Robert Eckel:	00:04	Welcome and thank you for joining us for the third podcast from the new and information podcast series on cardiovascular disease and diabetes for health care professionals. The goal of this series is to reduce cardiovascular disease death and incidents of heart attacks and strokes in people with diabetes and is based on the new collaborative initiative between the American Heart Association and the American Diabetes Association, Know Diabetes by Heart™.
Robert Eckel:	00:33	This series is brought to you by founding sponsors Boehringer Ingelheim and Eli Lilly and Company, Diabetes Alliance, and Novo Nordisk, and national sponsor, Sanofi. I'm Dr. Robert Eckel and joining me is Dr. Ronald Goldberg, and we'll be discussing the new American Heart Association's 2018 Cholesterol Guidelines and the implications for Type 2 diabetes.
Robert Eckel:	01:01	Good morning, Ron.
Ronald Goldberg:	01:02	Morning, Bob. It's a pleasure to be here.
Robert Eckel:	01:05	Well, good. Let's go ahead and kind of update ourselves and the audience who's going to be viewing this podcast on diabetes and cardiovascular disease. So let's begin by kind of looking at the updated guidelines. In primary prevention treatment intervention trials in people with diabetes, as in those without diabetes, span the age range of 40 to 75 years of age and LDL cholesterol levels between 70 and 189 milligrams per deciliter. Ron, have the 2018 guideline recommendations for initiating statin therapy for primary prevention of atherosclerotic cardiovascular disease or ASCVD in diabetes changed from the 2013 guidelines?
Ronald Goldberg:	01:49	This is an important question, Bob, because of course, this is going to cover the majority of patients that we see with diabetes. And the quick answer is that there really hasn't been any change. The clinical trial data have incorporated this age range, and so we don't know as much about clinical trial data outside of the age range.
Ronald Goldberg:	02:12	The only change I would maybe note was that looking at the evidence since 2013, there've been a couple more clinical trials in which the participants that were included were diabetes and there were no individuals without diabetes. So, there are now four clinical trials that have reported results in a population only with diabetes. It wasn't mixed up with individuals without diabetes. And so, I think their data is of the highest quality. And

		there is also a meta-analysis of these four clinical trials. So, the recommendation remains pretty much what it was in 2013, namely that in this age range with this LDL range from 70 to 189, which was the clinical trial inclusion criteria, moderate intensity statins are indicated in all of those individuals.
Robert Eckel:	03:07	One thing that comes up in patients with diabetes is that sometimes if a patient's 41 years of age, and let's say she or he with type 2 diabetes has very limited risk, often we turn to the ACC, or American College of Cardiology/AHA or American Heart Association ASCVD risk calculator. Diabetes is included as a risk factor in this calculator. So, would there be times wherein we might use the calculator rather than simply go ahead and prescribe a statin to a patient with diabetes if in fact their overall risk might be lower?
Ronald Goldberg:	03:42	That's another important question I think because it's become clear over the last five to ten years that the cardiovascular risk range in people with diabetes is not monolithic as we use to say in the days of the old guidelines. When diabetes was considered to be a coronary heart disease equivalent.
Ronald Goldberg:	04:03	It's clear that there's a range in the example you gave, an individual at the lower age range with short duration diabetes and no other risk factors. If you do the risk calculation using the calculator, their risk is often less than 5% in that small group.
Ronald Goldberg:	04:19	On the other hand, the vast majority of individuals in this age range have either intermediate or high risk and that was the reason that the guidelines recommended to proceeding with statin therapy in this group without making the decision, simply based upon the calculator, but to go ahead and do it. I think another consideration was that the life time risk and the trajectory in the rise of risk in this age group even in your 41-year-old individual is a lot higher than it is in those without diabetes.
Ronald Goldberg:	04:51	So, I think for all those reasons the original recommendation that we talked about of statin therapy for all is reasonable. However, because of the recognition that there's a wider range of risk in this group and a good number of individuals. Perhaps, 50% with high risk defined as a 20% risk of hard cardiovascular in points in 10 years. It seems reasonable to use the calculator because it adds more nuance to your decision.

Ronald Goldberg:	05:20	One last point I might make is in the new guidelines in general, and this was really an expansion of the 2013 guidelines. The importance of the physician/patient discussion was really emphasized because there is a lot of concern that sometimes comes from patients and you have to respond to this in the interest of trying to get optimal adherence. So, I think that's where the risk calculator can help you in your statin discussions.
Robert Eckel:	05:49	Well, I failed to mention that Dr. Goldberg was a member of the 2018 ACC/AHA guidelines podcast. So, he's right up to date having been part of the recommendations have been put forth. So, I think that what Ron has said is that, that's an unusual patient with diabetes in this age range who does not require a statin prescription but let's turn to where the guidelines may have changed in the respect to using a high intensity statin, Ron. Rather than just the moderate intensity statin therapy.
Ronald Goldberg:	06:18	Again, with respect to this and I should mention that this is a decision for the physician that is based on this strong evidence then we have been talking about for moderate statin therapy that is to say there still is no clinical trial testing high intensity statin therapy as a primary prevention approach in this age range. But as in the 2013 guidelines and as again repeated in the new guidelines, whether it preps a little bit more nuance that I'll get to in a second. The preference is for high intensity statin therapy based upon the following considerations.
Ronald Goldberg:	06:59	Number one, in the clinical trials with moderate statin therapy in diabetes that we talked about earlier. The residual risk in those who are statin treated was averaged in the meta-analysis of these trails at about 10% over 10 years. And so that is still a considerable risk that remains after moderate statin therapy and that will be one rational for wanting to perhaps use more intensive statin therapy and that idea is fully supported by the meta-analysis of all the statin trials now. By the cholesterol treatments trial collaboration this is a meta-analysis that has been going on now for some time. And their conclusion is that the benefit for statin therapy is strongly related with how much LDL lowering you achieve in individuals with elevated risk.
Ronald Goldberg:	07:54	So, this would seem to pertain to our 40-75-year-old group. Particularly as they get older or if they have other risk factors beyond diabetes alone. And the last bit of evidence to support this preference for high intensity statin therapy comes from the Jupiter trial. Which was done in patients who did not have

diabetes but did have in the placebo group a 13% hard end point of the ten years risk for coronary heart disease.

Ronald Goldberg: 08:26 And, in addition, this group had highish CRP levels which many of patients with type two diabetes have indicating an enhanced level of subclinical information. So, the benefit there was for high intensity statin therapy in Jupiter trial was a 47% reduction in the end point. Now, it should be stated that those individuals were age 50 among the men and 60 among the women. And, so, the guidelines include the suggestion that in the older age group, within the 40-75, particularly those with one or more risk factors or enhancing factors of which we'll talk about in a moment. That high intensity statin therapy is recommended.

Robert Eckel: 09:06 Well Ron that takes us on to the next level of intervention that the clinician needs to be considered. That's the addition of other cholesterol lowering agents. And, let's specifically identify ezetimibe as part of the improvement trial results. And the PCSK9 inhibitors those new injectable agents that markedly reduce cholesterol. When should the prescriber be considering these added agents in addition, to moderate or high intensity statin to lower LDL cholesterol in our patients with diabetes and heart disease risk?

Ronald Goldberg: 09:38 Well I think in response to that important question, your comment on the improvement trial is new data that we didn't have in 2013 demonstrating that in very high-risk individuals with acute coronary syndrome among whom a sizeable proportion had diabetes addition of the ezetimibe 40 milligrams of simvastatin further reduced risk as compared to the placebo comparator. And so, this together with further meta-analysis in particular one reported in 2016 demonstrating that non-statin and statin agents that lower LDL produce benefit along the same line relating LDL reduction to cardiovascular benefit. So, that ezetimibe then lay on that line obviously, it's a less potent LDL lowering drug. But it'd lay on the same line as the statins did in that relationship.

Ronald Goldberg: 10:32 And, so, the recommendation now is that it is reasonable. Particularly, among people with diabetes who don't have cardiovascular disease but who have a very high risk and the cut point there was the risk calculator demonstrating more than 20% of a ten-year event rate. That it would be reasonable to add ezetimibe to the maximum tolerated statin. The point there being of course, that not everybody even on maximum tolerated statins gets the LDL down by 50%. And, then there is a

		proportion of individuals who can't tolerate a maximum intensity statin therapy and therefore it's even less likely that they'll get to a really significant LDL reduction.
Ronald Goldberg:	11:14	So, based on that then to summarize an ASCVD risk Atherosclerotic Cardiovascular Disease risk of more than 20% in 10 years is reasonable to add ezetimibe to maximum tolerated statin. To reduce the LDL by 50% or more.
Robert Eckel:	11:30	So Ron, may I interrupt just a moment to indicate that if you looked at a subsequent publication from the Improve It trial you found out that patients with diabetes preferentially benefited from the ezetimibe addition. And if in fact the trial had been done without patients with diabetes the Improve It trial would not have been successful, so we may be seeing an additional benefited patient with diabetes in response to ezetimibe in terms of the primary outcome.
Ronald Goldberg:	11:56	That's an excellent point and thanks for bringing it up. You're absolutely right. So, I think that just strengthens this recommendation. If I can turn to PCSK9 inhibitors the guidelines will list strongly in supporting them and mostly because the database in diabetes is still fairly limited. Subsequent to the guidelines being established and finalized. The results of the diabetes subgroup analysis in the Fourier clinical trial which is testing the addition of a PCSK9 antagonistic evolocumab otherwise known as Repatha to statin therapy in individuals with cardiovascular disease. Which included a sizable number of people with diabetes and the benefit there was exactly the same in dimension to what we're seeing in those without diabetes and cardiovascular disease.
Ronald Goldberg:	12:49	So, we know that evolocumab does add a benefit to statin therapy. The issue that the group talked quite a bit about was just how does that look in terms of cost versus benefit? Because the estimate that was developed in terms of the benefit achieved with PCSK9 antagonists was at a rather high end of the relationship between cost and benefit. Therefore, was considered to be at a fairly low rate of value. When you try to evaluate the benefit versus the cost. And so, at this point there is no actual recommendation for the use of PCSK9 antagonists in participants with diabetes.
Robert Eckel:	13:33	So, while we're on a related question to PCSK9 inhibitor therapy in patients with risk and diabetes, is an LDL cholesterol go on an appropriate way for clinicians to perform or prescribe the PCSK9

		inhibitors? In other words, as some people say that an LDL should be as low as possible. And others would say that there's a plateau some place where an LDL lower than a certain level may not be additionally beneficial.
Robert Eckel:	13:57	Do you want to comment on that? Does an LDL zero predict no risk or do you think there's ultimately a level of LDL cholesterol where in fact the clinician should stop prescribing higher doses to get a level of zero?
Ronald Goldberg:	14:09	That's a great question Bob. And the quick answer to it is that, at this point there hasn't been a firm recommendation with respect to a target that is lower than 70 for example. Which is the target that is talked about in the guidelines for individuals with cardiovascular disease for example. And of course, our sizable proportion of our patients with diabetes fit in that category where they actually have cardiovascular disease or whether they fit in to the very high-risk group. Based upon the risk calculator in primary prevention.
Ronald Goldberg:	14:41	But you're absolutely right. I mean, the meta-analysis that was just recently reported by the cholesterol treatment trialers collaboration actually looked to see whether the benefit in a meta-analysis of clinical trials the same group of trials that were tested in earlier reports. Whether the benefit of statin therapy in individuals with LDL levels below 75 fell along the same line of benefit that they had demonstrated when they looked at the entire population. Whose mean LDL was 100 to 120 in that range and the answer is that it did. It really seemed to produce benefit all the way down to as low as 20 milligrams per deciliter. And importantly, they were not able to see any additional worsening of the side effect profile.
Ronald Goldberg:	15:29	So I think that we're entering an era where your question is highly relevant and may be answered in part by cost again versus benefit because to get LDL levels down into those very low ranges it may take a lot of therapy. If it does involve PCSK9 antagonists, then that's going to be expensive therapy. So, I know I haven't given you a hard answer but, I think I've tried to summarize what the new information is to guide physicians in their decision making.
Robert Eckel:	15:57	Well, let's turn our attention now Ron, to the elderly population. Defined here as a threshold of 75 years or older. This often comes up clinically in our older patients with type two diabetes. What about statin therapy in a setting in which

		the evidence doesn't give a strong indication for or against statin therapy? What did the committee feel is the best advice in terms of this population?
Ronald Goldberg:	16:20	I would divide the answer to that question Bob, into two. The situation where statin therapy has already been initiated at a point before the patient reaches their 71st birthday. And the question now becomes, just because they turned 75 should we discontinue the therapy. And the second part of the question is, what about individuals who are more than 75 who are found to have diabetes or have had diabetes but are not on statin therapy. And so, there's a slightly question, if I take the first one; should statin therapy that had been initiated before 75 be continued beyond 75? The argument against discontinuing it, I think is fairly strong. For a number of reasons.
Ronald Goldberg:	17:04	Firstly, we know that in observational studies of large diabetes databases, I'm thinking of a study for example from the UK done some years ago. In which the risk for cardiovascular disease was looked at over age. It's very clear that highest risk group are the individuals over 75. So, that's what the risk is, but in the end, you really would like to have clinical trial data. And, we don't have much.
Ronald Goldberg:	17:32	There was recently a publication of a meta-analysis of two clinical trials, the Jupiter trial that we've referred to earlier and the Hope Three trial which was a trial of primary prevention using rosuvastatin 10. Both of those trials did include a sizable number of individuals over the age of 70. So, we're not getting to 75, but we're clearly incorporating a fairly large population in the 70 to 80-year age group.
Ronald Goldberg:	17:59	And when they looked at the comparison between the benefit of statin therapy with either of those two drugs in that greater than 70 group, it was essentially the same as those who are younger. Furthermore, there was no greater rate of discontinuation of statin therapy in that greater than 70 group suggesting that the side effect profile. Which of course, becomes an important issue in older individuals. Since there are reasons to think that those individuals are more likely to get side effects.
Ronald Goldberg:	18:29	Another issue to think about in terms of discontinuing is the issue of longevity. You need time to get the benefit of statin therapy. I think this actually applies more to those individuals who are not in statin therapy and you're think about starting it.

		And most recently, there was a report published in the British Medical Journal, from a large Spanish group of individuals. Which included individuals in this 75+ age group. Both with and without diabetes. Who did not have cardiovascular disease to begin with. And there, it seemed like the only group that seemed to get benefit of age 70 and above age 75 but not above age 80 were those with diabetes.
Ronald Goldberg:	19:12	So, I think on the issue of continuation, I think it does involve a discussion with the patient to inform them that the data is less strong in this group but that for the reasons I've indicted, we would favor continuing it in most patients.
Ronald Goldberg:	19:26	On the issue of initiation, here we have absolutely no data. I think a consideration to be brought in to the conversation with a patient is the fact that, some patients who present with diabetes age more than 75 have just developed it for example. Or it's just been discovered. And you really don't have a good understanding of what their particular risk is. Although, again age is such a powerful risk factor for cardiovascular disease and having had a metabolic disturbance. For example, in the pre-diabetic range for many years in that age group, may actually raise their risk. I think there is perhaps a list to support as initiating statin therapy and it should be left to the judgment of the patient and the physician and their discussion.
Robert Eckel:	20:12	Alright Ron, let's turn to an age group that's quite different than our folks who are 75 and above. And that's the patients who are age 20 to 39. I mean with the obesity epidemic with much more type two diabetes now it is in younger people than we've ever seen before. The issues come up in that population but also in the type ones. Who are in the 25, 30-year age range. So, comment a little bit about statin prescriptions and people under the age of 40 and when you might consider them.
Ronald Goldberg:	20:42	As you say an increasing population certainly among those with type two diabetes in that age frame. And the problem is we have no interventional trial data. We do have a little bit developing data on risk for cardiovascular disease and the group in Colorado has been the forefront in studying subclinical Atherosclerosis in type one diabetes. So, I think it's a very relevant question.
Ronald Goldberg:	21:07	What data exists does suggest that the risk factor for cardiovascular disease in individuals in this age group with type two diabetes may actually be stronger than in type one

diabetes. It is not uncommon in individuals with 5 to 10 years of type two diabetes to already show evidence of microangiopathy.

Ronald Goldberg: 21:28 I mentioned microangiopathy here because of the data now that's I think fairly clear that the risk for cardiovascular disease in individuals in general, with diabetes is increased by any of the categorical forms of microangiopathy, retinopathy, neuropathy, both autonomic and peripheral neuropathy. And nephropathy whether we're talking about albuminuria with normal GFR or whether we're talking about individuals with reduced GFR below 60 without albuminuria. All of these entities have been shown to be associated with increased risk for cardiovascular disease beyond the standard risk factors. That is to say they are not going to be accounted for in the Heart Association, ACC risk calculator.

Ronald Goldberg: 22:17 So they might be viewed as enhancing factors that you need to think about. Not only in individuals with diabetes in general but, specifically to your question in this young age group where particularly as with duration of diabetes these complications start becoming evident. In fact, and, there have been observational studies of the risks of cardiovascular disease in the group under the age of 40. Starting at around late 20s and into the 30s that does suggest that duration of diabetes should be considered to be an enhancing factor. And the numbers that were suggested in the guidelines was ten years of type two diabetes. And 20 years of type one diabetes, where the risk starts to increase even though it may not reach even intermediate levels of risk.

Ronald Goldberg: 23:04 With caveat that very rapidly after that the risk starts increasing quite substantially. So, I think that the idea then, that when you look at an individual with diabetes under the age of 40, you should be thinking about their life time risk and the trajectory of rise of risk in your statin decision.

Ronald Goldberg: 23:23 I would simply complete the list of enhancing factors by mentioning that an ankle-brachial index of less than .9 is an independent risk factor. There's a large report now in individuals without cardiovascular disease who have ABIs of less than .9 or greater than 1.4 to show that it's an independent predictor not surprisingly, of first cardiovascular event.

Ronald Goldberg: 23:46 And then, the last point and this touches on an issue may be that we're going to spend a minute more on, is related to the

		coronary calcium score where any coronary calcium score grader than zero in this young age group should be viewed as an enhancing factor.
Ronald Goldberg:	24:01	So to summarize I think what you want to do again in the absence of intervention data is have a thoughtful patient physician discussion. In which, all of these issues are discussed. In order to come to a decision as to whether to proceed with statin therapy in the younger patient.
Robert Eckel:	24:18	So Ron, thank you very much. I think that the point that you needed to make there or which you made very, very clearly is the lack of information in the younger patient that's based on clinical trial evidence. So, this remains somewhat problematic and I think that you did mention too that I think the coronary artery calcium score is a tie breaker and put forward much more zealously in the revised guidelines and was present in the 2013 version.
Robert Eckel:	24:41	So, let me turn now to the last question. There's been a lot of press about the REDUCE-IT trial. Does that apply to people with diabetes and should the prescriber at this point be concerned about patients who have modest triglyceride elevations in type two diabetes, in terms of the value of EPA only versus no therapy until the FDA's made a decision on the indication.
Ronald Goldberg:	25:04	I'm pleased you brought it up Bob, and as you know, the results of the REDUCE-IT trial were only published in the last few weeks after we had completed our guideline development. And so, it couldn't be address in the guidelines, but I do feel that this is a really important clinical trial particularly in individuals with diabetes bearing in mind, that the population that they studied either had cardiovascular disease or they had a 30% primary prevention subgroup which consisted of individuals with diabetes and at least one risk factor.
Ronald Goldberg:	25:37	Not to forget also among those with cardiovascular disease a sizable proportion about a third, had diabetes as well. And so, we are looking forward to the analysis of the diabetes subgroup with and without cardiovascular disease. Which I think would be valuable for us in terms of, putting the final results into perspective. Having said that, it didn't look like there was much of a difference in the benefit of the icosapent ethyl, which is a purified fish oil preparation. And known by the brand name Vascepa. Which consists of pure EPA because as is well known

		the unpurified form of Omega3 fatty acid derived from fish is a mix of EPA and DHA.
Ronald Goldberg:	26:25	And the authors of the publication emphasized this point saying, this is the first clinical trial with four grams of this purified preparation that has reported and that the beneficial results of about a 25% reduction in cardiovascular events in individuals on statin therapy. And that had been due to the fact that this was due to a purified form of fish oil and not the mixture. Although, the fact is there isn't a comparative trial yet with the unpurified from the stand point of separation of EPA and DHA form of fish oil. And that's ongoing there's a trial ongoing.
Ronald Goldberg:	27:02	So, we look forward to that too. But to get to the clinical indications of this, now we have data to show that on top of statin therapy people with diabetes who have mild to moderate hypertriglyceridemia, will show a significant benefit. That's surprising. I think many of us in the field did not think it would be as sizable as it turned out to be. And importantly it didn't seem to be related directly to the triglycerides level to begin with. That is to say whether you are high or lower in the range of elevation between 200 and 400 didn't seem to influence the results nor whether or not the triglycerides were normalized seemed to influence the results.
Ronald Goldberg:	27:46	And so, this goes to then the question of how does EPA work? How did this benefit cardiovascular disease and of course, there's is fairly big literature now on a number of effects of Omega3 fatty acids on the atherogenic process. Whether it be anti-inflammatory, antithrombotic, in that regard there was always a question when you use high dose fish oil preparations as to where there was any bleeding. That didn't seem to be a significant problem certainly no serious bleeding side effect increase in the group on the fish oil preparation. And so, I think this has to influence our practicing approaches and certainly in my clinic I have begun to use it more extensively than I, perhaps might have.
Ronald Goldberg:	28:31	But it's one study and I think we await with great interest whether the less purified EPA DHA preparation at four grams will show the same results in that.
Robert Eckel:	28:43	Well like you Ron, I was very impressed with the results of the REDUCE-IT trial and remain uncertain about why EPA alone at high dose works in these patients. But nevertheless, the trial

		was very impressive with the results that at this point are subject to interpretation in terms of mechanism.
Robert Eckel:	28:59	So, I'd like to close and thank Dr. Goldberg for being on this podcast with me. Also, for the founding sponsors for this new collaborative initiative between the American Heart Association and the American Diabetes Association, known as Know Diabetes by Heart™. So, I want to thank the audience very much for listening to this podcast and please stay tuned for upcoming podcasts to follow. Thank you.