Suzanne Arnold: 00:04

Welcome and thank you for joining this podcast on the clinical management of stable coronary artery disease in patients with type two diabetes. This AHA scientific statement was recently released in April. The purpose of this ongoing series is to reduce cardiovascular deaths, heart attacks, strokes, and heart failure in people living with type two diabetes, and it's based on the collaborative initiative between the AHA and the American Diabetes Association. Know Diabetes by Heart™. This series is brought to you by founding sponsors, Boehringer Ingelheim and Eli Lilly Company, Diabetes Alliance and Novo Nordisk and national sponsors Sanofi and AstraZeneca and Bayer. I'm Suzanne Arnold. I'm chair of the writing group for the statement, and joining me are Doctors Prakash Deedwania, and Mikhail Kosiborod who also served on the writing group. Welcome to both of you.

Prakash Deedwania: 00:59

Thank you.

Mikhail Kosiborod: 01:00

Good to be with you.

Suzanne Arnold: 01:02

Well let's get right into this. Dr. Kosiborod, I kind of want to come to you first as far as why we thought that this scientific statement was really important to put forward understanding that we know that diabetes is a risk factor for coronary disease and other cardiovascular complications, but why now? Why was this important to do now?

Mikhail Kosiborod: 01:24

Yeah. No. That's a great question, Suzanne, and I think there are lots of reasons why now is the right time. Just to kind of take a step back, I would say the epidemic of type two diabetes and cardio metabolic disease in general, so essentially diabetes with cardiovascular complications is one of the most serious health threats certainly in the noncommunicable disease side of things that's facing both the United States and the world at large. There are hundreds of millions of patients with type two diabetes. That number is projected to increase dramatically over the next couple decades and of course that's coinciding with the epidemic of obesity that's driving a lot of this as well.

Mikhail Kosiborod: 02:04

Lots of reasons for this, but we really need to figure out how to both prevent cardiovascular complications in people with diabetes because cardiovascular disease remains the number one most common and the most morbid complication of type two diabetes. And then, unfortunately patients with type two diabetes already developed cardiovascular disease complications which is kind of what our statement focused on in people with diabetes and established

high risk carotid cardiovascular and coronary disease specifically. What can we do to optimize progressive secondary prevention and preventions?

Mikhail Kosiborod: 02:38

And, I would say the reason that the statement is important is not only because there are lots of people with diabetes and cardiovascular disease. It's also because we live in the world now where the number and type of interventions that have been shown to be efficacious, and have really had meaningful impact in reducing morbid and common events in people with type two diabetes like heart attacks, strokes, heart hospitalizations and so forth has grown dramatically over the past few years. We're really living in the world where we have a renaissance of these efficacious prevention therapies that at the same time implementation of what the guidelines tell us we should be doing to reduce that risk has been very poor.

Mikhail Kosiborod: 03:19

In fact as you all know, you and I authored a recent report in *Circulation* last year where we showed that the proportion of patients with diabetes and atherosclerotic cardiovascular disease are getting comprehensive optimal secondary prevention therapies, is considerable less than 10% nationally across hundreds of centers in the United States. That's not really a good performance record, and I think we really need to come together as a community and figure out how to do it better, so we can meaningfully reduce the risk of cardiovascular complications in this group especially of those that already have the disease.

Mikhail Kosiborod: 03:53

And we know that despite all the availability of efficacious treatments, the data from CDC suggests that the event rates are not going in the right direction, so we better figure out how to do it better.

Suzanne Arnold: 04:04

Absolutely. I think that we have found gaps in care in multiple places, and I think that particularly with diabetes and coronary disease, when the management can become very complicated, I think it's really helpful to have a statement such as this to try to lay things out for people a little bit more clearly. I think that as cardiologists, we've kind of left the management of diabetes to others, and I think we probably need to start owning it a little bit more.

Mikhail Kosiborod: 04:29

I would agree. I think the management of patients with diabetes and cardiovascular disease traditionally, right, has been kind of de-fragmented, which is that the cardiologist would kind of manage the heart if you will and the blood vessels, the cardiovascular aspect, and then their primary care physician or clinician or as a specialist like endocrinologist would manage the diabetes part, because diabetes was really looked at as glucose management, and we know that that's clearly no longer the case.

Mikhail Kosiborod: 04:59

All of this is connected as we'll I'm sure talk about during this podcast. Managing glucose is not enough. There are different ways of doing it and while there are lots of medications which lower blood glucose, there are some of those medicines that actually would have independent impact in cardiovascular events that may be highly beneficial, while others don't, and so, we really need to start looking at management of diabetes and cardiovascular disease together in a comprehensive fashion and cardiologists clearly you can be better educated about different treatment options that are available, trying to understand how diabetes as a disease entity impacts treatment options for our traditional cardiovascular therapies, but also become more active in selection to at least being part of the team that determines the selection of anti-diabetic agents that actually would have cardiovascular benefits as well.

Prakash Deedwania: 05:47

I think it's also; this is Prakash Deedwania. It's also important to emphasize that clearly many patients who have not been previously diagnosed with diabetes will come to the attention when they come with a cardiovascular event. The studies have shown that as many as 30 to 40% of the patients who come with acute coronary event or any kind of chronic coronary syndrome that we are discussing, they may be diagnosed for the first time with diabetes. About 30% of them will come with previously diagnosed diabetes, and another 30% or so, or there about will be diagnosed for the first time when we look carefully for the presence of diabetes.

Prakash Deedwania: 06:28

So, I think it's not only important, that cardiovascular specialists and their team needs to be involved, but in addition to that, if we miss the report of even the first time the patient is told they have diabetes and comprehensive risk reduction strategy isn't applied then we have missed a great opportunity, so I think it's very important for us to pay attention to all the points that we have emphasized in this scientific statement about the comprehensive risk reduction.

Prakash Deedwania: 06:56

And, as Mikhail mentioned, it goes beyond glucose control. We all know the importance of lipid management. We all know the importance of antithrombotic and anti-platelet agents, and of course various different treatment strategies for BP control. So, I think cardiologists play a pivotal role, and in my opinion any cardiac patient who has diabetes or even pre-diabetes, cardiologists should be intricately involved, because we can make lot more impact on their care and the importance of controlling diabetes than primary care physician or the real reason they have it and the endocrinologist.

Mikhail Kosiborod: 07:31

I'm glad that you bring up that point Prakash. We just recently published a manuscript where we looked at the data from St. Luke's Health System here in

Kansas City where Suzanne and I are and also Yale's New Haven Hospital in Connecticut, and we're going to combine our analysis to look at a very simple question which is if you look at a patient with diabetes and cardiovascular disease, who is likely to interact with a patient, if you will? Who is likely to come in contact with the patient in terms of health care? And what we found was, I'm not sure it's necessarily unexpected, but it's still interesting and informative, which is on average cardiologists are much more likely to see those patients than our endocrinology colleagues are, and about as likely to see them, if not more likely to see them, as our primary care colleagues are.

Mikhail Kosiborod: 08:20

And then, in certain cardiovascular disease states, like heart failure, we're maybe seven times more likely to see the patients than an endocrinologist, so we certainly have plenty of opportunities to intervene, and that's the reason why it's so critical for cardiologists to be involved and informed.

Prakash Deedwania: 08:34

I'm not surprised Mikhail that you found that. That is a general finding across the board, and not only that, it's important to emphasize that when a patient comes not undermining the authority or importance of consulting with other physicians in more in the care, but a cardiologist emphasizes that your risk of having a future cardiac event or any event that they might be exposed to is going to be substantially related to how we provide the comprehensive management of the cardio metabolic conditions that they have. They would be much more likely to listen to the cardiologist rather than just when somebody just says well, we need to control your glucose, because you have high glucose. I think one needs to relate it and who better can do it than a cardiologist and their cardio care team.

Suzanne Arnold: 09:17

So, I think that the importance of cardiologists being involved in the care of patients with diabetes is becoming even more clear as we go on, and I do want to kind of move into the meat of the scientific statement and kind of the actual recommendations that we made as a group, because I think those are important to kind of go through. From my perspective, I think we tried to split this up into kind of how does diabetes affect the care of a patient with coronary disease, and then also how does coronary disease affect the care of a patient with diabetes? And I think that kind of keeping those as kind of two separate topics, I thought was really informative.

Suzanne Arnold: 09:56

So, I think the first thing that we kind of talked about was just on antithrombotic. So, we know that patients with diabetes are more likely to clot. And so, I think that there's been a lot of data over the last several years showing that intensive antiplatelets can be really beneficial. Mikhail, can you kind of go through some of your thought process on how you treat patients with coronary

disease in terms of choosing, because there are so many different options out there, what do you think?

Mikhail Kosiborod: 10:27

Well, I think what we have learned over the years through all the different clinical trials and evidence that's been created is that there is very little question in my mind that patients with diabetes are at higher risk for thrombotic complications. So, certainly at higher risk in the setting of acute coronary syndrome, and at higher absolute risk during a period of time after an acute coronary syndrome, kind of in the convalescent phase and even long term. So, you know if you kind of think about therapy if you will, I think what we can say for certain is that somebody had an acute coronary symptom for example they absolutely need to be on a dual antiplatelet therapy for a prolonged period of time. At least 12 months, and that's what the guidelines would say.

Mikhail Kosiborod: 11:16

And then the question is what do you do afterwards, and I think what's emerged recently is that diabetes may be a potential effect modifier, if you will, but what do you do after? Do you continue a longer-term dual antiplatelet therapy for example in the patient who is one year after an acute coronary syndrome, and I would say that there is certainly data to suggest that that may be the case.

Mikhail Kosiborod: 11:39

So, if you look, for example, at data from the PEGASUS trial with ticagrelor, you know while the trial over all showed some ischemic benefit at the cost if you will of increased bleeding risks, patients with diabetes were at higher absolute risks for ischemic events. They got a greater absolute benefit with addition of ticagrelor, and while it's a post hoc analysis it needs to be taken with a grain of salt as there was even a mortality benefit in a subgroup of patients with type two diabetes.

Mikhail Kosiborod: 12:04

Again, not to over interpret these findings, but I think that's important. The other important piece of evidence is the data from THEMIS in PCI has just emerged. The largest trial of patients with type two diabetes ever conducted, close to 20,000 patients, over 19,000 patients with type two diabetes stable coronary disease, no prior myocardial infarction or ACS, and overall what we see with the data is that there is a modest reduction in ischemic event as a cost of significantly higher risk of bleeding so may not be the right treatment for everyone even with diabetes. But those patients who had a prior percutaneous intervention may have a little bit more of a favorable risk benefit profile. So,

Mikhail Kosiborod: 12:45

I think bottom line, what I would say when it comes to certainly antiplatelet therapy is I think diabetes is a risk modifier. We know that patients with diabetes have higher risk of thrombotic complications. They're risk of bleeding appears to be about same as everyone else. We have some conflicting data on that, so on average the benefit from more aggressive antiplatelet therapy, absolute benefit for sure maybe not a relative benefit for perhaps more aggressive and longer duration of antiplatelet therapy appears to be more favorable in people with diabetes than in those without.

Prakash Deedwania: 13:16

Mikhail just want to have a dialogue on this. I think there is no question that the role of antiplatelet drugs for secondary prevention is well established, but I think there has been a lot of controversy recently in the last two to three years with a number of studies and meta-analysis coming out showing that perhaps antiplatelet therapy in general really is not beneficial when we look at the risk benefit ratio it doesn't come out in favor of benefit even in diabetic patients for primary prevention. I do not hold that opinion. I still think it should be utilized, but I wonder what you think of that, what you and Suzanne both think of it, and are you using it routinely in your clinical practice for primary prevention? I do use it, but I individualize it. I don't use it as a universal approach, but I individualize it and I try to use whenever possible a medium dose.

Prakash Deedwania: 14:10

It's also known that a small dose like you usually use for primary prevention, the 75 or 81 mg is not effective in diabetics. We've had better evidence has shown that diabetic platelets are more resistant to anti platelet drugs, particularly the aspirin, and one needs to use little bit higher dose at least a medium dose. I'd like to hear your opinion because I think it would be really beneficial. There's a lot of controversy and confusion about that in the clinical arena.

Suzanne Arnold: 14:38

I definitely am using less aspirin for primary prevention than I have before. And, I think that the newer data really actually are pretty similar to the older data in terms of the counter balancing ischemic and bleeding complications, but I think that for me, I still use it for people who have other risk factors too. So, I definitely individualize treatments, but if they're a smoker and they have diabetes or if they have diabetes and an elevated corona calcium score, then those are people that I'm probably using it more in primary prevention, but I certainly am more cautious of not just using aspirin in everybody for primary prevention.

Mikhail Kosiborod: 15:15

This again, was not kind of our main focus for this statement, right? Because the statement was on people with already established coronary disease where there is no controversy, right? And antiplatelet are absolutely is indicated, but

you're right. I think the controversy is clear in the primary prevention stage and I think the question really is what is primary prevention, and how do we define it? But we all know that one patient with a quote unquote primary prevention group if not same as the other, and their risks may drastically vary depending on many things. I for one am a bit more thoughtful now than perhaps I was five years ago, about prescribing low-dose aspirin, for example.

Prakash Deedwania: 15:55

Yeah. But I think one can always argue what is your primary prevention in diabetic patients. Many diabetic patient has existing coronary artery disease. They may not be diagnosed, they could have had silent or latent disease and so on, but that's another discussion. I think all of us are together on this aspect. We individualize it and we are not using it as routinely as we used to do before, but it might still have a place in patients who are at very high risk.

Mikhail Kosiborod: 16:21

Yeah. I absolutely agree. I think we are all on the same page here, which clearly still has some role. I don't think it's a blanket prescription for anybody for diabetes maybe is the words that we used to think about it some time ago.

Suzanne Arnold: 16:33

Shifting back to secondary prevention which is obviously the focus of our statement, one of the things that I know that I'm doing much more now in terms of long term management is using risk scores such as the DAP score to help guide that. And the other thing that I've been doing a little bit more is using single agent core Benadryl. And just dropping aspirin. I feel like more and more long term we're seeing that that type of strategy may be an option.

Mikhail Kosiborod: 16:58

I think, Suzanne, that's a very interesting question, right, and what we're learning from some pieces of data and more and more is that if you're using a P2Y12 inhibitor, is it really a true value add with having aspirin on top of that, so at least some of the data that's emerging and now just to be clear, we're not talking about a 12 months period of time after ACS, but more for chronic disease management. Some of the data that is emerging would suggest that maybe there isn't all that much value add, but the risk of bleeding, we know it's higher. So, it’s clearly, I think, an area where hopefully more data will be emerging.

Suzanne Arnold: 17:34

Absolutely, and I feel like we're in a never-ending cycle of more and more data which is not a bad thing. So, just kind of shifting a little bit. I do want to kind of cover some of the other things that we talked about in the statement, to lipid management. And I think that, we certainly focused in this statement about high intensity statins are still really important, but what are of the other things

that we might be considering that we weren't before. So, Prakash, can you kind of go through how you think about lipid therapy for patients?

Prakash Deedwania: 18:04

Yeah. So, the lipid management is absolutely critical in patients with diabetes for a variety of reasons. Number one, we all are aware that patients with diabetes have multiple lipoprotein abnormalities. They may not have very high LDL, but whatever LDL they have it is highly atherogenic. Many people have referred that to be small dense LDL. Doesn't matter what you call it, but it is really very, very highly atherogenic lipid profile. They also have high triglyceride, which we also know in concert with LDL are also associated with significantly increases risk of cardiovascular event, and in addition to that they have post prandial hyperlipidemia et cetera.

Prakash Deedwania: 18:52

What is very important for the clinicians to know is that reducing LDL particularly by statin and other associated therapies as needed has been highly beneficial in patients with diabetes both for primary and secondary prevention that we are discussing as secondary prevention. And I think every study that has been done and looked at as well as the meta-analysis has shown that diabetic patients are really obtained significant benefit with as much or more reduction in cardiovascular events subsequent to utilization of statin therapy. We also know that from a very good study that I think all of us are aware, the STENO-2 trial where they showed a 50% reduction in cardiovascular events in a small group of diabetic patients who were treated with comprehensive risk reduction strategy, and that 70% of the benefit in the study was attributed to reducing LDL effectively.

Prakash Deedwania: 19:52

Also, we know from a number of studies recently for example, it's been IMPROVE-IT trial addition of ezetimibe was beneficial predominately in diabetic patients only, and if you excluded diabetic patients there was not as much benefit noticed, and this was in patients who have had preexisting recent coronary event, so I think it's important to realize that treatment of lipids in general is highly beneficial.

Prakash Deedwania: 20:21

We also look at the data recently, the data from the REDUCE-IT trial that had shown that additional treatment with EPA, eicosapentaene could be highly beneficial as well in patients who continue to have persistent high triglycerides. Furthermore, we have shown recently in a few papers that we have published on the FOURIER and other trials, that patients with diabetes who are unable to obtain the target LDL which in diabetic patients could be defined as either less than 70 or if you go with the American Association of Clinical Endocrinologists, the recommendation is less than 50 in diabetic patients with preexisting coronary artery disease, then sometimes it's very difficult to obtain that goal

with statin and ezetamibe therapy alone. And in those cases, one should not hesitate using PCSK9 inhibition with drugs that are currently available and have been proven to be quite effective.

Prakash Deedwania: 21:16

And now, we will soon have PCSK9 modifier that can be used every six months. So, I think there is really no excuse today for us to not have LDL reduction to the target goal in diabetic patients. And also, as I mentioned, it is important to realize that now we have a proven therapy for triglyceride reduction, but in addition to reducing LDL with eicosapentane and from the data that has now been seen in the REDUCE-IT trial, so I think, Suzanne and Mikhail, I routinely use a high intensity statin therapy in all diabetic patients, particularly in those who have had pre-existent coronary artery disease. And, further, provide supplementation in other therapies as I indicated with ezetimibe initially if I can attain the goal, and if needed with PCSK9 inhibitors in almost all of my patients with diabetes, because I think many therapies are beneficial but clearly lipid lowering therapy provides the biggest bang for the buck.

Mikhail Kosiborod: 22:19

I would say Suzanne, what we see certainly in registries that we've both been involved in, just to add to what Prakash just mentioned is that efficacious treatments unfortunately and frankly guideline recommendations are frequently not being implemented when it comes to lipid management, both LDL and otherwise. So, even, again, if you look at the GOULD registry for example, and people with diabetes and ASCVD, most patients are not on high intensity statins where they could say, there may be reasons for that, maybe the patients not tolerating it, but the bottom line is these are also patients whose LDLs that are not well controlled, so not anywhere close to what the guidelines say they should be at for somebody that high risk. I mean, there's no question there is some clinical interventions that regards that no question could be better, and we have a lot of tools to do better, and I think as long as we follow the guidelines and we treat high risk patients with appropriate degree of concern and we make sure that we use what we have available which are wonderful options for patient management to get LDL to target, will ultimately be better for our patients and we'll see a lower event rate.

Prakash Deedwania: 23:27

Yeah. Let me also emphasize Mikhail, because there has been a concern, and confusion around that, if you will, regarding the initial data that came out from JUPITER and other studies showing that patients who are getting medium to high intensity statin therapy could have higher risk of new onset diabetes. I think much has been written, and though, well established now, but I want to emphasize here for our listeners, that first of all the new onset diabetes risk is real, but the overall risk related to that are clouded with the event or the diabetes related complication is next to nil and clearly the benefit one gets with a statin therapy far, far outweighs any potential risks one could actually build up a concern about the new onset diabetes with high intensity statin therapy.

Prakash Deedwania: 24:19

Also, I want to emphasize, if that's a big concern, PCSK9 intervention with evolocumab or alirocumab, both of which are now available have no increased risk in diabetes or glycemic elevations. We have shown that in patients with diabetes. We have recently also shown that in patients with metabolic syndrome, who in previous studies have been shown to be the candidates that really do have the higher risk of developing new onset diabetes with statin therapy, but the main point I want to emphasize is that one should not, not prescribe the statin therapy because of that concern. And I think that concern has been wiped out, but I want to emphasize that because some people are still holding the statin therapy for that reason.

Suzanne Arnold: 25:07

I think that the other thing that I just want to make sure to emphasize is, I think it's been a little bit confusing for people as we've gone back and forth on guidelines, it's LDL less than 70 is all that matters, and then it's high density statins is all that matters and now it's kind of both. And, I still see people coming on relatively low doses of statins who have established coronary disease, but their LDL is 60 and so they say they're at goal, so I do want to make sure to emphasize that these lipid lowering medications at high intensity statins are important particularly to any patient who has established coronary disease regardless of diabetes and regardless of LDL.

Suzanne Arnold: 25:47

And I think that with the PCSK9 trials, it's actually been reassuring to see that these patients with really low LDLs are still doing well, so I think that that fear of the really low LDL has been reduced with some of those trials.

Prakash Deedwania: 26:01

We showed in the FOURIER trial that even when patient's LDL was down to 20 or 25 there was no worsening of glycemic parameters and certainly there was no increase in any sort of low LDL related side effects that people have been concerned about including any cognitive impairment.

Mikhail Kosiborod: 26:20

That's right, and EBBINGHOUSE sub study, right, in the FOURIER clearly showed that one could argue the duration of follow up was relatively short, but everything we've got to date does not suggest any neurologic issues or cognitive impairment issues with a very extensive battery of both clinician driven and patient reported outcomes, in terms of safety issues with very low LDL.

Suzanne Arnold: 26:49

Well, I certainly don't want to shortchange the discussion on glucose lowering medications, because I think that that was one of the really important parts of the scientific statement. I think that as cardiologists, we are often aware of some of the issues of endocrine thrombotic or lipid lowering or blood pressure

lowering, or things like that and those are all covered in the statement. The glycemic control section of this paper, I thought was something that was really important for us to be very detailed about and I do want to discuss that a little bit more, now. I think there's two major parts to this. I think the first is kind of what are the goals, beyond individual agents, what is an appropriate glycemic control goal in terms of A1C, because this is something that I know that I see a lot, and have to kind of argue with some primary care doctors about at times.

Suzanne Arnold: 27:40

Mikhail, what's your approach to, not taking into the individual agents, but just in terms of glycemic control and A1C, what's your approach?

Mikhail Kosiborod: 27:50

That's a great question and has been the subject of a lot of controversy of course over the years. And I think the bottom line message, Suzanne, is that those types of goals need to be individualized. And, I think over the years, major professional societies including American Diabetes Association has taken that very stance, which is, yes, hypoglycemic control is important. When patients have poor glycemic control which can cause and result in high risk of microvascular complications in people with type two diabetes which are important, right? Conditions like diabetic retinopathy, nephropathy, neuropathy, all connected to worse glycemic control.

Mikhail Kosiborod: 28:29

We know that some of these outcomes improve as glycemic control improves, so that remains an important goal of treatment, but you've got to balance that against the risks that may be involved with extremely aggressive management, especially in vulnerable patients, those that are older, those that have established macrovascular disease, cardiovascular disease may be at higher risk for hypoglycemic events. Kidney disease which we know is a risk modifier in that regard as well, and so, I think for the patient who is front of you it’s a really important consideration to have a patient clinician decision making process about what the goals of treatment should be, specifically focusing on hemoglobin, A1C and glucose control.

Mikhail Kosiborod: 29:10

So, in some patients, avoiding symptomatic hyperglycemia, and also avoiding symptomatic hypoglycemia is a very reasonable goal of management just from glucose centric standpoint. In other patients trying to get glucose control as low as possible as long as you can do it safely may be appropriate as well, so it really depends a whole lot on who's the patient that is in front of you?

Mikhail Kosiborod: 29:31

And the other piece which I'm sure we're going to get to shortly here is that just like with many other things that we've seen; it matters how you get there too. Especially in this day and age, it matters a lot. Lots of drugs have lowered

glucose, but some of those agents have cardiovascular benefits and others don't. Some of those agents promote weight loss, and others don't. Some of those agents cause hypoglycemia and others don't. Some of them do a better job of protecting the kidney for example independent of what the glucose blood but that's a mechanism. Not just necessarily hemoglobin, A1C control, and others don't. So, I think all of those have to play a real important role, both in terms of setting goals for the patient, which is the question you asked me, but also the choice that we give each agent.

Suzanne Arnold: 30:17

It really is important to recognize that a patient with diabetes and coronary disease is not the same across the board, so there are 50 year olds who have diabetes and coronary disease and you may treat those very differently than the 85 year old who you certainly worry much more about hyperglycemia, agents that cause hyperglycemia low blood sugars are incredibly hard on the body associated with more mortality, so as somebody who cares a lot about the treatment of elderly patients polypharmacy, things like that. I think that being cautious in that group of patients who are vulnerable, I think is something that is important. Prakash, you wanted to say something.

Prakash Deedwania: 30:57

Yeah. I wanted to echo what actually Mikhail said. That, I think, first of all, it is important to emphasize that a good control of glycemic parameters is beneficial both for clearly we know for microvascular but also for macrovascular events, the problem in the past has been the older drugs. The older drugs increase the risk of hypoglycemia significant hypoglycemia and many settings starting with the data from the ADVANCE and other studies have shown that when you have significant hypoglycemia then there is increased risk of cardiovascular death, and other complications, so the newer drugs that we have now, can be used safely and we can obtain the target hemoglobin A1C which should be in most patients with coronary artery disease should be around 7, not below 6.5 as has been recommended in the past, because there is probably not significant benefit, and the risk is much higher for having hypoglycemia.

Prakash Deedwania: 31:57

So, I think newer drugs are particularly beneficial, because the risk of hypoglycemia is much lower and I think the studies have shown convincingly now that the newer drugs such as SGLT2 inhibitors and when appropriate GLP-1 agonists are safe and they further can reduce the risk of cardiovascular events. I think we are moving into a new territory. I think I would call it a shifting paradigm about glucose management in patients with diabetes and cardiovascular disease.

Suzanne Arnold: 32:30

That's certainly a good segue into talking about how do you choose between these agents. There's been so much data coming out over the last few years regarding cardiovascular benefits, particularly with the SGLT2 inhibitors as well as the GLP-1 receptor agonists. Mikhail, how would you choose between these, or how do you prioritize?

Mikhail Kosiborod: 32:49

Excellent question, and of course something that has been incredibly clinically relevant in light of all the emerging data, and as you well know, Suzanne, these two classes of agents have been shown to have cardiovascular benefits, but they're not exactly the same. In fact, the profile in terms of cardiovascular benefits is very different.

Mikhail Kosiborod: 33:07

We know that the SGLT2 inhibitor was a shine if you will from cardiovascular benefits standpoint it's really prevention and treatment of heart failure, and we know from prevention kind of across the board actually regardless if patients have a ASCVD or not as long as they have type two diabetes and have established disease and multiple risk factors as these agents are effective and preventing heart failure, and at least when heart failure was reduced ejection fraction we know that they actually can be very effective in treating heart failure reducing the risk of cardiovascular deaths and worsened heart failure in the population very convincingly.

Mikhail Kosiborod: 33:40

We also know that these medications work very quickly, literally within a few weeks of randomization we see benefits in terms of heart failure prevention and heart failure treatment, and we also have learned now from more than one study that they can be remarkably effective in preventing the progression of diabetic kidney disease, which one could argue is not necessarily is in the purview of cardiologists, but I would say if you manage patients with diabetes that have ASCVD or heart failure in particular, kidney function is incredibly important, and preserving kidney function should be a very important consideration as well. So, that's the SGLT2 inhibitor.

Mikhail Kosiborod: 34:16

The GLP-1 RAs on the other hand are truly at least with the fair amount of data that we now have for those agents appear to be more on a atherosclerotic vascular disease progression pathway. It takes longer time to see benefits. The benefit primarily is what we call in cardiology MACE which is major adverse cardiac event essentially a cardiovascular death, non-fatal MI, non-fatal stroke, and actually especially on the stroke side of things show quite a bit of promise, so these agents also while both have shown SGLT2 inhibitors and GLP-1 receptor agents promote weight loss, and neither are by themselves have been associated with symptoms of hypoglycemia. GLP-1 receptor agonists in

particular once weekly can cause quite a bit of weight loss, so it's actually in some cases 10% or more body weight reduction, which can be very meaningful for our patients for a variety of reasons. And, of course the other thing is the safety profile and power ability and safety is different for different class of medications as well, which needs to be taken into account, so how do I make a decision? I would say there are some clear-cut cases where patients and it's actually consistent with guidelines.

Mikhail Kosiborod: 35:27

If you have somebody who has heart failure with reduced ejection fraction and if I have a patient with diabetes and heart failure with reduced ejection fraction given the substantial benefit from absolute risk reduction standpoint, even more in people with diabetes in a battery of test trials with those without diabetes there have been relative risk reductions is similar. I think you'd be hard pressed to find a reason why you would not start a patient like that on a SGLT2 inhibitor unless there is a contrary indication or if there is some other problems like access issues. If you have somebody who has significant diabetic kidney disease, the same story. The effect is quite remarkable, somewhere in the 30 to 50% reduction relative reduction in progression of kidney disease, so I think you'd be hard pressed to find a reason not to do that, not to start an SGLT2 inhibitor in somebody with diabetes and kidney disease, and of course many of these patients have combination of heart failure and CVD.

Mikhail Kosiborod: 36:18

On the other hand, if I have somebody who is primarily kind of an ASCVD phenotype if you will, microvascular coronary disease especially those patients has problems with being overweight or obese, and that's driving some of the symptomatology, maybe GLP-1 receptor agonist would be a better initial option. And, having said that, I think there is nothing clearly from a diabetes management at some point that says you can't use causations who don't have cardiovascular outcomes with a combination of SGLT2 inhibitors and GLP-1 RAs, and I'm not sure whether we are going to get any kind of data like that in the near future, but we certainly know they have complimentary effects on glycemic control, we know they have complimentary effects on blood pressure. We know they have complementary effects on weight. And, the mechanisms of action have such non overlapping that it's unlikely that they would not be complimentary from a cardiovascular standpoint either even though we can't prove it because we don't have the cardiovascular outcome data.

Mikhail Kosiborod: 37:15

Of course, access becomes even more of an issue when you combine more than one brand of therapy, but that's kind of in broad strokes as some would say kind of a decision making process is that I typically take when I see patients with diabetes and coronary disease, and other cardiovascular complications, and I think the patient, of course patient and patient preference is an important to that regard as well.

Prakash Deedwania: 37:37

I would completely agree with Mikhail's recommendation. I think if the cost was not a consideration, these drugs certainly would be used much more widely, but increasingly with the data that has become available, insurers and other agencies et cetera are approving these drugs when properly justified for diabetic patients, especially if one can emphasize the increased risk as many patients with diabetes are at. I think it is important to emphasize that the recent approval by FDA of dapagliflozin for heart failure therapy is also interesting, and it should be emphasized that SGLT2 inhibitors and dapagliflozin especially looked at patients with and without diabetes and showed similar benefit, but as Mikhail explained earlier, all SGLT2 inhibitors have been shown to reduce the risk of hospitalization for HF and other related events in patients with diabetes.

Prakash Deedwania: 38:32

So, I think it's a drug that I frankly use in patients with diabetes immediately after using metformin for glucose reduction, but also for the subsequent in cardiovascular protection. And this will have a special place in patients with coronary artery disease and hypertension who we know are going to be at substantially higher risk of heart failure in the setting of diabetes.

Suzanne Arnold: 38:56

I certainly echo everything that both of you have said. I think these are obviously very powerful drugs that we just have to find the way that we get our patients access to them in a very reasonable way. I think we're going to probably have to wrap this up. We didn't get to cover all of the pieces of the scientific statement, but I think we had some key highlights. I just want to give each of you the chance to give any last thoughts that you might have.

Mikhail Kosiborod: 39:23

Thanks, Suzanne. You know, I think, as you mentioned in the very beginning, this is a very timely statement. We need to figure out how to provide guideline directed comprehensive and aggressive cardiovascular risk reduction strategies and apply them appropriately to our patients with diabetes and cardiovascular disease. We're not doing, unfortunately a great job right now, if you look nationally, lots of these patients don't have the risk factors managed the way that they should. And unfortunately, that results in preventable events that can be avoided.

Mikhail Kosiborod: 39:55

And, the way to do it given the complexity of managing these patients, lots of different treatment options, I think what we really need to spend a lot of time thinking about, and working on, is how to effectively implement this at the point of care, and creating care teams, multidisciplinary care teams that include physicians, advanced practice providers, pharmacists, diabetes educators, nurses, and nurse navigators in the environments that centers on a patient and makes sure that we improve quality of life, reduce morbid events in this patient

population, and ultimately achieve our goal, which is for all of us is making our patients live longer and feel better.

Prakash Deedwania: 40:32

Thank you, Suzanne, for the great discussion, but I also like to emphasize in the end that beyond what we have discussed, it's critical for us to also control the blood pressure appropriately in patients with diabetes. If we look at the previous data, for last two decades, there has been emphasis on appropriate blood pressure control in patients with diabetes and despite the ongoing controversy about what is the ideal goal in patients with diabetes in terms of the systolic blood pressure I would still say as long as one can safely do it, lower is better, certainly the recent ACC, AHA guidelines emphasize the goal to be less than 130.

Prakash Deedwania: 41:16

One can argue there's not as much support about this from the studies that have been done in diabetic patients, but analysis from all the particular studies in meta-analysis have shown that lower blood pressure in patient with diabetes is cardio protective as long as can be safely done. So, that's very important, and this should be used in concert with the comprehensive risk reduction.

Prakash Deedwania: 41:42

I think we have discussed clearly and demonstrated that newer glucose lowering drugs which clearly have been under-utilized should be utilized more often as long as access is there and one should make the effort to get access to these newer drugs, and I think this newer strategy will clearly help us reduce the risk of subsequent and future cardiovascular events in patients with diabetes and coronary artery disease.

Suzanne Arnold: 42:06

Well thank you both so much for being on the podcast with me. It's been a great conversation. Clearly there's a lot more that we could cover here, but I encourage everyone in the audience to read the scientific statement. There's a lot to digest there, and we certainly need to take more control and more ownership of the patients who have diabetes that we take care of as cardiologists. So, thank you to the audience very much for listening, and please stay tuned for upcoming podcasts.