

Jennifer Green: 00:04

Welcome and thank you for joining the podcast where we will discuss the utilization of SGLT2 inhibitors and GLP-1 receptor agonist in the hospital setting and patients with indications for such therapy as described in the 2021 ADA Standards of Medical Care and current AHA guidelines, including the recent ASA/AHA recurrent stroke prevention guidelines. The purpose of this ongoing podcast series is ultimately to reduce cardiovascular deaths, heart attacks, strokes, and heart failure in people living with type 2 diabetes. And it's based on the collaborative initiative between the American Heart Association and the American Diabetes Association called Know Diabetes by Heart™. The 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 today is Dr. Neha Pagidipati who specializes in cardiovascular disease prevention. So welcome, Neha. I'm looking forward to our conversation today.

Neha Pagidipati: 01:11

Thank you so much for having me as well.

Jennifer Green: 01:14

So, we are primarily to focus on implementation of guideline-based care in the hospital setting today. And it's a hot topic, and it's really, I think a topic that deserves quite a lot of focus, both because we learned so much about newer diabetes medications.

Neha Pagidipati: 01:30

That's exactly right, Jennifer. I think when these agents SGLT2 inhibitors and GLP-1 receptor agonist just kind of stormed into the medical landscape after the 2008 FDA guidance, which mandated that antihyperglycemic therapies have trials, cardiovascular outcome trials, proving safety, and none of us expected the tremendous benefit that these agents would show. And I think we've spent the last several years as clinicians trying to deal with this avalanche of data that's coming at us. But I think it can be even more difficult to translate this knowledge into practice in the inpatient setting. And yet it's so important to do that, because when medications get started on the inpatient setting, patients are much more likely to stay on these therapies for the longer term.

Neha Pagidipati: 02:17

So, I guess maybe what we can do is start the conversation with just thinking about, well, why are we even talking about these classes of medications and how do we know that they're beneficial and in whom? And I wonder if you'd maybe talk us through a little bit of your understanding of and your thoughts around the benefits for the population of patients who have type 2 diabetes and either have known atherosclerotic cardiovascular disease or are at high risk of

cardiovascular disease because that's a particularly high-risk group and also very common, both in the outpatient and the inpatient setting.

Jennifer Green: 02:50

Yeah, very, very commonly encountered clinical scenarios in patients with both diabetes and those conditions. So, I think I'll give you how I think about these newer classes of drugs sort of in a nutshell. And bear with me, it may be that many of the listeners are already very familiar with this, but if someone is listening who isn't entirely familiar, it's not a bad idea to just go through this quickly. I'll start with the GLP-1 receptor agonists, because many of those agents when studied in patients with type 2 diabetes and evidence of atherosclerotic cardiovascular disease, and that included coronary disease, cerebrovascular disease, or peripheral vascular disease, GLP-1 receptor agonists, at least many of those in the class very clearly demonstrated the ability to reduce the risk of major adverse cardiovascular outcomes and interestingly in this patient population particularly stroke compared to placebo in the context of otherwise usual and appropriate guideline based care.

Jennifer Green: 03:52

So that's important to understand. Again, I'll give you my summary of what I understand about the SGLT2 inhibitors. In a similar patient population those agents were shown to have overall a beneficial effect on major adverse cardiovascular outcomes, but where they really shine is in their ability to reduce the risk of incident heart failure, and also to delay progression of kidney disease over time and not just delay or moderation of progression of albuminuria, which has been seen in most of the GLP-1 receptor agonist trials but in fact, not just that, but also a delay in progression to needing renal replacement therapy such as dialysis, or transplantation, or even renal or cardiovascular related deaths. So, we've really learned quite a lot about the outcomes and what kinds of patient populations may benefit most from these medications.

Neha Pagidipati: 04:51

That's extremely helpful, Jennifer. A tremendous, concise, but complete review of the data. And I think as the trials were on, we found that it wasn't just that initial population from EMPA-REG outcomes and from the LEADER study that you described a type 2 diabetes and atherosclerotic cardiovascular disease. It was also those with high-risk primary prevention and type 2 diabetes. But then it was also patients right with heart failure with reduced ejection fraction specifically. There've been trials now that have come out specifically with SGLT2 inhibitors and dapagliflozin in particular, looking at patients with heart failure with reduced ejection fraction, regardless of their status of diabetes and found to have tremendous benefits such that now we really consider SGLT2 inhibitors, particularly, again, DAPA and EMPA to be one of the four pillars of therapy for heart failure with reduced ejection fraction.

Neha Pagidipati: 05:44

So, this class of medications and specifically here, I'm referring to SGLT2 inhibitors, I think GLP-1 receptor agonists do not clearly have a heart failure benefit that we have seen convincingly but SGLT2 inhibitors clearly do. And in outpatient population, we see this benefit that as we will discuss is a very early benefit where the curve separate very quickly. And I think that will be very relevant for our conversation about initiation and the inpatient setting. Maybe, Jennifer, you can walk us through a little bit about how the patient population who benefits from these agents is expanded even further into those with chronic kidney disease with or without diabetes.

Jennifer Green: 06:24

Absolutely. So, the first trial of an SGLT2 inhibitor in a specifically chronic kidney disease or CKD population was the CREDENCE trial, which enrolled exclusively patients with type 2 diabetes and chronic kidney disease associated with significant albuminuria. And in that trial, very significant kidney and cardiovascular outcomes benefits were demonstrated. And then the next trial in that group was DAPA-CKD, which assessed the effects of dapagliflozin versus placebo in a CKD population. But interestingly, the patients may or may not have had diabetes and very similar outcomes benefits were seen.

Jennifer Green: 07:06

So very similar to those demonstrated in CREDENCE and with no evidence of a difference in beneficial outcomes, depending on whether or not the individual patients had diabetes. So, there's quite a lot of additional evidence accumulating that suggests that the benefits of these drugs, particularly the SGLT2 inhibitors, because we see the benefits really become evident very early after the drugs are started, they're really not mediated through glucose lowering. It's not entirely clear how they actually provide the benefit, which is interesting, but it's not a glycemic related effect. So, I think cardiologists, nephrologists, primary care physicians, we're all going to need to get really, really familiar with use of these medications. And I think we're going to see these; I hope prescribed much more broadly across different types of practice settings in the near future.

Dr. Neha Pagidipati: 08:01

Jennifer, that's an excellent point. These patients, they are really coming into contact with the health system in many different ways because they have diabetes, and heart disease and renal disease, so they're seeing their primary care doctors, nephrologists, endocrinologists, cardiologists, both in the inpatient and the outpatient setting. So, they're having all these touch points where you would think that there are many opportunities for patients to be able to start these medications and yet, unfortunately what we're seeing is that is just not happening. So, as you're well aware, Jennifer, we just recently did an analysis using HealthCore data, which is a population of patients who are commercially

insured in the United States and among 156,000 patients with type 2 diabetes and atherosclerotic cardiovascular disease, all of whom have an indication for a GLP-1 receptor agonist or an SGLT2 inhibitor, less than 10% of patients were on at least one of those classes of medications.

Neha Pagidipati:

08:56

So, there is a big discrepancy between what we know we should be doing for these patients and what we're actually doing. And I think something that we've learned, especially in the heart failure space is that the inpatient setting is really a moment of opportunity for these patients. It is a time when we have them on the inpatient side, we have time to think about them carefully, we're not rushed like we are in the outpatient setting and we really can initiate medications, teach them how to use them and then we know, again, from the heart failure side, that patients are much more likely to continue on these medications and adhere to them in the outpatient setting when they're started in the inpatient setting. And I wonder, Jennifer, if you've seen something similar in the endocrinology space, like we've seen in the heart failure space?

Jennifer Green:

09:43

That's really interesting. And I have not seen a lot of data recently pertaining to how particularly good or not good endocrinologists are at prescribing these medications to those with indications. We know that they are prescribing these medications at higher rates than many other types of physicians. But again, it's not entirely clear how they're doing in getting these medications into the hands and of patients with particular cardiovascular or kidney indications. The one thing I would note when we're focusing specifically on patients with diabetes, is that a very recent publication in *Diabetes Care* that looked at a very large primary care practice actually estimated that one third of all the patients with diabetes in that institutional setting actually had indications for use of a GLP-1 receptor agonist or SGLT2 inhibitor. So, we know that there's potential there. I completely agree that we really need to approach this clinical inertia we need to have a multi-pronged approach.

Jennifer Green:

10:42

And I think a hospitalization is a really wonderful time to take a step back and really look at the person's overall treatment regimen and take appropriate action to change their trajectory from there on out to keep them out of the hospital to keep their kidneys and their heart healthy. And I agree there are plenty of data from in particular heart failure studies that suggest that for example, prescriptions for spironolactone if provided to patients at discharge after a heart failure hospitalization were far more likely to have been filled within the next year than if that intervention were completely deferred to the outpatient setting. So, I think we need to think strategically about how to weave use of these medications safely and effectively in patient hospitalizations. But it's not entirely straightforward, there are potential side effects related to use of these medications that could be a concern and acutely ill patients.

Neha Pagidipati: 11:45

Those are great points, Jennifer. And I guess maybe what I'd like to do is think very practically, since you and I are both docs, we're both seeing patients in the clinic and in the hospital, maybe what we can do is talk a little bit about what are the potential concerns that people could have, and clinicians could have when thinking about initiating these medications in the inpatient setting. And maybe what we'll do is start with SGLT2 inhibitor therapy. Jennifer, when you think about a patient who is eligible for these therapies, so whether they have type 2 diabetes, an atherosclerotic chronic cardiovascular disease, whether they have chronic kidney disease or whether they have heart failure with reduced ejection fraction. What are some of the things that you consider when you're deciding whether or not to initiate an SGLT2 inhibitor in the hospital?

Jennifer Green: 12:30

I think the potential adverse effect of SGLT2 inhibitors that we hear about most often that would be relevant to the inpatient setting would be what's been described as Euglycemic DKA, which is just regular old DKA but with lower than typical glucose levels. And it's important to remember that patients with type 1 or type 2 diabetes can develop DKA if they're stressed enough or if conditions are right. So, this is pertinent to our type 2 population in the hospital. Now, this is a situation where often we can exercise, I think just good, common clinical sense. And sometimes it's helpful to think about when we use or don't use these medications, kind of along the lines of what we do with Metformin. So, we often stop Metformin in acutely ill patients who aren't eating or drinking normally, whose kidney function has deteriorated, who are very dehydrated.

Jennifer Green: 13:26

Those are sort of the same kinds of situations that would predispose someone with diabetes to DKA. So, I usually always stop SGLT2 inhibitors in someone who is ill enough to be hospitalized with an acute illness. And I also recommend that they be held in the outpatient setting if someone can't eat or drink normally. So, if someone's preparing for a colonoscopy, or they're fasting in advance of a planned procedure, or if they're just simply very ill and not particularly well hydrated. These are reasonable drugs either to temporarily stop in someone who's already on them or to wait to start until the person is less acutely ill is more clinically stable and adequately hydrated, eating and drinking. So that would be my greatest concern.

Neha Pagidipati: 14:13

What I'm hearing Jennifer is, when the patient walks in the door acutely ill from whatever it is, Cholecystitis, pneumonia, heart failure, and unstable in any way, that's not when you're thinking about starting the SGLT2 inhibitor, but once they stabilize or on the road to improvement, you're thinking about discharging them at some point, but they're hemodynamically stable and from a renal perspective they're stable and they're taking their POs and so and not

dehydrated, then it would be reasonable to start the SGLT2 inhibitor, even in patients with type 2 diabetes where you are thinking about the Euglycemic DKA risk.

Jennifer Green: 14:49

Absolutely. I think once they're stabilized a bit, I think they're very, very appropriate to start in the inpatient setting. But you do want to make sure that they've turned the corner and they're not likely to decompensate further during that hospitalization. And frankly, it's a little bit difficult sometimes to determine that with confidence. But I think really the key is just not to forget about the fact that the person needs to be on one of these medications and make sure it happens.

Neha Pagidipati: 15:14

Before they get discharged. And when we think about the heart failure population, really, I think we're realizing more and more that the heart failure population really lives on a spectrum. There's not that much difference between the outpatient, the person who is living in the community with heart failure who is volume up, maybe needs to come in for a dose of IV Lasix, and that patient who has had their acute decompensation has been hospitalized is now a day away from discharge.

Neha Pagidipati: 15:47

These patients live on the spectrum. So, the idea that they slightly volume decompensated, but not in the inpatient setting, that just doesn't make sense. We know that, especially with SGLT2 inhibitors for heart failure, the benefit is seen within 12 days. So, to not start it before discharge I think is not only bad in the sense of it will decrease the chances that the patient will get on the medication but will have a very acute impact on their health and their risk of rehospitalization. Because especially with heart failures, Jennifer, one in four patients with heart failure are going to get readmitted in the first thirty days.

Jennifer Green: 16:26

Right. I think it's a little premature to start people on SGLT2 inhibitors as they hit the cardiology floor with their acute heart failure decompensation but there are a number of trials underway really studying use of this class of drug in more acutely ill patients.

Neha Pagidipati: 16:47

It's so interesting, Jennifer. I disagree, I think we are, and we're doing it on the inpatient side. I think FDA doesn't mandate where these medications start. And I will tell you that having been in many discussions with heart failure physicians, they are starting it. Once a patient is hemodynamically in and from a renal perspective stabilized, we are starting it on the inpatient side before discharge. So, we're not starting-

Jennifer Green: 17:13

We agree, we agree. What I meant was when they show up and they're in distress and they're requiring a lot of supplemental oxygen and you need to pull a lot of fluid off in a short amount of time if you can, that's probably the setting in which I think it would be optimal to learn a little bit more. So, we actually agree.

Neha Pagidipati: 17:31

Well, see, I knew we agreed. I was so surprised. No, I think that you're exactly right. We don't know and we do not start these medications, like you said, when they show up and hit the floor and are unstable in any way and acutely decompensated. You're exactly right. But then being able to start it before they leave the hospital really gives them the best shot of not coming back into the hospital. What are your thoughts, Jennifer, on GLP-1 receptor agonists for that population that's mainly restricted to patients with type 2 diabetes? So of course, there is more of a chronic issue around weight management and there is benefit for GLP-1 receptor agonist in patients without diabetes who have obesity, but generally when we're thinking about it in the inpatient setting, we would be considering it in patients with type 2 diabetes. What are some of the considerations that you take into account when you're thinking about whether or not to start this on the inpatient side?

Jennifer Green: 18:20

Well, interestingly the story with GLP-1 receptor agonist in the hospital is a little bit different. So there actually have been a number of studies of hospitalized inpatients on both medical and surgical wards looking at strategies for glycemic control that consisted of either a GLP-1 receptor agonist, GLP-1 receptor agonist plus insulin or insulin alone. And in those trials, that really, again we're focused on in hospital glycemic control and not other outcomes, in general, the strategy was felt to be a safe and effective way to control diabetes. But I will tell you that that practice is not particularly common and what we see in the clinical trials and also in clinical practice is that at least a quarter of patients who start a GLP-1 receptor agonist will have some kind of GI side effects. And unfortunately, the GI side effects are most pronounced at the time of drug initiation or up-titration.

Jennifer Green: 19:19

So, if you're starting a drug in the hospital, that's when they're most likely to have nausea, vomiting, or maybe even diarrhea. And there are a lot of inpatient clinical settings where those kinds of side effects are not really going to be particularly helpful. And I would think particularly with diarrhea, which is such a common problem in the inpatient setting, you might be concerned, or even with nausea or vomiting that the patient has an ileus, has an infectious diarrhea, has some other kind of problem, not attributable to the medication that could be

troublesome. But that being said, patients might tolerate the medicine really very well and just sail through.

Jennifer Green: 19:54

So, I think there may be times and particularly where we might need to start thinking about it and where I have used this or initiated GLP-1 receptor agonist in the inpatient setting are in patients with cardiovascular or kidney complications who have contra-indications to SGLT2 inhibitors because their, for example, their eGFR is too low to permit use under current prescribing guidelines, or they have some other contraindication or intolerance of SGLT2 inhibitors. So, it doesn't mean that if you can't provide or start the SGLT2 inhibitor you just drop the ball. The GLP-1 receptor agonist needs to happen in those high-risk patients. So, it's not a bad idea to start them on it before they leave a hospital or make sure that they have the prescription when they're discharged.

Neha Pagidipati: 20:42

I completely agree, Jennifer. And I guess now what it kind of falls to is, we see the benefit of these two classes of agents in a wide variety of patients. These patients are coming in and out of the hospital all the time, unfortunately. And if we were to get them on these therapies, we could hopefully keep them out of the hospital. So, I guess the next question for us then to discuss is what are some strategies, some practical strategies that we could think about that would help folks think about these agents and get them started on patients before they leave the hospital.

Neha Pagidipati: 21:12

I can just start, something that we, and I cannot take credit for this, but some really excellent heart failure doctors at Duke where we are and some of the fellows actually who were very interested in quality of care improvement have initiated several strategies on the Duke side, one of which is having a heart failure dashboard within the EHR for patients that not only has all the information you would want about these patients, including their fluid status and how their blood pressure is doing and so forth, but also very clearly outlined whether they are on guideline directed medical therapy and that of course includes SGLT2 inhibitors.

Neha Pagidipati: 21:47

So, it really prompts clinicians to be thinking about it if they weren't already. And then another thing that's happening within the Duke Health System that I think is an excellent idea as well, is that there are kind of virtual consultations that are triggered that a patient with heart failure gets admitted into a medicine service or a non-cardiology service, they will actually contact that team and say, "Hey, you may want to think about initiating an SGLT2 inhibitors." So those are



just some examples that we're employing here specifically in the heart failure space. But I wonder if you have any other ideas before we wrap up.

Jennifer Green: 22:19

Yeah. I think first and most important is thinking about it, recognizing the sort of gap in the patient's care regimen or being reminded that the patient has a deficiency or a missing link in their overall care regimen. And I haven't seen it happen yet at our institution, but I know it's happened at other medical centers where it's really part of, for example, the clinical reminders that a person needs to be on one of these drugs, that they have an indication and it's an expected component of care. So, I'd like to see more of that happening and that happening more consistently. Ideally what I'd love to see for hospitals who would be at least a small group of people who are really focused on these cardio-metabolic patients who are very familiar with these medications can provide input, when necessary, in a very time sensitive fashion and figure out how to best incorporate these new medications into the regimen of people with diabetes, because that's where sometimes it's a little trickiest.

Jennifer Green: 23:24

What I'd hate to see is there being a lot of concern about how to incorporate this drug, how to adjust other background diabetes medications, and have that result in any sort of prolongation of care. So, I do think that hospitals are going to need to establish at least a small cohort of individuals who are really able to put this under their belt and be able to make recommendations and implement them quickly.

Jennifer Green: 23:47

One of the things that I think can be very helpful is having pharmacists as part of the team, because I think one of the problems we have and particularly at our institution, because people come from far and wide to stay there is that we may not have a drug on the formulary. So, for starting something in the inpatient setting, we don't know for certain if they're going to be able to access that same medication on the outside and I think pharmacists can be really incredibly helpful at figuring out what the best choice is going to be in the outpatient setting. And it's not always easy, but I think that they certainly have access to more information about formularies, for example, than we often do.

Neha Pagidipati: 24:29

Well, Jennifer, I hope that we have encouraged people to incorporate, if they haven't already kind of incorporate these agents into their own clinical practice. And for those who are already starting to incorporate it in the outpatient setting to think about it on the inpatient side before discharge. Because, again, I think that's a window of opportunity as we both said to actually get the medications onboard and have the patient stay on them in the long-term.

Neha Pagidipati: 24:55

Thanks everybody very much for listening and please stay tuned for upcoming podcasts.