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### Risk Reduction with GLP-1 RAs in Individuals with ASCVD and T2D: 2025 Update

#### Announcer:

Welcome to CME on ReachMD. This activity titled, "Risk Reduction with GLP-1 RAs in Individuals with ASCVD and T2D: 2025 Update" is provided by Voxmedia.

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#### Dr. McDonough:

This is CME on ReachMD, and I'm Dr. Brian McDonough, joining me to update you on risk reduction with glucagon-like peptide-1 receptor agonists, or GLP-1 RAs, in individuals with atherosclerotic cardiovascular disease, or ASCVD, and type 2 diabetes mellitus are Dr. Silvio Inzucchi and Darren McGuire.

Dr. Inzucchi is a Clinical Chief of the Section of Endocrinology, Medical Director of the Yale Diabetes Center, and Professor of Medicine at Yale University in New Haven, Connecticut.

Dr. McGuire is the Jere H. Mitchell Distinguished Chair in Cardiovascular Science and Distinguished Teaching Professor at the University of Texas Southwestern Medical Center in Dallas, Texas.

Dr. Inzucchi, Dr. McGuire, welcome to you both.

#### Dr. McGuire:

Thank you, Brian.

#### Dr. Inzucchi:

Thank you. Good to be here.

#### Dr. McDonough:

So why don't we start with you, Dr. Inzucchi; can you provide a little background on GLP-1 RAs, and then review the key trials of injectable GLP-1 RAs in patients with type 2 diabetes mellitus and high ASCVD risk?

#### Dr. Inzucchi:

Well, this is biology that's been studied for some 30 or 40 years. This is a so-called incretin axis, which is a communication between the GI tract and the endocrine pancreas. There are at least two incretin hormones; the most famous is GLP-1, a glucagon-like peptide-1. It has several effects on the endocrine pancreas, primarily when secreted by the GI tract in response to meal ingestion. It travels systemically and stimulates the beta cells of the endocrine pancreas to make more insulin and the alpha cells of the pancreas to make less glucagon. So that's a recipe for better blood glucose control—more insulin, less glucagon.

Now, the GLP-1 agonists have multiple other effects. They slow gastric emptying, and increase satiety, so they decrease caloric intake when used in individuals.

Those are the three major effects that seem to control blood glucose levels in patients with type 2 diabetes—optimizing endocrine secretion from the pancreas, reducing the introduction of new carbohydrates to the intestines through a slowing of gastric emptying, and reduction of food intake.

As it turns out, there are multiple other tissues, including the heart, the liver, and the kidney, that express GLP-1 receptors. There's been tremendous interest in this field as to whether a drug like a GLP-1 agonist might not only improve blood glucose levels and reduce hemoglobin A1c, but also have beneficial, perhaps indirect or maybe even direct effects on these other organs, including the heart. So the LEADER trial was the first to demonstrate that, in fact, when you lower glucose in a population of patients with type 2 diabetes at high cardiovascular risk, you not only do that, but you improve their cardiovascular outcome.

This was a 9,000-patient study using an older daily GLP-1 agonist known as liraglutide compared to placebo, reduced the risk of 3-point MACE, which is, as you know, major adverse cardiovascular events—reduced it by about 13 point %. That's a relative risk reduction.

The second trial that seemed to confirm the LEADER results was with a second GLP-1 receptor agonist known as dulaglutide, and that was a drug that had very similar effects to liraglutide. But the—patient population in REWIND was a bit different than in LEADER, in that there were many more patients with risk factors for cardiovascular disease but did not have overt cardiovascular events in their past history. This would be called more of a primary prevention population in this trial. Yet, similarly, the hazard ratio was 0.88, so a 12% relative risk reduction again in 3-point MACE versus placebo.

Now, since then, we've had weekly GLP-1 agonists come to market. The one that is of significant interest to many of us is semaglutide, which is the most commonly prescribed GLP-1 agonist at this point in time. And with this weekly formulation of a GLP-1 receptor agonist, we noted better effects, not only on hemoglobin A1c but also on body weight. So this appeared to be a more potent agonist than the two I showed you before—liraglutide and dulaglutide. In SUSTAIN-6, which was a smaller study, about 3,000 patients, there was a 26% relative risk reduction in MACE. This is an injectable version of semaglutide. And then PIONEER-6 actually studied an oral formulation of semaglutide, which we'll talk a little bit more about later on. And that also was a small study, again, about 3,000 patients, and showed a 21% relative risk reduction in MACE.

And then there are two additional studies I would just briefly mention. FLOW, which was a CKD study—it was a renal outcome study to determine whether semaglutide could reduce the risk of progression of CKD in a type 2 diabetes population. And the investigators did look at 3-point MACE, and in that more of a DKD population, they found an 18% relative risk reduction in MACE.

And finally, in SELECT, a unique study because weekly injectable semaglutide was used versus placebo. But here, we're dealing with a cohort of 17,000, the largest of the GLP-1 trials—17,000 patients with prior history of cardiovascular disease and many cardiovascular risk factors, but no diabetes. So if you had diabetes, you couldn't get into SELECT. And here, once again, we see a hazard ratio of 0.80, so a 20% relative risk reduction in MACE.

So obviously, there's been a lot of interest in this drug category because of its pervasive effects, not only in improving diabetes control but also on reducing cardiovascular risk.

The final point I'll make is that there had been a large meta-analysis that was published by Naveed Sattar, Professor at the University of Glasgow, a few years ago that summarized the effects of the class of GLP-1 agonists. This is across, at that time, eight trials, and the mean relative risk reduction in 3-point MACE was 14%. So across all these trials, when you pool all the data, you get about a 14% relative risk reduction in MACE, as well as a 13% relative risk reduction in cardiovascular mortality. So again, clearly, lots of interest in this emerging drug class. We're now at weekly formulations with substantive effects on A1c as well as BMI, but also, most importantly, for our cardiovascular patients, reductions in their future event rates for major cardiovascular occurrences.

**Dr. McDonough:**

With that background in mind, Dr. Inzucchi, can you summarize what the treatment guidelines say regarding the use of GLP-1 RAs for risk reduction in patients with type 2 diabetes mellitus and high ASCVD risk?

**Dr. Inzucchi:**

Well in the past, Brian, the recommendations from professional societies, including the American Diabetes Association, has been singularly focused in type 2 diabetes on glucose control—so-called glucose centrality. We knew that reducing glucose levels would improve microvascular disease risk, and therefore our goal as endocrinologists or primary care physicians caring for diabetes patients is to reduce hemoglobin A1c.

It wasn't until the large cardiovascular outcome trials began to be released, right around 2015, 2016, 2017, that we began to see that certain classes, including the GLP-1 agonists, actually had special effects on not only lowering blood glucose, but also improving cardiovascular outcomes. So over the subsequent 5 to 10 years, there's been a significant evolution of the treatment guidelines that now

favor certain medications in certain high-risk individuals who are at higher risk for cardiovascular disease as well as chronic kidney disease.

So in 2025, the so-called Standards of Care from the American Diabetes Association presented a new algorithm, which suggested that the best treatment for patients who have overt cardiovascular disease, or even had high-risk cardiovascular disease, would be either a GLP-1 receptor agonist or an SGLT2 inhibitor. This is a class we're not discussing today but has also been shown to reduce major adverse cardiovascular events.

In those patients who have ASCVD, either of those classes of medications would be favored, and in some circumstances, they could be used in combination because they clearly have unique mechanisms of action.

In a heart failure population, I think the data is stronger for the SGLT2 inhibitors. According to the ADA guidelines, that category would be favored, although there are emerging data of the benefits of the GLP-1 agonists as well, in a HFpEF population—that would be heart failure with preserved ejection fraction.

And finally, in patients with chronic kidney disease, the favored class would be the SGLT2 inhibitors because of their benefits in that patient population, but also to consider a GLP-1 agonist that has also had proven benefits in diabetic kidney disease, including a drug like semaglutide.

So there's been a significant shift in our guidelines in high-risk populations, favoring either a GLP-1 agonist or an SGLT2 inhibitor in these categories of patients.

**Dr. McDonough:**

Turning to you now, Dr. McGuire, is there an unmet need for additional information on the effectiveness of oral GLP-1 RA therapy?

**Dr. McGuire:**

Yeah. So as Silvio has mentioned, all of the outcomes trials we've had to date, and three of the injectables have FDA product-labeled indications, and as Silvio mentioned, level 1A recommendations from the guidelines, both the endocrinology and the cardiology guidelines.

We have a lot of patients who are just resistant or completely refuse to take an injection. And we have prescribers who perceive that it's cumbersome to prescribe an injectable therapy.

For whatever reasons, people who have indication and access to a GLP-1 receptor agonist, but don't want to take the injection, we now have an oral formulation, oral semaglutide, and we've just completed, presented and published the SOUL trial results that tested oral semaglutide versus placebo in people with type 2 diabetes and either ASCVD and/or diabetic kidney disease. We showed, with oral semaglutide in an almost 10,000-patient study that oral semaglutide reproduced almost precisely the meta-analysis of the class of medications—a 14% relative risk reduction with oral semaglutide for cardiovascular death, MI, and stroke.

We've now got an oral option with proven efficacy. It will enter the guidelines. These data are relatively new. The FDA hasn't acted on them yet, but it's almost certain that oral semaglutide will get the same cardiovascular indication and product label as the injectables—semaglutide, liraglutide, and dulaglutide—have presently. And it now enters the arsenal of evidence-based GLP-1 receptor agonists.

I'm going to push back a little bit on Silvio—he talked about hemoglobin A1c over and over again, but we're not treating glucose with these medications. As a cardiologist, we're treating cardiovascular risk. This is cardiovascular death, MI, and stroke. And I think Silvio will agree that little, if any, of the cardiovascular benefits of these drugs are glucose-related. These drugs are changing atherosclerotic cardiovascular disease well before glucose becomes controlled and well before weight is lost.

We see in the SELECT trial that Silvio mentioned in people with overweight and obesity without even having diabetes, is that the 3-point MACE outcome immediately separated within the first weeks to months of the trial and before weight was lost, before glucose was controlled. So there's something way, way above glucose that these drugs are treating.

And to that point, as a cardiologist, I will say these are squarely in the cardiology toolbox, just like we were with statins in the mid-90s, is we have to be prescribing them as cardiologists for cardiovascular risk mitigation. What we do in our clinic is send a private note to the primary care doc or even the endocrinologist who's managing the glucose, saying we've started a GLP-1 receptor agonist, we will continue to defer glucose management to you. We make sure we're not stepping on toes, but we're using these for cardiovascular risk mitigation—completely independent of hemoglobin A1c considerations.

**Dr. McDonough:**

Given that background, Dr. McGuire, can you please provide the details surrounding the evaluation of the oral GLP-1 RA semaglutide in the SOUL trial and the key efficacy and safety findings?

**Dr. McGuire:**

We started the SOUL trial in 2016—9 years ago. It was a 7.5-year-long project, and median follow-up in the trial of over 4 years. We enrolled 9,650 people with type 2 diabetes and high cardiovascular risk. Independent of glucose control, patients in the trial were able to be treated with open-label therapies for glucose management. This was not a glucose management trial; it was testing a dose of a drug—semaglutide, oral—versus placebo.

We were testing the oral formulation. This is the first small peptide—first peptide we've ever, in all of medicine, been able to deliver through the GI tract, through a very sophisticated tablet formulation that has an absorption enhancer. The tablet is sticky in an acidic environment and actually sticks to the gastric mucosa, and the point of contact is the only place that drug is delivered. So the bioavailability of this tablet of semaglutide is only about 0.8% on average, which means 99.2% of the drug is excreted in the feces. It's a highly inefficient delivery system.

Despite that, we were able, in almost a 10,000-patient trial, to show that patients could take the drug as prescribed, and get pharmacologic doses of the drug.

We didn't just measure cardiovascular outcomes; we also measured A1c and body weight and inflammation—all of the things that we expect to change with exposure to GLP-1 receptor agonists. They all went in the expected direction. We proved that this tablet can be taken over a long period of time in a large population, and generate the same cardiovascular risk reductions as we see with the injectables.

**Dr. McDonough:**

Well, Dr. McGuire, can you please describe how a patient should take the oral semaglutide?

**Dr. McGuire:**

It's a very specific prescription. It's very much like thyroid replacement therapy. Patients are encouraged to take the tablet after at least an 8-hour fast, so for most people, that's first thing in the morning. They can take it with no more than 4 ounces of water, and then for 30 minutes not eat or drink anything. They can do everything else in the morning. They can go for their jog or brush their teeth or take their shower. So it's not terribly cumbersome, but it is a little bit different than an average tablet prescription. But again, despite this little bit of complexity of the administration of it, in this big trial, we were able to demonstrate that patients were able to actually take the medicine and get the medicine on board.

**Dr. McDonough:**

For those just joining us, this is CME on ReachMD. I'm Dr. Brian McDonough, and we're providing an update to you on risk reduction with GLP-1 RAs in individuals with ASCVD and type 2 diabetes mellitus with Dr. Silvio Inzucchi and Darren McGuire.

Dr. McGuire, what are the key insights from the 2025 updated meta-analysis of GLP-1 RA cardiovascular outcome trials, which now includes the SOUL trial?

**Dr. McGuire:**

When we presented and published in March the primary results of SOUL at the American College of Cardiology, and on the same day, we also published an updated meta-analysis that Naveed Sattar led as well.

What we were able to show is we added to his previous meta-analysis now the data from SOUL, and also Silvio had mentioned the FLOW trial—the FLOW trial of injectable semaglutide in people with diabetes and diabetic kidney disease. We updated it with two additional trials showing pretty much the same thing across the class—is that the pooled estimate didn't change from the previous meta-analysis: a 14% class-wide cardiovascular risk reduction.

As Silvio has mentioned, in the US and around the world, liraglutide, semaglutide, and dulaglutide all have regulatory product label indications for cardiovascular risk reduction that are independent of glucose considerations. We are confident that oral semaglutide will join that group of GLP-1 receptor agonists as options for people at high cardiovascular risk to reduce cardiovascular death, MI, and stroke.

**Dr. McDonough:**

Doctors Inzucchi and McGuire, what do you think is the impact on patient care based on the results of the SOUL trial? Where does oral semaglutide fit in the management of these patients? And how might the results affect updated guidelines?

**Dr. Inzucchi:**

Well, I'll start, Brian. I think that this is just another option. We have had several of the GLP-1 agonists being positive for cardiovascular risk reduction, as we've seen with the meta-analyses. And now we have oral semaglutide, which joins the club, basically. What will

happen to the guidelines? I don't know for sure, but I suspect that it will be included, because it's a GLP-1 agonist that has proven benefits. It's just remarkable that with the point estimate of 0.86 that we found in SOUL, that Darren just showed you, a 14% relative risk reduction is precisely the risk reduction that we now see in the largest meta-analysis when you pool all of these GLP-1 receptor agonist trials together. So I think that's really, really meaningful for our patients.

**Dr. McGuire:**

I completely agree. For whatever reason, the people who should be getting GLP-1 receptor agonists but historically have not chosen to take the injection, we do now have a very viable option for an oral formulation. For people who are willing to take the injection, I would pick the injection over the tablet every time, just because of the predictable bioavailability.

I co-chaired the SOUL trial, and we all agreed on the messaging, is that this is a second option. The first option should be the injection. But there are a lot of people who just won't take the injection or prescribers who won't prescribe it. So this opens up, and we've seen already, within months, regions increasing their uptake of GLP-1 receptor agonists by the penetrance of oral semaglutide now being prescribed for those people who weren't willing to take the injections.

**Dr. McDonough:**

It's an interesting point too, Dr. McGuire—I know when you prescribe, you were talking about similar to thyroid medications—that you actually take the semaglutide, you wait 30 minutes, and you have to take your other medications after 30 minutes as well, right? You can't do them all at once?

**Dr. McGuire:**

Right, exactly. Because you'll probably be taking more water as you're taking if you're taking more tablets. It's not that the other medications will interact with semaglutide, but you really just want this to be taken on an empty stomach. Literally, the tablet has to bind to the gastric mucosa. It's a 30-minute pause, and it's not onerous. So I think patients can easily learn how to do that.

**Dr. McDonough:**

Well, certainly well worth any plus with the benefits. But let's continue. Dr. Inzucchi and McGuire, as clinicians taking care of type 2 diabetes mellitus patients with ASCVD risk, how do you determine between a sodium-glucose co-transporter 2 inhibitor, or an SGLT2 inhibitor, an injectable GLP-1 RA, or an oral GLP-1 RA? Lots of choices.

**Dr. Inzucchi:**

I'll go first. It's a really interesting question, and we deal with this in clinic all the time. I think that even though the ADA guidelines don't distinguish between the GLP-1 agonists and the SGLT2 inhibitor in the ASCVD population—and that's because, when you look at the pooled estimates from the various meta-analyses of both of these classes, you get something in the range of 11 to 14% relative risk reduction, numerically perhaps larger with the GLP-1 receptor agonist trials. But they've really never been compared head-to-head, so we don't know.

Having said that, I think most of us feel that, particularly when you look at the components of MACE, across the board reductions in stroke and MI and cardiovascular mortality, that speaks more to an anti-atherosclerotic effect from the GLP-1 agonist, whereas with the SGLT2s, you see a larger effect on cardiovascular mortality, some on MI, and virtually nothing on stroke.

So it's still a little bit unclear how the SGLT2 inhibitors are modulating the MACE events. It may be more of a hemodynamic effect than one that is truly anti-atherosclerotic. Whether that matters to the patient, I'm not sure—they want to reduce MACE irrespective of the mechanism. But this speaks to the potential for combination therapy using both of these drugs. It's an expensive undertaking, but the mechanisms are very, very different, and they probably have additive effects.

In a heart failure population, I think clearly I would favor an SGLT2 inhibitor because there's just a large evidence base behind that statement—both in a HFpEF population, as mentioned before. There's some evidence of GLP-1 agonists having benefits in HFpEF, but also with the SGLT2s in a HFrEF population with reduced ejection fraction. And I think those data are incontrovertible.

Finally, when we talk about a CKD population, I think both drugs have benefits, but perhaps more studies and a larger evidence base with the SGLT2 inhibitor.

So in my practice, if it's just ASCVD, I favor a GLP-1. If it's just heart failure, I favor an SGLT2. Just CKD, I favor an SGLT2. But as we all know, these are artificial choices because many of these patients have two or three of these conditions at the same time, and therefore, very often, we'll use these drugs in combination.

**Dr. McGuire:**

I'll take over from that last comment; I think the diabetes community gets this wrong in their guidance, where they say either or. I had the privilege of being the author of the antihyperglycemic section of the European Society of Cardiology guidelines for diabetes, and we

unequivocally endorse both; it's not either or, it's both.

When we talk about medicines for HFREF, we don't say a beta blocker either or RAAS inhibition, either or MRA. It's not true to the data. The diabetes guidance standards of care now say either or, and then check an A1c and add the other one if you need more glucose control. None of our trials were glucose control trials. It's in the guidance—I don't understand what the ADA is doing. It's both.

**Dr. Inzucchi:**

I think that might stem from the tradition of considering a glucose-lowering medication, of the same category, irrespective of the mechanism of action. I think we're condemned to that way of thinking. But I agree with you—their actions are completely different. They have nothing to do with hemoglobin A1c. We'll take the A1c reduction, right? If you have it.

**Dr. McGuire:**

Don't get me wrong. You and I have talked about this for decades, it's absolutely—it's important to treat the hyperglycemia. Absolutely. And you get some of that with these two agents. I think true to the data is you use both of these, and then you see if you need additional glucose control, and you add the other favorable options. But we don't want to predicate the decision to use these, and it's not either or, it's both.

**Dr. McDonough:**

I've got to tell you too, as somebody who teaches in a residency program in family practice, what you're talking about is so real, because we get these patients—I know Dr. Inzucchi was saying, you don't get the patient with either or, one or the other—you get somebody with a combined picture. And we're looking at the heart failure, we're looking at blood sugar, we're looking at everything together. And it's really interesting to talk about the use, the potential combination use.

And I want to ask Dr. McGuire that; the role for combination therapy of GLP-1 RA and SGLT2s, and who are the patients where combination therapy of the two could be used?

**Dr. McGuire:**

As a cardiologist, I have a biased patient exposure, but most of the people who come to my clinic have some level of cardiovascular disease. I work in the Parkland Health System in Dallas, the safety net hospital, and in my cardiology clinic, we have 45% with diabetes. So almost all of my patients have an indication for these medications.

Fortunately, even though we're a county safety net hospital, we have unrestricted access to SGLT2 inhibitors and GLP-1 receptor agonists. We did a cut of our data just recently. Our penetrance of these two medications is 79% in my clinic. The population—the US average in cardiology clinics is single digits. But we are early adopters, and we're using these drugs routinely as cardiovascular medicines. Again, sending messages to their glucose-managing prescribers: please, we'll defer the fine-tuning of their glucose management to you, but just understand we're using these medicines for cardiovascular risk reduction.

**Dr. McDonough:**

So now that we've covered—we've covered a lot—before we close, I know there's more. I'd like to hear two or three take-home messages from each of you. Maybe Dr. Inzucchi, we can start with you. And I'm sure there's a lot to say.

**Dr. Inzucchi:**

There certainly is. I think the first take-home message from SOUL is that the risk reduction for MACE that we've seen in all the other—or, I should say, most of the other GLP-1 receptor agonists cardiovascular outcome trials has been confirmed with this oral formulation of semaglutide. So as we mentioned before, it is an option for many of our patients.

And the second, more globally, is this movement over the past decade, beginning in the 2015 to 2017 era, where we began to see these very large clinical trials—both with SGLT2s as well as the GLP-1 agonists—getting published, showing glycemic-independent effects of glucose-lowering medications. I use that terminology only because they were originally developed as glucose-lowering drugs, but we know that they're much, much more than that. So this movement away from this singular focus on glucose and treating the patient with type 2 diabetes holistically, understanding their very high risk of cardiovascular events, and those with diabetic kidney disease, a progression to end-stage renal disease. And now we have exciting tools to finally be able to mitigate that risk over time.

**Dr. McGuire:**

I'll pile on. So I've worked in this space in diabetes, and more recently obesity for 30 years. Silvio and I have worked together in most of that time. We worked together on the leadership committee of the SOUL trial, and the academic leadership, but also the clinical care of these patients has become very much a partnership. It's not the diabetologist, and it's not the cardiologist—it's all of us have the responsibility to holistically care for these patients, and that's been really rewarding. And Brian, bringing in the family practice and the primary care discipline, we all have this responsibility to treat these patients to their cardiovascular risk.

We just have to adopt these as standard care for clinical risk mitigation.

We're not treating a biomarker with these medications; we're treating the patient's risk. So it's all of our responsibility to get them. Now having an oral formulation will take a lot of the hurdles away from either prescribers and/or the patients who just want to take a tablet.

**Dr. McDonough:**

Well, as a primary care physician, I appreciate the great work both of you are doing, because you can really see changes. We see it in our patients. I mean, it's amazing and wonderful to watch. And you have the studies, but then you see reality day to day. And I do see a lot of potential and a lot of work being done on that. So anything else either of you wanted to mention, or?

**Dr. McGuire:**

No, I think this has been great. It's been a great conversation. I think it's important to get this information in front of as many people as we can, and just continue to hold the hands of the people who have the responsibility to prescribe these medicines. And it is changing practice, and we will continue to do that.

**Dr. Inzucchi:**

The only thing I might add is that there are newer formulations of GLP-1 agonists that are coming down the pike that appear to be even stronger in terms of glucose-lowering effects and their effects on obesity. Whether they have more potent effects on cardiovascular risk reduction, I don't think we will know, but it's a very exciting time to be managing patients with type 2 diabetes.

**Dr. McGuire:**

Yeah, and I'm glad you brought that up. I almost forgot to mention it, but just today, we have the top-line press release from the SURPASS CVOT trial. I was on the executive committee of this trial—this study, tirzepatide, the dual GLP-1/GIP agonist, once-weekly injectable. We tested it against an active, proven comparator, dulaglutide, and we achieved—in the press release, it's in the public domain as of this morning—that we achieved statistical non-inferiority against dulaglutide, with the point estimate for cardiovascular death, MI, and stroke of 0.92, so directionally favorable. So A highly significant non-inferiority finding against a proven active comparator. And all-cause mortality was statistically reduced with tirzepatide versus dulaglutide. So we'll see those data presented and published by the end of this year. But that was a 13,000-patient trial that we just finished and got the results of this morning.

**Dr. McDonough:**

Well, with those key take-home messages in mind, I want to thank both my guests, Dr. Silvio Inzucchi and Darren McGuire. Dr. Inzucchi, Dr. McGuire, it was great speaking with both of you today.

**Dr. McGuire:**

Alright, thanks so much, Brian. Thanks, Silvio.

**Dr. Inzucchi:**

Thank you.

**Announcer:**

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