National Institute of Diabetes and Digestive and Kidney Diseases

The new weight loss medications Who should we treat?

Jonathan Krakoff, MD

Chief Obesity and Diabetes Clinical Research Unit

NIDDK-Phoenix

National Institute of Diabetes and Digestive and Kidney Diseases

OUTLINE

- Evidence that weight loss has health benefits
- Does it make sense to focus treatment on individuals with more elevated BMI?
- Options to treat
- What new treatments are out there?

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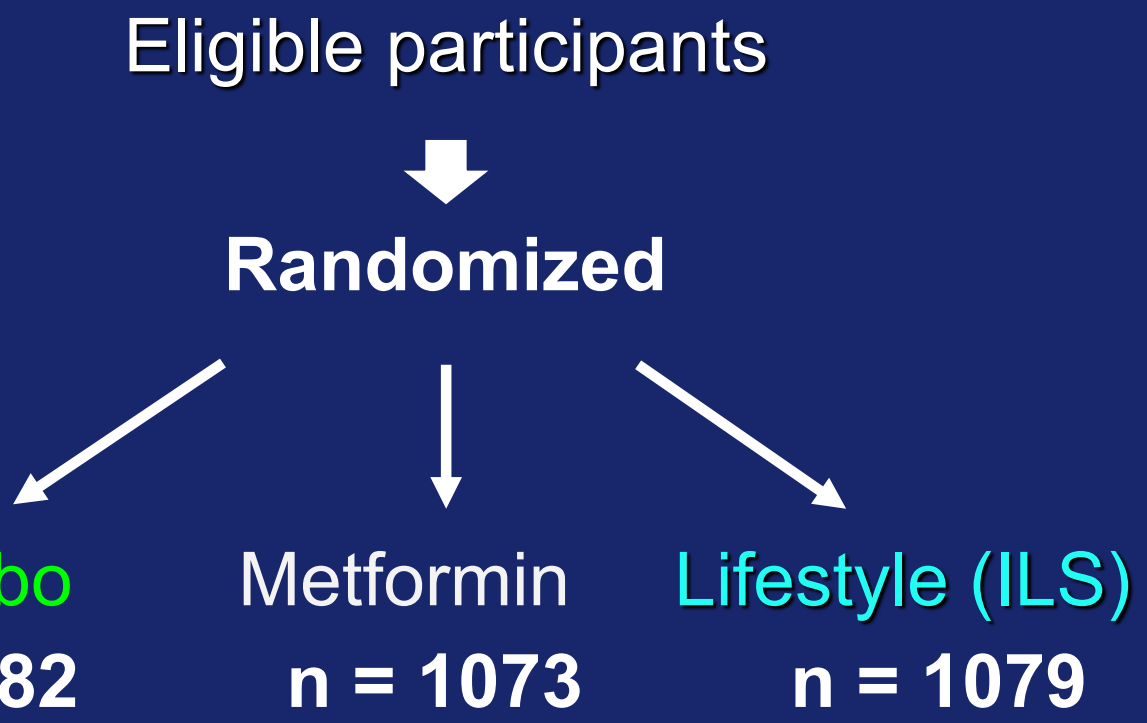
DIABETES PREVENTION PROGRAM



DPP: *NEJM* 346: 393-403, 2002

Total n = 3,234

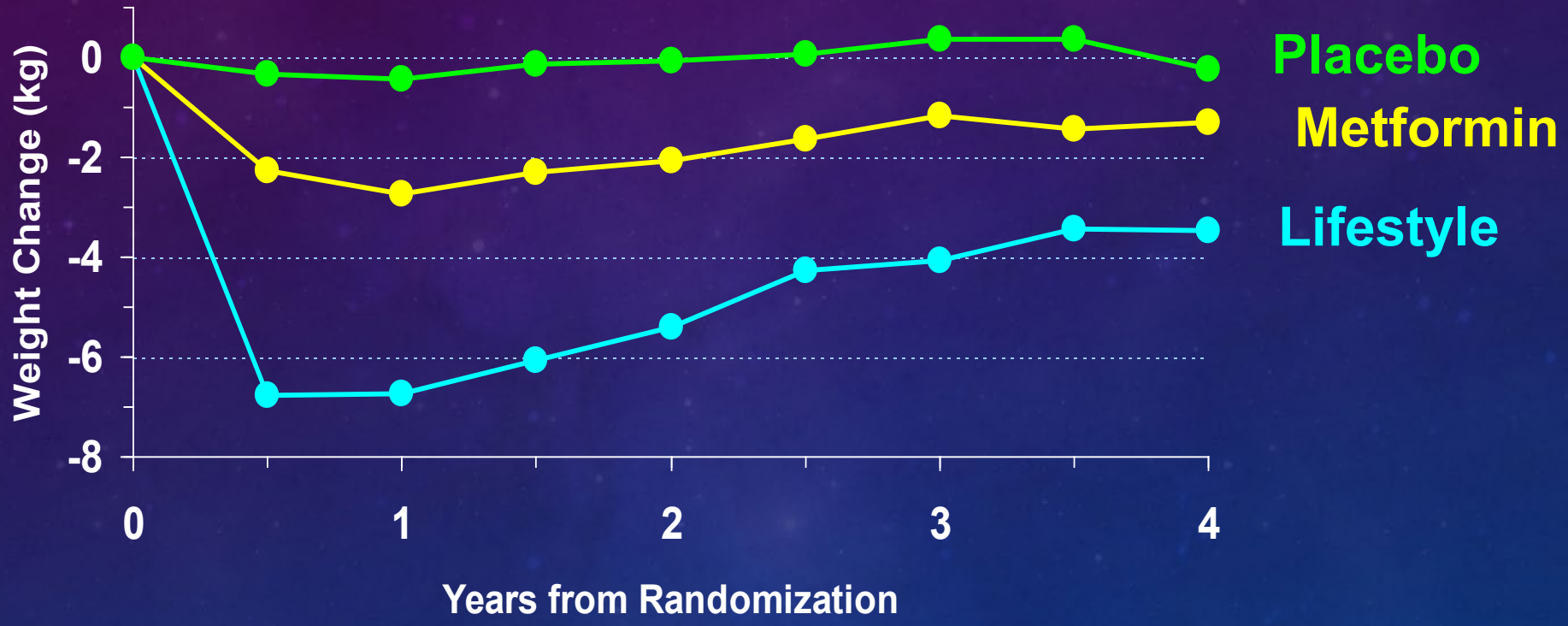
LIFESTYLE INTERVENTION

An intensive program with the following specific goals:

- ≥ 7% loss of body weight and maintenance of weight loss
- ≥ 150 minutes per week of physical activity

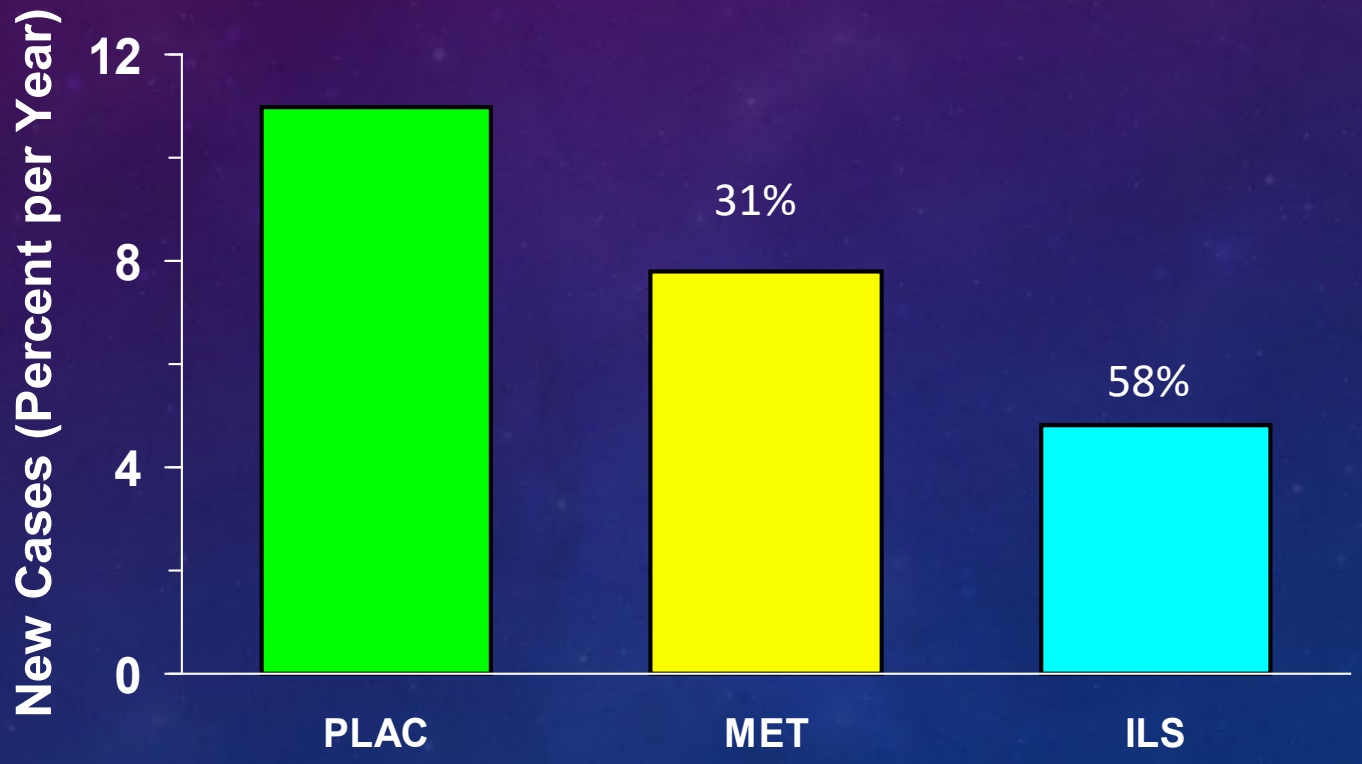
NEJM, 2002

MEAN WEIGHT CHANGE IN THE DPP

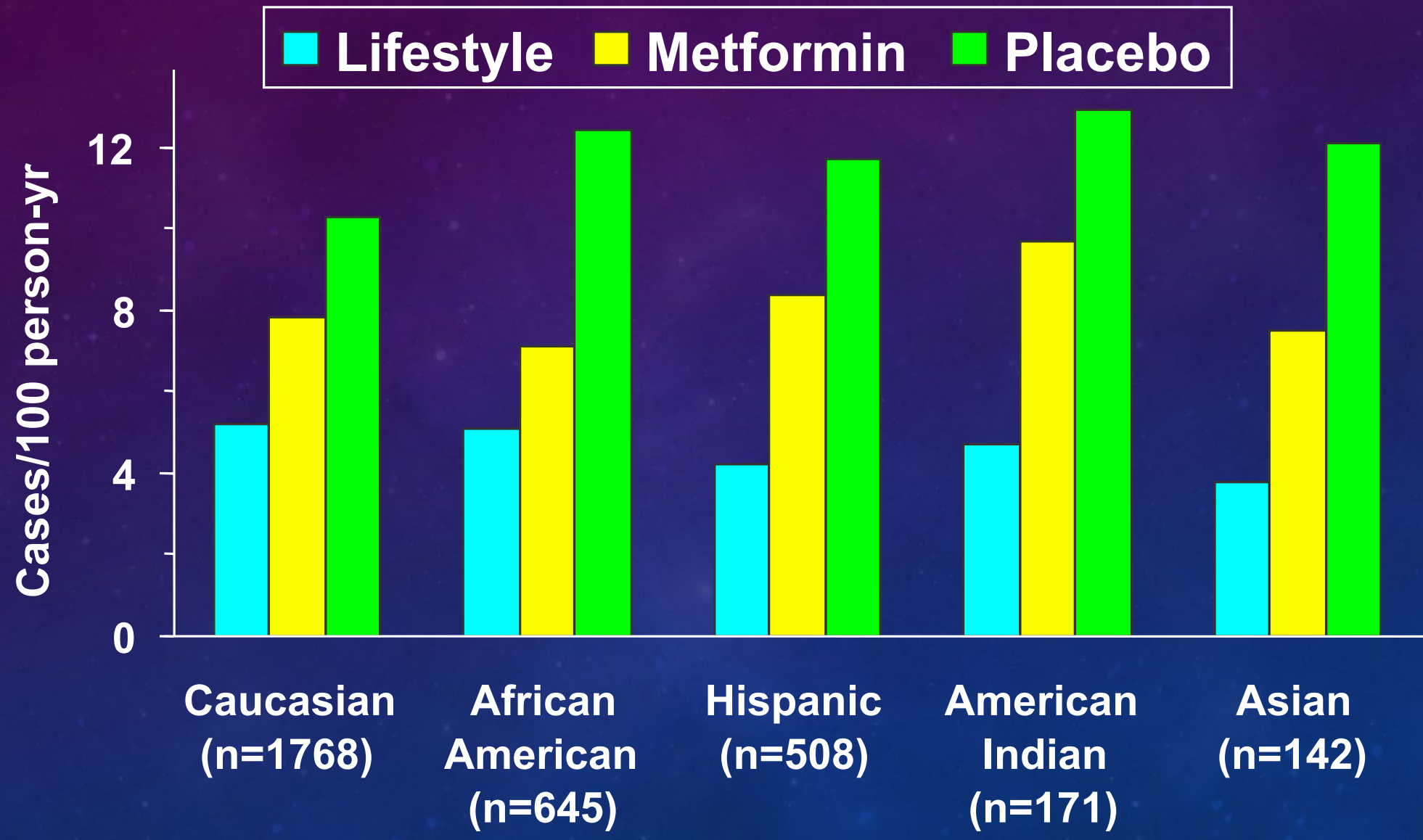


DPP: *NEJM* 346: 393-403, 2002

METFORMIN AND LIFESTYLE REDUCED INCIDENCE OF DIABETES

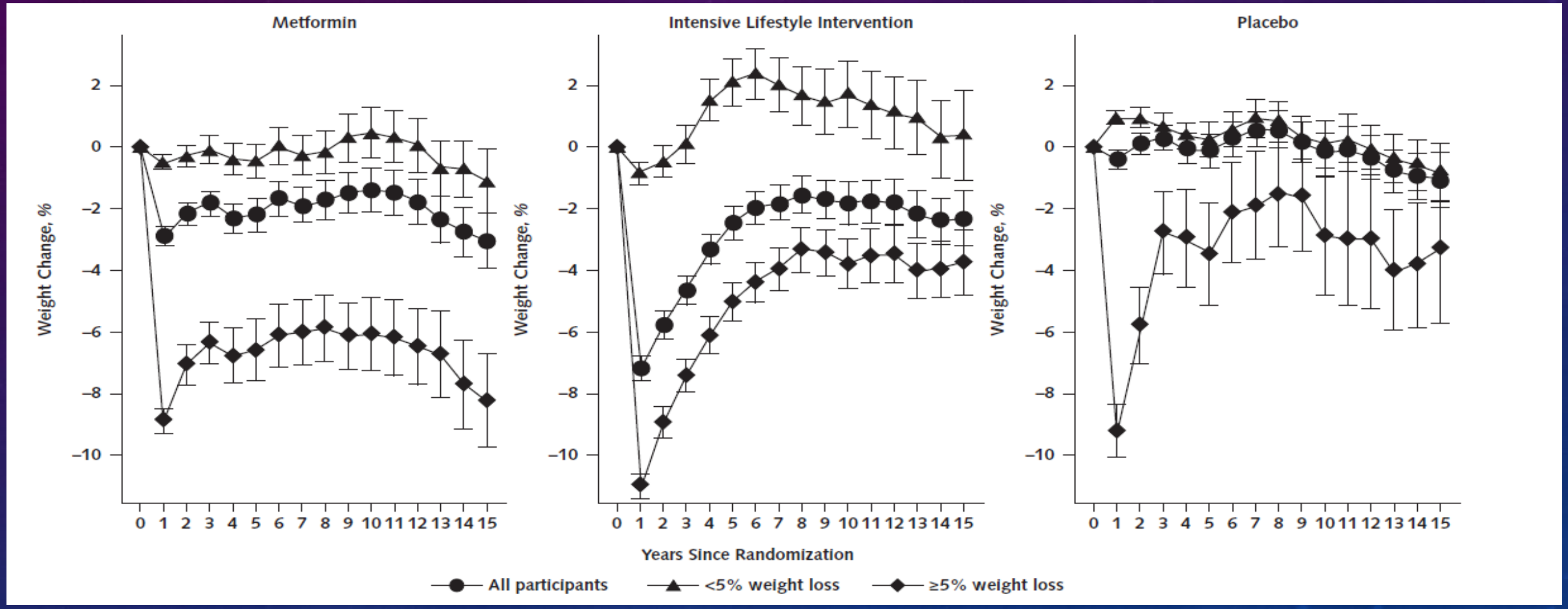


DIABETES INCIDENCE RATES BY ETHNICITY



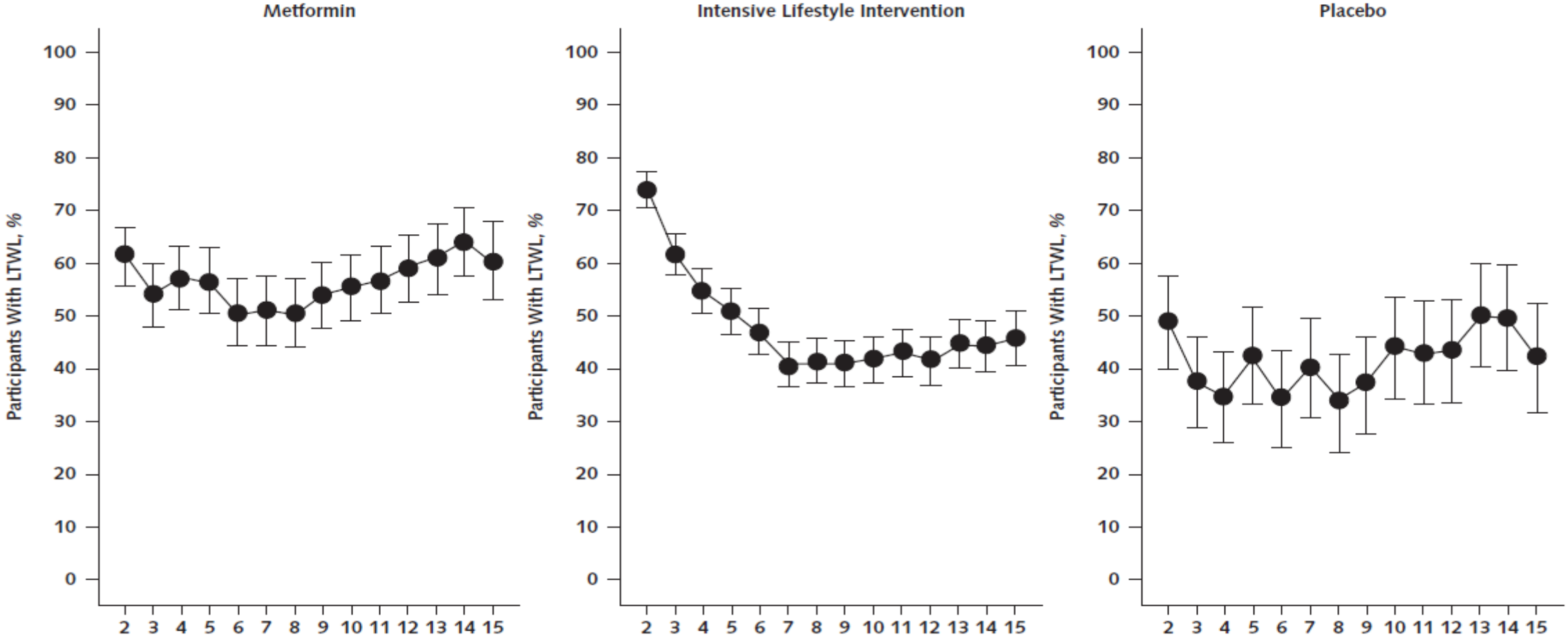
The DPP Research Group, *NEJM 346*:393-403, 2002

LONG TERM WEIGHT LOSS IN DIABETES PREVENTION OUTCOME STUDY



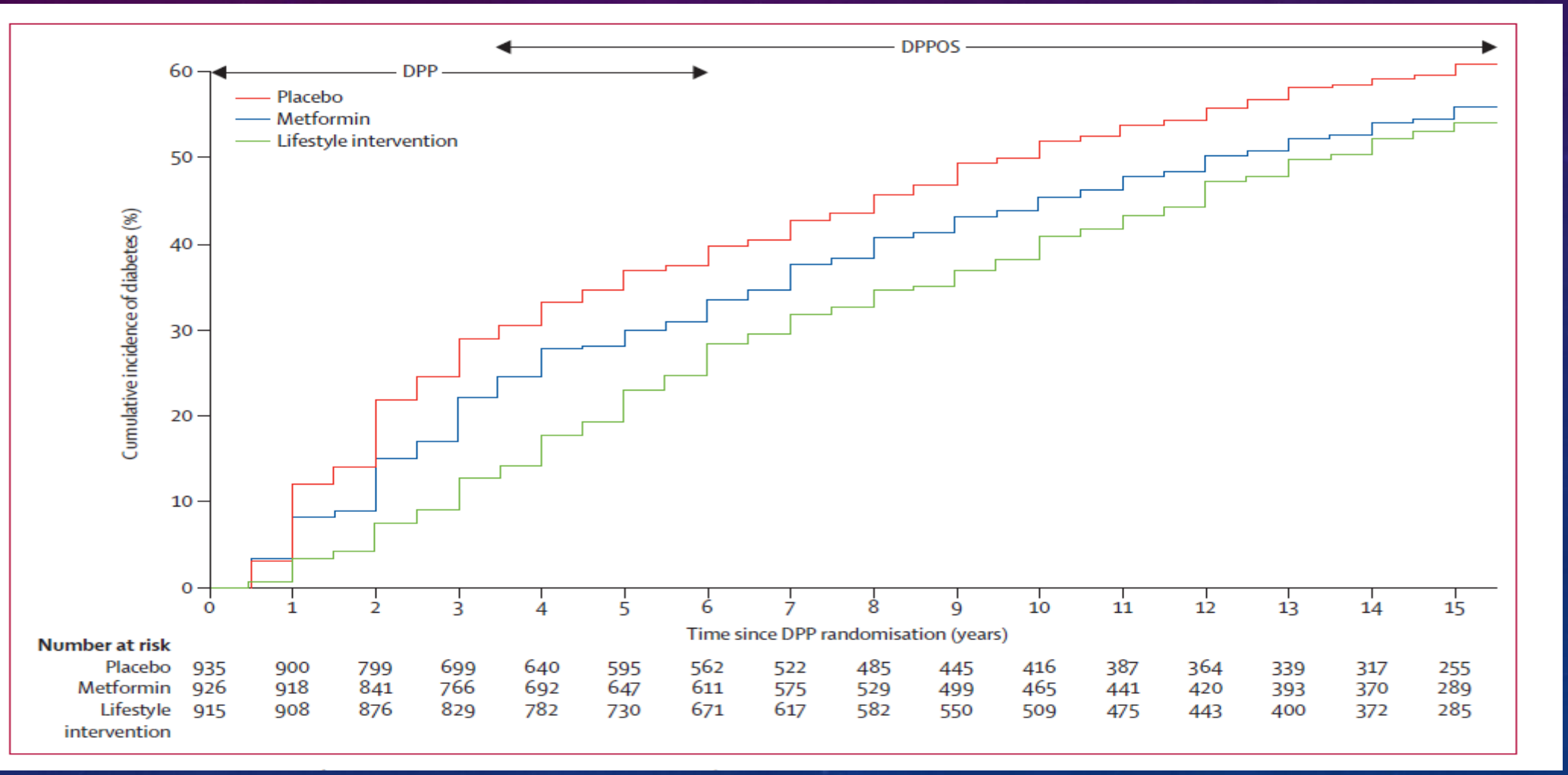
Apolzan et al Annals of Int Med 2019

METFORMIN ACHIEVES BEST LONG TERM WEIGHT LOSS (>5%)



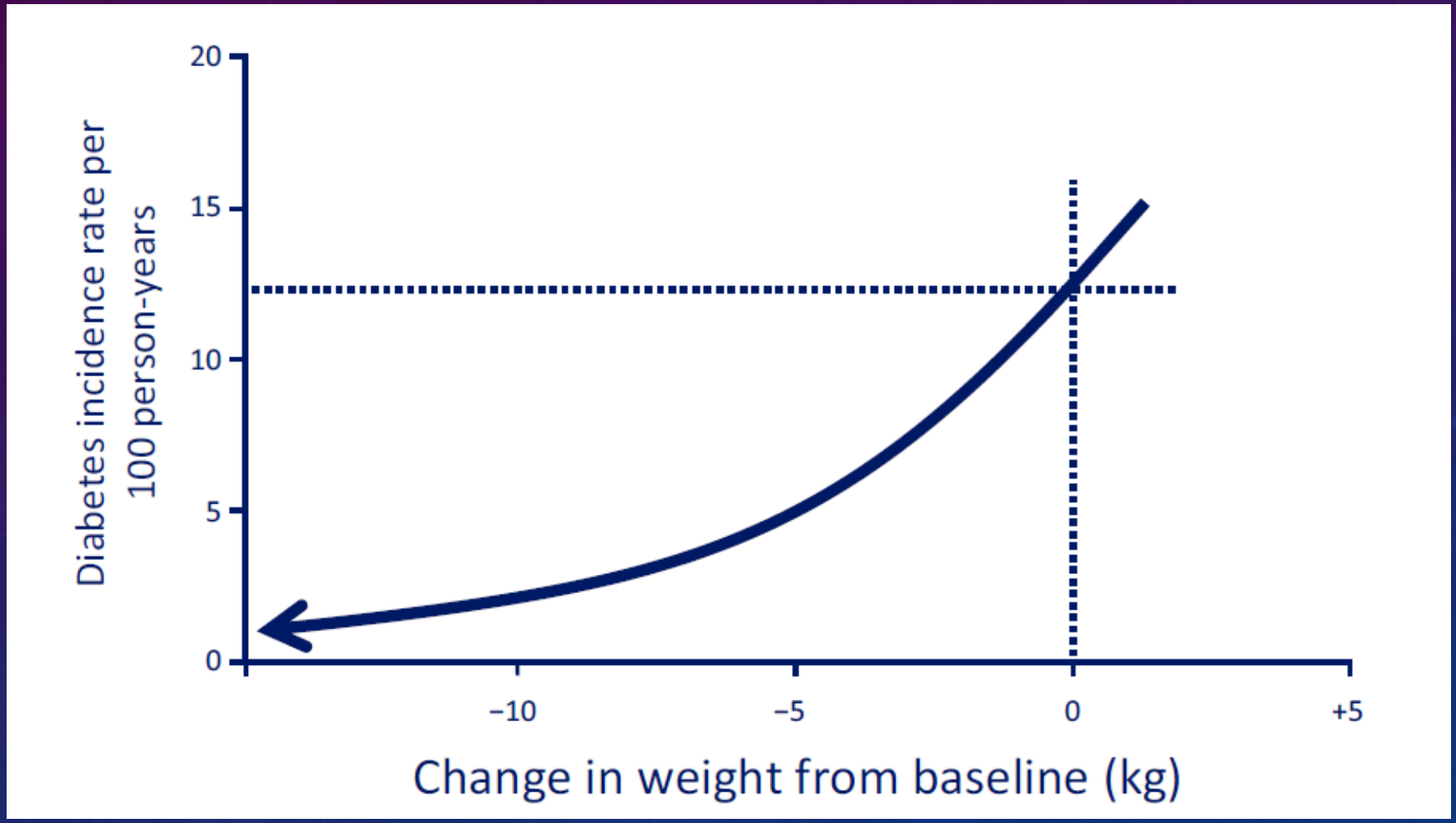
Apolzan et al Annals of Int Med 2019

INTENSIVE LIFESTYLE AND METFORMIN DELAY DEVELOPMENT OF T2DM



DPPOS Lancet 2015

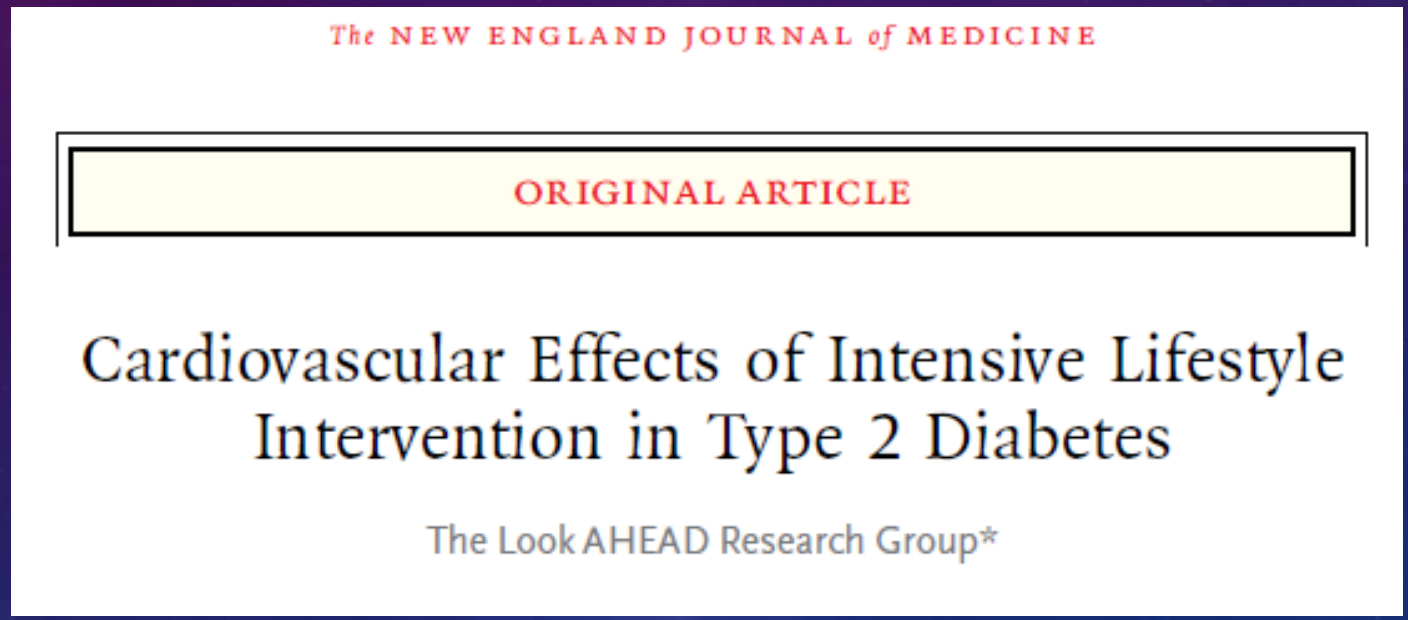
DIABETES PREVENTION PROGRAM EXPERIENCE



Every kg of weight loss associated with 16% reduction in risk to progression of T2DM

Ryan D Current Obesity Reports 2017

ACTION FOR HEALTH IN DIABETES (LOOK AHEAD)



The NEW ENGLAND JOURNAL of MEDICINE

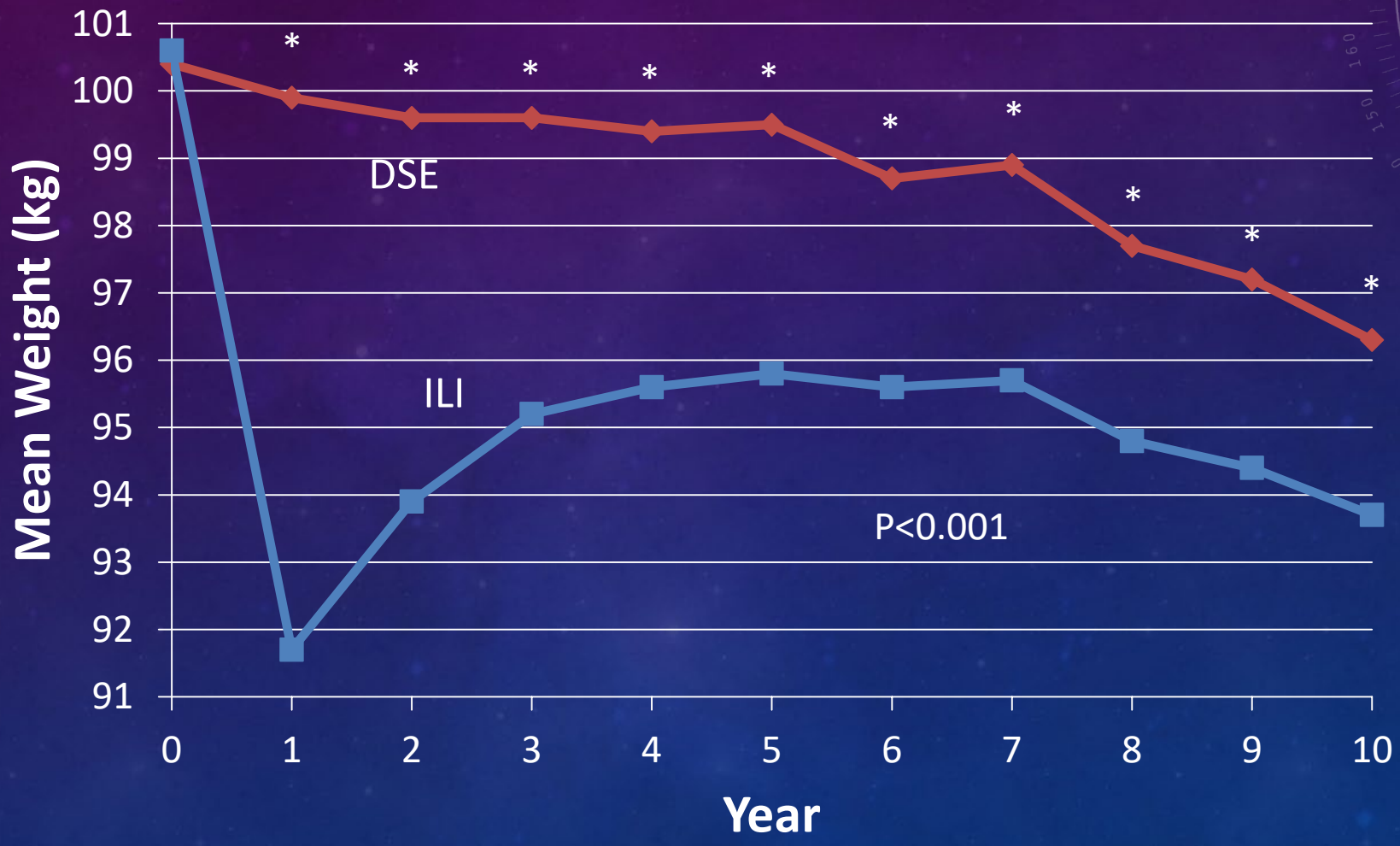
ORIGINAL ARTICLE

Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes

The Look AHEAD Research Group*

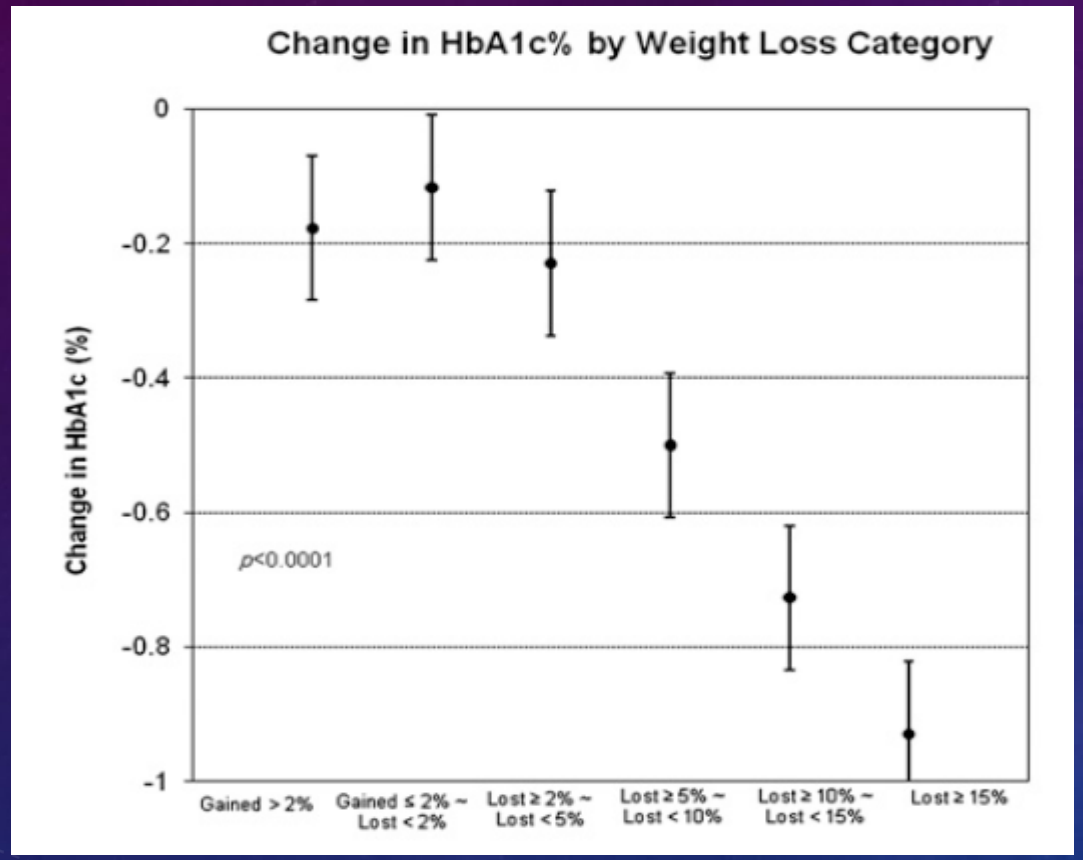
Look AHEAD Research Group, *NEJM* 2013

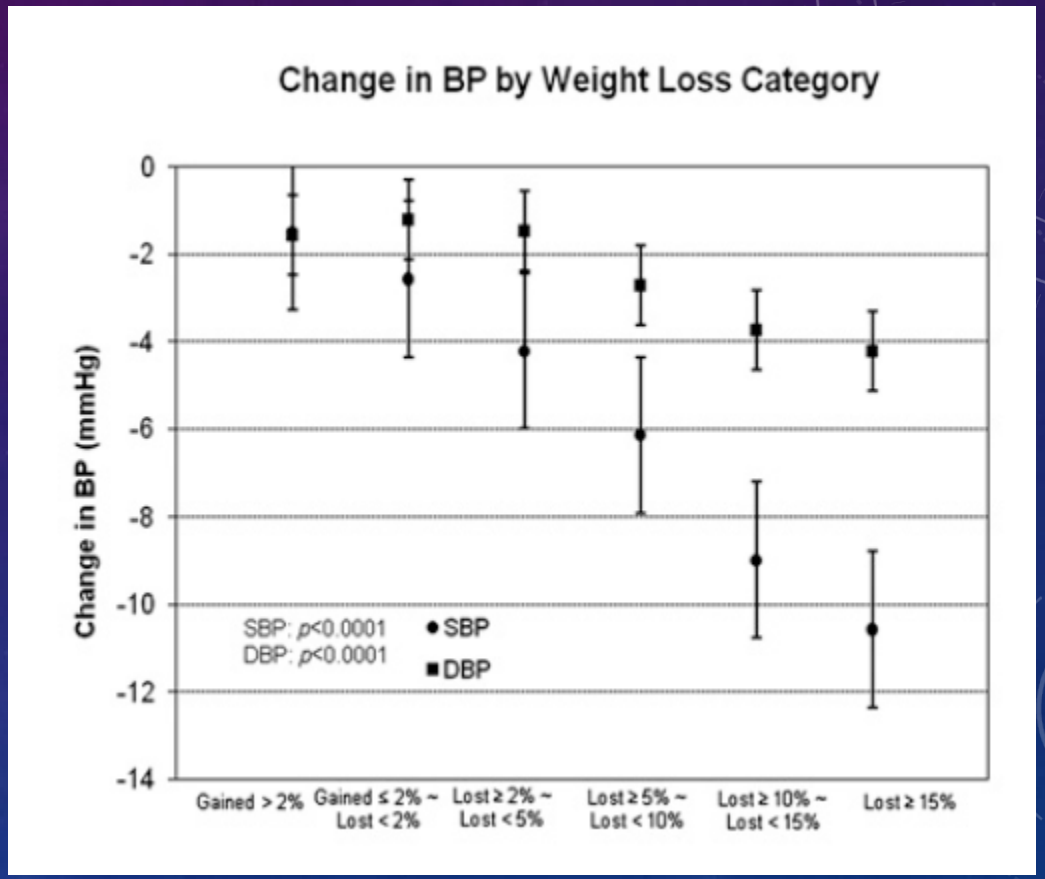
WEIGHT CHANGE



Look AHEAD Research Group, *NEJM* 2013

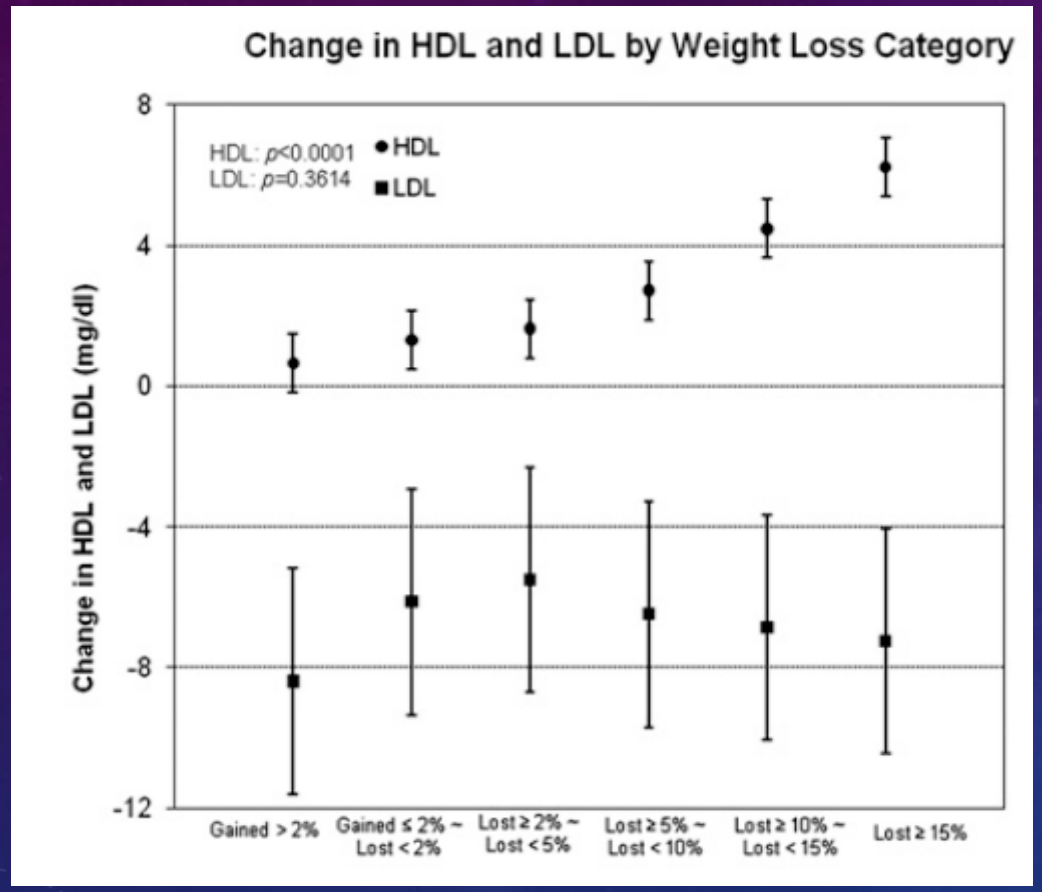
MODEST WEIGHT LOSS CAN IMPROVE CVD RISK FACTORS

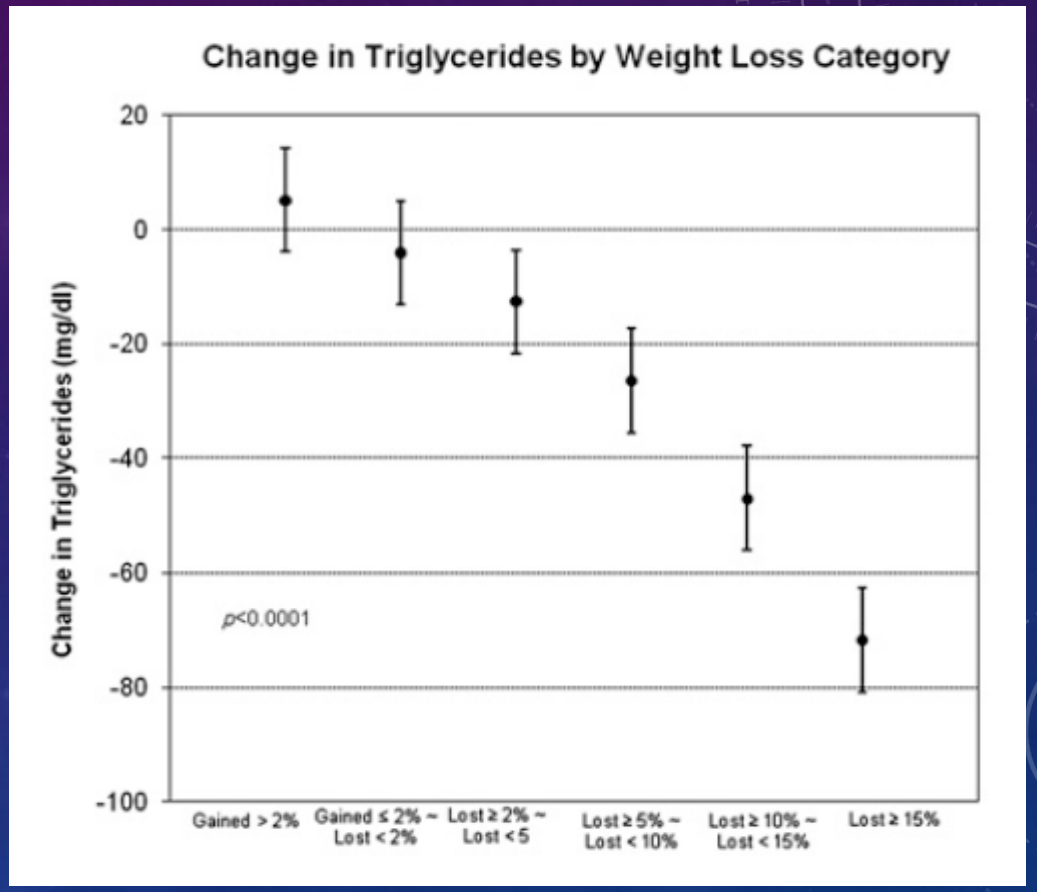




Wing RR et al Look AHEAD Research Group, *Diabetes Care* 2011

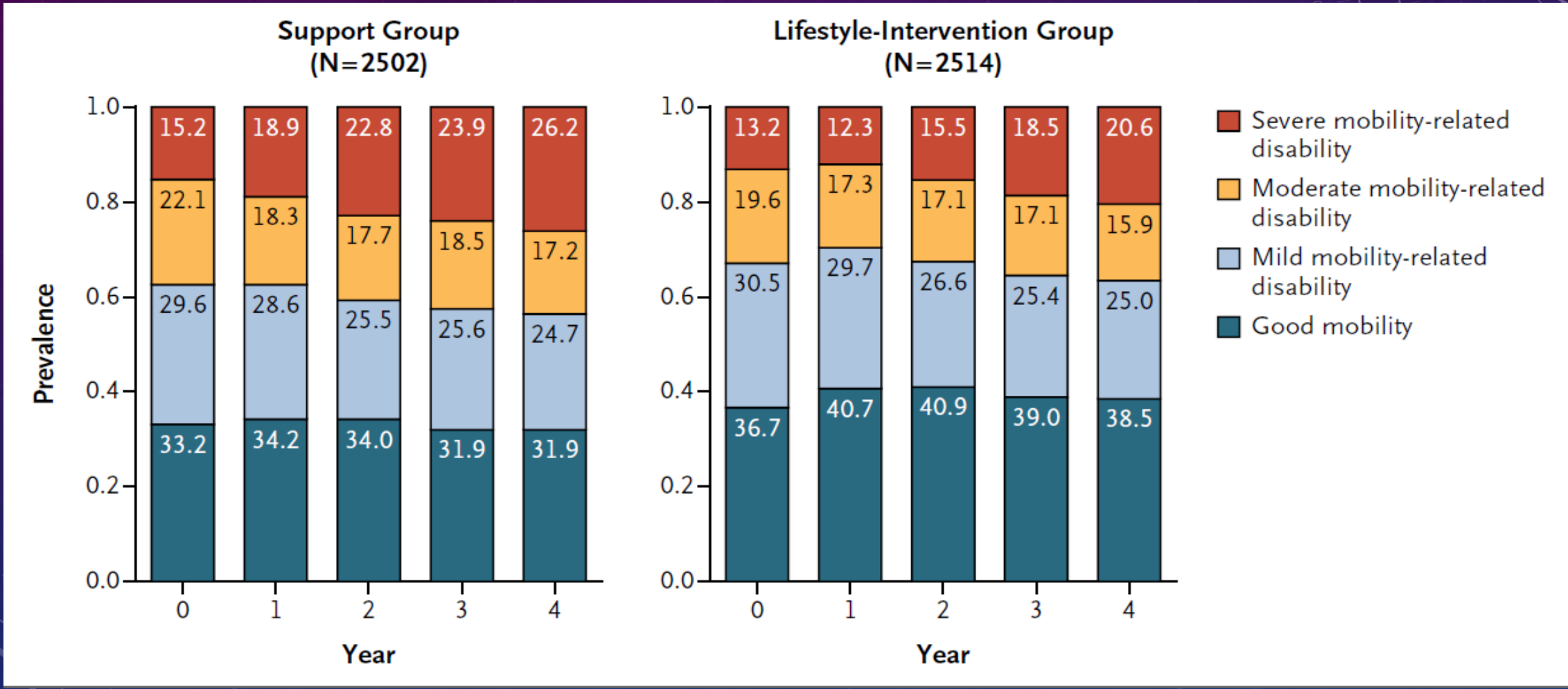
MODEST WEIGHT LOSS CAN IMPROVE CVD RISK FACTORS





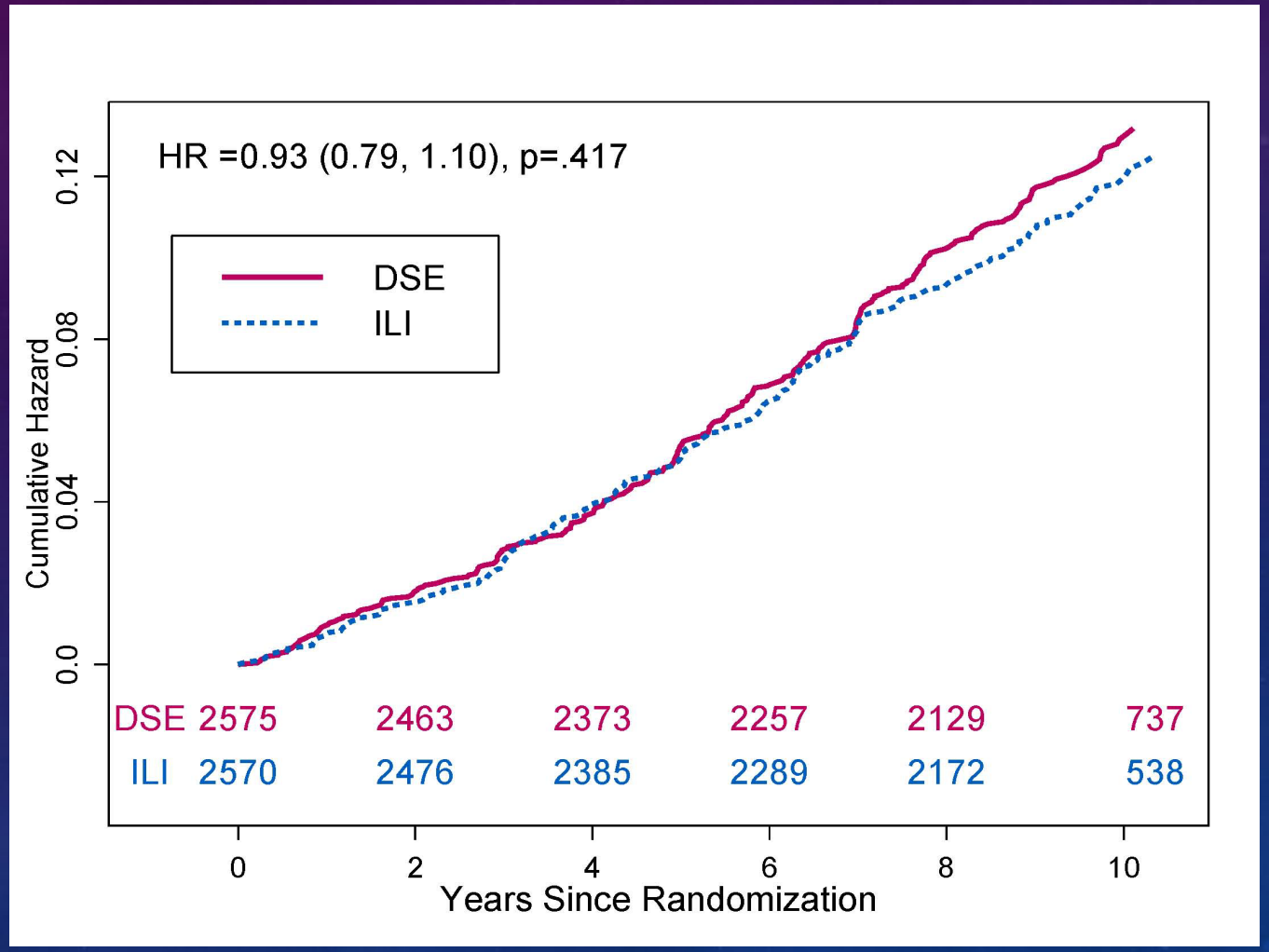
Wing RR et al Look AHEAD Research Group, *Diabetes Care* 2011

WEIGHT LOSS PRESERVES MOBILITY



Rejeski WJ and Look AHEAD Research Group, *NEJM* 2012

NO DIFFERENCE IN CVD EVENTS BETWEEN WEIGHT LOSS VS. SUPPORT GROUP



Look AHEAD Research Group, *NEJM* 2013

OUTLINE

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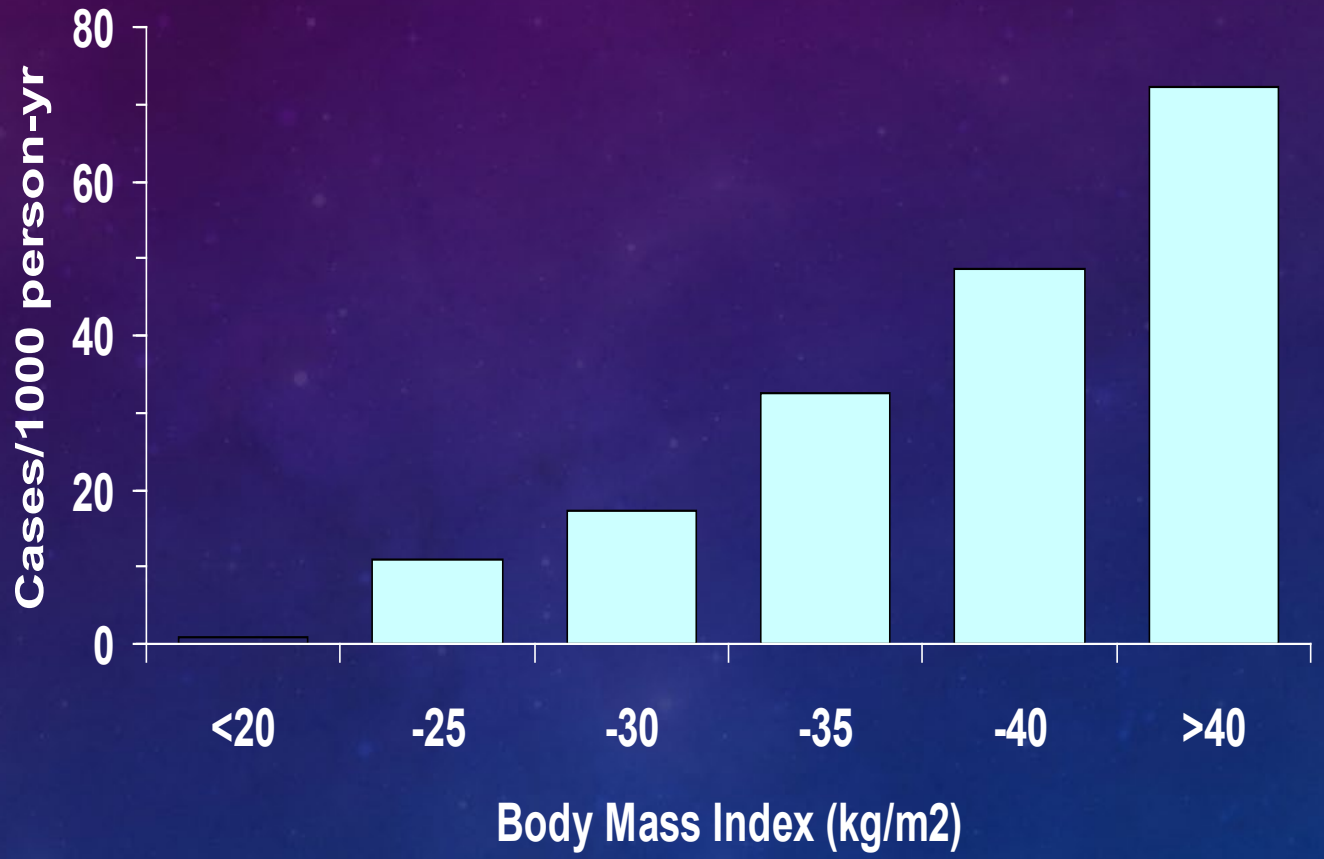
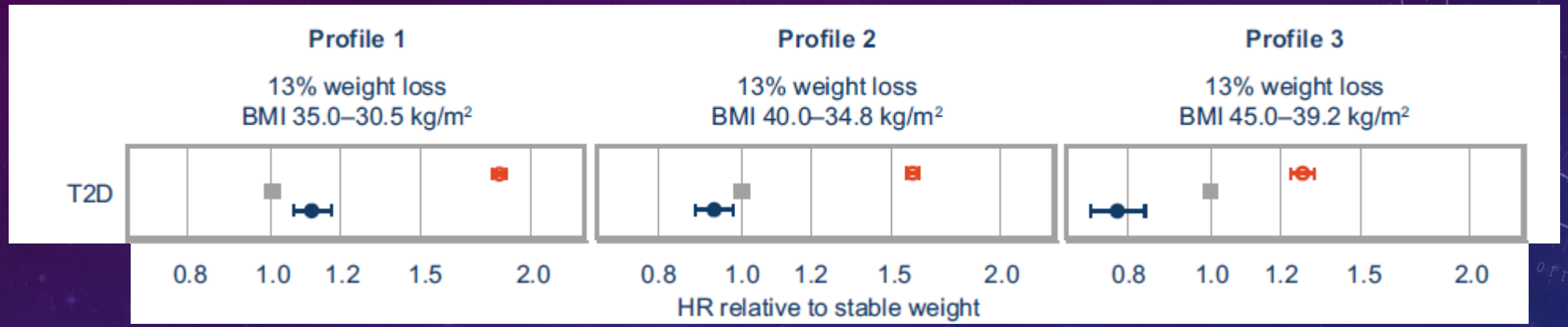
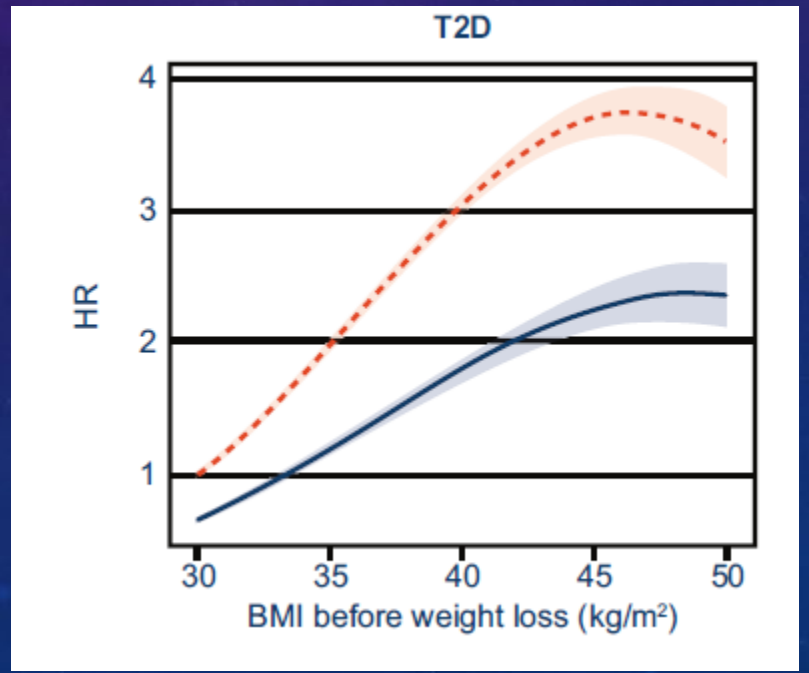
Incidence of Diabetes by BMI



Knowler WC et al: Am J Epidem, 1981

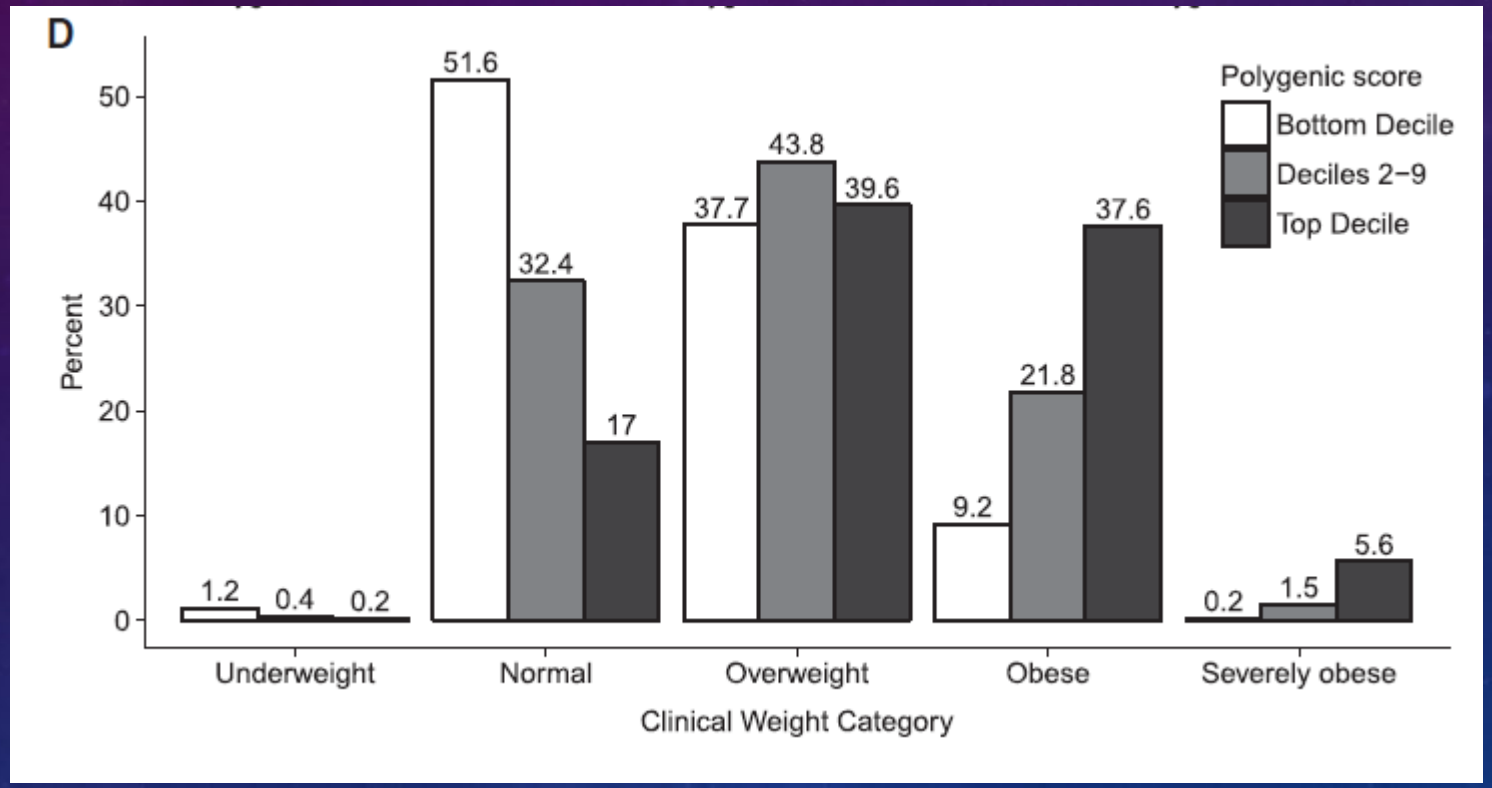
SIMILAR WEIGHT LOSS ACCRUES GREATER BENEFIT AGAINST DEVELOPMENT OF T2DM AT HIGHER INITIAL BMI





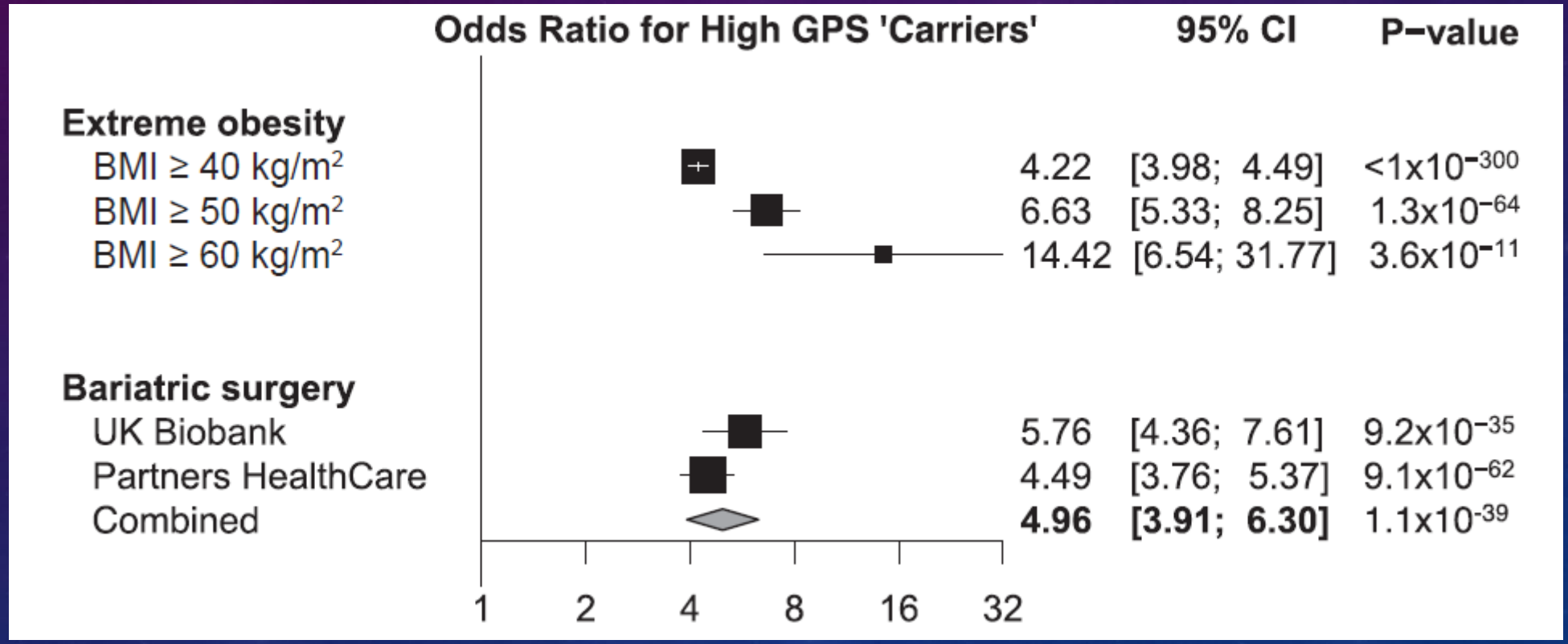
Haase IJO 2021

HIGHER PREVALENCE OF OBESITY AND SEVERE OBESITY IN TOP DECILE OF POLYGENIC RISK SCORE



Khera A. V. et al Cell 2019

ODDS RATIO OF BEING IN HIGHEST DECILE FOR POLYGENIC SCORE INCREASES WITH BMI



Khera A. V. et al Cell 2019

OUTLINE

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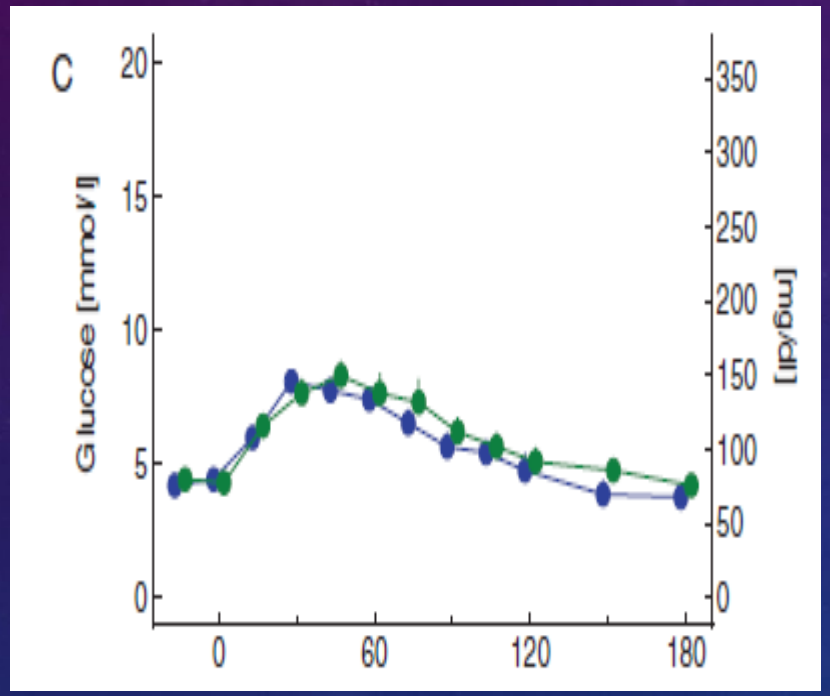
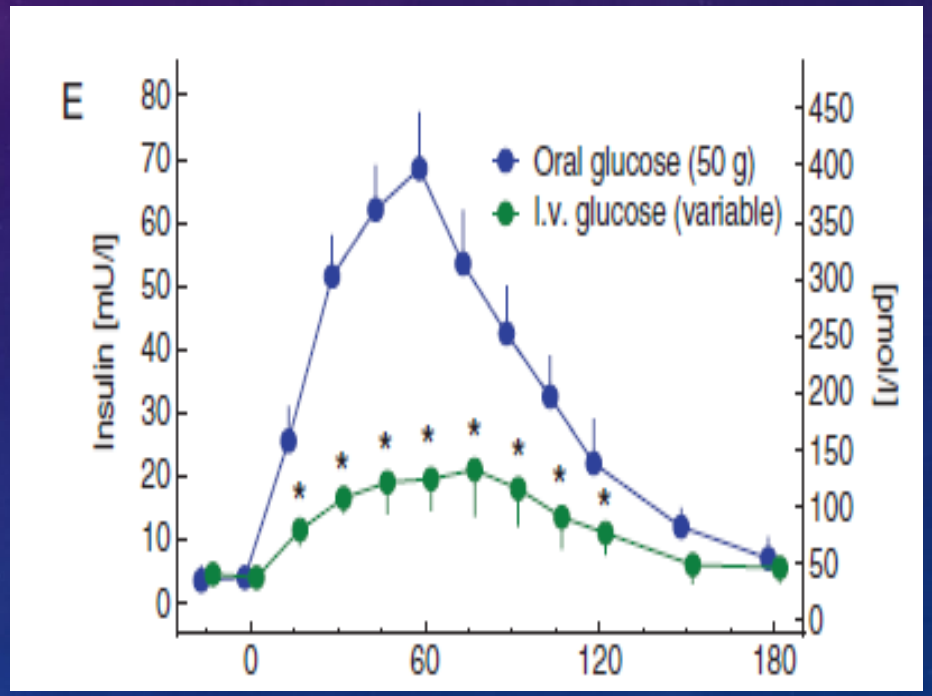
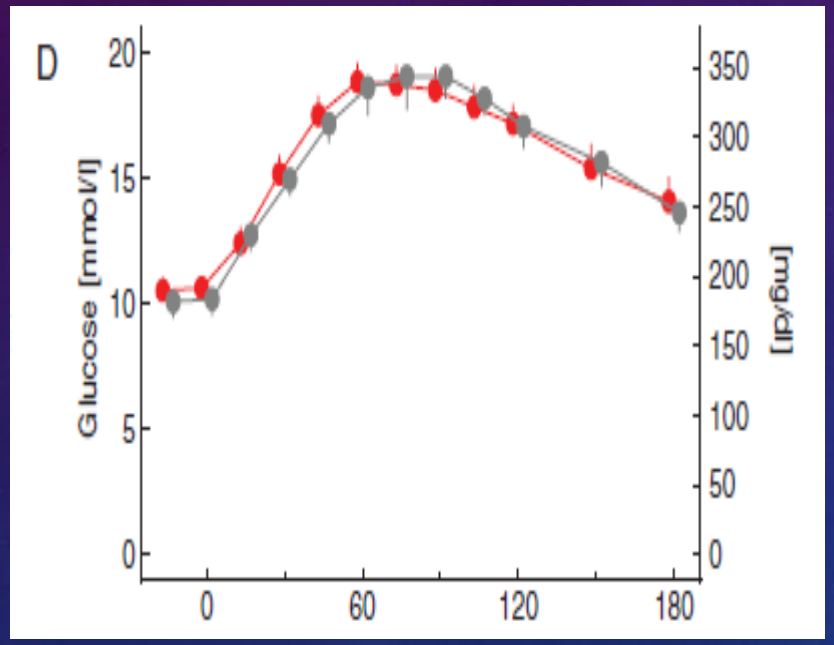
INCRETIN EFFECT

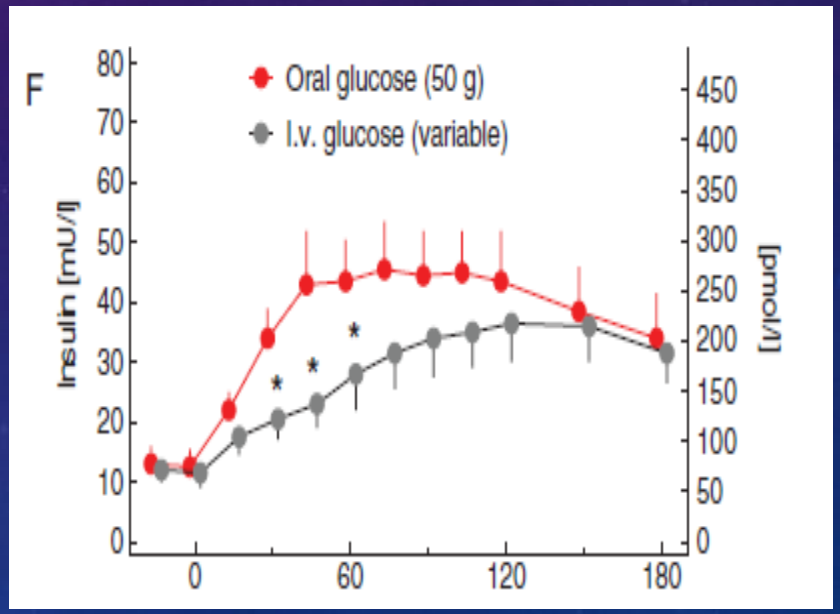




Nauck MA Diabetes Obesity Metabolism 2018

INCRETIN EFFECT IS DIMINISHED IN TYPE 2 DIABETES





Nauck MA Diabetes Obesity Metabolism 2018

INCRETINS

Glucagon like peptide-1 (GLP1)

-secreted in L cells of small intestine (ileum)

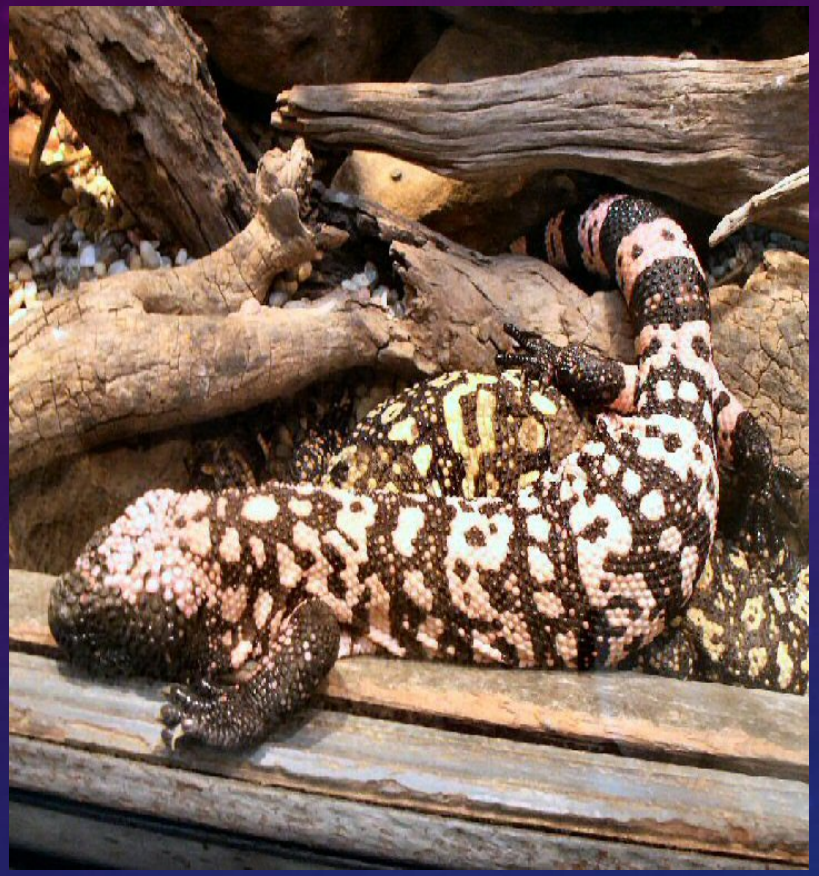
Glucose-dependent insulinotropic polypeptide (GIP)

-secreted in K cells duodenum and jejunum

Both are insulinotropic and stimulate insulin secretion from pancreatic beta cells and reduce glucagon release

Both are rapidly degraded by DPP IV enzyme

GILA MONSTER AND JOHN ENG



Long periods without eating
Does eat, maintain constant glucoses

Hormones from Gila monster lead to pancreatic enlargement

Identified a peptide called exendin-4

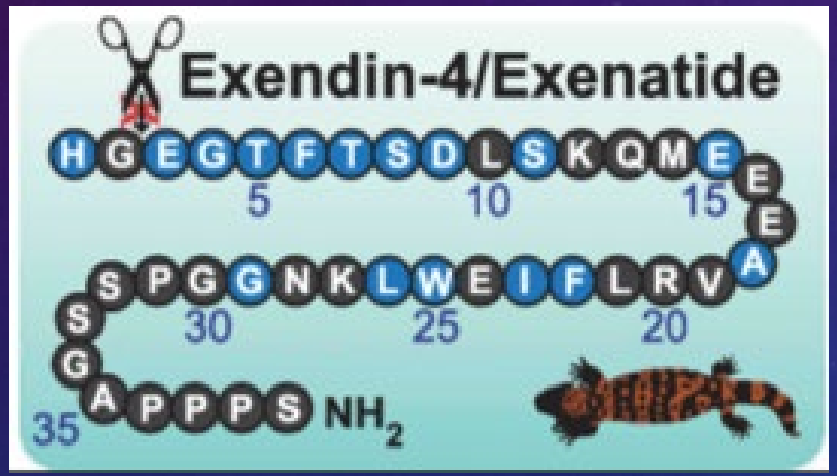
53% homologus to glucagon like peptide-1 (GLP-1)

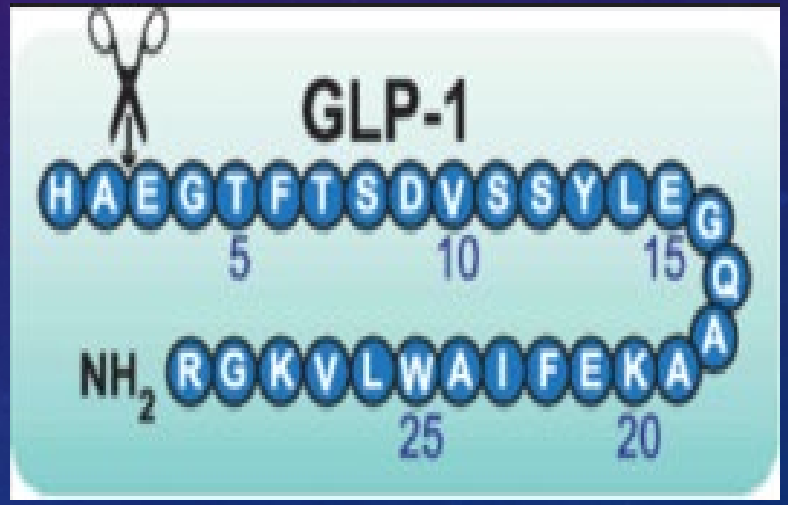
Similar in function
GLP-1 lasts only minutes, exendin-4 for hours

EXENDIN-4 VS. GLP-1

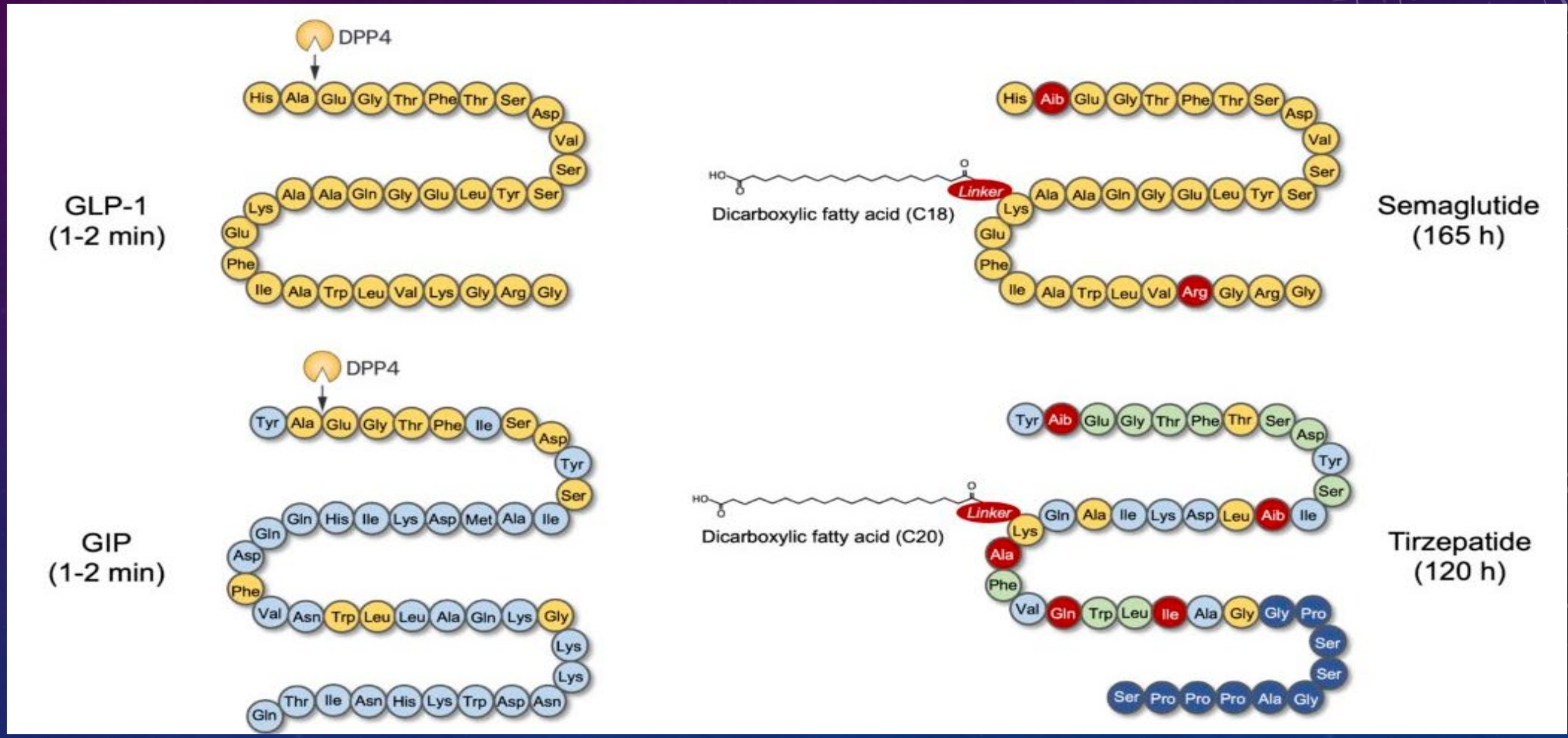
GLP-1 is degraded quickly by DPP IV enzyme

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

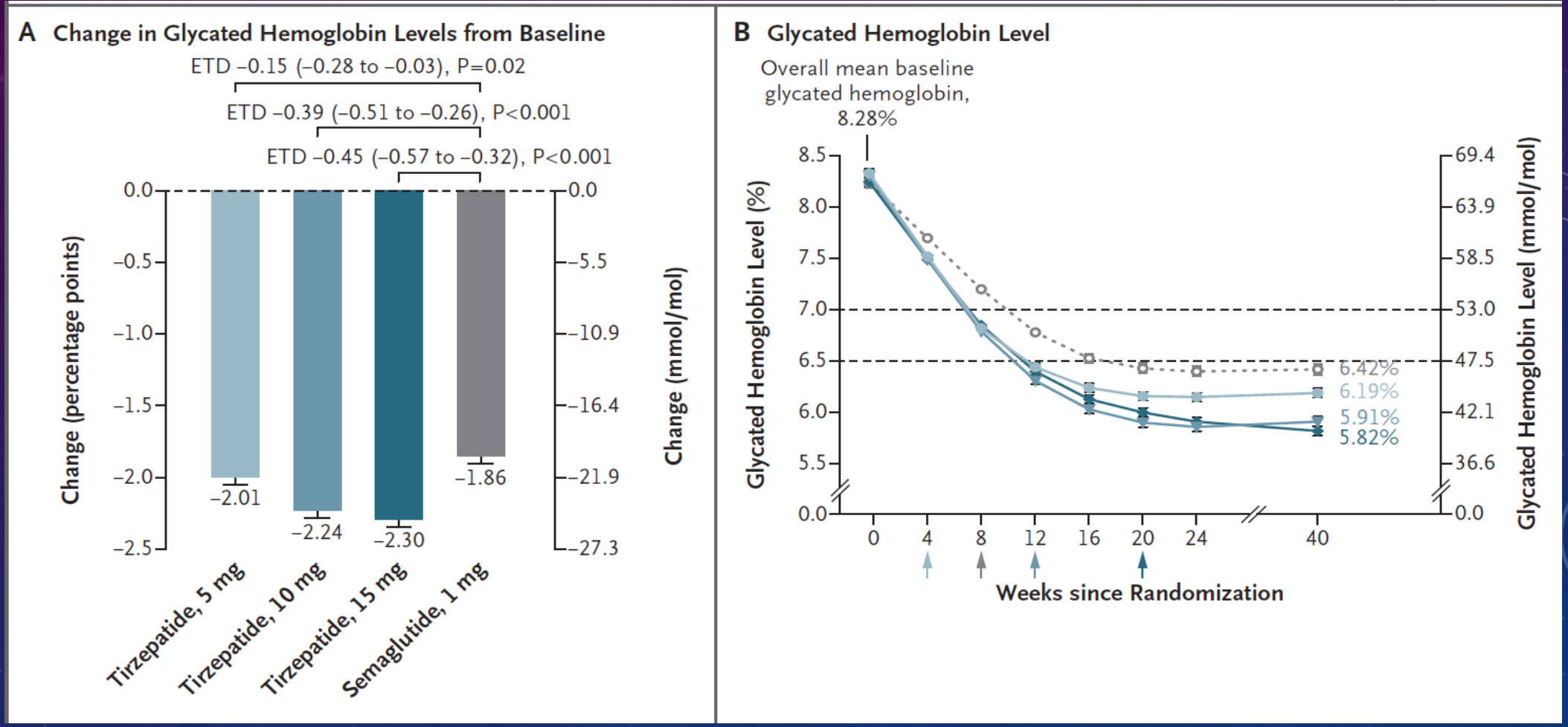




STRUCTURES OF SEMAGLUTIDE AND TIRZEPATIDE



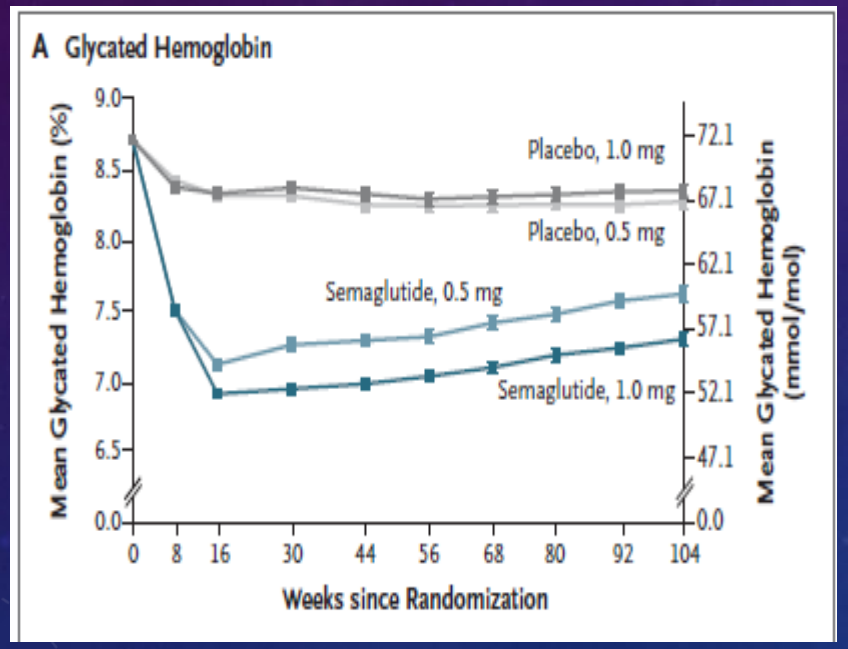
BOTH SEMAGLUTIDE AND TIRZEPATIDE ARE EFFECTIVE AT IMPROVING GLYCEMIA

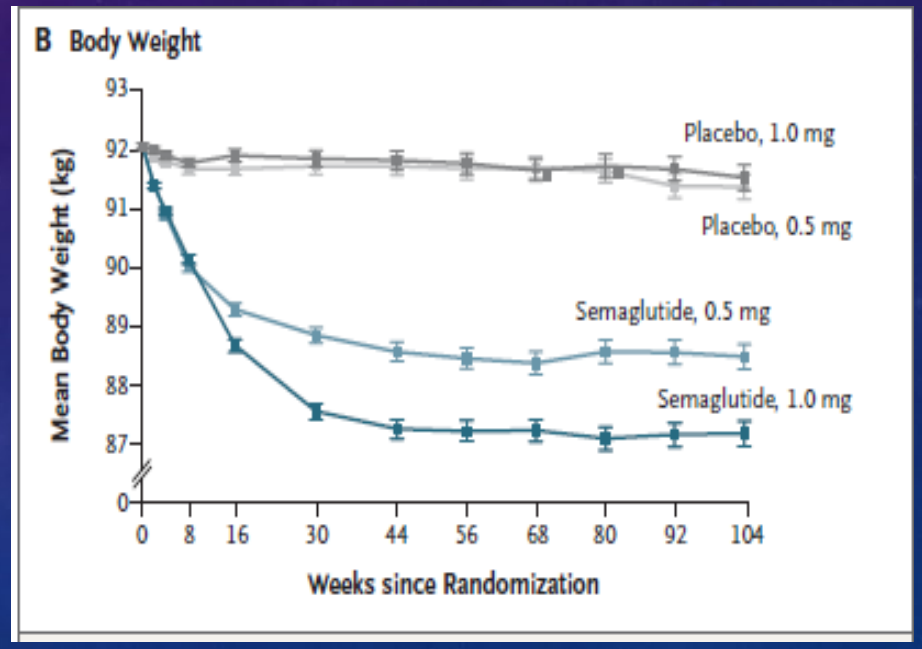


Frias JP and SURPASS-2, NEJM, 2021

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

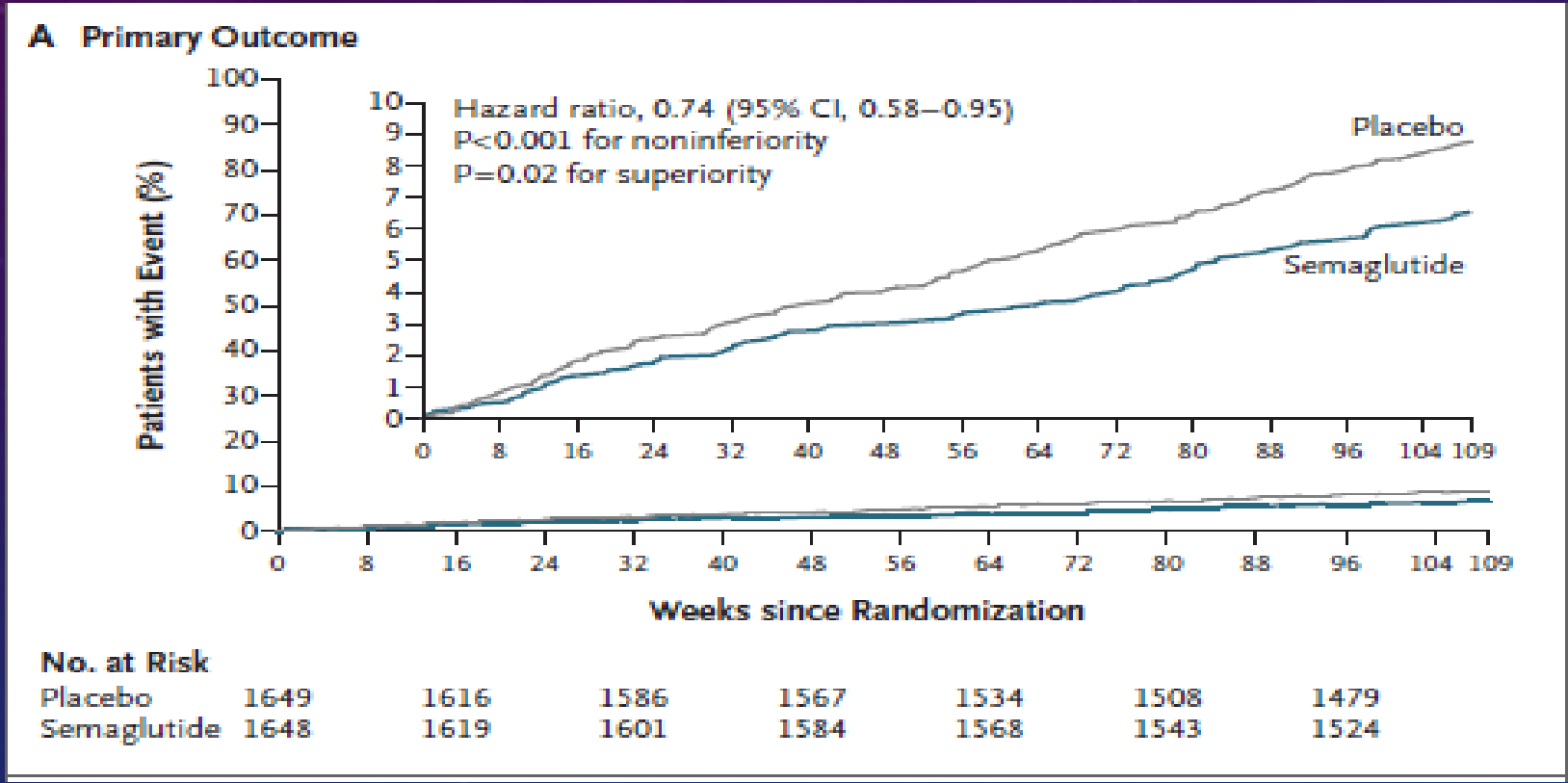
Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*





Marso SP et al SUSTAIN-6 NEJM 2016

SEMAGLUTIDE REDUCED CVD RISK IN INDIVIDUALS WITH TYPE 2 DIABETES

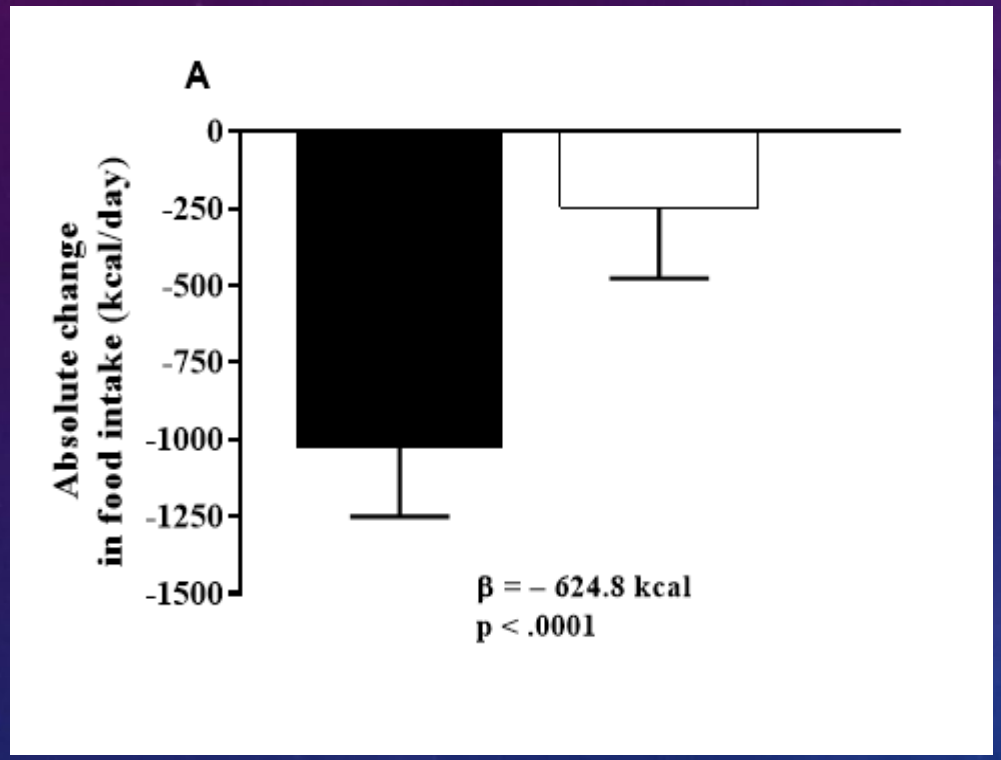


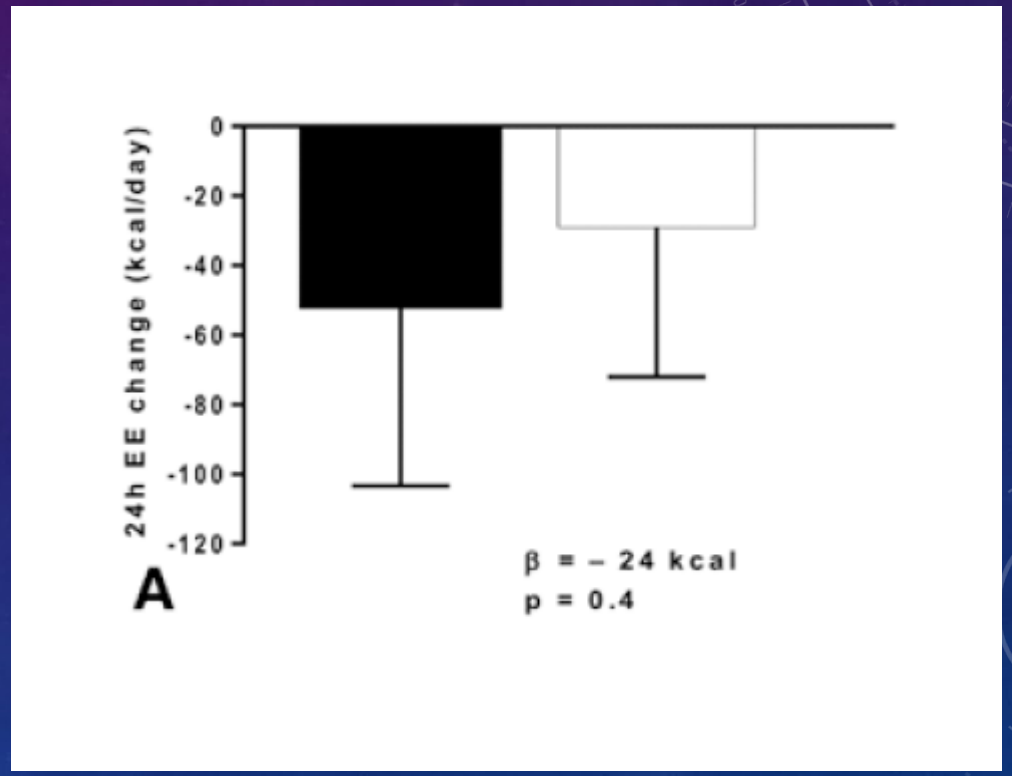
Marso SP et al SUSTAIN-6 NEJM 2016

EXTRA PANCREATIC EFFECTS OF INCRETINS

- Slows gastric emptying
- Reduces cravings or ruminations about food
- Increases oxidation of lipids

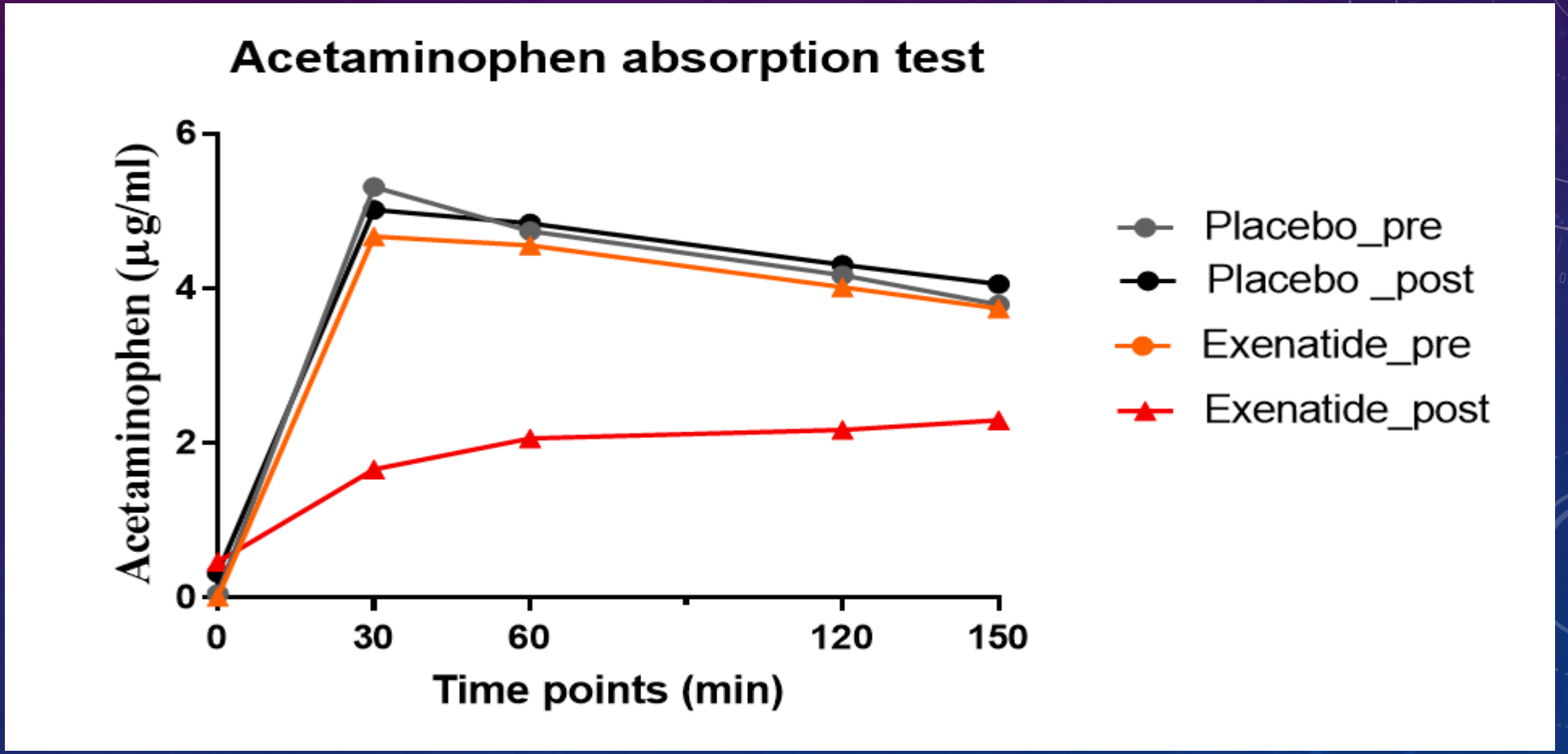
REDUCTION OF FOOD INTAKE BUT NO CHANGES IN ENERGY EXPENDITURE WITH EXENATIDE





Basolo A, Krakoff J et al Metabolism 2018

EXENATIDE REDUCES GASTRIC EMPTYING



Basolo A and Krakoff J

POPULATION SELECTED IN SEMAGLUTIDE AND WEIGHT LOSS STUDY

BMI ≥ 30 kg/m²

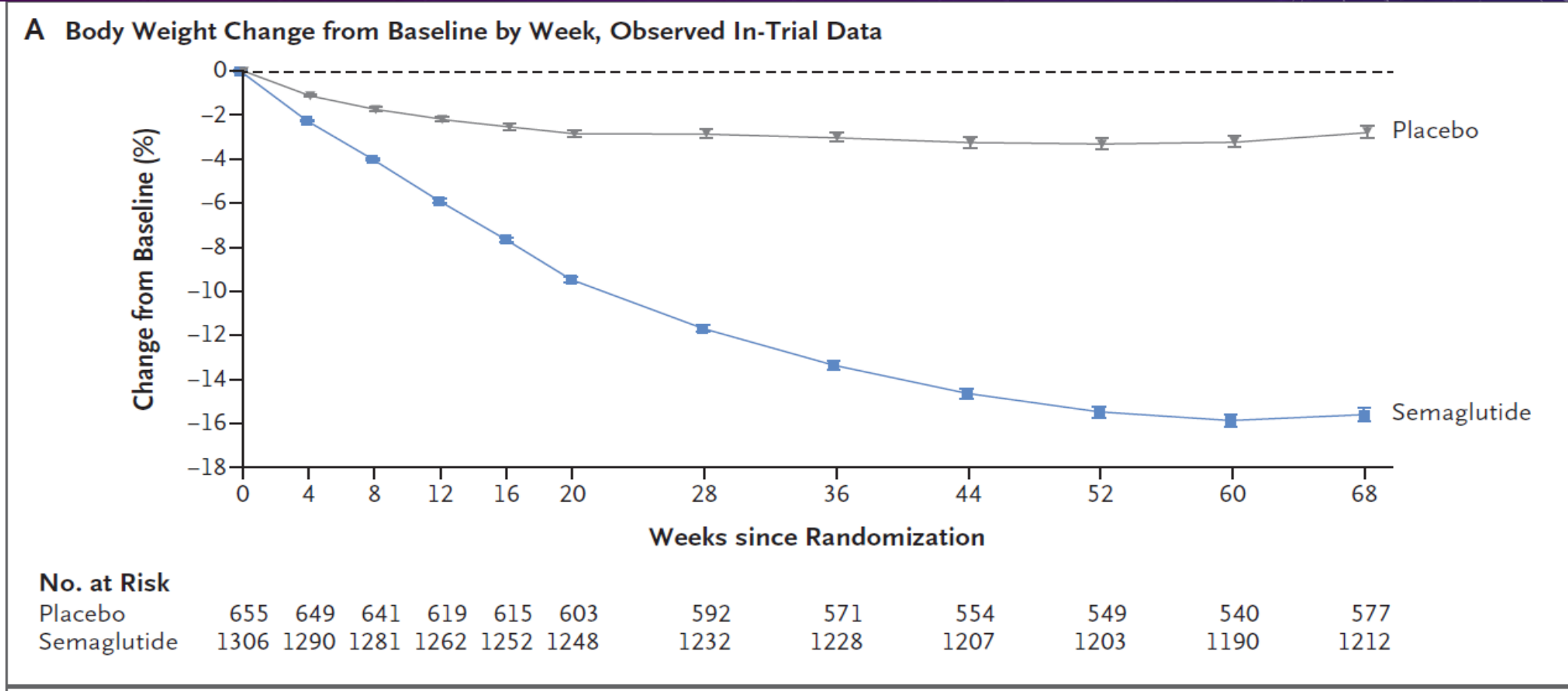
BMI ≥ 27 kg/m² with

- Hypertension
- Hyperlipidemia
- Obstructive Sleep Apnea
- Known cardiovascular disease

Excluded: Individuals with type 2 diabetes (A1c ≥ 6.5%)

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

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



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

SECONDARY ENDPOINT IMPROVEMENT AND ADVERSE EVENTS

Improvements:

Systolic blood pressure ~8 mm Hg

Diastolic blood pressure ~3 mm Hg

Physical functioning

Serious Adverse events:

9.6% in semaglutide vs. 6.4%

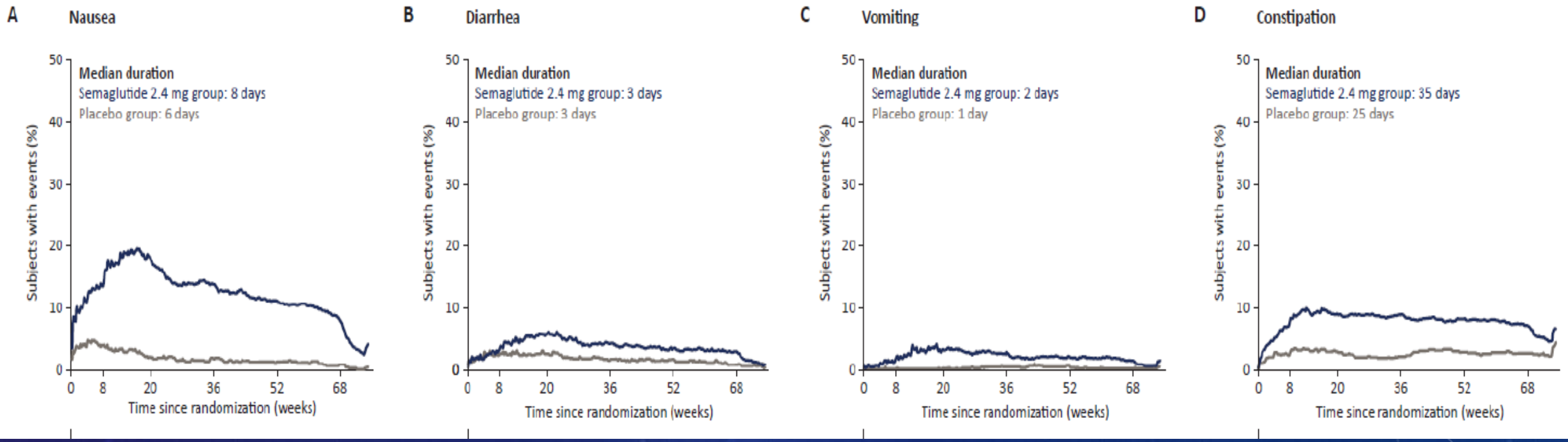
Serious GI 1.4 vs. 0%

Gallbladder 2.4 vs. 1.2%

Only 3 cases of mild pancreatitis in semaglutide group

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

EXPECTED GI SIDE EFFECTS FOR SEMAGLUTIDE DURING STUDY



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

WHY WAS THIS SO SURPRISING?

Weight loss medication field is littered with promising meds that failed

-T3 and ephedra: increased mortality

-Fenfluramine/Phentermine: great weight loss, cardiac valve disease

-Rimonabant: good weight loss, increase in anxiety and suicide risk

-Orlistat: yeah it works, but…

POPULATION SELECTED IN TIRZEPATIDE AND WEIGHT LOSS STUDY

BMI ≥ 30 kg/m²

BMI ≥ 27 kg/m² with

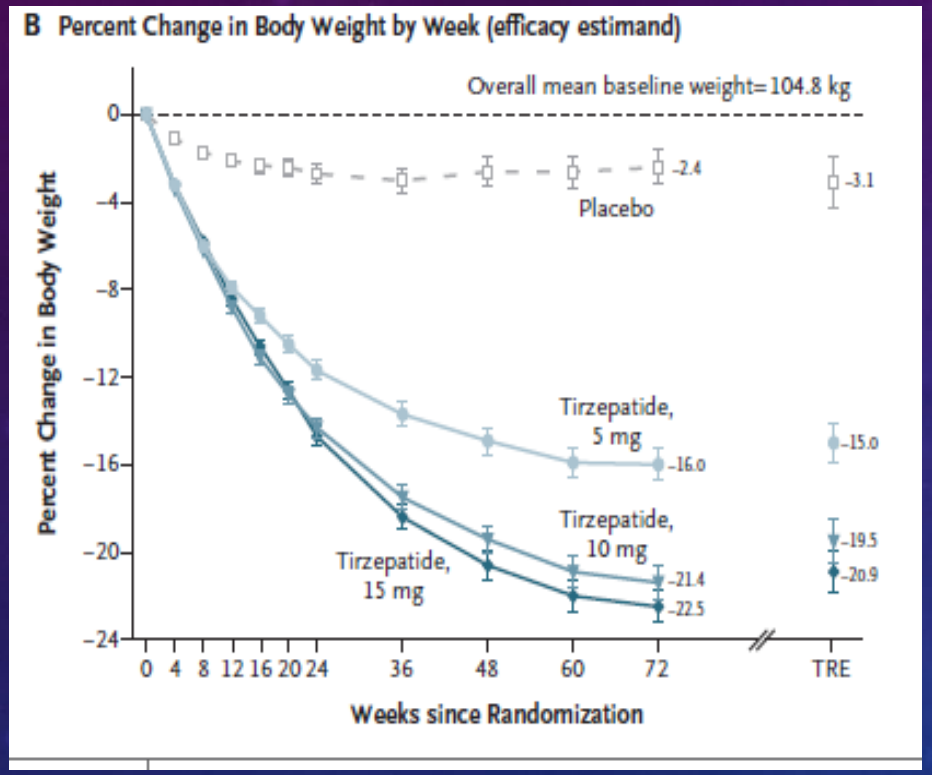
- Hypertension
- Hyperlipidemia
- Obstructive Sleep Apnea
- Known cardiovascular disease

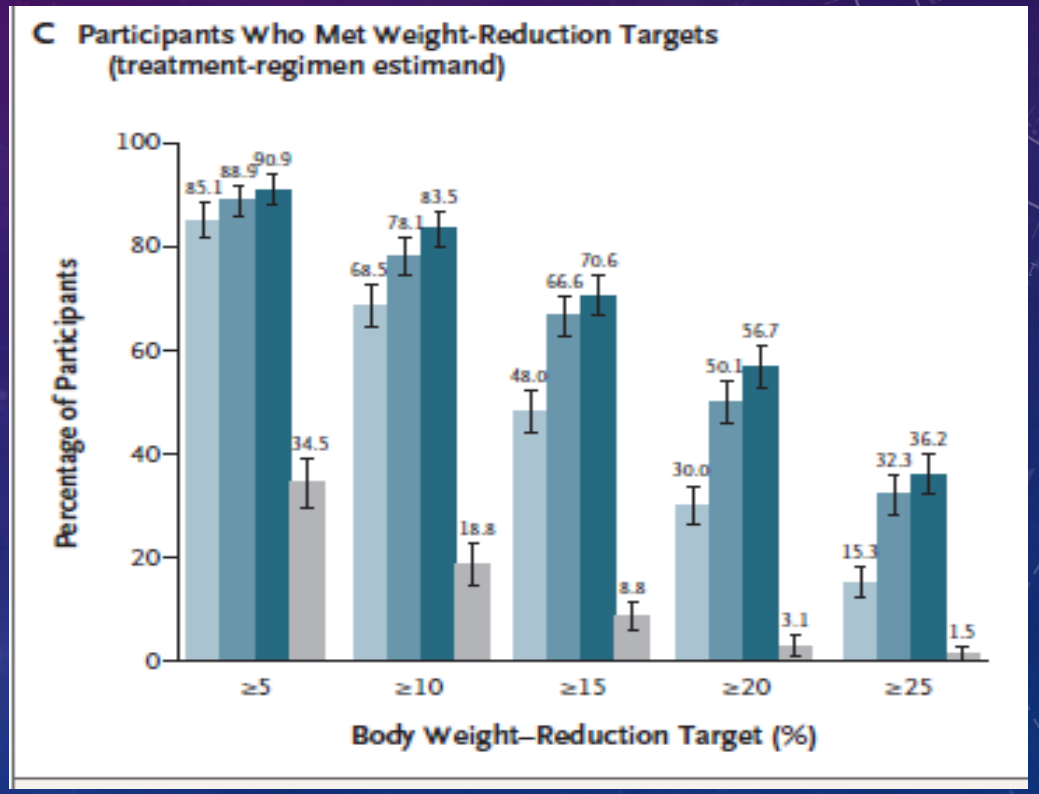
Excluded: Individuals with type 2 diabetes (A1c ≥ 6.5%)

Change in weight of 5 kg within 90 days

Jastreboff AM et al and SURMOUNT-1 trial, *NEJM* 2022

TIRZEPATIDE INDUCES >20% WEIGHT LOSS





Jasterboff AM and SURMOUNT-1 Trial, *NEJM* 2022

SECONDARY ENDPOINT IMPROVEMENT AND ADVERSE EVENTS

Improvements:

Systolic blood pressure ~6 mm Hg

Diastolic blood pressure ~4 mm Hg

Triglycerides ~ 20 mg/dl

HDL increase ~ 9 mg/dl

Serious Adverse events:

5.1-6.8% across all treatment groups

Serious GI 4.7/7.1/6.2% in tirzepatide groups vs. 2.6% in placebo

No significant difference in gallbladder disease

1 case of pancreatitis in each group (including placebo)

Jastreboff AM et al SURMOUNT-1 study NEJM 2022

MAIN RESULTS

Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes

A. Michael Lincoff, M.D., Kirstine Brown-Frandsen, M.D., Helen M. Colhoun, M.D., John Deanfield, M.D., Scott S. Emerson, M.D., Ph.D., Sille Esbjerg, M.Sc., Søren Hardt-Lindberg, M.D., Ph.D., G. Kees Hovingh, M.D., Ph.D., Steven E. Kahn, M.B., Ch.B., Robert F. Kushner, M.D., Ildiko Lingvay, M.D., M.P.H., Tugce K. Oral, M.D., Marie M. Michelsen, M.D., Ph.D., Jorge Plutzky, M.D., Christoffer W. Tornøe, Ph.D., and Donna H. Ryan, M.D., for the SELECT Trial Investigators*

Lincoff AM and SELECT investigators, NEJM 2024

POPULATION SELECTED IN SEMAGLUTIDE CVD OUTCOMES STUDY

Age ≥ 45 years

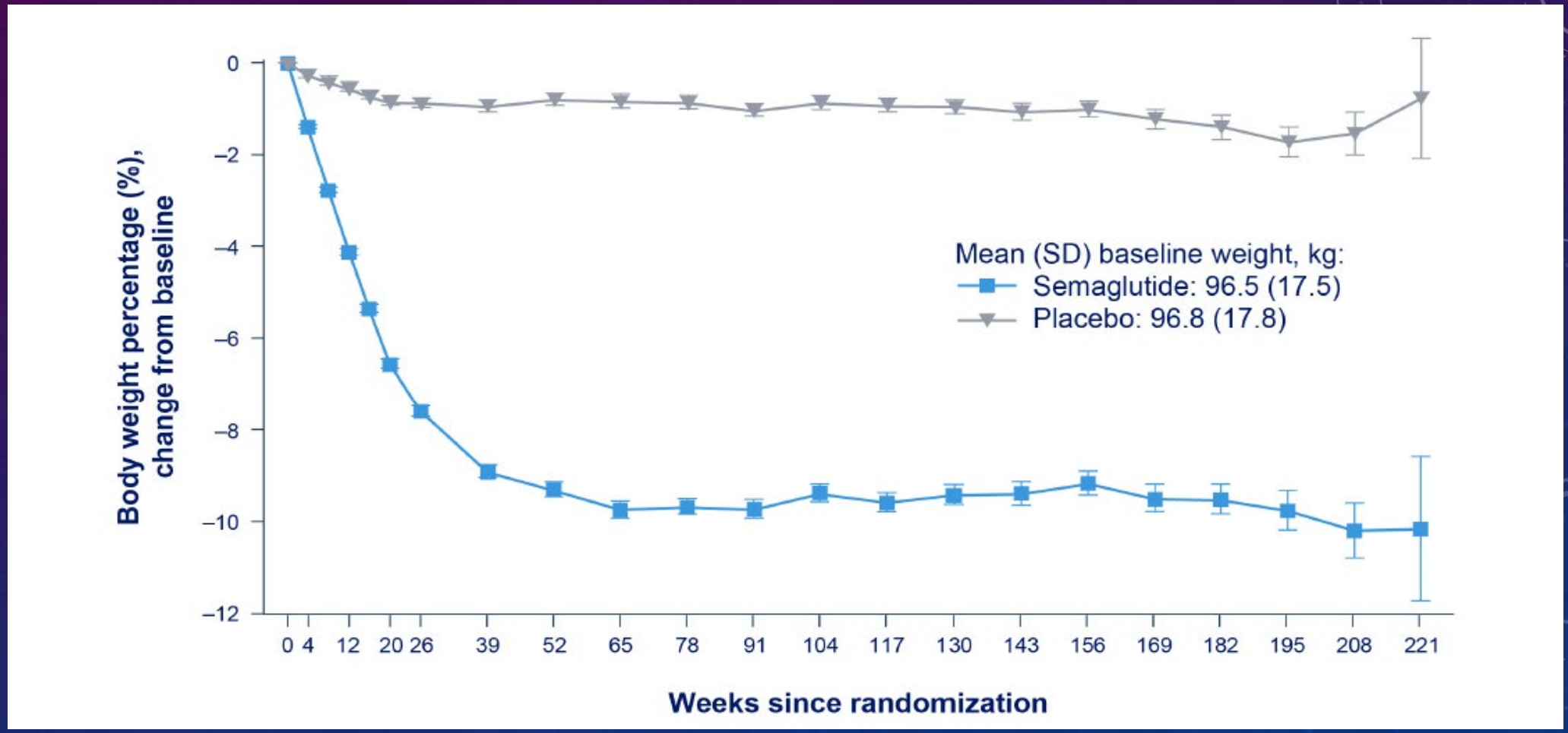
BMI ≥ 27 kg/m² with Cardiovascular disease

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

Excluded: Individuals with type 2 diabetes (A1c ≥ 6.5%)

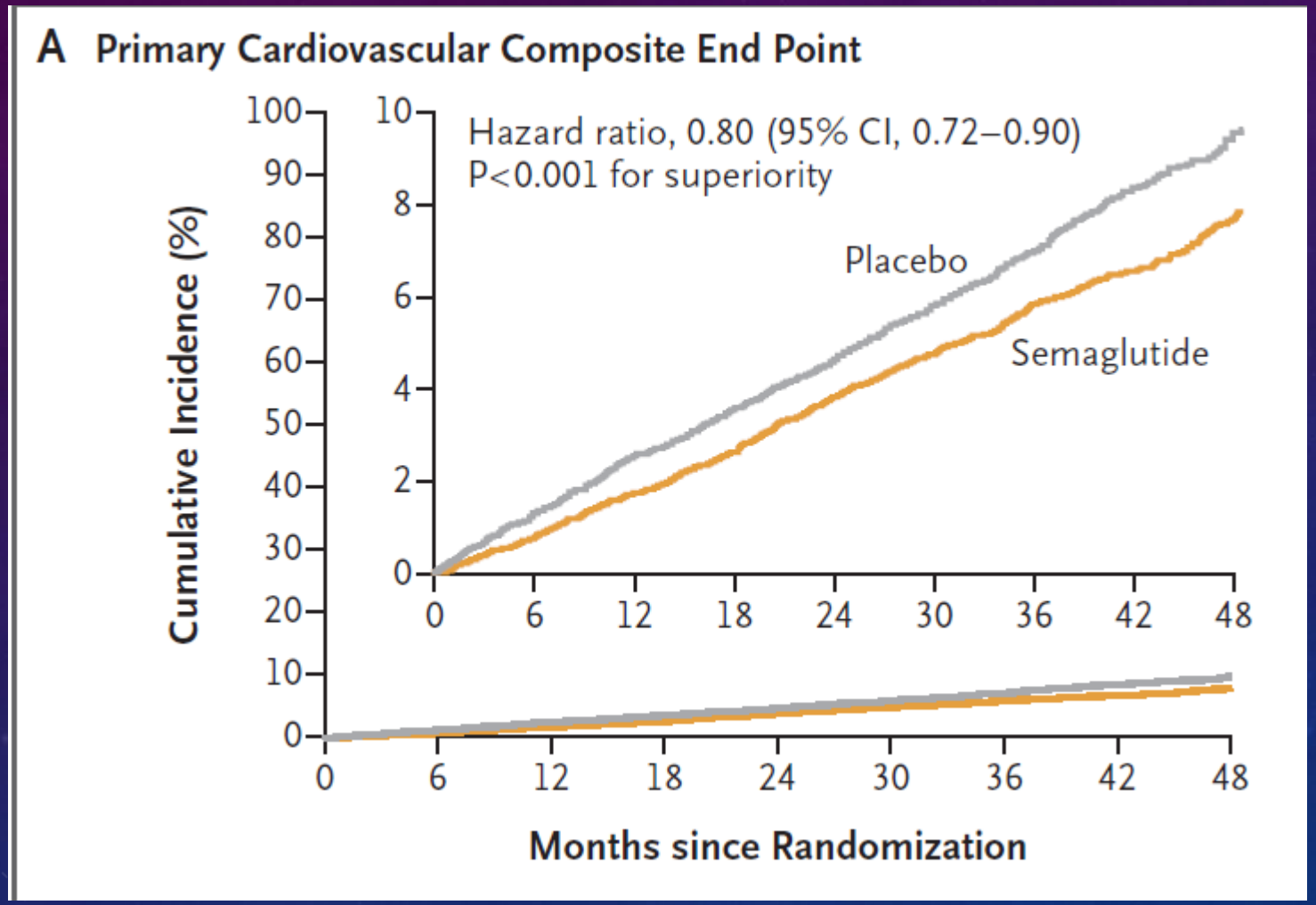
Lincoff AM et al and SELECT TRIAL, *NEJM* 2024

WEIGHT CHANGE IN SEMAGLUTIDE CVD OUTCOME STUDY



Lincoff AM and SELECT investigators, NEJM 2024

SEMAGLUTIDE DECREASES CVD EVENTS BY 20%



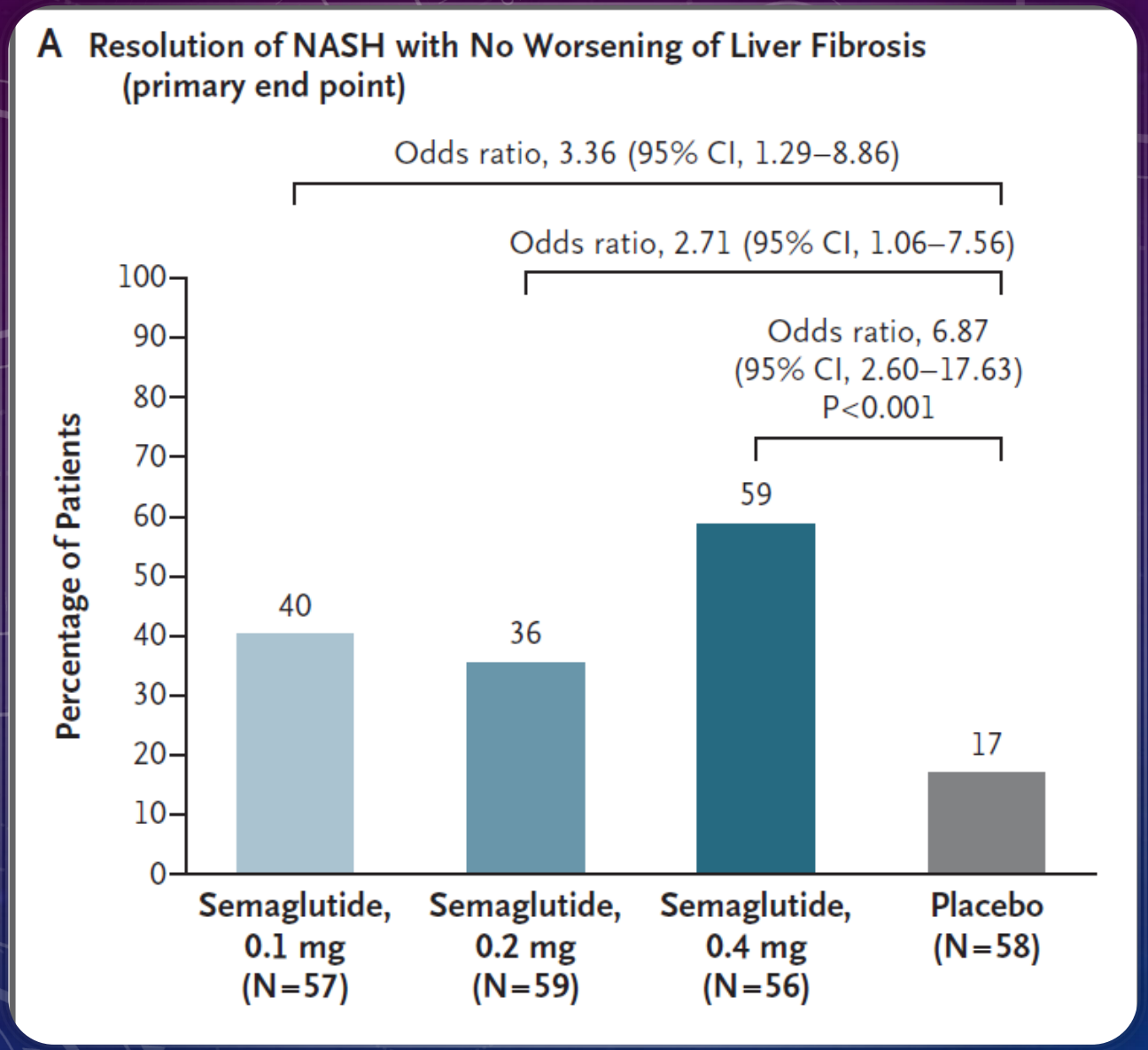
Age >45, BMI ≥ 27 kg/m²
Established CVD

N=8803 semaglutide;
8801=placebo
Mean age=61.6 yrs
Mean BMI=33.3 kg/m²

Mean weight loss 9.4%

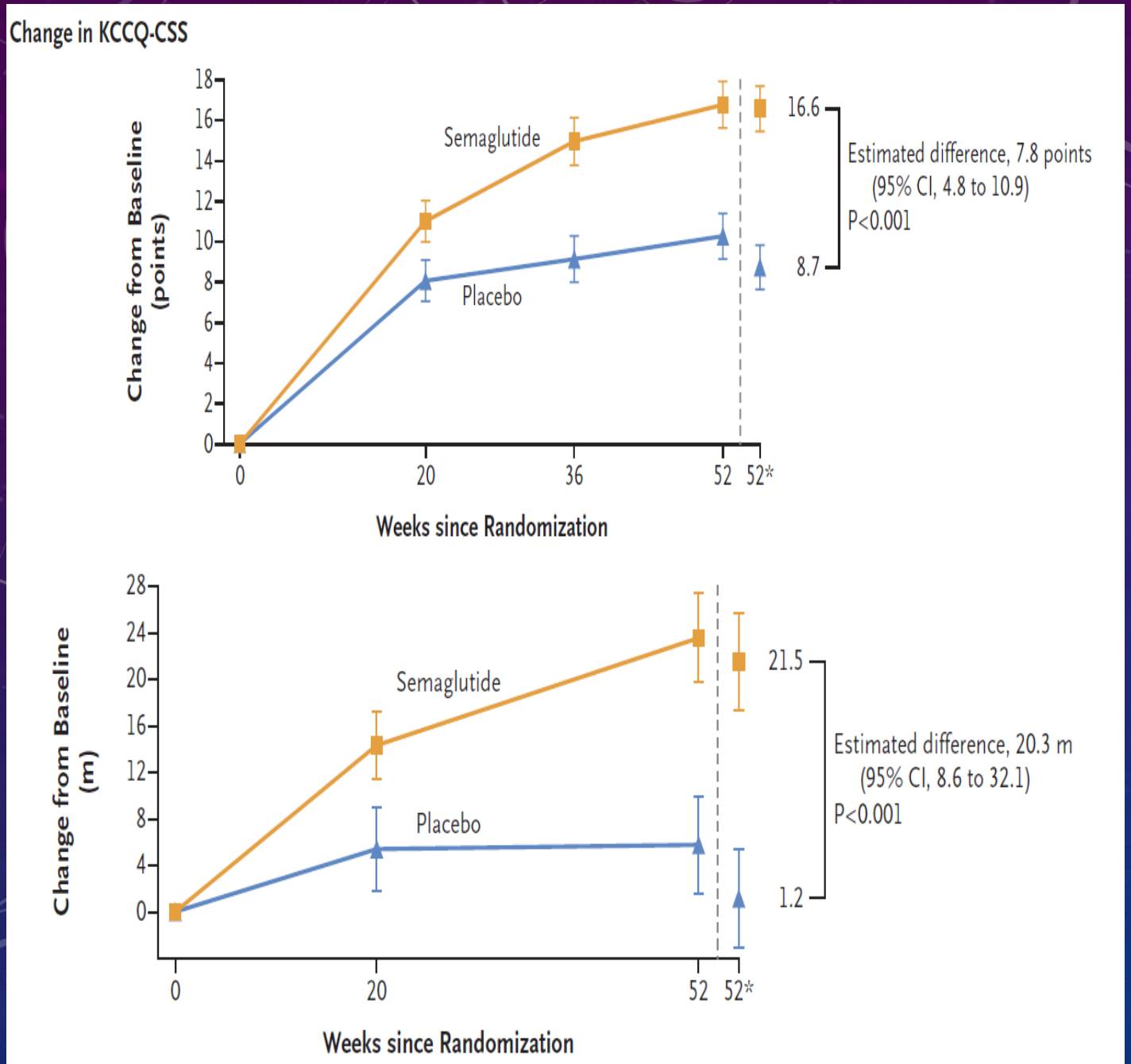
Lincoff AM and SELECT Trial, *NEJM* 2024

OTHER OUTCOMES WITH SEMAGLUTIDE: NON-ALCOHOLIC STEATOHEPATITIS



NEWSOME PN ET AL, NEJM 2021

OTHER OUTCOMES WITH SEMAGLUTIDE: IMPROVEMENT CHF SYMPTOMS IN THOSE WITH PRESERVED EJECTION FRACTION



KOSIBROD MN ET AL, NEJM 2023

OUTLINE

- Evidence that weight loss has health benefits
- Does it make sense to focus treatment on individuals with more elevated BMI?
- Options to treat
- What new treatments are out there?

MORE MEDICATIONS ARE ON THE WAY

Tirzepatide: combines GLP-1 and GIP, considered dual agonist

Other dual agonists: combine GLP-1 and Glucagon agonists

- 8-17% weight loss in initial studies

Triple agonists under study: (GLP-1, Glucagon and GIP agonists)

- Retratutide (Lilly) 24% weight loss

Gustegell et al Diabetes Therapeutics 2024

INCREASINGLY WE WILL SEE DRUGS TARGETING SPECIFIC GENETIC ALIGNED MECHANISMS

Individuals with monogenic forms of obesity:

Rare and include:

Leptin deficiency

treat with leptin (metreleptin)

Propiomelanocortin deficiency (POMC)

Proprotein convertase subtilisin/kexin type 1 deficiency (PCSK1)

Bardet-Biedl syndrome

Leptin receptor deficiency

treat with setmelanotide (Melanocortin 4 agonist, increases satiety)

WHO SHOULD WE TREAT?

PLUSES

- VERY EFFECTIVE
- ESTABLISHING A GOOD RECORD OF SAFETY
- SIDE EFFECTS ARE PREDICTABLE
- EMERGING HARD ENDPOINTS FOR BENEFIT
  - CVD, NASH, HEART FAILURE

MINUSES

- COSTS
- AVAILABILITY AND DEMAND
- LIFELONG THERAPIES
- RELIANCE ON MEDICATION AT EXPENSE OF INVESTMENT IN HIGH QUALITY FOODS AND EXERCISE

WHO TO TREAT?

- Current FDA guidelines say: “anyone BMI ≥ 30 or ≥ 27 kg/m² with co-morbidities who has attempted lifestyle intervention”

- Practical considerations:
  - Higher BMI more likely to have greater genetic component and greater risk of co-morbidities (type 2 diabetes in particular)
  - Associated co-morbidities may drive therapy
  - Patient investment and goals

REASONABLE STARTING POINT

Develop a multi-disciplinary team that provides a consistent message

- clinician, pharmacist and lifestyle interventionist (dietician, physical therapy, exercise physiologist or anyone who provides lifestyle modification counseling)

Offer treatment to those with BMI ≥40 or 45 kg/m² without co-morbidities

Consider offering at lower BMI (35 kg/m²??) to those who have CVD or NASH


QUESTIONS?