

- Janani Rangaswami: 00:04
Welcome and thank you for joining this podcast, Know Diabetes by Heart™, a collaborative initiative between the American Heart Association and the American Diabetes Association. My name is Janani Rangaswami, and I'm a nephrologist with the Einstein Health System in Philadelphia and Vice Chair of the Kidney Council of the AHA. The purpose of this podcast series is to reduce cardiovascular deaths, heart attacks, strokes, and heart failure in people living with type 2 diabetes.
- Janani Rangaswami: 00:36
Today's episode discusses the recent AHA scientific statement on cardiorenal protection with the newer antihyperglycemic agents in patients with diabetes and chronic kidney disease, which I had the pleasure of chairing and co-authoring with several distinguished authors in the cardiorenal metabolic space. This scientific statement was recently published in *Circulation* and is a work product of the Kidney Council and supported by four other AHA councils. This podcast series is brought to you by founding sponsors, Boehringer Ingelheim, Eli Lilly and Company Diabetes Alliance and Novo Nordisk, and national sponsors, Sanofi, AstraZeneca and Bayer. Joining me today are Professor Katherine Tuttle and Dr. Muthiah Vaduganathan who both served on the writing group of this statement.
- Janani Rangaswami: 01:29
Professor Tuttle is an endocrinologist and nephrologist by trade. She is the executive director for research at Providence Healthcare, the co-principal investigator of the Institute of Translational Health Sciences, and professor of medicine at the University of Washington. Dr. Muthiah Vaduganathan is a cardiologist and clinical investigator at Brigham and Women's Hospital and Harvard Medical School with well-established expertise in the cardio-metabolic space. Doctors Tuttle and Vaduganathan, welcome to this podcast and thank you for being here today.
- Muthiah
Vaduganathan: 02:06
Thank you for having us. It's really a privilege.
- Katherine Tuttle: 02:09
Yes. Thank you very much. Great to be with you today.
- Janani Rangaswami: 02:12
So, before we actually start the discussion, I just wanted to give a little bit of a backdrop about why the AHA felt the need for this statement. So as we know, chronic kidney disease in patients with type 2 diabetes is a major public health problem and is a leading cause of end-stage kidney disease in the United States and worldwide. Despite current standard of care therapies, there still remains a disproportionately high burden of cardiovascular disease in this population, accounting for high morbidity, mortality and healthcare resource utilization.

Lifestyle modification, optimization of glycemic targets and blood pressure control, statins, and the use of inhibitors of the renin-angiotensin system have been the cornerstone of treatment for patients with type 2 diabetes and CKD for several decades. However, substantial residual disease burden of cardiovascular disease and end-stage kidney disease remain even in optimally managed patients.

Janani Rangaswami: 03:13

In this backdrop, the new classes of antihyperglycemic agents, including the SGLT-2 inhibitors and the GLP-1 RAs have demonstrated significant reductions in cardiovascular and kidney adverse outcomes in patients with type two diabetes and CKD, and they represent a paradigm shift in the approach to cardio-renal risk reductions in this patient population. So that's why the AHA, and particularly the Kidney Council, felt the need to put out a statement in a multi-disciplinary fashion involving nephrologists, cardiologists and endocrinologists, to be able to summarize the latest science in the field, offer guidance to these three specialty communities as well as to the internal medicine community, and to offer guidance on how multidisciplinary care models can be implemented.

Janani Rangaswami: 04:04

So, one of the first points we made in the statement was to accurately define end stage CKD, for which measurements of both eGFR as well as urine microalbumin are necessary. And the other group made this point, because in the real world practice, routine assessments of microalbuminuria are somewhat erratic, and especially when performed by non-nephrologists. It's also somewhat underappreciated that both components, eGFR and urine microalbumin, independently influence cardiovascular risks. So Dr. Vaduganathan, we have summarized in this paper that the SGLT2-I trials have consistently shown cardiorenal benefits across eGFR strata, as well as albuminuria strata. However, do you think that the message for the added value added by measurement of urine microalbumin and GFR has percolated in the cardiology community in the evaluation of cardiovascular risk? And if not, what do you think we can do to ensure that urine albumin measurement is a part of routine CVD assessment profiles?

Muthiah
Vaduganathan:

05:11

Thank you so much for that wonderful introduction to this topic and for that segue into initial topic of risk assessment. I think that in cardiology, we have a number of tools to aid in risk assessment, whether that's clinical parameters, excellent biomarkers, blood-based biomarkers. I think that there's a real opportunity to add kidney markers of risks that not only allow for incremental risk identification, but also may identify key patients who may respond more favorably to certain therapies. Many of the existing therapies in the cardiovascular domain, especially for high risk entities like heart failure, unfortunately are limited when we get to low eGFR states, and I think that this is another plug that this high-risk intersection is an important one, not only to

detect early, but to track over time. And these patients may be special candidates for some of these newer therapies.

Muthiah

Vaduganathan:

06:15

The second question that you asked about, how do we actually get this more broadly disseminated and how do we actually get more routine measurement, especially with respect to albuminuria status implemented in cardiovascular practices? I echo your sentiments that these measurements are incomplete. They're erratic, they're infrequent and often are never done in cardiovascular practices. I think it comes down to actually processes of care. I think that in built in our structures of routine ambulatory practice, I think we actually don't have the equipment, for instance, in many of our practices to actually make measurements of urine microalbumin ratios. So I think that shifting that, especially as we move to better recognition, that none of these entities exist alone. These are highly overlapping entities and those high risk patients at the intersections are the ones that we need to pay special focus to and may target for newer therapies.

Janani Rangaswami:

07:16

I completely agree with you, and I really think it cannot be emphasized enough that these kidney markers are such an important tool in identifying that high risk phenotype and introducing early therapies rather than allow the patient to develop advanced disease and then try to pull them out of an advanced cardiorenal phenotype. Dr. Tuttle, I would like to get your thoughts on the pivotal DAPA-CKD trial that reported after the timeline of our statements summary. For the audience briefly, this was a trial that included 4,304 participants with any GFR in the range of 25 to 75 mL per minute and a urine albumin to creatinine ratio between 200 milligrams up to 5000 to receive dapagliflozin 10 milligram, once a day, or placebo. The primary outcome was a composite of a sustained decline in eGFR of at least 50% end stage kidney disease or death from kidney or cardiovascular causes.

Janani Rangaswami:

08:17

Notably the trial was stopped early due to efficacy with a mean follow-up of 2.4 years. The DAPA group experienced a 39% relative risk reduction for the primary composite outcome with an impressive NNT of 19. The hazards for key secondary outcomes were also lower with DAPA versus placebo, including for the composite of death from cardiovascular causes or hospitalization for heart failure and death. The effects were similar in those with and without type two diabetes, and the known safety profile of DAPA was confirmed. Dr. Tuttle, do these results surprise you in any way, especially in the non-diabetic CKD group, and between CREDENCE and the data from DAPA-CKD? Can we now say that the SGLT2 inhibitors are definitely first-line therapy and standard of care across the board in patients with CKD regardless of diabetes status? And finally, do you foresee any role in the emerging knowledge of the non-albuminuric diabetic kidney disease phenotype, which wasn't particularly addressed in either of these two trials?

Katherine Tuttle: 09:26

Well, thank you very much for those very compelling questions. And if I may take a moment, I would really like to say I was very heartened to hear a cardiologist speak to the importance of identifying and stratifying by CKD risk. And I want to make a couple of points related to this emphasis on cardiorenal metabolic medicine. If we look at patients with diabetes, kidney disease is still one of the most common complications. It's still occurs in a third of type one and 40% of type two. So first off, this is very common and one of the most severe complications. And with regard to cardiovascular risk, several years ago we published a population-based study out of NHANES (National Health and Nutrition Examination Survey), which showed that in patients with type two diabetes, almost all the excess cardiovascular risk was confined to the group with albuminuria, low GFR or both. So it is time to recognize that if we want to focus on cardiovascular risk reduction, these are the highest risk patients. And I think that that has not been well appreciated if you will, even within the subtyping of which diabetic patients are at highest risk. And then finally, among people who survive cardiovascular events, it still is the most common cause of kidney failure worldwide.

Katherine Tuttle: 10:46

So, this is really the intersection of a very, very important outcome for many people, especially considering the other pandemic of diabetes. We have 476 million people in the world now with a projection to 700 million by 2045. So this is a big deal. And the other thing is, it hearkens to the fact that what we know about diabetes prevention has not translated in any meaningful way to communities. And while certainly that should be a focus, in the meantime, we're going to have another pandemic of people with diabetes, which means diabetic complications, and it means serious morbidity and mortality. So I really welcome this opportunity to realize that we're all looking at the same patients from a different lens and bringing it together to treat them properly.

Katherine Tuttle: 11:32

Now to the SGLT2 inhibitors, this is breakthrough therapy. We have been hearing about this since the initial results of the CV outcome trials, which were done for safety of these agents and focused on atherosclerotic or MACE events and not only showed safety, but superiority. However, following that the really striking benefits have been on heart failure and on kidney failure. I won't recap for this audience the benefits on heart failure, and we'll hear a little bit more about that later, but to the point of the two kidney disease outcome trials, CREDENCE and DAPA-CKD that you mentioned, I mean, these really are in the field of nephrology breakthrough trials. Another sort of contextual issue I'd like to point out is, both of these trials were stopped early for overwhelming efficacy. And in the field of nephrology, we've had trials stopped, but almost always for safety and occasionally for futility. These were the first trials ever stopped for overwhelming efficacy. So that is a huge success right there.

Katherine Tuttle: 12:32

And basically as you pointed out, DAPA-CKD extended the type of patients who were treated with an SGLT2 inhibitor to non-diabetic patients in about a third, and also lowered the GFR criteria from 30 in CREDENCE to 25 in DAPA-CKD, and then also lowered the albuminuria entry criteria from 300 to 200. So we sort of see this indication creep. But you cited the main results for the trial. If you look across any therapeutic area, to see reductions in major disease end points, whether they're in cardiovascular disease, kidney disease, cancer, I don't care, to see risk reductions on top of the best we have today of 40% is almost unprecedented. And then second, in nephrology, prior to the SGLT2 inhibitors, we have had no drugs that have been shown to prevent death in the CKD population. Mortality is the ultimate end point from any condition, and to see a 30% relative risk reduction in mortality is stunning. And that's why it's currently in a breakthrough status with the FDA under consideration to move this therapy quickly to patients, because the mortality risk is enormous.

Katherine Tuttle: 13:47

The most common cause of death in patients diabetes and CKD is cardiovascular disease, it's about half. About a third are infections. And again, context. In the COVID-19 era, where these patients are very high risk, that mortality risk may shift a little bit, but right now what we can act upon is the cardiovascular risk. So if we could reduce mortality in this very high risk group for death, and among the living preserve function, heart function and kidney function, this is a real win for patients because it means staying alive and staying well, which is what we have so desperately needed. So I guess that's more than enough to say and I'll stop and welcome comments from my colleagues here.

Janani Rangaswami: 14:30

I think that it was very well put, Kathy. Like you said, the nephrology field has had a drought for a very long time, almost two decades since IDNT and RENAAL, to get to the point where we have another therapy that has been shown to slow down progression to end stage disease. And just considering the impact it could potentially have on healthcare economics, on quality of life and patient satisfaction, like you said, the true winner here is the patients. So thanks for that very nice overview of how the field is where it is today, to the point where we now have data from the DAPA-CKD trial.

Janani Rangaswami: 15:07

So, Dr. Vaduganathan, as this audience knows, the burden of cardiovascular disease is disproportionately high in CKD, particularly the heart failure phenotype in that combination of patients with diabetes and CKD. To that end, the recent EMPEROR-Reduced trial was received with a lot of excitement at the ESC meeting in 2020, and it confirmed several key findings from DAPA heart failure from last year, including the benefit in patients with heart failure with reduced ejection fraction without diabetes. However, there was some interesting nuances and differences in the baseline risk of the enrolled patient

groups between DAPA heart failure and EMPEROR-Reduced, and also some differences in baseline guideline directed medical therapy use patterns. And notably, one of the things that caught interest was the lack of the effect on cardiovascular death reduction with EMPEROR-Reduced when compared to DAPA heart failure, where that was seen. So can you help tease out some of the subtle differences and shed light on why we might've seen some of these results?

Muthiah

Vaduganathan:

16:18

You know, I think we can all remember in fall of 2015, when EMPEROR outcome thread out where exactly we were and how surprised we were, especially with respect to certain end points, including heart failure. And I think the real success of this field has been how rapid it has moved and pursued threads of efficacy in kidney disease and heart failure. And we've had the benefit of seeing now two randomized clinical trials in dedicated populations of chronic heart failure with reduced ejection fraction. The first was the DAPA Heart Failure trial that read out in 2019. And then just a year later, we have EMPEROR-Reduced, a second randomized clinical trial also in heart failure with reduced ejection fraction. And I would say at a high level, both files had very concordant findings. Substantial reductions in composites of cardiovascular death or heart failure hospitalization, they both had remarkably consistent effects in large subsets of patients with and without diabetes, and they had remarkably consistent effects, irrespective of background use of best available therapies for heart failure. And so they fundamentally have shifted the available therapeutics in this space and have added an additional pillar of disease modifying therapy for heart failure with reduced ejection.

Muthiah

Vaduganathan:

17:50

Now, as you had mentioned, there are differences between these trials that should be acknowledged. EMPEROR-Reduced enrolled a higher risk patient population, partially driven by their inclusion criteria in the clinical trial, in which eGFRs were allowed down to 20, the natriuretic peptide cutoffs were higher for inclusion. And so because of this, the overall risk of the population was substantially higher. And because of that as well, the absolute risk reduction seen in the trial were more substantial with respect to cardiovascular death or heart failure hospitalization.

Muthiah

Vaduganathan:

18:29

Now DAPA heart failure in contrast studied a more stabilized chronic heart failure population in which there was a higher proportion of NYHA class two patients with lower, on average, natriuretic peptide levels. And in this trial, they showed substantial reductions, relative risk reductions, in the primary composite endpoint, and they showed a nominal reduction in all-cause mortality. Now because of the specific hierarchy of testing, this couldn't be claimed statistically significant, but it did meet P values less than 0.05. Now in contrast, EMPEROR-Reduced had a non-significant reduction in cardiovascular death. Now when pooling data and looking at the totality of evidence, there did

not appear to be any statistical heterogeneity in these assessments. And that's my takeaway, that these are very comparable overall risk assessments and risk reductions. The subtle differences in the clinical trial findings likely can be explained by differences in inclusion criteria and the study designs.

Muthiah

Vaduganathan:

19:37

Importantly, both therapies did show a substantial slowing in the decline in eGFR. And this is a real remarkable finding to me. It was a real pleasure to see that in a heart failure clinical trial program to have a pre-specified secondary endpoint as an eGFR slope is really unheard of, a testament to how the progress in this field and the recognition of the intersection and overlap of these entities. And EMPEROR-Reduced is probably one of the first, if not the first, randomized clinical trial of a chronic heart failure population in which a therapeutic substantially significantly slowed the decline in eGFR a pre-specified endpoint in a randomized clinical trial. And so, again, remarkable progress on both fronts. I think we have a lot to look forward to coming up in heart failure and other domains. We have several randomized clinical trials examining the use of these therapies amongst patients with acute heart failure, many hospitalized for heart failure. In addition, there are dedicated randomized clinical trials evaluating both empagliflozin and dapagliflozin, as well as canagliflozin in patients with heart failure with preserved ejection fraction, a tremendous high risk entity encompassing about 50% of the total heart failure population without available therapeutics at present. So I think we'll learn a lot more about the overall scope of how these therapies can be deployed and also how to best get them to our highest risk patients.

Janani Rangaswami:

21:15

Thank you. That was such a nice and detailed explanation. Dr. Tuttle I want to quickly switch over briefly to cover the role of the GLP-1 RAs in our patients with CKD. One of the group of patients that nephrologists and even endocrinologists routinely struggle with is the patient with moderate to advanced CKD and the introduction and maintenance of these novel antihyperglycemic agents in that group of patients. Now we do know from both CREDENCE and from DAPA-CKD that the SGLT2 inhibitors, once initiated, can be continued all the way to the initiation of renal replacement therapy. However, the GLPs also have a really good track record in that very vulnerable and brittle advanced CKD population and with a favorable risk profile. So what is your approach to managing this patient with, say, a GFR in the low twenties? I've heard you speak about using the stratified approach to begin with an SGLT2 and convert at some point to a GLP, is that still true after the data that we've seen with CREDENCE and DAPA-CKD, any guidance as an endocrinologist on this question?

Katherine Tuttle:

22:28

Yes. I view the GLP-1 receptor agonist as really complimentary to SGLT2 inhibitors. And what's exciting is we're getting to where we have a portfolio of therapies so we can tailor the right treatment to the right patient at the right time, our aspiration for precision medicine. So the GLP-1's can be used in

patients with lower GFR for glucose lowering, whereas the SGLT2 inhibitors are certainly organ protective, again, heart and kidney at lower GFRs, but they aren't very effective for glucose lowering. And so when a patient with advanced CKD needs glucose lowering, they're an excellent choice. They're not associated with hypoglycemia. And in fact, in AWARD-7 that we conducted, there was a 50% reduction compared to insulin glargine as basal therapy for major hypoglycemic events, which is really the limiting factor in getting good glycemic control in advanced CKD. Also from the standpoint of patient convenience, they're given as one shot a week without dose adjustment. And these are people who have very complex medical regimens and anything that can make it simpler for the patient is a good idea, so there's very good patient acceptance of these therapies.

Katherine Tuttle: 23:39

With regard to heart and kidney protection, we did show in AWARD-7 that the GLP-1 receptor agonist in patients with type 2 diabetes and CKD prevented GFR decline over one year, whereas the insulin treated patients had a predicted decline of three to four ml per minute per year, which is about what we would expect in that advanced stage of CKD. So there've been some subsequent analysis out of LEADER and now SUSTAIN-6 showing similarly that even in those CV outcome trials where there were just a few patients with advanced CKD, the evidence is pointing toward preservation of GFR, especially at more advanced CKD stages. So we don't have as much evidence as for SGLT2 inhibitors, but the data from AWARD-7, LEADER and SUSTAIN-6 has actually led to a new phase three clinical trial called FLOW, which is actually testing semaglutide in a classic DKD population, very similar to CREDENCE, for kidney disease outcomes. But importantly, it's sort of the reciprocal of the heart failure trials, the major cardiovascular events, MACE and heart failure events are important secondary end points.

Katherine Tuttle: 24:50

But what we do see in the GLP-1 class is more of an effect on atherosclerotic disease and really a neutral effect on heart failure. But it's important to keep studying that as much as anything for safety as secondary end points, but we would expect that more likely than not, if there's a cardiovascular benefit, it will be on the atherosclerotic end points as it has been for other populations. So that also is helpful in terms of tailoring therapy, depending on the patient phenotype. So we will find out if they're actually renal protective from FLOW, or we'll learn more about that. But in the meantime, they're very effective agents. And you asked two important questions with regard to, do we switch patients now? I think based on what we've learned from DAPA-CKD and CREDENCE, is not unless they have a side effect. But remember, patients with advanced CKD are also more likely to have side effects via ketoacidosis or genital mycotic infections and so forth. So the other thing is the safety profile of these agents looks really good in advanced CKD. I think the main time I would switch a patient from an SGLT2 to a GLP-1 at a GFR below 30 would be if there's a side effect or for some other reason, the patient can't take an SGLT2 inhibitor.

Katherine Tuttle: 26:05

And then the other question you raised earlier was, what about the non-albuminuric patient with low GFR? What we know about those individuals is even though they have very low GFR, they're still at lower risk of even CKD progression in the same patient at the same GFR with albuminuria. But that said, in the EMPA-KIDNEY trial, back to SGLT2s, we are including patients without albuminuria, so we will find out there. And in AWARD-7, now back to the GLP-1 receptor antagonists, we did include non-albuminuric patients. They were only about a third of the population and we didn't detect an effect on GFR, but they hardly had any GFR decline. If you look at the macroalbuminuric group, it was actually six mil per minute per year. And the normal microalbuminuric group, about three, and in the normal albuminuric group, about two. So that's why we got the overall decline of three to four. But it's in the macroalbuminuric group where we can show the biggest benefit on GFR because they're declining. You can't, in a short trial with a limited number of people, detect an effect if the parameter's not changing very much.

Katherine Tuttle: 27:20

So I wouldn't say it's evidence of absence, rather it's absence of evidence, but that's where the large trials like FLOW, that'll have somewhere around 3,500 participants followed, the anticipated trial time is five years, will have a lot more data on the effect on GFR decline, as well as cardiovascular and kidney disease end points.

Janani Rangaswami: 27:41

Thanks so much. Finally, in our statement we also made an important point of the cardiorenal metabolic multi-disciplinary care model. It's very obvious that the data are clear in terms of these agents being cardio and kidney protective, however, there are huge gaps in implementation, especially in patients that need them the most, the highest risk population of patients. Several barriers exist across so many different interfaces. Many of them are system-based, just the healthcare structure in general, fragmentation of care between specialists, knowledge gaps, therapeutic inertia, the reluctance of specialists to try to kind of cross specialty boundaries and embrace new knowledge to incorporate into the cardio-metabolic risk reduction of their patients. So I really hope that our statement plays some role in catalyzing the concept of these cardiorenal metabolic care models. And to that end, I really think our statement work itself was a great example of multidisciplinary work and collaboration. We just had some of the best people. And thank you so much as well as to Dr. Vaduganathan for your contributions, not just to the discussion today, but the fact that you've enriched the statement so much.

Janani Rangaswami: 28:58

So, with that, we conclude this discussion on the cardiorenal benefit scientific statement in patients with type two diabetes and CKD. Thanks to the audience

for your time and for listening, and stay tuned for upcoming podcasts from the series, Know Diabetes by Heart™. Thank you.