

Jorge Plutzky: 00:04

Welcome and thank you for joining this podcast on managing cardiovascular risk and renal risk in patients with diabetes. This discussion is based on new science that came out during the recently concluded American Heart Association Scientific Sessions 2020. The purpose of this ongoing series is to ultimately reduce cardiovascular deaths, heart attacks, and strokes, as well as heart failure in people living with type 2 diabetes.

Jorge Plutzky: 00:30

It's based on an exciting collaborative initiative between the American Heart Association and the American Diabetes Association, Know Diabetes by Heart™. It's a valuable resource for both patients and physicians. This is the professional education podcast series, and 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 and AstraZeneca and Bayer.

Jorge Plutzky: 00:58

My name is Jorge Plutzky. I am a cardiologist and the Director of Preventative Cardiology at the Brigham Women's Hospital. We've had a longstanding interest in the intersection between diabetes and heart disease. It's exciting to be able to discuss some of the ongoing advances in this area. And, I'm also very excited to have joining me today Dr. Neha Pagidipati from Duke. Neha, thank you. Welcome. And, why don't you tell us a word or two about yourself?

Neha Pagidipati: 01:26

Thank you so much, Dr. Plutzky. It's really an honor for me to be able to speak with you today. As you said, my name is Neha Pagidipati, and I am a cardiologist at Duke. My focus is on cardiometabolic disease prevention, and I've been fortunate to be the Director of the Duke Cardiometabolic Prevention Program. And, I also do a lot of work in clinical research and in implementation science in this field. So, it's a huge honor for me to be speaking with you today.

Jorge Plutzky: 01:49

It's great to have you here, and I certainly want to talk to you about what you're doing at Duke there since I know you're doing some innovative approaches, and I think it's very timely in terms of what we're dealing with. But, it's really, I think you agree, Neha, as we've talked about, an incredibly exciting time in this cardiometabolic space. I think the AHA 2020 continued to reinforce that. We've really entered into a whole new era about the management of diabetes, how we think about diabetes, and most importantly about how we manage cardiovascular risk in those patients. We've known for a long time that that risk is present, and yet for decades, we have failed to make inroads on reducing cardiovascular risk by treating diabetes. We knew that the risk was there with people with diabetes who'd never had a cardiovascular event, but yet, paradoxically, as you treated their diabetes outcomes, didn't get better.

Jorge Plutzky: 02:44

And that really has changed over the last few years. It's really a revolution in this area with the advent of these two classes of medicines, the SGLT2 inhibitors and the GLP-1 receptor agonists with data that really came out of first proving that they were safe in terms of not causing more cardiovascular disease. Those studies one after another showed benefit of actually reducing cardiovascular events with both those agents. And, I think at the AHA, we saw how that discussion is continuing to evolve. Would you agree with me that we're really into new uncharted territories about how to continue to leverage these new insights and understand how to use them?

Neha Pagidipati: 03:29

Absolutely. I completely agree, and I think it's just an unbelievably exciting time for cardiologists who are managing patients with type 2 diabetes, for the primary care doctors and the endocrinologists who have always treated them, and for the patients themselves. And, I completely agree with you. It's like a complete paradigm shift, I would say, just in observing the AHA and the dialogue around cardiovascular risk in patients with type 2 diabetes over the last several years at each AHA. There's been a huge evolution in that discussion going from, as you said, the discussion around A1C lowering not actually providing any macrovascular benefit, to now, sessions that are titled, "Do cardiologists need to manage diabetes. Yes we do." And, several prominent leaders in the field such as yourself and others promoting this concept of cardiometabolic disease and that cardiologists really need to take a prominent role in helping to manage the cardiovascular risk in patients with type 2 diabetes. So, I completely agree. There's been a huge shift in the dialogue, and I think it's very exciting.

Jorge Plutzky: 04:31

One of the sessions at the AHA really was oriented trying to be a primer on the subject because a lot of cardiologists and their practices, people involved, nurse practitioners, nurses, and beyond trying to get their heads around this. And, one of the interesting issues is the barriers to cardiologists taking this on. I know in the comments we got in one of the sessions, someone asked, "Why should we be doing this as cardiologists? Why isn't this falling to endocrinologists and internists?" And, I think it's an important point. And, I was glad that it was asked because it really highlights the issue. The fact is that there are not enough endocrinologists out there to really handle the problem. There's many, many more cardiologists.

Jorge Plutzky: 05:12

And, at the end of the day, in addition to the other barriers we might cite about people saying, "Well, I didn't train for this. I'm not familiar with the issues. I don't know how to get reimbursement. I'm worried about causing a problem." We're so weaned on do no harm that the fact is that at the day, the outcomes with both the SGLT2 inhibitors and GLP-1 receptor agonists are cardiovascular

outcomes. And, so I think these are endpoints that we own. And, so as you assemble all those issues, not enough endocrinologists, they're looking at this as a cardiovascular outcome, and internist looking for guidance, I think that we really have to step up and begin embracing all the various issues and coming up with strategies for solving them. Do you encounter that hesitation in the Duke system or in North Carolina about whether or not cardiologists are willing to treat and use these agents?

Neha Pagidipati:

06:04

You make excellent points. And yes, absolutely. We actually did a study within the Duke Health System that we published last year. And, we did a survey of primary care physicians, endocrinologists, and cardiologists across the health system. And, obviously this is representative of large tertiary, quaternary academic health systems, but I think it was still telling nonetheless. We asked providers what their comfort levels were with their knowledge around SGLT2 inhibitors and GLP-1 receptor agonists, whether or not they prescribed those agents, and what they thought the barriers were. And, we saw stark differences between the different groups of providers. So, the primary care physicians and endocrinologists seemed relatively comfortable prescribing these agents. Their main concern and barrier they felt was the cost, which is obviously understandable. These are very expensive agents.

Neha Pagidipati:

06:53

Cardiologists, on the other hand, felt hugely uncomfortable with these agents and were less clear on who to prescribe them and how to do it and felt very worried about muddying the antihyperglycemic regimen of patients. And, obviously this data was about a year and a half old, but I fear that things have not changed all that much or at least enough. So, we absolutely see that here, too. And, I think it's being seen around the nation. And, you make an excellent point. I mean, we also looked at data from a large medical insurance population, the HealthCorps dataset. And, we looked at over 150,000 patients with type 2 diabetes and atherosclerotic cardiovascular disease. And, when you look at them, 70% of them had been seen by a cardiovascular specialist in the last one year, but less than 16% were seen by an endocrinologist. So, your point is exactly spot on, Dr. Plutzky, that these patients are definitely being seen by cardiologists much more than endocrinologist.

Neha Pagidipati:

07:48

And, of course, they're being seen by primary care physicians as well. But, I see some parallels to the statin story. Right? Because statins weren't initially considered cardiovascular drugs either. They were much more in the endocrinologist and primary care space, but their benefit was clearly a cardiovascular benefit. And, I think when cardiologists began to take some ownership of initiating and following and managing the patients on these medications, then I think that the usage greatly increased. So, my hope is that something similar will and should happen with these two agents that are clearly cardiovascular risk reduction agents.

Jorge Plutzky: 08:25

One of the topics of the discussion that came up with the AHA and came out of the strategy and a perspective that we've arrived at here at the Brigham is the idea that there's a spectrum of engagement of cardiologists with these topics. And, I think that spectrum gives room for people who just don't feel comfortable with it, which would be at the far end that you have to be aware of the data and that, at the very least, in a patient with diabetes who would from these agents, that you begin engaging with primary care physicians and endocrinologists on the topic, raising it in your communications and in emails and follow-up about, how about initial SGLT2 inhibitor, GLP-1 receptor agonist for this patient, because then you're at least advancing the discussion, and it's certainly a very easy entry point.

Jorge Plutzky: 09:17

And then, you progress from there to becoming familiar with the use of the agents and the appropriate use and when to be cautious, finding partners to work with, which is a broader strategy we've used of having an endocrinologist oversee and serve as a resource for our decision making, and then ultimately becoming comfortable with prescribing the agents oneself including getting the support needed for prior authorization and all those challenges. But, if you look at it as a spectrum then it also allows cardiologists to step into that stream at whatever point they feel comfortable.

Jorge Plutzky: 09:54

We find the younger people coming out of their training, closer to their Internal Medicine training, feel even more comfortable. In our own studies, we had one cardiologist who led the rest in terms of his use of these agents. And, so in our studies and asking him, "Why was that the case?" He said, "Well, that's easy. That's the clinic I do with the fellow." And the fellow was in training. But, the point would be that once you step into that stream, that you can then move downstream as you get more comfortable, more familiar with them. Although we certainly see many cardiologists in our system who feel very comfortable with it and are now using the drugs, and these agents are quite safe and well tolerated.

Neha Pagidipati: 10:38

That's absolutely right. I mean, I think you're exactly right that people have varying levels of comfort, not just with these agents but with starting new therapies and adopting new therapies into their practice in general. And, I think you're right. I think we've seen something similar at Duke in terms of the younger folks maybe being quicker to adopt. But, obviously we see a lot of variability in that. I think that as physicians begin to prescribe at least once, there's something of a feeling of it... Once you break that barrier and you prescribed at least once and you realize that things are okay, I think that there is a lot more comfort after that point. But, I think people need to have support in

order to do that because fundamentally, like you're saying, every doctor is doing their best and they just want to do what's right and not harm the patient.

Neha Pagidipati:

11:23

And I think there's some amount of fear when you're starting something that you've never done before. But I think as more programs like this, like Know Diabetes by Heart™, and other educational programs enter into the mainstream cardiovascular specialists consciousness, my hope is that that fear gets decreased. You know, we can talk about, and as we've already discussed, some of the barriers that cardiologist fields are prescribing these drugs, but clearly I think one of the issues is that their information is coming so fast and furious. There's this huge avalanche of data, which is very exciting for the field and for patients, but it can be hard to digest all of it and to know how to adopt it into your clinical practice. So, again, programs like this, like Know Diabetes by Heart™, I think are really critical to helping clinicians out in practice learn how to adopt these therapies.

Jorge Plutzky:

12:14

Yeah. Well, one of the things that helps with that, that certainly was reviewed at the AHA, is the incorporation of use of these agents into guidelines and guidelines, consensus statements, coming from ACC and AHA and trusted resources for us looking to the AHA and programs like this for information. Where we see that now incorporated into guidelines, and the ADA and these consensus statements look to try and parse out what direction you'd go in terms of GLP-1 and SGLT2 inhibitors. What's your overarching perspective as someone who's sitting across from a patient with diabetes who maybe is not at optimal control, has already had a coronary intervention, in terms of deciding about adding these drugs. Guidelines would have us think a lot about heart failure versus a more of a cardiovascular event risk. What's your perspective on that in terms of advising people about how to approach that decision-making?

Neha Pagidipati:

13:13

Yeah, it's a great question and something that comes up clinically all the time, and we think that there may be benefitted to using both. We don't know if they're synergistic, but they probably would be complimentary on both types of agents because they act in completely different ways. And, we think that obviously cost is such a big barrier that most patients or many patients that may not be feasible for them. So, if you have to choose one, the way that I generally think about it is if a patient has heart failure or significant renal disease, I am often thinking about the SGLT2 inhibitor because I think the data is so convincing with SGLT2 inhibitors, especially for heart failure with reduced ejection fraction. We don't yet have much data in the preserved ejection fraction population though obviously some data came out at the AHA, which we can discuss. But, especially in the patients with reduced ejection fraction, there is such a clear and really a huge benefit with SGLT2 inhibitors.

Neha Pagidipati: 14:09

And, that benefit happens very early on after starting the medication. So, if the patient has heart failure, especially with reduced ejection fraction, and/or has a low EGFR, especially above the 20 range, then I'm often leaning towards the SGLT2 inhibitors because in addition to the weight loss and the slight blood pressure lowering and the A1C lowering, and in secondary prevention patients that may benefit, there's a heart failure benefit and then a clear renal disease benefit, which I think is extremely important.

Neha Pagidipati: 14:41

We as cardiologists see renal disease really as a barrier to so many of the therapies that we want to institute for our patients with cardiovascular disease, especially those with heart failure. And, I think that this class of agents provide a way for us to address all of those different organ systems at once. But, for the patients who maybe primarily have a lot of atherosclerotic disease, have had an MI or multiple atherosclerotic disease events, and especially those who are interested in losing weight, I think the weight loss effect of GLP-1 receptor agonist is quite substantial as well as their A1C lowering. And, for those patients, I do consider a GLP-1 receptor agonist. What are your thoughts on that? I'm curious how you manage that decision-making in your own clinical practice.

Jorge Plutzky: 15:23

You know, I'm right with you, and that's really what these consensus statements and guidelines have gone, that the patient with heart failure and reduced ejection fraction, SGLT2 inhibitor can be warranted to separation of the curves. And, the trials are really quite striking how early there's benefit. And, that in the patient where their course is much more aligned with recurrent cardiovascular events, and especially in the setting of obesity, that a GLP-1 receptor agonist can be appropriate. I think one of the things we're saying can actually be reassuring to cardiologists that they start thinking about this in patients with diabetes and following labels and guidelines is that the next wave of studies are already underway and coming. And, that includes looking at these agents in people who don't have diabetes. It really highlights the fact that the drugs in and of themselves don't cause hypoglycemia. You have to be careful adding them on to someone who has a complicated regimen and maybe with weight loss with these agents that now you might get into those issues. But, in and of themselves, they don't cause those problems.

Jorge Plutzky: 16:26

So, we're seeing studies in people at high cardiovascular risk with obesity, for example, with GLP-1 receptor agonists, and then looking at the SGLT2 inhibitors and how they might be relevant to people who don't yet have diabetes. One of the exciting things at the AHA, which is always the case as we see new data roll out, were some of the new findings that came out of the AHA. I'd love to pick your brain about your take on those and the studies that highlighted additional

potential mechanisms around SGLT2 inhibitors and also mineralocorticoid receptor antagonists. We had a study with finerenone and CKD and type 2 diabetes and FIDELIO just came out in the New England Journal. Can I get your take on that study?

Neha Pagidipati:

17:11

Yeah, I mean, I think the AHA was extremely exciting for the kind of cardiovascular and metabolic disease space. So, as you mentioned, the FIDELIO-DKD study came out which randomized patients with both type 2 diabetes and diabetic kidney disease to finerenone, which is a non-steroidal selective mineralocorticoid receptor antagonist, and it significantly decreased the risk of cardiovascular death, MI stroke, or heart failure hospitalization by about 14%. And, this is an extremely high risk population, so anything that we can do to maximize their benefit and minimize their poor outcomes is extremely important. So, I think that was an extremely exciting study, and I'm excited to see where that goes. And, then in addition, as you mentioned, there was a pair of trials, the SCORED and the SOLOIST-WHF trials, and both of these tested the agent sotagliflozin in patients with type 2 diabetes, but different comorbidities. And, sotagliflozin is a dual SGLT1 and SGLT2 inhibitor. The SGLT2 part inhibits sodium reabsorption in the kidney, just like all the other SGLT2s, but the SGLT1 inhibition component also delays glucose uptake through the intestines.

Neha Pagidipati:

18:19

And, so in these studies, the SCORE study looked at patients with type 2 diabetes and diabetic kidney disease, and it found that there was a significant benefit with sotagliflozin, that there was a 26% reduction in cardiovascular death, heart failure, hospitalization, and urgent heart failure visits. And, then in the SOLOIST-WHF trial, that study looked at patients with type 2 diabetes and heart failure, both preserved and reduced ejection fraction, who were acutely ill. They had worsening heart failure, and they were stabilized in the hospital. They were off drips. They were off oxygen. But, they started the agent either in the hospital or within three days after leaving. And, there, too, there was a 33% reduction in the composite of CV deaths or hospitalizations or urgent visits for heart failure. So, this is not an agent that is on the market, and it's unclear yet whether it will be on the market. But, I do think that this highlights how rapidly the field is changing and how exciting it is for these patients who really continue to have high residual risks for both cardiovascular disease, heart failure, and renal outcome.

Jorge Plutzky:

19:18

Yeah. Really it is quite striking just how that front continues to move. I think one could say that in general mineralocorticoid receptor antagonists are not used as much as they could be, and the finerenone data highlights an opportunity for benefit there and continues to draw our attention to CKD. I almost feels as if we're beginning to recognize CKD in the way we start thinking about diabetes in terms of what it really means for risk. It's just not another box that you check, but really outcomes in CKD are really very poor and they need help. They need

intervention. So, now we have something on that front. And then, it's amazing to see the sotagliflozin data in a drug that's not on the market, but expands the possibility that maybe inhibiting SGLT2 one, which is in the gut and preventing reabsorption there, does that add another component of benefit in people with renal dysfunction?

Jorge Plutzky: 20:17

We know that the SGLT2 inhibitors work, even people with compromised renal function, but whether you get some additional benefit by inhibiting the process in the gut, that remains to be completely established, especially now that sotagliflozin has this positive outcome data. The question is what incremental benefit is there, and will that come forward?

Jorge Plutzky: 20:36

But I think more globally what those two trials are pointing us to is intervening earlier, moving upstream. Tell me about adding these agents in the patients that you're about to discharge from the hospital with acute heart failure, that there's an opportunity there. We're going to have some studies addressing that with some of the drugs that are on the market. And also, recognizing that aspect of CKD. I think that brings us around to where we are as we look forward to 2021 on many different fronts. But, I think we're going to have an ongoing drive here to integrate our practices, break out some of our own molds to have cardiologists thinking about and managing diabetes, to engaging more with our endocrinology colleagues and getting advice as we need it and help, and referring as necessary, and also interacting more and more with the nephrology community and kidney disease, and that's ultimately going to improve outcomes for patients.

Neha Pagidipati: 21:37

Absolutely.

Jorge Plutzky: 21:38

Well, it's been a pleasure talking with you. I bet it's warmer in Durham today than it is in Boston, but I won't hold that against you. I'll just appreciate all your insights and having a chance to have this discussion with you and furthering the Know Diabetes by Heart™ program. Thanks to all of you for listening, and please stay tuned for upcoming podcasts from Know Diabetes by Heart™. It really is an excellent resource, both for you and for your patients. So, I would encourage you to direct your patients to all the resources available through this program.