Title: EASD 22: SURMOUNT-MMO: Tirzepatide in Obese Type II Diabetes Patients

Participant: Dr Steven Nissen

Date: 10 October 2022

Please note that the text below has not been copyedited.

- I'm Dr. Steve Nissen. I'm the Chief Academic Officer of the Heart and Vascular Institute at the Cleveland Clinic, and we're going to talk today about tirzepatide and the SURMOUNT trial, which is a very large trial designed to determine the effect tirzepatide on major cardiovascular and other metabolic outcomes in patients with obesity.

What was the rationale behind this study?

First of all, it's important to understand that tirzepatide is a unique drug. It is the first dual GLP/GIP agonist.
And in a study known as SURMOUNT-1, tirzepatide produced at the end of 72 weeks, a remarkable 22.5% reduction in body weight. This is a larger reduction in body weight than has ever been seen before with any drug and it did so with a good safety profile.
So that gives us now the opportunity to study tirzepatide in a large population with obesity who do not have diabetes.
Although tirzepatide has been approved for treatment of diabetes, it has not yet been approved for obesity and has not yet been shown to have a favourable outcome result in patients without diabetes, with obesity.

What is the mechanism of action of Tirzepatide?

It's a complicated mechanism, but it involves two hormones, two gut hormones, GLP-1 and GIP. It is believed that tirzepatide has more effect on GIP than GLP-1. And this gut hormone has very profound effects on the intake of food and also in a variety of peripheral tissues.
And so what we have here is a combination drug, single molecule with the combination of effects that affect these two very important gut hormones.

What was the study design?

So, we sought to study patients that have obesity, that is defined as a body mass index of greater than 27 kilogrammes per metre squared, and significant cardiovascular risk either primary prevention patients, and I'll define that in a moment, or secondary prevention patients.
Now, all of these patients are patients with obesity that do not have diabetes.
For primary prevention, it's women greater than age 55 or men greater than age 50 with at least three additional risk factors, or women greater than 70 and men greater than 65 with at least two risk factors such as hypertension, smoking, dyslipidemia, and others.

The secondary prevention population is very straightforward. It's individuals over the age of 40 with established cardiovascular disease defined as coronary artery disease, cerebral vascular disease, or peripheral arterial disease. That constitutes the study population.

What were the main outcomes?

The primary outcome of interest is a composite, and in this composite includes all-cause mortality, nonfatal MI, nonfatal stroke, coronary revascularization, and heart failure events that result in hospitalisation or urgent visits.
The reason that we use this five-component endpoint is that data from a number of studies, including some very large studies performed here at the Cleveland Clinic by myself and my colleague Dr. Ali Aminian, show that obesity has adverse effects on many outcomes, including these five very important cardiometabolic outcomes.

How should these findings impact practice?

Right now, there are no drugs to treat obesity with established benefits on cardiovascular outcomes. It is amazing that after all these years of attempts at development of obesity drugs, one after another of these drugs has failed. The examples of the failures are extraordinary. I mean, we had the Fen-phen disaster with valvular heart disease, lorcaserin was withdrawn because of malignancy, rimonabant withdrawn for psychiatric effects, and then the others simply failed to show any cardiovascular benefits.
So if we can be successful, we can treat this extraordinary epidemic that is now sweeping the world of obesity and obesity-related morbidity and mortality. We have no tools that have been shown to be effective, with perhaps the exception of bariatric surgery, at improving outcomes.
Tirzepatide, when this trial is done, if we are successful, we'll have the evidence necessary to show the medical community that obesity is a reversible risk factor for atherosclerotic cardiovascular disease and for other outcomes.
And I might add that we have very important secondary outcomes in this trial including time to onset of type 2 diabetes, decline in eGFR or renal death, very important to look at the renal outcomes, and a variety of measures of quality of life.
Our hope is that we can both improve the quality of life for these patients but more importantly, reduce the morbidity and mortality due to obesity.

What are your take-home messages?

Well, first of all, the take home message is that we have got to tackle the obesity epidemic. It is reversing all the great progress we've made over many years in reducing the risk of cardiovascular disease. And there's a set of clear evidence that obesity is now undermining the public health efforts. We made great progress.
We've got people to stop smoking, we came up with drugs to lower blood pressure and to lower cholesterol, but all of that has now being challenged by the obesity epidemic.

So my take home message is we need to treat the obesity epidemic but we need evidence, and we have a drug now that can produce remarkable weight loss. We now need to show whether or not it can actually reverse the increases in atherosclerotic events and other adverse outcomes related to obesity.