George Bakris: 00:04

Welcome and thank you for joining this podcast where we will discuss updates made in the 2021 ADA *Standards of Care* that are related to metformin use and considerations for when the guideline recommends, considering the use of SGLT-2 inhibitors and GLP-1 receptor agonists, independent of A1C or metformin use.

George Bakris: 00:29

The purpose of this ongoing podcast series is to reduce cardiovascular deaths, heart attacks, strokes, and heart failure in people living with type two 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, as well as Company Diabetes Alliance, and Novo Nordisk and national sponsors, Sanofi, as well as AstraZeneca and Bayer. I'm Dr. George Bakris, a nephrologist specializing in the diagnosis and reduction of high blood pressure, particularly in complicated and refractory cases.

George Bakris: 01:17

Joining me are Dr. Neda Rasouli , whose specialties include internal medicine, endocrinology, diabetes, and metabolism, and Dr.Cecilia Low Wang, who also specializes in endocrinology and diabetes and metabolism. So welcome ladies and thank you for being here. We have a number of issues that have come up and have been in the limelight of discussions for a long period of time. So, Cecilia, I want to start with you. Are there any data supporting synergy of metformin on anything other than glycemic control and in line with this, are there data from properly designed clinical trials to show metformin reduces mortality?

Cecilia Low Wang: 02:05

Thanks George. I think this is such a great topic. It's, very hot right now, and there's been a lot of voices calling for us not to start with metformin. So, I took this opportunity to look into the literature and see what I could find, because I know that we often referred to the UK-PDS as an example of why we should keep metformin in the lineup. I was able to find a couple of studies, and so one is a secondary analysis of a trial of another drug. So, looking at metformin non-users and users and a trial called TREAT, which was a trial of patients with diabetes and CKD. TREAT stands for Trial to Reduce Cardiovascular Events with Aranesp (or darbepoetin). Looking at this trial of about 3,400 non-users and 600 users of metformin, there was actually an effect found with metformin. It was found to be independently associated with reduced risk of all-cause mortality, with a hazard ratio of 0.49. The cardiovascular death hazard ratio was also 0.49, the cardiovascular composite hazard ratio was 0.67. So that was pretty dramatic. I didn't expect to find that.

Cecilia Low Wang: 03:18

There was another study that I found called SPREAD DIMCAD. This was published in *Diabetes Care* in 2013, Effects of metformin versus glipizide on cardiovascular outcomes. This was in patients with type 2 diabetes and known coronary artery disease. What's interesting about this one was that although, this is a small trial, only about 300 patients with type 2 diabetes with coronary artery disease, it was multicenter randomized, double blind, and placebo controlled. The only issue is that I couldn't tell from the paper whether the outcomes were adjudicated, but when comparing patients who were on metformin, 1.5 grams a day, versus patients who were on Glipizide, 30 milligrams a day for three years, the primary end point, (time to composite of recurrent cardiovascular events, including cardiovascular death, death from any cause non-fatal MIA, non-fatal stroke or arterial revascularization), was actually a difference between groups. And so, the adjusted hazard ratio for the composite outcome for patients who were on metformin was 0.54, pretty dramatic compared to Glipizide. So that was about all I could really find, and of course there are some secondary analyses of other trials, but these two stood out for me.

George Bakris: 04:31

Cecilia, doing this comparison as they did in these trials, first of all, I'm not sure they were adequately powered, but let's pretend that they were. Comparing metformin to a sulfonylurea is like comparing somebody with an IQ of 130 to somebody with an IQ of 90. Of course, they won. Congratulations. I mean, are we surprised? Even more recent trials with a sulfonylureas fail to show any benefit in terms of cardiovascular outcomes. So, I'm going to set that up and ask Neda, what are your thoughts about these trials? Do they cut the mustard, or should we consider them? I mean, they've been considered in the past. So, what do you think?

Cecilia Low Wang: 05:12

Actually, I have to interject here because I can't leave that bait hanging because I think that's an important question. I think that when we're trying to figure out the question of, “Should metformin be considered first-line therapy or not?”, there are so many other things that we're balancing as well as the effects from these trials. One of the trials I mentioned was metformin versus Glipizide. The other one was an analysis of metformin versus nothing. No metformin. And so, I think that I take your point that if we're going to compare metformin with something such as, a sulfonyurea with no known cardiovascular benefit, that's one thing. I think the next question then is what about metformin compared to other agents with proven cardiovascular benefits?

George Bakris: 06:00

Absolutely, spot on, no argument there.

Neda Rasouli: 06:04

Thank you, Cecilia, for summarizing a lot of data on trials with metformin. But we all agree that none of these trials were designed or powered to study effects of metformin on cardio renal endpoints similar to the CV outcome trials done for new glycemia lowering medications. As you know, UKPDS trial has provided us with some data supporting the cardioprotective effects of metformin. But metformin data from UKPDS was from a relatively small sample size, and it was not designed to evaluate the effects of metformin on diabetes complications such as CV outcome independent of glycemic control.

I am not aware of any ongoing study to evaluate effects of metformin on CV events, and I don't think that such a trial is going to happen in the future. You might have heard of VA Impact study. This is a prospective double-blinded trial designed to study effects of metformin vs. placebo on cardiovascular events in prediabetes. This trial is currently recruiting at several VA hospitals. After completion of this trial, we will learn whether metformin could prevent CV events in patients with prediabetes and established CVD or at risk for CVD.

George Bakris: 07:26

Absolutely, absolutely. Well, definitely something to look forward to without any question. So, Neda while I've got you here, let me ask you the next question. Given the recent ADA EASD guideline, metformin is always first in treating diabetes. Hence all trials are added to metformin. It's been argued that there's additivity on cardiovascular and renal events. Do you believe this?

Neda Rasouli: 07:52

This is an interesting question and you're absolutely correct that majority of patients in the large cardiovascular outcome trials had metformin as background treatment for diabetes.

Let's review some of the data. For example, empagliflozin and liraglutide both showed cardioprotective effects independent of glycemic control. In EMPA-REG trial, 74% of the patients were on metformin at the time of randomization. In LEADER trial, 76% were on metformin at baseline. So, majority of patients, roughly 3 quarters, were on metformin at baseline when randomized to the study medication. Now the question is whether the presence of metformin in the background is needed for the cardioprotective effects of, for example, empagliflozin and liraglutide? Obviously, those trials were not designed or powered to answer this specific question, but there has been several post-hoc analysis trying to figure out whether background treatment with metformin makes a difference.

The post-hoc analysis of the large CV outcome trials with GLP-1 reported no significant differences between metformin users as compared to non-users. The post-hoc analysis of SGLT2i trials (such as CANVAS or EMPA REG trials) reported

that people who were not on metformin at baseline had better cardioprotective effects. The effect was small and disappeared in some after adjustments. Whether the differences were due to metformin as a background medication or due to the differences in the baseline characteristics of metformin users vs. non-users we still don't have the answer for that and yet to be determined.

To give you a short answer, I do not believe that the cardiorenal benefits of newer glycemic lowering medications are dependent on metformin use in the background.

George Bakris: 10:00

Right, and you made some very good points and I just want to emphasize the fact that all of these analyses that you've mentioned, and there's been others as well, to say that these are underpowered is an understatement. We really don't know, and you really will never find the answer going back because the majority of people by far more than 80, 90% are going to be on metformin and so it's very difficult to get any kind of hint. Now, Cecilia, I'm coming back to you, given the relative paucity of data on CV outcomes and limitations of the use based on kidney function, why is metformin first line? Is it price? I heard it's free in some markets. So, is that what's driving this? It certainly can't be renal protection that's for sure. So, what are your thoughts?

Cecilia Low Wang: 10:47

I think that what you and Neda have both said, is correct that we're, probably never really going to know how or whether or not metformin has an independent effect and also are these effects additive to the newer agents. But I think that metformin cost is a big issue. So, we know that the newer drugs are quite expensive and if they're not covered well, the out-of-pocket cost for patients is quite high and that metformin is relatively harmless. So, it doesn't cause a hypoglycemia when taken alone without insulin or sulfonylurea or glinides, it doesn't cause weight gain and, in some patients, will cause a little bit of weight loss. Then the other thing is that the mechanism of action of metformin is different from the other classes and so those are some different reasons that metformin, I think is still first-line besides the fact that it's incredibly inexpensive, but I don't really know, because those are my speculations. And I'd love to hear other thoughts.

George Bakris: 11:46

Neda, what are your thoughts on that?

Neda Rasouli: 11:47

Let's talk a little bit about the history of metformin. Metformin was recommended as the first line of treatment for diabetes in 2004 by IDF (International Diabetes Foundation). This recommendation was made due to efficacy and safety data for metformin. At the time, metformin was the most

commonly used anti-diabetes medication. It was later in 2009 when ADA recommended the use of metformin as a first line of treatment for diabetes.

The rationale for this recommendation was mainly data supporting safety and efficacy of metformin. As we all know metformin is not associated with any weight gain or hypoglycemia as seen in sulfonylurea and as a bonus it is not an expensive medication. Now that we have several newer glycemic lowering medications with additive effects on top of glycemic lowering properties, it is time to re-visit these recommendations.

George Bakris: 12:51

I think one of the key issues here is that metformin was a very good drug to get glycemic control under control and microvascular complications of course are driven in large part by that. We really had nothing until the SGLT-2's and the GLP-1's that showed substantial reduction in cardiovascular events and that was never the focus. I think the uproar now, and I'm speaking, not only as a nephrologist, but as a nephrologist who does diabetic kidney disease research. Our cardiology colleagues have said, "My God, what is going on here"? You've got drugs that can reduce glucose just as effectively. They don't cause hypoglycemia. They've got far greater benefits and you're wedded to metformin. What is it, wake up? So, this is kind of the background for the audience. If they're not knowing this to be aware of this.

George Bakris: 13:45

Now Neda, since I've got you, metformin is broadly combined with other classes of glucose lowering agents, like sulfonylureas and the DPP-4 inhibitors, which by the way, also failed to show any benefit on mortality benefit. Given that these classes have never been shown to have any CV risk reduction, was it appropriate in retrospect, especially since the benefit of price is gone when you combine these with metformin because they're more expensive, the DPP-4 is I'm speaking specifically of. So, knowing what we have now, would you rethink this? Would you discontinue these combinations and provide other combinations? What are your thoughts on this?

Neda Rasouli: 14:29

You're specifically talking about a fixed dose combination?

George Bakris: 14:34

Yes.

Neda Rasouli: 14:35

These fixed-dose combinations have been made to improve patients' compliance and help with co-pay. But, because of the fixed dose ratio, it might be a challenge for the providers to adjust the dose due to less flexibilities.

As you know, we have almost every single drug in the market in combination with metformin. For example, different sulfonylureas, DPP4 inhibitors, or SGLT2

inhibitors, all come in preparation of fixed dose combination with metformin. We even have combination of three medications in one pill which includes metformin, a DPP4 inhibitor, and a SGLT2 inhibitor. Personally, I don't use the fixed-dose combination pills, but I think they have their own place. After you choose the right medication and the right dose for your patient, then you can convert them to an equivalent fixed-dose combination pill to improve compliance or co-pay. So, I don't recommend removing any of these combination fixed-dose medications from market, but I encourage the provider to personalize diabetes care based on the patients characteristics and their preference and then or if appropriate use these fixed-dose combinations.

George Bakris: 15:57

I understand. I understand. I was asking you to speculate more because yes, I agree with you. I don't think these are going to be immediately taken off the shelves, they're there and they've been there, but I think it's something knowing that we have a lot more data now and a lot better data than we had going back 15 years, you know, the question would be really, would you change this? Is it worth changing? Because again, these combos are all focused on glycemic control and really nothing else cause they had nothing else to offer.

Neda Rasouli: 16:29

And we have combination of metformin, with canogliflozin with dapagliflozin and empagliflozin, all of that and ertugliflozin. So those combinations are available, and the problem is we are not using SGLT-2 as much as we are supposed to.

George Bakris: 16:46

No question about that. Cecilia, I'm going to ask you the next question, but before I do, do you have anything to add to this?

Cecilia Low Wang: 16:52

Not really. I agree with what's been said. I think that there's probably no utility for the metformin and sulfonylureas and metformin and DPP-4 inhibitor combinations because you do remove that price or cost benefit with these combination agents. There's really nothing compelling to drive DPP-4 inhibitor use. And I think right now, and for sulfonylureas, it's mainly the cost and people are comfortable using sulfonylurea because they've been around for so long. I think for the DPP-4s what I see and hear is that primary care physicians tend to use them because there aren't many side effects and there's no hypoglycemia with DPP-4 inhibitors and costs of course is still an issue. So, I think it's just level of comfort and co-morbidities and side effects that people are also looking at.

George Bakris: 17:43

Yeah. You're spot on with that. That's absolutely true. All right, so now let me ask you this. I'm going to move away a little bit and get a little deeper here. We really don't know how metformin works in spite of the fact that it's been around for decades. We don't know how it works in specifically lowering glucose. We know it affects the gut microbiome. We know it has multiple other things. One of the recent assertions from observational data are that it lowers the risk of cancer. So, what are your thoughts about this? Is this true? Is this hype, what's going on with that?

Cecilia Low Wang: 18:16

I'm glad you brought this up because that might be yet another reason that metformin's going to stick around for a lot longer, besides the reasons that we already mentioned. So there has been a lot of observational data that suggests that metformin may reduce the risk for cancer specific mortality, as well as all-cause mortality in patients with cancers associated with insulin resistance. So, for example, colon cancer, prostate cancer are two of the main ones. So here again, I searched for some trials, because a lot of that is observational it's retrospective. I was able to find a small phase three trial that enrolled about 500 patients who had colorectal adenomas, and this is published in *Lancet Oncology* in 2016. So, this was a multicenter double-blind placebo controlled randomized phase three trial of patients receiving very low dose metformin, 250 milligrams a day versus placebo followed over the course of, I think it was the only one year and looked at recurrence of adenoma and found a decreased risk in patients on metformin.

Cecilia Low Wang: 19:23

So really very surprising small numbers, but interesting. There's another trial that is ongoing called the ASAMET trial, a randomized phase 2 double-blind placebo-controlled multicenter two by two factorial biomarker study, looking at tertiary prevention in stage one to three colorectal cancer with low dose aspirin and metformin. So, we'll have to see what those results look like, but I know that there are other trials ongoing. For example, at the Anschutz Campus , we are just about to start a pragmatic trial of metformin use in patients with prostate cancer and overweight, obesity and or glucose intolerance. So, we'll see, there may be some effects of metformin, even though it's such an old drug, there's still some surprises.

George Bakris: 20:12

Let me ask you an unsure, but related question, and only because I'm very interested in this myself. That is the gut microbiome is changed by this drug, there's evidence for that, and could it be, and this is pure speculation, but could it be that the bacterial shift is less inflammatory and somehow is reducing the inflammation that could be going on in specific cell beds? I know you don't know the answer to that, but I'm just asking you to see if you agree or disagree with that.

Cecilia Low Wang: 20:47

I think it's possible and so it's an intriguing possibility. To me, I think one of the other interesting possibilities, although with the super low dose metformin of, 250 milligrams, I don't think this would be the mechanism, is reduction of insulin resistance. So that's another potential mechanism.

George Bakris: 21:03

Okay, very good. Now I have in my hand, the last question, and you're both going to get a shot at this. I'm going to start with Neda. Should metformin remain the anchor to initiate glucose lowering therapy and diabetes since two trials in advanced CKD and four trials in high cardiovascular risk patients with diabetes show that SGLT-2 inhibitors reduce cardiovascular risk and chronic kidney disease progression, independent of glycemic control?

Neda Rasouli: 21:38

George, you left the most important question for the last. In different words, you are asking "should we still prescribe metformin as a first line of treatment?"

I believe there are three groups of patients who benefit from SGLT-2 and GLP-1 beyond their glycemic lowering effects. These groups are those with established ASCVD, #2 patients with heart failure and reduced ejection fraction, and finally those patients with reduced eGFR and albuminuria. In this specific population, we should start either GLP-1 RA or SGLT2i depending on the patient profile. If they happen to be drug naïve patients with diabetes, then the question is should we start metformin first and then consider these medications. In these three groups that I mentioned, I personally give priorities to either SGLT2i or GLP-1 RA and will consider adding metformin for glycemic lowering effect if needed in the future. From a practical standpoint, if your patient has to wait for prior authorization or insurance approval, then I will consider metformin while waiting to get approval for these newer medications.

But for those patients, outside these three groups that I mentioned before, depending on the risk assessment, I will start metformin and consider SGLT2i and GLP-1 RA later because at this point, we don't have enough evidence that SGLT2i or GLP-1 RA can be used as a primary prevention in those without any established ASCVD.

George Bakris: 23:25

Okay, very good, so Cecilia, what do you think?

Cecilia Low Wang: 23:28

I completely agree with what Neda has said. I think that we have had the benefit of these really well conducted, large scale cardiovascular outcome trials for our DPP-4 inhibitors, our GLP-1 receptor agonists, and our SGLT-2 inhibitors and the cardio renal benefits of all of the SGLT-2 inhibitors and the vast majority of the

GLP-1 receptor agonists is incredibly compelling. But I think that it's really important to look at the populations that were enrolled in the trials and the ones that benefited.

Cecilia Low Wang: 24:03

So, I completely agree that the three groups that I would target for not starting metformin first-line are the ones with known atherosclerotic cardiovascular disease, known heart failure with reduced ejection fraction or with CKD. So that still leaves a large number of other patients and so I don't think that we can make a great argument for the other patients, to not start with metformin, but I think that again, we have to be very careful about clinical inertia. We can't leave people sitting there untreated as we try other things and so, as we're trying to think about our care in our diabetes patients, of course, we're also focusing on blood pressure, we're focusing on other elements of cardiovascular risk we're looking at lifestyle, and these antihyperglycemic are yet another part of the puzzle, but I think that I would target those three main groups of patients for not starting metformin first-line.

George Bakris: 25:03

So, I'm very happy to hear both of you independently say this, you need to know the group that listens to these podcasts needs to know that when we put the 2021 guideline together, one of the things that, because believe me, we grappled with this for a long time. We basically came down as a compromise and said, okay, look, you want to start with metformin. That's fine. We don't care. If you have high cardiovascular risk and or presence of kidney disease and or presence of heart failure, you must start with an SGLT-2, and if not tolerated a GLP-1, and this way we hopefully made the distinction between there's glucose, okay, that's fine. But in the meantime, these people are very high risk and that's not going to get you where you need to be. You need to be on these agents as well.

George Bakris: 25:58

We didn't make a big deal out of the people that fell out of that, it was much lower risk. And I think you're right. I mean, people have asked me about prophylaxing these people against events, and there is no evidence that really supports that. Just like there's no evidence by the way, for the group supporting ACE inhibitor use or ARB use and people that don't have kidney disease to protect them against developing kidney disease. So, I think you've stretched the point too far. Any final words you want to say before I close this up.

Neda Rasouli: 26:29

George, I want to make one last comment. The prevalence of heart failure in patients with diabetes is extremely underestimated and frequently unrecognized. It is important to think about heart failure symptoms or signs when we see a patient with diabetes and screen high risk patients for heart

failure because diagnosis of heart failure will affect the choice of anti-diabetes medication and it might improve cardiovascular comorbidities in patients.

George Bakris: 27:02

Excellent point, excellent point. Thank you very much.

Cecilia Low Wang: 27:05

Thanks, and I would like to make one last point as well, I've really enjoyed this conversation and I do want to remind our listeners that atherosclerotic cardiovascular disease isn't just the heart. It also includes the brain and of course the limbs, and so, asking about peripheral artery disease and making sure that that's on your radar as well is so important.

George Bakris: 27:26

Excellent points. Thank you very much, ladies. It's been a real joy and thank you very much for listening and stay tuned for upcoming podcasts. Have a good day.