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Why cardiologists should be interested in obesity and its treatment

Dr. Deanfield:
My name is Professor John Deanfield from University College in London, and I'm going to talk to you today about why cardiologists should be interested in obesity and its management.

Now we all know that there is a worldwide epidemic of obesity, which is having huge impact on the health of the population. And obesity is associated with multiple chronic conditions, and you can see them listed on this slide here. But most importantly for us as cardiologists, it is cardiovascular disease that dominates the adverse clinical outcomes when weight starts to go up in the population. And it's an extraordinary fact that increased BMI leads to premature death in more than 4 million people around the world, with more than 2/3 of those deaths linked to cardiovascular disease and its complications.

Now their interest in obesity has increased enormously in the last few years because we now have the capacity not just to see the complications of obesity and try to manage it with lifestyle change, but we have some specific therapies that really can address a weight loss in our patients in clinical practice. And GLP-1 receptor agonists have been a breakthrough in this field. And recently, data has emerged to show that if you treat patients with cardiovascular disease with these drugs, you can have a real impact on their cardiovascular outcome. Now probably the most important trial that has been published recently on this is the SELECT trial. This was a very large trial of more than 17,000 patients with pre-existing cardiovascular disease who had a BMI of 27 or greater to get into the trial. They had prior myocardial infarction, stroke, or peripheral arterial disease, and they were randomized to semaglutide 2.4 mg once weekly, or placebo. And this was an event-driven trial to understand the impact on MACE.

Now these are the data for the primary outcomes in the SELECT trial. You can see on the top left a 20% reduction in MACE events, the primary cardiovascular outcome. And importantly, death from cardiovascular causes, heart failure, composite endpoints, and indeed, interestingly, death from any cause, were also reduced in this trial.

Now, SELECT patients were not untreated patients; they actually were very well treated with conventional therapy as they went into the trial. Almost all of them were on statins, many were on platelet aggregation inhibitors, beta blockers, ACE inhibitors, and the like. And the 20% reduction in cardiovascular events occurred on top of that good background therapy.

Now it's intriguing to ask the question, what was it in the trial that resulted in that improvement in cardiovascular outcome? What was the effect of the drug in terms of mediating those clinical benefits? Well, the traditional cardiovascular risk factors were indeed reduced in SELECT. You can see here on the left the change in blood pressure, a modest and sustained lowering of blood pressure. You can see on the right that inflammatory markers like CRP were also reduced in the trial. And lipid profiles were also improved in the trial.

Glucose control was also improved. The SELECT population did not have diabetes, but many of them had prediabetes with disturbed glycemic control. You can see that in the trial, the patients who received semaglutide 2.4 mg once weekly, were less likely to increase their HbA1c during the course of the trial than those who received placebo. In fact, their glycemic control improved when they received the active medication.

Now we're still in the stage of trying to understand what it is about GLP-1 receptor agonists that mediates this important improvement in

cardiovascular outcome, and it's probably a little bit more complicated than just weight loss or those traditional cardiovascular risk factors. Many things change when patients take GLP-1 receptor agonists, and one of the things that changes are the way in which they eat, not just what they eat and how much they eat. You can see here, interesting data to show that patients who are on these drugs change their diet for the better, with a marked improvement in healthy foods rather than their traditional diet, and this may be part of the way in which their cardiovascular outcome is benefited.

Now what does this mean for clinical practice? Well, it is going to change the care of our patients with cardiovascular disease. On top of standard care treatment, you've seen a 20% reduction in MACE with these drugs with benefit on multiple cardiovascular endpoints. And in association with that, a benefit for the patient is a sustained significant reduction in their body weight, as you see here. In SELECT, it was almost 10% reduction in body weight sustained throughout the trial.

Importantly, there are side effects from these drugs, but they're not severe, and they did not impact on the clinical outcome of these of the patients in the trial. Safety data was also reassuring. There were no differences in some of the conditions that had been worried about in terms of the use of drugs in patients with obesity. And specifically, none of the complications that have been observed in the past were seen in greater numbers in this trial.

Now this is already changing the way in which we think about clinical practice and the use of weight loss therapies. GLP-1 receptor agonists and other emerging therapies I'm going to show you are altering clinical practice quickly, and the guideline committees are beginning to understand this and incorporate these data into their recommendations. The first was NICE in the UK, who, in March 2023, advocated the use of semaglutide for managing overweight and obesity. The American Heart Association followed shortly with a presidential advisory. Recently, the FDA have licensed another drug, tirzepatide, for weight management. And just recently this year, in March, the FDA approved semaglutide for reduction of cardiovascular risk. What this is going to do is make us think about the way in which we deal with weight management in our patients, and in particular those with cardiovascular disease.

And here are some issues that we need to consider. When should we start treatment for weight and managing cardiovascular risk? Which cardiovascular disease patients will benefit the most? How much weight do we aim to lose, and is this related to the cardiovascular benefit? And of course, when we start these drugs, do we have to continue them long-term? Can we stop them? And might we manage rebound that occurs in terms of weight when these drugs are stopped? Of course, there is the important issue about whether or not we should be medicalizing the population to manage their weight and how we relate the use of these drugs to lifestyle changes that we advocate for our patients. The cost to the healthcare system is going to be more than insubstantial. And we have to think about this against the cost of obesity and cardiovascular disease. Not only is this a health problem, but this is a problem for the economy and society at large, because health inequalities and workforce productivity are really important targets for managing health in the population, as well as just the immediate health outcomes.

Now drugs like semaglutide are the beginning of a new field that is opening up in terms of weight loss medication strategies. There are a whole host of trials currently underway looking at different ways in which medications can enable patients to lose substantial amount of weight. This is going to be a really interesting area to follow in the next couple of years.

You see here on the left, the tirzepatide data showing that if you add an agonist, it's a dual agonist, not just a GLP-1 receptor agonist, you can see that there is substantial weight loss, quite rapidly in the trial data. And on the right, you can start to see how combination of different agents, like the combination of a GLP-1 receptor agonist and an amylin agonist will increase the way in which we can induce weight loss and do it rather rapidly.

A triple-hormone-receptor agonist has already been tested and published in clinical trials. You see here, a phase 2 trial with this agent published recently in the *New England Journal of Medicine*, showing a 25% change in body weight achieved within 1 year; remarkable data for medical therapy of a weight loss.

Now I've been talking about MACE as an outcome, but actually the most important new relationship that is emerging with adiposity is the relationship between BMI and heart failure. On the left you see in the ARIC data, the relationship between BMI and cardiovascular outcomes, with a markedly increased hazard of cardiovascular events occurring as weight increases and in relationship to heart failure. That's not only the number of patients with heart failure that we've perhaps underestimated, but the increase in adiposity is changing the spectrum of the clinical presentation of heart failure as well. It's not heart failure with reduced ejection fraction that is substantially related to the presence of obesity, but is heart failure with preserved ejection fraction, and this is becoming the dominant presentation of heart failure in our clinical practice.

Recent data has shown that if you give GLP-1 receptor agonists to patients with heart failure and preserved ejection fraction, you can improve their quality of life measures and their exercise performance in a very impressive way. On the left, you see the Step-HFpEF data with patients who do not have diabetes, looking at questionnaire data of quality of life and exercise performance, a significant

improvement in those metrics with semaglutide. And just last month, we saw similar data in patients who had heart failure but also had diabetes.

Just in the near future, I'm going to show data from the SELECT trial at a major conference, which shows hard endpoints of morbidity and mortality in these patients with heart failure, both with HFpEF and with HFrEF. Interesting data that will also change clinical practice.

Now when we talk about weight management in our patients, we talk about it in patients who already have cardiovascular disease, and perhaps the only criticism of SELECT is that it is not a primary cardiovascular prevention trial; it is a trial of patients who already had cardiovascular disease. So perhaps we've missed the boat in preventing their cardiovascular disease by earlier management of their risk profile and indeed their obesity. So I would suggest that, as a target, we should be thinking about managing obesity much earlier than we currently do, not just to treat its consequences, but to prevent cardiovascular disease, type 2 diabetes, from emerging in our patients.

We should start much earlier than perhaps we currently think. These are really sobering data looking at the impact of obesity as it emerges in young people. On the left, you see data to show that if a child is obese or overweight at the age of 2, they have a high probability, more than 80%, of being obese and overweight at the age of 35. These changes occur very early, and the patterns related to future weight are occurring already in childhood. Now this is not a benign change. You can see on the right in another study published in the *New England Journal of Medicine*, that the impact of adiposity in teenagers is quite substantial in terms of future cardiovascular morbidity and mortality. And this is largely driven by the development of hypertension and diabetes in these patients who are overweight or obese from an early age.

WHO's statistics are sobering, more than 50% of today's children will be living with obesity at the age of 35 years. This is the next generation of our clinical patients with future cardiovascular disease.

So cardiologists should really care about the management of obesity. It's now changing the cardiometabolic landscape, which is driving cardiovascular disease and indeed, other diseases like diabetes and kidney disease in our patients, and this is having important adverse impact on their clinical outcome. It affects a significant and increasing proportion of patients that we see already in our clinical practice. Now, very excitingly, we're able to change that relationship for the future, not only with lifestyle advice, but now with novel treatment agents. The SELECT trial shows benefit of cardiovascular outcomes in patients with obesity and cardiovascular disease even before they develop diabetes. And it's going to be very interesting to understand the mechanisms that underpin this improved clinical outcome. GLP-1 receptor agonists enable significant and sustained weight loss, which can transform clinical care, but also prevent, as I've shown you and suggested, future diseases. These are much more than just obesity treatments. They're agents for metabolic disease prevention. This change in practice has the potential to revolutionize healthcare very broadly by treating the causes of cardiometabolic disease with far-reaching benefits, not just for our patients today, but also future patients and the economy and society more broadly.

Thank you very much for your attention.