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Semaglutide Reduces CV Events in Non-Diabetic, Overweight Patients

Dr. Wysham:
Welcome to *Diabetes Discourse* on ReachMD. I'm Dr. Carol Wysham, and joining us to talk about a recently published study focusing on semaglutide and cardiovascular outcomes in patients who are overweight or obese but don't have diabetes is Dr. Michael Lincoff. Dr. Lincoff is the first author of the study and is Vice Chairman of the Department of Cardiovascular Medicine and a Professor of Medicine at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University.

Dr. Lincoff, thanks for speaking with me today.

Dr. Lincoff:
It's my pleasure. Thank you for having me.

Dr. Wysham:
Well, let's start off. Dr. Lincoff, can you tell us about the background behind the importance of doing this study?

Dr. Lincoff:
So as you know, the prevalence of overweight and obesity is exploding worldwide. It's estimated that in 10 years, half of the world's population will be overweight or will have obesity. And there's growing evidence that overweight and obesity are associated with increased cardiovascular risk not only mediated with the traditional risk factors, but also independently. And yet there is no intervention that's been shown to reduce that cardiovascular risk that's associated with overweight and obesity.

Now the GLP-1 receptor agonists were shown in the large-scale trials that were initially being conducted for cardiovascular safety among patients with diabetes to actually reduce cardiovascular events. That and the SGLT2 inhibitors are the only classes of drugs that have been shown to do that. And so the natural question that arose from that, particularly since those drugs also lead to substantial weight loss, is would it influence the cardiovascular risk associated with overweight and obesity even among patients who did not have type 2 diabetes. And that was the rationale for conducting this study.

Dr. Wysham:
Well, that's very important, and I certainly agree with your perspective on this. So let's get into the study. Can you describe the patient population and study design?

Dr. Lincoff:
Sure. So this was a large-scale, multicenter, multinational randomized trial. It enrolled patients who had overweight or obesity, as defined by a body mass index of greater than 27, and who had preexisting cardiovascular disease but who did not have diabetes. So patients qualified for the criteria of cardiovascular disease if they had a previous myocardial infarction, a previous stroke, or symptomatic peripheral arterial disease. And then their exclusion for diabetes was either an established diagnosis of type 1 or type 2 diabetes or a hemoglobin A1C of 6.5 percent or greater at screening, or they were being treated with a glucose-lowering drug, so those patients were excluded. And then we had other exclusions that were related more toward some safety issues, so patients who had chronic pancreatitis or within a few months of acute pancreatitis were excluded along with patients who had severe class 4 heart failure, patients who were going to undergo a revascularization, or patients who were within 60 days of an acute ischemic event. They could be enrolled later but not in the immediate period thereafter.

Dr. Wysham:

Great. And how about the study design?

Dr. Lincoff:
So it was a randomized trial. The intent was to have the power to detect a 17 percent reduction in the primary endpoint. The primary endpoint was the hard clinical endpoint of cardiovascular death, myocardial infarction, or stroke. So this was calculated to require about 17,500 patients who were randomized double-blind to receive either semaglutide, which was at the dose of 2.4 mg (the weight reduction dose), or placebo. The semaglutide doses increased in steps over a period of four months, with sham titrations in the placebo arm. It was an event-driven trial with the intent of reaching a total of about 1,700 events.

Importantly, because these patients all had cardiovascular disease, this was on top of guidelines for evidence-based therapy for cardiovascular disease, so patients were all being treated appropriately for their hypertension, hyperlipidemia, and heart failure if they had it, etc., so this was superimposed on that standard of care.

Dr. Wysham:
So with that background in mind can you zero in on the results? What were the key findings?

Dr. Lincoff:
As a preliminary, the underlying standard of care was confirmed to have been good, so the vast majority, nearly 90 percent, were on statins; their mean LDL cholesterol at baseline was 78 mg per deciliter; their blood pressure was 131 mm mean, which for a large scale international trial is very good control. Interestingly, 2/3 of the patients had prediabetes, and around 70 percent of patients met criteria for actually being overweight. That is a body mass index of greater than 30.

So among that group of patients, the primary endpoint, that is the cardiovascular death, myocardial infarction, or stroke, was reduced by 20 percent—so the hazard ratio is .80—and we had an event rate of 8 percent in the placebo group and 6.5 percent in the semaglutide group. And importantly, the survival curves diverged very early after initiation of treatment, much earlier than we'd expect or that we've seen in recent trials, for example, of lipid-lowering therapy, etc. and just continued to diverge throughout. We had three secondary endpoints that were controlled for multiplicity, statistically controlled. The first of those, which was death from cardiovascular causes, was not significantly reduced. The hazard ratio was .85, and the upper limit of the confidence interval wasn't significant. We had a heart failure composite, which was cardiovascular death plus hospitalization or urgent visit for heart failure, for which the hazard ratio was .82 with an upper limit of the confidence level of .96, and an all-cause mortality had a hazard ratio of .81 with an upper limit of confidence interval of .93. So we couldn't test because it was sequential P values for those, but they certainly met nominal criteria for significance.

And then we also showed significant reductions in the risk of developing diabetes. The hazard ratio of reaching an A1C of greater than 6.5 percent was .27, so a nearly over 70 percent reduction in progression to diabetes and a substantial proportion of patients actually had regression of their A1C on therapy to levels that no longer met criteria for prediabetes as well. We saw changes in the biomarkers that you'd expect: falls in blood pressure, falls in glucose levels, falls in CRP, and reductions in triglycerides, and so those were all consistent. And virtually all of the cardiovascular endpoints were in a similar direction. And importantly, all subgroups were in the same direction.

Dr. Wysham:
So for those of you just tuning in, you're listening to *Diabetes Discourse* on ReachMD. I'm Dr. Carol Wysham, and today I'm speaking with Dr. Michael Lincoff about his study on semaglutide and cardiovascular outcomes in patients who are obese or overweight but do not have diabetes.

So if we continue reviewing the key findings, Dr. Lincoff, can you discuss the observed adverse events that were associated with semaglutide and how they compared to placebo?

Dr. Lincoff:
The primary adverse event was that of gastrointestinal intolerance, but they didn't meet the criteria for serious adverse events, but gastrointestinal intolerance, particularly during the period while patients were uptitrating the dose the first four months or so, was more common and led to steady drug discontinuation in 10 percent of the patients receiving semaglutide as compared to 2 percent in the patients receiving placebo. So despite our willingness as part of the trial protocol to slow down titration or even let people stabilize at the lower titration and not reach the target of 2.4 mg, still about 10 percent of patients were intolerant on that basis. We saw a slight increase in cholelithiasis of gallbladder, gallstones, 2.8 versus 2.3 percent. Importantly, we didn't see any increase in the risk of pancreatitis, and we actually adjudicated that with source documentation.

Dr. Wysham:
Well, considering the observed reduction in cardiovascular events in these patients, how do you think this data might change clinical

practice in the future?

Dr. Lincoff:
Well, I think it should and will have a substantial impact. A lot will depend upon access, but to put this in perspective, this 20 percent decrease in the primary outcome was on top of evidence-based therapies for ischemic heart disease, so it was on top of patients receiving statins, receiving aspirin, receiving antihypertensives, beta blockers, ACE inhibitors, etc. So an incremental 20 percent reduction is a big deal in modern cardiovascular care, and it does apply to a large number of patients. A substantial portion of our practice would meet the criteria in terms of the body mass index who aren't already eligible or weren't before this trial on the basis of a diagnosis of type 2 diabetes. So I think this is a substantial proportion of patients and is a substantial treatment effect that certainly warrants consideration.

So what this does is it establishes a new modifiable cardiovascular risk factor for specialists who take care of patients with cardiovascular disease. We previously have evidence that by treating hypertension, by treating diabetes, by treating hyperlipidemia, thrombosis, etc. that we know that we reduce cardiovascular events. And now we have overweight and obesity as something that we can address with a therapy specifically directed at weight management that also, and perhaps even more importantly, reduces cardiovascular events.

Dr. Wysham:
I wanted to let the audience know that the FDA has recently given approval for the weight reduction doses of semaglutide for reduction of cardiovascular events in patients with obesity and overweight but without diabetes. I think that really speaks to the importance of this study. And there's indications from Medicare that this is going to be covered, so I'm very excited about having this available in the future.

Dr. Lincoff:
Yeah, that's a key development because the biggest barrier right now is that no payers cover medications for weight loss, but with the FDA recognizing and acknowledging with their approval of the indication for cardiovascular risk reduction, this becomes, hopefully, a different story, as with the approval of these drugs for diabetes where the approval is for reduction in cardiovascular events associated with diabetes. We hope now that the FDA approval will lead to more in the way of not only Medicare but commercial insurers, etc. willing to cover these drugs and make them available to patients with overweight and obesity. Right now, they're cost-prohibitive without coverage for most people.

Dr. Wysham:
Well, before we close, any additional thoughts you'd like to share with the audience today?

Dr. Lincoff:
So the main summary that I take as a cardiovascular specialist, as a cardiologist, is that just as we've had to move and share management and think of the management of patients with diabetes from the standpoint of the drugs that influence the cardiovascular risk, this now moves us to be looking at the risk factors of overweight and obesity; this has become one of the risk factors that we now have to take responsibility for and be active in advocating or prescribing the medications that reduce their cardiovascular risk.

Dr. Wysham:
Well, this has been a really interesting conversation today, and I'd like to thank my guest, Dr. Michael Lincoff, for sharing his findings on semaglutide and cardiovascular outcomes in patients with obesity or overweight without diabetes. Dr. Lincoff, it was great speaking with you today.

Dr. Lincoff:
Thank you very much.

Dr. Wysham:
For ReachMD, I'm Dr. Carol Wysham. To access this and other episodes from our series, visit *Diabetes Discourse* at ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.