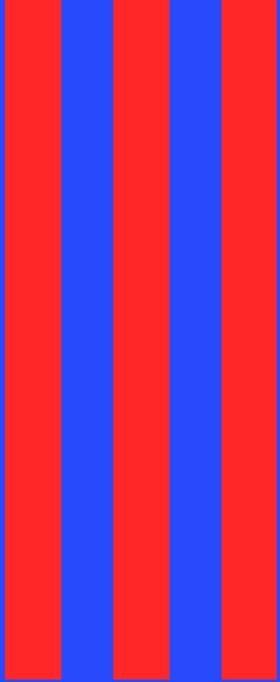


# Management of Pre-diabetes



**Shadrach Smith, MD**  
**President, Midwest Obesity Society**



# Introduction

- Diagnosis
- Incidence
- Pathogenesis
- Treatment
  - Diet
  - Medical Management



**GLUCOSE LEVELS CHART**

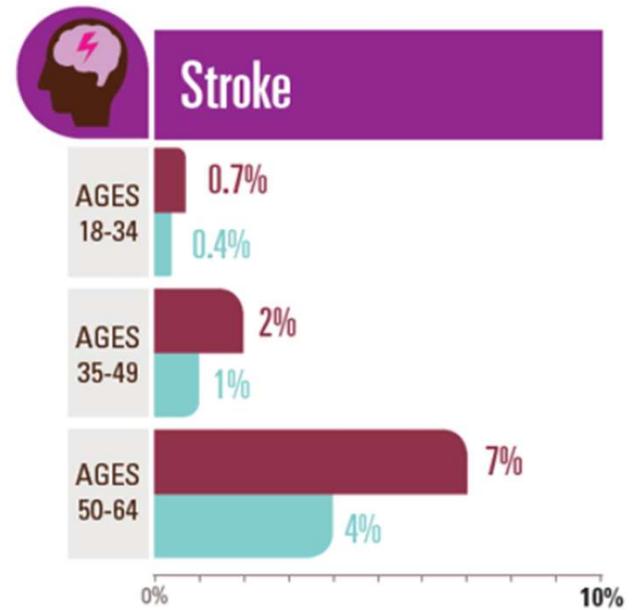
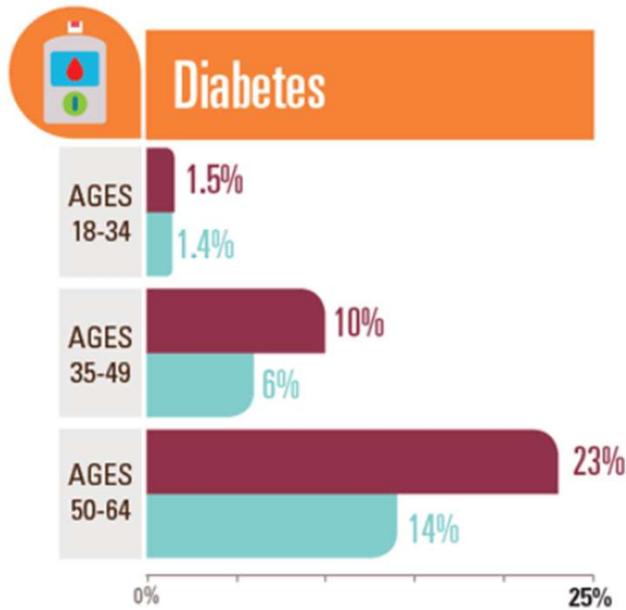
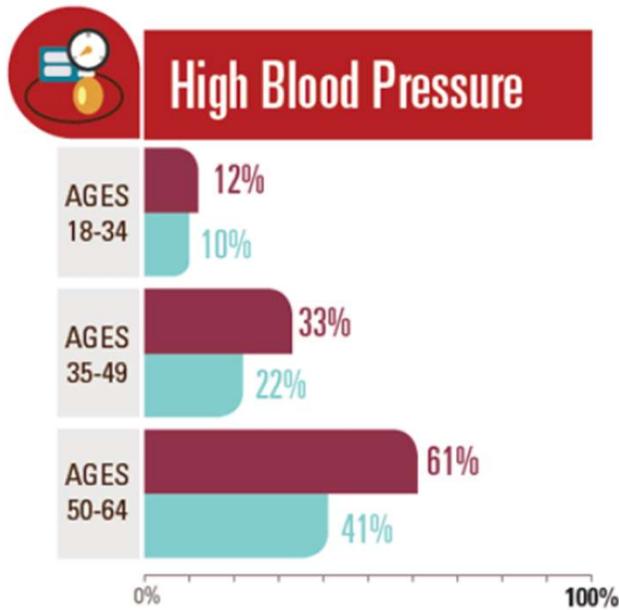
## Table 1

Top 10 causes of death for black men compared with black women, white men, and white women, 2013. Data taken from Reference [57](#)

<b>Cause of death</b>	<b>Black men</b>	<b>Black women</b>	<b>White men</b>	<b>White women</b>
Heart disease	1	1	1	1
Malignant neoplasms	2	2	2	2
Unintentional injury	3	7	3	6
Cerebrovascular diseases	4	3	5	4
Homicide	5	NA	NA	NA
Diabetes mellitus	6	4	6	7
Chronic lower respiratory disease	7	5	4	3
Nephritis, nephrotic syndrome, and nephrosis	8	6	-	9
Septicemia	9	9	-	10
Influenza and pneumonia	10	-	9	8

NA, not applicable.

# Common Chronic (TIME-related)



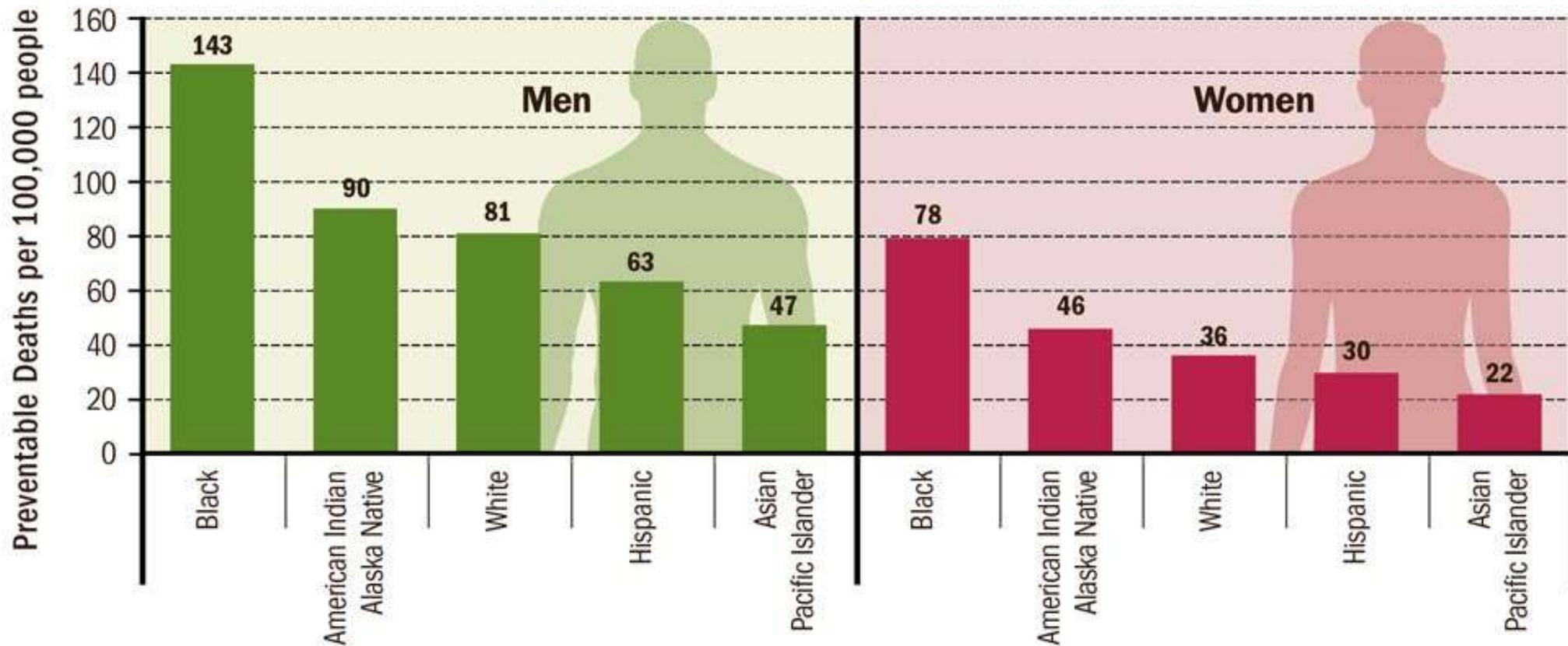
**African American**

**White**

*African Americans and whites include Hispanic and non-Hispanic origin.*

SOURCE: Behavioral Risk Factor Surveillance System, 2015.

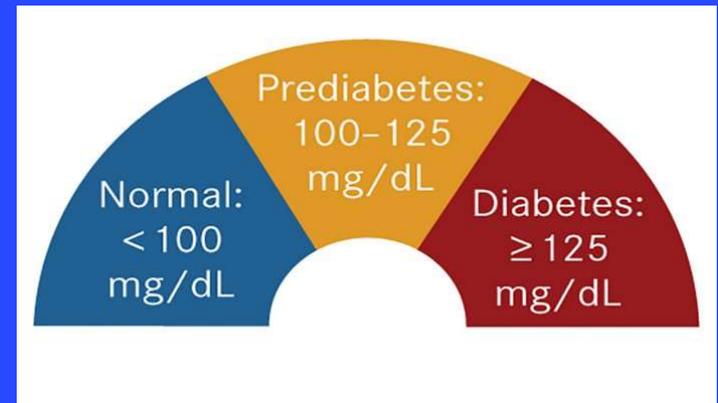
## Black men are at highest risk of dying early from heart disease and stroke



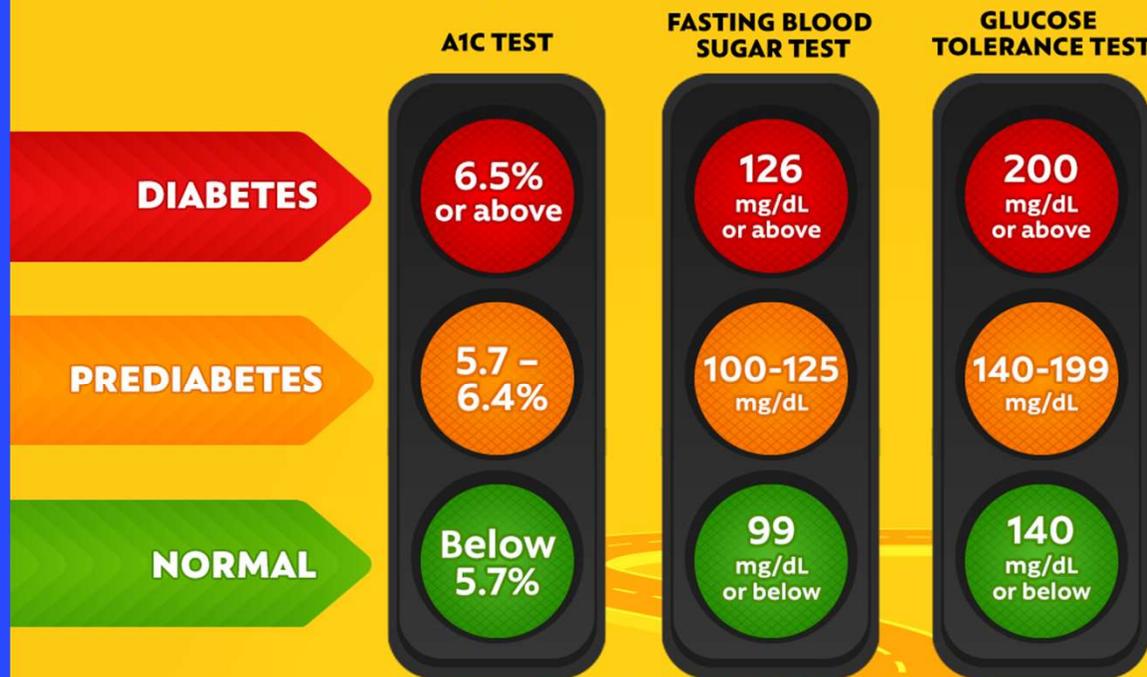
SOURCE: National Vital Statistics System, US Census Bureau, 2010.

# Feasibility of Preventing Type 2 Diabetes

- There is a long period of glucose intolerance that precedes the development of diabetes
- Screening tests can identify persons at high risk
- There are safe, potentially effective interventions that can address modifiable risk factors:
  - Obesity
  - Body fat distribution
  - Physical inactivity
  - High blood glucose



# THE ROAD TO TYPE 2 DIABETES



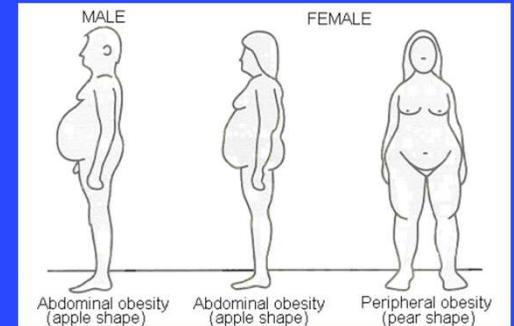
Source: American Diabetes Association



# Pre-diabetes (Synonyms)

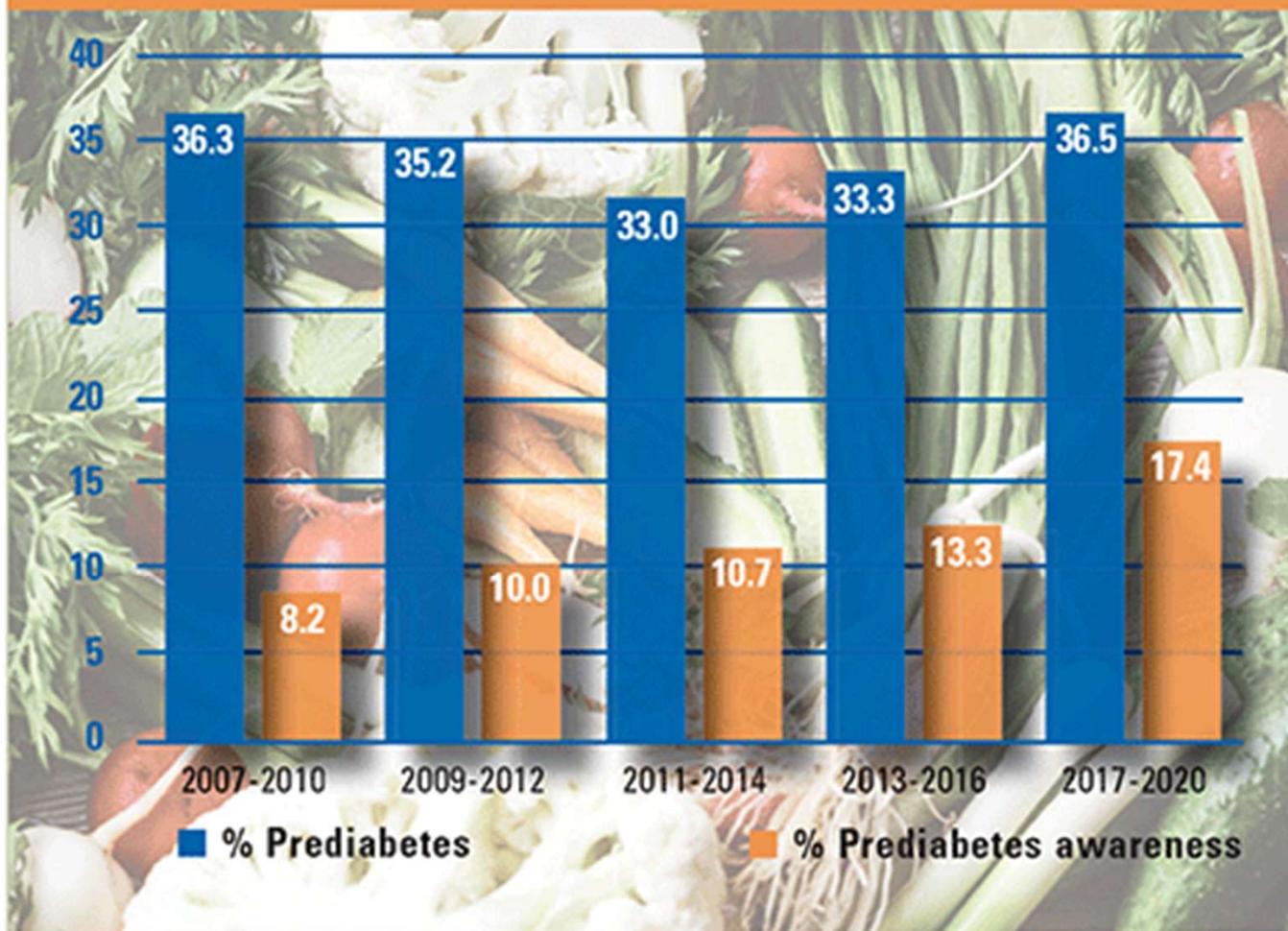
- **Prediabetes**

Impaired fasting glucose (IFG)  
Impaired glucose tolerance (IGT)  
Borderline diabetes

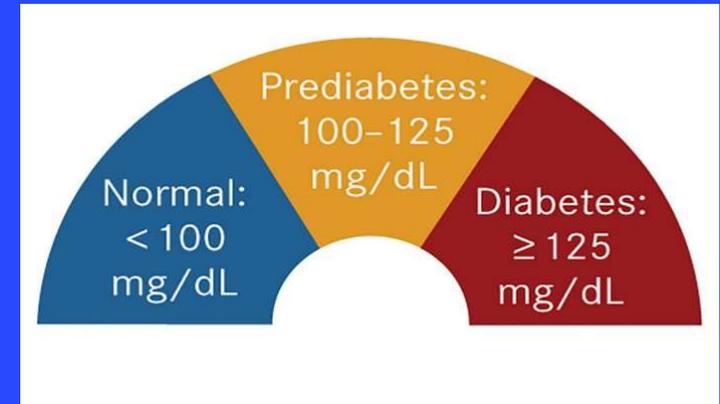


- **Metabolic syndrome** (*3 or more of the following*)
  - Increase waist size (Men >40 in and Women >35 in)
  - Elevated blood pressure > 135/85
  - Low HDL cholesterol (Men <40 and Women <50)
  - Elevated triglycerides >150
  - Fasting glucose  $\geq$  100
- **Insulin Resistance Syndrome**

## Age-Adjusted Prevalence and Awareness of Prediabetes in U.S. Adults Aged $\geq 18$ Years

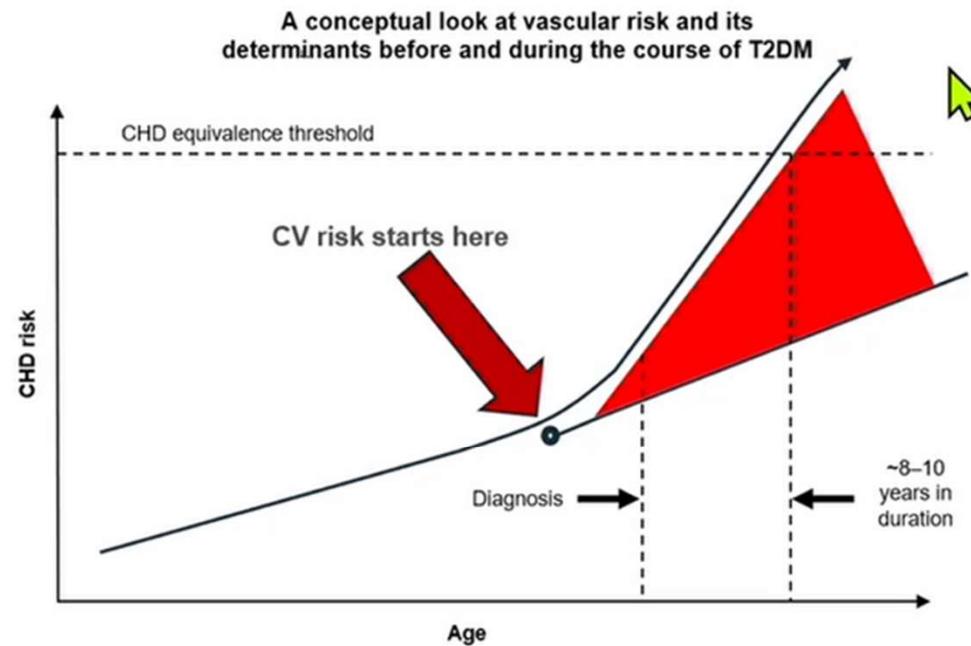


# Prediabetes

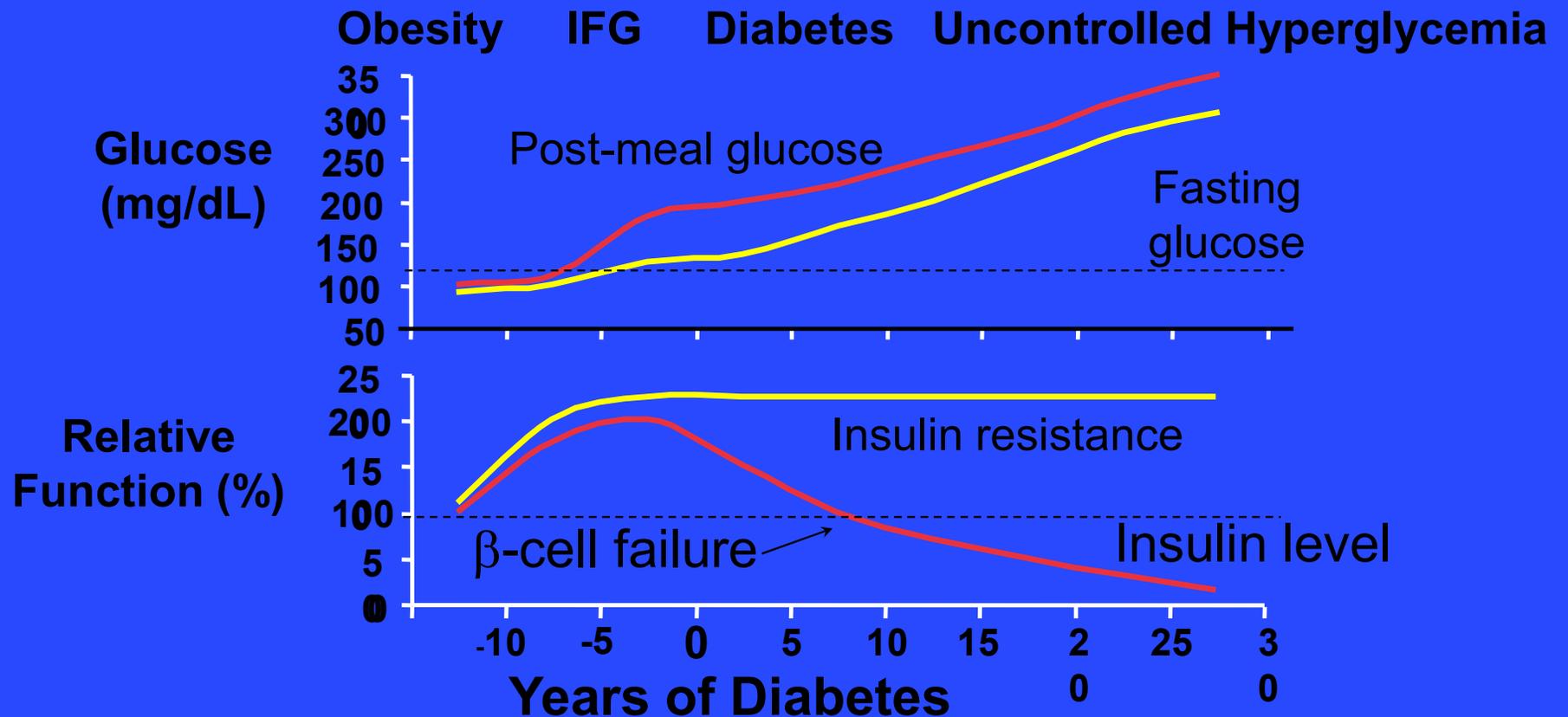


- Epidemiologic evidence suggests that the complications of T2D begin early in the progression from NGT to frank diabetes
- Prediabetes and diabetes are conditions in which early detection is appropriate, because
  - Duration of hyperglycemia is a predictor of adverse outcomes
  - There are effective interventions to prevent disease progression and to reduce complications

## The CV risk continuum in T2DM: CV risk starts before diagnosis of diabetes



# Insulin Resistance- A Precursor to Type 2 Diabetes



IFG=impaired fasting glucose.

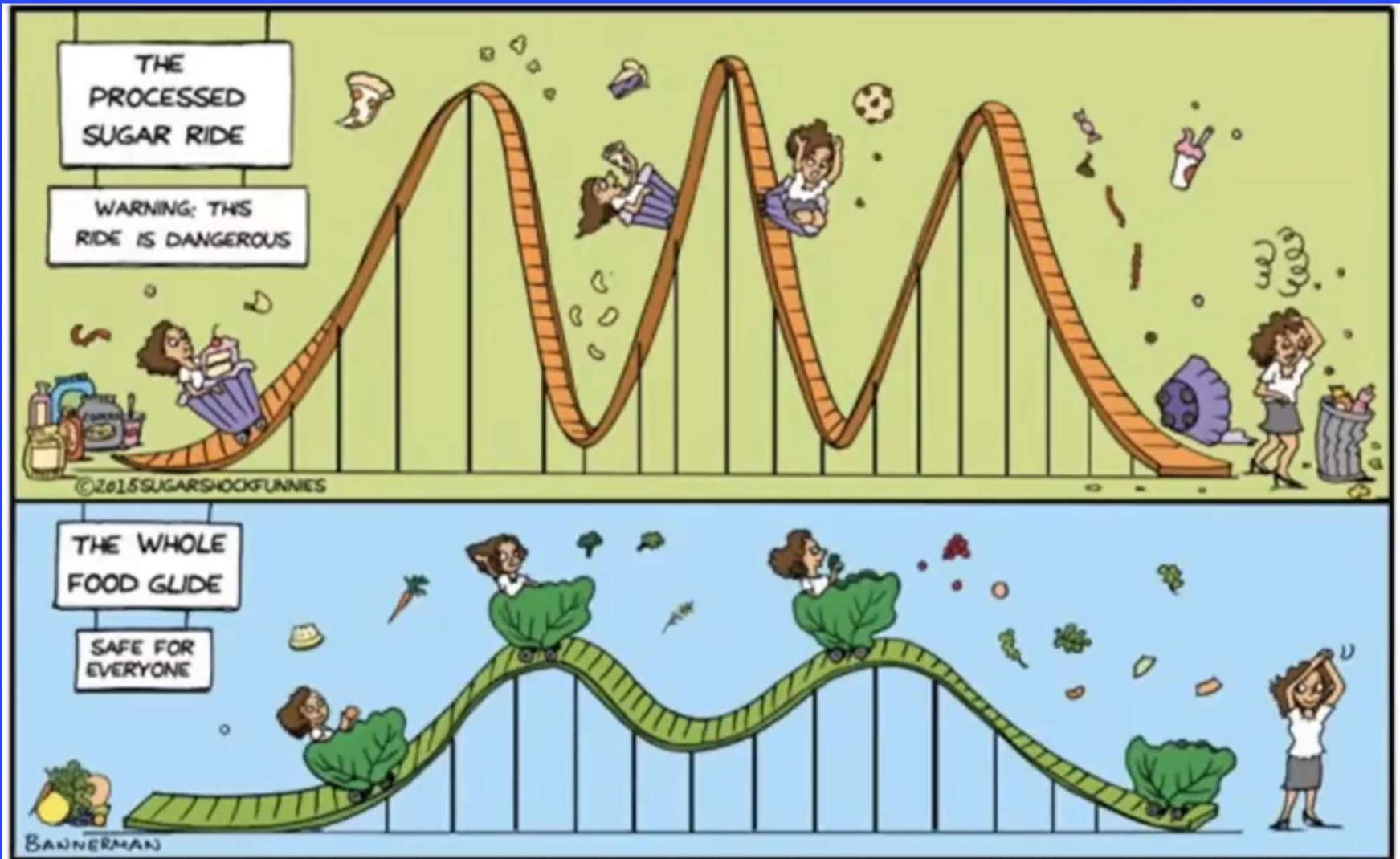
Adapted from International Diabetes Center (IDC), Minneapolis, Minnesota.

# Feasibility of Preventing Type 2 Diabetes

- There is a long period of glucose intolerance that precedes the development of diabetes
- Screening tests can identify persons at high risk
- There are safe, potentially effective interventions that can address modifiable risk factors:
  - Obesity
  - Body fat distribution
  - Physical inactivity
  - High blood glucose

# WHAT CAUSES INSULIN RESISTANCE? THE Lifestyle CURE



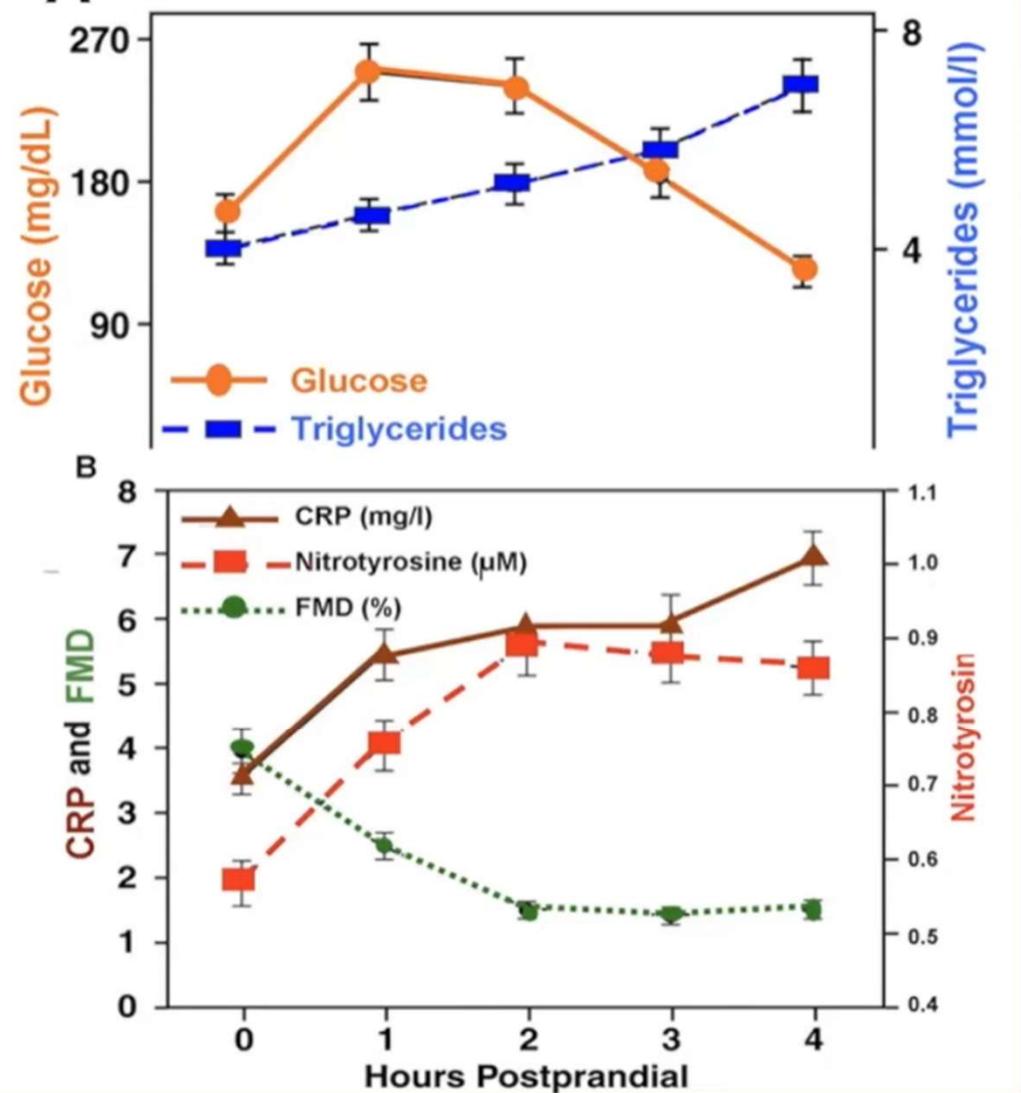


Concept: Connie Bennett Art: Isabella Bannerman

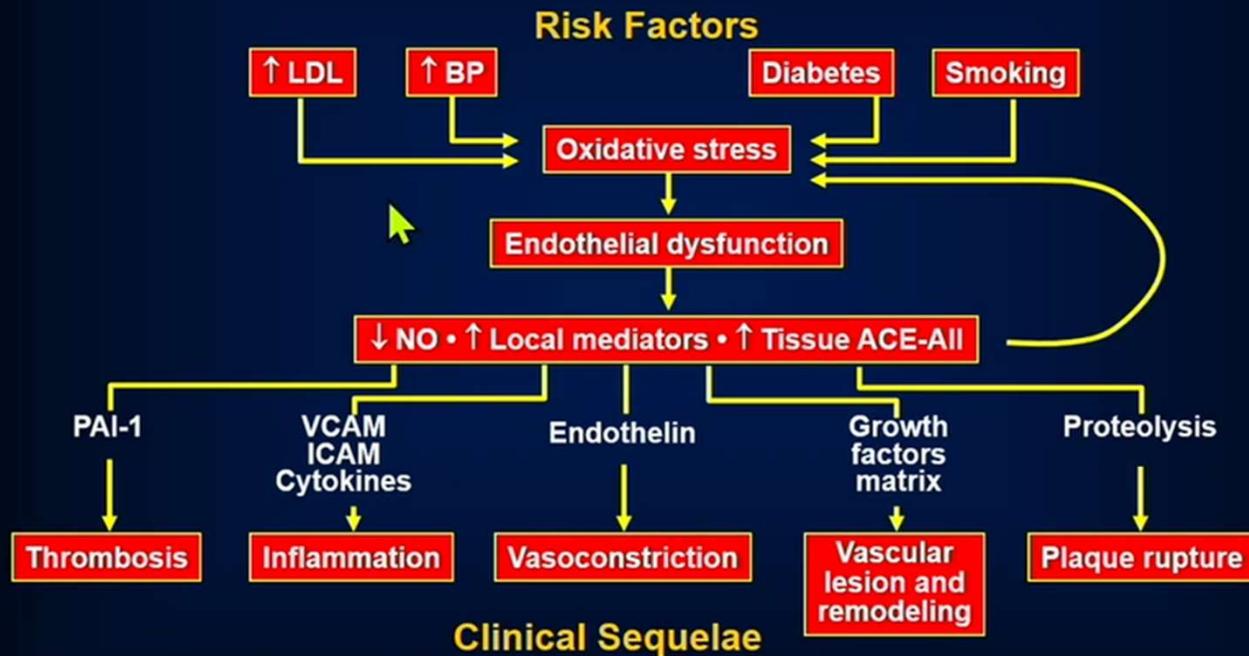
[www.Connie-Bennett.com](http://www.Connie-Bennett.com)

# Post-Prandial Stress

Post prandial stress: The immediate deleterious effects of a beverage containing 75 g glucose mixed with 700 kcal/m<sup>2</sup> of whipping cream. Within 2 to 4 h glucose and triglyceride levels double, causing immediate oxidant stress (nitrotyrosine), inflammation (C-reactive protein [CRP]), resulting in deterioration in endothelial function. 56 FMD % = Flow mediated dilation



# Unifying Model

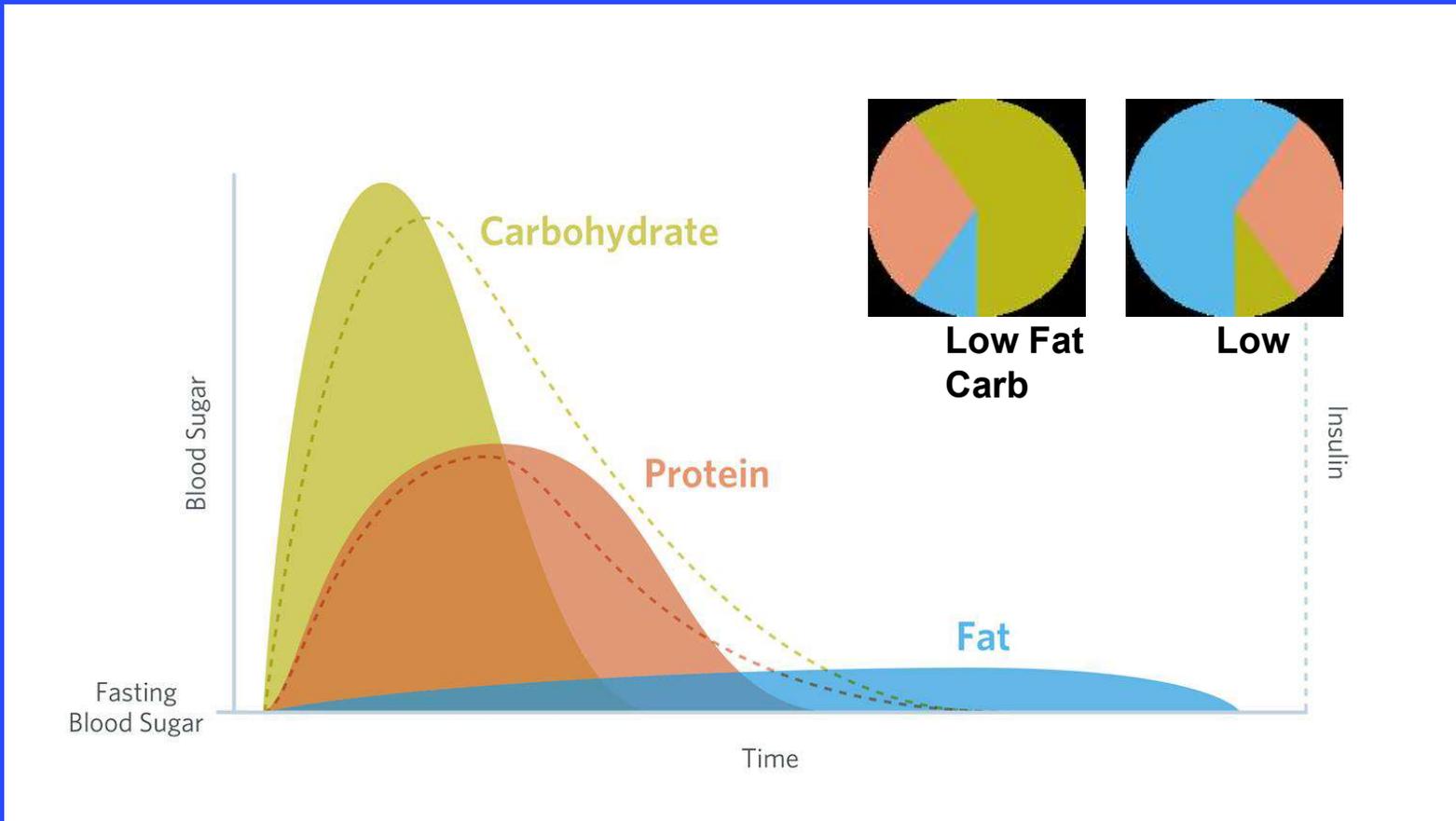


## Clinical Sequelae

NO=nitric oxide; All=angiotensin II; VCAM=vascular cell adhesion molecule;  
ICAM=intracellular adhesion molecule.

Dzau VJ et al. *Am J Cardiol.* 1997;80:331-391.

# Glucose and Insulin Response to Macronutrients



# Why Manage Disease Early

- Prevention is better than cure
- Halt Progress of Disease

*Diabetes- decrease beta cell decline*

*HTN - halt vascular remodeling and stiffening*

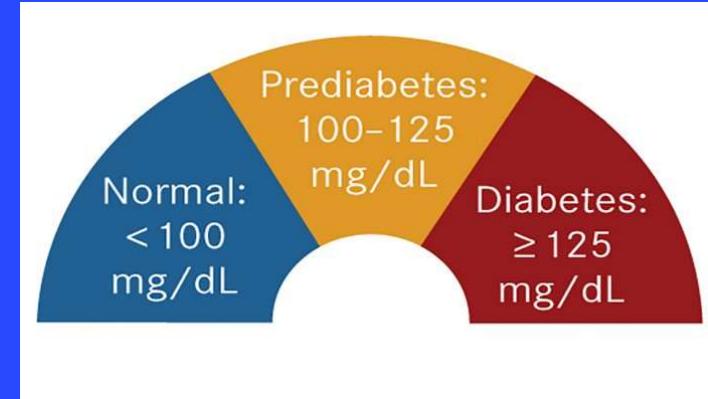
*Kidney- halt processes that cause GFR decline*

*Nerves – halt progressive decline*

- Prevent complications of disease
- Keep people healthy longer

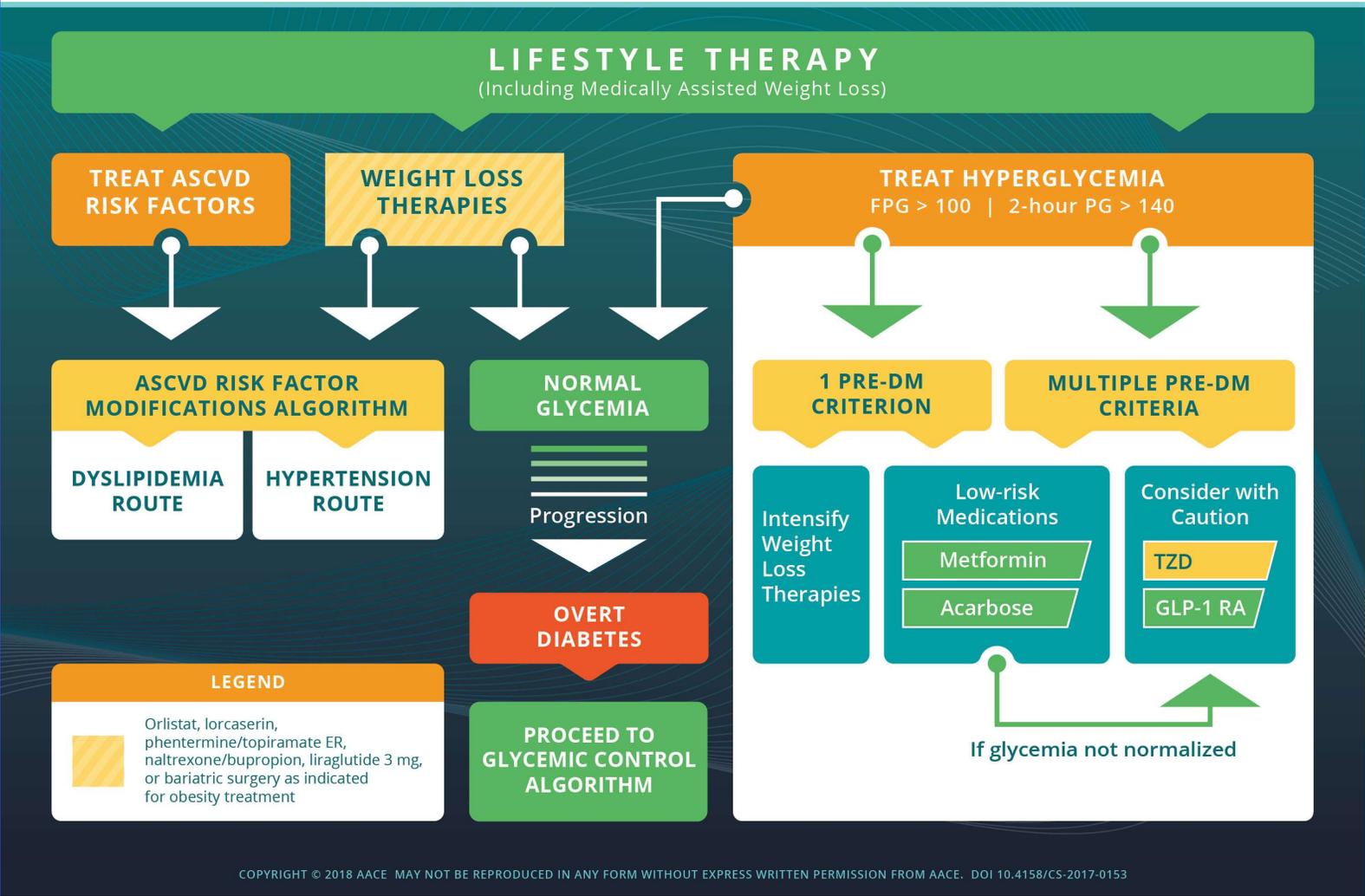
# Interventions to Reduce Risks Associated With Prediabetes

- Therapeutic lifestyle management is the cornerstone of all prevention efforts
- No pharmacologic agents are currently approved for the management of prediabetes
  - Pharmacotherapy targeted at glucose may be considered in high-risk patients after individual risk-benefit analysis



# Prediabetes Algorithm

IFG (100–125) | IGT (140–199) | METABOLIC SYNDROME (NCEP 2001)



# AACE Prediabetes Consensus Statement: Summary

- Untreated individuals with prediabetes are at increased risk for diabetes as well as for micro- and macrovascular complications
- Treatment goals are to prevent deterioration in glucose levels and modify other risk factors such as obesity, hypertension, and dyslipidemia
  - The same blood pressure and lipid goals are suggested for prediabetes and diabetes
- Intensive lifestyle management is the cornerstone of all prevention efforts; pharmacotherapy targeted at glucose may be considered in high-risk patients

Handelsman YH, et al. *Endocr Pract.* 2015;21(suppl 1):1-87.

Garber AJ, et al. *Endocr Pract.* 2008;14:933-946.

# **Prevention of Diabetes: Lifestyle Studies**

Prediabetes Management

# Prevention of T2D: Selected Lifestyle Modification Trials

Study	Country	N	Baseline BMI (kg/m <sup>2</sup> )	Intervention period (years)	RRR (%)	NNT
Diabetes Prevention Program	USA	3234	34.0	2.8	58	21
Diabetes Prevention Study	Finland	523	31	4	39	22
Da Qing	China	577	25.8	6	51	30

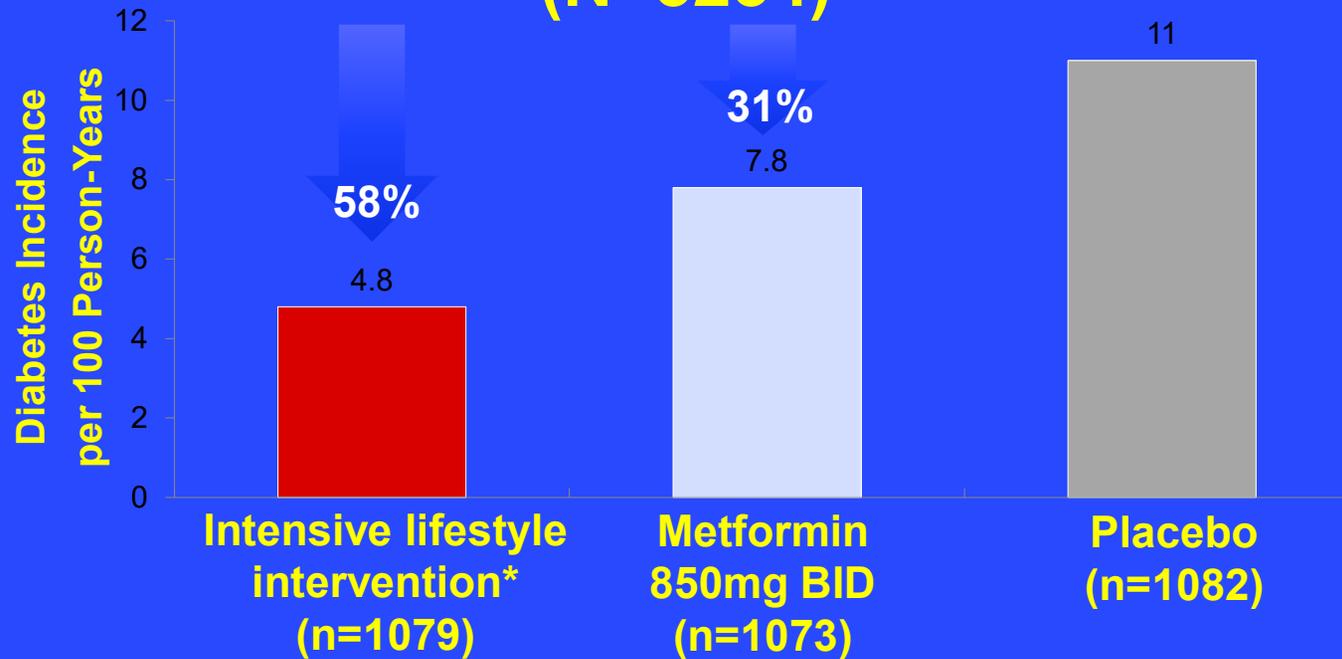
NNT, number needed to treat; RRR, relative risk reduction; T2D, type 2 diabetes.

DPP Research Group. *N Engl J Med.* 2002;346:393-403. Eriksson J, et al. *Diabetologia.* 1999;42:793-801.

Li G, et al. *Lancet.* 2008;371:1783-1789. Lindstrom J, et al. *Lancet.* 2006;368:1673-1679.

# Intensive Lifestyle Intervention Effectively Prevents Progression From IGT to T2D

## Diabetes Prevention Program (N=3234)



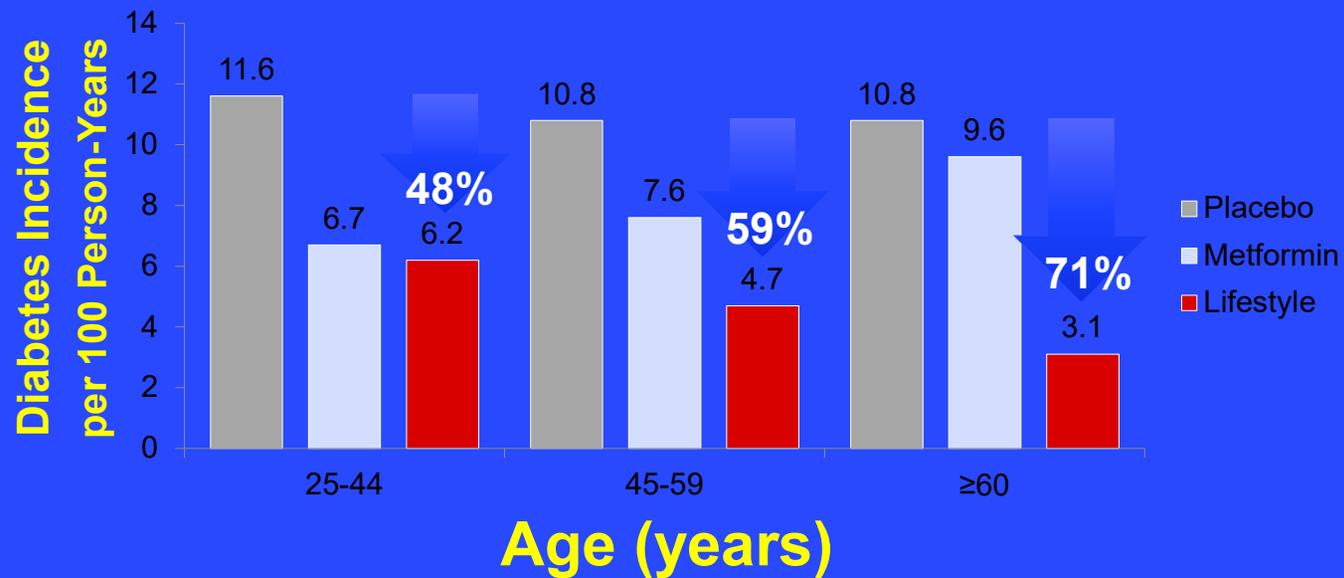
\*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and  $\geq 150$  min/week moderate intensity exercise.

IGT, impaired glucose tolerance; T2D, type 2 diabetes.

DPP Research Group. *N Engl J Med.* 2002;346:393-403.

# Lifestyle Intervention More Effectively Prevents Diabetes as Populations Age

## Diabetes Prevention Program (N=3234)

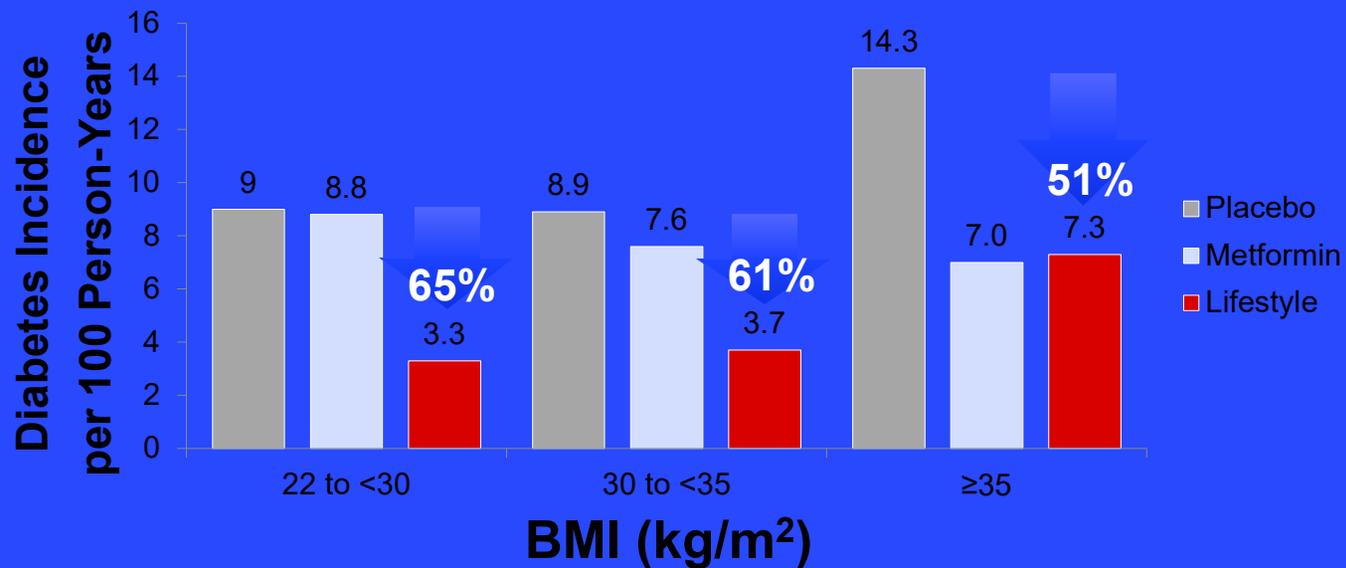


\*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise .

DPP Research Group. *N Engl J Med.* 2002;346:393-403.

# Effectiveness of Lifestyle Intervention for Diabetes Prevention Wanes as Weight Increases

## Diabetes Prevention Program (N=3234)

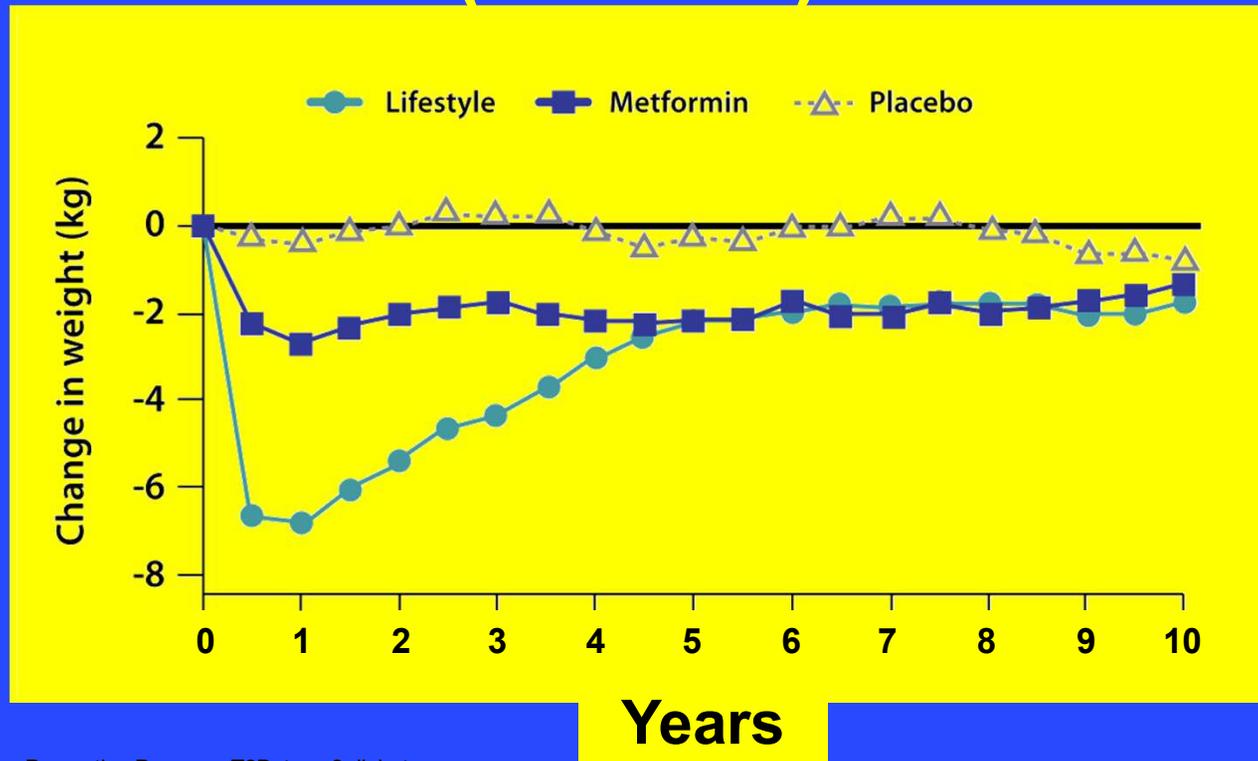


\*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise.

DPP Research Group. *N Engl J Med.* 2002;346:393-403.

# Maintenance of Long-Term Weight Loss

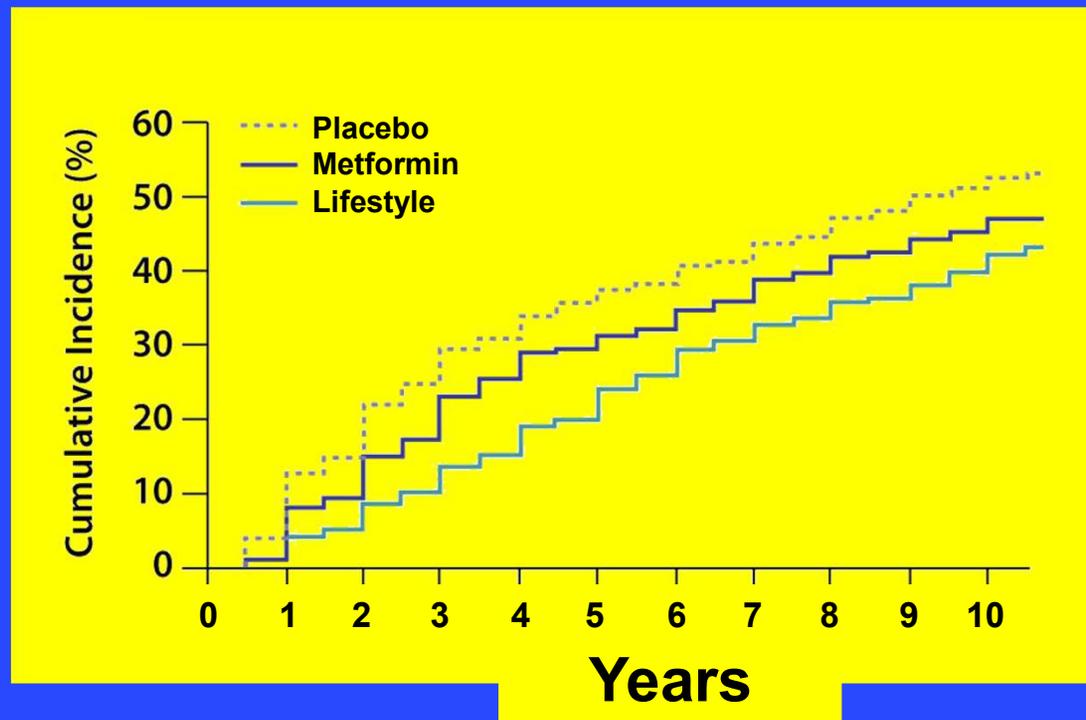
## DPP Outcomes Study (N=2766)



DPP, Diabetes Prevention Program; T2D, type 2 diabetes.  
DPP Research Group. *Lancet*. 2009;374:1677-1686.

# 10-Year Incidence of T2D

## DPP Outcomes Study- (N=2766)



DPP, Diabetes Prevention Program; T2D, type 2 diabetes.

DPP Research Group. *Lancet*. 2009;374:1677-1686.

# **Prevention of Diabetes: Pharmacotherapy and surgical Studies**

Prediabetes Management

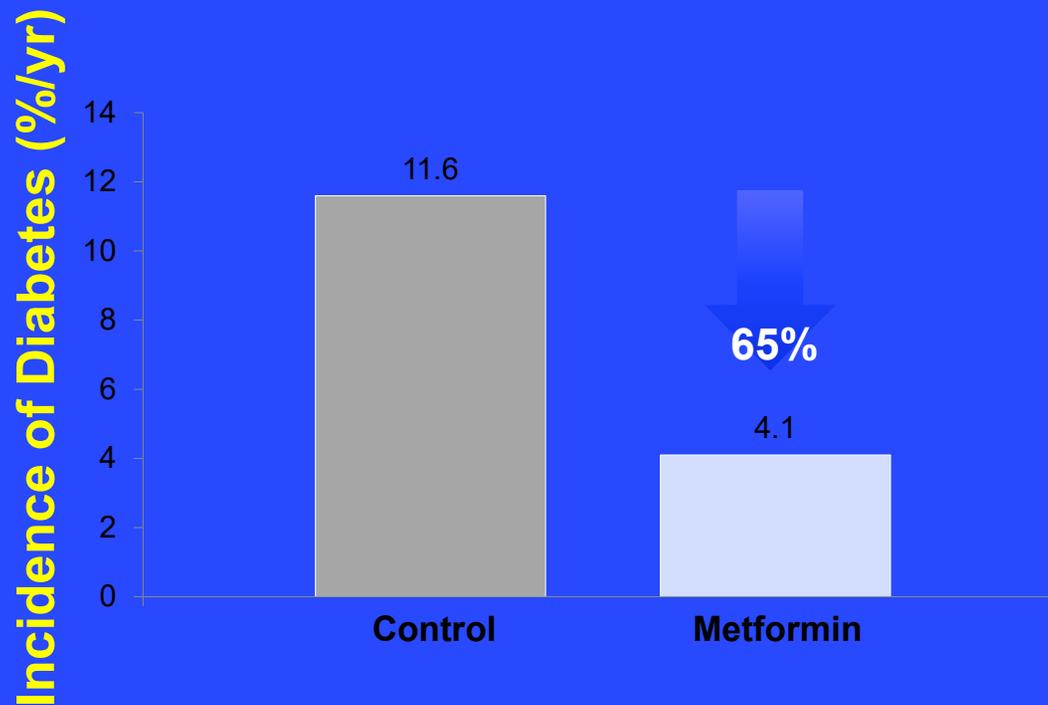
# Medical and Surgical Interventions Shown to Delay or Prevent T2D

Intervention	Follow-up Period	Reduction in Risk of T2D (P value vs placebo)
Antihyperglycemic agents		
Metformin <sup>1</sup>	2.8 years	31% ( $P < 0.001$ )
Acarbose <sup>2</sup>	3.3 years	25% ( $P = 0.0015$ )
Pioglitazone <sup>3</sup>	2.4 years	72% ( $P < 0.001$ )
Rosiglitazone <sup>4</sup>	3.0 years	60% ( $P < 0.0001$ )
Weight loss interventions		
Orlistat <sup>5</sup>	4 years	37% ( $P = 0.0032$ )
Phentermine/topiramate <sup>6</sup>	2 years	79% ( $P < 0.05$ )
Bariatric surgery <sup>7</sup>	10 years	75% ( $P < 0.001$ )

T2D, type 2 diabetes.

1. DPP Research Group. *N Engl J Med.* 2002;346:393-403.
2. STOP-NIDDM Trial Research Group. *Lancet.* 2002;359:2072-2077.
3. DeFronzo RA, et al. *N Engl J Med.* 2011;364:1104-15.
4. DREAM Trial Investigators. *Lancet.* 2006;368:1096-1105.
5. Torgerson JS, et al. *Diabetes Care.* 2004;27:155-161.
6. Garvey WT, et al. *Diabetes Care.* 2014;37:912-921.
7. Sjostrom L, et al. *N Engl J Med.* 2004;351:2683-2693.

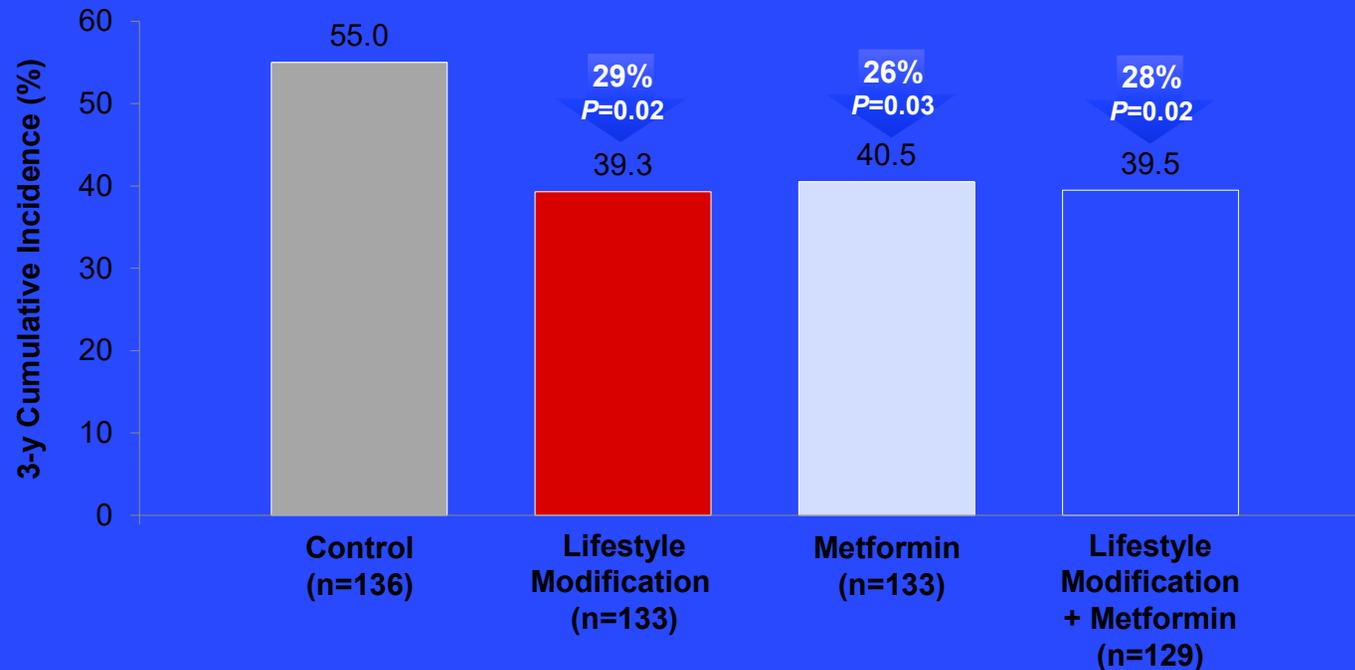
# The Effect of Metformin on the Progression of IGT to Diabetes Mellitus



IGT, impaired glucose tolerance; RRR, relative risk reduction.

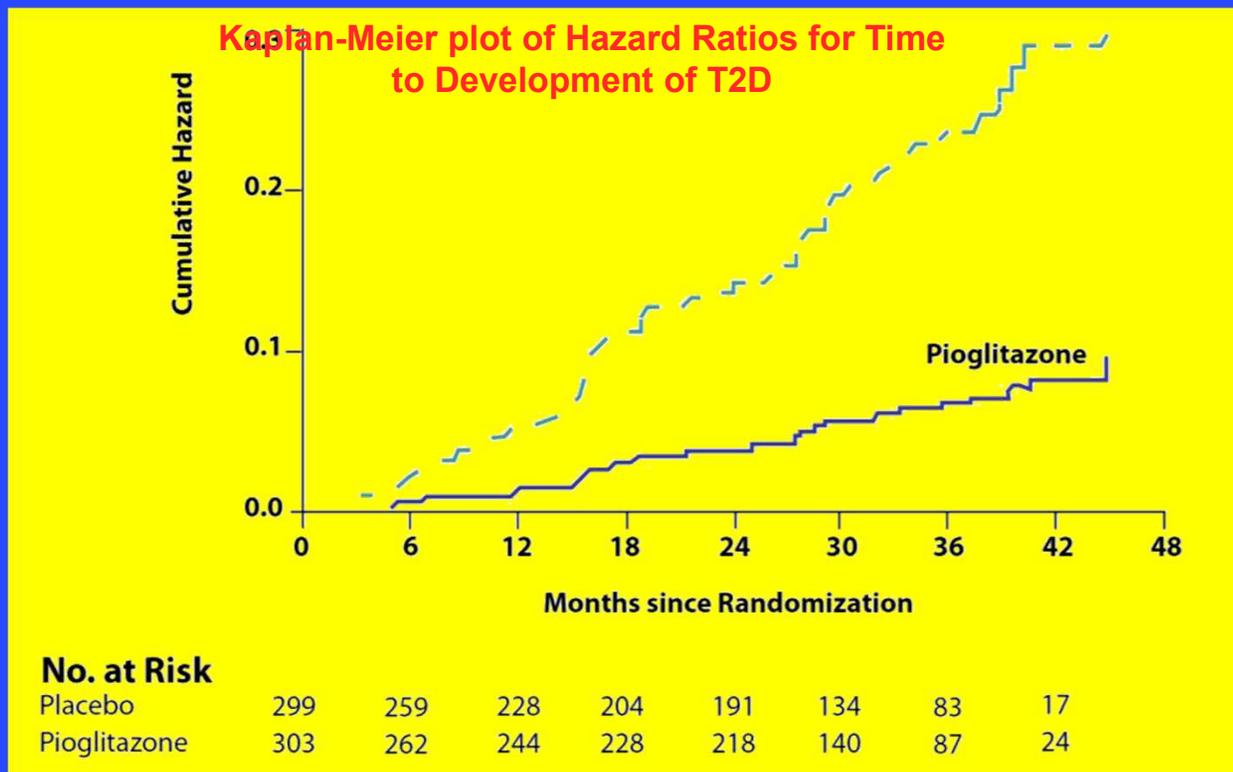
Yang W, et al. *Chin J Endocrinol Metab.* 2001;17:131-136.

# Effect of Lifestyle Modification and Metformin on Cumulative Diabetes Incidence



DPP, Diabetes Prevention Program; LSM, lifestyle modification; MET, metformin; RRR, relative risk reduction.  
Ramachandran A, et al. *Diabetologia*. 2006;49:289-297.

# Effect of Pioglitazone on Development of T2D in Patients with IGT



ACT NOW, Actos Now for the Prevention of Diabetes; IGT, impaired glucose tolerance; T2D, type 2 diabetes.

DeFronzo RA, et al. *N Engl J Med.* 2011;364:1104-1115.

# Special Considerations for Thiazolidinedione Use in Patients With Prediabetes

- Because of the known adverse effects of the TZDs, these agents should be considered only for patients at the greatest risk of developing future diabetes and those failing more conventional therapies

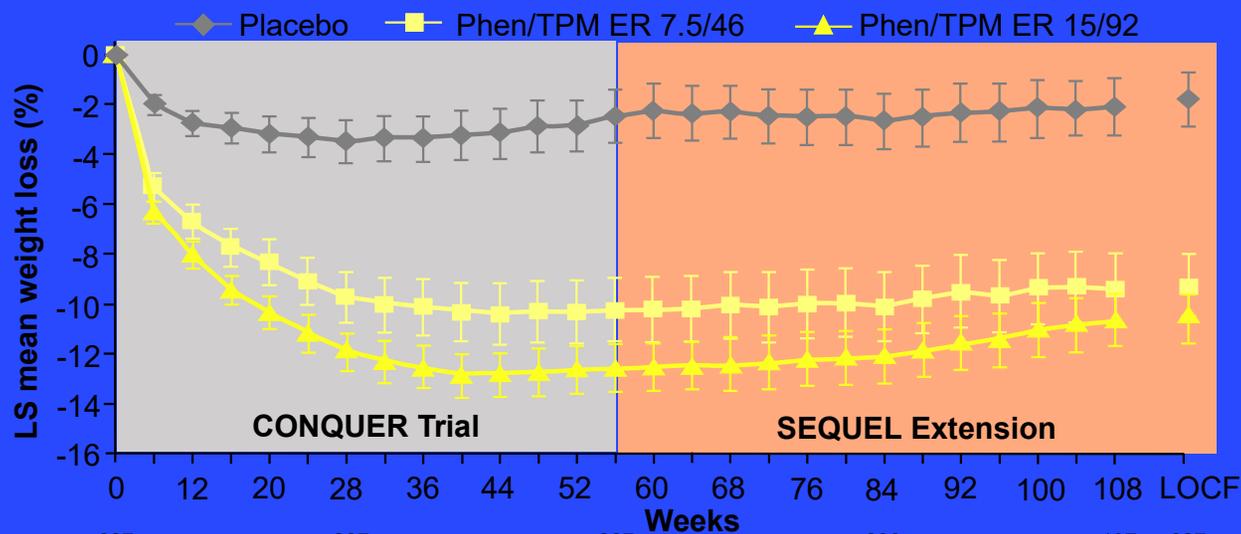
# Effects of Exenatide and Lifestyle Modification on Body Weight and Glucose Tolerance in Obese Patients With and Without Prediabetes

- Patients
  - N=152, weight 108.6 +/- 23.0 kg, BMI 39.6 +/- 7.0 kg/m<sup>2</sup> (IGT or IFG 25%)
- Design
  - 24-week randomized controlled trial: exenatide or placebo plus lifestyle intervention
- Results:
  - Exenatide-treated patients lost 5.1 kg from baseline vs 1.6 kg with placebo ( $P<0.001$ )
  - Both groups reduced their daily caloric intake
  - IGT or IFG normalized at end point in 77% and 56% of exenatide and placebo subjects, respectively

BMI, body mass index; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Rosenstock J, et al. *Diabetes Care*. 2010;33:1173-1175.

# Effect of Phentermine/Topiramate ER on Weight Loss in Obese Adults Over 2 Years



Placebo n:	227	227	227	208	197	227
Phen/TPM 7.5/46 n:	153	152	153	137	129	153
Phen/TPM 15/92 n:	295	295	295	268	248	295

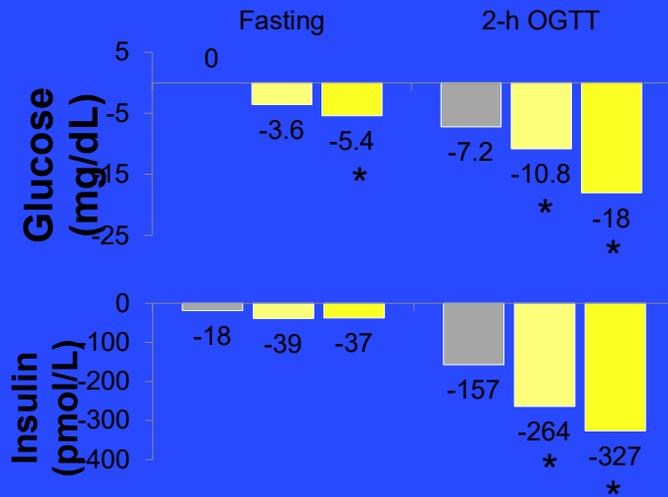
Data are shown with mean (95% CI).

Phen/TPM ER, phentermine/topiramate extended release.

Garvey WT, et al. *Am J Clin Nutr.* 2012;95:297-308.

# Effects of Phentermine/Topiramate ER on Glucose, Insulin, and Progression to T2D

## Glucose and Insulin



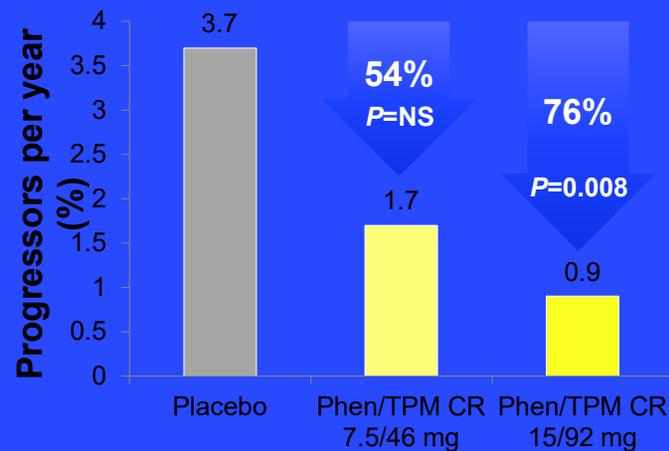
■ Placebo    ■ Phen/TPM ER 7.5/46 mg    ■ Phen/TPM ER 15/92 mg

\* $P \leq 0.005$  vs placebo.

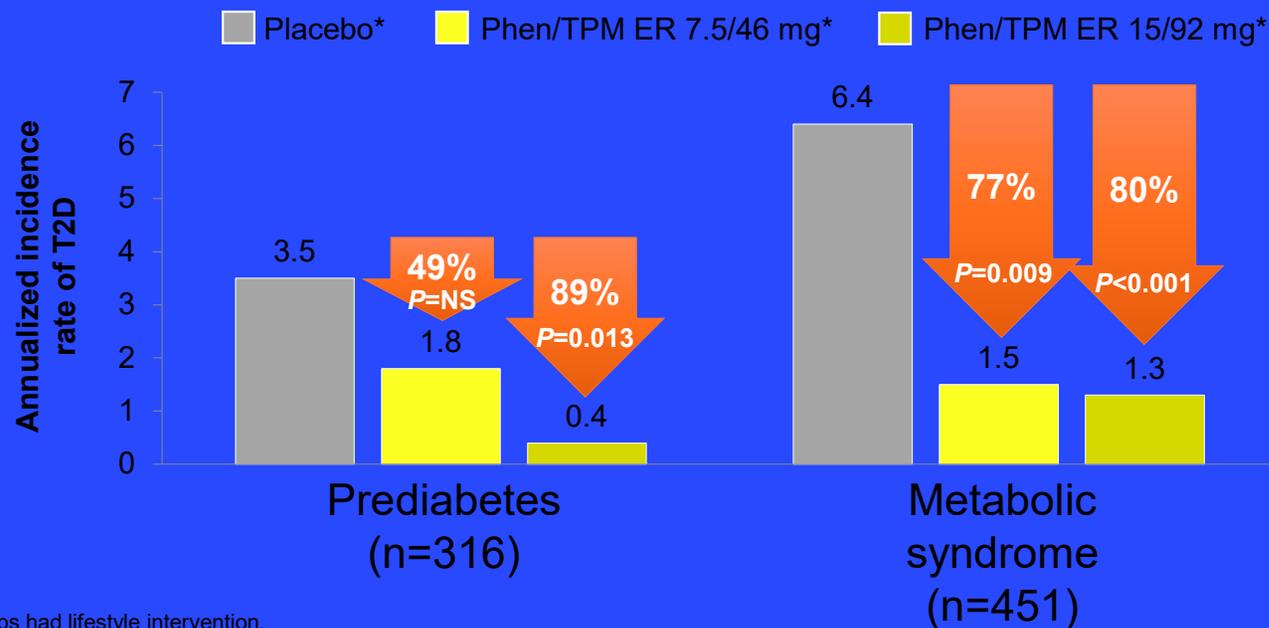
NS, not significant; Phen/TPM ER, phentermine/topiramate extended release; T2D, type 2 diabetes.

Garvey WT, et al. *Am J Clin Nutr.* 2012;95:297-308.

## Annualized Incidence of T2D



# Effects of Phentermine/Topiramate ER in Patients at High Risk of Developing T2D

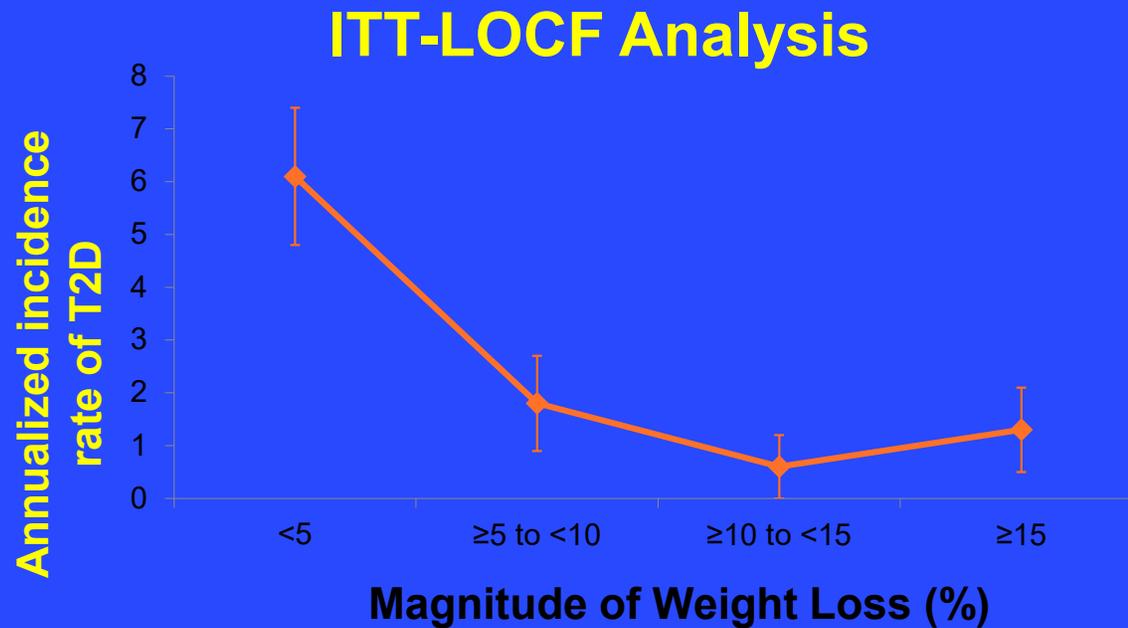


\*All groups had lifestyle intervention.

NS, not significant; Phen/TPM ER, phentermine/topiramate extended release; T2D, type 2 diabetes.

Garvey WT, et al. *Diabetes Care*. 2014;37:912-921.

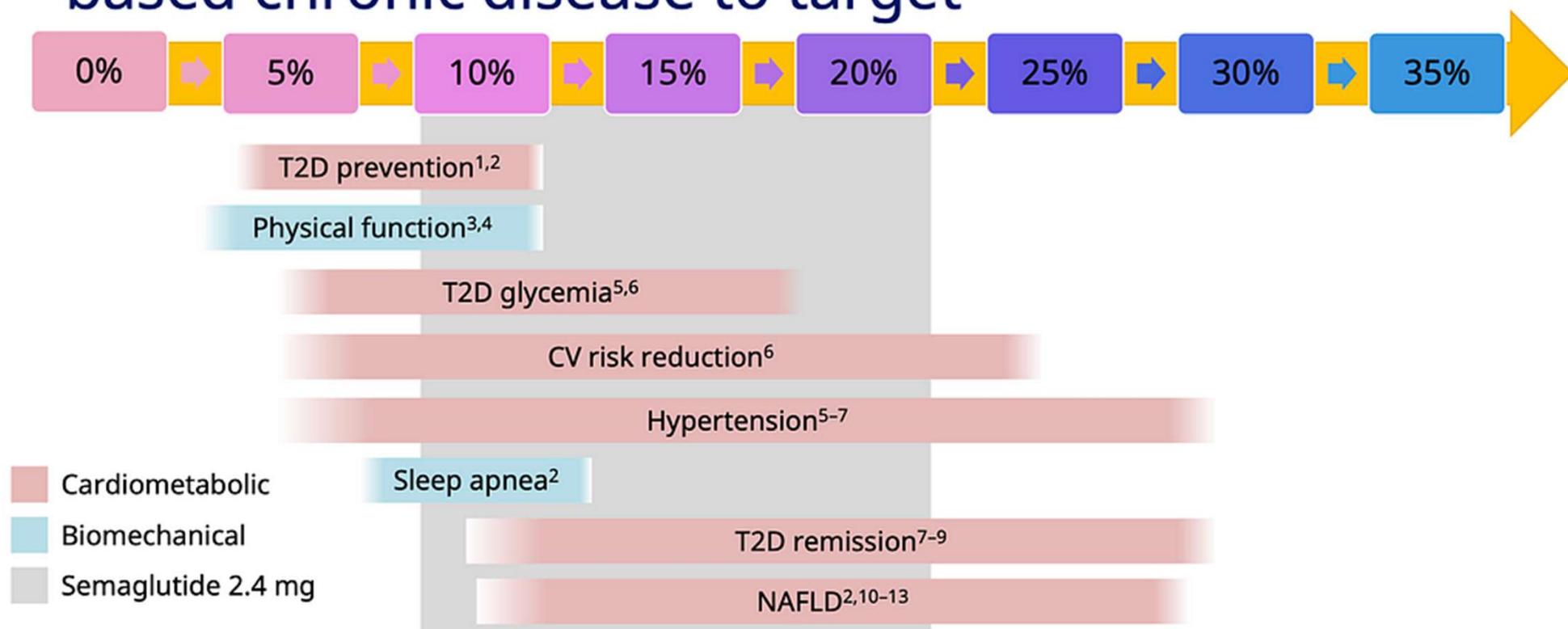
# Relationship Between Weight Loss and Prevention of Type 2 Diabetes



ITT, intent to treat; LOCF, last observation carried forward.

Garvey WT, et al. *Diabetes Care*. 2014;37:912-921.

# Semaglutide 2.4 mg: treating obesity/adiposity-based chronic disease to target

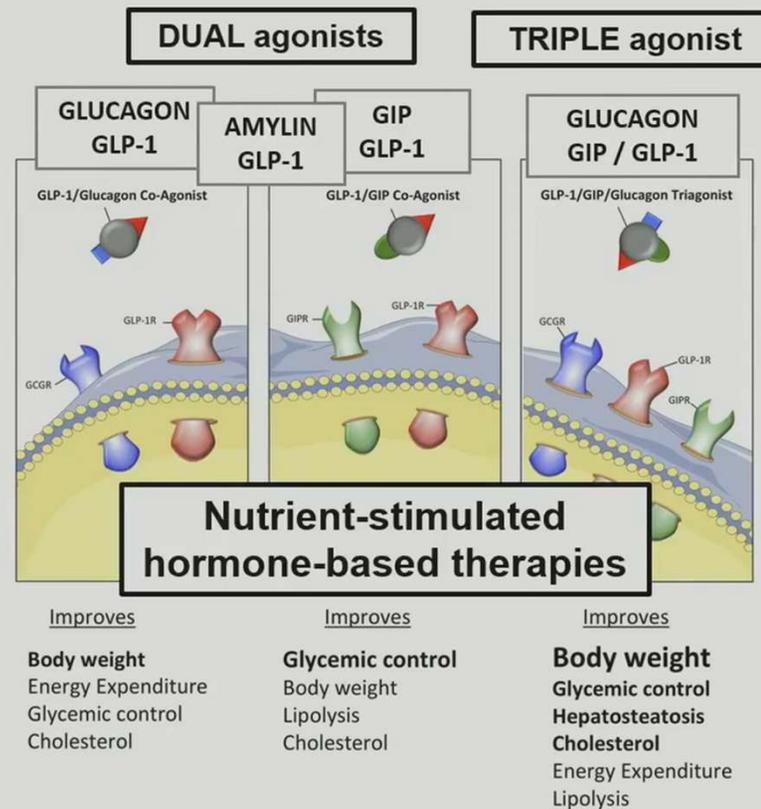
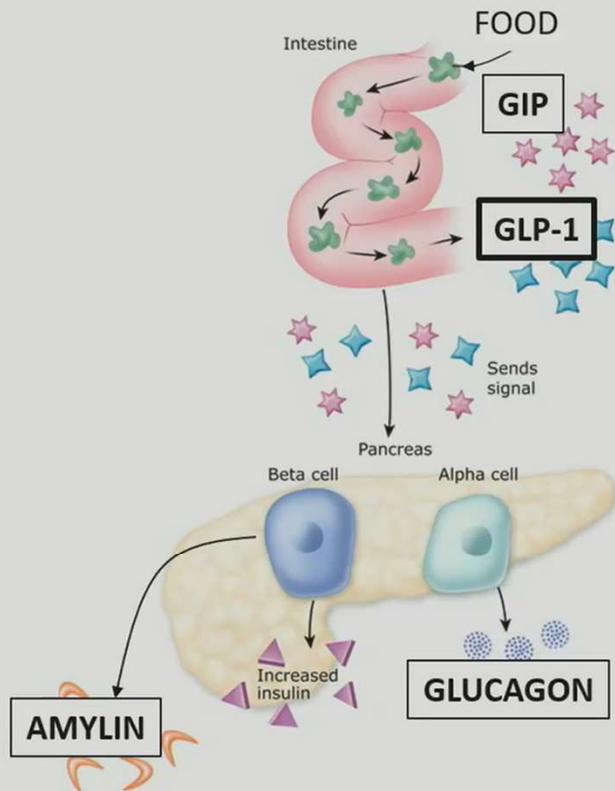


CV, cardiovascular; NAFLD, non-alcoholic fatty liver disease; T2D, type 2 diabetes.

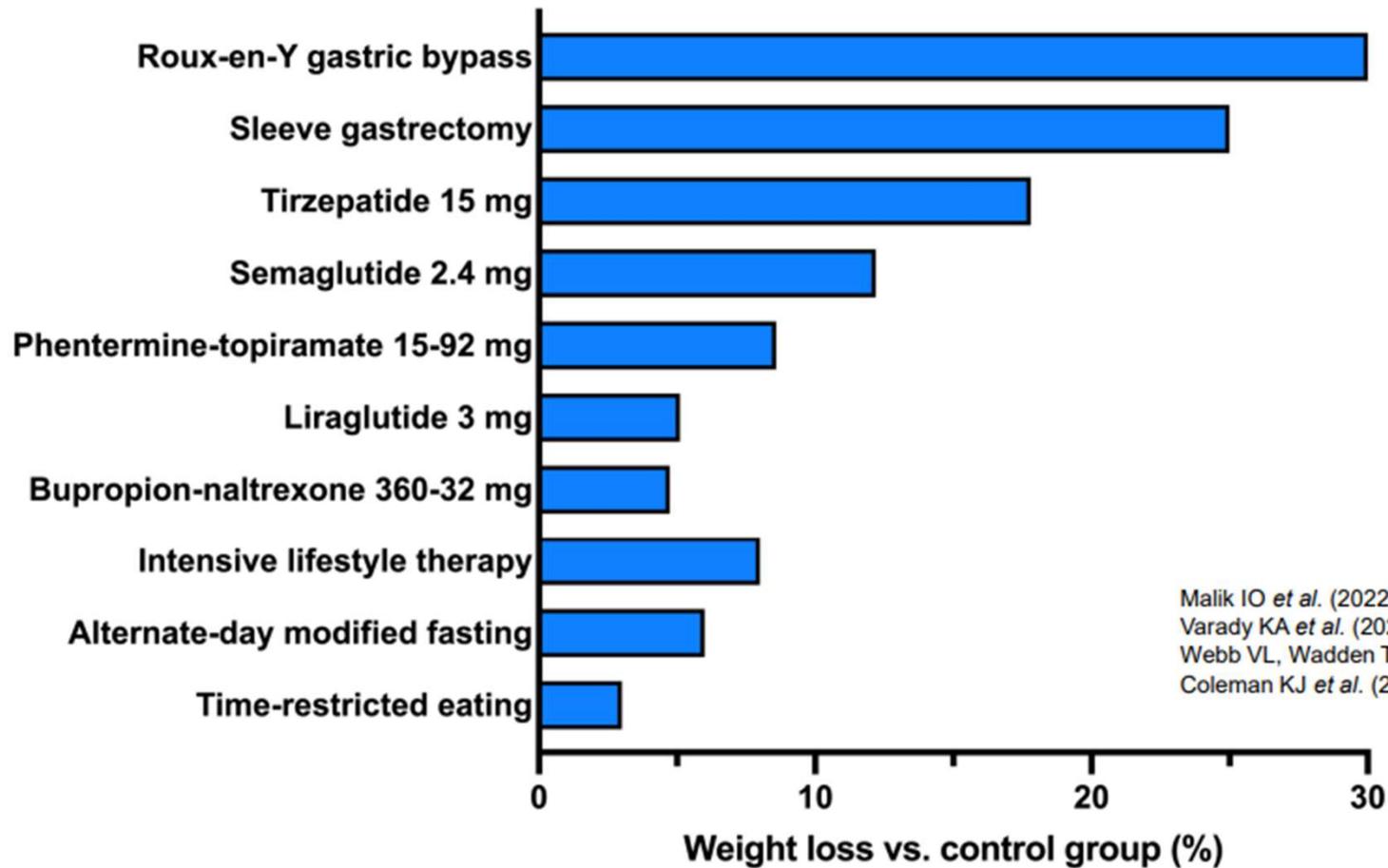
1. Knowler, et al. *N Engl J Med.* 2002;346:393-403; 2. Cefalu WT, et al. *Diabetes Care.* 2015;38:1567-82; 3. Christensen R, et al. *Osteoarthritis Cartilage.* 2005;13:20-7; 4. Bliddal, et al. *Obes Revs.* 2014;15:578-86; 5. Wing RR, et al. *Diabetes Care.* 2011;34:1481-6; 6. Ooi GJ, et al. *Int J Obes.* 2017;41:902-8; 7. Courcoulas AP, et al. *JAMA Surg.* 2018;153:427-34; 8. Lean MJ, et al. *Lancet.* 2018;391:541-51; 9. Dambha-Miller H, et al. *Diabet Med.* 2020;37:681-88; 10. Vilar-Gomez, et al. *Gastroenterology.* 2015;149:367-78; 11. Koutoukidis DA, et al. *Metabolism.* 2021;115:154455. 12. Promrat K, et al. *Hepatology.* 2010;51:121-9; 13. Liu X, et al. *Obes Surg.* 2007;17:486-92.

Garvey W.T, et al. Presented at the 39<sup>th</sup> Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1-5, 2021.

# Nutrient-stimulated hormone (NuSH)-based therapies



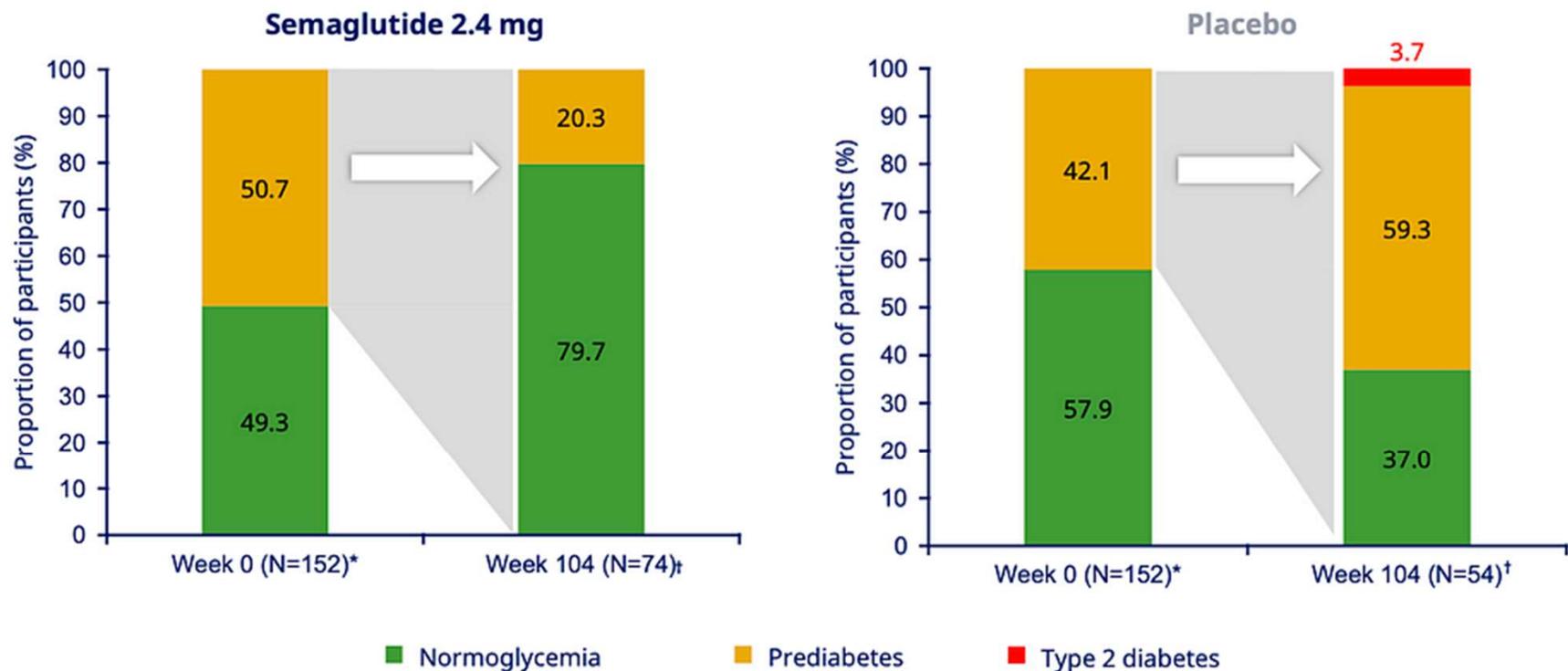
# Efficacy of TRE compared to other obesity therapies



Malik IO *et al.* (2022) *Obesity* 30(9):1718-1721  
Varady KA *et al.* (2022) *Nat Rev Endocrinol* 18:309-321  
Webb VL, Wadden TA. (2017) *Gastroenterol* 152(7):1752-1764  
Coleman KJ *et al.* (2022) *JAMA Surg* 157(10):897-906.

# Shift from baseline to week 104 in glycemic status

## Participants with prediabetes at baseline



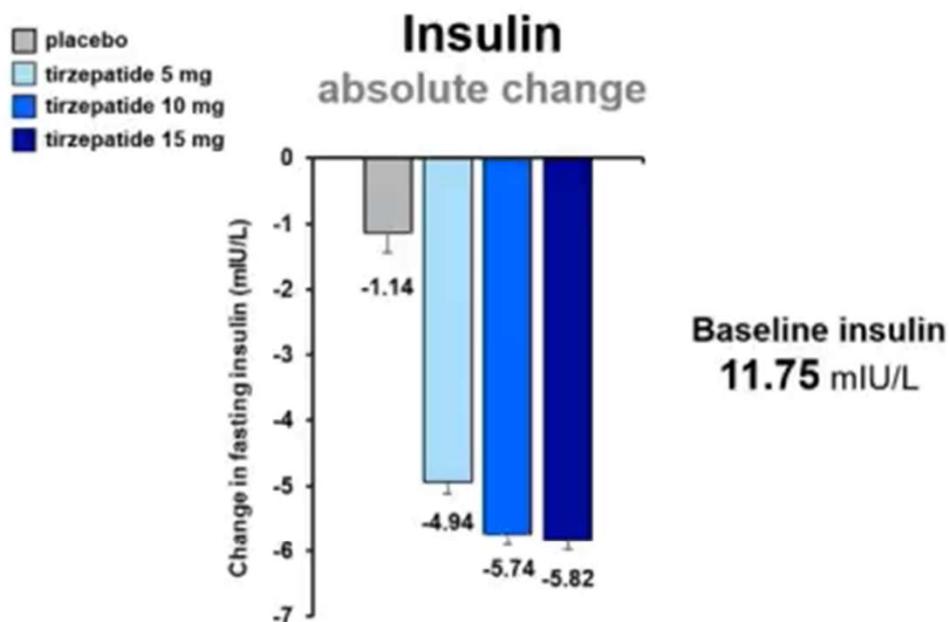
Data are observed data during the in-trial period (regardless of treatment discontinuation or rescue intervention). Glycemic category was evaluated by the investigator based on all available relevant information (e.g. concomitant medication, medical records, and blood glucose parameters) in accordance with American Diabetes Association definitions.

\*Number of participants in overall population; †Number of participants with prediabetes at baseline and evaluable data at week 104.

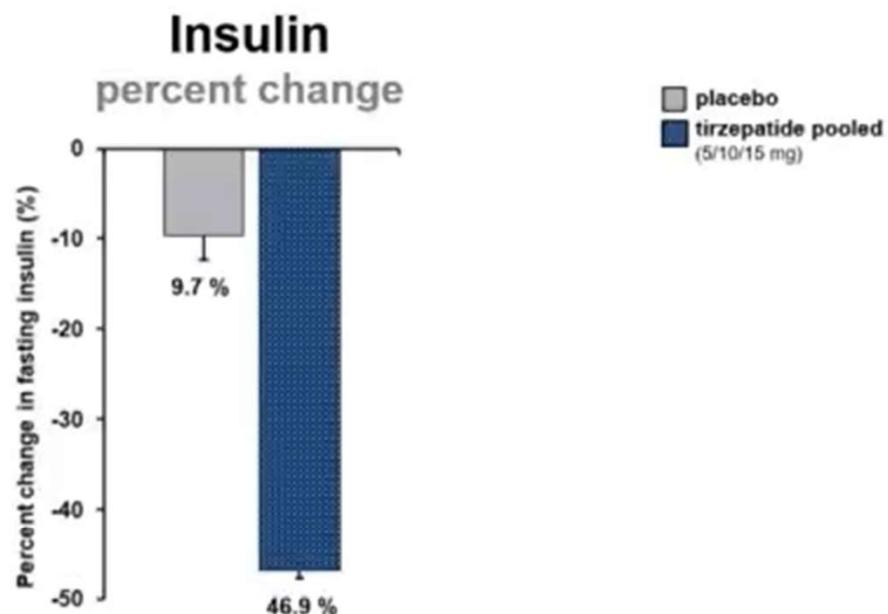
Garvey W.T, et al. Presented at the 39<sup>th</sup> Annual Meeting of The Obesity Society (TOS) held at ObesityWeek®, virtual meeting, November 1-5, 2021.

# Change in Fasting Insulin

On Treatment  
Efficacy Estimand



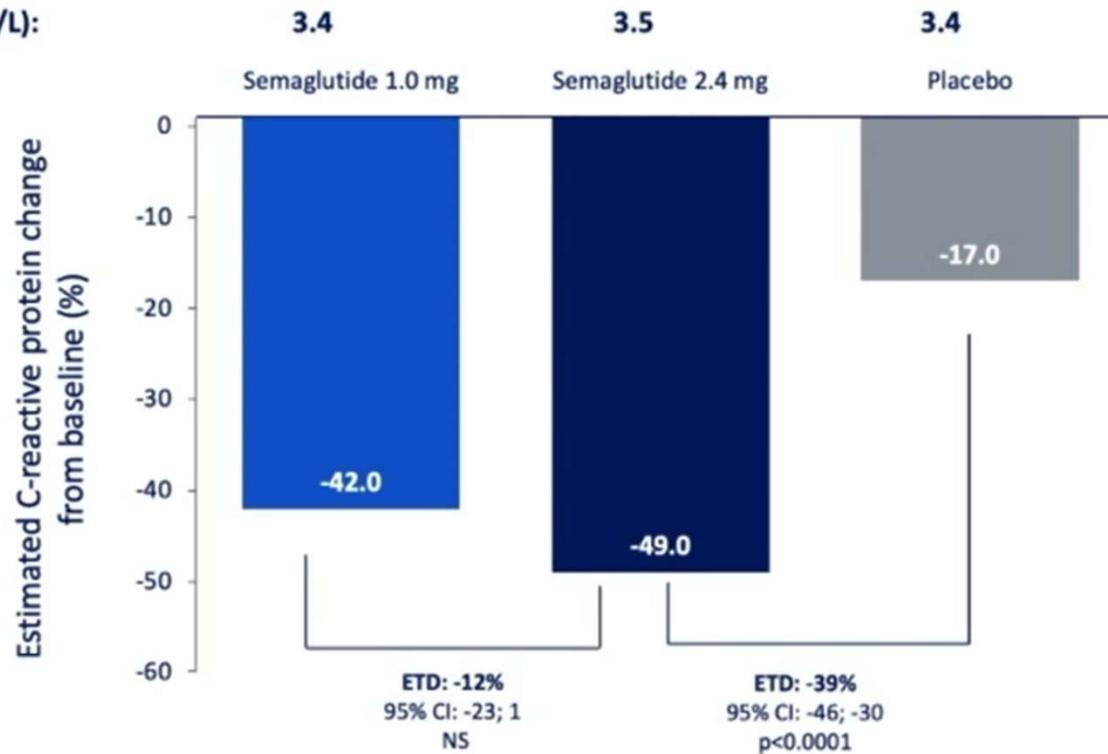
Fasting insulin levels decreased by 4-5 mIU/L with tirzepatide



Fasting insulin decreased by nearly 47% with tirzepatide

## STEP 2: Change in C-reactive protein

Mean at baseline (mg/L):

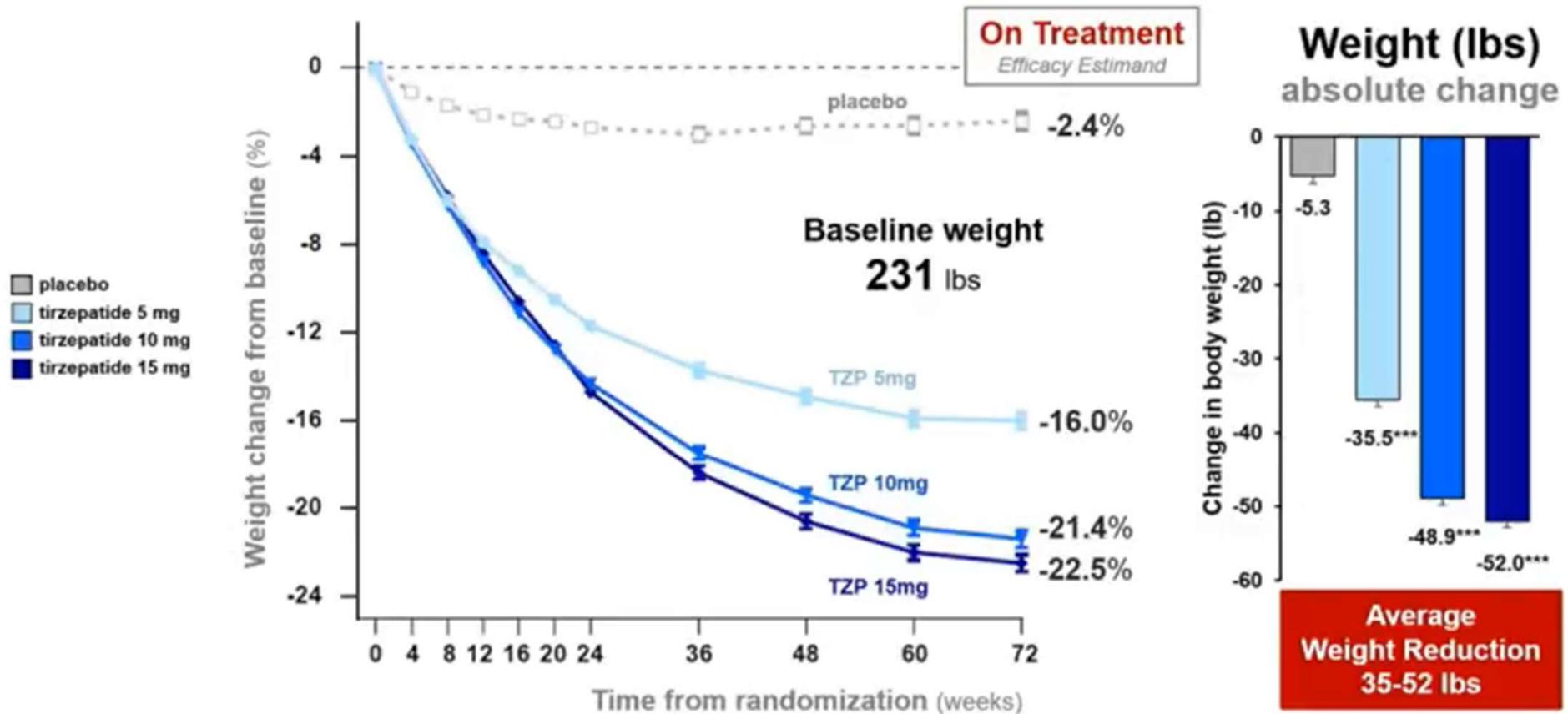


Estimated data for the treatment policy estimand.

CI, confidence interval; ETD, estimated treatment ratio; NS, not significant.

Davies M et al. *Lancet* 2021; doi: 10.1016/S0140-6736(21)00213-0. Online ahead of print.

# Weight Reduction Over 72 weeks: absolute change



# Tirzepatide

---

- Weight loss of 15-22.5% depending on dose
- Up to 96% of participants achieved  $\geq 5\%$  weight reduction, with up to 63% of participants  $\geq 20\%$  weight reduction, up to 40%  $\geq 25\%$  weight reduction
- Significant improvement in all cardiometabolic risk factors:
  - Systolic/Diastolic blood pressure
  - Fasting glucose and HbA1c
  - Lipids
  - Liver enzymes (AST, ALT)
  - Waist circumference
  - Fasting insulin
- 95.3% of participants on tirzepatide with prediabetes at baseline reverted to normoglycemia at week 72 as compared to 61% of those on placebo and diet

ADA Scientific Sessions  
June 26, 2023



# Retatrutide Obesity: Efficacy and Safety Results of the 48-week Obesity Phase 2 Trial

**Ania M. Jastreboff, MD, PhD**

**Associate Professor, Yale University**

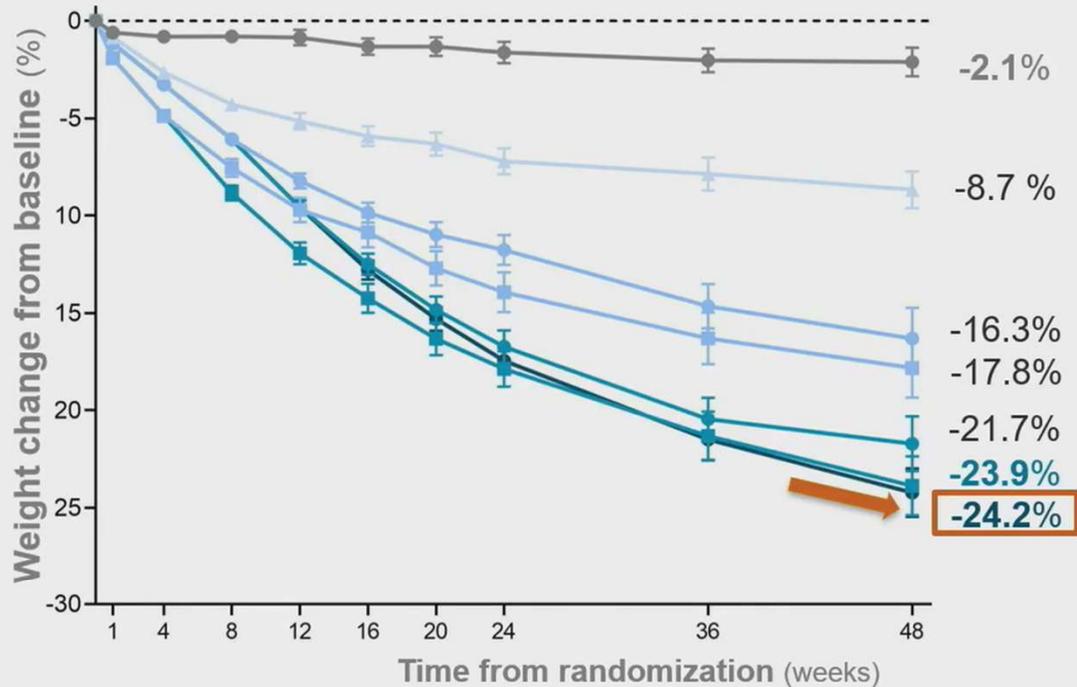
Internal Medicine, Endocrinology & Metabolism  
Pediatrics, Pediatric Endocrinology  
Director, Yale Obesity Research Center (Y-Weight)  
Board of Directors (ABOM)

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Yale SCHOOL OF MEDICINE



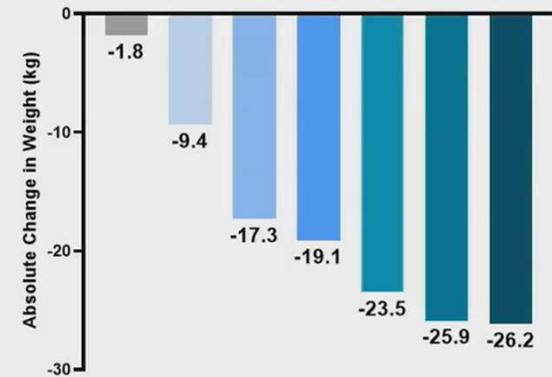
# Weight Reduction Over 48 Weeks – Key Secondary Outcome



- Placebo
- RETA 1 mg
- RETA 4 mg [ID 2 mg]
- RETA 4 mg [ID 4 mg]
- RETA 8 mg [ID 2 mg]
- RETA 8 mg [ID 4 mg]
- RETA 12 mg [ID 2 mg]

**Average weight reduction of 24.2% with 48 weeks of treatment with retatrutide (12 mg)**

**Weight (kg) absolute change at 48 weeks**



**Average Weight Reduction 26 kg / 58 lbs at 48 weeks**

Baseline weight 107 kg / 237.4 lbs

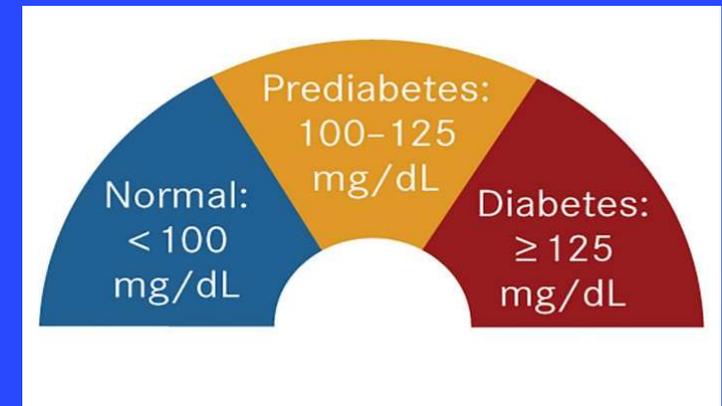
# Summary

- **Prediabetes**  
Increasing Incidence
- **Pathogenesis-**  
Insulin Resistance
- **Treatment-** can reverse Pre-diabetes  
Diet- Goal is to prevent spikes in glucose  
Medical Management-  
- goals are treat insulin resistance and obesity



**GLUCOSE LEVELS CHART**

# Prediabetes



- Epidemiologic evidence suggests that the complications of T2D begin early in the progression from NGT to frank diabetes
- Prediabetes and diabetes are conditions in which early detection is appropriate, because
  - Duration of hyperglycemia is a predictor of adverse outcomes
  - There are effective interventions to prevent disease progression and to reduce complications

# Thank you

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