

## KDBH Podcast #4: Heart Failure Management in Patients with T2D and CVD

Nancy Albert: 00:04

Welcome and thank you for joining this podcast on heart failure management and patients with type two diabetes and cardiovascular disease. 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 American Heart Association and the American Diabetes Association, Know Diabetes by Heart™. This series is brought to you by founding sponsors, Boehringer Ingelheim, Eli Lilly and Company, Diabetes Alliance, and Novo Nordisk, and national sponsor, Sanofi, and AstraZeneca and Bayer. And I'd also like to thank the Heart Failure Society of America for working with us in advancing care to Know Diabetes by Heart.™ I'm Dr. Nancy Albert, clinical nurse specialist, and a research scientist in heart failure. Joining me is Dr. Mikhail Kosiborod, a cardiologist, an expert in the fields of diabetes, cardiovascular diseases, cardio-metabolic and cardio renal syndromes and quality care and outcomes. Good afternoon, Dr. Kosiborod.

Mikhail Kosiborod: 01:14

Hi Nancy. How are you? It's great to be with you.

Nancy Albert: 01:17

Yeah. It's great to be here today. I thought that before we actually jump into diabetes and cardiovascular disease, we could begin our discussion about COVID-19 and its impact on the care of patients with heart failure, since it's such a hot topic right now. Would you like to give us a little bit of an overview?

Mikhail Kosiborod: 01:36

Yes. Obviously it's a very important topic and I guess I would preface by saying that the most important issue to kind of keep in mind is that obviously the situation is evolving and changing almost on a daily basis and what we think we know today may be different a few days from now or a week from now. So, it's situations that we need to continue to keep an eye on very carefully. What is very clear and it's that kind of picture was already emerging from China where the epidemic started, that is clearly merging from Europe and United States, that first of all patients that have underlying cardiovascular disease and/or type two diabetes and that cardiovascular disease, of course, includes both arteriosclerotic cardiovascular disease and heart failure, and those that have type two diabetes or combination of these factors are clearly at higher risk for disease progression and severe complications.

Mikhail Kosiborod: 02:32

They're also at higher risk for death in a setting of COVID-19. So, it is not entirely clear at this point whether people with type two diabetes or cardiovascular disease, including heart failure, are necessarily at higher risk for contracting the disease, but it is very clear as it is they do contract the disease the risk of having complications and death is considerably higher. Several fall higher than those patients that don't have type two diabetes or cardiovascular disease and as

specifically when it comes to heart failure, I think there are a number of additional considerations here. One, of course, is again the risk of the patients who develop severe complications and death. That clearly is the case in patients with heart failure and they need to be, therefore, very careful and monitored if they're diagnosed with having SARS-CoV-2 infection. The other, of course, is this whole issue about running angiotensin aldosterone system blockers, including ACE inhibitors, ARB, sacubitril-valsartan which we use as a standard of care now in patients with heart failure and reduced ejection fraction.

Mikhail Kosiborod: 03:30

As you know, Nancy, there was a lot of controversy recently. There was a question raised whether these medications would potentially increase the risk of acquiring the infection, with SARS-CoV-2 or potentially increase the risk of complications if somebody does contract the disease and this is a complex question.

Mikhail Kosiborod: 03:46

What we can say at this point is that we certainly have no evidence to suggest that running angiotensin aldosterone blockers either increase the risk of infection or increase the risk of complications. The relationship between those agents and the ACE 2 receptor, which is the receptor that the virus seems to use to enter the body and then starts replicating and causing damage is very, very complex. It's not simplistic and it's actually possible that, in fact, these agents, RAS blockers possibly may actually be beneficial. We don't know.

Mikhail Kosiborod: 04:20

We don't know if they maybe neutral so it's too early as this point to say anything since we have no data. Was there is any increased risk of eyes infection with complications in patients that are on RAS blockers. What is very clear is that we know these agents can be lifesaving in people with heart failure and reduced ejection fraction and therefore all of the professional societies in cardiology including ACC, AHA, and Heart Failure Society, which issued a recent joint statement, as well as, the European side of cardiology. Issued statements clearly recommending that at this point until we know more, it is not advised to just continue RAS blockers because the risk of discontinuation certainly within patients with heart failure and reduced ejection fraction we know is there. That was, there is any increased risk on a virus side of the equation. It's very unclear.

Nancy Albert: 05:09

Right, and I'll just add a few things and that is if there's any patients listening to this podcast, you know, we know that these patients are at higher risk and prevention is key and so we would really encourage everybody to follow the national guidelines that we've been all hearing for multiple weeks now. Stay at home. Follow precautions in terms of social distancing practices. Continue your treatment plan, as you just heard. Don't change it up right now and unless you've spoken to your healthcare provider, so that includes your medication

plan, your standard clinical practice in terms of how you take care of yourself during the day. We know that physical activity and healthy eating habits are good even though people are staying home more, that doesn't mean to start eating more. And also if you need to see your provider check and see if your provider has telehealth services so that you may be able to connect with them without having to leave the house and step aside that social distancing that we want to keep.

Mikhail Kosiborod: 06:07

Oh, that's absolutely right, Nancy, and the other thing I would mention too since you mentioned kind of the dietary component, is that in the middle of this pandemic is continues to be very important to kind of maintain your low sodium healthy diet, especially in patients with heart failure because none of the fundamentals have, changed. So, you know, staying on your medicines, as you pointed out, and not changing medications without connecting with your healthcare team for heart failure and continuing to maintain your lifestyle. Healthy lifestyle habits are critically important.

Nancy Albert: 06:39

Agree completely. Well, let's go ahead and change gears a little bit and talk a little bit about heart failure management in patients with type two diabetes and cardiovascular disease. So, Mikhail, can you just give an overview and highlight some of the current epidemiology around cardiovascular disease, heart failure, and concurrent type two diabetes? What's the magnitude of the problem so that our audience really gets a sense of how important this theme is?

Mikhail Kosiborod: 07:06

Well, I think what we can say for sure is that both types of diabetes, as well as, cardiovascular disease and especially heart failure are epidemics globally, right? So, these noncommunicable diseases, are really one of the key public health threats across the globe. There are millions of patients with type two diabetes. It is actually estimated that that number will increase substantially within the next 25 to 30 years. And what we do know is that diabetes, whether type one and type two and of course type two is a lot more common, is a key risk factor. One of the key risk factors going back to Framingham Heart Study for development of atherosclerotic cardiovascular disease, as well as, heart failure. And what we also now is that if you develop heart failure in the setting of type two diabetes, your outcomes are really very poor.

Mikhail Kosiborod: 07:56

In fact, if we look at older patients with type two diabetes that develop heart failure in compared to those who remain free of heart failure, the risk is comparable to some malignancies like lung cancer. So, it's really a highly morbid disease and that underlines the importance of actually prevention of cardiovascular disease and heart failure in people with diabetes. So, the best we really can do and should do is to prevent it from happening in the first place

because the outcomes are so bad. And then the next best thing of course, is that if have the patient already developed heart failure in the setting of type two diabetes. The next critical important thing is to try to treat it in a very multifaceted, aggressive fashion to reduce the risk of death and complications due to heart failure.

Nancy Albert:

08:38

Right. And I'll just add one little comment and that is that for people listening, when we're talking about heart failure, we're not just talking about heart failure and reduced ejection fraction. We're also talking about patients who have heart failure and preserved ejection fraction. So, whether the ejection fraction is normal, mid-range or high, patients with heart failure are at equal risk of having more comorbidities, more complications, and a higher risk of death. So, we need to keep that in mind for all of our patients about the elevated risk.

Mikhail Kosiborod:

09:09

And just to add to that Nancy. It is also true that type two diabetes is a risk factor for developing heart failure regardless of which type of heart failure it is, reduced or preserved ejection fraction.

Nancy Albert:

09:19

So, let's talk a little bit about the American Heart Association and the American Diabetes Association guidelines and standards for care of treatment screening and management of type two diabetes. So, we're going to focus just on type two diabetes right now and we know that there are many different things to consider. I'll start off talking a little bit about the nonmedical care just as a reminder for everybody and then we'll hopefully have, Mikhail and I both talk about some of the drug therapies out there today. So, we just need to keep in mind that when we talk about the goals of care of managing type two diabetes, especially in patients who also have cardiovascular disease, that we need to remember that lifestyle is really important. Are patients getting out and exercising? Are our patients following a diet that is the right diet for somebody with diabetes and heart disease? Are they keeping their hemoglobin A1C levels at a level that is considered a standard of care? What is our weight?

Nancy Albert:

10:18

We know patients have an increased risk as they get older. We also need to consider factors, such as, internal motivation and how we can work with our individual patients to ensure that they're following the best practices out there depending on their motivation level and trying to make it work with them. And for our patients with depression, we know that people who are depressed oftentimes are less likely to be adherent to evidence-based therapy. So, what can we do to think about depression, motivation? And then finally the socioeconomic context. Because we know there's a lot of people in the United States, especially now with COVID-19 and many people having been furloughed or having lost their jobs, that they may have to make very careful choices about

how they spend the money they do bring in. So, we just need to think a little bit about the goals of care in terms of optimizing quality of life.

Nancy Albert:

11:11

In addition to the medical or medication therapies we're going to be talking about. We would hope that most of our patients are involved in shared decision making with their providers so that patients are getting answers to questions and the providers are giving options of care so that patients really best understand why it is that we may want them on a newer drug versus an older agent, as an example.

Nancy Albert:

11:37

When it comes to drug therapies, the market has really opened up since about 2015 in terms of newer therapies on the market. Mikhail, do you want to summarize a little bit about the different diabetes medications that are available so that our audience can get an idea of what is first line of therapy and then what we should consider next in our patients who have diabetes and cardiovascular disease?

Mikhail Kosiborod:

12:01

Right, so just to maybe very briefly mention, too, Nancy is that, of course, if you look at the standards of care, for example, standards of care for patients with diabetes from the American Diabetes Association. Of course, the risk factor medication both for secondary and primary prevention and risk reduction are multifaceted and comprehensive and they don't just focus on medications that were initially developed for glucose lowering, but now if you're to have cardiovascular benefit, such as, sodium glucose co-transporter-2 inhibitors, so SGLT-2 inhibitors and glucagon-like peptide-1 receptor agonist, so GLP-1 receptor agonist. But there are really comprehensive sections that have to do with the lifestyles, that have to do with blood pressure, with lipids, and, of course, there have been developments and new data that are applicable to all of those facets of risk management. So, I would just encourage everybody to look at that document because I think it's really as always very comprehensive and we know that comprehensive risk reduction and multifaceted approach to care in terms of prevention is critical.

Mikhail Kosiborod:

12:59

Now kind of specifically focusing on the glucose lowering medications, or at least medications that were developed for glucose lowering initially, and then have been shown to have cardiovascular benefit. There is a dedicated section in the standards of care and essentially, I guess, to cut to the chase if you will. The bottom line is the past decade of cardiovascular outcomes trials that were initially mandated by the U.S. Food and Drug Administration to show safety of new medications and novel drugs for type two diabetes really created a wealth of evidence. Now this intersection of type two diabetes and cardiovascular disease is one of the most evidence-based areas in the entirety of internal

medicine in large part because of the decade of cardiovascular outcomes trials. And what we clearly learned from just cardiovascular outcome trials is that different medications, while that they developed for glucose lowering while they may all lower blood glucose and hemoglobin A1C and now it's the same when it comes to cardiovascular risk reduction.

Mikhail Kosiborod:

13:56

Some medications that have been studied were shown to be safe from a cardiovascular standpoint like DPP4 inhibitors perhaps, which are very popular medications for management of type two diabetes, but do not appear to provide cardiovascular benefit and are neutral from a cardiovascular standpoint similar to placebo. Whereas two classes of medications developed for glucose lowering, again SGLT-2 inhibitors and GLP-1 receptor agonists clearly had been shown to have cardiovascular benefits. Now what we know from just cardiovascular outcome trials in patients with type two diabetes is these two classes are not exactly the same as GLT-2 inhibitors specifically. Their biggest effects appear to be on prevention of heart failure. In fact, a majority of patients in these trials, while they all had type two diabetes and most had atherosclerotic cardiovascular disease, the majority did not have heart failure at baseline and so there was a very robust reduction with SGLT-2 inhibitors compared with placebo in the risk of hospitalization for heart failure and that appears to be primarily prevention of heart failure in patients that didn't previously have it.

Mikhail Kosiborod:

14:52

So if you think about it in the ACC/AHA classes of heart failure, this is essentially taking patients with class A and B heart failure which means that they either have risk factors like type two diabetes or possibly structural heart abnormalities and then preventing these patients from progressing to stage C heart failure, which is where we actually see symptoms of heart failure, such as, shortness of breath and social intolerance, low extreme edema and so forth. So, these agents, again, and that appears to be a class effect all appear to significantly reduce the risk of this if you will, progression of heart failure from stage A and B to stage C and appear to be very effective in preventing heart failure in people with type two diabetes. And that evidence is now reflected in the standard of care. What was not known with SGLT-2 inhibitors when the last iteration of standards of care had emerged was whether they can also be used as effective treatments for patients that already have established heart failure.

Mikhail Kosiborod:

15:43

And there is some new evidence that just came out that we'll probably come back to and specifically DAPA-HF trial in that patient population. What we also know from the cardiovascular outcome trials in type two diabetes is that SGLT-2 inhibitors also appear to have a modest, but significant effect on reducing the risk of major adverse cardiovascular events, which include events like myocardial infarction, stroke, and that's from cardiovascular causes and for that specific purpose. It appears as the higher the risk of the patients, the greater

potential reduction in those major adverse cardiovascular events, which we abbreviate as MACE. Fact on heart failure that we see in these outcome trials, appears to be very early. Literally within weeks of randomization and I think that again speaks to the mechanism of action. We've done a lot of work to try to understand the mechanism of benefit and that work is still ongoing in many mechanistic studies.

Mikhail Kosiborod: 16:32

For GLP-1 receptor agonist, the benefit that appears to be primarily in reduction in atherosclerotic atherothrombotic events like myocardial infarction, stroke, death from cardiovascular causes with very little effect on heart failure and the benefit it appears to be, it takes a little bit longer to emerge. Again, suggesting that that's more of an effect on atherosclerotic vascular disease progression, black regression, if you will, versus the more of a human dynamic effect, which is what we see with the SGLT-2 inhibitors. Now, what I will say is that most of these agents are now being increasingly emphasized in multiple societies' guidelines and they're also featured, of course, as you would expect in a standards of care as medications that you should consider for cardiovascular risk reduction, not just for glucose lowering, but specifically for cardiovascular risk reduction, especially in patients with type two diabetes and established cardiovascular disease.

Nancy Albert: 17:21

Right, and if we have patients with heart failure, would you suggest that the SGLT-2 inhibitors would supersede the GLP-1 receptor antagonists' agonists?

Mikhail Kosiborod: 17:32

Well. What's the again the most recent iteration of the standards of care state is that these medications may also benefit patients that already have heart failure, established heart failure, but again, when the document was published, of course, the results of the DAPA-HF trial were just emerging and what that trial showed for the first time in the very conclusively, in my opinion, is that SGLT-2 inhibitors and specifically in patients with established heart failure and reduced ejection fraction who are already optimally managed with guideline directed medical therapy for heart failure with reduced ejection fraction, definitely significantly reduced the risk of death or worsening heart failure by 26% with very small number needed to treat over a treatment period of just 18 months. And that benefit was interestingly enough, essentially identical in patients regardless of whether they did or did not have type two diabetes.

Mikhail Kosiborod: 18:26

So roughly 45% of patients in that trial had type two diabetes, 55% did not, and the effects of and the beneficial effects in this primary outcome of dying from cardiovascular causes of worsening heart failure events was essentially exactly the same. And people with or without type two diabetes indicating that the benefit of this agents in patients with heart failure, are likely completely

independent of glycemia and hemoglobin A1C or any changes from the hemoglobin A1C. So, my prediction would be that these data will be incorporated in future iterations of standards of care as well as incorporating another societies' guidelines specifically as those for heart failure management.

Mikhail Kosiborod: 19:03

That has not transpired yet, but that's only because the trial was just published a few months ago. So, I think that's very important data, very exciting data for patients that have heart failure with reduced ejection fraction regardless of whether they have type two diabetes or not.

Mikhail Kosiborod: 19:15

Now going back to your question, Nancy, I think the joint consensus document from American Diabetes Association and European Association for the Study of Diabetes already is giving preference Even before DAPA-HF trial data emerged already was giving preference to have SGLT-2 inhibitors in people with heart failure, in individuals that have type two diabetes and established heart failure already. And clearly these data will only further strengthen those types of recommendations going forward.

Nancy Albert: 19:41

Right. It seems like after metformin being the first line of therapy in patients with heart failure, the next preference was SGLT-2 inhibitors and I think it's because it does. We know it has an impact on blood pressure control, arterial stiffness, vascular resistance, and even microvascular remodeling. And it'll be interesting to learn if we can actually find the exact mechanism of action. We know that there's been many proposed benefits in our patients with heart failure, whether it's ion hemostasis or calcium handling or reduction of cardiac oxidative stress or even vascular inflammation. So, it'll be very interesting down the road to learn how we will best use these. And we know that the guidelines for heart failure are in the process of being revised so hopefully before the end of 2020 we'll have a strong consensus out there about how to use these drugs.

Mikhail Kosiborod: 20:34

Nancy, just to introduce maybe a little bit of a controversial point here is that, I guess, one could make an argument given the fact that we now know SGLT-2 inhibitors at least dapagliflozin for the time being. In fact has a benefit on cardiovascular and all-cause mortality and also worsening heart failure in people that have type two diabetes and heart failure with reduced ejection fraction was in fact it should be first line therapy in those types of patients that have type two diabetes and known heart failure with reduced ejection fraction that need a medication for glucose lowering and maybe it should come even before metformin, because for metformin, certainly in heart failure, we do not have any trial data and there's only data we have comes from observational studies and, at best, is and maybe suggestive, but certainly not convincing or definitive.



The European guidelines have already kind of taken that leap and in fact have suggested that's exactly that be done.

Mikhail Kosiborod: 21:27

We have not yet followed this in the American guidelines from either diabetes societies or cardiovascular societies and I think it'll be very interesting to see how that evolves as we continuing to get more data on the role of SGLT-2 inhibitors from heart failure. We, of course, have a number of heart failure trials both in patients with heart failure and reduced ejection fraction and in those with heart failure and preserved ejection fraction, which, of course, is extremely interesting because as of right now we don't have any established medications that have really been proven to be disease-modifying in heart failure and preserved ejection fraction. So, it will be a very interesting field and will be fascinating to see how it evolves and how it impacts the guidelines.

Nancy Albert: 22:05

I agree completely. I think it'll be wonderful for our healthcare providers and, also, for our patients to get a better handle on how we can do a better job of improving the lives of our patients and also their quality of life. So, I guess we'll have to just wait and see a little bit longer, but hopefully we'll be getting new knowledge and new information soon. Let's hone in a little bit on screening for these patients. What should the primary care provider be screening for and how do they manage and reduce the heart failure risk in their patients with type two diabetes?

Mikhail Kosiborod: 22:37

Well I think, Nancy, you know we need to kind of come back to the fundamentals, which is, I know there is a lot of discussion about should you be using random theoretic peptides like NT-proB NT or echo cardiographs for screening patients with type 2 diabetes that may be at risk for developing heart failure. To me, it's the most important saying, and I think where's the ball gets dropped frequently, is just a simple good medical history combined with a good physical exam. Medical history perhaps being the most important because frequently we either are not inquisitive enough. We just ask patients how they're doing, and they say, okay and we don't really delve in. I can't tell you how many times that occurred to me in my own practice where asking the patients if they feel okay and they would say yes and then you start probing and asking what happens when they walk or go up the stairs and you do, in fact, find out they get short of breath quite easily, but because they're sedentary and they don't do it on a regular basis, it's not something that they will bring up on their own.

Mikhail Kosiborod: 23:32

So, I think that is a critical part. I think good physical exam is a critical part. And the other piece I would say is if you are screening questions on the medical history suggesting social intolerance or shortness of breath with physical activity

that does need to be aggressively investigated in people with type two diabetes because they have high risk and all of those things I mentioned kind of earlier including brain natriuretic peptides and echocardiography could be very useful. There are some caveats with using both of those modalities, in terms of screening patients for heart failure, but certainly if interpreted and used correctly, that can be very helpful in patients that appear to exhibit some symptoms suggested for perhaps unrecognized heart failure.

Nancy Albert:

24:11

Great. So, when we think about trying to prevent unwanted complications, one of the things I always think about is how we can help our healthcare providers do a better job of managing patients with cardiovascular disease and comorbidities like diabetes. And we're very fortunate right now that the American Heart Association has a Get with the Guidelines® Heart Failure program and they've included emerging performance measures which can help sites track and get feedback on how well they're doing in their own hospital systems or in their own clinical practices. In terms of managing patients with diabetes, are they checking hemoglobin A1C? Are they looking for complications, etc.? And then we also know that the Target: Type 2 Diabetes<sup>SM</sup> program is a new quality improvement in recognition opportunity that organizations can get involved in in terms of providing outpatient care related to type two diabetes and cardiovascular risk factors.

Nancy Albert:

25:10

And so, it's brought to us by the American Heart Association and the Know Diabetes by Heart™. And so we just need to keep in mind that there are resources available for healthcare providers to help them do a better job of monitoring their own quality care and looking at different performance measures to see if they're really providing care at what we would call guideline levels or optimized care so that we can do the best job for our patients. One of the things that we may want to talk about more though is what is needed for health care systems and/or providers to be successful beyond just giving the right drugs at the right doses?

Mikhail Kosiborod:

25:51

Well, I think one of the problems we deal with, especially when we talk about prevention with the primary secondary prevention in patients with type two diabetes, that is they're at high risk for developing cardiovascular complications, including heart failure or already have the disease condition. You know, unfortunately our current preventative care strategies or clinical care delivery models, really is a better term, are not very well aligned to incentivize the clinicians to do the right saying prevention unfortunately frequently gets kind of put on the back burner because there may be urgent issues that patients need to address, especially with their primary care physicians or clinicians. As there is limited time to see a patient, there are lots of potential treatment options, which is a good problem to have, but it still requires a pretty detailed conversation with a patient for shared decision making.

Mikhail Kosiborod: 26:42

So, I think what ends up happening, unfortunately we see a lot of clinical inertia. I can tell you, for example, you know we recently published this paper in *Circulation* from the registries that we're involved in across 120 centers in the U.S. looking at people whose type two diabetes and atherosclerotic cardiovascular disease, and what we see is that only a tiny fraction of those patients, less than 10%, actually receiving what we would consider to be optimal guideline directed care with a multifaceted comprehensive risk reduction. And I think that's a testament to the fact that there is a lot of clinical inertia and there is not a good alignment of incentives to prioritize prevention. And I think given how big of an issue it is, the burdens that we are already experiencing and about to experience in a much greater way from cardio metabolic conditions like type two diabetes and its associated comorbidities, we need to think carefully about what we can do better. How can we realign incentives and how we can really come up with a better clinical delivery model that prioritizes multidisciplinary team-based comprehensive cardiovascular risk reduction.

Nancy Albert: 27:43

Right. I agree completely and it's very sad to hear a statistic like less than 10% of patients are receiving optimal medical care. One of the things I always think about is I try to remind my patients and my colleagues that patients are only in a hospital environment or even in a clinical setting about 1% of the time, the other 99% of the time they're at home. And so, we do need to figure out how we can give our patients more control of their care and help them to understand that they are in control of their care. They have to manage themselves and we need to figure out how to go about it in a way that they understand what we're asking them to do and that they're willing to take those actions even beyond taking medications day in and day out.

Nancy Albert: 28:27

Well, I know we've only got about five minutes left and what I'd like to do is ask you to talk a little bit about how we prevent worsening or existing kidney disease, because you have a background in that regard. We know renal function is both important to heart failure patients and diabetes because they're both at increased risk for renal complications. So, can you give any thoughts to us to help our providers and patients out there when considering kidney disease in the mix?

Mikhail Kosiborod: 28:54

Yeah, and I assume, Nancy, that you're talking about diabetes related chronic kidney disease and, of course, that's another very common and morbid complication of type two diabetes and has a significant impact on patient outcomes, both progression of kidney disease. Those patients, of course, with chronic kidney disease and diabetes are also at high risk for both atherosclerotic cardiovascular disease complications and heart failure. So, it's not just progression of kidney disease that we need to keep in mind, but also

cardiovascular events and, in fact, cardiovascular events is what kills most patients with diabetes and chronic kidney disease. In fact, even more so than the impacts of chronic disease progression has, and, of course, it also has substantial impact on their health status and quality of life. The important thing to keep in mind is, first of all, patients with type two diabetes need to be screened consistently for chronic kidney disease and that includes both assessment of glomerular filtration rate, estimated GFR, and also albuminuria and proteinuria, which is a huge risk factor for both kidney disease progression and cardiovascular disease events.

Mikhail Kosiborod: 29:55

The second is, we do have effective treatments now for treating diabetic kidney disease and preventing disease progression. One class of those agents is running angiotensin blockers. So both ACE inhibitors and ARBs have been shown previously and are now recommended in the guidelines for prevention of diabetic kidney disease or diabetes related kidney disease progression and while many patients with type two diabetes receive those medications, it is still underused and we need to do better in that regard.

Mikhail Kosiborod: 30:25

The second more recent and very exciting development is a sodium glucose co-transporter 2 inhibitors, SGLT-2 inhibitors that we already talked about in terms of the effects on heart failure, also, had been shown to be significantly beneficial when it comes to prevention of diabetes related chronic kidney disease progression. So the CREDENCE trial that was presented and published last year showed that canagliflozin one of the SGLT-2 inhibitors can significantly reduce by about 30% the risk of heart kidney endpoints such as doubling of serum creatinine and progression 10 stage kidney disease, initiation of renal replacement therapy or death from kidney causes or kidney related death. And that was despite the fact that almost everybody in that study was already on RAS blockers.

Mikhail Kosiborod: 31:11

So, this is on top off and through some of the different mechanisms that RAS blockers is doing in terms of how they a prevent kidney complications and progression of kidney disease. A very recent development is actually that the second trial, DAPA-CKD with dapagliflozin another agent in the SGLT-2 inhibitor class.

Mikhail Kosiborod: 31:30

That trial was just stopped prematurely by the data monitoring committee due to overwhelming efficacy. Now unlike CREDENCE which enrolled only people with type two diabetes related CKD, the DAPA-CKD trial enrolled patients both with and without diabetes. We don't have any details. We don't know what those results look like specifically in terms of numbers and whether they differentiate people, with or without diabetes in terms of CKD progression. But

we will be eagerly awaiting those data. So bottom line is I think we now have several effective interventions to prevent the progression of this very morbid complication of type two diabetes and at least one of these agents, possibly a class of agents like SGLT-2 inhibitors may potentially have an effect. And even on peoples that have non diabetes related CKD. But again, we don't have any details and we need to await the data from that trial before we can make those conclusions.

Nancy Albert:

32:18

Well, that helps us leave this podcast on a very high note that there may be more to come down the road in terms of cardiovascular disease and diabetes and kidney dysfunction so that's great to hear. Well, I want to thank Dr. Mikhail Kosiborod for joining me today, and I'd like to thank everybody for listening and to stay tuned for upcoming podcasts.