

KDBH Podcast #2: Management and Treatment of Diabetes to Prevent Cardiovascular Disease in the new American Diabetes Association's 2019 Standards of Care

- Ron Goldberg: 00:04 Welcome and thank you for joining us for the second podcast from the new and informative podcast series on cardiovascular disease and diabetes for healthcare professionals. The goal of this series is to reduce cardiovascular death and incidents of heart attacks and strokes in people with diabetes and is based on the new collaborative initiative between the American Heart Association and American Diabetes Association called Know Diabetes by Heart.
- Ron Goldberg: 00:33 This series is brought to you by founding sponsors, Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance and Novo Nordisk and the national sponsor, Sanofi. I'm Dr. Ron Goldberg and joining me is Dr. Chris Cannon. We will discuss how cardiovascular disease is addressed in the new American Diabetes Association's 2019 Standards of Care.
- Ron Goldberg: 01:01 So to begin with, Chris, it might be useful for our listeners to get a feel for what's new in our thinking about atherosclerotic vascular disease in people with diabetes.
- Chris Cannon: 01:14 Well, thanks very much. A delight to join and a really exciting time in the field with lots of new therapies and then guidance on how to approach patients and really get the best therapies to the best patients. Now, I think in general we've known that atherosclerotic cardiovascular disease is the major complication of diabetes. But with all of the cardiovascular outcome trials, we now have a lot of new data on exact event rates, and so our awareness of the risk of heart attack, stroke, and death from diabetes I think is more acute. And another new thing that's come to light is the risk of developing heart failure. This goes along probably a lot of diastolic dysfunction in diabetes, but one that thankfully all of these are modifiable with some of the new therapies.
- Chris Cannon: 02:09 So I think increasing awareness of the very high cardiovascular risk and then a focus on aiming to prevent cardiovascular events as a goal of therapy is really a new point of emphasis in the guidelines.
- Ron Goldberg: 02:25 That's great, Chris. It's sort of follows from there then that if we can prevent diabetes, obviously that is the earliest way to try to prevent cardiovascular disease in diabetes. Wouldn't you agree?
- Chris Cannon: 02:38 Yes. This is certainly a major time point that you could avoid all these complications. Indeed, I saw just a news story of someone who lost 400 pounds because the doctor told him he had prediabetes, and he didn't want to get diabetes. That's exactly

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the type of awareness that patients can really intervene in lifestyle with dietary changes and exercise as the key as a way to avoid developing diabetes in the first place and then the complications from it.

Chris Cannon: 03:11 There's also been data available on early use of metformin in patients with prediabetes, and so that can be another way of trying to avoid development of full-blown diabetes. But a real focus is on lifestyle changes with diet and exercise that we all try and emphasize and work with our patients to figure out what could work for them.

Ron Goldberg: 03:35 Right. So, unfortunately, we're confronted all the time with people who have developed diabetes, and I think it's true to say, isn't it, that over the last few years, we've come to appreciate that the risk of cardiovascular disease in diabetes is not as monolithic as it used to be, that there's quite a wide variation and risk. And so I think it will be important to say something about how the physician should evaluate the patient and what are the keys to help assess that risk.

Chris Cannon: 04:07 This is a terrific point, and I think one that in the new guidelines we do make some emphasis on exactly this, of what are the risks and specifically focusing on those risks so that we can then tailor therapies for that. And, so, one simple thing is used in patients in general for primary prevention is calculating the ASCVD risk score, so that is what is the 10-year risk of developing a fatal or non-fatal MI or stroke. This was based on the Framingham Risk Score originally but updated, and it's been seen that this score can be helpful even in patients with diabetes. And in part, it will identify very high-risk patients where if you have diabetes and say a risk score of 20% or higher, that you would be treated as if you have known coronary disease. So this can be a real starting point to quantify a bit the risk in this case of MI or stroke or death from either of those.

Chris Cannon: 05:17 There are many other assessments, and so there's some discussion now and wider use and more studies of calcium scoring as a way to further risk stratify patients. This is a way of actually imaging whether the process of atherosclerosis has started in the heart arteries, and so it's a really direct way of seeing what's happening for a given patient. So, there've been a host of studies, including in patients with diabetes, showing that the more calcium that's identified in the calcium score, that score can range from zero, meaning no atherosclerosis developing, or all the way over a thousand. And the higher that

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amount of calcium, then the higher the risk of developing a cardiovascular event.

Chris Cannon: 06:08 There haven't been strategy trials of using that number to change the therapies, but it's been seen and now in other guidelines for cholesterol management, has been cited as a way to, if you are uncertain about a patient's risk and want to decide on how intensively to treat them, that calcium scoring is the new test that's gaining wider acceptance.

Ron Goldberg: 06:33 I know that in talking to patients and other physicians, one of the issues knowing how high the risk of cardiovascular disease in diabetes is, is how intensively they should screen patients for ischemia or coronary heart disease, and therefore it will be important to hear your thoughts about whether you think that's fruitful or not.

Chris Cannon: 06:54 It's a terrific question. Screening interestingly goes in two flavors of one, looking at the function, so a stress test for example, or imaging atherosclerosis and more of the anatomy of the coronaries. In general, screening asymptomatic patients has not been seen to be helpful in directing care so that doing a routine stress test, say, every few years would generally not be recommended. I think in patients with diabetes, symptoms can often be a little bit atypical or masked, and so one does have to have a high level of suspicion if patients have exertional dyspnea, that would immediately raise questions about whether ischemia is developed. So being careful on are there any subtle symptoms, and if so, then that would direct a functional test like a stress test. But then the calcium scoring would be another way of screening patients and there it's not recommended, but I think it's a tool that in selected cases can be helpful.

Ron Goldberg: 08:05 And then perhaps a final point in this particular area is the increasing recognition of the importance of renal insufficiency. Would you say a few things about that?

Chris Cannon: 08:17 Well, this is another key thing. In part, we all know that we have to get an ACE inhibitor going to protect the kidneys for patients with diabetes, although that has really been seen more in patients with some level of albuminuria, and so we realize that actually doing a formal assessment of what stage of chronic kidney disease or CKD a patient, can again help focus therapy. The exciting thing that we'll come to is some of the new agents can impact and beneficially the progression of renal disease. So we have new therapies that can improve renal function over

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time. And, so, we've included in the assessment section all the different things to look for in the history and physical, but then also to do these assessments and say what is the ASCVD risk score and then what is the stage of chronic kidney disease if normal or more advanced. That can again raise awareness to say, "Oh, I can't forget about directed therapy to prevent renal progression of disease."

Ron Goldberg: 09:26 Right. So okay, we've done our assessment. We've tried to develop a sense of how much risk this particular individual has, and so we have one or more or none if we're fortunate, if the patient is fortunate, abnormal risk factor. So the question then becomes, what's new with regard to management of classical risk factors such as hypertension, dyslipidemia, the use of aspirin for example?

Chris Cannon: 09:53 Well, interestingly, there is some new data, both in more intensive and less intensive, across the different other risk factors. It's a key point for starters to just say that in the management of a patient with diabetes, there's a focus on glycemic control, but then on these other risk factors. Indeed, the focus, as we said in the very beginning, now in preventing cardiovascular events is the goal, not just each individual target.

Chris Cannon: 10:22 But for blood pressure, the last year for patients with or without diabetes, the American College of Cardiology and the American Heart Association had new long-awaited guidelines that set a lower threshold for the target for management and said that blood pressure elevations are no longer just 140/90 but even 130 would be a stage one of hypertension, and so a question of what should be the target. So in patients with diabetes, of course we had the ACCORD Trial that didn't find a big benefit of more intensive blood pressure lowering, but in the SPRINT Trial without diabetes, there was a benefit of a lower blood pressure target of 120.

Chris Cannon: 11:09 And, so, in the recommendations, we note that there should be individualization of the blood pressure target. In the higher-risk patients, you'd aim for a lower target and aim systolic of 120 or so, but in the lower-risk patient, you'd want to avoid going to low because it can have consequences. A second major risk factor is obviously lipid management, and there over recent years, all the various guidelines are getting more and more intensive. And, so here we have for a general patient primary prevention use of a statin is recommended. And then for anyone with known atherosclerotic cardiovascular disease, intensive statin therapy is recommended, and then add on non-

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statin therapy if the LDL remains above 70. And, so that would be with ezetimibe and in some cases one might need a PCSK9 inhibitor, and so intensive lipid management has been seen to have really great benefits in patients with diabetes.

Ron Goldberg: 12:14 Can I ask in regard to statin therapy or other lipid-lowering agents, one of the questions that often comes up particular in our aging population with diabetes as well of course is the fact that there are now more young patients with type 2 diabetes, is what to do in people over the age of 75 on the one end and under the age of 40. How are physicians to think about that?

Chris Cannon: 12:42 Excellent question, and guidelines have called out those two sides of the spectrum. I think in short, patients over the age of 75 should receive as intensive therapy. The level of evidence from the trials is a bit more modest in that there are fewer patients over the age of 75 in all the trials, but the benefits actually are bigger in absolute terms of all of these interventions. And so in short, do the same thing as you would otherwise in patients 75 years or older.

Chris Cannon: 13:15 For younger patients, I think you generally also try and do the same thing, although patients will be lower risk, and over the first 10 years, it's a very low risk of developing a cardiovascular event. So there, it's more of a discussion that's encouraged to talk about the risk, try and run some of the ways of assessing risk, perhaps the risk score only works if it's age 40, but one can run that score nonetheless, and then think about other risk-modifying tools. But to certainly consider statin therapy as you would if the patients were 40 or older.

Ron Goldberg: 13:57 The other thing that always caused confusion over the years, maybe it's a little clearer now, is because so many of our patients have hypertriglyceridemia, whether we should add fibrates to a statin. Any thoughts about that?

Chris Cannon: 14:10 Well, it's a fascinating area in high triglycerides. So unfortunately, there was not a benefit seen in the trials with fibrates overall. Subgroup analyses of some of these have suggested maybe benefit if the triglycerides are high and the HDL is low. But as of 10 days ago, there is a new intervention that had striking results with the icosapent ethyl or EPA preparation of omega-3 at a high dose of four grams was seen to have a huge benefit, like 25% to 30% reduction in cardiovascular death and MI and really striking results. This is brand new. It has not made it into any guideline but is a big development in the area of high triglycerides. I think reviewing,

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it's the REDUCE-IT Trial, but that will be something that will have to make it into the living updates for the guidelines are now being adopted so that new important trials and advances like this could be incorporated more than just the annual update.

- Ron Goldberg: 15:23 Thanks for that really clear and complete evaluation of hypertension and dyslipidemia management and its new development. What about aspirin? This has always been a somewhat ticklish area in terms of who to give aspirin to and who not to and what the risks are. Would you care to comment on that?
- Chris Cannon: 15:40 Well, yeah this is another fascinating area where here we're getting a little bit less intensive interestingly. So just this year, this fall, there were three large trials and one was dedicated to patients with diabetes, a huge 18,000-patient trial that Oxford ran called the ASCEND Trial looking at aspirin for primary prevention. And, they found a benefit of about 12% reduction in events, but they found a similar increase, about a 1% absolute increase in the risk of bleeding. The number of heart attacks or strokes avoided was equal to the number of bleeds created, and so the net benefit was kind of neutral.
- Chris Cannon: 16:29 Now, some of the bleeds were gastrointestinal bleeds. So if one took a proton pump inhibitor, could perhaps prevent that. But we settled on the notion that this should be a discussion between the patients and clinician to sort out the benefit and risk for an individual patient. And, so, it's no longer a straight-up decision of, "Oh yeah, diabetes, and you have a certain level of risk. You should take aspirin," that one really has to consider carefully the benefit and the risk to see what would be helpful.
- Chris Cannon: 17:06 I think another study had patients over the age of 70, and there, there was more risk and no benefits seen. And so age advances, interestingly the risk increases, and so one pulls down may indeed avoid aspirin for primary prevention again. For secondary prevention, if you've had a heart attack or stroke, obviously then aspirin has been proven many times over and is still fully recommended for use.
- Ron Goldberg: 17:34 Given the increased risk for thrombosis that people with diabetes are said to have, is there a place for more than aspirin in terms of antiplatelet therapy?
- Chris Cannon: 17:46 Well, certainly in secondary prevention, so if you've had a stent, obviously you'll get a P2Y12 inhibitor and clopidogrel is the main

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one in addition to aspirin. And other combinations in secondary prevention have shown great promise. And, so, a new combination just recently approved of a quarter dose of rivaroxaban plus aspirin was seen to have big benefits on mortality, and MI, and stroke in a broad population of patients with known vascular disease including patients with diabetes, but it also has a higher risk of bleeding.

Chris Cannon: 18:24

So in the secondary prevention realm, an add-on therapy of either two antiplatelet agents or antiplatelet and a low-dose anticoagulant have been seen to be beneficial. But that same benefit/risk calculation is something that will go into the decision making.

Ron Goldberg: 18:42

Thanks. That really, although it's still a little unclear, it certainly helps I think in deciding about when to use aspirin and when not. So in a way, we've left the best for last in terms of positive developments over the last few years, and of course I'm referring here to the new antihyperglycemic agents, which as you well know, in a way we learned about the cardiovascular effects from the FDA insisting that all new antidiabetic drugs undergo cardiovascular testing. And of course, I'm referring to the GLP-1 receptor agonists and the SGLT2 antagonists. So perhaps you'd like to begin with the GLP-1 agonists and tell us where their place might be or even begin with a sort of general discussion of where these agents fit in to our antihyperglycemic armamentariums.

Chris Cannon: 19:36

Well, as you said, this is such an exciting time, and it seems like every other week there's a new large trial that shows a benefit on prevention of cardiovascular events. And so for many years, it was all about managing the glucose, and we assumed that was helpful. Then we found in some of the other classes of the DPB4 class, really no apparent benefit in terms of reducing death or heart attack or stroke. But then beginning with empagliflozin in the SGLT2 class, but then also with liraglutide in the GLP-1 receptor agonist class, that reductions in cardiovascular events were seen over the three to five years of follow-up in these trials, and so a clinical benefit that was observed over a short period of time with management with these two classes of drugs.

Chris Cannon: 20:30

And what's been so exciting is that this has now been replicated in three different trials with the SGLT2 altogether and now five trials with GLP-1 receptor agonists have had positive benefit on cardiovascular events, and so really striking benefit that's seen. Interestingly with the SGLT2, it seems to be for both

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atherosclerotic events and for heart failure prevention. so a fascinating benefit. And actually a third aspect that I mentioned in the beginning was a prevention of progression of renal disease, so a kidney benefit as well.

- Chris Cannon: 21:11 The prevention of cardiovascular events seems to be more in those with known atherosclerotic disease, but prevention of heart failure and CKD progression, that seems to be more across the board regardless of whether you've had a prior MI or stroke with the SGLT2 class. For GLP-1 receptor agonists, the benefit on cardiovascular events has been seen, also a kidney benefit has been suggested in some of the analyses. But no difference in heart failure with that class of drugs.
- Chris Cannon: 21:44 So this is now a well evidence-based two classes of drugs that have led to a big shift in the management algorithms for choosing glycemic agents in diabetes where the patient characteristics are the main driver for choosing the classes of drugs. And, so, this was really mentioned a little bit last year in the ADA document, but in the new ADA/EASD document in the upcoming ADA Standards of Care, this has now been a major shift in how we choose therapies, with these two classes of drugs really moving to the head of the class for these patients with atherosclerotic cardiovascular disease, heart failure, or CKD.
- Ron Goldberg: 22:33 So just to be clear, in patients without any evidence of heart disease or renal disease, should these drugs be still thought of as possibly preventing cardiovascular disease and therefore be considered? Or should their use be focused more at those individuals who are already presenting with some atherosclerotic cardiovascular disease or renal disease?
- Chris Cannon: 22:56 I think the latter for the moment. And, so, the algorithm is a very nice one where in approaching the glycemic management, obviously lifestyle intervention is a base approach and then metformin is recommended as the first line therapy. There hasn't been a study that's gone head to head against that to try and displace metformin, so that becomes the base therapy. And then the next question to ask is, does a patient have known ASCVD? And if so, then either of these two classes is recommended as the next line of therapy.
- Chris Cannon: 23:35 The second question is, does a patient have heart failure or chronic kidney disease? And if so, again the SGLT2 is the preference, and the GLP-1 as the backup are the recommended therapies. Then still more patient characteristics to help drive



the therapy. But there we have evidence of clinical benefit once we get past those patients, so the patients without known heart disease. There we start looking at other factors to try and choose therapy. And, so, the next one that's recommended is whether weight loss is a key focus of the management program overall. And if so, there are then two classes of drugs that could be recommended, including the GLP-1 receptor agonists, probably the most potent, and the SGLT2s are really helpful there.

Chris Cannon: 24:30 A fourth characteristic then is whether hypoglycemia is a worry. And that of course is a worry for a lot of patients. Sulfonylureas and insulin are obviously the two classes of drugs that contribute to hypoglycemia, but there are then four different classes that could be recommended if hypoglycemia is a worry. And then a final thing is that cost is obviously a key thing, and so there are even recommendations put in for cost. It's a cascade where you have base therapy, questions about do you have ASCVD or heart failure or chronic kidney disease, where you would choose specific therapies, and then if not, then you'd start looking at the patient and other goals of therapy to try and choose amongst the different classes.

Chris Cannon: 25:18 So a very different approach than the more hemoglobin A1c titration approach that was the key focus. And so pretty exciting I think because many of these class choices can lead to clinical benefit.

Ron Goldberg: 25:35 So Chris, we've reached a point then where, would this be correct, that these effects are probably class effects? The GLP-1 receptor agonists as a class and the SGLT2 antagonists? And since they seem to be having somewhat different effects on the cardiovascular system, it raises the question as to whether combination therapy might have additive effects. Do we know anything about that?

Chris Cannon: 26:00 Well, I don't know that anyone comes out and declares it's a class effect, but the consistency across all these different trials I think in each of these two different classes to me does suggest a class effect. The very short-acting GLP-1 receptor agonists have not been seen to have clinical benefit, and so the ELIXA Trial and the lixisenatide was the agent there. That's been the one exception so far. And, so, the longer-acting agents for the GLP-1 receptor agonists seem to be where the class effect is there. Some differences between the different trials, but I think in general the classes do seem to have very positive clinical effects.

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- Chris Cannon: 26:43 I should note that the evidence on the benefit for heart failure has thus far been seen in patients with known atherosclerotic cardiovascular disease largely, although some recently seen without it in the DECLARE Trial, but not specifically in patients who start out with heart failure. It's really been prevention of development of heart failure in a broad population. And, so, there are specific trials now going on in patients with documented heart failure as a major component of their cardiac disease. And, so, lots of new trials are emerging from all the evidence to date that we have some really clinically beneficial classes of drugs.
- Ron Goldberg: 27:27 Well, sadly our time is up. I know we could go on talking about this for a good deal longer. It is such a fascinating area, and I want to thank you sincerely for helping to make us understand it and to our listeners to thank them for listening and please to stay tuned for upcoming podcasts.
- Chris Cannon: 27:45 Thanks very much.