



National Institute of  
Diabetes and Digestive  
and Kidney Diseases

# Exploring the new weight loss medications Are they the right fit?

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National Institute of  
Diabetes and Digestive  
and Kidney Diseases

# OUTLINE



How do we assess weight? Why is it important?



Obesity is NOT a lack of will power



Is there benefit to losing weight?



The story of our new weight loss medications

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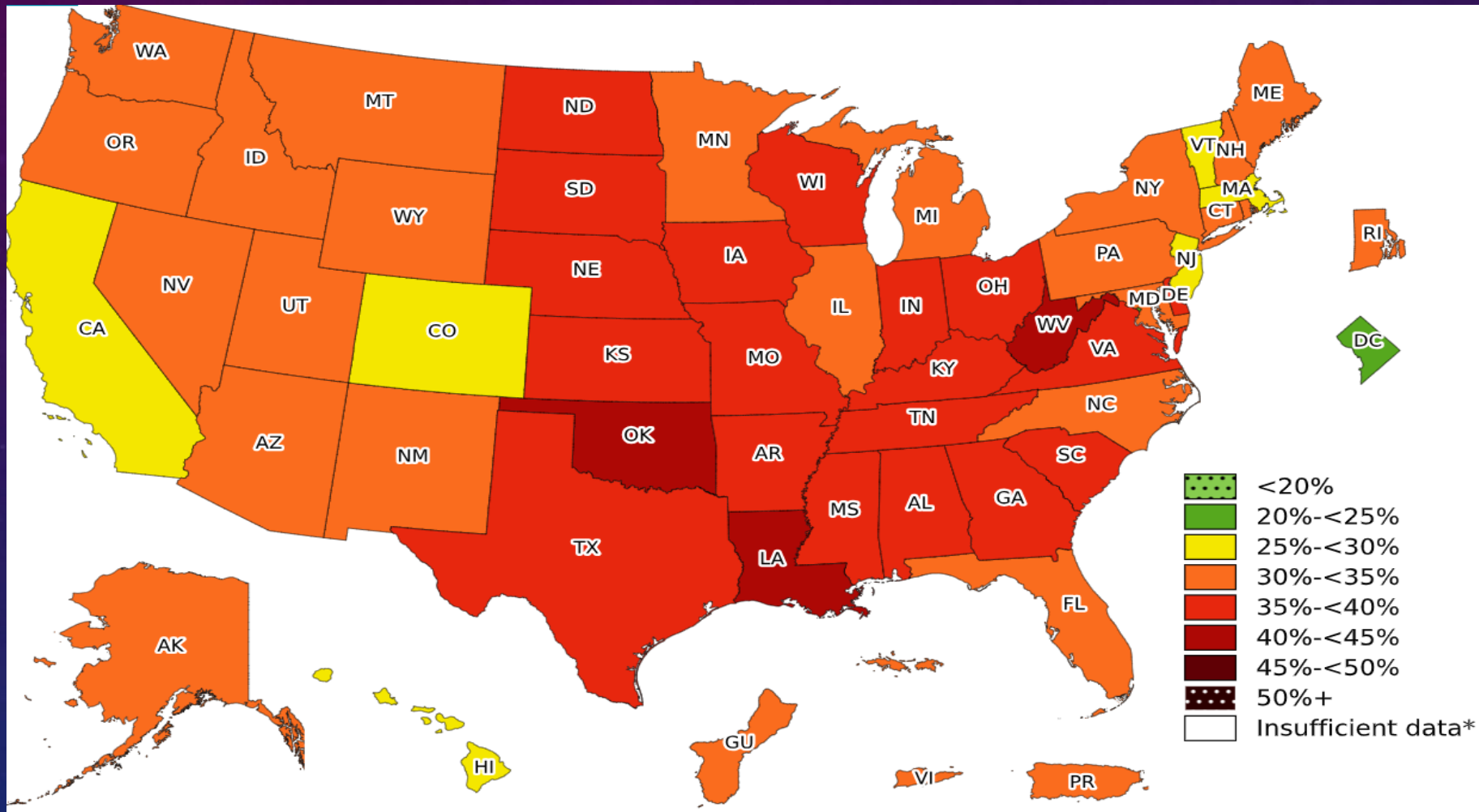


Is there benefit to losing weight?



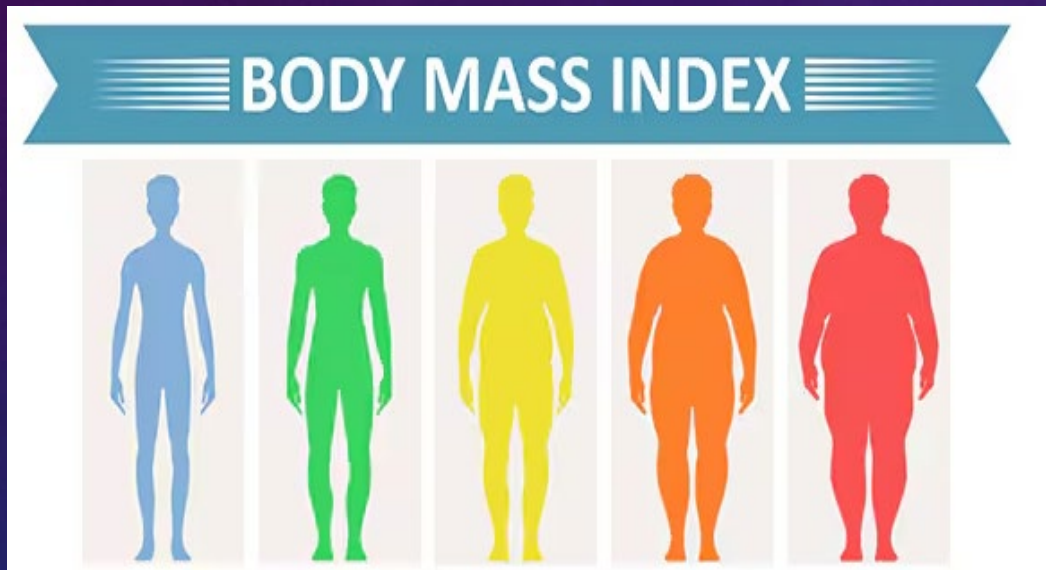
The story of our new weight loss medications

# OBESITY (BMI $\geq$ 30 KG/M<sup>2</sup>) BY STATE



From CDC

# WHAT IS BODY MASS INDEX?



- Your weight divided by your height
- Estimate of amount of body fat
- Helps clinicians understand possible future health concerns

# YOU CAN DIRECTLY MEASURE BODY FAT BY DEXA SCAN (DUAL-ENERGY X-RAY ABSORPTIOMETRY)

DEXA scan



Body fat by Dexa



# YOU CAN MEASURE BODY FAT BY BIOELECTRICAL IMPEDANCE ANALYSIS (BIA)

BIA device (example)



Body fat by BIA

- Small electrical current
- Electrical current flows at different rates thru body depending on amount of water
- Adipose (fat) tissue conducts less (slower) than other tissues

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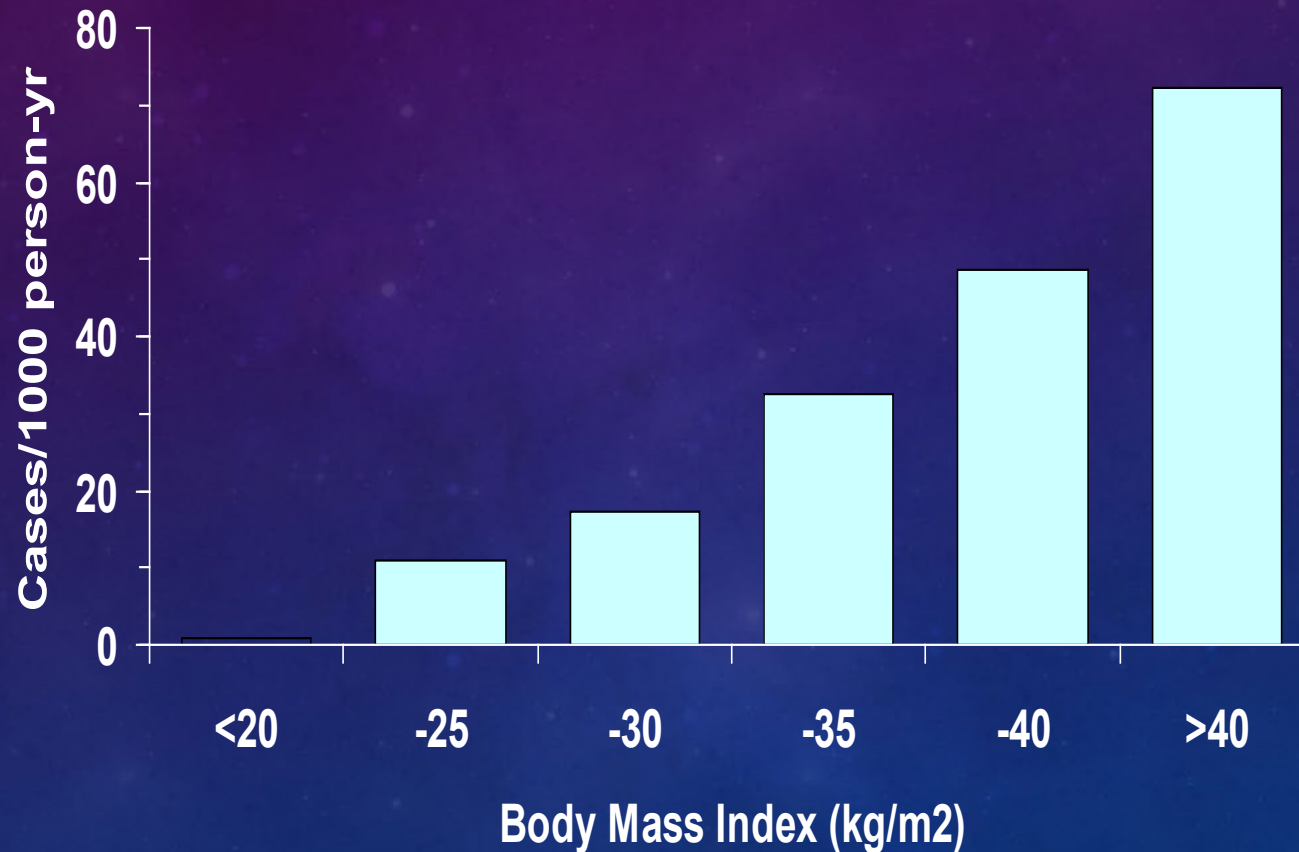
Is there benefit to losing weight?



How did we get to these new medications and who should take them?

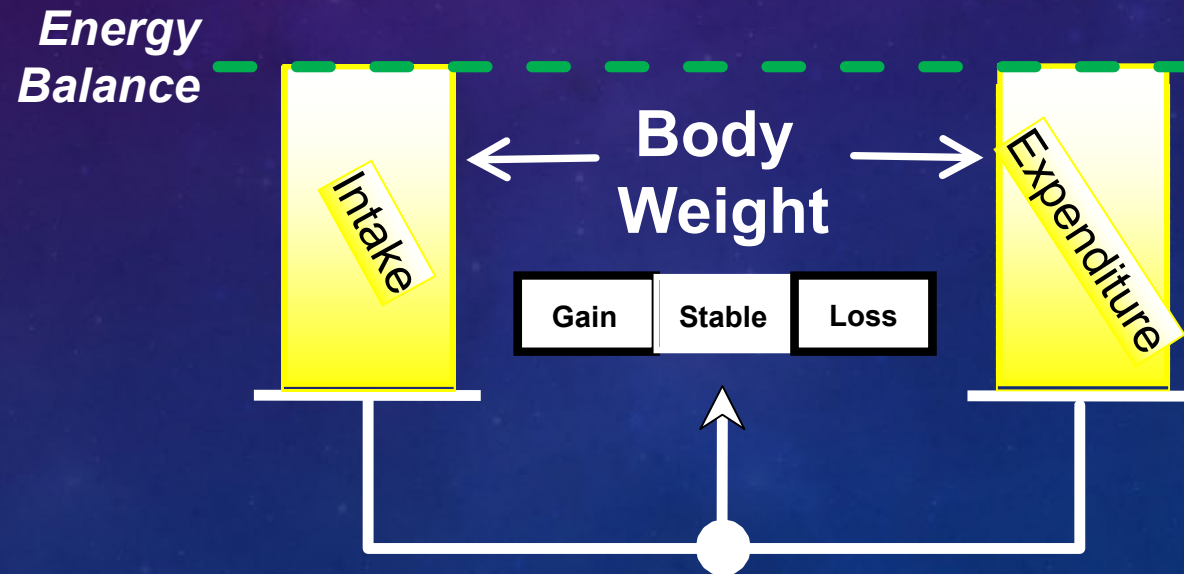
# Body mass index is like a vital sign

## Provides information about disease risk



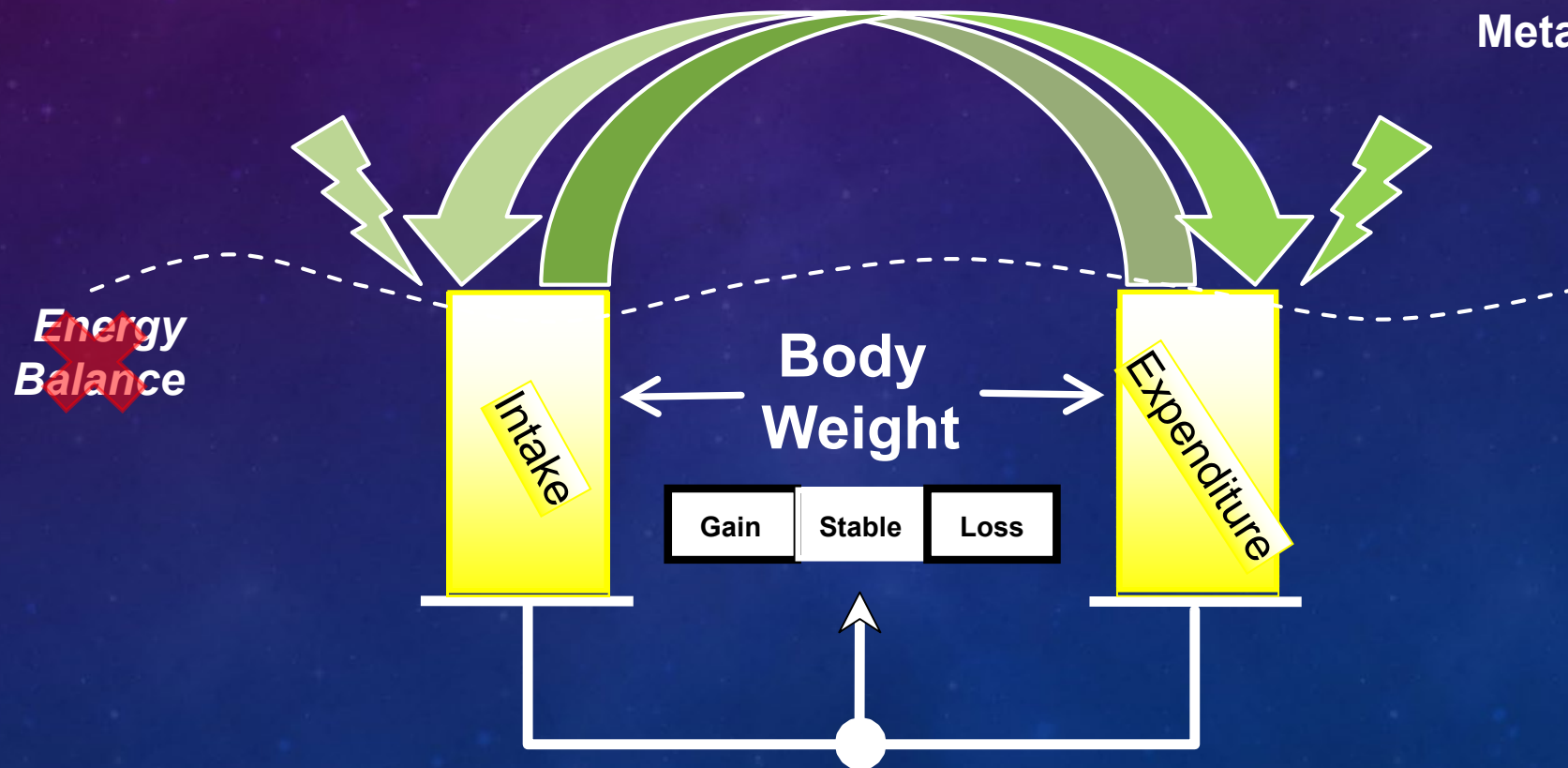
# BODY WEIGHT IS GOVERNED BY STRAIGHT FORWARD IDEA OF ENERGY BALANCE

Calories in=calories out



# MULTIPLE FACTORS AFFECT ENERGY BALANCE

Genetic  
Environmental  
Lifestyle  
Socioeconomic  
Behavioral  
Hormones  
Metabolic



# OBESITY IS A COMPLEX PROBLEM WITH OVERLAPPING CAUSES

- Genetic
  - 45-70% of predisposition to obesity is heritable
  - 1200 genes linked to obesity
- Environmental
  - Neighborhood
  - Psychological stress
  - Gut microbiome
  - In utero
- Sedentary Lifestyle
  - Cars, TV, internet
- Socio economic status
  - Food insecurity
  - Unpredictability
- Behavioral
  - Eating
  - Sleep patterns
- Hormones
  - Secreted from adipose (fat) tissue
  - Secreted from the gut
- Metabolic
  - How body burns calories in response to diet and overeating
  - How body burns calories in response to weight loss or gain

# RECOGNIZING WEIGHT STIGMA

## Definition and consequences

Social devaluation due to excess weight

Results in misconceptions and biases about underlying causes

Affect job and educational prospects

Impairs empathy of healthcare professionals

Impairs effectiveness of interventions

Has health effects

## Addressing

- Make physical environment is comfortable
- Be mindful of language
- Adopt a non-judgmental framework for counseling
  - Ask
  - Assess
  - Advise
  - Agree
  - Assist

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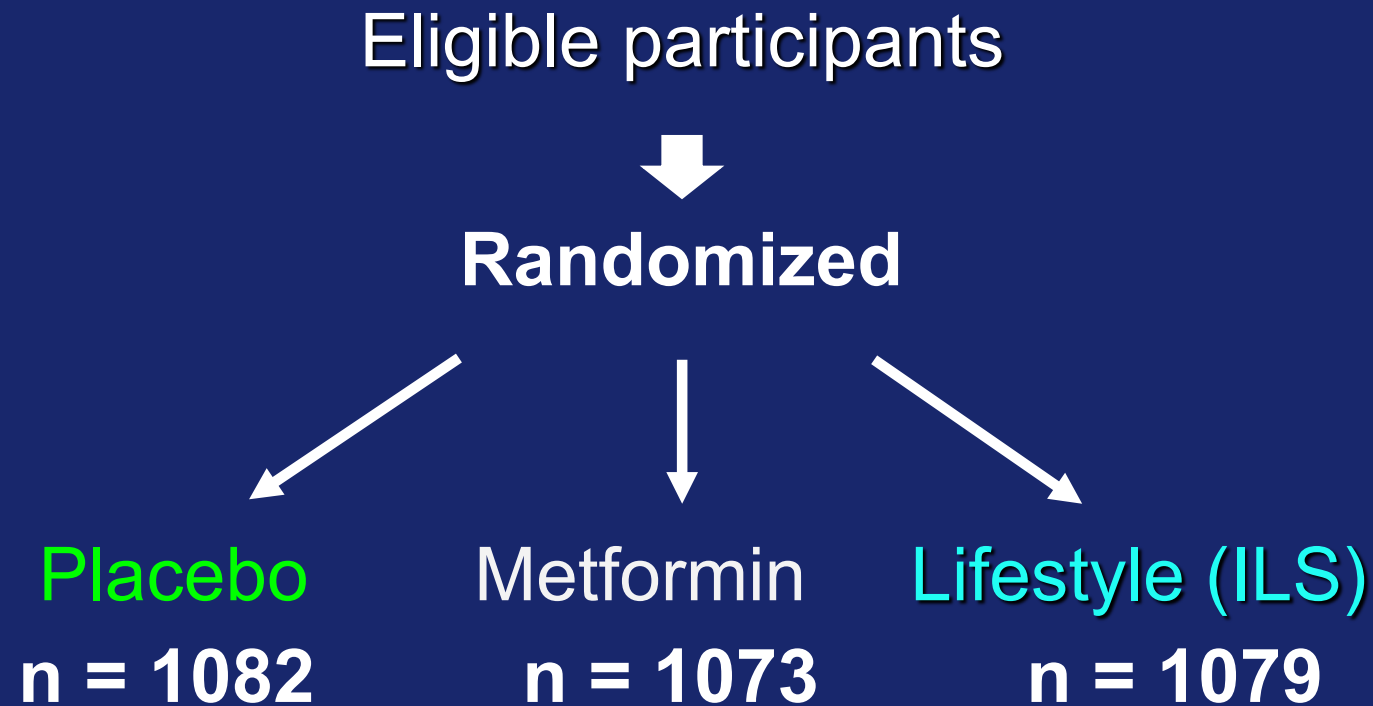


The story of our new weight loss medications

# HEALTH BENEFITS OF WEIGHT LOSS

- Weight loss goals may be unrealistic
- Start with idea that 5% weight loss can produce health benefits

# DIABETES PREVENTION PROGRAM

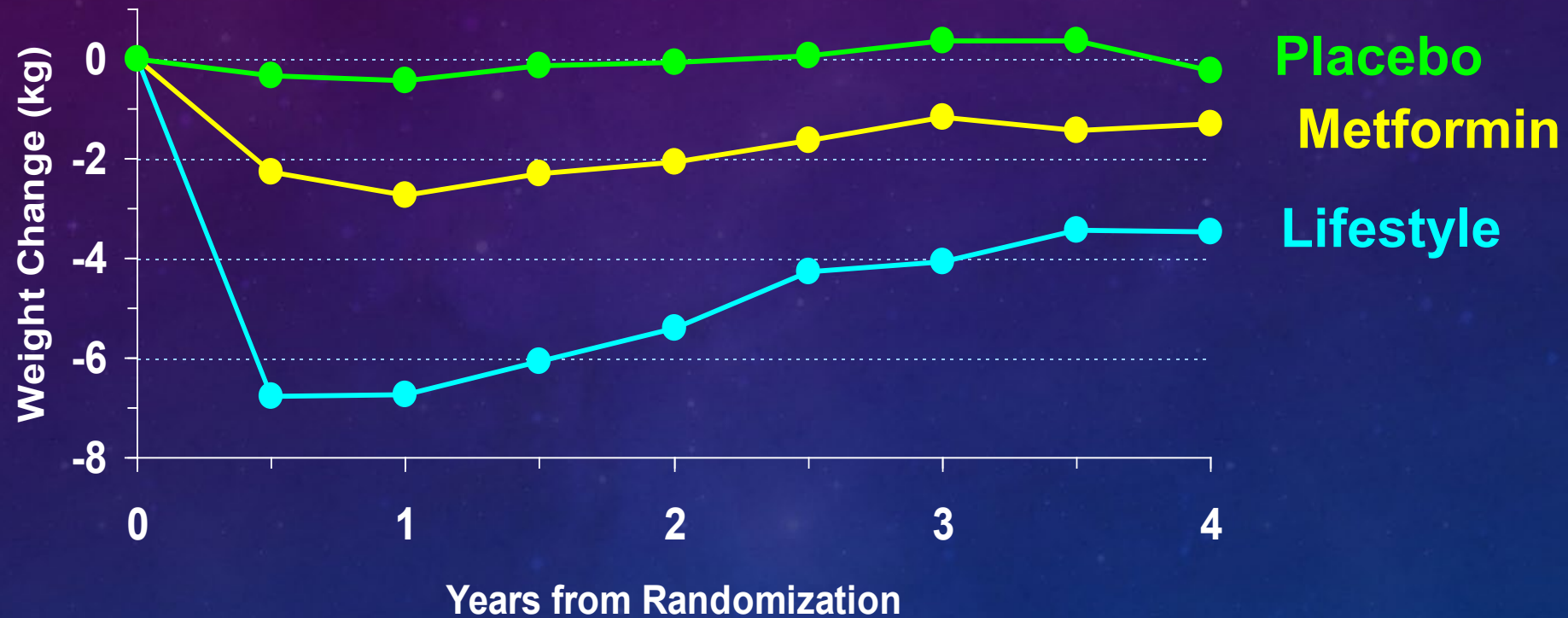


# LIFESTYLE INTERVENTION

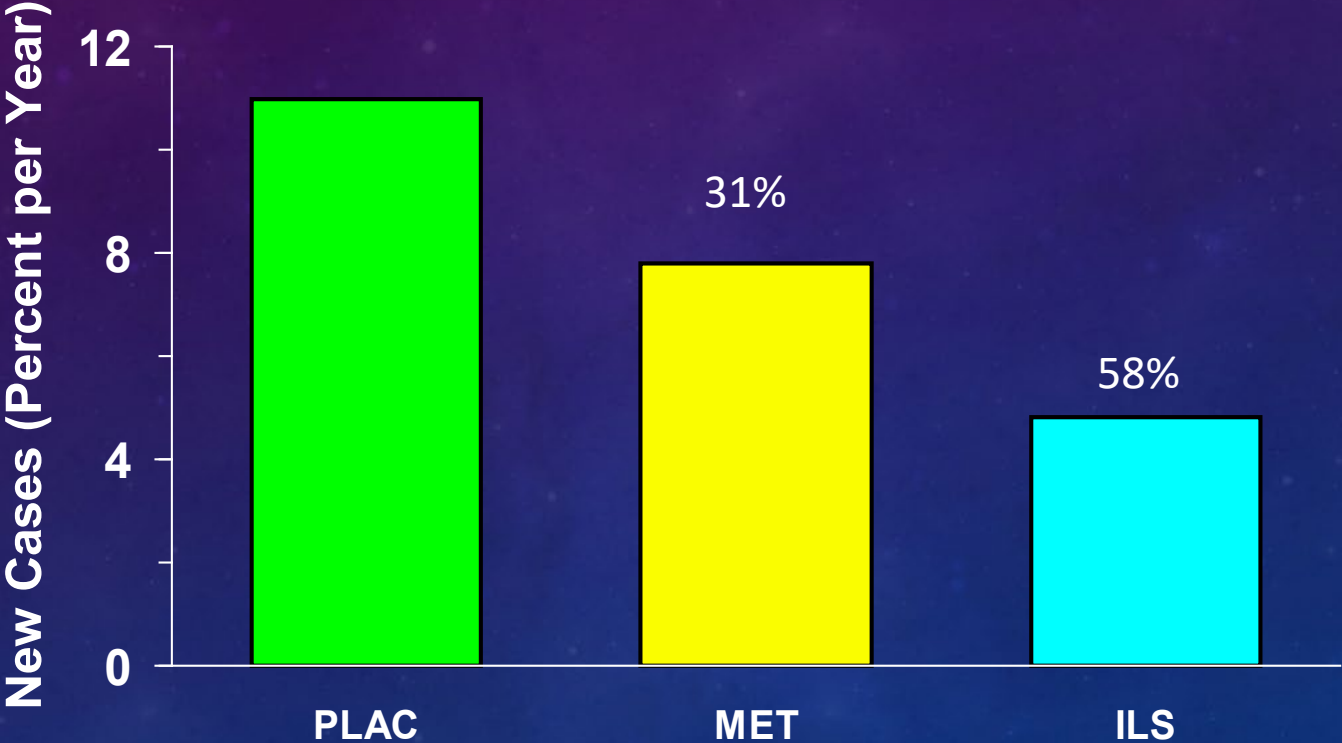
An intensive program with the following specific goals:

- $\geq 7\%$  loss of body weight and maintenance of weight loss
- $\geq 150$  minutes per week of physical activity

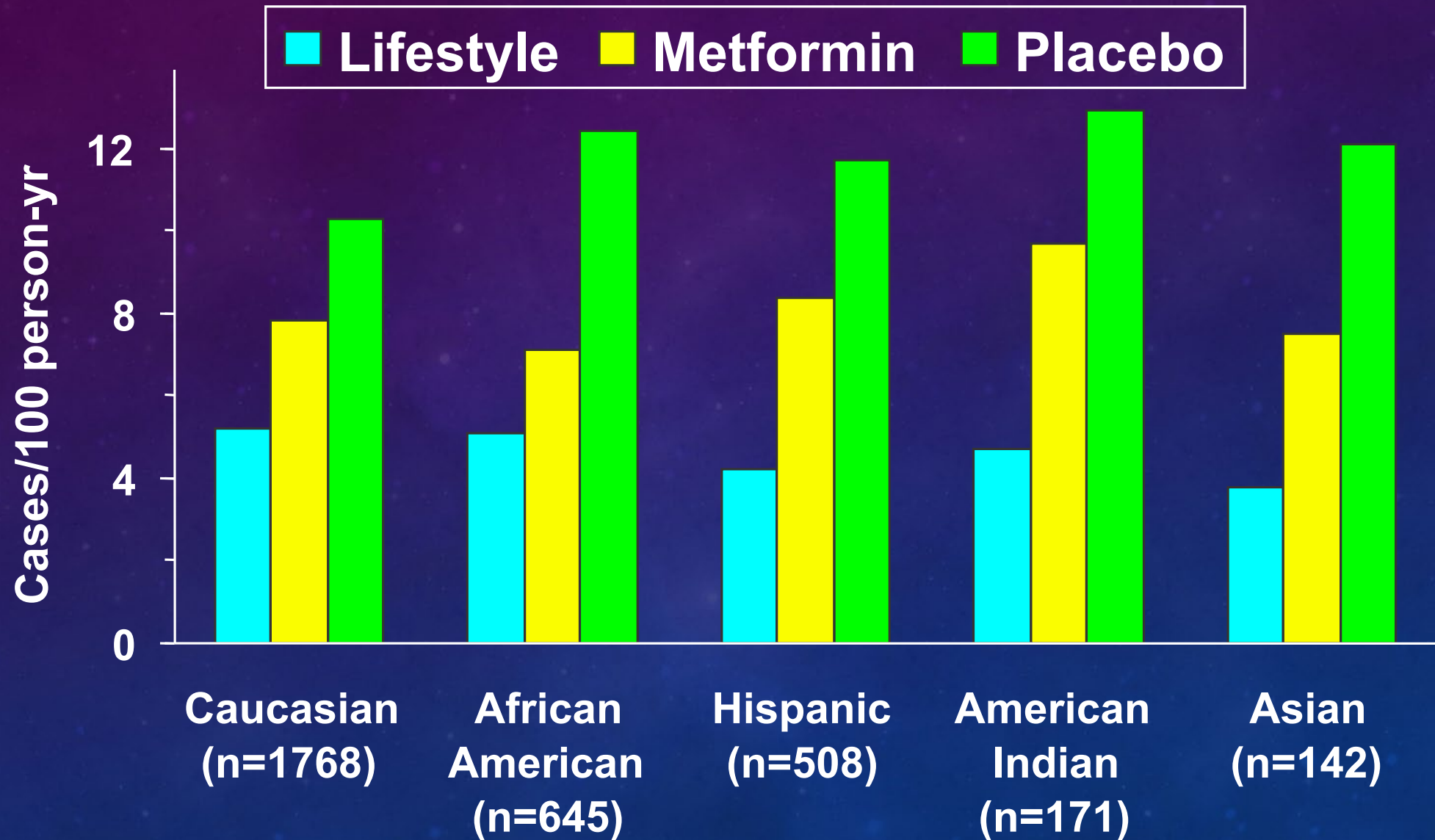
# MEAN WEIGHT CHANGE IN THE DPP



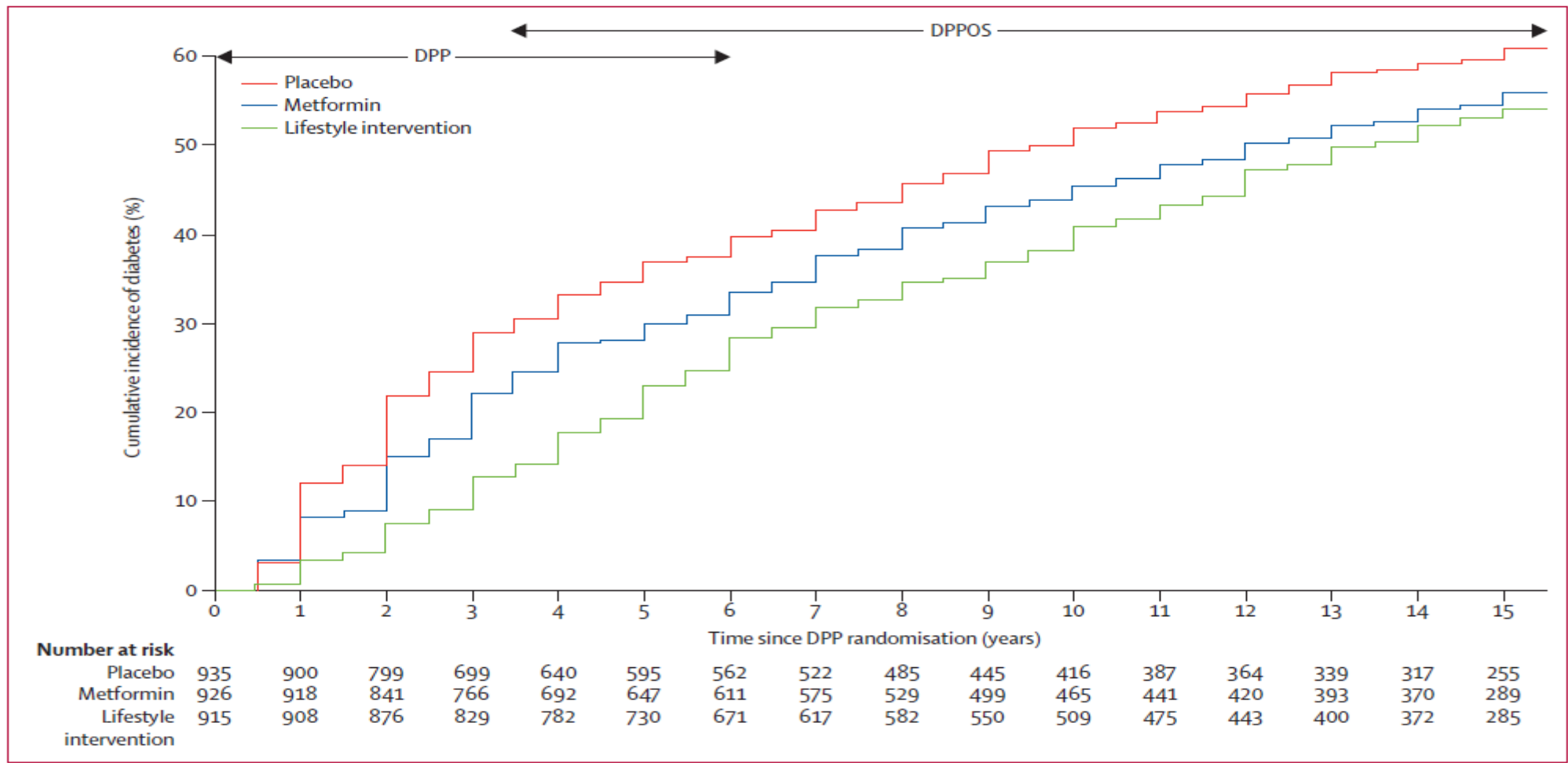
# METFORMIN AND LIFESTYLE REDUCED INCIDENCE OF DIABETES



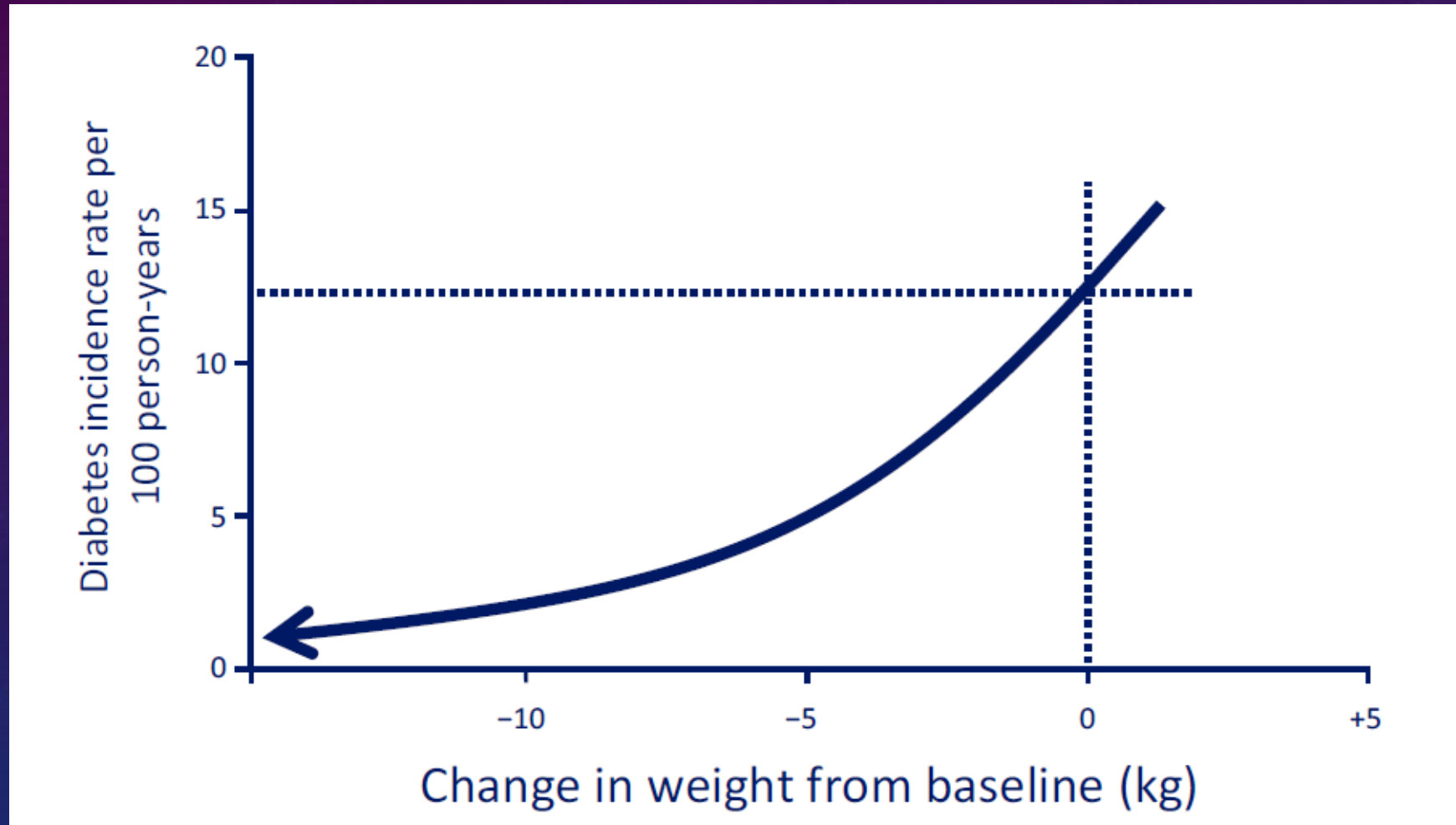
# DIABETES INCIDENCE RATES BY ETHNICITY



# DELAY IN DEVELOPMENT OF DIABETES EXTENDED TO 15 YEARS



# EVERY 1 KG (2.2 POUNDS OF WEIGHT LOSS) REDUCED DIABETES RISK BY 16%



# ACTION FOR HEALTH IN DIABETES (LOOK AHEAD)

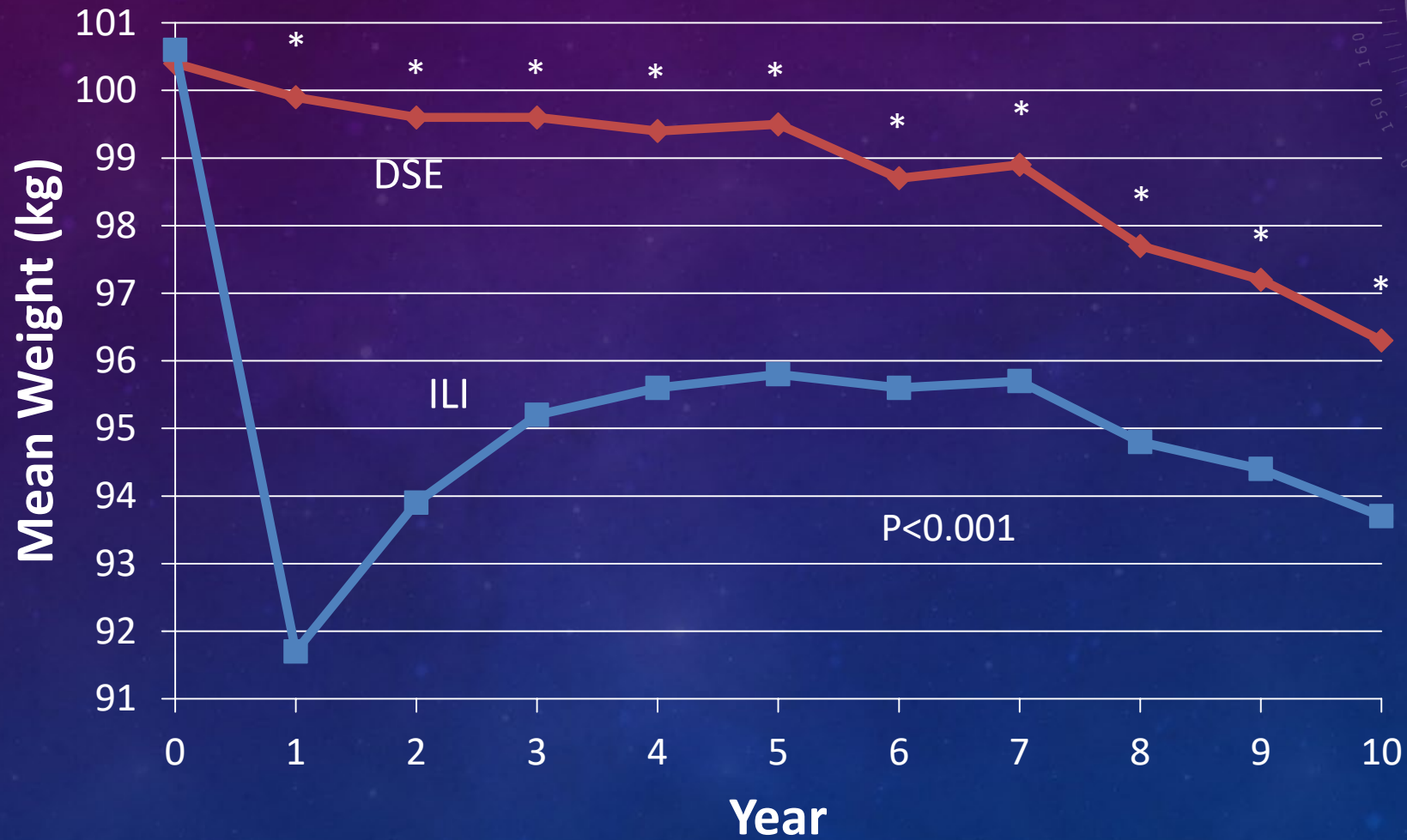
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

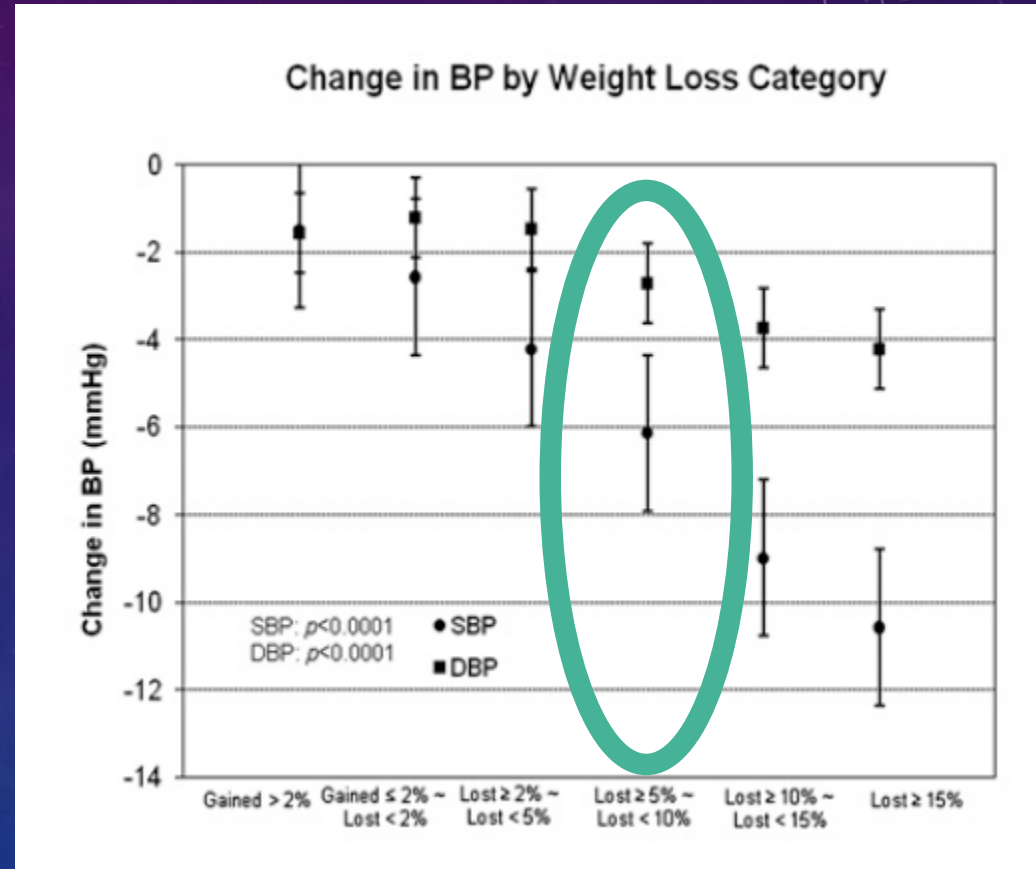
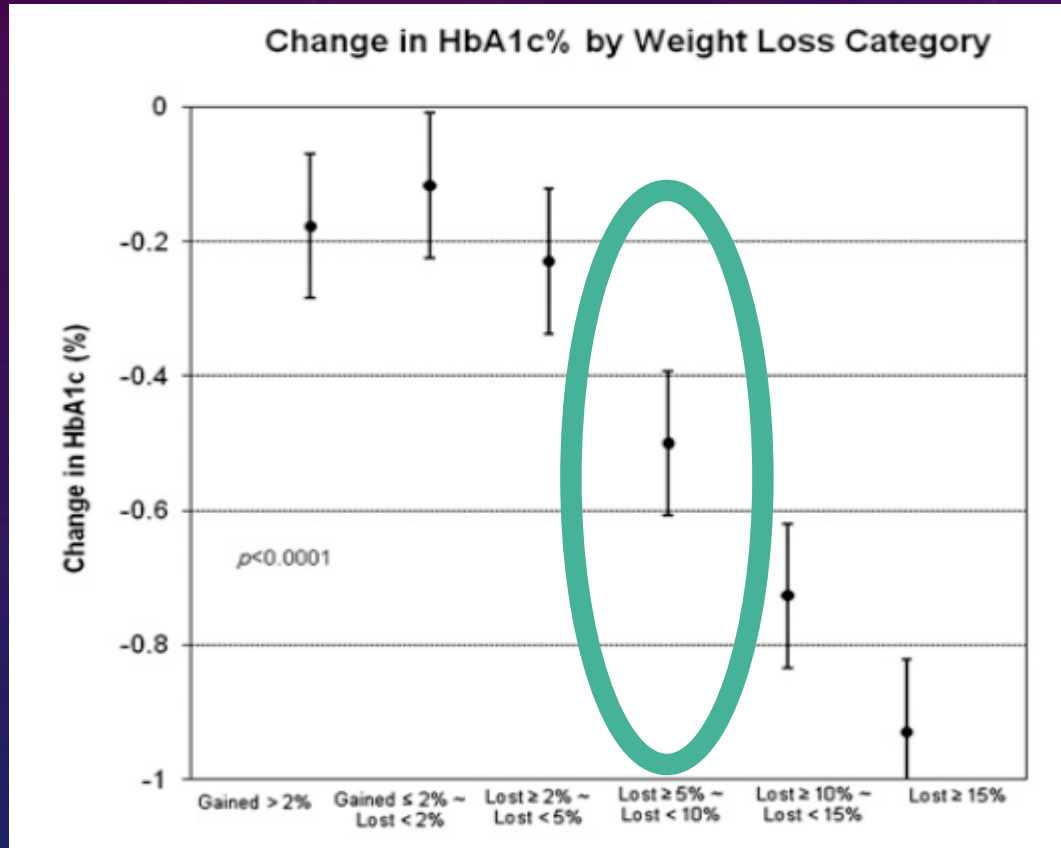
The Look AHEAD Research Group\*

# WEIGHT CHANGE

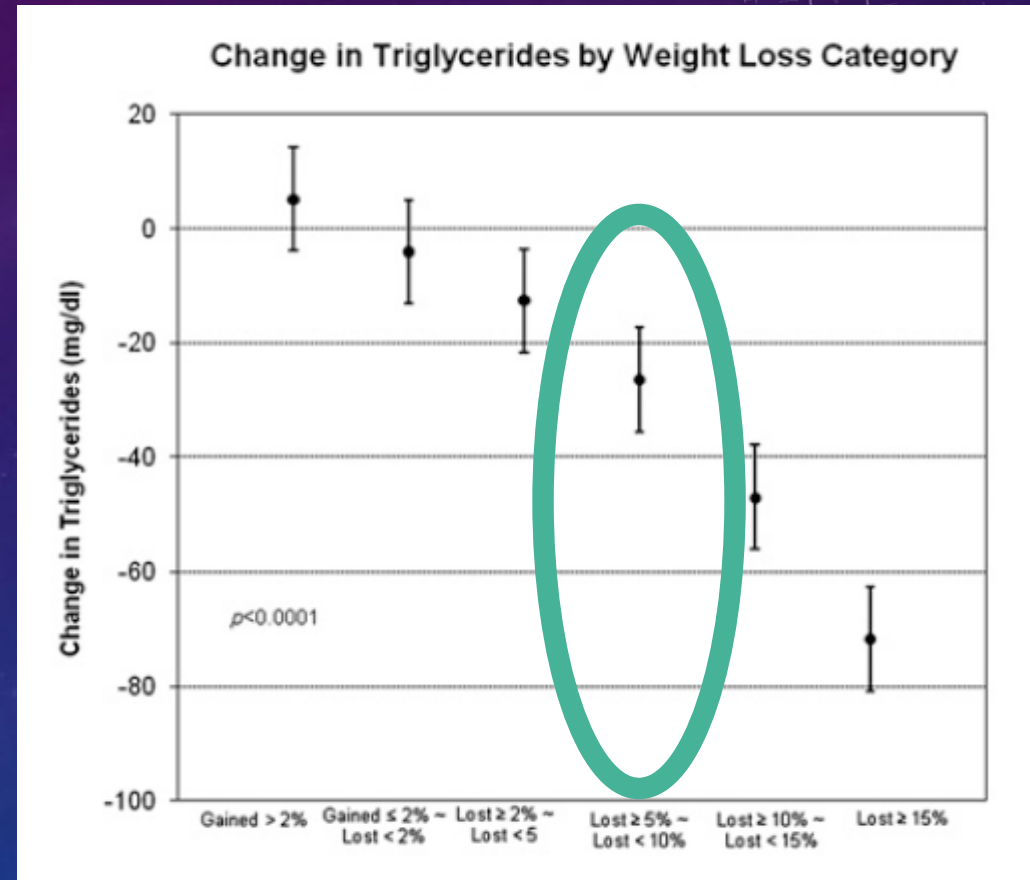
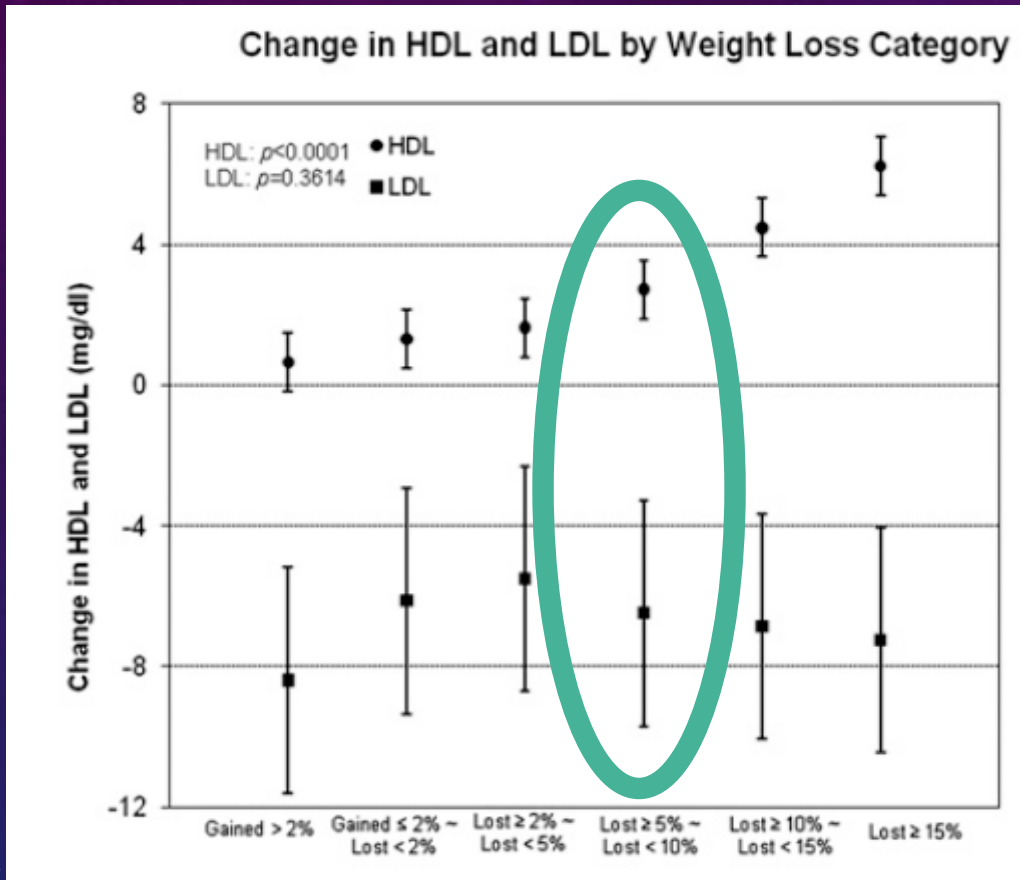


Look AHEAD Research Group, *NEJM* 2013

# OVER 5% WEIGHT LOSS IMPROVES BLOOD SUGARS AND BLOOD PRESSURE



# 5% WEIGHT LOSS IMPROVES CHOLESTEROL AND TRIGLYCERIDES



# WEIGHT LOSS IMPROVES FUNCTION

- Symptoms of knee osteoarthritis improve
- Distance walking improves
- Decline in mobility decreases
- Back pain improves (less evidence)

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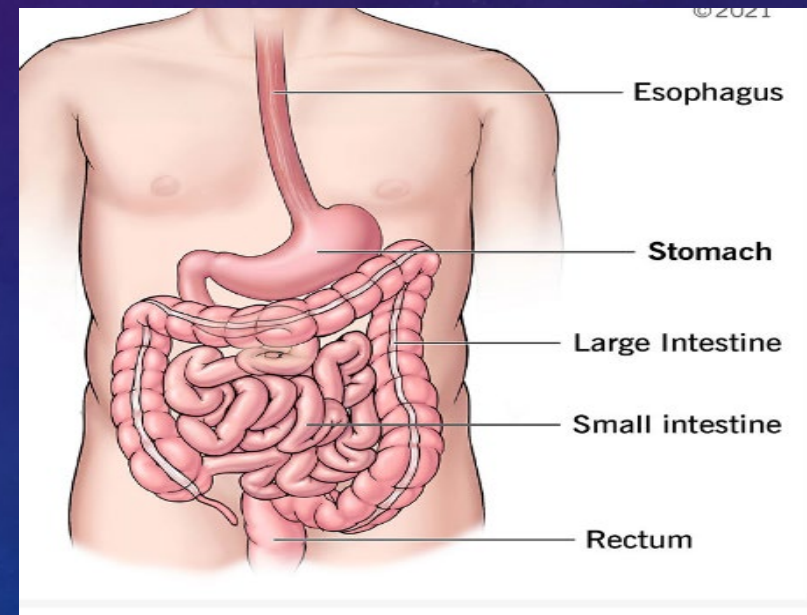
The story of our new weight loss medications

# THE STORY

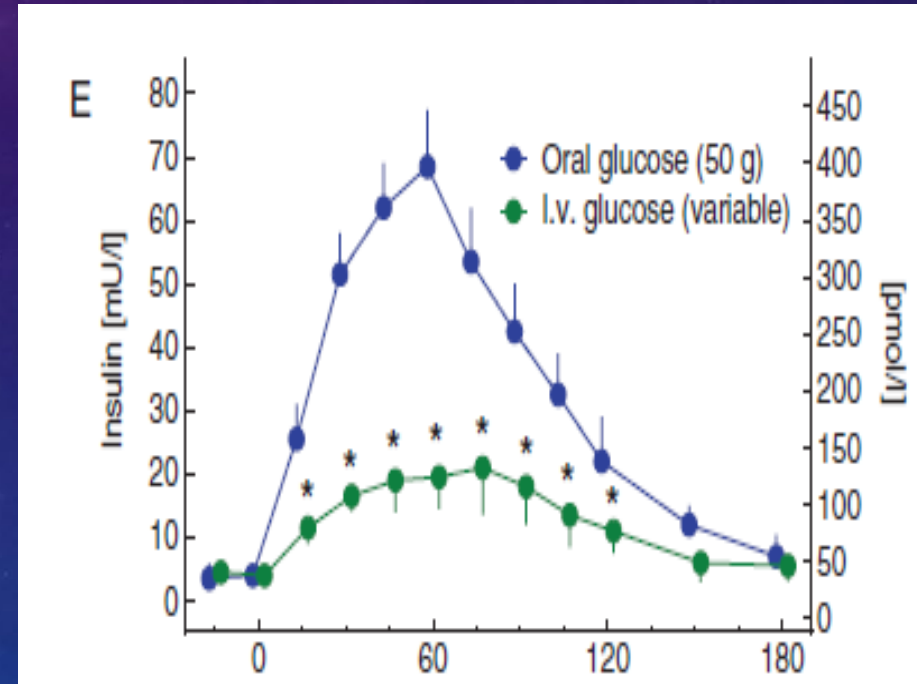
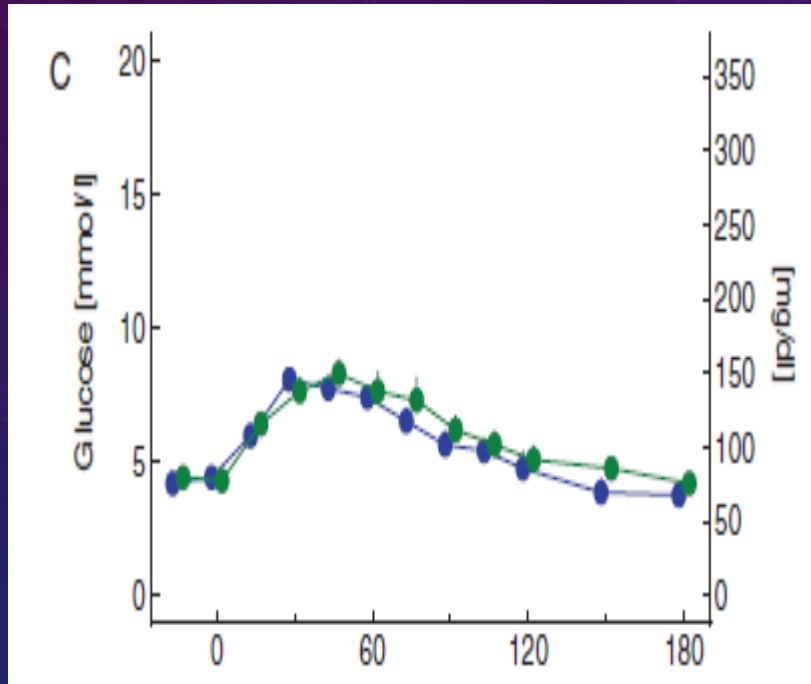
## The Gila Monster



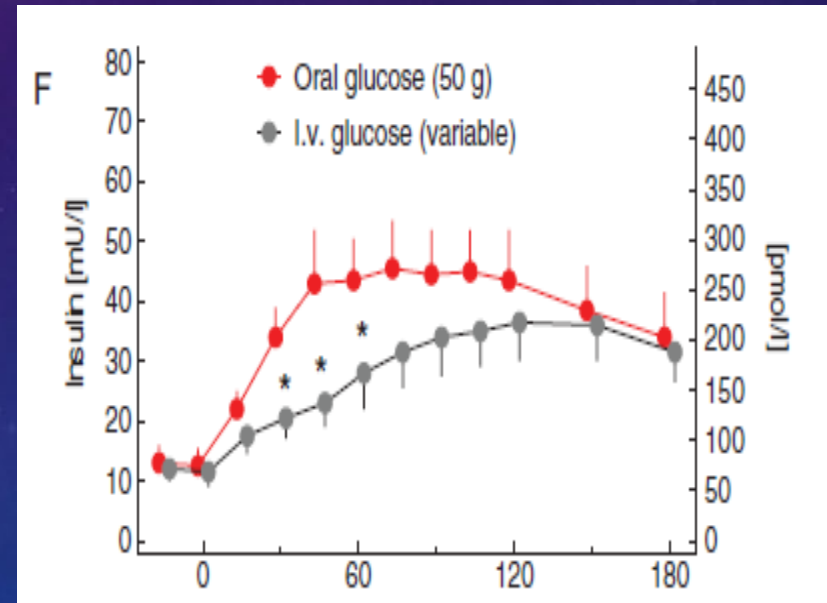
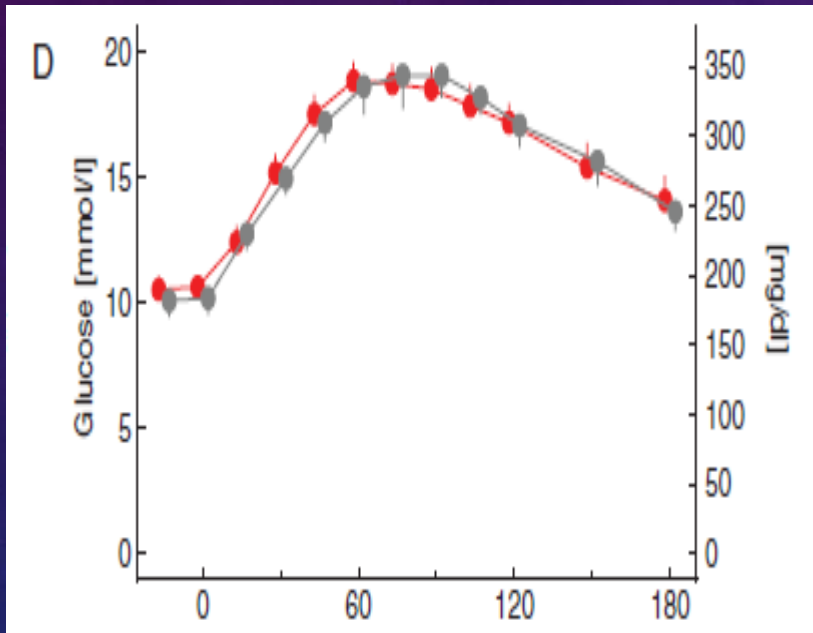
## The Human Gut



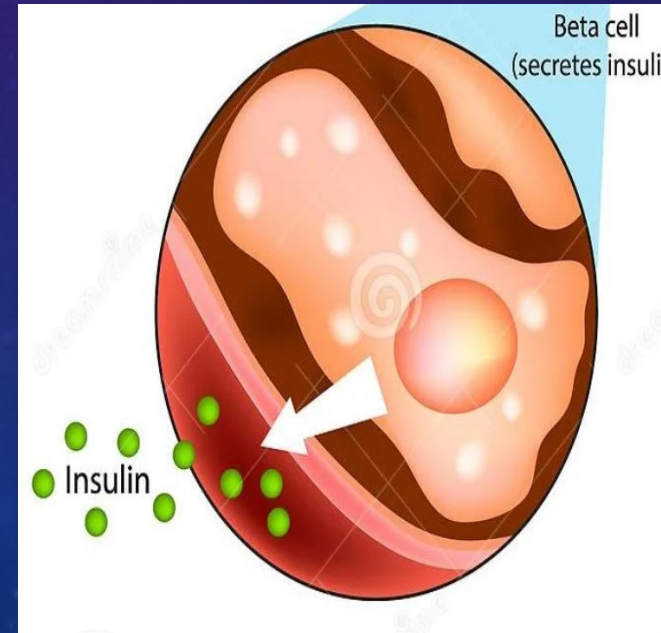
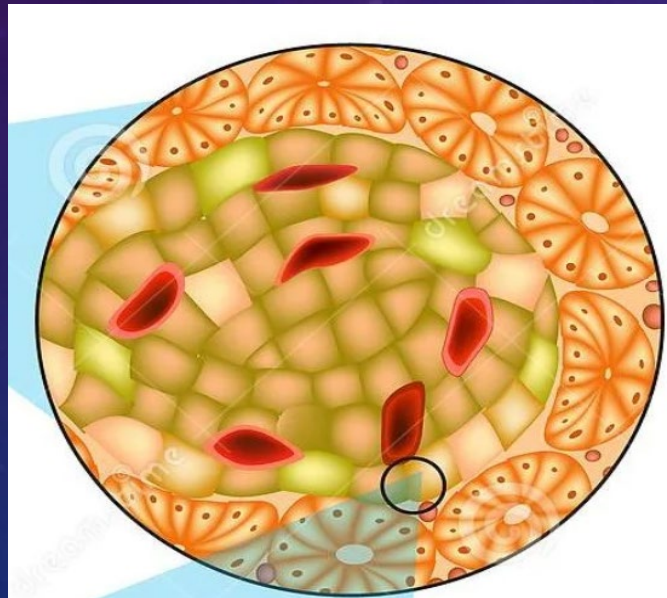
# THE BODY PRODUCES MORE INSULIN WHEN YOU GIVE SUGAR BY MOUTH VERSUS THROUGH THE VEIN



# THIS PROCESS IS IMPAIRED IN INDIVIDUAL WITH TYPE 2 DIABETES



# INSULIN IS MADE AND SECRETED FROM PANCREAS



# THESE SUBSTANCES ARE MADE BY THE GUT AND CALLED: INCRETINS

Glucagon like peptide-1 (GLP1)

-secreted in small intestine (L cells of the ileum)

Glucose-dependent insulinotropic polypeptide (GIP)

-secreted in small intestine duodenum and jejunum (K cells)

Both stimulate insulin secretion from pancreatic beta cells

# WHY NOT JUST USE THESE FOR TREATING DIABETES?

The problem is these are both chewed up (degraded) very quickly by an enzyme

That enzyme is called DPP 4

So you need something similar that is resistant to this enzyme

# ENTER THE GILA MONSTER



Long periods without eating  
Does eat, maintain constant glucoses

Hormones from Gila monster led to  
pancreatic enlargement

# ENTER DR. JOHN ENG IN 1990



He was interested in how the Gila Monster could increase size of its pancreas and maintain blood sugars

Found a hormone in the saliva of the Gila Monster

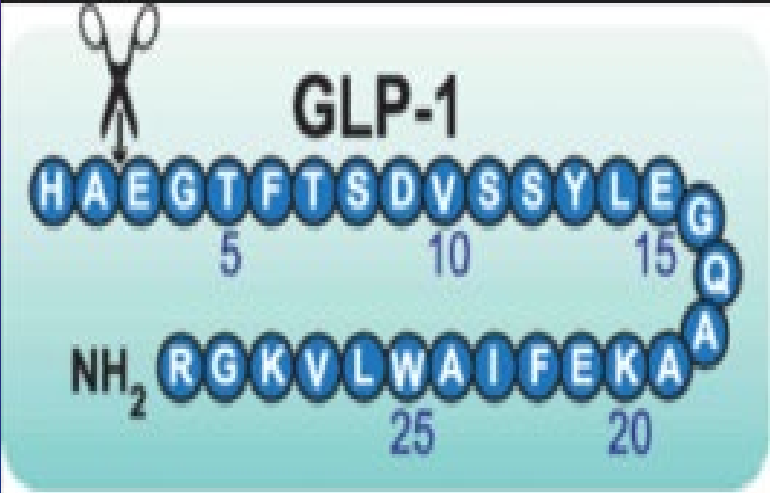
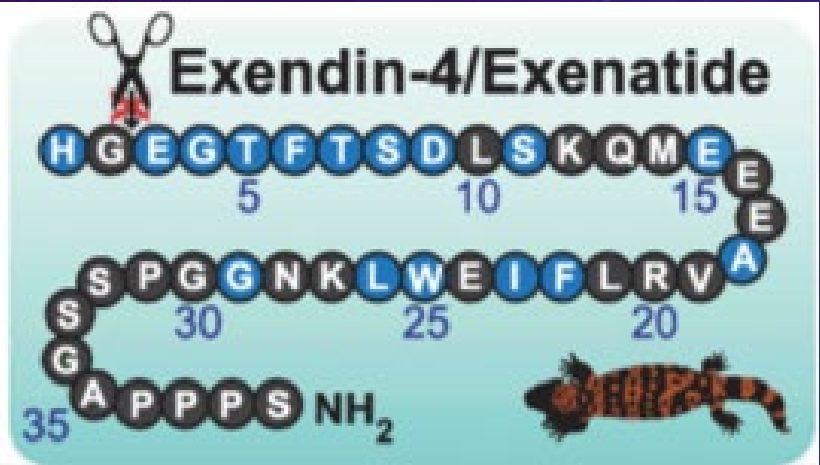
This compound stimulated insulin release

It was also looked very much like one of the human incretins: GLP-1

# EXENDIN-4 VS. GLP-1

GLP-1 is degraded quickly by DPP IV enzyme

Exendin-4 is resistant  
Exenatide was first GLP-1 analog



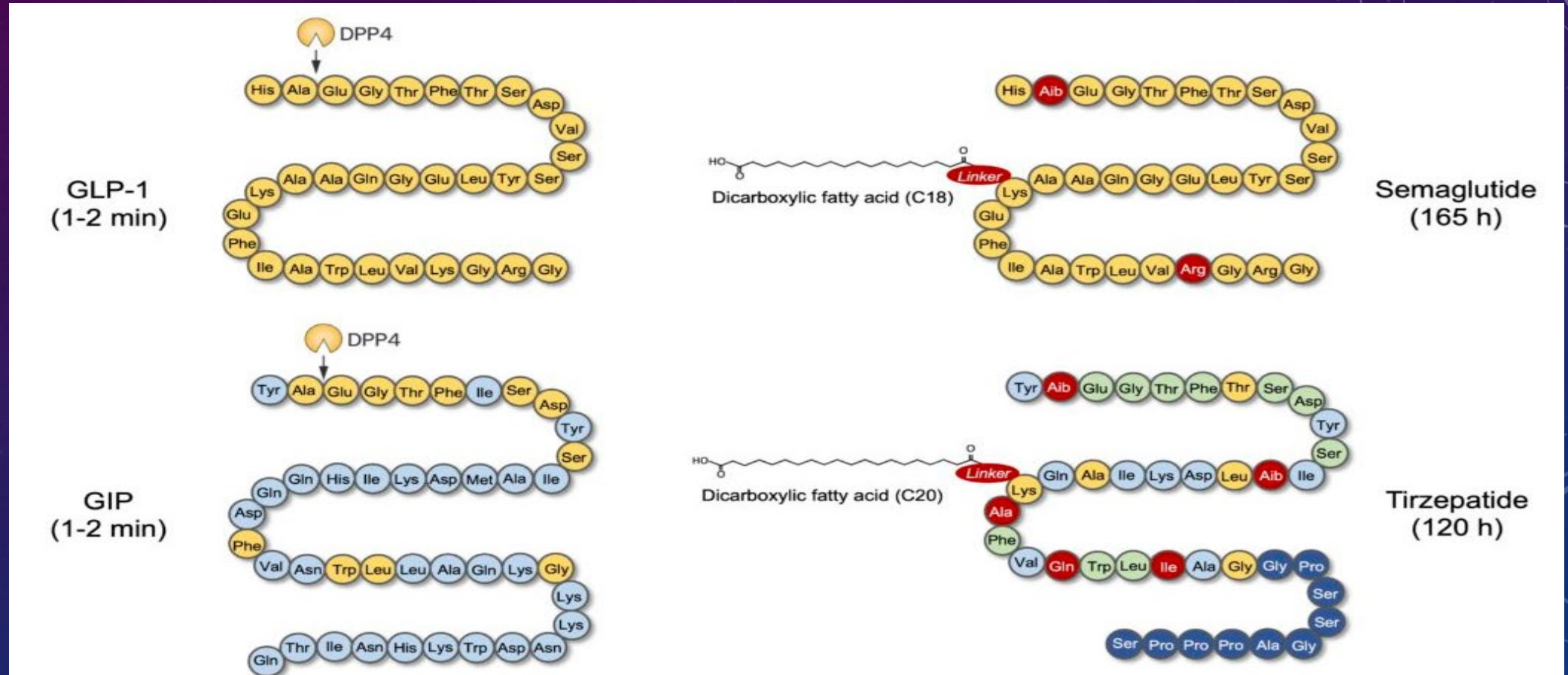
# FIRST (OF MANY) GLP-1 ANALOGS



Improved blood sugars in people with type 2 diabetes

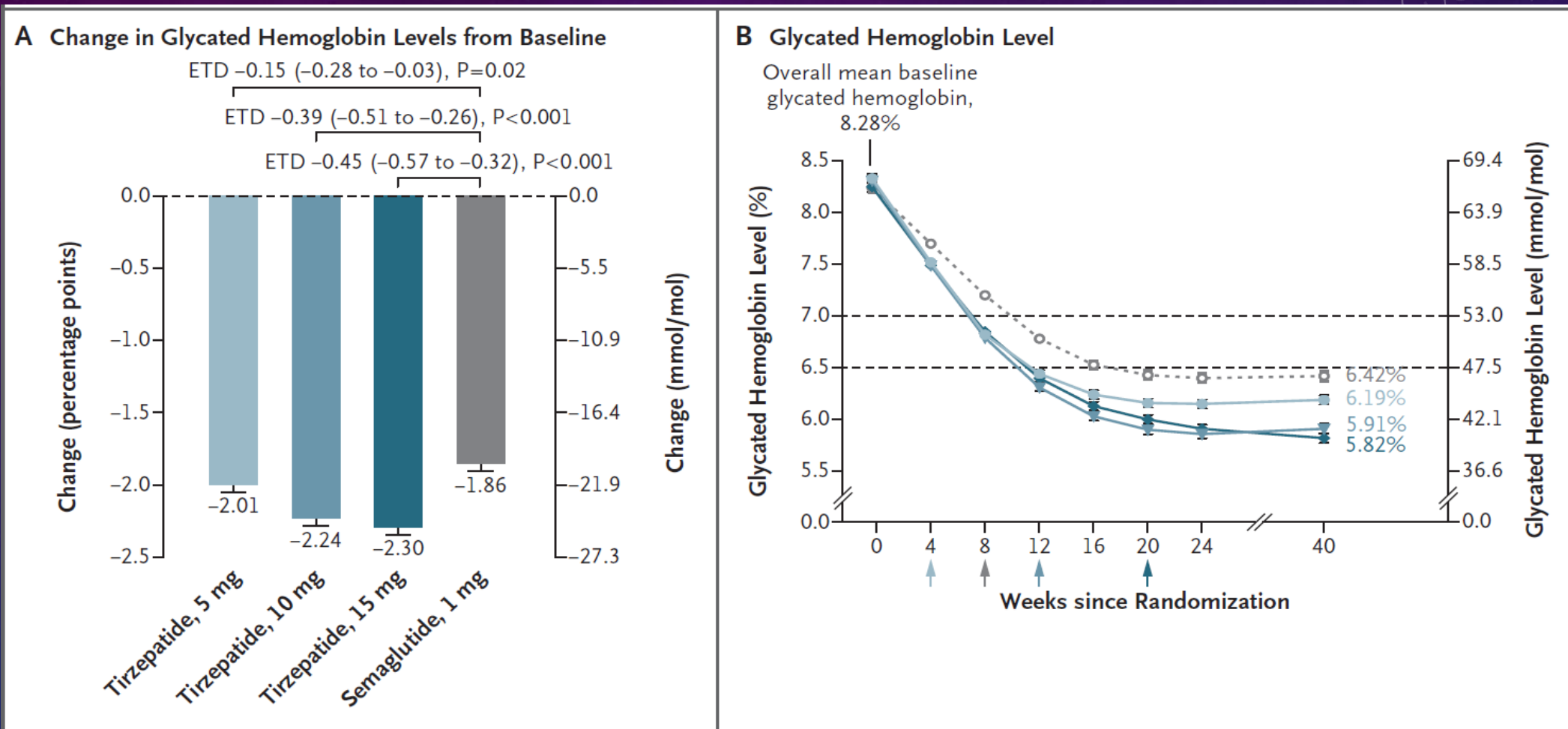
Original formulation had to be taken twice a day

# DEVELOPMENT OF MANY NEW MEDICATIONS: INCLUDING SEMAGLUTIDE AND TIRZEPATIDE



All modified to resist being broken down by the DPP 4 enzyme AND to last a week

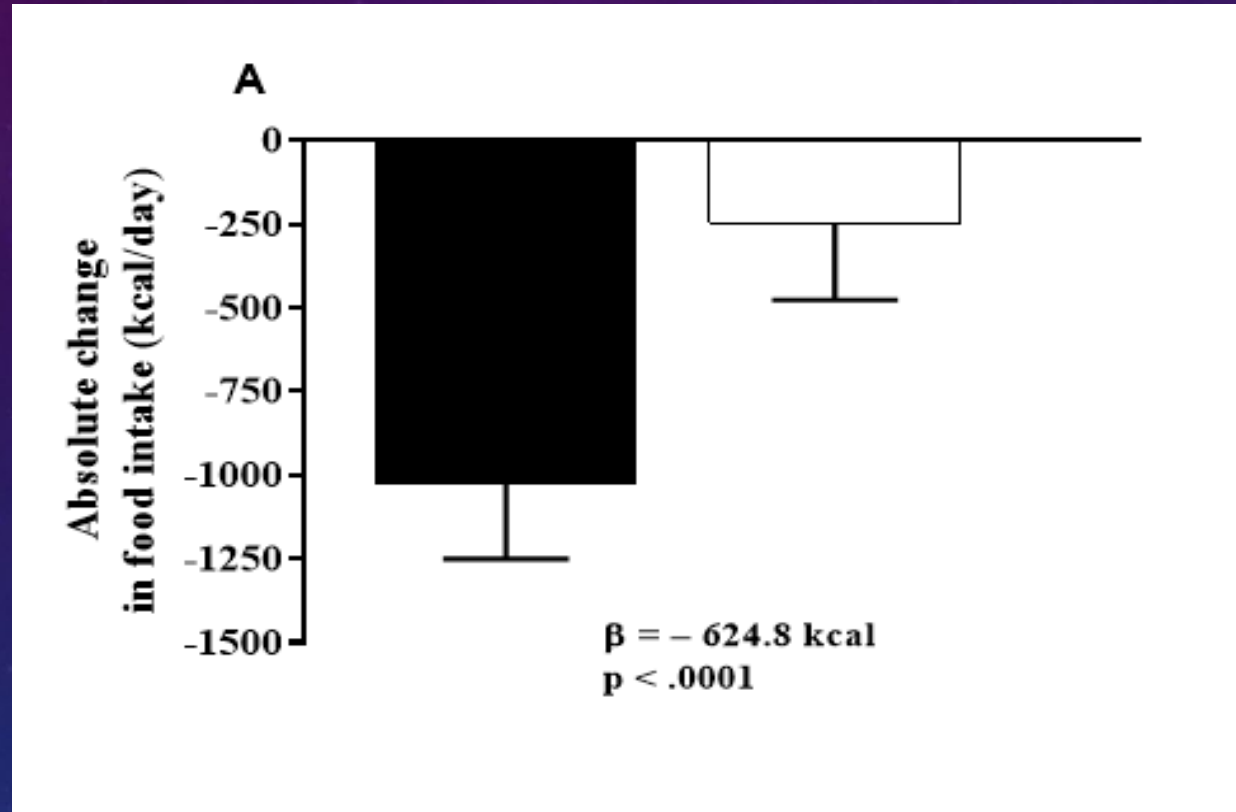
# BOTH SEMAGLUTIDE AND TIRZEPATIDE IMPROVE BLOOD SUGARS



# EFFECTS OF THESE MEDICATIONS BEYOND HELPING BLOOD SUGAR

- Slows stomach emptying
- Reduces cravings or ruminations about food

# EXENATIDE REDUCES HOW MUCH FOOD INDIVIDUALS EAT



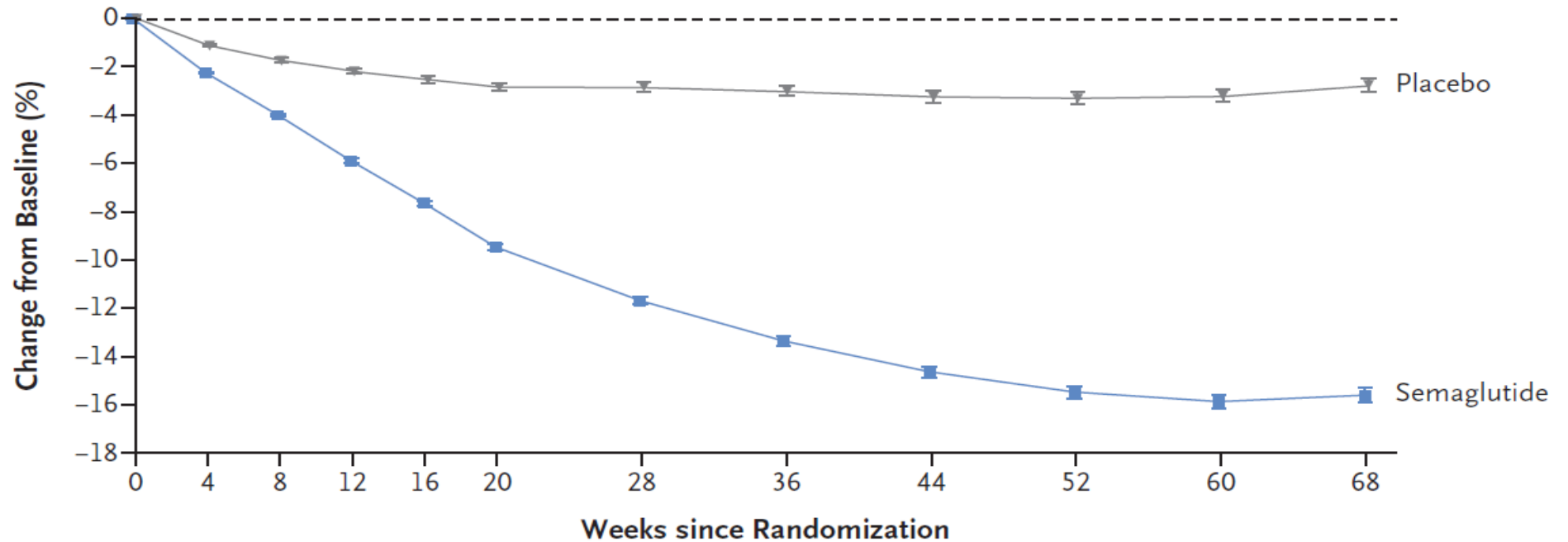


# KNOWING THIS: INVESTIGATING EFFECT OF THESE MEDICATIONS ON WEIGHT LOSS

Wilding JPH et al and STEP-1 trial, *NEJM* 2021

# SEMAGLUTIDE INDUCES MEANT 18% WEIGHT LOSS IN THOSE WITH OBESITY WITHOUT DIABETES

A Body Weight Change from Baseline by Week, Observed In-Trial Data



**No. at Risk**

Placebo	655	649	641	619	615	603	592	571	554	549	540	577
Semaglutide	1306	1290	1281	1262	1252	1248	1232	1228	1207	1203	1190	1212

Wilding JPH et al and STEP-1 trial, *NEJM* 2021

# OTHER HEALTH IMPROVEMENTS AND SIDE EFFECTS

## Improvements:

Systolic blood pressure ~8 mm Hg

Diastolic blood pressure ~3 mm Hg

Physical functioning

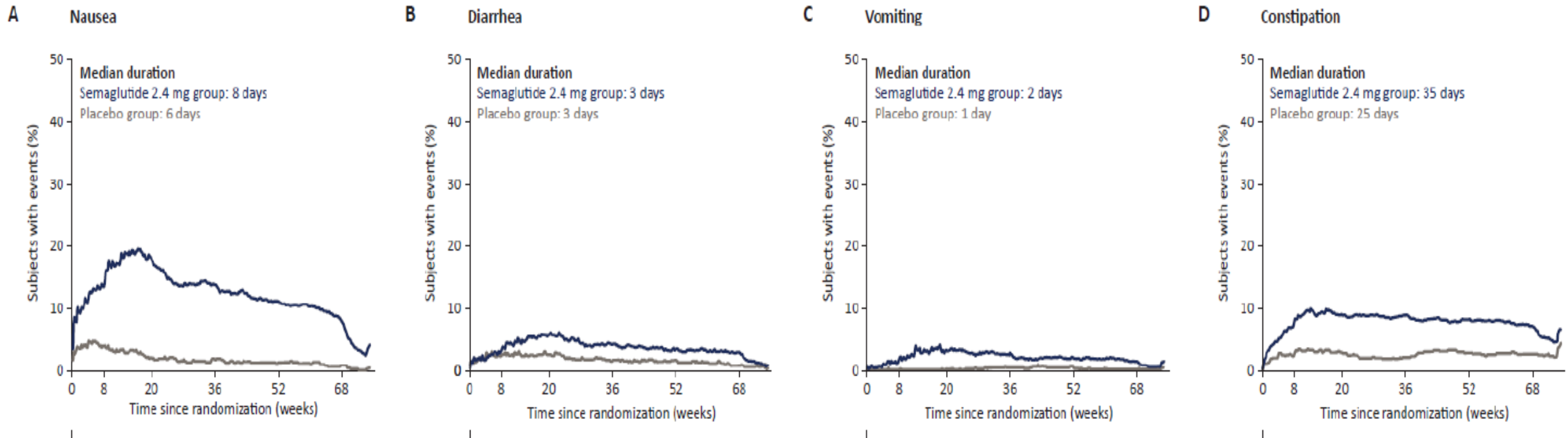
## Side effects

More GI side effects in those on semaglutide

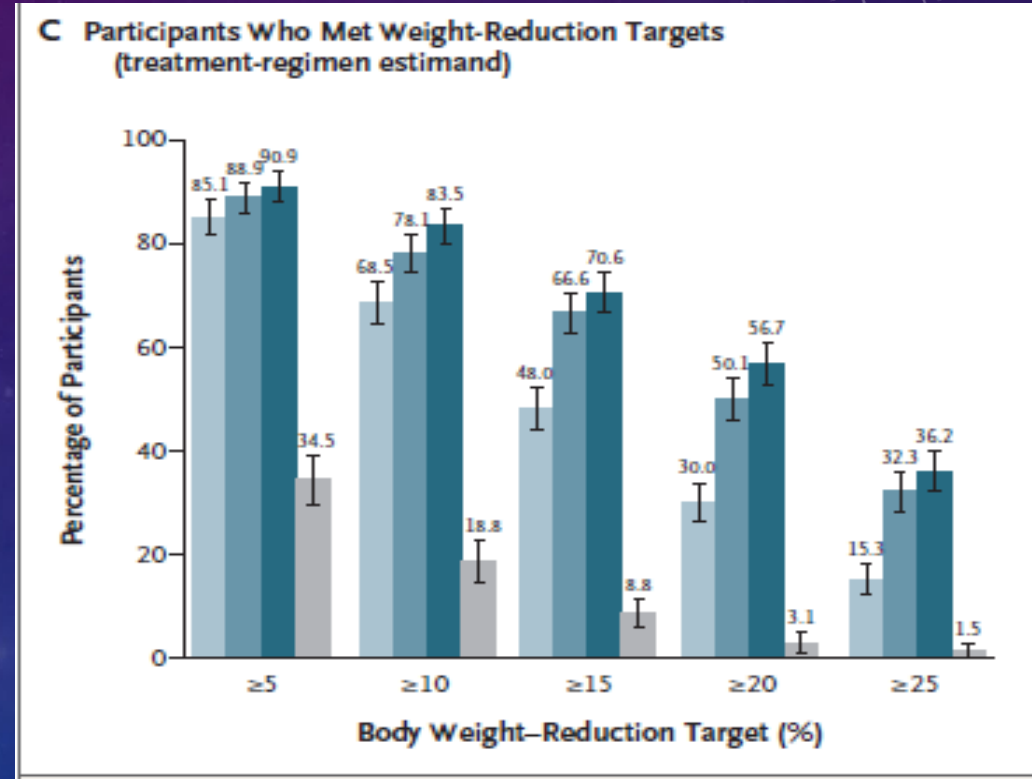
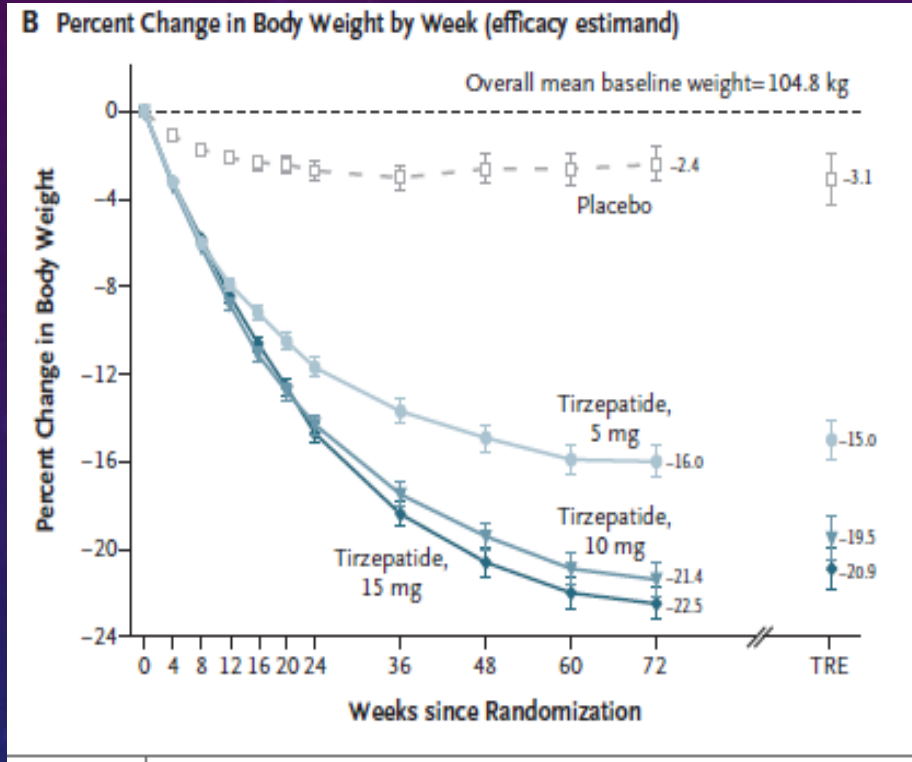
More gallbladder disease

No increase in pancreatitis

# AS YOU WOULD EXPECT FROM SOMETHING THAT SLOWED STOMACH EMPTYING THERE WAS MORE NAUSEA



# TIRZEPATIDE INDUCES >20% WEIGHT LOSS



# OTHER HEALTH BENEFITS AND SIDE EFFECTS

## Improvements:

Systolic blood pressure ~6 mm Hg

Diastolic blood pressure ~4 mm Hg

Triglycerides ~ 20 mg/dl

HDL increase ~ 9 mg/dl

## Side effects:

More stomach side effects in tirzepatide group

No significant difference in gallbladder disease or pancreatitis

# SEMAGLUTIDE STUDIED IN INDIVIDUALS WHO ALREADY HAD HEART DISEASE, STROKE OR CIRCULATORY ISSUES

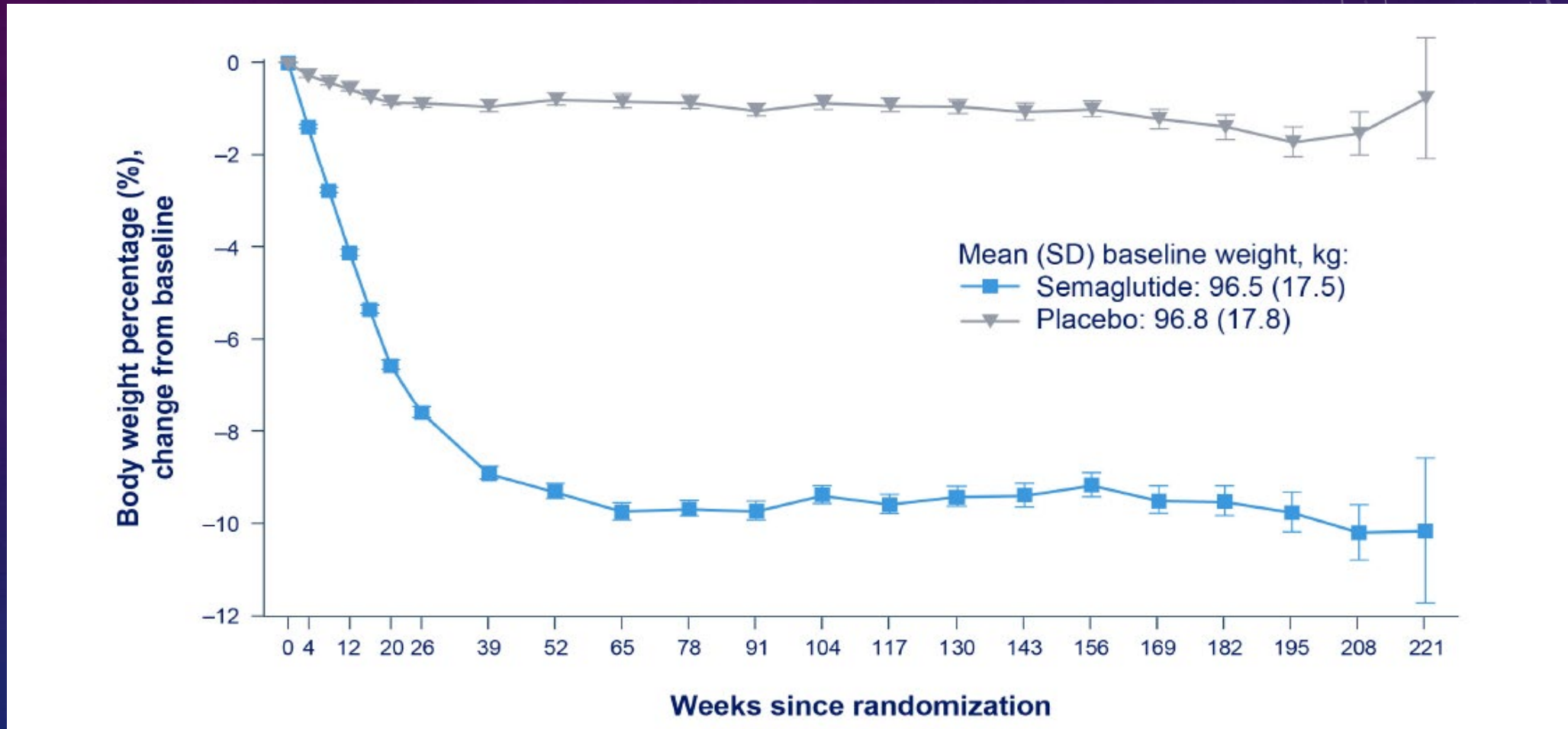
Age  $\geq$  45 years

BMI  $\geq$  27 kg/m<sup>2</sup> with Cardiovascular disease

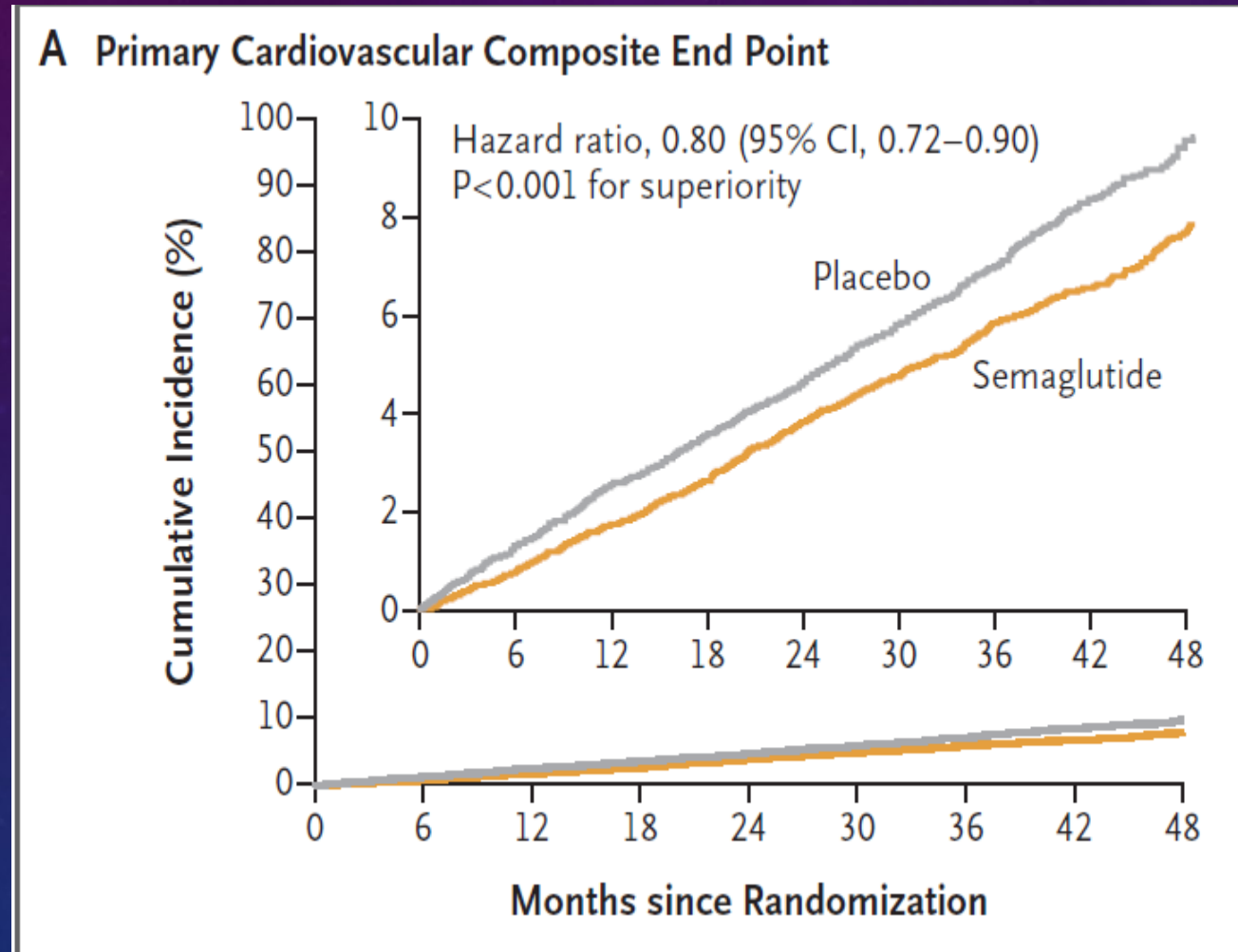
H/o myocardial infarction, CVA or symptomatic peripheral artery disease

Excluded: Individuals with type 2 diabetes (A1c  $\geq$  6.5%)

# THOSE WHO RECEIVED SEMAGLUTIDE LOST WEIGHT



# SEMAGLUTIDE DECREASED HEART ATTACK, STROKE AND DEATH BY HEART ATTACK OR STROKE BY 20%



In those with established Cardiovascular disease

# ARE THESE MEDICATIONS THE RIGHT FIT FOR ME?

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Have this conversation with your treating clinician

Weight management is a long-term process with long term goals

Medical treatment is like that for other chronic conditions

Have improvement in your health in mind



QUESTIONS?