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**Understanding ASCVD Progression in Patients with Type 2 Diabetes, and Strategies to Assess its Risk**

Rodica Busui: Hello, and thank you so much for joining us on this podcast on understanding the atherosclerotic cardiovascular disease, or ASCVD progression in people with type two diabetes, as well as strategies to assess its risk. We'll also discuss the

[00:00:25] COORDINATE study. This podcast is a continuation of our series to reduce cardiovascular deaths, heart attacks, heart failure, kidney disease, and strokes in people living with type two diabetes, and is based on the collaborative initiative between the American Heart Association (AHA) and the American Diabetes Association (ADA), Know Diabetes by Heart. This series is brought to you by founding sponsor Novo Nordisk and national sponsor Bayer. I'm Rodica Busui

[00:01:00] professor of diabetes and vice chair of clinical research in the Department of Internal Medicine, Director of the Clinical Research Mentoring in the Caswell Diabetes Institute at University of Michigan. Joining me are Dr. Neha Pagidipati, Associate Professor of Medicine and Cardiovascular Disease Specialist at Duke University, and member of the Duke Clinical Research Institute. And Dr. Jennifer Green, board certified endocrinologist, Professor of Medicine in the Division of

[00:01:30] Endocrinology Metabolism Nutrition at Duke University, and member of the Duke Clinical Research Institute. Let's get started.

We prepared objectives to address this topic, and the first one is to discuss strategies to assess the risk of atherosclerotic cardiovascular disease in people with type two diabetes. And I am quite pleased to invite Dr. Neha Pagidipati to

[00:02:00] share some of her expertise with us on this topic. Neha.

Neha Pagidipati: Sure. Thank you so much. And Rodica, thank you for having me. I'm so honored to be here doing this podcast with you all and talking about one of my favorite things, which is prevention of heart disease, and of heart disease progression, especially in patients with diabetes. In some ways, the first question that we

[00:02:23] should be asking is, do patients with type two diabetes need to be risk stratified? Or is diabetes in and of itself a CAD (coronary artery disease) equivalent? Right? And that was then thought for so long. We thought if you have diabetes, you have the same risk of having a heart attack as somebody who's had a heart attack in the past. And I think a lot of that came from a paper in the late 90s out of Finland, I believe, that showed in that particular population, that patients with

diabetes had a similar risk for future heart disease as patients who had already had an MI (myocardial infarction).

[00:02:56] But I think what we've realized, through many studies, many meta-analyses, that there is no one type of patient with diabetes. There is no one type of or one level of cardiovascular disease risk in a patient with diabetes. It's a very heterogeneous population, and therefore the way that we need to think about their risk also needs to be tailored to that individual's risk. I think lots of studies
[00:03:22] have shown that patients with differing levels of other traditional risk factors, like hypertension, dyslipidemia, and so forth, that matters, right? And so, it isn't only if they have diabetes, they have one level of risk. It matters looking at the entire person. And so, I think when we think about ways to risk stratify an individual with type two diabetes, yes, obviously your ears perk up when you hear that they have diabetes because you know that their risk is increased, but then you also need to look at their other traditional risk factors.

[00:03:52] And so, as I mentioned, we think about hypertension, dyslipidemia, weight, family history, and so forth. But then we also need to think about some of the other less traditional risk factors that we are increasingly becoming aware are important, both in patients with diabetes and without, including chronic kidney disease, which significantly increases the risk of heart disease. And of course, patients with diabetes have a risk of kidney disease, as well as other things. Like if it was a woman, did she have hypertension in pregnancy? Is it an individual of
[00:04:23] South Asian ethnicity? These are all risk enhancing factors to be considered in terms of risk stratification. But then there are also diabetes specific kind of risk factors like the length of time that the person has had diabetes, whether or not they have albuminuria or retinopathy. So, I guess my overarching framework is that it should be personalized to the patient with type two diabetes, and that we should consider traditional risk factors, some less traditional risk factors, and also diabetes specific risk factors.

[00:04:52]
Rodica Busui: Thank you so much, Neha. And I would like to invite Dr. Jennifer Green to provide her perspective. Jennifer, what do you think about what Neha has just shared with us? And how do you apply these thoughts in your clinical practice when you see people with type two diabetes?

Jennifer Green: Yeah, that's a really good question. And I do think it's true that we do tend to sit
[00:05:13] up and pay attention when we know that someone has diabetes because we know that fundamentally, they are at high risk for cardiovascular events, even if they've not had one in the past. But from my perspective, my ability to impact that risk, to mitigate that risk is so much greater now than it has been in the past. We know that the traditional modalities to address cardiovascular risk, for
[00:05:53] example, controlling blood pressure, lipids, blood sugar, have been very effective in decades past, in particular in reducing the risk of acute MI and stroke. But even with, I would say perfect or optimal management of those traditional risk factors, we really haven't been able to reduce the cardiovascular risk of people

with type two diabetes to that of people without diabetes. And that's ultimately the goal, right?

[00:06:22] So now we do need to be very cognizant of the fact that these foundational therapies, although remaining critically important in the foundation of risk reduction, are really just the starting point for people with type two diabetes. And we need to think beyond that to look at, for example, the American Diabetes Association or the American Heart Association's particular guidelines or algorithms for the care of the person with multiple risk factors for ASCVD, and
[00:07:00] make sure that we are doing everything we can therapeutically, and of course, lifestyle wise to make sure that we have reduced that cardiovascular risk to I guess as little as it can be, or as close to the person, the risk of the person without diabetes as is possible. And our ability to do that has expanded dramatically in the past 10 years, for example.

[00:07:21]
Rodica Busui: Well, thank you so much for both of your perspectives. And I would like to bring up a couple of additional thoughts, especially when we talk about re-stratification and a personalized approach. We also have witnessed more recently that several large cohorts of people with diabetes, and actually observational general population cohorts identified that women with diabetes seems to have an unbalanced high risk, higher risk impact for atherosclerotic
[00:07:55] cardiovascular disease, as well as other cardiovascular complications when compared with men. And this type of data has emerged including here in US from the MESA (Multi-Ethnic Study of Atherosclerosis) and enhanced cohorts, and definitely from the European large populations, like the Swedish and the Scottish Registry. So, what do you think that may drive actually this higher risk in
[00:08:16] women with diabetes in general? And how should we actually educate our clinicians regarding this differentiated risk? Is it something that we need to do more?

Neha Pagidipati: I can start. You're exactly right. The risk that is imparted by type two diabetes is greater for women than it is for men. In general, women and men with type two diabetes have a greater risk than their counterparts without diabetes, but that imbalance in the risk imparted by type two diabetes for women over men is
[00:08:52] something that's not entirely clear to me. There have been a lot of hypotheses, whether it's related to differences in hormones or what. But I have to say I don't think we have a clear answer to that. What is clear is that we need to be very aggressive about the preventive management of both women and men, but in this case, particularly women who have type two diabetes, and having them and their clinicians understand what their future risk is. In general, we tend to underestimate the risk of women and their risk for future heart disease.

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That's something that the AHA has been fighting against for a very long time with their Go Red for Women campaign, and that is particularly so in patients with type two diabetes as well. So, when I see a woman who has type two diabetes, I am very clear about discussing with her, what her risk for future heart disease is. Even if she doesn't have a lot of the other traditional risk factors, she now does

have a very strong risk factor for cardiovascular disease. And I treat her
[00:9:49] aggressively in terms of the preventive therapies according to guidelines. So, we get her blood pressure down less than 130 over 80. We get her LDL (low-density protein) down as low as possible on at least a moderate, if not usually a high intensity statin. We addressed her weight. And then we also address the other, like I said, non-traditional risk factors. I like to understand what her lipoprotein(a) is. And that's a whole other field that we can get into, but these are other kinds of risk factors that could be additive and important in understanding her future risk.

[00:10:21]
Rodica Busui: Yeah, great. Thank you so much. In fact, actually, the risk seems to be as high in women with type one diabetes, even if we are concentrating this podcast on type two, but that observation holds true for women with type one diabetes as well. So, Jennifer, what are your thoughts regarding potential reasons behind and what do you do in your practice to optimize, or actually minimize the risk of women with diabetes?

[00:10:50]
Jennifer Green: Right, to minimize the risk. Well, first of all, I'll answer the minimization question last, but this is a really interesting subject matter, and I agree that we don't know the rationale. Some of the interesting theories that I've seen proposed are that in a relative sense, for example, women need to gain more weight than men do to develop to meaningfully increase their risk of type two diabetes, so they may be
[00:11:19] in a relative sense, heavier when they develop diabetes, which is obviously a risk factor in and of itself. And there's also a theory that women therefore spend more time or more years in the state of pre-diabetes, which of course is an unfavorable metabolic state, than do men in their pathway or timeline to type two diabetes. So, they may have already had a greater number of years or a
[00:11:49] greater burden of exposure to a dysmetabolic state before they develop type two diabetes than do men.

And then of course, women have what seemed to be special risk factors for the development of cardiovascular disease. For example, gestational diabetes is known to be associated with, for example, the presence of coronary calcium in women, even if they don't have type two diabetes or pre-diabetes later in life.
[00:12:17] So, women have a particular set, I think, of risks that can occur early in life and maybe particularly detrimental. The other thing that I would point out is that when we looked at outcomes in the EXSCEL trial, which is the cardiovascular outcomes trial of extended release exenatide, we compared outcomes in women versus men. And it was a really interesting opportunity to do that because that trial enrolled people with established ASCVD, but also with multiple risk factors.
[00:12:50] And what we found when we compared the outcomes of women to men in that study was that in people who had multiple risk factors, women did better than men.

So, if we look specifically at people who hadn't had a diagnosis of a cardiovascular event or established ASCVD, women did better. However, once

[00:13:20] women had, in particular, a coronary event, once they had an MI, their risk of a future event was comparable to men. So whatever supposed advantage from a cardiovascular perspective has been reported with women who have type two diabetes compared to men, that seemed, at least in that cohort of individuals, to be eliminated once a woman had an event. So, to me, what that means is

[00:13:43] women's risk must be recognized, and we must be really focused on a preventative sense. Because if we can keep their cardiovascular risk to a minimum before they actually have an event, that's probably the sweet spot from a therapeutic perspective. But again, there are study after study showing that women's risk factors are not either treated or not treated as well as men. So, we must recognize, and our female patients must recognize that that risk is present, and that it must be addressed appropriately.

[00:14:21]

Rodica Busui: Yeah, absolutely. So, to summarize, definitely we have all agreed that having a personalized approach for our patients is key to try to identify, as early as possible, all the associated risk factors that may drive an additional risk increase

[00:14:45] in our patient populations, and definitely making sure that women are evaluated and are provided with as aggressive treatment, if not more aggressive for all the associated risk factors including diabetes. To kind of recap and close this initial objective, I was wondering whether in your practice you use any other

[00:15:18] modalities including relying on some specific biomarkers. I think you mentioned very briefly potential biomarkers that may guide your level of aggressiveness in implementing therapy. So, are there any specific biomarkers that you may use, especially when you want to convince patients or clinicians about the need of a more aggressive approach?

Neha Pagidipati: That's a great question. And I have to say that when I start with risk stratification,

[00:15:52] I abide by the 2018 ACC/AHA cholesterol guidelines, which recommend using the PCE, the pool cohort equations, risk scores in both patients with and without diabetes. There are many risk scores out there, some that were developed only in patients with type two diabetes, but it's never been clear to me that they necessarily provide better risk stratification than what we have with the PCE. But then beyond that, there are, as I was mentioning, several additional risk factors

[00:16:20] that you could consider that really are relevant in patients both with and without diabetes. I think that, like I said, the diabetes specific risk factors are really around albuminuria, retinopathy, neuropathy, the length of time that the patient's had diabetes. But other biomarkers, as you pointed out, could be relevant in both patients with and without diabetes.

So, for example, as I mentioned, lipoprotein(a) is very clearly a risk factor for cardiovascular disease in both patients with and without type two diabetes. That

[00:16:51] can be helpful in understanding how aggressive to be in risk management. I would also say that there are other biomarkers that have been studied extensively, especially in patients with diabetes, like proBNP (PRO-B-TYPE NATRIURETIC PEPtide), high sensitivity troponin, and so forth. And those have been shown to be clear risk markers in patients with type two diabetes, but what we don't know is whether or not modifying your preventive therapy based on

[00:17:19] these risk markers, especially on a population, whether or not that improves heart outcomes. So clearly we need clinical trials, but there is a lot of observational data to suggest that some of those biomarkers might be helpful. And then of course, I'd be remiss if I didn't mention coronary artery calcium scoring and in both patients with and without type two diabetes, this can be an incredibly useful tool to get additional data on that patient, that particular patient's ASCVD risk.

[00:17:49] It's not just based on a population level approach. That's very individualized for that population, understanding what their Agatston score is. And then a lot of data, as I think Jennifer and Rodica, you both mentioned, has been shown in patients with type two diabetes, this can be particularly useful in helping to understand that patient's risk for future cardiovascular disease. So, it's not a biomarker. It's an imaging marker, but I think increasingly, it's being utilized. What I will say is that still, insurance companies across the nation do not cover it. And so, it has to be an out-of-pocket expense, which is frankly ridiculous because [00:18:19] the patients who are at most risk are the patients who are probably least likely to be able to access that. And so, it's not something I kind of mandate for my patients, of course, because you can't do that. It is a cost, but it is something that I offer as a potential option if they are interested.

Rodica Busui: Jennifer, any additional thoughts?

Jennifer Green: [00:18:49] Yeah. In all honesty, my clinic population is really a population of individuals who are very clearly at very high risk, so I'm not often in a position where I need to add some of these emerging biomarkers to what I understand about that individual because I already have very clear indications to treat them intensively. But I do think that that is very helpful, perhaps most particularly in younger individuals with type two diabetes, for example, where their risk is commonly [00:19:22] underappreciated. And in fact, if those individuals are to develop kidney disease or cardiovascular disease, or both, very early in life or early in their lifespan with type two diabetes, it's very clear that, in particular, there'll be a significant reduction in their life expectancy. So those individuals, I think we need to be [00:19:50] very, very thoughtful in assessing their risk to not assume that they're going to do well or better than older people because they're young. In fact, their prognosis is worse.

So, in my mind, that's the kind of population, which, again, is probably seen most often in the primary care setting where the use of those particular biomarkers might be exceptionally helpful in determining whether or not you need to treat someone a bit more aggressively than might otherwise be apparent.

[00:20:20]
Neha Pagidipati: I just wanted to underscore really quickly something that Jennifer said, which I think is one of the most important points that I think we can make. And there was an excellent article. I had nothing to do with it, so I can promote it. It was an excellent article in JACC (Journal of the American College of Cardiology) that was published in October of this past year by Dr. Gyldenkerne and colleagues, and

they used a huge Danish cohort and they looked to understand what the 10-year atherosclerotic cardiovascular disease risk of patients with newly diagnosed
[00:20:46] diabetes was. And it was fascinating because of course, they found that if you have diabetes, you're at higher risk than somebody who doesn't. But in particular, where that risk was increased was in the young. So that increased risk for cardiovascular disease was much greater if you were young than if you were above the age of 80.

And what they found was that individuals who were diagnosed, at a younger age, with type two diabetes, developed cardiovascular disease between 10 and 12
[00:21:16] years younger than patients who did not have diabetes. So that idea of understanding the risk that inherently a young person has when they develop type two diabetes. Their trajectory when they've been diagnosed with type two diabetes has just dramatically changed. Their kind of trajectory and their risk pattern has dramatically changed, and we have to be very aggressive when we understand it's not just about lowering their A1C. It's about managing that whole person and their cardiovascular risk.

[00:21:45]
Rodica Busui: Yeah, that's an amazing comment that you have made, and it's so relevant, particularly when we know that even more so than in Europe, here in US, we are facing an unacceptably high number of youth with type two diabetes, kids and adolescents that are being diagnosed with type two diabetes. And we also have pretty strong evidence, at least from two large cohorts, both today in search demonstrating that these kids have a very different constellation of
[00:22:18] cardiovascular risk factors, and actually risk of developing all type of complications including cardiovascular disease. So therefore, a message of aggressiveness and clearly identifying as part of the re-stratification, the age of diagnosis of type two diabetes and not overlooking someone who is young, it's a very strong message. And in a way, that actually makes a very nice segue into our
[00:22:46] next objective because we all agree we need to be aggressive. We need to apply a personalized approach and understand the complexity of each given patient that we see in our clinic, and definitely not overlooking women or people who by standards that were applicable 15 or 10 years ago were considered too young for being at risk.

So that's an important message. However, we all know that despite our
[00:23:14] guidelines, and the American Heart Association and the American Diabetes Association have, particularly the American Diabetes Association that has the entire spectrum of management of people with diabetes, are updating their guidelines in line with the most recent levels of evidence and all these discoveries that have been made. And yet we all know that the guideline
[00:23:43] implementation at the point of care lags behind substantially. So, what can we do? And let's review perhaps some of the evidence that we have acquired more recently regarding ways of implementing the evidence and implementing the guidelines into clinical care at large. Jennifer, would you like to start?

Jennifer Green: [00:24:14] Yes, I'd be very happy to. Thank you so much for the opportunity to discuss the trial COORDINATE-Diabetes. I love talking about this trial, and I really try to work it into almost every presentation or scientific discussion that I have because it was such an important study. And of course, we were all involved in with... We all had key roles in that trial, but it's a very simple study. And the impetus behind the design and conduct of this study was the recognition that people with type [00:24:45] two diabetes and established atherosclerotic cardiovascular disease were not receiving standard of care risk reduction therapies. And that became even particularly noticeable when, for example, the outcomes benefits associated with use of SGLT2 (sodium-glucose cortransporter-2) inhibitors and GLP-1 (glucagon-like peptide) receptor agonist became evident. And so really, the gap [00:25:12] between optimal care and delivery care became even wider. So, COORDINATE-Diabetes was an implementation study which was specifically conducted at cardiology clinics throughout the United States. And those cardiology clinics were randomized.

The clinics themselves were randomized, either to their usual practice when they were provided with copies of contemporary care guidelines for patients with type two diabetes and atherosclerotic cardiovascular disease. And then of [00:25:47] course, the other group was randomized to our trial intervention, both of the sets of clinics then enrolled patients with type two diabetes, and again, established atherosclerotic cardiovascular disease at their location. The trial intervention, again, was designed specifically to determine the effects on the intervention of the rate or proportion of such individuals enrolled at the sites [00:26:16] that we're receiving at the end of study, which was either six, or usually 12 months, all three of high intensity statin therapy, an ACE (angiotensin-converting enzyme) or ARB (angiotensin receptor blockers), or an SGLT2 inhibitor, or GLP-1 receptor agonist as a component of their diabetes care. And we expected the cardiologist to be essentially in charge of making sure that all three of these therapies were prescribed to the patients enrolled, all of whom had indications for all of these therapies.

[00:26:48] It's important to understand that our intervention in the study was really very simple and something that could be reproduced anywhere. So essentially, what we did was at the intervention sites or intervention clinics, we worked with them to discuss and assess their local barriers to the delivery of optimal comprehensive guideline-based care. We second worked with them to develop strategies to overcome the barriers, although for the most part, they needed to [00:27:17] do this locally and independently because their barriers were their barriers. And we couldn't tell them how best to overcome, and they needed to sort that out themselves. And we also stressed coordination of care between the enrolled participants, many clinicians or providers. So, we knew that the cardiologist wasn't necessarily going to be able to do this on their own. They needed to collaborate that, you generally had a point person locally who either was an [00:27:45] endocrinologist, or someone experienced in diabetes care to help with that local decision making.

And then finally, and I don't know if this was most important, but critically important, we continually and regularly assessed the proportion of individuals enrolled at the individual clinics and assessed if they were on all three of those important guideline-based therapies. We provided this information to the clinics.

[00:28:15] We showed them how they were looking overall and how they were comparing to the other intervention sites so that they could really be on top of how well, or perhaps not well, they were delivering guideline-based therapy. And at the end of the day, just to sum it up, we did find that this fairly simple but important intervention very, very significantly increased the delivery of this multifactorial

[00:28:46] guideline-based therapy, again, consisting of high intensity statin ACE or ARB or guideline directed diabetes medications, very significantly compared to the set of sites that proceeded with their usual care delivery as they had been doing it.

So, we do hope that this in turn would translate into improved outcomes. The

[00:29:10] trial itself was not powered to detect whether or not there was a significant reduction in clinical cardiovascular events in the enrolled population. We did see a nominal reduction in the rate of important cardiovascular and other outcomes in the patients enrolled at the intervention site, but it was not a statistically significant difference. But we knew that going into the study, but still certainly promising, is what we would expect to see if we increase the delivery of this

[00:29:48] indicated care. So that's a long summary, but that's the snapshot of what we did.

Rodica Busui: So, Neha, do you have something more to add? We are almost approaching the end of our podcast, but from your perspective, if there is an additional point that you may want to highlight that Jennifer hasn't done that yet.

Neha Pagidipati: Thanks, Rodica. Jennifer gave an amazing summary. I guess the only thing that I'll

[00:30:18] just highlight, or underscore is that anybody can do this intervention. This was not something that was only something that could be done in the context of a clinical trial or only something that could be done at Duke, for example. It really was something that anybody who has a passion for improving care in their clinic can do this. And it's really simple. First of all, you can go to our website to get all the tools that we used. All of the information that we use is on coordinatediabetes.org, and you can go to that website and get everything that

[00:30:48] we did. But really, it came down to those simple principles that Jennifer said. What are the barriers to providing optimal care? Let's come up with solutions, local solutions to addressing those barriers, which may include having a pharmacist help us. It may include giving the clinician a little snapshot of the medications that the patient should be on that they're not on before they walk into the room.

And then let's give that data back to our clinicians and say, "Great, you're doing

[00:31:15] better," or "You're not doing so much better.” That works. And so, I just want to underscore that this is something that anybody can do, and if it doesn't get disseminated, then there was no point of the study. It really is something that the only good outcome is if people adopt it.

Rodica Busui: Yes, and I would also like to highlight that COORDINATE, it's another example of what's the future in diabetes management in general should be, which is a team

[00:31:45] approach. We are so much more powerful when we work together. And we demonstrated that, in fact, the spectrum of care, whether our cardiologist and endocrinologist, nurse practitioner, clinical pharmacists, educators, nurses, they can also effectively work together. And it is for the benefit of our patients because this is what drives all of us, and I'm sure all of you. There are ways to

[00:32:14] implement this evidence that we continuously generate, and the guidelines can be easily applied in practice, particularly when we rely on teams. We are all colleagues. And that is COORDINATE. It's yet another example that this team approach can be very successful in managing our patients based on the evidence, based on their risk, and also taking into account their personalized features.

[00:32:47] And with that, I would like to thank you so much to Neha and Jennifer for their expert opinions and sharing some of the wealth of their expertise. And thank you all for listening. This concludes the podcast, and we would like to hear from you. If you have any suggestions for future contact, please email

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