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### Diabetes and Cardiovascular Risk: New Thinking, New Opportunities

#### Narrator:

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Your host is Dr. John Russell.

#### Dr. Russell:

Diabetes is a major global health emergency affecting approximately 415 million adults and contributing to 5 million deaths each year. Cardiovascular disease is a serious complication of type 2 diabetes, contributing to the majority of morbidity and mortality in this population. Recent findings from large-scale cardiovascular outcome trials with antihyperglycemic agents have shown that some type 2 diabetes treatments, beyond their glycemic control, can provide cardiometabolic benefits and may open the door for an even more successful outcome management.

This is CME on ReachMD, and I'm Dr. John Russell. Joining me today is Dr. Jack Leahy. Dr. Leahy is Professor of Medicine and Sarah Nichols Gruenig Green and Gold Professor of Diabetes Reach and Co-Chief for the Division of Endocrinology, Diabetes, and Metabolism at the University of Vermont College of Medicine in Burlington, Vermont.

Dr. Leahy, welcome to the program.

#### Dr. Leahy:

John, it's a pleasure.

#### Dr. Russell:

So there's been a lot of recent discussion about cardiovascular protection linked to certain diabetes medicines. Could you summarize the important background information on this issue?

#### Dr. Leahy:

John, this has been a huge topic, and in many ways, I think we should go back in history a little bit. From my perspective, the sort of modern era, if I think about it in terms of trying to intervene in terms of either microvascular or macrovascular complications in diabetes, goes back to the '90s. The famous trial for type 1 diabetes was the Diabetes Control and Complications Trial in the early '90s, and the trial in type 2 diabetes is the UKPDS, the United Kingdom Prospective Diabetes Study. Now all of those were designed on trying to improve blood glucose control the best they could at that time, and then look at outcomes, in terms of microvascular and macrovascular events in a reasonably healthy population. And in the type 2 diabetes studies, they found this dramatic improvement in microvascular complications—really, really impressive—and they did see an improvement in the rate of myocardial infarction, and it was not trivial; it was 16% reduction, but there wasn't a statistical significance. And I think what happened with that is the general feeling of the medical world was, "Well, it's probably not blood glucose control per se that's really going to deal with the issue of cardiovascular disease." And

part of that was because there was a blood pressure arm in that study as well, and that did show some cardiovascular benefits.

So, we skip ahead a few years, and actually, those same studies, the DCCT and the UKPDS studies, had a followup where about 10 years later they looked at the population, and the stunning observation was that after about a year of the study, everybody kind of got together in terms of the same hemoglobin A1c value, but 10 years later there was now clear protection against cardiovascular disease and even microvascular complications, something that's been called metabolic memory. And so, that actually got people very excited about blood glucose control early in the course. It has a hugely important cardiovascular benefit.

So then the next step was to try a similar thing in people farther along in the disease, which is with established cardiovascular disease. They ended up, again, trying intensive blood glucose control studies, and they were a disappointment, and, in fact, even a little scary because one of the them, the ACCORD trial, showed some risks by intensive blood glucose control in those individuals. And so what ended up happening is the medical world again, sort of turned to thinking about blood pressure and lipids and smoking and aspirin and all these things being the dominant way to try and improve cardiovascular risks in type 2 diabetes, not so much blood glucose control.

Now along with this, it turns out there's data that supports there really has been improvement in cardiovascular disease in type 2 diabetes over the years, probably reflecting medical care just getting better. We have data from the U.S. which has shown a clear reduction in cardiovascular disease in type 2 diabetes until about 2010, and we have really interesting data from Sweden that was recently published that again has shown gradual improvements that absolutely parallels a non-diabetic population. But still the problem is there's about a 2- or 3-fold higher risk of cardiovascular disease in type 2 diabetes, so we continue focused on trying to figure out how to improve that.

Dr. Russell:

So you and I practice in a world right now where we've never had more choices before for our type 2 diabetics. What are all these choices, and how do they fit into this discussion?

Dr. Leahy:

Well, that's been the important question. Pharma keeps bringing us new drugs, and along with improving blood glucose control—that's wonderful—but I think we'd like to know that there's a downstream positive health effect of these drugs, not simply better blood glucose values. So virtually every class of medicines that's out there, data has appeared that's told us something about cardiovascular risks. They're not always dedicated cardiovascular trials, but just along the way, one of the outcomes of different trials may be cardiovascular things, and so you kind of get this reputation about what the drugs show us. And as a general statement, until recently, the results have been sort of disappointing. Really no class of our usual medicines has clearly shown a cardiovascular benefit—maybe a little bit with metformin, maybe a little bit in a study with pioglitazone, but as a general statement, nothing really dramatic. And even more problematic is, I think we've steered away from realizing that cardiovascular disease is not simply angina and CABG and stents and these kinds of things. A huge element of cardiovascular disease now is heart failure, of which we really have struggled trying to figure out what to do. And when you look at those same classes of medicines in terms of maybe benefiting heart failure, there's been huge disappointment with even the couple of the drugs showing problems. TZDs and insulin sensitizers are the most famous ones in terms of promoting risks of heart failure and edema, and even a newer class of drugs, the dipeptidyl peptidase 4, the DPP-4 inhibitors, have also shown risks in terms of heart failure. And so in summary, our diabetes medicines in general, until recently, have been really kind of disappointments in terms of making a big impact in lowering the risks of cardiovascular disease.

Dr. Russell:

So our paradigm shifted in 2008 though, because the FDA required that all new diabetes medicines perform these dedicated cardiovascular outcome trials, so why was this so important?

Dr. Leahy:

Well, that was an interesting time. You may or may not remember that there was about a 3-year time frame where there was a huge focus on the possibility that one of the insulin sensitizers, rosiglitazone, might actually cause cardiovascular risks and raise the risk of myocardial infarction in patients with diabetes, which was a pretty scary thought. And so that was very public, talked about a lot, and discussed by very powerful people. And the sum end of that is the FDA realized that this would not be acceptable. We just can't have diabetes drugs that cause cardiovascular risks. And so, in 2008, the FDA came down with a dictum, which continues to be followed, which requires all new diabetes drugs to prove that they have no unacceptable increase in cardiovascular risk. And they provided pretty clear guidelines how that was going to be tested, that companies needed to do dedicated cardiovascular outcome trials, often referred to as CVOTs, and these were to be done using a protocol which was to study non-inferiority versus placebo in addition to standard of care in a high-risk population with cardiovascular disease and diabetes—really important phrases there. There had to be a dedicated study. It had to look at cardiovascular outcomes, and it had to look specifically in patients at high risk for cardiovascular disease. They talked about how the protocol should be done, and typically these are done looking at a composite outcome, which is typically looking at

something called a 3-point MACE, which is 3 elements of cardiovascular disease, and MACE stands for Major Adverse Cardiovascular Events. And so most of these trials are powered to look at a combination of cardiovascular death or new nonfatal MI or new nonfatal stroke, although a few of the studies add a fourth element. And they also provided a really important guide as to when these studies had to be done, that when a company's developing a new drug, during the registration studies, all the different studies that are done against different comparators to see how the label's going to end up, that if the relative risk of cardiovascular disease with the new drug versus all these other trials was more than 80%, i.e. a 1.8 relative risk, the cardiovascular outcome trial must be done before the drug could come onto the market. Alternatively, if the risk was 1.3 to 1.8, then the drug could be approved to come on the market, but the company would have to do a cardiovascular-dedicated trial after it's being marketed.

The last thing I would say about these studies, there's a lot of them now, and we talk about them because they're so hugely important. They're a little bit misunderstood because of the difference in designs, the difference in patient populations, a lot of things. One, it's really hard to compare one trial against another in terms of a lot of specifics. Secondly, they're not really powered for subgroup analysis, so we've got to be a little careful in picking and choosing among the data. And most importantly, these are high-risk individuals with cardiovascular disease, often with existing cardiovascular disease. We cannot presume or say that whatever positive results we get would be true in people who don't have cardiovascular disease. We don't know about these drugs in primary prevention.

And so just as an example, so the FDA mandated this in 2008, these studies started to appear, and the first ones that appeared were a GLP-1 receptor agonist drug called lixisenatide, and what you see was safety in what they're trying to show, so there was no increase in cardiovascular events. Three DPP-4 inhibitor drugs then appeared, the gliptin drugs, which also showed safety in terms of the MACE cardiovascular outcomes, but with one big surprise; because if you look at the trial using saxagliptin, what was shown is a significantly higher risk of admission to the hospital for heart failure. And that's actually carried over to that whole class now. Even though not all of those drugs have shown us that result, a black box warning on those drugs now refers to a higher rate of heart failure because of these trials. So you begin to see how important these trials are for really giving us information about cardiovascular health.

Dr. Russell:

So then we get to 2015 as these studies are rolling out, and something very unexpectedly comes out, correct?

Dr. Leahy:

Totally, and in fact, amazingly. Up until that time, all the trials had been showing safety, which is what the FDA wanted, but in fact, I think what we were hoping was that someone would find a drug that actually has some cardiovascular protection, that would lower the risk of cardiovascular events in people who are really at risk with this disease. And so in 2015, the first study did come out using a new class of medicines called the SGLT-2 inhibitors, and it did, in fact, show cardiovascular protection. The drug was empagliflozin, and the study is called EMPA REG. So I think what we should do is sort of start to describe what these drugs are, and then we should talk about the trials.

So the SGLT-2 inhibitors are those drugs that we talk about that are once-a-day oral medications that work by essentially promoting glycosuria. So this protein, SGLT-2, is an important glucose transporter that's in the proximal part of the renal tubule, and that's what takes our filtrate, what goes through the glomerulus into the early tubules, and takes the glucose which is in there and puts it back into the serum. So it's part of the biology which is really to return all the glucose back into the blood so that our urine is absent of glucose. Of course, we all know that blood glucose values can be high, so we can kind of exceed that threshold, and part of the biology in terms of compensation when blood sugars are fairly high is to have some glycosuria, but that requires a pretty high glucose. So what these drugs do is to inhibit the action of the SGLT-2 protein. They don't hurt it. They don't destroy it. They simply, what I call, trick it, so now all of a sudden you don't take the glucose back into the blood, you put it out into the urine, and that ends up having interesting effects for a person with diabetes. One, it will clearly improve blood glucose values. I don't think that's a big surprise. But also, you're peeing out glucose, which is calories, so people often lose some weight. You pee out salt and water along with the glucose, which means blood pressure tends to improve. So they have a pretty attractive profile in terms of what they do.

So the design of this trial is a classic cardiovascular outcome trial. And so what you see is about 7,000 individuals all with known cardiovascular disease were randomized. Half of them got placebo, and the other half got 1 of 2 doses of empagliflozin, and it doesn't really matter that 2 doses were used because those results were combined in the final comparison. And so what you see is the primary outcome was a standard 3-point MACE, which was a composite of either death from cardiovascular disease, a new nonfatal myocardial infarction, or new nonfatal stroke. And what the results showed is a 14% reduction in the composite 3-point MACE. And this was just actually amazing for us because this was the first drug after all of these trials which clearly showed a proven benefit in terms of reducing cardiovascular disease.

When you actually look at those results, what you see is much of the improvement occurred because of reduction in both cardiovascular death or death from any cause—pretty good to have—but there are also some other really surprising results. The first was that when

you look at rates of hospitalization for heart failure, that also was hugely reduced, 35% in these individuals. And the second thing that was so interesting and surprising is that all of these benefits occurred really quickly. Within being on the drug for 2 or 3 or 4 weeks, already there starts to be a divergence in the risks, and benefits occur by that early time.

The next thing that made this study really interesting is there was a second study which looked at renal risks in the patients that were in this trial. So everybody who had a GFR above 30 was then looked at in terms of the placebo group or the empagliflozin group and in terms of their renal outcomes. So what was seen is that early on when people started this drug because probably of a diuretic effect, there was a reduction in GFR, but then that stabilized, and in fact, with time, the normal slow loss of GFR that occurs in people with type 2 diabetes just stopped. There was stabilization of renal function over the years of the trial using this drug. And when you looked at a composite outcome again of renal issues—doubling of creatinine, renal replacement, new onset of overt proteinuria, death from renal disease—that reduced almost 50% in people who were on the SGLT-2 inhibitor. So these 2 trials together just caused enormous excitement about issues related to both cardiovascular and renal protection with this drug.

So, of course, the next issue was: Well, was this actually unique to empagliflozin, or did we think it was going to have something to do with the class in general? And so a subsequent study with another drug, canagliflozin, has come out. These are called the CANVAS trials—pretty similar protocol, although with some subtle differences. This one actually has 2 trials that are put together to give us the CANVAS trials. One was a relatively short trial of just a couple of years, and one was a longer trial of about 5 years. They did that to get enough outcomes, and also because the longer trial there was a little concern that the data had already been reported to the FDA, so they needed new data.

The second thing that's a little bit different is in this trial a third of the individuals did not have known cardiovascular disease. They had, instead, an age along with high-risk cardiovascular risk factors. But it doesn't really matter, because what you get is again that same 14% reduction in terms of the risks of the 3-point MACE. The pattern of how that occurred was a little bit different. It wasn't only death. It was kind of all of the issues within composite death. But also what this trial showed was a 30% reduction in heart failure and a 40% reduction in the renal composite, so collectively, amazing and really important results in terms of renal and cardiovascular protection with these drugs.

Dr. Russell:

So, Dr. Leahy, you talked about studies involving 2 different SGLT-2 inhibitors. Are you going to expect that this will be a class effect with other drugs in this group?

Dr. Leahy:

Well, this is always the important question. And, in fact, whoever brings out a new one of these drugs is going to need to do a cardiovascular outcome trial and prove it, but I think the general perception right now is "yes." And one of the things that's helped a lot is there's a real-world study that's been published. Real-world studies are really important, because when you do a randomized clinical trial, you realize these are pretty rigorous conditions that all the patients go into, and whether you're going to get the same kind of results in the real world is always open to a little bit of discussion.

So there's this trial which is called CVD-REAL Study, and so what this study was was to go to databases from 6 specific countries—the U.S. and Norway and Denmark and Sweden and Germany and the United Kingdom—and in all of them to identify patients who had been newly started on SGLT-2 inhibitors and compare them to people who were matched controls who didn't start on these drugs, and then the databases were studied for outcomes in terms of heart failure and death and those important things. The baseline of these patients is kind of important, because as you see and look at it, relatively small history of cardiovascular disease, only 13%, a very small history of heart failure, only 3%, and the makeup of the studies is a lot of people were on canagliflozin, also on dapagliflozin, relatively small group on empagliflozin, because of the 3 drugs, that's the newest one. And what was found in this study when you put all 6 of them together is a very similar 40% reduction of heart failure, a 50% reduction in all-cause death, and no big difference among countries. This is sort of the general finding in all of the countries, so very similar, and I think our perception is there's a really high chance that additional SGLT-2 inhibitors that come onto the market will have similar kinds of benefits.

Dr. Russell:

So you mentioned earlier about the heart failure benefits being seen fairly early in the studies. Why do you think that happened?

Dr. Leahy:

Well, this has been the question. You can imagine, as soon as the EMPA REG trial was presented—it turns out it was presented at a big meeting and then published that same week in the New England Journal—there was immediate discussion. "Well, how does that work? How do you actually give a drug and see an improvement in heart failure within a few weeks?" So initially the idea was, well, it lowers blood pressure; maybe that's the outcome. But it lowers blood pressure modestly, not nearly enough to see those benefits. And then the next discussion that went on for a significant amount of time is maybe it has to do with ketone bodies, because one of the

biology of these drugs is they promote an increase in circulating ketones. It just has to do with how these drugs affect certain hormones. It's not a bad thing, frankly. But ketones are known to be an available fuel for heart cells that are a little bit sick. And so ketones can actually serve to provide fuel, and so the idea was, "Well, maybe that's the reason." And then I think the general consensus was, "Probably not." The newest reason which has a lot of investigational support now is it's probably a diuretic effect, and these are pretty reasonable diuretics. And even on top of a known diuretic, it seems to be the major effect of these drugs, and that's why they work so quickly.

Dr. Russell:

So for our colleagues who've not used medicine from this class, what would be some of the safety things that you would have them watch for in their practice?

Dr. Leahy:

Well, I think our feeling is these are pretty safe drugs, and they're convenient drugs. You take them once a day as a tablet. That's pretty nice. Secondly, the side effects are reasonably predictable. By promoting glycosuria, you have a risk of increase in urinary tract infections and also genital yeast infections, especially vaginal yeast infections. I think we know that. And just from a clinical practice experience, it's probably more in terms of vaginal yeast infections. I would say on average I'm probably getting 10 to 20% of my women who go on one of these drugs will have some kind of yeast infection, occasionally more than one, often in women who've had yeast infections before. In terms of men, the male equivalent is balanitis. Balanitis is a little more clinically worrisome, I think. And an important thing to realize is the risk of that is much higher in men who are not circumcised than in men who are circumcised. But even so, the overall risk is pretty modest. There is a risk of hypotension, and I think some providers are afraid of that, because that was one of the early things we talked about. In some elderly patients who are already on diuretics, their blood pressure can drop quite a bit. You've got to be careful. But the reality is this is really a very minor effect in clinical practice in most of the patients we use it in.

One thing that was noticed in the CANVAS trials, those trials I talked about which is using canagliflozin, was about a doubling of the rate of amputation. And this has had a lot of publicity, a lot of people talking about it, and the FDA has emphasized this within the product insert related to this drug because it hasn't really been noted with any of the other SGLT-2 inhibitors so far. But when you look at the data, very modest risk of amputation in the control group, which was doubled, so still a pretty modest risk. We're talking about mostly toe amputations, partial foot amputations, very rare higher than that, and almost all of those people had a history of toe amputations or some other foot amputation or known peripheral vascular disease or known peripheral neuropathy. And so I think the way we typically think about this is to use canagliflozin in particular in caution with patients who carry any of those prior diagnoses.

Now there is one issue that has come up related to these drugs that has been an interesting issue and a surprising issue is something called euglycemic diabetic ketoacidosis. It was identified about a year or more ago that a few patients with type 1 diabetes, a few patients with type 2 diabetes, could be on these drugs. They would go into frank metabolic acidosis with ketone production, all the things we would think about in terms of ketoacidosis, except their blood sugars would not be as high as one would expect because you've got an agent that's promoting you pee glucose out. And so the only important thing there is we needed to teach primary care doctors and to teach emergency room doctors that if someone is on one of these drugs and they're having nausea and vomiting, they're not doing well, one really needs to look at an anion gap and look at ketone levels to make sure that's not the issue, and that's usually handled by better hydration and giving insulin back. It's pretty rare, but it's real.

Dr. Russell:

There are patients out there who have this as a natural defect, correct?

Dr. Leahy:

It's a complicated issue because we really don't have any predictive factors right now that identify who is at most risk to have this happen. We tend to think about it's probably more in type 1 and it's frequently in someone who's on one of these drugs; they're maybe getting a little sick; they're cutting back on their insulin dosages because they're worried about getting hypoglycemic if they're not taking in much carbohydrate; and then the balance of insulin to a hormone called glucagon starts to move into the range where you'll start to convert fat into ketones and ketoacids. And again, in that situation it's mostly to give fluid back and give insulin back, and that will reverse the whole process.

Dr. Russell:

So how should our clinician partners think about starting to integrate this class of medicines into their practices?

Dr. Leahy:

Well, John, you have to understand that, for me, this is such an exciting time because we couldn't have had this conversation 2 or 3 years ago because there wasn't really any conversation to have, and now we have a couple of classes of drugs which have been proven to have cardiovascular benefits in patients with existing cardiovascular disease. We've talked at length today about one class which is

the SGLT-2 inhibitors. There's also data to the different, but it's profound data using another class of medicines, which is the GLP-1 receptor agonist. Not all of those drugs, but a couple of those, liraglutide and semaglutide, have also shown positive cardiovascular protection.

So in terms of how I think about this, what I want our providers to know is that there are class effects, I believe, related to SGLT-2 inhibitors, and they are profound: a dramatic and a rapid reduction in clinically significant heart failure in our patients, so much so that there's some discussion these drugs might actually be useful for heart failure protection in people who don't have diabetes—and there are actually clinical trials that are underway to test that—secondly, a dramatic reduction in the onset and progression of chronic kidney disease, and even in people who don't have known kidney issues. This may be one of the most dramatic findings with these drugs. It's really amazing. And then there probably is an important reduction in overall death. That's what these data seem to imply.

The drugs, for the most part, are easy to take. They're safe with very few side effects, except for the ones we talked about. And so my feeling is that we should think about these drugs in anyone who has known cardiovascular disease with type 2 diabetes. And that is, in fact, what our specialty organizations are saying. You may know that the American Diabetes Association publishes new standards of care every January, so we're pretty newly into the new group, and for the first time they have changed their recommendations for second-line therapy after metformin. And what they now currently say is if someone's failing metformin and you need to add another drug, if they have known cardiovascular disease, they should be put on one of the classes of medicines that are known to have cardiovascular protection including the SGLT-2's or one of them.

There is one caution I would say though. I think these data come out and there's kind of an inclination of some providers to tell patients, "Well, I know you don't have any cardiac disease, but there are these new drugs out there. They're so cool. They're so great. And I think we should give them to you for cardiac protection." The data we have is totally in people at high risk for cardiovascular disease or known cardiovascular disease, and we can't advertise to our patients as primary prevention. This is really secondary intervention, but it's profound. And my message to my primary care colleagues is that as you now moving into prescribing the newer drugs for diabetes, if someone's a patient with either renal or cardiovascular issues, these are really an important class of medicine to be familiar with and use.

Dr. Russell:

Well, it's very exciting information, and with that I'd like to thank our guest, Dr. Jack Leahy, for discussing New Therapeutic Developments for Diabetes Based on Cardiovascular Risk. Dr. Leahy, thank you so much for being on the program today.

Dr. Leahy:

John, it's a pleasure. Thank you.

Narrator:

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