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MARY First of all, let's just start-- there was some good news this past year, with this publication in *The New England*
KORYTKOWSKI: *Journal of Medicine* showing that there have been significant decreases in the risk of myocardial infarction here, stroke, amputation, renal disease, and deaths from hyperglycemic crises in people with diabetes. And when you compare that to a population that does not have diabetes, it's been certainly more significant improvements.

However, if you look at the y-axis here, looking at the rate per 10,000 individuals, for people with diabetes, the risk of cardiovascular disease has decreased from about 150 for MIs down to about 75, where it's remained fairly constant at 8 to 10 per 10,000 people in the population without diabetes. So diabetes still remains a major risk factor for cardiovascular disease, and we're looking for ways to minimize the impact of diabetes on cardiovascular outcomes. Let's see.

The prevalence of diabetes, as you all know, is increasing along with the increasing prevalence of obesity. So this line here would be the rising prevalence of obesity, with which it's now estimated that 35% of the population in the United States is obese, meaning that they have a body mass index of 30 or above. There has been some good news lately that the prevalence of obesity is leveling off, but it's leveling off in a non-minority, relatively affluent population. It is not leveling off in minority populations and in less affluent populations. So they are continuing to take a hit from this.

But you can see here that the prevalence of diabetes has increased from 5% of the population all the way up to close to 10% of the population now, where this last data comes from, from 2005 to 2010. And then, this really just emphasizes the issue of age and race that I talked about earlier. So I just want to keep moving ahead.

So with this rising prevalence of diabetes, there's going to be a rising prevalence of cardiovascular disease in both morbidity and mortality. And we look at drugs for treating these things. We look at a lot of interventions for identifying markers. But when it really comes down to it, lifestyle intervention is really the backbone of any therapy we use to treat people with diabetes. Diet and exercise is listed as the number one therapeutic intervention, usually associated with metformin, unless there's contraindications.

And why is this? Well, the majority of non-surgical weight loss studies-- and so Look AHEAD intervened, because they looked at, the majority of non-surgical weight loss studies have been of short duration. The beneficial effects of weight loss in prior studies did not really focus on their impact in cardiovascular events. And if somebody does go for surgery, their success is predicated on their ability to follow a regimen of ongoing diet and exercise. There's nothing magical about surgery. It just allows for more rapid weight loss early. But if this person doesn't intervene, themselves, with diet and exercise, they're going to regain the weight.

So Look AHEAD came along with the primary objective here, was to examine the long-term effects of an intensive lifestyle intervention program, compared with a program of diabetes support and education in overweight subjects with type 2 diabetes. The goal here in the intensive lifestyle intervention was to achieve and maintain a weight loss of 10% with the combination of decreases in caloric intake and increases in physical activity.

The primary outcome, the primary outcome-- and this is where these studies sort of get themselves in trouble-- was this composite of cardiovascular death with fatal MI and stroke, non-fatal MI and stroke, or angina requiring hospitalization, which was added at two years, when the number of events in these first two categories wasn't achieving what was expected. Fortunately, there were multiple other outcomes that were investigated. This included risk factors, glycemic control and complications, overall health, bone health, quality of life, psychological outcomes, as well as cost effectiveness studies.

The types of subjects recruited for this study, there were over 2,500 subjects in each arm that actually maintained compliance with the study for the duration of the study. These are patients that you see in your office. The average age was 59, about 60% female. The racial composition, there were 16% African-American. So minorities were well-represented. The BMI was obese, with a BMI of 36.

They were under fairly good control when they came in, with A1Cs at study entry of 7.3% to 7.2%-- so maybe a little different from what we see in our practices, meaning that this was a motivated population for this type of study. About 16% of patients were already using insulin. And about another 13% already had a history of underlying cardiovascular disease. Pittsburgh was one of the sites. Pittsburgh was one of the more robust sites for the Look AHEAD study, with close to 500 participants, who are continuing to be followed.

So, now, what are the components? We talk about lifestyle intervention all the time. But just what is lifestyle intervention, and how do we go about doing that? If it works so well, why aren't we more effective at it? Well, this is what it was in the Look AHEAD study. People who weighed less than 250 pounds were instructed to restrict their calories to 1,200 to 1,500 calories per day. If they weighed more than 250 pounds, they were restricted to 1,500 to 1800 calories per day.

And the way they did this is with the use of meal replacements for two meals a day for the initial part, for months one through six, with one snack bar, or food bar, so that was a contained caloric intake. They were allowed to have a sensible dinner. And of course, that can have a lot of different definitions for people. And the intake of fresh fruits and vegetables was encouraged. For the second half of the year, they were continued with one meal replacement shake for one meal each day, two sensible meals, and encouraged intake of fruits and vegetables.

Physical activity-- a little different from the Diabetes Prevention Program that recommended a minimum of 150 minutes of exercise per week. They recommended 175 minutes per week of moderate intensity exercise, which could include walking. And walking is what most people did.

There was group instructions on the use of daily activities to increase energy expenditure, such as taking stairs instead of elevators, such as parking far away from the grocery store rather than close to the grocery store. Even fidgeting is associated with more-- people who fidget burn more calories than people who don't fidget. So I'll understand if you all start fidgeting right now. And all participants were given pedometers, and they were given a goal of 10,000 steps to walk each day.

In this group, they had group and individual sessions with nutritionists, exercise specialists, and behavior therapists-- certainly well beyond what most of us have in our practices. Each participant had a lifestyle coordinator for the duration of the study. And there were periodic refresher courses and national campaigns to promote compliance with the study.

Those in diabetes support and education got even a little bit more than what we usually do in clinical practice. They received three classes per year that provided some social support and reviewed dietary approaches to weight loss, exercise approaches to weight loss, and issues related to living with diabetes in general, addressing some of the stress issues that are involved. They had an annual study visit and there were periodic phone calls. This was not a pharmacologic study, so people were just taking whatever they were taking anyway. That was independent of the study.

The one-year results of this trial were actually very encouraging, with those in the intensive lifestyle intervention losing close to 9% of their body weight at one year and having about a three-fold improvement in their fitness level than those in the diabetes support and education group. However, by four years, we were already seeing a falloff. But many of the weight loss trials have not really gone much beyond six months to a year.

So this initial weight loss at one year was associated with a regain of weight over time. But they did not go back to baseline. They remained well below baseline. The fitness level that was so good at one year also declined over the next year, but still remained significantly better than in those in the diabetes support and education group.

One myth that Look AHEAD addressed was one of the myths of, when we tell our patients to lose weight, we tell them to take it slow and just lose weight gradually over time. Well, here there were different patterns of weight loss. And they compared to people who lost the most weight at one year, moderate amounts of weight loss, versus a little bit of weight loss. And it was interesting that those who lost the most weight, even though they also regained weight, they were the ones who were more likely to keep the weight off at four years. So the myth that large, rapid weight loss early is associated with poor long-term weight loss can be demythified, I guess.

Another change that was found-- this is results at four years. They looked at the percentage of patients who had changes in their mobility and disability scores. And just to walk you through this, the orange bars here reflect patients who have severe mobility-related disability. And the blue bars here at the bottom-- if I can get the cursor there-- represent patients who have good mobility. So they're really completely functional.

And as you can see, the percentage of patients who had good mobility remained fairly constant in the diabetes support and education group, but more developed significant disability. While in the intensive lifestyle intervention group, more of them developed good mobility. And fewer patients went on to develop severe mobility-related disability over time.

So the Look AHEAD intensive lifestyle intervention ended in September of 2012. And this was because of the study futility, meaning they were not really seeing major differences in the two groups for cardiovascular outcomes, which was the primary outcome for the study. So it was thought there was really no point in carrying this out any longer, although participants continue to be followed longitudinally to see if there are long-term benefits of this assignment to an intensive lifestyle intervention. So these results will be coming out over time.

The results were published in *The New England Journal* exactly a year ago. And this is really the composite outcome. So it almost doesn't matter who's what color. Because you can see there's two groups here, there's no difference in the primary composite outcome between those receiving diabetes support and education and those receiving the intervention. The rate of cardiovascular events was similar.

When they did subgroup analysis, similar to some of the more recent cardiovascular trials that I will review very briefly, there was possibly a trend towards a benefit in patients who had no evidence of cardiovascular disease at baseline. But this did not reach statistical significance, as the line is crossing one here.

So the question is, is this just a time to throw up our hands again and say, is this another negative study from the NIH looking at cardiovascular disease in people with diabetes. And should we have just left well enough alone and not spent all this money, because-- just another study. We've had plenty now. We've had the ADVANCE trial, the ACCORD trial, the Veterans Affairs Diabetes Trial, where the differences in cardiovascular events was really similar between the intensively treated and the control groups.

And in fact, in the ACCORD trial, that was even stopped earlier because of a non-significant trend toward more cardiovascular events in the intensively treated group. Although, each of these studies were pharmacologic trials. That was really trying to drive the A1C to a certain level, where Look AHEAD was not really trying to drive the A1C. The focus here was more on weight loss.

Fortunately, as I mentioned earlier, the Look AHEAD trial had other outcomes that were investigated in addition to cardiovascular outcomes. And I'm going to go through some of what I have listed here in the time that remains.

So one thing that happened is, these patients were under relatively good control to begin with, and they went under better control with a more significant reduction in those in the intensive lifestyle arm, again, with a trend upward, which has been seen in many long-term trials, pharmacologic trials of people with type 2 diabetes, but still remaining significantly different from the diabetes support and education group, where it remained fairly consistent. And there was a little uptick in their A1C at the study end, with about a difference of about 0.4% percent at the study end. But there was more remission of type 2 diabetes in those in the intensive lifestyle intervention group.

There was also a 31% reduction in the risk of advanced kidney disease, defined using KDIGO criteria, and a 14% reduction in the risk of diabetic retinopathy in those in the intensive lifestyle group.

Changes in weight-- again, this is a long term weight loss study, with patients being followed for an average of 10 years. And although there is a gradual downward trend in weight in the diabetes support and education group and a gradual regain of weight in the intensive lifestyle intervention group, those in the intensive lifestyle intervention still have about a 5-kilogram difference from the diabetes support and education group at 10 years. So this is long-term weight loss, which can be beneficial. Waist circumference, which has also been listed as a marker of cardiovascular risk-- initial loss with the weight, gradual regain, but still significantly lower in the intensive group.

A sub-study of the Look AHEAD trial was the Sleep AHEAD trial, in which a subset of close to 300 patients from several, but not all, of the centers were studied for the presence of sleep apnea. The presence of sleep apnea was actually very high in this population.

And they were randomized within this group. They were already randomized. But they wanted to see what their outcomes were for sleep apnea according to assignment to diabetes support in education or intensive lifestyle. And the Apnea-Hypopnea Index was actually at a moderately high to severe level, with anything greater than 5 is mild, anything greater than 15 is moderate. And the average here was 23 episodes per hour for this group of patients.

What happened is-- the dark bars are the intensive lifestyle group. The white bars are the diabetes support and education. So more of these patients with the diabetes support group remained the same. More of those in the intensive lifestyle intervention improved. And there was probably a similar percentage worsening, which was small in both groups.

The changes in the Apnea-Hypopnea Index did change according to the amount of weight loss achieved with those-- really not much of a difference occurring with those losing less than 10 kilograms. But the significant improvements were in those who lost 10 kilograms of body weight or more.

Another outcome that was investigated was the presence of urinary incontinence in women. This was a group with an average age of 59. And it was an obese group. There's a higher prevalence of urinary incontinence in this group. They were matched at baseline for the prevalence of symptoms. At one year, it was significantly lower in the intensive group. And the incidence at one year was lower, but the resolution was a little higher. But the only one that met significance was the one-year incidence.

The other thing that was investigated was the prevalence of depression. And they looked at this in a couple of different ways. They looked at changes in the Becton Dickinson inventory scores for those with and without depression, according to whether they were in the diabetes support and education group here or the intensive lifestyle intervention group here. And it looks like those in the intensive lifestyle intervention had greater-- if they had depression at baseline, they had greater improvements in their scores than those without depression at baseline that exceeded the improvements seen in the diabetes support and education group.

They also looked to see if depression, if the presence of depression at baseline, affected the ability of these patients to lose weight. And as you can see, those with and without depression lost similar amounts of weight with the intensive lifestyle intervention, and similar in the diabetes support and education group, where there was a much lower weight loss.

What about the adverse events with weight loss? The incidence of severe hypoglycemia did not differ between groups. The incidence of fractures that have been observed in some trials, primarily with some of the medications, did not differ. The risk of amputations, congestive heart failure, or gallstones, which have been reported in some weight loss studies, did not differ between the groups. And these were reported as the number of events per 100 person years.

So in conclusion, this intensive lifestyle intervention that focused on weight loss did not reduce the rate of cardiovascular events in these overweight and obese adults who were at high risk for cardiovascular disease, but it did improve glycemic control. It did improve sleep apnea indices. It did improve quality of life, although I took the slide out. It did reduce the incidence and prevalence of depression. It did allow for remission of type 2 diabetes in a higher percentage of individuals. And it did reduce the risk of urinary incontinence among overweight and obese women.

So what can the take-home messages be for you from this study? So what can we as health care professionals do about this obesity epidemic that is causing an epidemic in diabetes and other metabolic disorders? Well, one thing we can do is we can actually tell our patients that they are overweight or obese. We can actually tell our non-obese patients how to stay that way. And I think we don't talk about that enough.

We think, well, we have to wait till people are overweight or obese to start saying anything to them. But I think we want to tell our patients who are lean to stay lean and not let themselves gain weight, and give them the tools for how to prevent that. And we can learn more about how to prescribe dietary interventions and exercise, which I think is very important.

So what can we tell our patients? Well, we can give them caloric goals. So, again, we can use what look ahead used-- 1,200 to 1,500 calories per day for those weighing less than 250 pounds, 1,500 to 1,800 calories for those weighing more than 250 pounds. An alternative is to recommend 10 calories per pound per day plus or minus 20%, which allows for the individual variability there is in metabolic rates. Like, some people find weight loss easier than others, which is known. Men find weight loss easier than women, which is known.

And recommending an increase in physical activity-- again, it doesn't have to be jogging. It doesn't have to be lap swimming. It can be going out for a walk. And there are some patients who say that they're afraid to go out for a walk where they live. They just don't feel comfortable, or it gets dark. They can walk in front of their television set. They can put on their favorite program, and they can walk in place for 15 minutes at a time, twice a day. They don't even have to go outside.

They can exercise in their own homes. And I think we have to tell them that, just because they're not going outside, doesn't mean they can't be active. 30 minutes a day, five days a week is the minimum. More is better.

One study that you'll probably hear about a little bit tomorrow from Dr. Conroy-- but this was actually a diabetes prevention program that was performed in Finland that was very similar to the Diabetes Prevention Trial done here in the United States. But they looked at five measures of success. It was patients who lost 5% of their body weight during the study, lowered their fat intake, lowered their intake of saturated fat, increased fiber intake, and they actually exercised for four hours per week.

And they looked to see who achieved these five measures and who didn't. And they actually looked at it both in their control group as well as their intensive lifestyle intervention group. If they achieved none of these five indicators-- actually, the intervention group actually had a little bit of a higher incidence of diabetes than those in the control group. But after this, whether or not they were in the control group or the intervention group, there was a significant reduction in the incidence of diabetes-- which was the primary outcome here-- where it got close to zero if they were compliant with all five measures.

So, just like to summarize with this quote that "an ailment treatable by diet alone should not be treated otherwise." I'm not saying we shouldn't use pharmacologic therapy for our patients with diabetes, but we should definitely be emphasizing the therapeutic lifestyle intervention as well. I would suggest that we use police tape around some of the fast food restaurants and not just murder and accident scenes. Because it is scary, what it's doing to us in the United States as well as around the world. So I thank you for your attention.