[MUSIC PLAYING]

[APPLAUSE]

NOOR KHAN: Hello, everyone. Thank you for the invitation to speak. We have a lot of material to cover, so I'm going to get started. And hopefully I'm going to be able to advance these slides. Yes, success.

So these are our disclosures, and these are the objectives for today's talk. We will be presenting a list of articles published in 2023 mostly. And we will also present a few landmark studies published in 2022. There were a lot of studies to go through that were worthy of inclusion. And we did our best to include material that's going to be most relevant to you and most practical.

I'm going first, and I'm covering everything but medicines. And as you may be able to guess, I had to really limit the number of articles that I could include. I do want to start with a case, though, to illustrate the studies I have selected.

So this case is based on a composite of patients I have seen in my practice, Mrs. P, a 46-year-old white lady. She has a BMI of 31, an elevated abdominal circumference of 39 inches. Her blood pressure is elevated today, as it has been on prior visits.

And she attributes her recent weight gain to a sedentary lifestyle, a high-stress job, and poor sleep habits. Selected labs and investigations done in the last six months include HbA1c in the prediabetes range and dyslipidemia with a high triglyceride/low HDL pattern. An echo checked for dyspnea on exertion and shortness of breath showed left ventricular hypertrophy.

Mindful of the experiences that our patients have in the health-care setting, you ask her if it's OK to discuss how her weight may be impacting her health. She really appreciates that you ask permission, and she says she is glad that you brought it up. She also asks you about recent news reports that body mass index may not even be very accurate.

So our patient is probably talking about the American Medical Association statement that got a lot of media attention in June 2023. The American Medical Association put out a new statement and a policy in June asking individuals, professionals, insurance companies to not over-rely on body mass index. BMI does correlate significantly with the amount of fat mass in the general population but starts losing predictability when you start applying it to individuals. And someone with the same BMI may have really very different adiposity, metabolic risk factors based on body composition, shape, and ethnicity.

The American Medical Association recommends using other risk factors in conjunction with BMI. Some of these may be hard to measure in the clinical setting, like body adiposity, body composition. But certainly waist circumference, especially for a BMI between 25 and 34.9, is something that we can very easily measure in our patients, and also assessing for genetic risks and metabolic risk factors as well within the realm of routine practice.

So the first question we're going to ask is, does BMI predict all-cause mortality? And I'm going to talk about this study published in July 2023. We do have older studies that have tried to answer the question of whether body mass index is associated with mortality. However, these are older studies, and they used population cohorts mostly from the 20th century.

The US population today is different. We have a higher BMI. We've seen a more than 10-year improvement in life expectancy. We have a very different ethnic makeup, and we have better access to treatment for obesity comorbid conditions. So this study was designed to address this gap in knowledge and lack of reliable data for the contemporary US adult population.

The study investigators looked at the National Health Interview Survey, which is a nationally representative survey conducted 1999 to 2018. And they used recorded body mass index calculated from self-reported heights and weights in adults and linked that to the mortality statistics from the National Death Index. And this allowed them to make inferences regarding all-cause mortality and BMI.

The reference category that they used was determined to be a BMI of 22.5 to 24.9, essentially a normal body mass index, and they compared other strata to this reference category. And they looked at the association between mortality and adiposity as defined by body mass index in various populations, including women and men younger than 65, older than 65, and various ethnicities.

So this is the makeup of the study. More than 500,000 individuals were included in the study. It was fairly representative of the current US adult population except I was actually a little surprised to see the 42% smoking at least 100 cigarettes in their life. That's a little higher than what we typically see these days.

And then these are some of the selected results. So this table shows the all-cause mortality. BMI 22.5 to 24.9 was the reference. And interestingly, unlike older population cohort studies, an elevated all-cause mortality was not seen in the overweight range. So you do not see elevated mortality for BMI 25 to 27.4 and also BMI 27.5 to 29.9. Both those references include 1.

Increase in mortality was seen for a body mass index of 30 and above. And not surprisingly, you also see increase in unadjusted all-cause mortality for individuals with a very low body mass index. These patterns became even more apparent after they adjusted for covariates. And they also limited analysis to participants not dying in the first two years to avoid confounding by illness-related weight loss, and they found the same pattern. And the same pattern of an increase in mortality at a higher BMI than earlier studies had suggested of 30 was seen in a wide swath of the population.

And the next few slides will show some of those. So this is for male and female participants of the study. And for both men and women, increase in all-cause mortality was once again seen at a body mass index of 30 and above.

And then this is an interesting slide. It shows the association between body mass index and all-cause mortality by race and ethnicity. Interestingly, for white adult Americans at a higher BMI, all-cause mortality was actually higher than for Black and Hispanics.

But then again, if you look at this panel more closely, for Hispanic Americans at a BMI of 25 to 29.9, a trend towards increased all-cause mortality was seen. So this is just a hypothesis-generating study, but it does show some interesting differences in all-cause mortality and body mass index amongst different ethnicities, which is what we expected. But interesting findings there.

So this slide is also very interesting. And it looks on the left at the BMI in women and men younger than 65, and then on the left, on the right, the mortality rate in women and men older than 65. And what we see over here is that at least in older adults, mortality rate did not start increasing until a body mass index of 35. So this study suggested that a higher BMI was actually protective in older adults.

So in conclusion, this study of the contemporary US adult population suggests body mass index in the overweight range is generally not associated with an increased risk of all-cause mortality. And in older adults, body mass index may not increase mortality independent of other risk factors in adults with a BMI of 25 to 34.9. And this study also highlights the potential limitations of using body mass index in capturing true adiposity.

All right, so the next question we're going to ask is, does treating obesity improve comorbidities? And there were many studies over here that could have made the grade. And I chose to focus on this study that was just published in September last month in the *New England Journal of Medicine.*

Before we move on to the study, I want to draw your attention to obesity paradox. I'm sure this is a term that you are familiar with. Previous observational reports suggest that a higher BMI is actually protective in patients with certain chronic conditions, including heart failure. And weight loss is associated with a worse prognosis. And this is the obesity paradox.

However, these prior observational data did not distinguish between unintentional versus intentional weight loss. So what happens with CHF, congestive heart failure, with intentional weight loss strategies that we are using today for reduction of weight? And that brings us to this trial published in September 2023.

So HFpEF, heart failure preserved ejection fraction, accounts for more than half of all cases of heart failure in the US. And the majority of patients with HFpEF also have either overweight or obesity. Excess adiposity is not simply a coexisting condition, but may actually play a role in the development and progression of the condition.

So in this trial investigators, looked at the effect of semaglutide, 2.4 milligrams weekly, versus placebo on functions and symptoms in patients with HFpEF and obesity. So this was a randomized, double-blind, placebo-controlled, industry-sponsored trial. It was conducted in multiple sites in 13 countries across four continents.

And the inclusion criteria were subjects with HFpEF, EF more than 45%, and NYHA class II, III, or IV. They also looked at functional scores using the Kansas City Cardiomyopathy Questionnaire and included in the study individuals who had a score less than 90, a lower score indicating more symptoms, and a higher score indicates less symptoms. And they also looked at six-minute walk distance of at least 100 meters. Subjects were excluded if they had diabetes or had recent significant weight loss prior to screening.

So this first slide for results shows the primary endpoints. And panel A is functional improvement in the Kansas City Cardiomyopathy Questionnaire. And panel B is change in body weight.

And as you can see, both for symptom score and also change in body weight, semaglutide, the semaglutide group did significantly better than the placebo group. The semaglutide group lost about 11% more weight than placebo and had about an eight-point improvement in the Kansas City Cardiomyopathy Questionnaire score. And both the change in the score and the change in weight, as you can see in these graphs, seems to correlate temporally with each other.

Secondary endpoints include a change in six-minute walk distance, which favored the semaglutide group for a distance of 20 meters, and a change in C-reactive protein. And there was about a 37% reduction in semaglutide versus placebo group for change in C-reactive protein.

There were also less adverse events seen in the semaglutide group. And this was mostly attributed to cardiovascular events. And the investigators felt that along with the decrease in CRP levels that I just showed you, there was also a reduction in systolic blood pressure and NT-proBNP. And they felt that some of the semaglutide effects may have been because of its anti-inflammatory and hemodynamic effect and not just weight loss. However, the extent to which each of these weight loss versus hemodynamic effects contributed to CHF improvement is really not known and something that should be studied further.

So this study was an interesting trial that goes against the obesity paradox that we have seen in prior studies. And intentional weight loss in HFpEF does seem to lead to improvement at least over a year, in both symptoms and function.

So coming back to our case, Mrs. P appreciates the information you've provided on how her weight may be impacting her health. And she would like to start with lifestyle interventions first. She tells you she is seldom hungry in the morning, yet she forces herself to eat something. And she wants to ask your opinion about time-restricted eating.

So time-restricted eating is a popular dietary strategy, especially in the health-care world. None of us has time for breakfast. And I'm going to talk about this study published in June of 2023 in the *Annals* that looked at a racially diverse population and used a strategy of time-restricted eating, importantly without calorie counting, versus daily caloric restriction.

So what is TRE? Time-restricted eating, or TRE, requires restricting your caloric consumption to a certain period of the day. Either six hours or eight hours are common protocols. And eating over this narrower portion of the day actually leads to consumption of less calories, so about 300 to 500 kilocalories less consumed.

Individuals who do TRE, unless it's a research setting, are typically not counting their calories. This is in contrast to daily caloric restriction, in which they are monitoring their caloric intake. So little research has actually been done in the US adult population on this strategy, especially little long-term research.

So this was a one-year randomized controlled trial. It was a single-center trial done in Chicago. and They looked at a TRE window of eight hours, noon to 8:00 PM, versus caloric restriction of 25% calories daily versus a control group that was eating ad libitum. They looked at body weight and cardiometabolic risk factors. And the hypothesis was that the TRE group would achieve greater weight loss and insulin sensitivity over 12 months compared to caloric restriction and control.

Inclusion criteria were adults between ages of 18 and 65 and a BMI between 30 and 50 and a very long list of exclusion criteria, which was actually one of the limitations of the study. The study was designed as such. Eventually, 90 people were randomized to three groups, TRE, daily caloric restriction, or control.

In the first six months of the 12-month study was the weight loss phase. And the next six months of this 12-month study was the weight maintenance phase. Assessments were done at baseline, six months, and 12 months. And there were 30 subjects in each of these groups.

Let's talk a little bit more about what the TRE six-month weight loss phase looked like. So the eating window, like I said, was eight hours, noon to 8:00 PM. But participants were not required to monitor caloric intake. They could eat whatever food they had at home. There were no restrictions on types, quantities of food consumed.

In the fasting window, they could drink plenty of water or energy-free drinks, including up to two diet sodas per day. And then in the weight maintenance phase, the eating window was widened to 10 hours, 10:00 AM to 8:00 PM, once again, no requirements to monitor caloric intake.

And for the caloric restriction group, there was a 25% calorie restriction in the weight loss, six months. And then after the first six months, when they went into the weight maintenance phase, their new caloric requirements were, again, calculated based on their new weight. And they were asked to eat 100% of their new caloric requirements.

So these are some of the baseline characteristics. So one of the weaknesses of the study was mostly women. Also very few white adult patients, subjects were in this study. Other parameters, including body composition, bone density, lipids, cardiometabolic factors were all quite well matched between the three groups.

So let's look at some of the results. And this graph shows weight loss. In the first six months during the weight loss period, both participants in the TRE and the CR group lost weight, an equivalent amount of weight, about 4.6 for the time-restricted eating, TRE, group, and 5.4 kilograms for the caloric restriction group. And there was no statistical difference between these two weights. In the weight maintenance period, both groups maintained most of the weight that they lost.

If you look at adherence, please don't compare the adherence numbers on the slide directly to each other because they had different references. The TRE groups reported actually a high adherence. They were able to adhere to their time-restricted eating window for six out of seven days a week for about 87% of the days over that 12-month period. In the caloric restriction group, 61% of study participants reported meeting their caloric goals.

Mean calorie deficit was actually similar in both groups, for 425 per day in the TRE group in the first six months, and 405 kilocalories per day in the caloric restriction group. So this calorie deficit in the TRE group was achieved without them actually counting calories and just by restricting when they ate. Both the active interventions led to reductions in fat mass, waist circumference, and BMI, but no reduction in lean mass, visceral fat mass, or bone mineral density. And the TRE group was associated with increased insulin sensitivity compared to the control but not compared with caloric restriction.

So in conclusion, this interesting trial compared effects of TRE without intentional energy restriction with that of daily caloric restriction. And this is how it's different from some of the other time-restricted eating studies that you may have read. There were no serious adverse events in any of the group. And this suggests that TRE may be an effective and feasible regimen for sustained weight loss in a culturally diverse population that may also have limited tools and finances to buy all different types of food.

Limitations, small, single center, nonblinded, mostly women. They did not actually measure energy expenditure. They just estimated it based on calculated equations. And there were also a lot of exclusion criteria, excluding a lot of comorbid conditions that we would be interested in treating in patients with obesity and overweight.

All right, so how am I doing for time? All right. So I have about six minutes to cover the next two papers. And I'm going to talk about surgical and procedural interventions for weight loss and cardiometabolic risk.

So this first one is the endoscopic sleeve gastroplasty for treatment of obesity study. And this is a reversible endoluminal organ-sparing bariatric procedure that has been found to be effective for weight loss, 16.5% weight loss in one large meta-analysis published in 2020. So this study looked at the efficacy and safety of this endoscopic sleeve gastroplasty procedure.

It was a multicenter randomized trial, again, industry sponsored. And it included individuals who were adults with BMIs in the 30 or 40 range who agreed to comply with the lifelong dietary restrictions. If you're interested in recommending this procedure to your patients, please look at those dietary restrictions. They are quite intense. And the placebo group was moderate lifestyle interventions. And the intervention group was ESG plus moderate lifestyle interventions.

So for the first 52 weeks, patients in the ESG group were followed, and then continued for another 52 weeks for a total of 104. At the 52-week mark, some patients in the ESG group did require retightening. And that was about four individuals in that group.

In the control group, in the lifestyle modifications only group, participants were offered crossover to receive ESG if they did not meet their weight loss goals and then were followed for another 52 weeks. So the trial was a total of 104 weeks. And this panel shows the weight loss. As you can see, the ESG group lost significantly more weight than the lifestyle modifications only group. And then when the lifestyle modification only group was offered ESG, the weight loss became pretty similar in both groups.

So this is an important slide to spend some time on. And it shows improvement in comorbidities. So all comorbidities listed over here except hyperlipidemia improved significantly in the ESG group compared to the control. And of note, at least for diabetes, in the first 52 weeks, when the controls were not offered ESG, there was a worsening seen in glycemic parameters. So this slide suggests that ESG was better as far as comorbid improvement compared to usual lifestyle interventions.

And then this slide shows the side effects. As expected in the beginning post ESG, there were a lot of side effects. But by the time we got to 52 weeks, the side effects fell off significantly, indicating that at least in this population, the procedure was tolerated well. So in conclusion, ESG with lifestyle compared with lifestyle alone led not just to weight loss, but also improvement in comorbid conditions and also higher participant satisfaction.

GERD incidence was also not increased in the ESG group. And of note, even though the control group did have some worsening of metabolic health during this time period, sample size was inadequate to draw conclusions for that.

All right, the last study I'm going to talk about is a 10-year analysis of the SLEEVEPASS randomized clinical trial. So if you're not familiar with this trial, this is one of the largest randomized controlled trials comparing laparoscopic sleeve gastrectomy to laparoscopic Roux-en-Y gastric bypass. And there have been a number of articles published from this trial.

And this article that I'm going to talk about provides 10-year outcomes. And it focuses on that question that we are now seeing. We're seeing a lot of reflux, even some suggestion that Barrett's esophagus may be increased after a sleeve gastrectomy. So this 10-year analysis really looked at comorbidities and reflux.

So briefly about the initial trial, multicenter, multisurgeon, open-label randomized clinical equivalence trial with 240 patients. And the primary endpoint of the trial was weight loss defined by percentage axis weight loss. And the secondary endpoint was the total weight loss. I'm going to show data on total weight loss because it's easier for us nonsurgeons to understand. And they also looked at comorbidity remission and improvement. For the 10-year analysis, the one that I'm going to show you, the added assessment of GERD symptoms, PPI use, and Barrett's esophagus specifically.

So this panel shows weight loss. The darker gray over here at the bottom is sleeve gastrectomy. And the line just above that is laparoscopic Roux-en-Y. At least for weight loss, even though a trend towards improvement in weight loss was seen with the Roux-en-Y, the study was actually not powered to detect this difference. So we can't say whether one was superior to the other based on this data as far as weight loss.

And then looking at comorbid conditions also, both for diabetes, dyslipidemia, and sleep apnea, laparoscopic sleeve and laparoscopic Roux-en-Y ruined led to significant remission. This is not improvement. These are remission rates at 10 years. The only condition for which Roux-en-Y was superior to sleeve was hypertension as far as remission.

One of the points to note, diabetes is something we often treat. No remission was seen in any group in patients who had diabetes for more than 10 years at the time of randomization. So this suggests that if you are considering these procedures for diabetes remission, do it early.

PPI intake, as expected, was more in the sleeve gastrectomy group, and so was the GERD score, quality of life score. It was worse in the sleeve gastrectomy group. Interestingly, in this study at least, that signal towards increased Barrett's esophagus for sleeve versus Roux-en-Y was not seen. So this was reassuring. As far as complications for Roux-en-Y-- for sleeve, of course, it's reflux. And then for Roux-en-Y, it was mostly internal herniations.

So this study shows that both sleeve and Roux-en-Y done laparoscopically resulted in significant sustained weight loss, resulted in remission of a significant number of patients with diabetes, dyslipidemia, or sleep apnea. Hypertension remission was more in the Roux-en-Y group. The prevalence of de novo Barrett's was the same. And esophagitis reflux symptoms, PPI use was significantly more after LSG. All right, thank you very much. I'm going to hand it over to Dave.

[APPLAUSE]

DAVID ROMETO: All right. Thank you, Noor. That was fantastic. And so I will be-- excuse me. I will be addressing the antiobesity medication portion of this talk. And I'm going to get through a few more papers than you saw in the first half. So I'm not going to get into as much detail to different trials.

But just to show you a quick summary of what we're going to be talking about are the more recently published phase III studies of semaglutide 2.4 subcutaneous and then the semaglutide higher dose oral trials and tirzepatide 15 subcutaneous for weight loss, which is different from their phase III trials for the treatment of diabetes. And then we're going to talk about some phase II trials of medications in the pipeline that have not yet been approved for anything yet. So we have not seen an FDA approval of these kinds of medications. And lastly, we're going to talk about the combination of antiobesity medicines and bariatric surgery. So good to have that update from Dr. Khan.

So semaglutide 2.4, this is the STEP 5 trial. And the novelty of this trial is it's a two-year duration trial, where the initial trials were in the 68-week range. So we now have 104. So 304 subjects with meeting the criteria for antiobesity medication without diabetes.

And the lifestyle arm, which I'm going to talk about in most of these trials because we can compare them. Was meeting with an RD or equivalent every four weeks for the duration of the trial, aiming for a 500-calorie deficit on the diet side, 150 minutes a week of physical activity. And this group was recording these things daily.

You see that 80%, almost 81% of the subjects were women, with a starting average BMI almost of 39. And I'll also show the waist circumference, as we talked about the importance of that independent of BMI, 45.6 inches. And we see here on the right 15.2% weight loss at two years. And if you look at that 68-week mark, they were just a little over 16% weight loss. So a significant preservation of that little over one-year weight loss effect at the two-year mark.

And the other thing that's reported in weight loss trials is what percent of the population achieved a certain threshold of percent weight loss? So they presented the 15% weight loss achieved in slightly over 50% of the population and a loss of 5.7 inches from the waist circumference. So that's the first one.

So moving on, and we're going to compare these numbers to each other just so you understand that, once weekly semaglutide in adolescents, this is called STEP-TEENS. Subjects were 12 to just under 18 years old. The BMI is defined by the growth chart and being over the 95th percentile. And again, most of these patients did not have diabetes. It wasn't an exclusion. But only 8 out of the 201 had a diagnosis of diabetes at the start of the trial.

There was a 12-week lifestyle run-in. But after the start of the medication, subjects were on a 60-minute of moderate to high-intensity physical activity per day without any specific calorie or volume of food restrictions. We have now 63% female in this study, BMI around 38. And the average age was 15.5. But the majority of the patients, 2/3 of the patients were in the upper half of that range, 15 to 17 years old.

And the percent weight loss results here-- and I'm showing, by the way, the intention-to-treat or treatment regimen as demand results because I don't want to oversell the results and just use that as a standard across all the trials that we're reporting. So a 14.7% weight loss. When you look at the percent BMI change in adults, those numbers should be the same because they're not changing height. In pediatrics, they're still growing. So we actually see 16.1% decline in BMI in the pediatric population.

And didn't have time to present this paper, but also about a year ago, a year and a half ago, phentermine topiramate in teens was studied and showed a 7.1% decline in BMI. Different trials, not randomized. But that's a significant magnitude of difference. And 37% subjects achieving greater than 20% weight loss, a 5-inch loss of the waist circumference. So this is the first time a pediatric trial of any weight loss intervention has matched the adult magnitude of weight loss. So very, very important.

And on the right here, I just like showing when you see this the waterfall plot of seeing each individual subject. And even in the control arm, you say, oh, they didn't lose any weight. Well, half of them gained weight, and half of them lost weight, and it averaged out. So there is this spread even in any intervention. But you see very few people did not lose weight in the study arm.

Moving on to semaglutide 50 milligrams PO-- so you may have had experience with semaglutide 3, 7 and 14 milligrams PO for the treatment of diabetes. So this is now a significantly higher dose for the treatment of obesity. And this is the peptide itself in tablet form. And it needs to be consumed on an empty stomach first thing in the morning with a little bit of water and no drinks and no other medications and no food for at least 30 minutes. So some significant rules to follow there, even harder to follow than thyroid hormone replacement. And they did tweak the contents of the tablet compared to Rybelsus to try to get better absorption of the much higher dose.

So their clinical trial, OASIS-1, is the phase III trial in obesity. Again, type II diabetes was excluded. And they have 68-week data here. Again, lifestyle intervention was meeting every four weeks, 500-calorie deficit, 150 minutes a week of physical activity. Took about 16 weeks to titrate the dose.

So they went right from 14 to 25, and then four weeks later, 25 to 50 in the escalation. 74% women, BMI around 37. And looking at this graph at six to eight weeks, 15.1% weight loss, 34% achieving greater than 20% weight loss, so basically showing very similar results in the intention-to-treat data as semaglutide 2.4 in adults and teens. So the conclusion here is basically 50 milligrams is the oral efficacy equivalent of the 2.4 milligram semaglutide injection weekly, which, of course, would be a benefit to people who won't or can't give themselves injections.

Next up is PIONEER PLUS. And this is oral semaglutide in that dose range for patients with diabetes. The difference is this was not a weight loss trial. This is the diabetes trial for getting this approved for diabetes in this range. And so there was no lifestyle arm or component of increasing exercise or eating fewer calories or even improving the quality of the diet involved in this.

Also notable, in a diabetes trial, you see this trend. There is no predominance of females in diabetes trials. They're split. And actually, this one was 43% women. And the BMI cutoff is lower, a BMI over 25. And so we see an average BMI of 33.7. So you're already starting off with different demographics.

And when we look at the results, at 68 weeks, 9.8% weight loss. So there is a noticeable history of the same intervention causing less weight loss in people with diabetes. But you do have to factor in, what is the mix of sex in the subjects, and what is the starting BMI? And we'll see a little bit more of that later. But greater than 44% with greater than 10% weight loss, they're not even reporting 15% and 20% weight loss because it's not a weight loss trial.

We also see the A1C comes down a little more than 2 points. And that also leveled off after six months while the weight continued to fall. And I'm mentioning the diabetes outcomes because this medication was cut for time from the endocrine presentation earlier this year.

Moving on to tirzepatide, so tirzepatide is the first dual agonist, GLP-1 and GIP, in the same single peptide. It was actually based off the GIP peptide. So it has more homology in its sequence but adjusted to also stimulate the GLP-1 receptor. It has stronger affinity for GIP than it does for GLP-1, also adjusted to avoid DPP degradation and added the 20-carbon chain for binding to albumin to increase the half-life to make it a weekly injection.

So the clinical trials, phase III, are called SURMOUNT when you see tirzepatide in weight loss trials. So that means they are in a lifestyle intervention with the RD, 500-calorie deficit, 150 minutes of exercise, patients without diabetes, of course. Now, it takes 21 weeks to reach the full dose in the escalation if you've started patients on Mounjaro for diabetes, four weeks each on multiple doses. And again, predominance of females in the trial and an average BMI of 38 with a 45-inch waist circumference.

So we see at 72 weeks that the treatment regimen estimated is 20.9. But you may have been quoting the 22.5 of the on treatment results at that period of time. 57.6% with a greater than 20% weight loss and, again, a loss of 5.7 inches off the waist circumference. So we are seeing here about a 5% increase in total body weight loss compared to the semaglutide trials and an additional 25% of the population reaching the 20% weight loss threshold.

SURMOUNT-2 is in a diabetes population, but it is a weight loss trial, not a diabetes trial. So they're also meeting frequently for calorie restriction and exercise targets. And they note also three-day diet and exercise log reviewed at each visit.

But yet because it is a diabetes trial, somehow they hit the 51% female mark. And so they were more evenly distributed on sex. And BMI was a little bit lower at 35.7. And we look at those results, and we see a 14.7% weight loss and 30.8 achieving a 20% weight loss. So we're basically seeing similar results in this trial as in tirzepatide in people with diabetes as we see in semaglutide for people who don't have diabetes, just to compare those numbers.

All right, so now we're going to get to what's in the pipeline? What are the medications that we may have approved in the next two years or so to be the new thing that we consider prescribing to our patients and fight for insurance coverage?

So cagrilintide, cagrilintide, and cagrilintide in combination with semaglutide-- cagrilintide is a amylin analog. And amylin analogs, you may know about pramlintide under the name Symlin, which is a three-times-a-day before-meal subcutaneous shot for the treatment of diabetes, type 1 or type 2 on insulin, that does control blood sugar, decreases how much insulin you have to take, and causes some weight loss, including through delayed gastric emptying.

But analogs also target the calcitonin family G-protein receptors. So calcitonin we know from coming from the thyroid cells, C cells, and medullary thyroid cancer. So these receptors in the brain stimulating them actually does result in weight loss centrally in energy expenditure and food intake.

So cagrilintide is a once a week. So it's altered. So it can also be a once-a-week shot for long-term action. So it's not going up and down when you eat, but it's always there, like the GLP-1 agonists.

The data by itself, these two trials were from 2021. I'm just showing them as background, that cagrilintide by itself in subjects without diabetes who were not trying to lose weight-- there was no lifestyle arm-- lost almost 11% at 26 weeks. And Novo Nordisk, who owned the molecule at the time, said, well, this isn't going to beat these other pipeline drugs that are out. But it is a different mechanism. So let's just combine it with a GLP-1 agonist and sell it as a package deal.

So they combined it with semaglutide, which they already owned, and knew the 2.4 was the right dose. So the next trial here was cagrilintide and semaglutide in combination. And they achieved 17.1% in 20 weeks. So this is very rapid weight loss, of course, compared to everything else we've talked about so far today.

So the update is that they did publish their type 2 diabetes phase II trial of what we call CagriSema. And this is two molecules just in the same shot. It's not one molecule stimulating both receptors. 92 subjects with type 2 diabetes. And again, the titration path is the same as that for semaglutide in terms of those doses. And they're in the same dose. 2.4 is the peak dose.

And there was no lifestyle component. This is just being given to people with diabetes to control their diabetes. Again, 42% female, so we have that diabetes ratio there. And we see 15.6% weight loss at 32 weeks, so already equal to or better than tirzepatide in that duration, in a shorter duration of time. 54% with greater than 15% weight loss. And they're not talking about waist circumference in these diabetes trials.

They did put them on continuous glucose monitor. So you see this data here in the lower right. So significantly better timing range on the combination than on the medication separately. And you see that nice lower average but also tighter variability on the continuous glucose monitor data. And the A1C fall, because this was a diabetes trial, was 2.2.

Interestingly also that Cagri by itself and Sema by itself achieved the weight loss there in the middle upper section. If you add those two numbers together, CagriSema achieves a more than additive result, at least at the 32-week mark in this trial. So this may actually be a synergistic combination of medications. But we'll need the one to one-and-a-half-year data to see where that flushes out.

Next up, orforglipron-- Dr. Hahn mentioned this in her diabetes update earlier this year. So this is an oral nonpeptide GLP-1 receptor agonist. So you see the molecule there. That is not a string of amino acids. And so this tablet does not need to be absorbed through the stomach wall. So it does not need to be taken with all of these following rules, like the oral semaglutide needs to.

And its agonism at the GLP receptor is actually different than the GLP-1 peptides, which is favoring a cyclic AMP pathway. So that may be more beneficial in terms of sensitization to stimulating the receptor constantly.

So in the orforglipron phase II trials in patients without diabetes, they were enrolled in a lifestyle component, but it did not specify frequency of visits or calorie targets or physical activity targets in the description. And we have 26 and 36-week endpoint data. The 26-week data, we've got 12.6% weight loss at 26 weeks.

And in the 36-week data, we got 14.7% data at 36 weeks, with 48% achieving greater than 15% weight loss. So this is reaching that number earlier than oral semaglutide. So it's at least equivalent. And we'll need the one-year-plus data to see what the long-term difference is between these two oral GLP-1 agonist therapies.

In type 2 diabetes, orforglipron-- and I'm going to be mispronouncing this word for two years at least-- orforglipron, this is a diabetes trial. Again, the lifestyle component was just healthy eating, not something aiming at weight loss. And we have 26-week data on this. And the starting BMI was 23. So there's a significant number of patients without-- subjects without obesity in this trial. Again, a low percentage of female subjects, only 39%.

And so we see 9.6% weight loss at 26 weeks, so you can say compared to 12.6 in the nondiabetic population. But again, the BMI range is different, and the percentage of women is different. And a unsatisfactory 2.9 inches loss of the waist circumference.

Moving on, the next step, the triple agonist-- so we have GLP-1, GIP, and now glucagon, one peptide stimulating all three receptors and creating new effects that were not present in the dual agonist. And these are affecting energy expenditure, definitely in the animal models, still being studied in the human models, humans.

And this is called retatrutide. So retatrutide phase II studies just came out in August of this year. And again-- I'm sorry, I went up instead of down-- retatrutide phase II trials in patients without diabetes, 24 and 48-week data. There is a 12-week titration to the full dose. So you can get there significantly faster than tirzepatide.

And from the lifestyle component, there were visits with RD, just saying following US guidelines on healthy diet and physical activity. There was no specific 500-calorie deficit involved. But the US guidelines are the 150 minutes a week target.

And this is interesting, as I've been prepping for this reveal through this talk, is this is a nondiabetes trial, but they achieved 48% female, 52% male in the people enrolling in the trial. And we see 24% weight loss, 63% achieving greater than 20% weight loss, so another 4% to 5% increase compared to the prior agent, the dual agonist.

Notable here, they do show the difference between men and women in the bottom here, with women achieving 28% and men achieving 21% weight loss. So that's also the big reveal of why the percent of subjects who are men and women can affect your average weight loss results in the trial and also the BMI range, BMI over 35 achieving 26%, BMI under 35 achieving 21%-- 22%. Why? If you have less fat to lose, you end up having no fat left, and you can't lose any more because you already lost 25% of your weight or 22% of your weight. So the heavier you are, the more chance you have of losing 25% plus of your weight.

And men have different body composition than women. So they may be losing the same percentage of their fat, but it shows up as a different percent of their weight. In terms of retatrutide in type 2 diabetes, again, still a short trial, 36 weeks, 17.2% weight loss. And they actually had more women in this trial.

So I want to speed up here for the last paper. But if you do line up everything on this chart, you do see phentermine, topiramate, and also liraglutide have this 10% weight loss range, semaglutide, oral/subcutaneous, and orforglipron, right now we're in the 15% weight loss range. CagriSema and retatrutide are better than that. But the data are in less than a year. So we don't know where they're going to end up.

And bariatric surgery, depending on the trial and the population, is in the 30% to 38% weight loss range. So we don't know if CagriSema or retatrutide is going to break into that matching sleeve gastrectomy data or not. And until it's a head-to-head trial, it really won't mean anything.

And lastly, antiobesity medication in addition to bariatric surgery-- this was earlier this year, all bariatric surgeries, so sleeve gastrectomy, gastric bypass, and lap band. And this was a retrospective study. And they looked at patients who after they had bariatric surgery and regained some weight were started on semaglutide 1 milligram or liraglutide 3 milligrams and followed them up for a year. And we see that semaglutide average weight loss was 12.9%. Liraglutide 3 milligrams was 8.77%.

And so these medicines definitely work to lose weight after you've had a bariatric surgery. This idea of already have a lot of GLP-1, so they won't do anything, that is a false premise and disproven. But when you break it down by which surgery they had, the gastric bypass patients actually had more like a 15% to 16% weight loss with semaglutide.

And people over 55 also had a higher amount of weight loss than people under 55. So you're seeing some differences there. And sleeve gastrectomy was 12%, 13%. And the lap band was weighing it down with a 9% weight loss. So that's the end of my content.