Welcome and thank you for joining us on our kickoff podcast for the 2020 Know Diabetes by Heart podcast series. The purpose of this ongoing series is to reduce cardiovascular deaths, heart attacks, strokes and heart failure in people 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. This series is brought to you by founding sponsors, Boehringer Ingelheim and Eli Lilly and Company Diabetes Alliance and Novo Nordisk, and national sponsors, Sanofi, AstraZeneca and Bayer. I'm Dr. Jennifer Green, an endocrinologist and diabetes and metabolism specialist, and joining me is Dr. David Aguilar, a cardiologist who is also board certified in internal medicine. We will discuss how the American Diabetes Association's 2020 Standards of Care guidelines have changed and implications for practice. Dr. Aguilar, it may be a good time to start by discussing what hasn't changed. Were there any important principles in the new Standards of Care that you thought were maintained and important to highlight before we move into the changes?

Well, Dr. Green, I think this is obviously such an important document that helps us take care of our patients who have Type 2 diabetes and cardiovascular risk, and like similar publications or previous iterations of the guidelines, they really emphasize a patient-centered approach, to help physicians and healthcare providers really match the choice of pharmacologic therapy or lifestyle modification to lower risk associated with diabetes, specifically cardiovascular risks in specific patients. So I think it echoes what we've seen in previous guidelines, really finding the right therapies, the right interventions and strategies for the right patients. And what's important about these, is that the treatment decisions, be it lifestyle interventions, behavioral modification or pharmacologic therapy, really focus on the patient's risk factor profile. Do they have cardiovascular disease? What cardiovascular risks do they have, as well as the strategy that we're implementing, be it blood pressure control, lipid-lowering therapy, or antihyperglycemic medications to lower their overall risk.

Right, so I think one of the important overarching themes that remain in the Standards of Care is an emphasis upon individualization of care for each patient in setting glycemic targets, and then really constructing a regimen of medical care which best suits that person based on their individual needs and any particular micro- or macro-vascular complications that they might have. Before we move on, I would mention that there is still a recommendation to use Metformin as the preferred first agent for the treatment of Type 2 diabetes, and we'll come back
to that when we dive into this a little bit more deeply later in today's podcast. Section 10, which focuses on cardiovascular disease and risk management really continues to emphasize the large benefits or the significant benefits that are achieved when we address multiple cardiovascular risk factors in an individual patient, and should be targeted according to their risk profile. Were there any particular recommendations as far as management of these cardiovascular risks that you found to be most important for our listening audience?

David Aguilar: 03:38 I think it's really important to remember that many of these risk factors, they don't occur in isolation, and when we approach patients, they have several risk factors. So although we often speak of hypertension or lipid-lowering therapy or diabetes individually to set our recommendations, I think one point that the Standards of Care makes emphasizes the need to target all risk factors. We might be good at achieving one goal, but really we're going to have our greatest success if we can reach several goals, and really taking a multifaceted approach to target multiple interventions. We know that many of our patients have hyperlipidemia, hypertension, as well as their glycemic agent, smoking status, their level of physical activity, and really it takes a multifaceted approach, and I think the guidelines really highlight this point.

Jennifer Green: 04:27 Right, and I think it's important to recognize that each person's individual cardiovascular risk profile will not remain static, and we have so many young people who are being diagnosed with Type 2 diabetes. As they're living many, many years with the condition, their estimated risk for cardiovascular events will continually evolve. So I think it's important for the individual practitioner to regularly reassess each individual's risk and make sure that they're receiving guideline-directed interventions to keep them as healthy as possible. There certainly our blood pressure targets, which are covered in the Standards of Care. I don't think that those have changed dramatically.

Jennifer Green: 05:42 I think that's fairly unchanged from previously. However, there have been a fair number of changes in the recommendations for lipid management, and in particular the recommendations around statin therapy, and those revisions have been made to achieve consistency with the 2018 ACC, AHA, et cetera, multi-society guideline on the management of blood cholesterol. So, readers will see in the Standards of Care that that document in particular is referenced as the guidelines for use of lipid-lowering therapies have become relatively complex. But this again is in an attempt to better customize and better individualize recommended therapies for each patient based on
their personal risk. Were there any particular trials with respect to lipid-lowering approaches that you've found interesting or important to highlight in this new version, Dr. Aguilar?

David Aguilar: 06:42 It has been an exciting year for lipid-lowering therapy, and I think probably the biggest trial that has been incorporated into the Standards of Medical Care and Diabetes document is the REDUCE-IT trial. As you know, this was a study using icosapent ethyl in patients who either had atherosclerotic cardiovascular disease, or a cohort of individuals who were high risk, who specifically had diabetes and showed benefit associated with the use of this medication on top of a statin in both individuals, an entire cohort including those with diabetes. So this now has been incorporated in the Standards of Care, where the use of icosapent ethyl in patients who have diabetes but who have controlled LDL cholesterol with the statin, but still have elevated triglycerides, triglycerides between 135 and 499 to reduce the risk of cardiovascular disease. So, this is an important update that is now present in the Standards of Care.

Jennifer Green: 07:37 Right, it's really become a situation where we have a wide array of tools to reduce cardiovascular risk in individuals with Type 2 diabetes. I would note that this is a recommendation to consider use of icosapent ethyl in these individuals, and not a firm recommendation, as I think we're all, I think, trying to figure out how to best incorporate these newer treatment options into each individual patient's regimen. But certainly that represents a very good therapeutic option for individuals who are considered to be at very high risk for recurrent events. I think one thing that readers will absolutely notice when they're reviewing Section 10 again, the cardiovascular section of the Standards of Care, is how much expansion there has been in the inclusion of data and information pertaining to the cardiovascular outcomes trials of individual diabetes medications in patients with Type 2 diabetes. And the information has been reorganized and summarized in an attempt to make the results a little bit more understandable and useful to practitioners.

Jennifer Green: 08:51 I would note that some very late breaking trials, for example, the Carolina [inaudible 00:08:57] heart failure trial, those results were not available in time for incorporation into this annual update. However, the living standards are now considered, frankly, a living document, so they'll be updated regularly in between the annual issues, so we can expect to see that updated information included fairly early next year. One of the things that I had noticed was that in prior issues of the Standards of Care, Metformin does remain the recommended...
first line therapy, which should be initiated at the time of diagnosis of Type 2 diabetes. But importantly for patients who also have established cardiovascular disease, chronic kidney disease or heart failure, or who are at very high risk for those conditions, for those patients, the addition of an SGLT-2 inhibitor or GLP-1 receptor agonist with a demonstrated cardiovascular benefit no longer depends upon the need for additional glucose lowering.

Jennifer Green: 09:53 So, for example, if a patient with Type 2 diabetes and established coronary disease has a well-controlled A1C on Metformin monotherapy, he or she should still have an SGLT-2 inhibitor or a GLP-1 receptor agonist added for cardiovascular risk reduction, even if they don't need that additional drug to reach their individualized hemoglobin A1C target. So Dr. Aguilar, what do you think about that? Is that a reasonable change from your perspective, or do you feel like it may not even have been aggressive enough?

David Aguilar: 10:28 I think it is a reasonable change, and Dr. Green, it has been a remarkable few years and things are moving fast as far as the amount of information that we currently have. If you reflect back and think of cardiovascular outcome trials a decade ago, we had very few patients, and now it's estimated that there may be over 200,000 individuals who've been enrolled in the cardiovascular outcome trials, which now form the basis of how we're treating our patients. And I do think that this recommendation is an extension of those trials, which really move beyond A1C in lowering cardiovascular risk.

David Aguilar: 10:59 So I find it important particularly as we individualize treatment, and I may just ask you as well, as an endocrinologist, when we see a patient who has an A1C that's well controlled, and in target and we're adding an SGLT-2 inhibitor or a GLP-1 receptor agonist which hasn't been shown to have proven cardiovascular benefit, are there suggestions that you might give a practicing PCP or a cardiologist who is considering adding these medications in someone who's controlled on other therapies beyond Metformin?

Jennifer Green: 11:30 That's a great question, and this is a very common clinical scenario, and I think all of us need to become comfortable with essentially making room in the diabetes medication regimen for these beneficial agents in high risk patients, if they're not already taking one. And so for example, some of the main principles to keep in mind would be if you have a patient who's on a sulfonyl urea or insulin, take a look at their A1C, see if they're having any hypoglycemia. If A1C is already a goal and or
if they're already having issues with low blood sugars, then those medication doses will need to be reduced or potentially even discontinued in order to safely make room for the addition of an SGLT-2 inhibitor or a GLP-1 receptor agonist. I personally, if the patient doesn't need additional glucose lowering and the hypoglycemia is not a major issue, I will often consider cost in deciding which medication I'm going to discontinue in order to incorporate use of the beneficial new medication.

Jennifer Green: 12:40 But you can certainly take other factors into consideration. If a person's on a drug that they're not tolerating particularly well, that's a great choice for discontinuation, so that you can adopt and include the use of this newer medication. We don't have enough time on this podcast to really review all of the considerations, but of course, for example, SGLT-2 inhibitors have a diuretic effect, so I'm always cautious about what the blood pressure is at baseline and whether or not the person's taking a lot of other diuretics or perhaps other antihypertensives that might need to be reduced in concert with the initiation of an SGL-2 inhibitor. But I think what's really important is for people to think about this, and start doing it potentially in lower risk patients first so that they achieve some experience and really gain confidence in their ability to use these medications safely.

David Aguilar: 13:38 So as we think about the guideline and the recommendation for the treatment of reaching for these medications, even in patients who are controlled on their A1C, we still need to pay attention to where they are, and then echoed through the document are the risks associated with hypoglycemia. So as a practitioner, you're saying we still need to pay attention and be cognizant of it and perhaps withdraw medications that could increase the risk of hypoglycemia over time.

Jennifer Green: 14:04 Right, and I think that's not necessarily because hypoglycemia itself would be responsible for increasing the risk of cardiovascular events, but really more the fact that hypoglycemia itself is inherently dangerous and something to be avoided. And much of the time, we can make changes that allow us to add new agents to reduce cardiovascular risk safely. But it's a matter of, I think, just putting this into practice and doing it regularly so that it almost becomes an automatic approach to the clinical care of these patients. I would mention that when you look at the figure in Section Nine that indicates how these new drugs should be adopted in patients with cardiovascular disease, heart failure, or chronic kidney disease, when you look at the portion of the figure that refers to patients with atherosclerotic cardiovascular disease, we have
the option of using either a GLP-1 receptor agonist or SGLT-2 inhibitor as equivalent choices in that group of patients, and that's really because at present we have no head-to-head cardiovascular outcomes trials comparing the benefits of an SGLT-2 inhibitor compared to a GLP-1 receptor agonist in that group of patients.

Jennifer Green: 15:23 I think what's important to remember is those classes of drugs provide benefits to such patients, but really it's the types of benefits that are provided that differ between the two classes of medications, but either option is quite reasonable. I think it's interesting to note that the body of literature and amount of evidence available now for heart failure prevention and for outcomes benefit in patients with chronic kidney disease with the use of SGLT-2 inhibitors continues to grow, in particular with incorporation of the DECLARE-TIMI 58 and CREDENCE trials. Do you have any thoughts or insights about this very interesting direction that cardiovascular outcomes trials have taken in recent years?

David Aguilar: 16:09 So I think the literature with the SGLT-2 inhibitors in patients who have chronic kidney disease is very exciting, particularly as we think historically of what we've had, not only for cardiovascular outcomes, but for renal outcomes, when we think of issues or medications that we've had for renal protection in patients who have diabetic kidney disease, for example. Historically, we've had inhibitors of the renin–angiotensin system, ACE inhibitors or angiotensin receptor blockers, and these medications have shown benefit in patients who have chronic kidney disease, specifically the CREDENCE study. And not only did it benefit their kidney disease, but it also benefited their cardiovascular outcomes.

David Aguilar: 16:44 So I think we're in a special era related to renal protection and these medications. And then to further that also with heart failure, this is a special time for the prevention of heart failure with these agents. In previous renditions of Standards of Care, if we went back several years and we looked for heart failure, we would always be concerned about harm. For example, thiazolidinediones and fluid retention and how these medications were limited in people who had heart failure because of increased rates of heart failure hospitalization.

David Aguilar: 17:11 And now we have these medications which really are consistent with the SGLT-2 inhibitors that they have a special role in the prevention of heart failure, and all three studies, in the DECLARE cardiovascular outcome study, the CANVAS program as well as EMPA-REG outcome study, where the SGLT-2
inhibitors were associated with reduction in heart failure hospitalization. So I think that's very exciting and kind of a great area of interest.

Jennifer Green: 17:35 Right, and it's particularly exciting that we're identifying evidence of benefit in who are really our sickest patients, patients with heart failure and patients with chronic kidney disease for whom treatment options often become fairly limited. And we'll expect to see a great deal more information about the effects of agents in these particular classes of patients moving forward.

David Aguilar: 18:02 Dr. Green, one thing that I find interesting and important is that we do have a lot of data now on patients who have established atherosclerotic disease, who have risk factors or chronic kidney disease, and now even some with heart failure, in how we incorporate the presence of these diseases in deciding on starting certain therapies. But in the absence of high-risk features such as known heart disease or known heart failure or known kidney disease, the guidelines say that we don't have a lot of data on which to base decisions. And so the guidelines again echo this idea of individualizing and sharing our decisions with our patients, be it a need for cost, or if weight is an issue, or hypoglycemia, that we choose different agents.

David Aguilar: 18:45 There have been some observational studies which have echoed, for example, the benefits with SGLT-2 inhibitors that have been seen in CV outcome trials. In these observational studies, the risk of having a heart attack is much lower in people who've never had one compared to secondary prevention, so the absolute risk reduction is lower, although the relative risk here is very similar to the studies that we've seen with cardiovascular outcome trials. I was wondering if you had thought of this and how we extend what we've seen with the cardiovascular outcome trials to perhaps our lower risk patients which we may see in the clinic.

Jennifer Green: 19:18 Yeah, that's a great question, and I agree that this is a clinical management issue that is very commonly encountered. When you think about optimal strategies or optimal care pathways for patients with Type 2 diabetes who do not yet have cardiovascular or renal complications of their disease, but who have many risk factors for the same, it's hard to apply the current clinical trials evidence to that decision making. There is, however, some movement in that direction and I think the best example of this is in the REWIND cardiovascular outcomes trial of the GLP-1 receptor agonists dulaglutide, and that particular trial enrolled a very significant percentage of patients who
would be considered a primary prevention population. And importantly, the patients who were assigned to dulaglutide had a very significant reduction in the rate of their primary cardiovascular outcome compared to individuals who were assigned to placebo in that trial.

Jennifer Green: 20:27 And when they looked specifically at the outcome in the primary and secondary prevention populations, it was clear that dulaglutide was effective in significantly reducing the risk of cardiovascular complications in the primary prevention population. So I think that data is accumulating to support preferential use of particular agents in high-risk patients who have not yet experienced major complications of their disease, but agree that it can be difficult to really figure out the patient population for whom these interventions should be selectively deployed. But hopefully we will learn a considerable amount more about this in the future.

Jennifer Green: 21:14 Well, this has been a very interesting conversation and unfortunately, it's not possible for us to have covered all the changes in this individual podcast, but I think in conclusion, we both agree that delivery of guideline-based care in these high cardiovascular risk patients with diabetes is of very significant importance, and we now have many tools to address these multiple aspects of cardiovascular risk. I would note, though, that recently-published data suggests that delivery of this care and clinical practice remains suboptimal, so we need to emphasize that cardiovascular risk reduction in patients with diabetes is a shared responsibility. It doesn't belong exclusively to general medical doctors, endocrinologists, or to cardiologists, and in attention appears needed to address gaps in care and increase everyone's familiarity with use of these beneficial diabetes medications. Thank you very much for listening and stay tuned for upcoming podcasts. And if you missed the previous series, please go to knowdiabetesbyheart.org podcast series to listen to the other podcasts.