New Science from AHA Scientific Sessions 2022 - CVD Risk Management in Patients with T2D

Jane Reusch: Thank you for joining this podcast on the latest science highlighting strategies for cardiovascular disease risk management in patients with type 2 diabetes, released at the American Heart Association's Scientific Sessions this year. This podcast is a continuation of our series to reduce cardiovascular deaths, heart attacks, strokes and heart failure in people living with type 2 diabetes and is based on a collaborative initiative between the American Heart Association and the American Diabetes Association, known as Know Diabetes by Heart. This series is brought to you by founding sponsor, Novo Nordisk, and national sponsor, Bayer.

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I am Jane Reusch, Professor of Medicine, Bioengineering and Integrative Physiology, and the Associate Director of the Ludeman Family Center for Women's Health Research at the Anschutz Medical Campus at the University of Colorado. And joining the podcast are doctors Nathan Wong, Professor of Medicine and Director Heart Disease Prevention Program at the University of California at Irvine, and Dr. Chiadi Ndumele, Director of Obesity and Cardiometabolic Research for the Johns Hopkins Cardiology.

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Nathan Wong: Thank you very much Dr. Reusch.

[00:01:30] One of the important themes of this meeting was the problem certainly with multiple risk factor control and actually disparities in achieving this in terms of trying to optimize cardiovascular risk in people with diabetes. And one of the sessions that I think is important to actually highlight is one that we did that specifically focused on this and the implications of the Know Diabetes by Heart initiative. We talked about how there are limitations in current cardiovascular risk assessment strategies, such as from the various risk scores, they many times

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[00:03:04] don't include certain diabetes specific factors that might affect outcomes. Only about one in five people with diabetes are at acceptable targets for three key parameters that the Know Diabetes by Heart initiative focuses on, namely LDL cholesterol, blood pressure, and A1C. But obviously, there's many other factors. And if you actually look at those, for example, if you add in non-smoking status, having a non-obese body mass index, you're at even a lower percentage at these targets. And we talked about how actually there's a fair amount of evidence that suggests that if you are at target for these factors in particular, you can actually reduce cardiovascular event risk by more than 50%.

[00:03:30] Peter Gaede talked about the Steno-2 study that showed that intensive multiple risk factor intervention reduced cardiovascular events over eight years by 53%. And then if you extended this actually after the trial phase to 13 years, you had about 20% reductions in mortality. And he also emphasized that he was able to show that you actually can extend life, cardiovascular free life by eight years if you're at these multiple risk factor goals. So, I think this is a very, very important message.

[00:04:35] Joshua Joseph then discussed the key pillars for risk reduction in people with diabetes. He specifically focused on lifestyle management, anti-thrombotic, glycemic lipid management, and health equity. And importantly, what was discussed was the importance of health equity issues and social determinants of health to making sure that we're accomplishing these risk reductions in an equitable fashion. 40% of our people with diabetes are not on any of these evidence-based therapies. And only 10% are actually on three key evidence-based therapies, namely statins, either an ACE inhibitor or ARB, as well as either an SGLT2 inhibitor or a GLP-1. Yeah, actually a receptor agonist.

[00:05:32] Sadiya Khan pointed out that it's extremely important that we maximize opportunities to prevent diabetes. And she, in particular, reminded us of the implications of the diabetes prevention program. And another very important point was how some of our underserved ethnic communities, in particular, Hispanic individuals and non-Hispanic Black adults, are diagnosed with diabetes five to seven years earlier than actually other groups. One very important point that I wanted to mention that she also reminded us of was that there's a fair amount of evidence that shows that in order to be successful, and this is going to be a theme throughout, is that we have to have a team-based approach. And we

[00:06:20] need at least 10 contacts of six months duration or more in order to be successful. So, it's no longer sufficient just to see the patient once or twice and

talk to them about their risk, but we have to keep on this through actually multiple visits.

[00:07:00] Certainly, there were also some important late breaks in clinical trials. And I guess I can say a little bit about the PROMINENT trial, one of those that I found most interesting?

Jane Reusch: Yeah. So why don't you, in a couple minutes, tell us about the PROMINENT trial. And then we're going to move to how this call to action, from the sessions that you have just gone over, really is going to need to be implemented. And some barriers. And we're going to hear a little bit more about that from Dr. Ndumele.

Nathan Wong:

[00:08:02] The PROMINENT study that involved chemo fibrate, that's a PPAR-alpha modulator. And the actual goal of this trial was to examine people with type 2 diabetes who had mild to moderate hypertriglyceridemia, and in particular, also had a low HDL cholesterol. Because from the past trials, this subgroup seemed to benefit. So, this involved over 10,000 patients and they looked at the composite of non-fatal MI ischemic stroke, coronary revascularization, or actually cardiovascular death. They found there was absolutely no difference in the primary composite endpoint, nor in any of the components of the primary composite endpoint. So, a hazard ratio of 1.03. Far from being statistically significant.

[00:09:16] And part of why this trial might have been negative, was that there was actually an increase in LDL cholesterol in the actual pemafibrate groups. So, some of us feel that that may have counteracted any possible benefit from lowering triglycerides. So, this trial, I think, was very important because it really, many of us feel, was kind of the nail in the coffin. At least for trying to show whether the management of hypertriglyceridemia from fibrate therapy specifically would actually reduce cardiovascular events. Certainly, in people with very high triglycerides. Remember, fibrates still have an important role for preventing acute pancreatitis, but at least most of us feel that there is no longer a role for fibrate therapy for prevention of cardiovascular events in people with moderately high triglyceride levels.

Jane Reusch: Well, thank you, Nathan. And Chiadi, I know that you were, I think, chairman of a session that was a flipped classroom talking about the barriers in actually getting optimized cardiovascular risk reduction. And we would love it if you'd tell us a little bit more about that session.

Chiadi Ndumele: Thank you, Jane. And thank you, Nathan.

[00:10:30] Nathan really helpfully described the fact that there's a lot of great science out there. There's a lot of wonderful studies out there. There's also even a lot of great guidance from AHA and ADA and KDIGO and ESC. But the real question is, how are we going to get this actually implemented in kind of real world clinical and real-world community settings? And the flipped classroom, which was actually led by Ian Neeland, one of my colleagues in the Scientific Sessions Programming Committee, that session really kind of turned the tables. Instead of us kind of lecturing two folks, they kind of put all the guidance out there and

[00:11:09] then had more of a discussion with the experts on how are we actually going to make this work in real world settings. It was a nice case-based session where there was a discussion of the kind of patients, we commonly see with multiple uncontrolled multi-system challenges.

[00:11:30] But one of the big first steps was this question of therapeutic inertia and moving past. People have been historically on lots of therapies that don't have some of the cardiovascular outcome's benefits. So how we kind of transition individuals towards moving them towards some of these therapies, like the GLP-1 receptor agonists and SGLT2 inhibitors and think about the different things that we're trying to accomplish. There's also some very important gaps to consider. So, for example, in that at-risk patient, where are we actually prioritizing the SGLT2? Where are we actually prioritizing the GLP-1? Where are we saying we need to be on both? Where are we taking some additional steps for renal protection? There's clearly a need to start focusing on some of these newer therapies, and that was one very important part of the discussion.

[00:12:37] Clearly, we are at a stage where thinking about this in a siloed fashion, as Nathan alluded to, is not making sense anymore. We really need to think about this in terms of shared ownership and integrated care models. And the panelists for this session really went across all the disciplines. We had folks who were cardiologists, but then also nephrologists and endocrinologists. And clearly, there needs to be also really nice engagement of internists. But on top of that, we need to also be thinking about who are the other individuals who need to be included in this care team to actually make these guidelines and these

approaches a reality. What kind of navigators, what kind of lay persons in the community do we need to support care for individuals? We should all be owning this patient and we should all have these shared goals and be working together to accomplish those.

[00:13:37] I think the biggest barrier that came up time and time again is getting these therapies to patients. We know there's a lot of coverage challenges with getting some of these newer therapies to patients and the question of how to do that, but there were very interesting lessons. So, there's a Cardiometabolic Care Alliance. And Mikhail Kosiborod actually did some really helpful discussions bringing on some of his care models towards helping individuals navigate coverage and navigate getting some of these therapies and the way they work with various organizations to make sure individuals get connected to the therapies they need and to address coverage gaps. I think what I'd love to see more of as we move forward is not only more specific guidance's on those individuals who are at risk and thinking about prevention in this kind of people with kidney disease and people with metabolic disease, but then also how we actually make this equitable in the community setting. How we deal with these people who have lots of barriers, and how we deal with these coverage challenges.

Jane Reusch: I think that one of the things that we can put together from these two sort of approaches is what we need to get done and what we can get done. And to really identify those gaps of research. And also, of the medical care infrastructure that could allow us to get from what should be happening to what can be happening.

[00:15:11] But I would say one of the most compelling graphs about residual risk that I have seen is in the failure to get blood pressure, glucose and cholesterol addressed at all in people living with diabetes. So, from the Steno-2 study, what was really exciting and then also unnerving in looking at your data, Nathan, was that we are not getting this job done. But just in a panel of 160 patients, he was able to show that even addressing blood pressure, cholesterol, and glucose, not perfectly, not even getting to his goals, he was already achieving that 60 to 70% improvement over time.

So that we have to be messaging when we give a lecture about residual risk and the need to use these newer transformative therapies, we need not to leave anything on the field when it comes to more bread and butter, easily accessible in populations at very high risk without good medical medication security, access

to care, other barriers to care. We need to really just emphasize the ABCs. The guidance that is now aligned from the AHA, ADA, ACC, ESC, you meet a person with existing coronary disease or heart failure, they need to go exactly on these transformative medicines right away.

Nathan Wong: Oh yeah. Well, I was just going to comment that there's many, many other factors. Like lifestyle factors particularly, trying to achieve weight control, physical activity. And a whole list of social determinants of health that are responsible for much of this risk factor reduction.

Jane Reusch: Yeah.

Chiadi Ndumele: And I think it's important to just highlight that this therapeutic approach was not just medications. As you're saying, there was intensive lifestyle modification at the core to address all of the other aspects of residual risk. And then targeted pharmacotherapies to help further achieve those goals. The people we're going to miss are those individuals who are most marginalized, who have the most barriers. And we really need to think about in clinical environments, but also in the community setting, how do we best support that holistic care for these individuals at risk? That's really going to be the way we move the needle on addressing risk in this population.

Jane Reusch: Yeah, absolutely. And so, let's move to heart failure because there was a lot of work on heart failure, and particularly cardiometabolic risk for accelerating heart failure.

Chiadi Ndumele: [00:18:00] We had some really interesting discussions on heart failure, and particularly in relation to diabetes. So, we're all probably most of us are familiar with the SOLOIST-WHF trial, which is the combined SGLT1 and SGLT2 inhibition with the dramatic impact on cardiovascular events, particularly heart failure and hospitalization and mortality. So, this was an interesting post hoc analysis of SOLOIST-WHF that focused on those individuals who got therapy just before or at the time of discharge and demonstrated a really dramatic impact on short-term events. So, 30-day re-hospitalizations and 90 days both re-hospitalizations and mortality and cardiovascular events in those persons really indicating, as [00:18:44] you're just describing, this question of a delay, that there's probably going to end up being some benefit to kind of early institution of these therapies where we know we're going to have the greatest benefit.

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In terms of another trial, DECLARE-TIMI 58, there was a very interesting study looking at biomarkers and demonstrating the variability of NT-proBNP in particular. There was also some for troponin, but there was remarkable variability of NT-proBNP over six months in relation to receiving SGLT2 inhibition. And that basically those individuals who had the greatest increase in the NT-proBNP over time and/or the greater increase in troponin over time, and certainly both had dramatically increased risk for developing heart failure. So, it actually speaks to the idea that these biomarkers could actually help us in some kind of precision ways in thinking about how we understand people's responses and thinking about monitoring for longer term heart failure risk.

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And then on another side of biomarkers, we had some interesting proteomic data from the ARIC study demonstrating some very interesting relations of proteomics in diabetes to heart failure and finding a series of proteins that seemed to be specifically associated with the development of heart failure among individuals with diabetes. So that is very interesting because that could be setting the stage for some future either prediction approaches, or even future therapeutic approaches that may be specific to kind of diabetic cardiomyopathy or the development of heart failure and diabetes.

Jane Reusch:

Yes. And along that line there was a - even though it had been presented, the top line results had been presented elsewhere, there were some of the breakdown products of EMPA-KIDNEY presented. And I wondered if you could tell us a little bit about that?

Chiadi Ndumele:

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Yeah, we had some really interesting late breaking science. So, the EMPA-KIDNEY trial was a really helpful addition. We know now that the SGLT2 inhibitors are helpful among individuals at risk for developing heart failure. We know that we see some real benefits among individuals with existing heart failure. But now the EMPA-KIDNEY actually expanded this now to thinking about patients who just are selected based on CKD. A portion of them having diabetes, a portion of them having CVD, but not all of them. And really it was based on CKD and seeing do we see a reduction in the composite of progression of kidney disease and cardiovascular events. Importantly, most of the outcome benefit over two years was driven by the reduction in chronic kidney disease prevention. But the composite overall outcome was strikingly positive and speaks to the fact that now we should be thinking of these agents and people not just based on diabetes, but also in individuals with CKD.

Jane Reusch: [00:22:03] Yeah. And I think in terms of really sort of thinking through what we're learning and thematically and why Know Diabetes by Heart is such an important initiative is we're seeing that an agent that was originally designed for glucose lowering is having renal effects, is having cardiac effects, and is really bringing together the integrative physiology of diabetes metabolic syndrome and this sort of composite cardiorenal, cardiometabolic renal.

[00:22:30] I did want to then move to one of the root causes of excess cardiorenal disease in the population, which is obesity. That it is really important if we want to have true remission of diabetes or prevention of cardiovascular events. We learned from metabolic surgery studies that it was - you really needed to get to about a 10 to 15% weight loss and you needed that to be a durable weight loss in order to really prevent cardiovascular renal disease progression, fatty liver disease progression. And we didn't really have pharmacological strategies to achieve those goals.

Chiadi Ndumele: [00:23:42] I think that this is a whole new landscape for obesity pharmacotherapy. And with the higher dose GLP-1 receptor agonists, as we saw in the really powerful STEP 1 trial, we are seeing that we are able to hit that threshold that you're describing, where we might expect to see cardiovascular benefit with these agents and being fairly well tolerated in that setting. So, a dramatic impact of the high dose semaglutide. And then now we have the tirzepatide, GLP-1 GIP receptor agonists showing even greater weight loss and seeming to be durable as well. All of these are associated with improvements in multiple metabolic risk factors in this degree that we would expect to see. But now we're going to be looking to understand what that means from a cardiovascular event's standpoint. Next year we're going to have, I think, a very exciting next step, which is the SELECT trial, which will be focused on the use of high dose semaglutide GLP-1 receptor agonist in individuals with just cardiovascular disease and obesity, without diabetes.

Jane Reusch: [00:24:33] So, let's talk about one of the really big goals of Know Diabetes by Heart, which is to get all of this incredible new data and emerging data to the patients at risk. Let's say we've gotten all of the cardiovascular disease sort of standard ABCs; we have them to goal. People know what to eat, they're eating what they're supposed to eat, they're sleeping when they're supposed to sleep, they're not sitting in a chair, and they are doing physical activity. So, these are fantastic things that we've gotten done, we've gotten accomplished, we've interfered with

the community, we have changed the status quo. What are the barriers to the use of these new agents, both on the practice side as well as on the patient side?

Chiadi Ndumele: [00:25:30] Currently, obesity, which is the underpinning of most of what we're talking about, is dramatically under addressed in clinical encounters. And part of that is because of several things. One is just physician comfort and know how. And this is not something that we've traditionally emphasized within our kind of medical education or continuing medical education approaches. So, I think that's something that we can continue to do. And I think the guidance of the updated guidelines helps from that standpoint as well. I also think that we have a lot of stigma around these challenges, and particularly in clinical environments as well. And I think doing a better job of understanding that these are challenges that are complex and there's often a lot of social determinants and physiologic determinants that go into the development of obesity and the maintenance of that over time that go beyond just individual responsibility and choice.

[00:26:36] And I think that there are real challenges in terms of coverage. And barriers, particularly for those individuals who are in more marginalized communities and have more challenges with access. So, there's a lot of questions I see around the questions of social determinants and coverage. I think we need to be incorporating that into more of our models and thinking about that as we're engaging with these individuals. But then also saying, "How can we actually circumvent or overcome these coverage gaps for these agents?" I think that's going to be a key imperative because once we start - particularly if we see improvements in cardiovascular event rates, this is going to be a huge imperative to make sure we're getting this to the people who need it most.

Jane Reusch: [00:27:42] Yeah. So Chiadi, let's follow up on that. You have quite a bit of expertise in social determinants of health. And is there something that you might recommend, a tool that you might recommend to help people identify patients at the highest risk? Because physicians just like they're uncomfortable talking with a patient about obesity or even understanding the language about - is it okay if we talk about obesity? Let's talk about strategies. What are you worried about? We are also very poor as practitioners in asking the questions about social determinants of health. And that is embedded stigma, that that's really important. So, can you recommend a tool that we might make available on the Know Diabetes by Heart website that we could use? A simple screening tool in clinic?

Chiadi Ndumele: We don't have actually great tools that are specifically focused on those individuals with diabetes. But I do think that there are a couple of holistic tools,

[00:28:00] some from CDC, some from NIH, that are kind of focused more on just holistic assessments of everything, from kind of food insecurity to barriers in the kind of neighborhood setting, that kind of get at the broader assessment of social determinants of health. So, we're thinking more and more about taking into account social vulnerability indexes and area deprivation indexes and some of the kind of epidemiologic tools that we're starting to use in populations to better refine our calibration and prediction of risk as well. But I do think that as a general rule, we need to be thinking a little bit more about what are the factors that are preventing individuals from meaningfully engaging with the health system. And then also being able to have a healthy lifestyle and access some of these newer therapies that we're talking about.

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Jane Reusch: And I think that this is an area where the guidelines sometimes get in the way of patient care. So, the ADA, the ACC, the AHA, ESC all have guidelines. And there are very subtle differences in some of these statements, but the bottom line is we need to be addressing blood pressure. So, the language after the SPRINT trial, many of the guidelines evolved to say 130 over 80 would be your target, particularly in people with diabetes and hypertension. Actually all hypertension. And so that 130 over 80 guideline has increased the global prevalence of hypertension, which is the leading promoter of all cardiovascular death globally. I think it was 1.3 billion people having a hypertension diagnosis.

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Now, if you get into the details of this guidance when you're monitoring people and you're seeing their blood pressure go up, first, you need to measure the blood pressure correctly. Second, you need to be working with the person, as you've heard throughout this conversation on lifestyle changes, on decreasing salt in the diet, on increasing physical activity, decreasing sedentary time. And then you need to start medications. You need to not delay. Just like we as diabetologists are saying, "I don't want to delay lowering your A1C." I don't want to delay lowering your blood pressure. But it doesn't mean I don't want to delay giving you a medication for your blood pressure. What I need to do is treat your blood pressure and follow it up. And if you have particularly cardiovascular risk and persistent blood pressure higher than 130 over 80 or even above 140 over 90, then you're going to go early to a medication because if somebody then miraculously loses weight or intentionally loses weight, we are then going to be able to stop some of those medications.

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[00:31:24] But we don't want to delay initiating medications. So, it's not that anybody should be okay with 140 over 90, it's that these conversations need to be happening. Even as you see blood pressure creeping up from one 120 to one

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130, you're having these conversations about behavioral interventions. If they have other conditions that require medications, you may choose a medication that also lowers blood pressure. And then in the right person who needs blood pressure lowering, you need to treat them. And if their blood pressure is even higher, 160 over 90 or something like that, you might use a combination blood pressure lowering agent. So, the point is, get that blood pressure addressed. Not, "What is the subtlety?" If somebody's hovering between 130 over 80 and 140 over 90, you need to be addressing their blood pressure. And not waiting until the next visit.

Nathan Wong:

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Yeah. And we have to emphasize to our patients that hypertension is the leading cause of death in the world. And it also reminds me to point out that what we don't oftentimes appreciate is that many of these individuals, even if they're in the 130 range, may have masked hypertension, which is more common in people with diabetes and metabolic syndrome. So, their blood pressure is elevated at night and during the day, maybe more so than in the clinics.

Chiadi Ndumele:

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In terms of a screening tool, one tool from a social determinant's standpoint is the Accountable Health Communities Social Needs Screening Tool. That could be a nice starter for getting a holistic assessment of social determinants of health. And I think it's something helpful - a validated tool to apply in clinical practice.

And I just wanted to - I forgot to touch on one late break in clinical trial that was important, which is the RESPECT-EPA trial, where the fibrates may not be quite as effective. So, it seems to support -that was a helpful trial that seems to support the EPA aspect of cardiovascular risk reduction.

Jane Reusch:

So excess obesity in these high-risk populations with food insecurity. So maybe a comment here on those questions.

Chiadi Ndumele:

So, we need to understand that the greatest cardiometabolic risk we often see in marginalized communities. We need to be doing broader screens of social determinants of health. And we probably also need to investigate beyond an integrated care team and individuals outside of that team that can further address barriers. So, kind of patient navigators and community health workers, other kind of persons in the care team that can more broadly address these challenges that people in our most marginalized communities face. So, I think we

need to at least be thinking about this as part of our care for optimal care for patients in our clinical and community populations.

Jane Reusch: So, thank you to our sponsors for allowing us to put together these programs. This was a broad ranging conversation of a meeting where the AHA is now having many, many more sessions related to cardiometabolic health.

[00:34:56] This concludes the podcast, and we want to hear from you. If you have a suggestion for future content, email knowdiabetesbyheart@diabetes.org. It is our mission to reach as many listeners as possible with this lifesaving information. If you enjoyed this podcast and are listening on iTunes or Google Play, don't forget to leave us a rating and subscribe. Thank you very much for listening today and stay tuned for upcoming podcasts.