

# **Metformin for Prevention and Treatment of Type 2 Diabetes**

**William C. Knowler, MD, DrPH  
National Institutes of Health  
Phoenix, Arizona**

**Navajo Nation Human Research Review  
Board Research Conference  
Window Rock  
October 18, 2017**

# Medicines Used in Treating Type 2 Diabetes

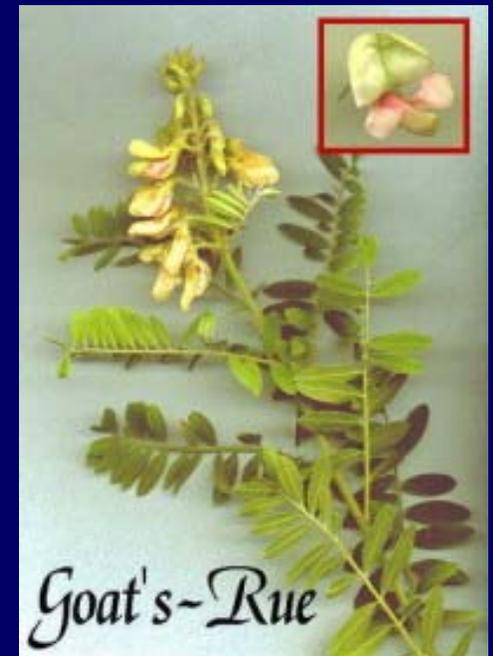
- **Metformin**
- **Insulin secretagogues**
  - **Sulfonylureas**
  - **Meglitinides**
- **Thiazolidinediones**
- **Alpha-glucosidase inhibitors**
- **DPP-4 inhibitors**
- **GLP-1 agonists**
- **SGLT2 inhibitors**
- **Insulin**
- **Weight-loss drugs**

# Medicines Used in Treating Type 2 Diabetes

- **Metformin: 1<sup>st</sup> recommended drug**
- **Insulin secretagogues**
  - Sulfonylureas
  - Meglitinides
- **Thiazolidinediones**
- **Alpha-glucosidase inhibitors**
- **DPP-4 inhibitors**
- **GLP-1 agonists**
- **SGLT2 inhibitors**
- **Insulin**
- **Weight-loss drugs**

# History of Biguanides

- Goat's rue / French lilac (guanidine) used for diabetes in medieval Europe
- Guanidine-derived compounds tried in 1920s but too toxic
- Biguanides **metformin** & phenformin introduced 1950s
- Phenformin withdrawn in U.S.A. in 1977 due to lactic acidosis
- **Metformin** approved in U.S.A. in 1995



# What Does Metformin Do?

- **Suppresses glucose production by the liver**
- **Lowers fasting glucose**

# Advantages and Disadvantages of Metformin

## Advantages

- Long experience
- Rare hypoglycemia
- May lower cardiovascular disease
- Greater effect on lowering HbA1c
- Modest weight loss
- Low cost

## Disadvantages

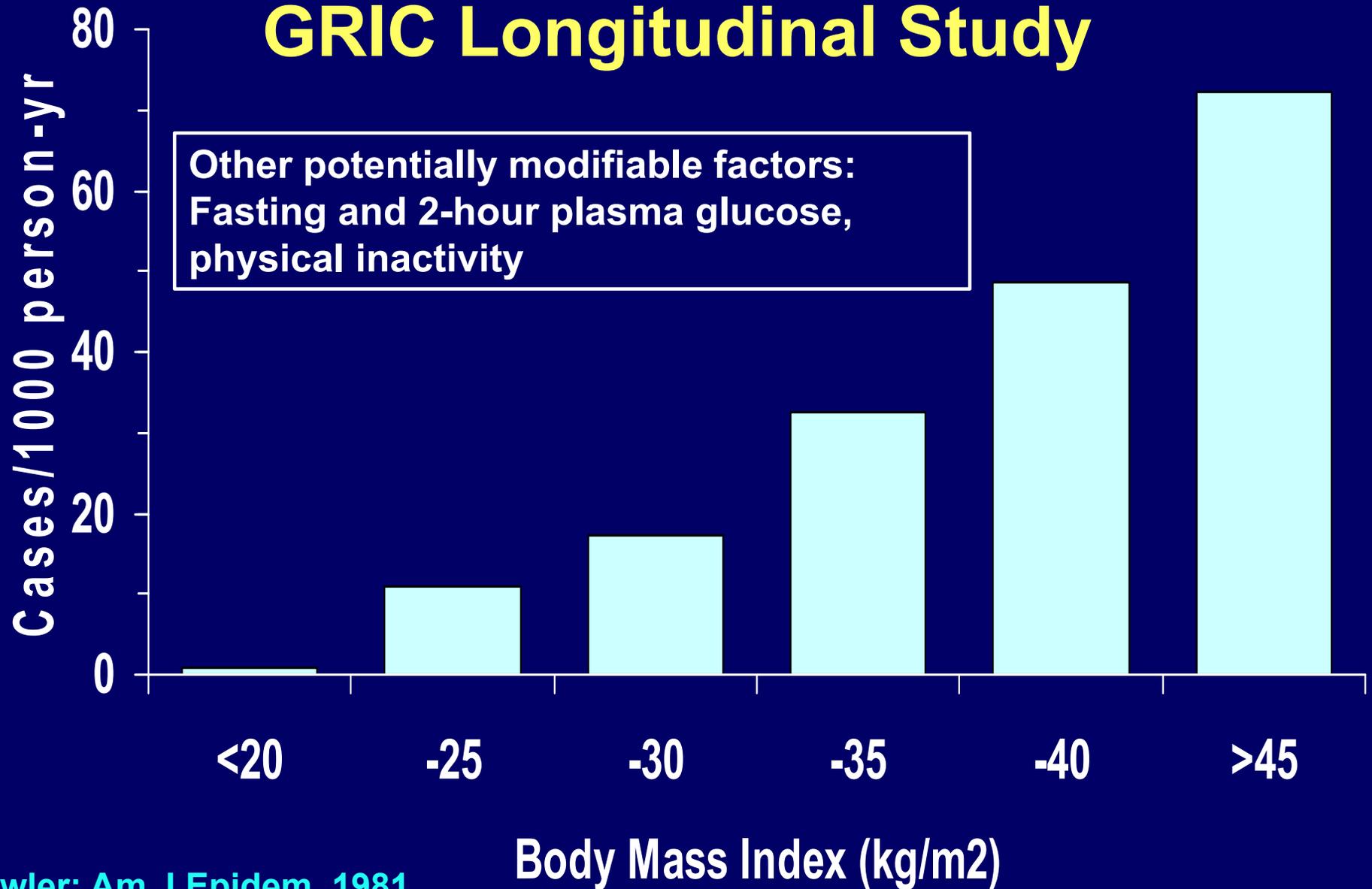
- Gastrointestinal side effects
- Vitamin B12 deficiency
- Not used in advanced kidney disease
- Lactic acidosis (?)

Adapted from American Diabetes Association: Diabetes Care 2017

# **In the 1990s We Thought Type 2 Diabetes Could Be Prevented**

- **Why did we think so?**
- **Was there a role for drugs such as metformin?**

# Incidence of Diabetes by BMI in Adults GRIC Longitudinal Study

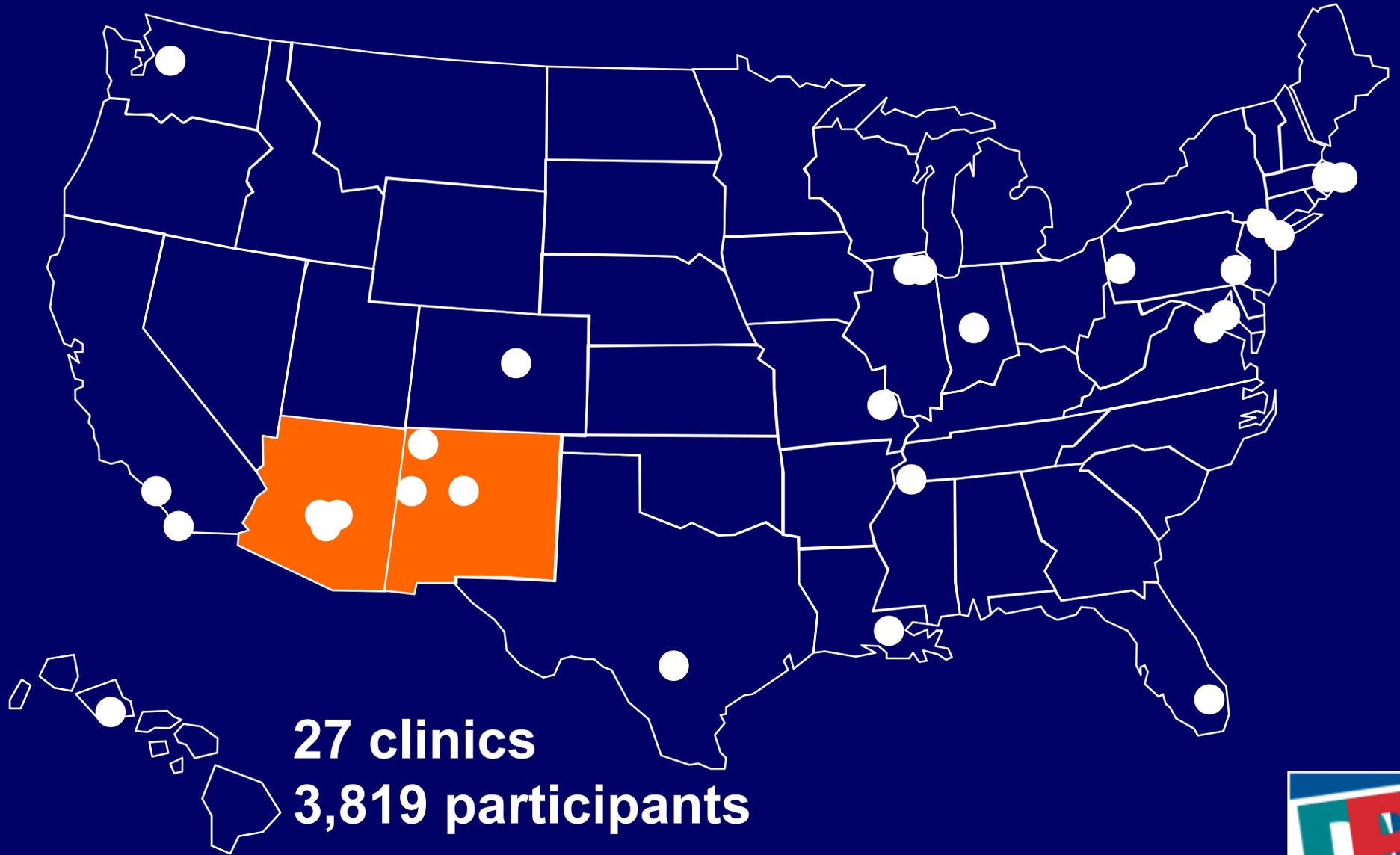


Knowler: Am J Epidem, 1981

# Diabetes Prevention Program (DPP)

- **Multicenter randomized clinical trial in U.S.A.**
- **Hypothesis: Type 2 diabetes can be prevented or delayed by treating modifiable risk factors: obesity, inactivity, insulin resistance, elevated glucose**
- **Nondiabetic adults at high risk of type 2 diabetes**
- **1996 – 2001 with long-term follow-up**

# Diabetes Prevention Program Clinics

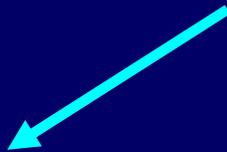


# DPP Study Treatment Groups

Randomize (n = 3,234)



Standard lifestyle teaching



**Intensive  
Lifestyle**  
(n = 1079)



**Metformin**  
850 mg BID  
(n = 1073)



**Placebo**  
(n = 1082)



# The DPP

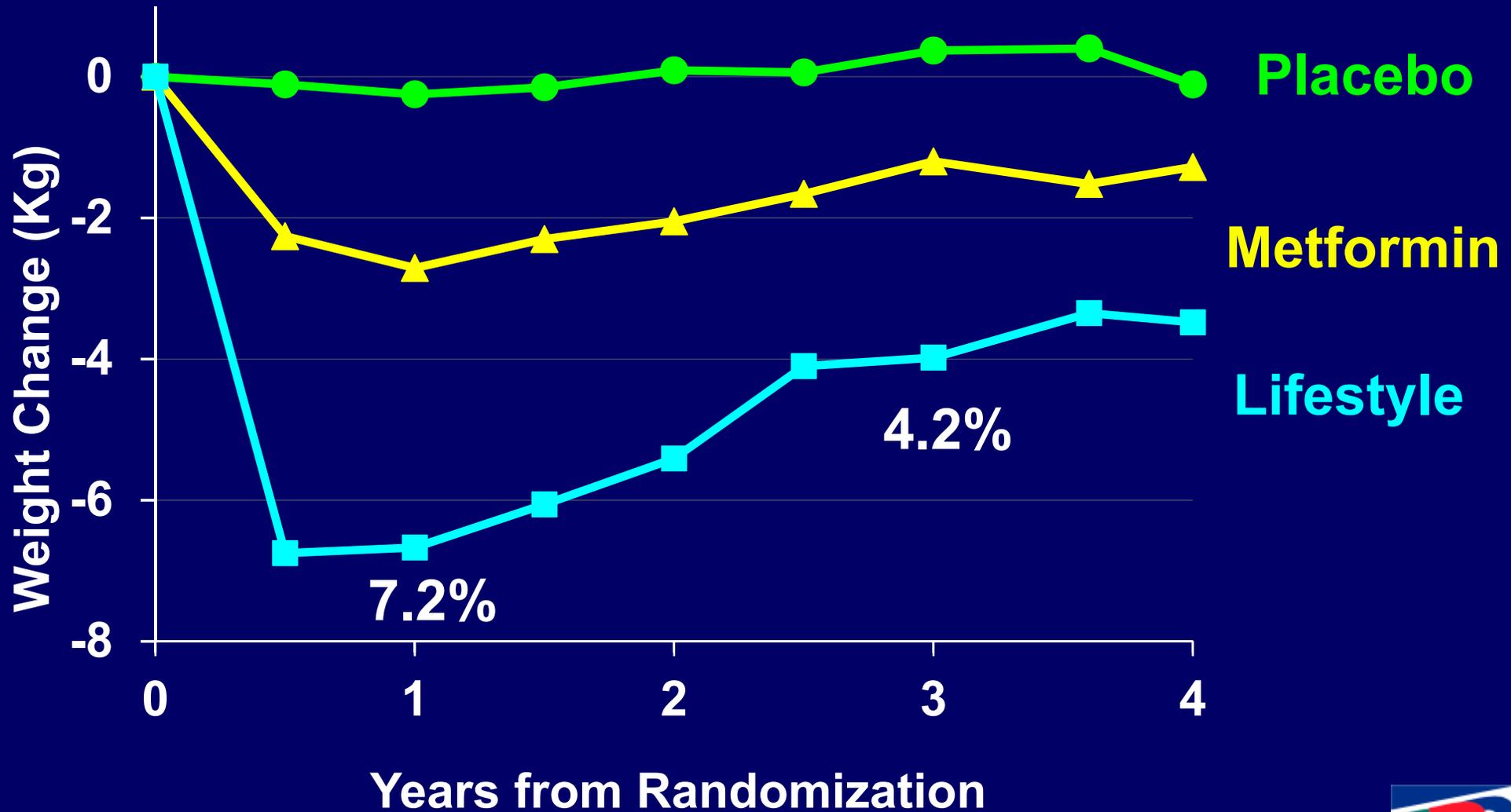
## Intensive Lifestyle Intervention

An intensive program with the following specific goals:

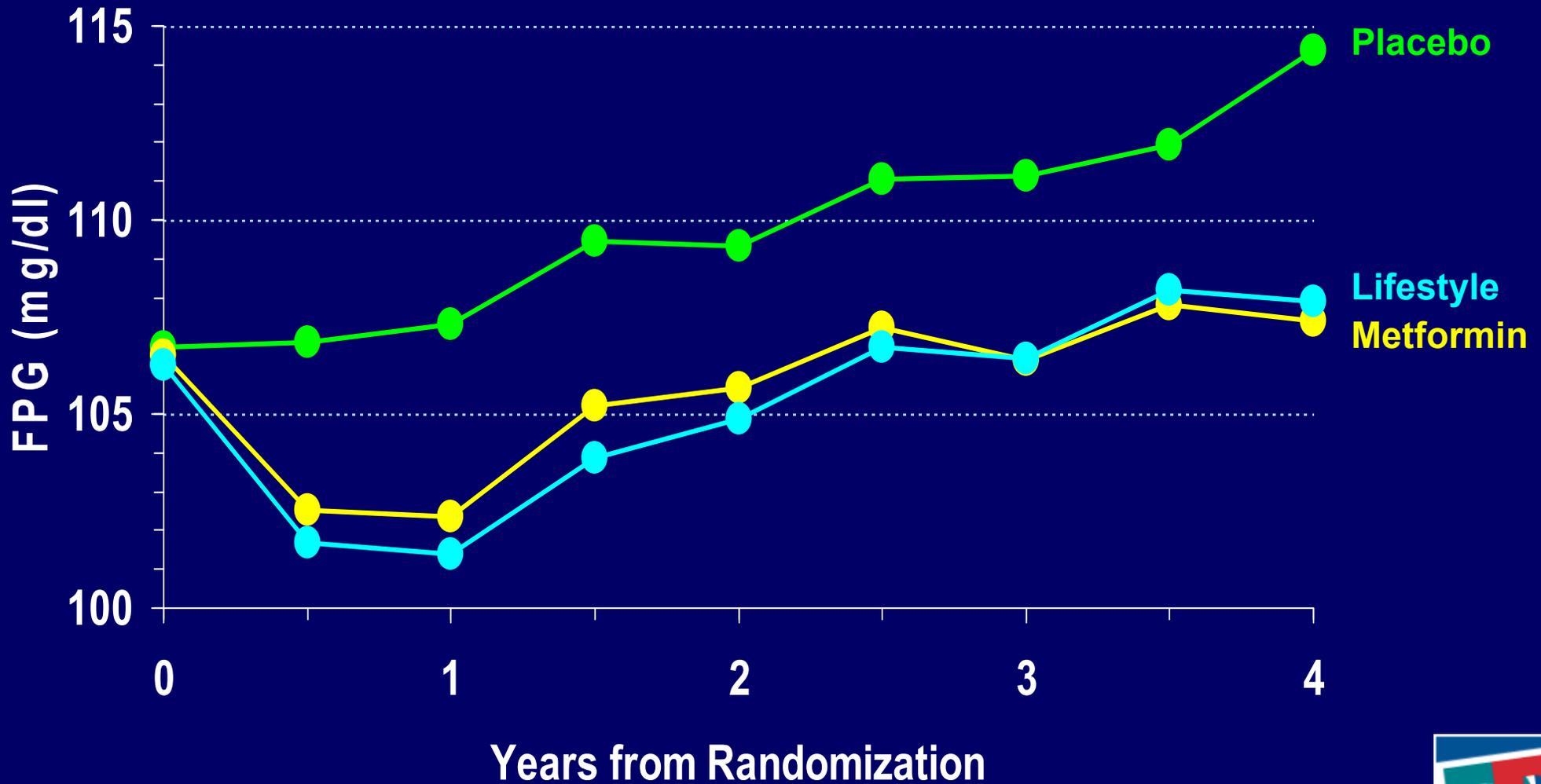
- $\geq 7\%$  loss of body weight and maintenance of weight loss
- $\geq 150$  minutes per week of physical activity



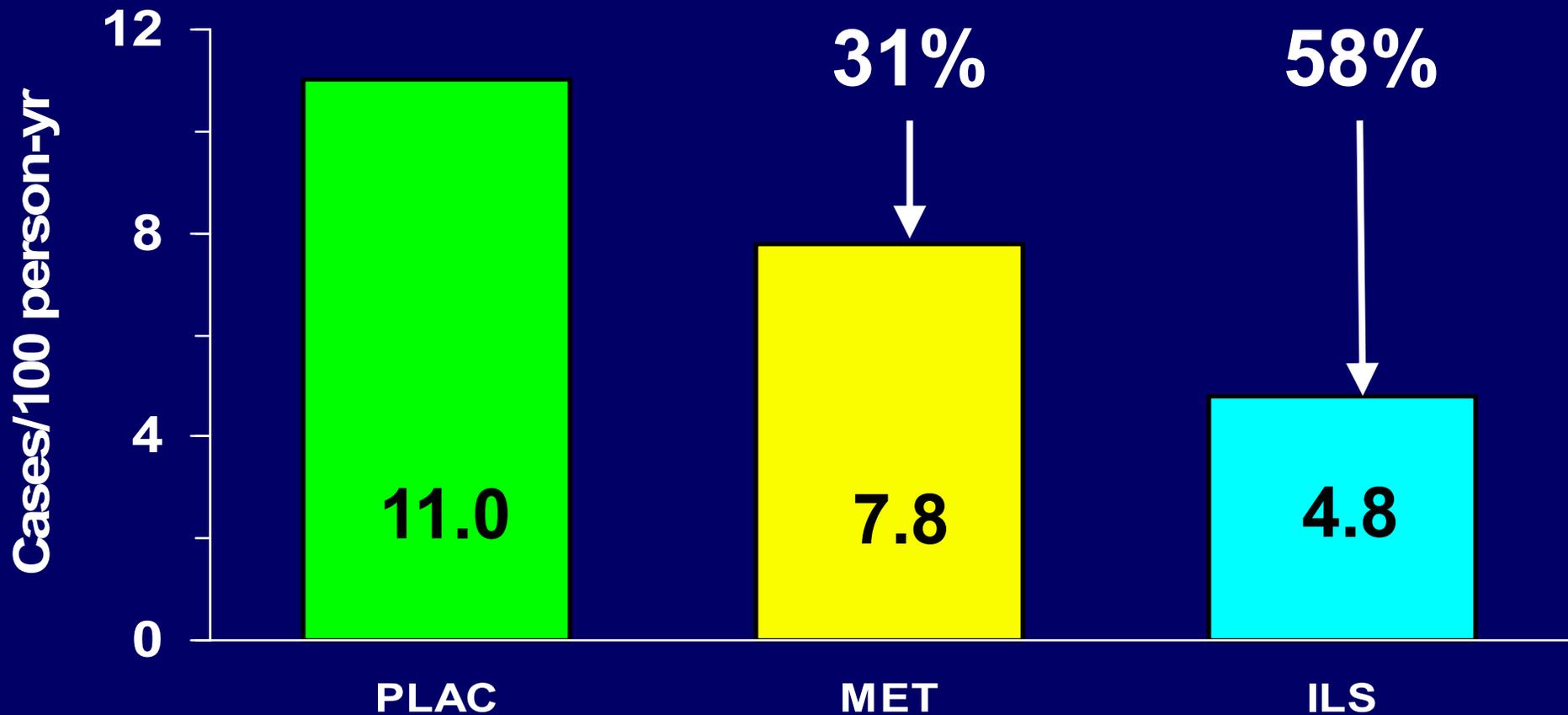
# Mean Weight Change from Baseline



# Changes in Fasting Plasma Glucose by Treatment Group

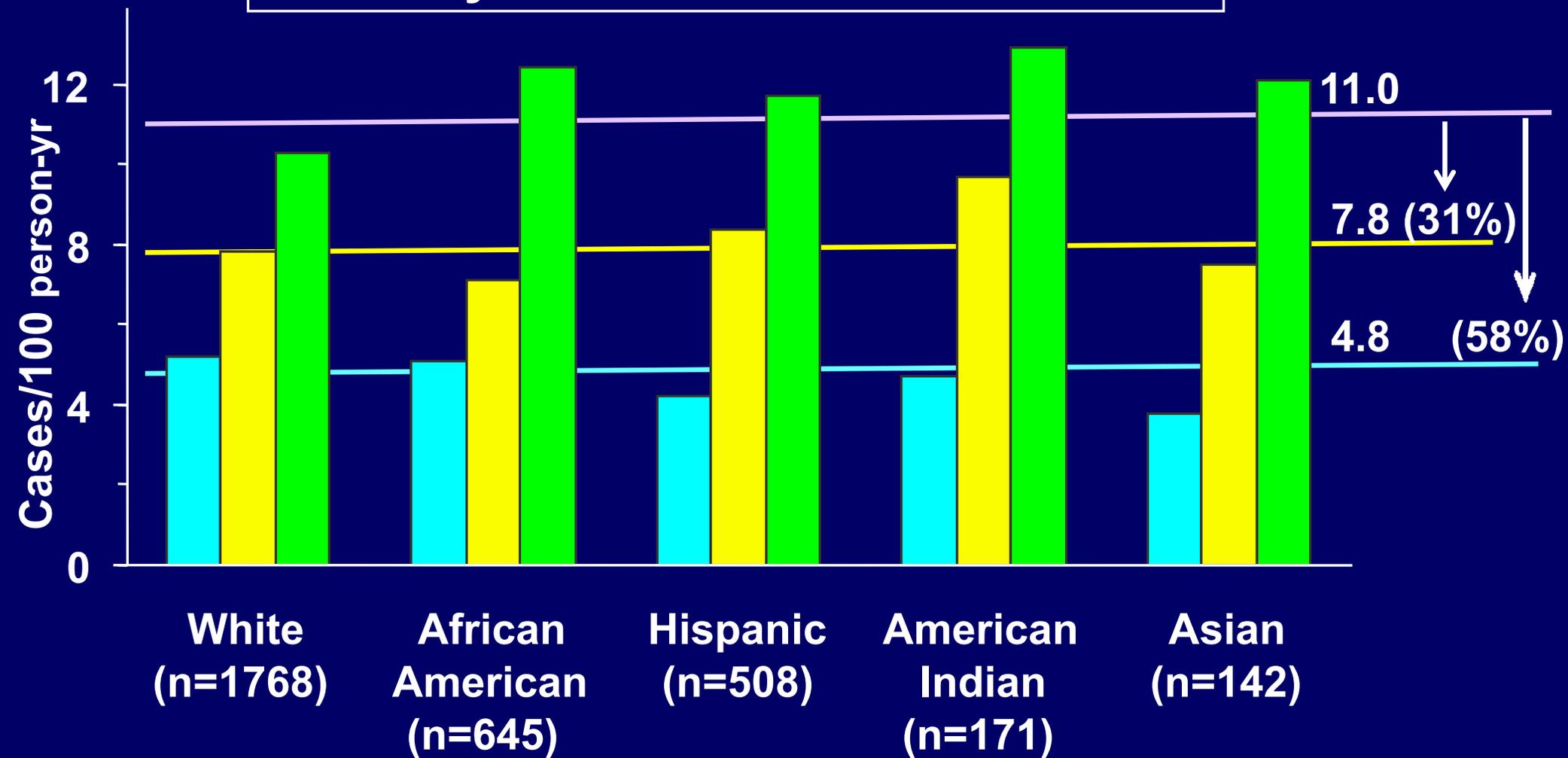


# Diabetes Incidence Rates in DPP

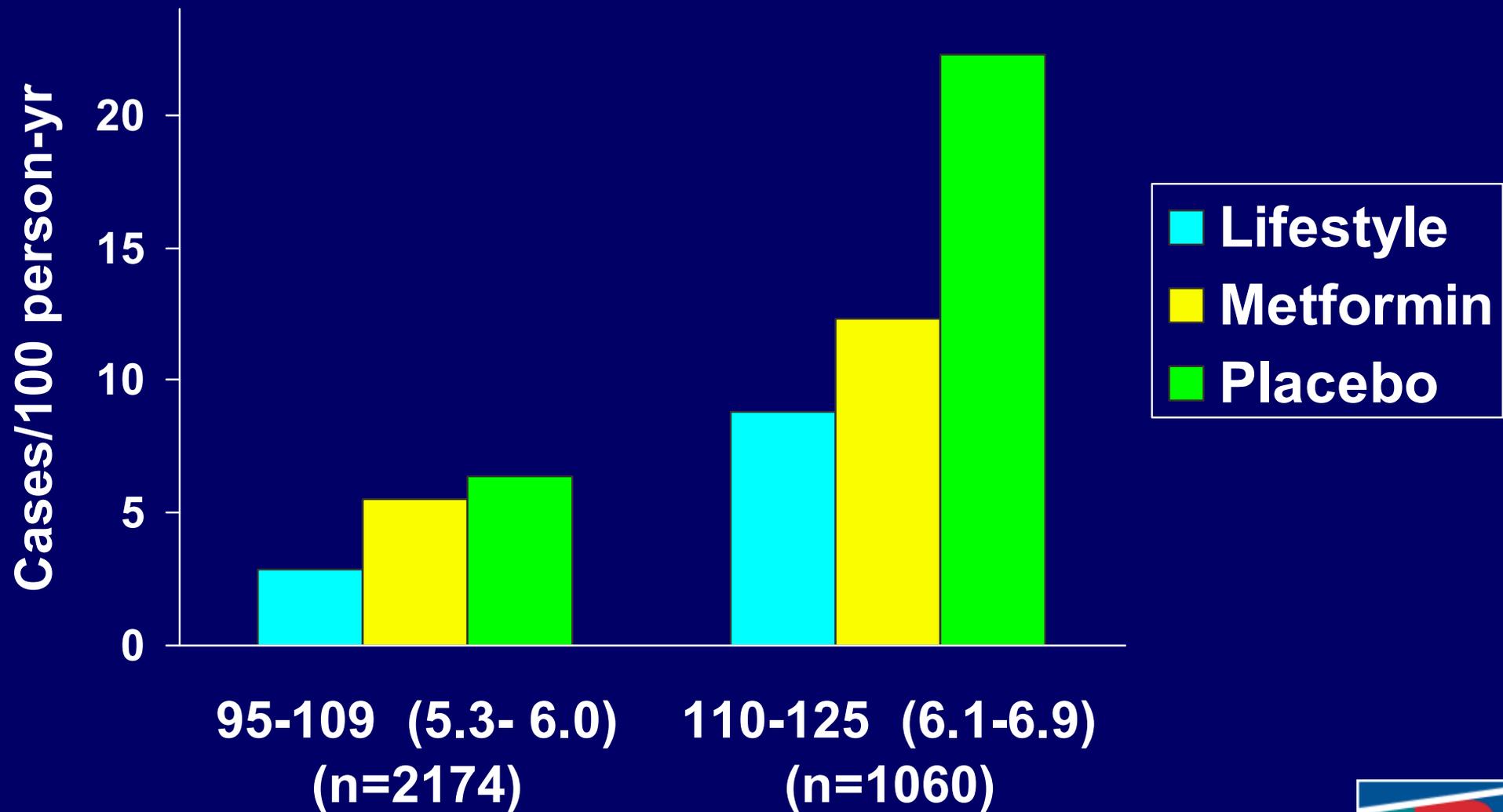


# DPP: Diabetes Incidence by Race/Ethnicity

■ Lifestyle ■ Metformin ■ Placebo



# Diabetes Incidence Rates by Fasting Glucose



NEJM, 2002

Fasting Plasma Glucose: mg/dl (mmol/l)



# **DPP: Unanswered Questions After 3 Years**

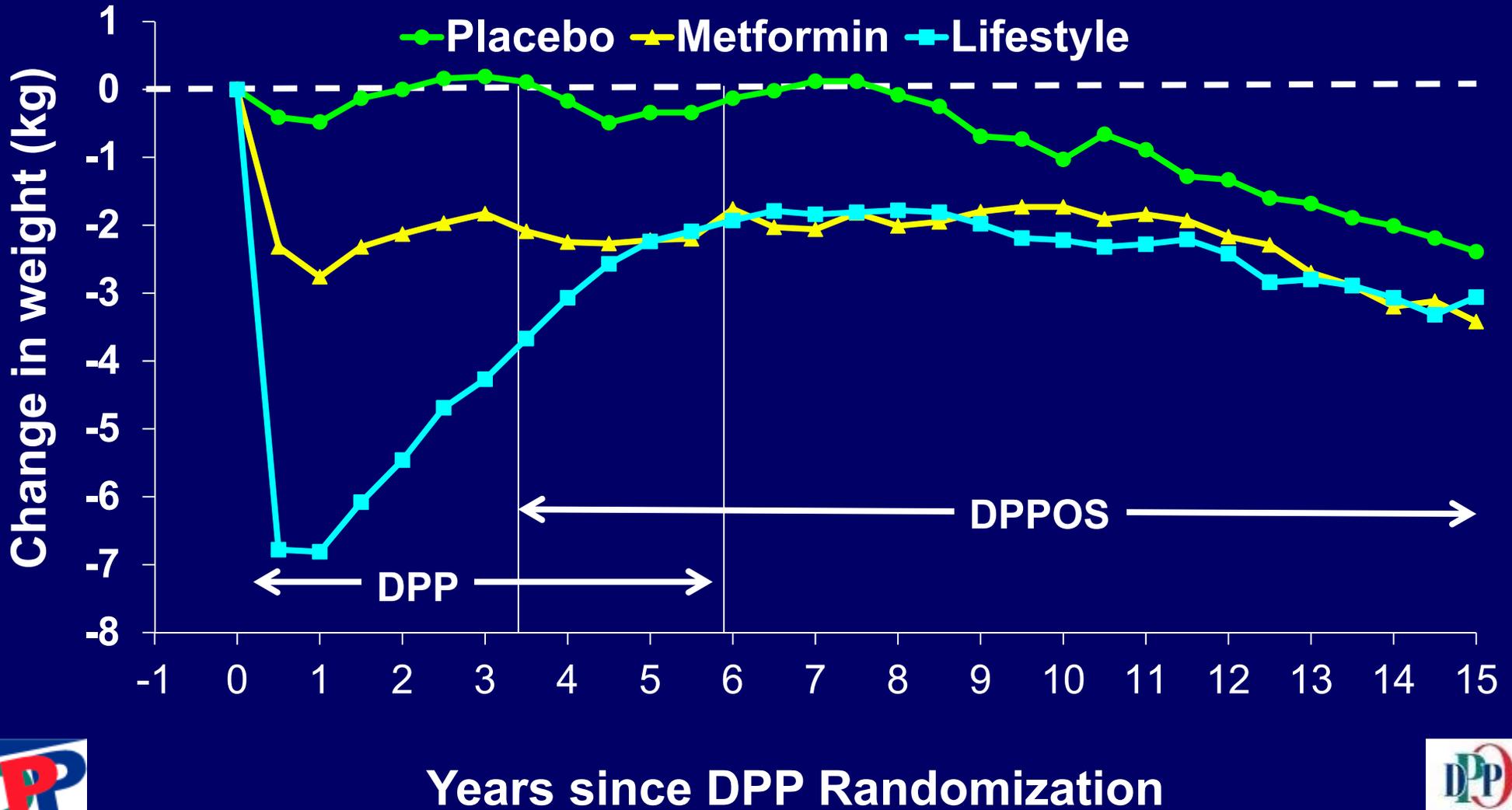
- **How long will weight loss and prevention last?**
- **Effects on “patient-centered” outcomes: micro- and macro-vascular disease, quality of life, longevity**
- **Cost-effectiveness**

# **DPPOS Protocol Changes Mandated by Treatment Effects**

- **Unmask drug assignments and study results**
- **Discontinue placebo & continue metformin**
- **Group lifestyle intervention for all participants**

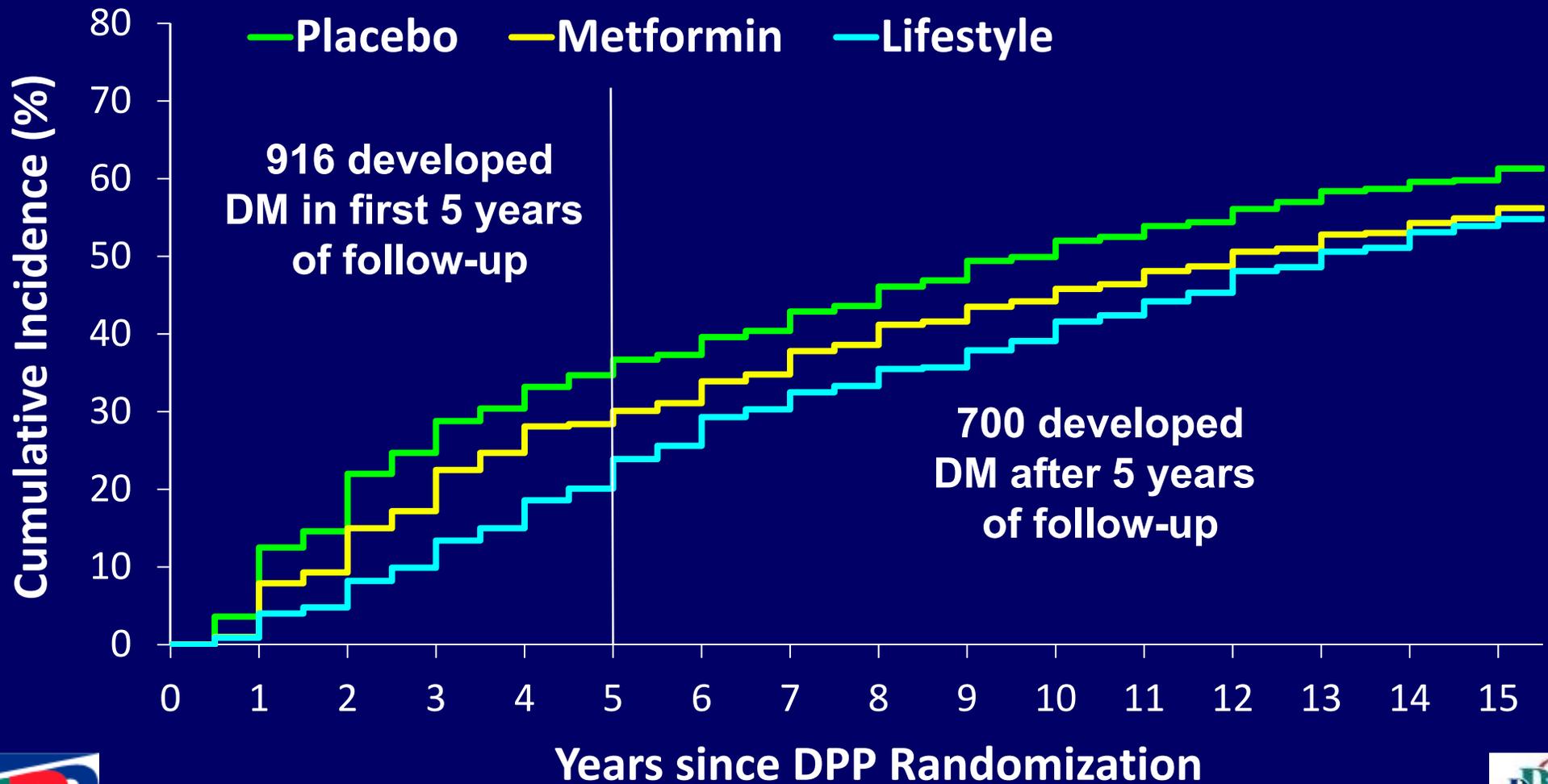
# DPPOS Results

## Weight Loss



# Cumulative Incidence of Diabetes

## DPP and DPPOS: All participants



916 developed DM in first 5 years of follow-up

700 developed DM after 5 years of follow-up



# Coronary Artery Calcification Severity\* in DPPOS



Circulation, 2017

\* Age-adjusted geometric mean severity, Agatston Units



# Other Long-term Effects of Metformin in the DPPPOS

- **Cost saving: reduction in medical care costs outside the study were greater than the cost of the metformin intervention**
- **Increased rate of vitamin B12 deficiency (a known side effect)**
- **No effect on cognitive function (memory and thinking)**

# **DPPPOS Phase 3 (2016-2025)**

## **Aims**

- **Long-term effects of metformin, started during pre-diabetes, on**
  - **Cardiovascular events (heart, stroke)**
  - **Cancer incidence**
- **Long-term effects of metformin or lifestyle on diabetes complications (eye, kidney, physical and cognitive function) and further diabetes**

# **Conclusion**

## **Metformin for Diabetes Prevention**

- **Although lifestyle changes (weight loss and increased physical activity) had the greatest effect on diabetes prevention, metformin was also effective, and not everyone can lose weight**
- **Metformin may have other long-term benefits**
- **Thank you volunteers in the DPPOS and other medical research programs for teaching us ways to improve health**

**The End**

