

# **Should We Treat “Prediabetes”**

**International Conference on Diabetes and Metabolism**

**Asian Association for the Study of Diabetes**

**Seoul, Korea**

**8 November 2013**

**William C. Knowler, MD, DrPH**

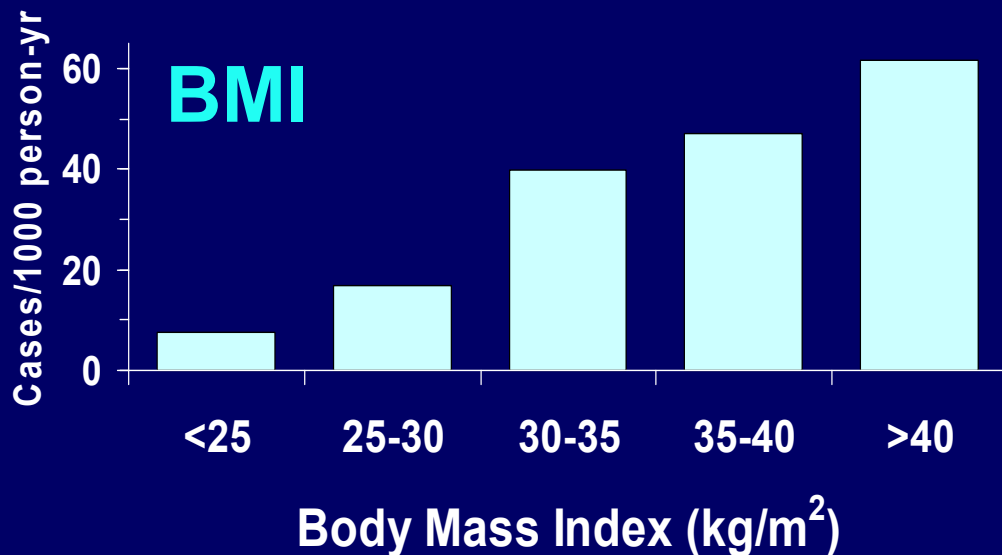
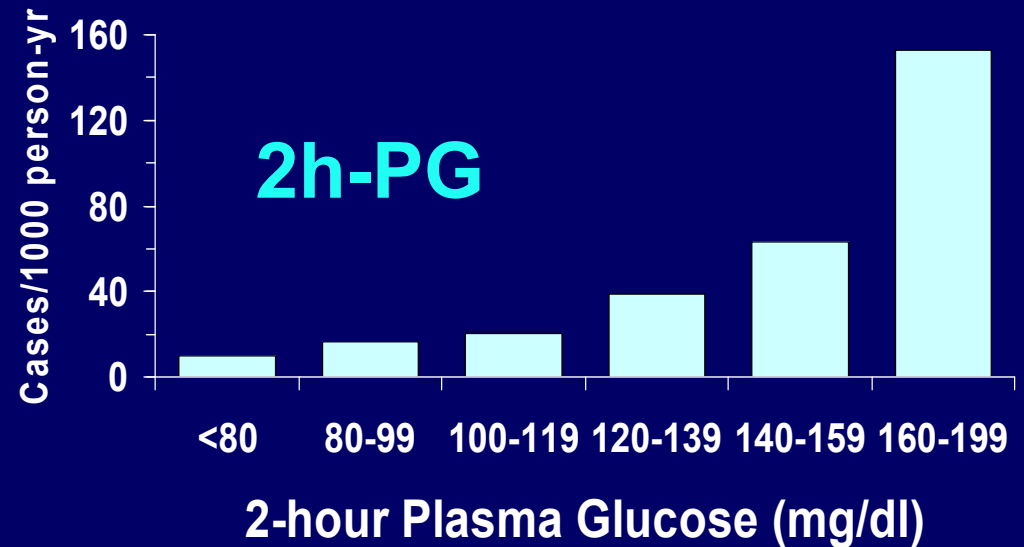
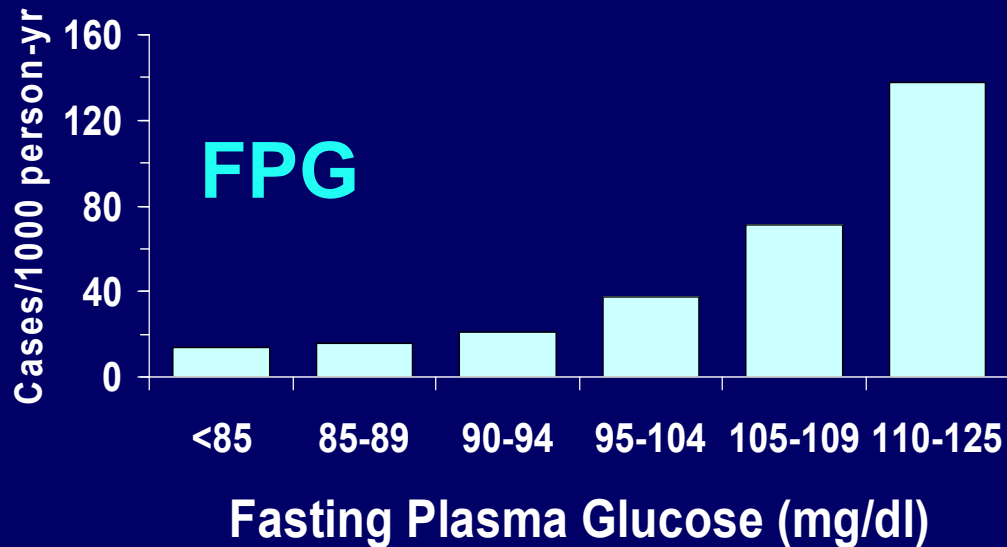
**National Institute of Diabetes and Digestive Diseases**

**Phoenix AZ, USA**

# What Is “Prediabetes”?

- Time prior to diabetes (only retrospective)
- ADA: impaired glucose regulation
  - Impaired fasting glucose
  - Impaired glucose tolerance
  - Elevated HbA<sub>1c</sub>
- Does it always lead to diabetes?  
(Is “prediabetes” always pre diabetes?)

# Predictors of Type 2 Diabetes in Adult Pima Indians



## Other major predictors:

- Parental diabetes ([Am J Epi 1981](#))
- Intrauterine environment ([Diabetes 1988](#))
- Serum insulin ([NEJM 1988](#); [Diab Met Rev 1990](#))
- Physical inactivity ([Am J Epi 2003](#))
- Serum adiponectin but not inflammatory markers ([Lancet 2002](#); [Diabetes Care 2003](#))
- Arsenic exposure ([Am J Epi 2013](#))
- Genetics

# **What Do We Hope to Accomplish by Treating “Prediabetes”?**

- **Prevent or delay development of diabetes**
- **Prevent complications of diabetes**
- **Prevent cardiovascular disease**
- **Reduce health care costs**
- **Extend life**

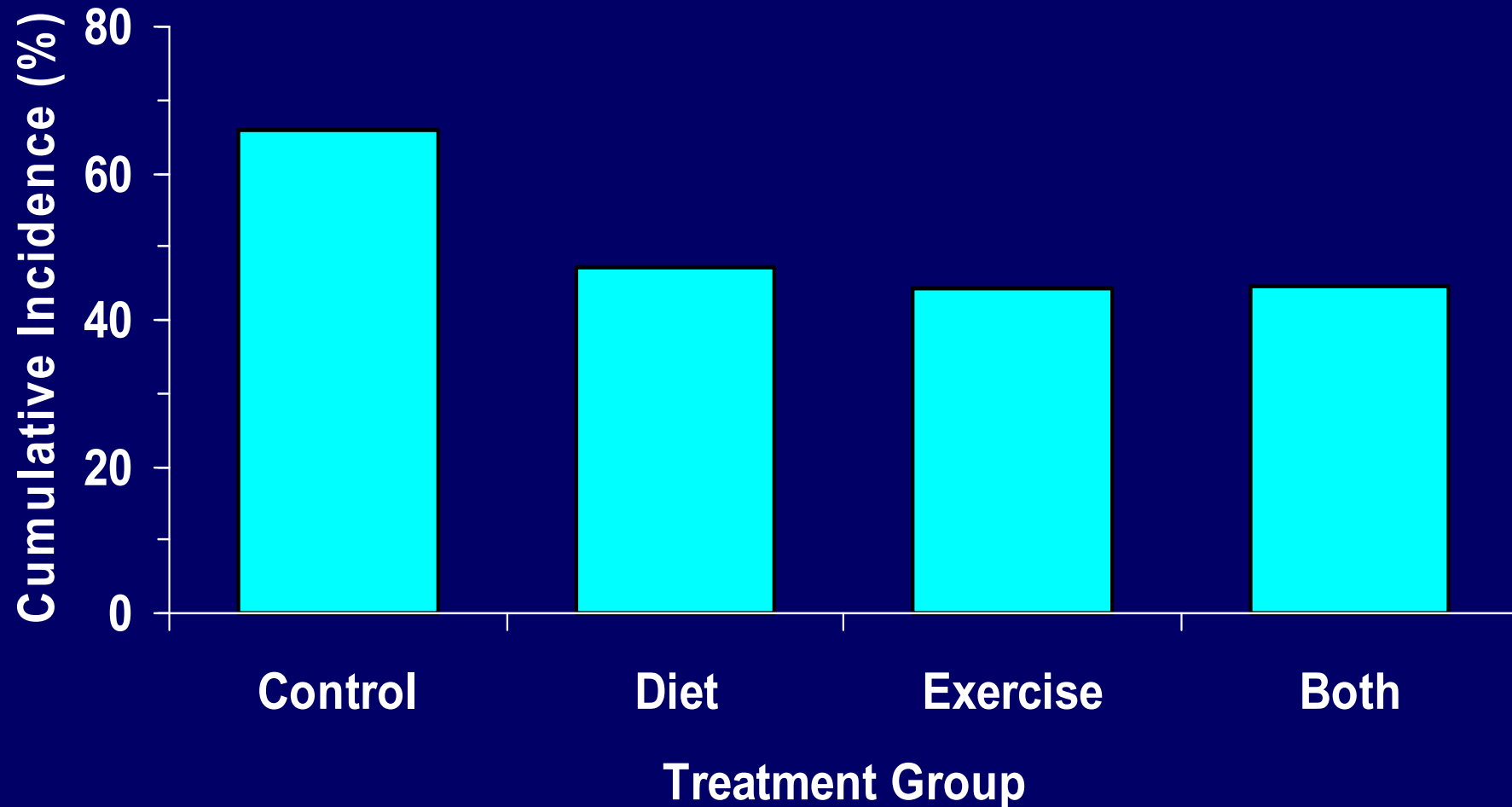
# Feasibility of Preventing Type 2 Diabetes

- The development of diabetes is preceded by a long period of impaired glucose regulation
- Screening tests can identify persons at high risk
- Safe, effective interventions can address modifiable risk factors:  
obesity, physical inactivity, elevated fasting or post-load glucose, insulin resistance, impaired insulin secretion
- Early drug trials (1970s) inconclusive – samples too small.

# Da Qing Clinical Trial

- 110,660 screened, age  $\geq 25$
- 577 with IGT
- 530 randomized by clinic (n=33)
  - Control group
  - Diet only
  - Exercise only
  - Diet & exercise
- Followed 6 years for diabetes

# 6-Year Incidence of Diabetes in Da Qing Clinical Trial

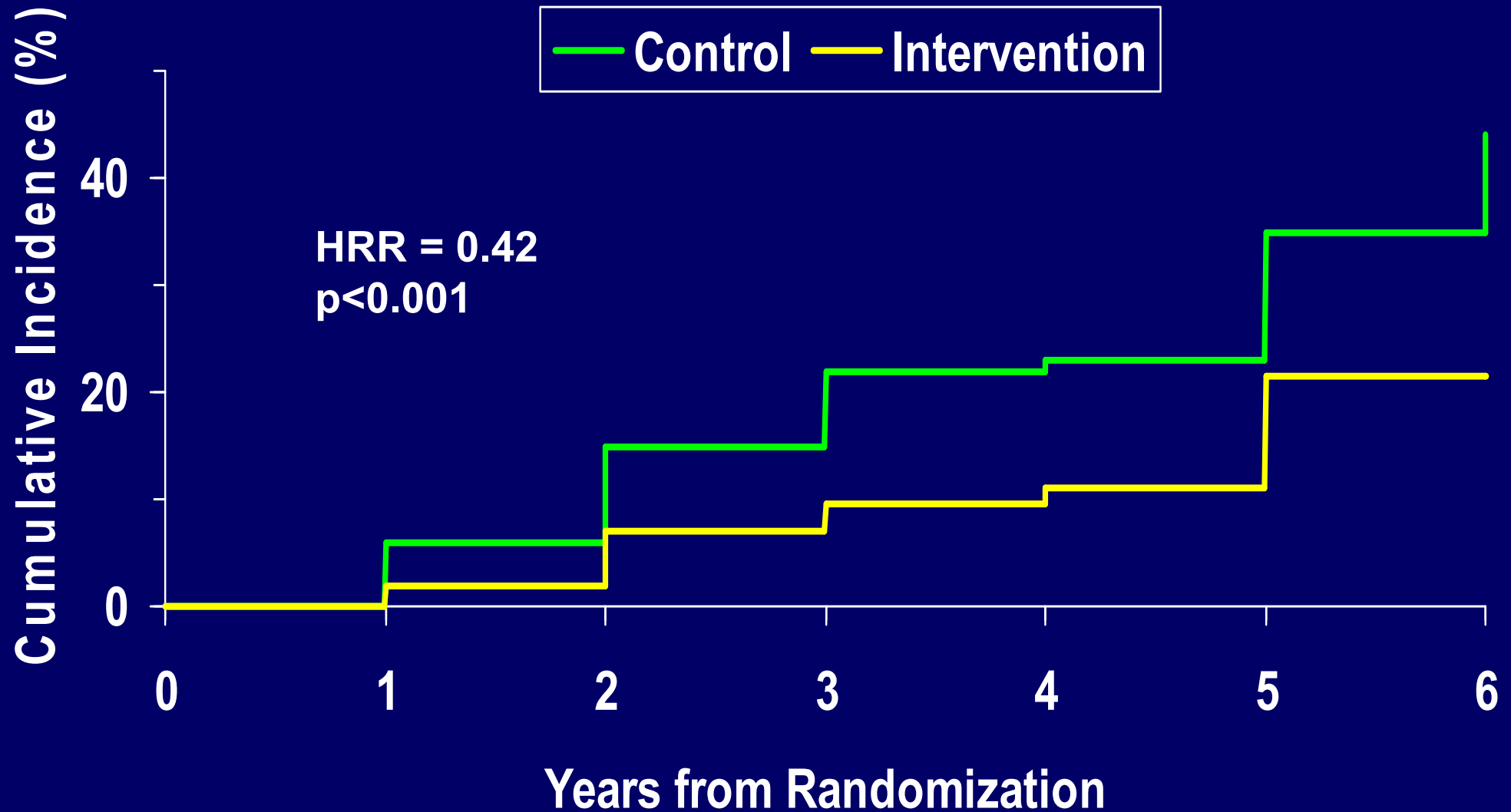


# Finnish Diabetes Prevention Study

- 522 in 5 centers with
  - Age 40-65 years
  - BMI  $\geq$  25 kg/m<sup>2</sup>
  - IGT
- Randomized to
  - Intervention  
(weight loss, diet changes, exercise)
  - Control
- Primary outcome: diabetes  
(1985 WHO criteria)



# Diabetes Incidence in the Finnish DPS



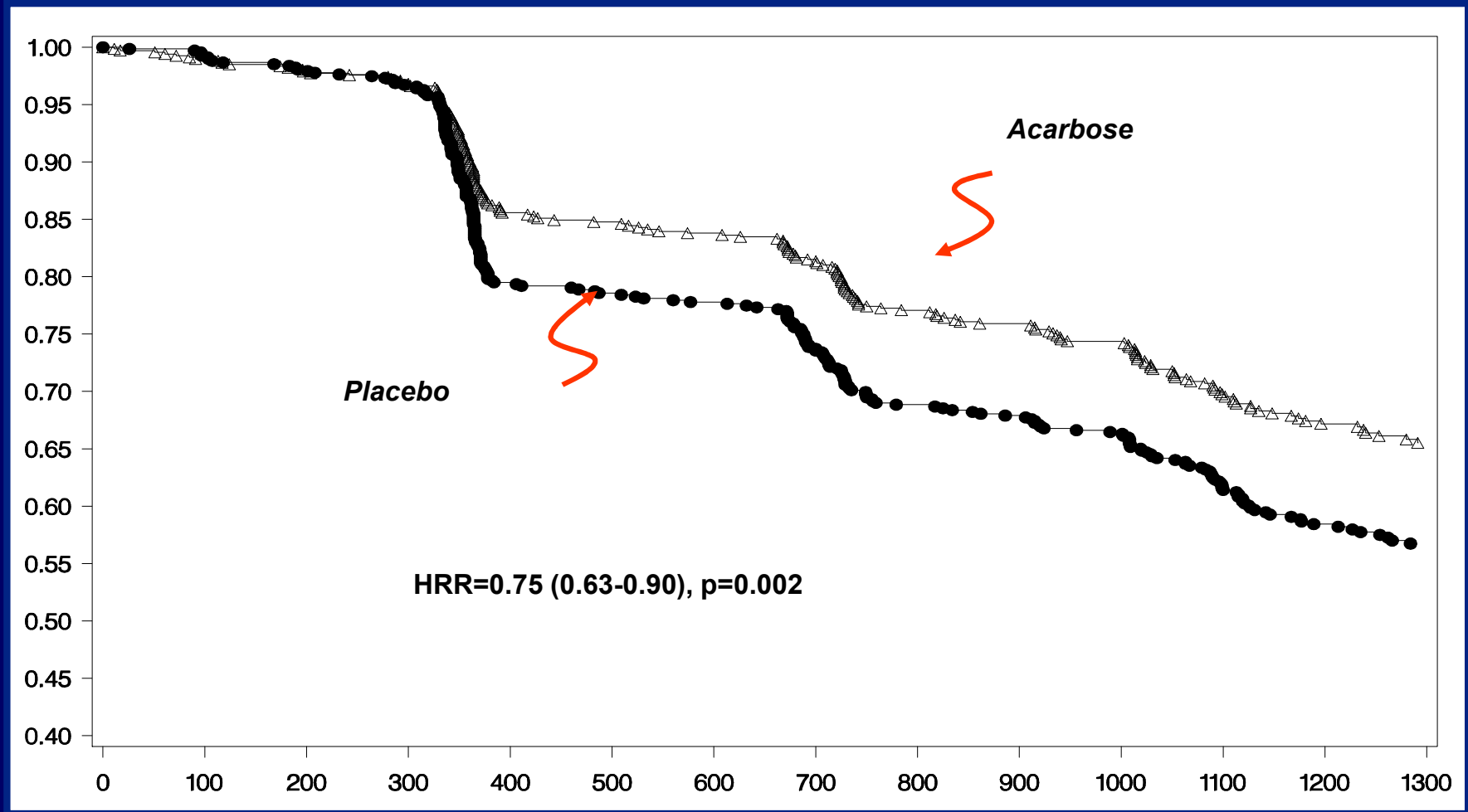
Tuomilehto, et al *NEJM* 2001;344:1343-50

# Stop-NIDDM

- International, multicenter (n=1,429)
- FPG  $\geq$  5.6 mmol/l & 2hrPG  $\geq$  7.8 mmol/l
- Randomized to acarbose or placebo
- Primary outcome
  - Diabetes by 1997 ADA criteria
- Secondary outcomes
  - Glucose tolerance
  - Insulin sensitivity and secretion
  - CVD

# The Effect of Acarbose on the Progression of IGT to Diabetes: Stop-NIDDM

Diabetes-free Survival



Days after randomisation

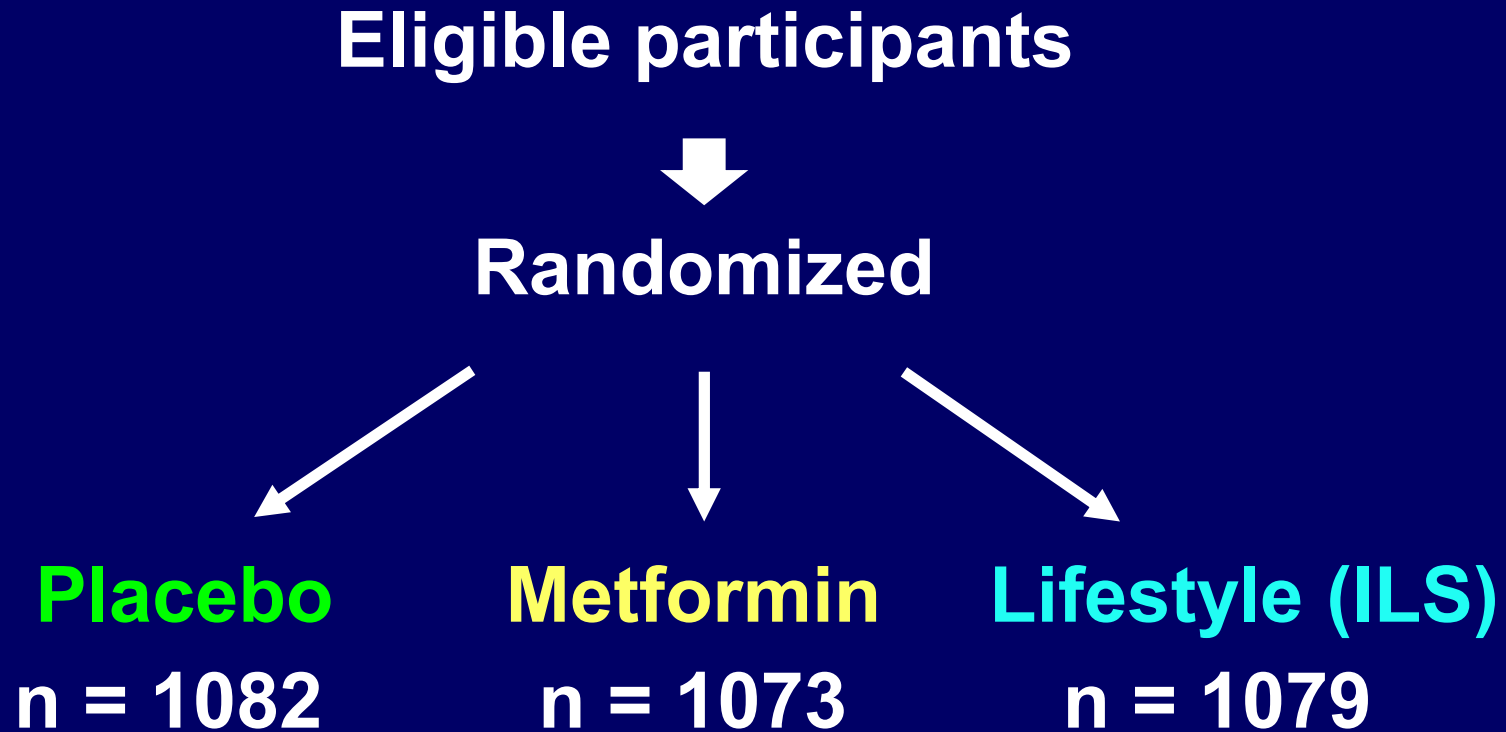
# Diabetes Prevention Program (DPP)

- **Multicenter randomized clinical trial in U.S.A.**
- **Hypothesis: Type 2 diabetes can be prevented or delayed by treating modifiable risk factors**
- **Persons at high risk of type 2 diabetes**
- **1996 – 2001 with long-term follow-up to 2014**

# Diabetes Prevention Program (DPP) Eligibility and Outcome

- Age  $\geq$  25 years
- Plasma glucose
  - Fasting 5.3- <7.0 mmol/l (95-125 mg/dl)  
and
  - 2 hour 7.8- <11.1 mmol/l (140-199 mg/dl)
- Body mass index  $\geq$  24 kg/m<sup>2</sup>
- Primary outcome: diabetes by FPG (6 mo.) or OGTT (annual)

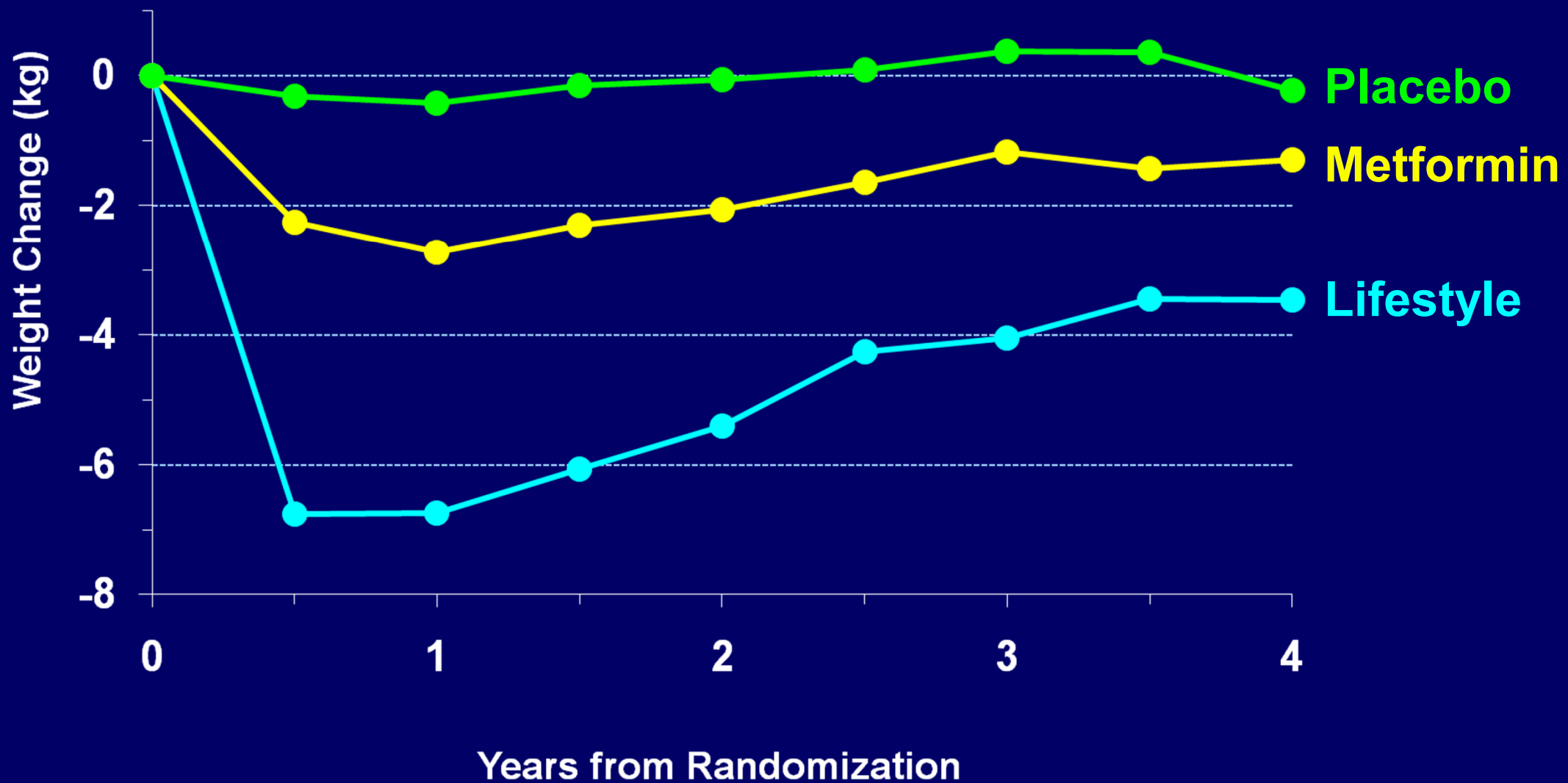
# Diabetes Prevention Program



NEJM 346: 393-403, 2002

Total n = 3,234

# Mean Weight Change in the DPP



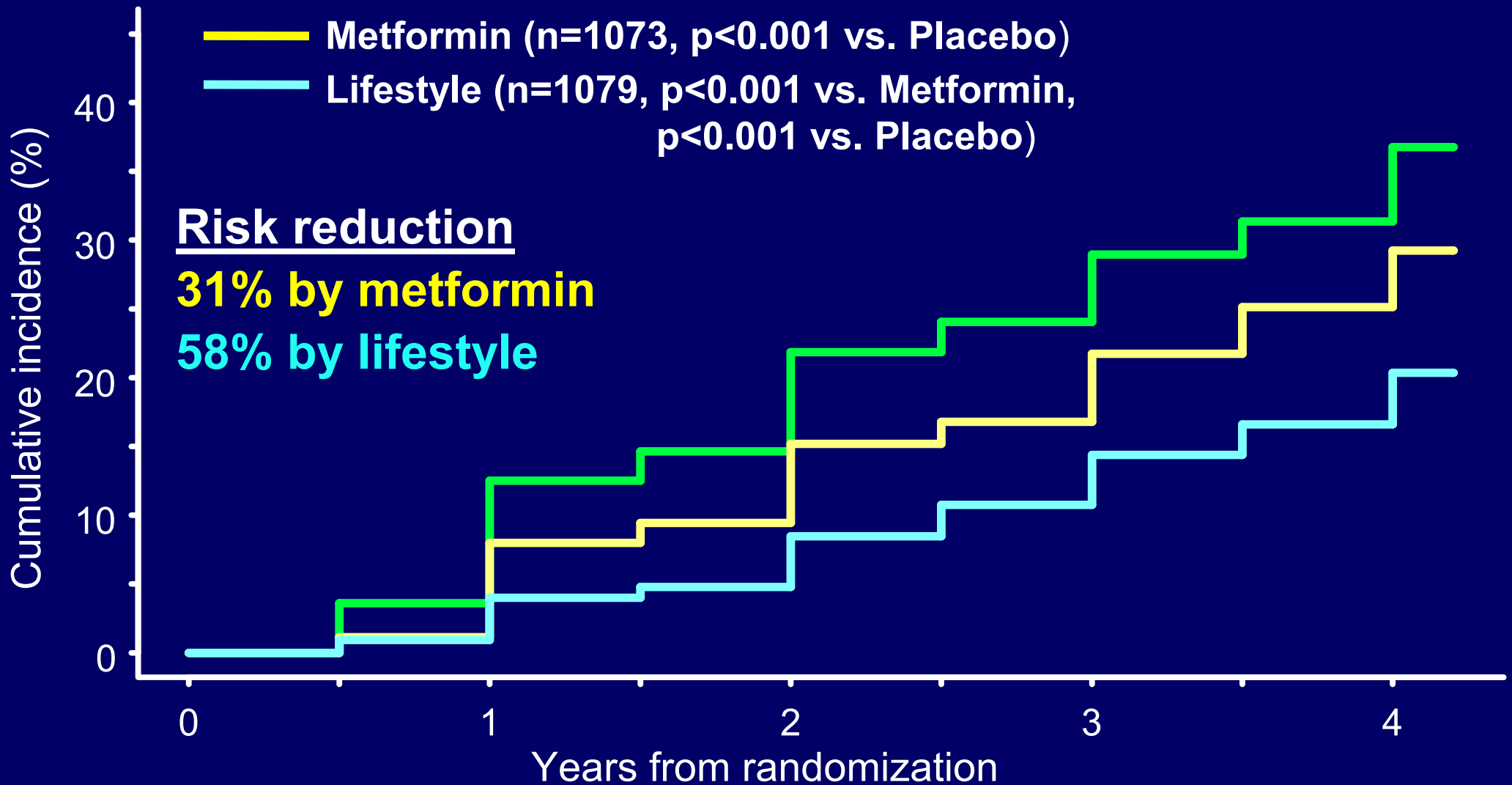
# DPP Incidence of Diabetes

- Placebo (n=1082)
- Metformin (n=1073, p<0.001 vs. Placebo)
- Lifestyle (n=1079, p<0.001 vs. Metformin, p<0.001 vs. Placebo)

## Risk reduction

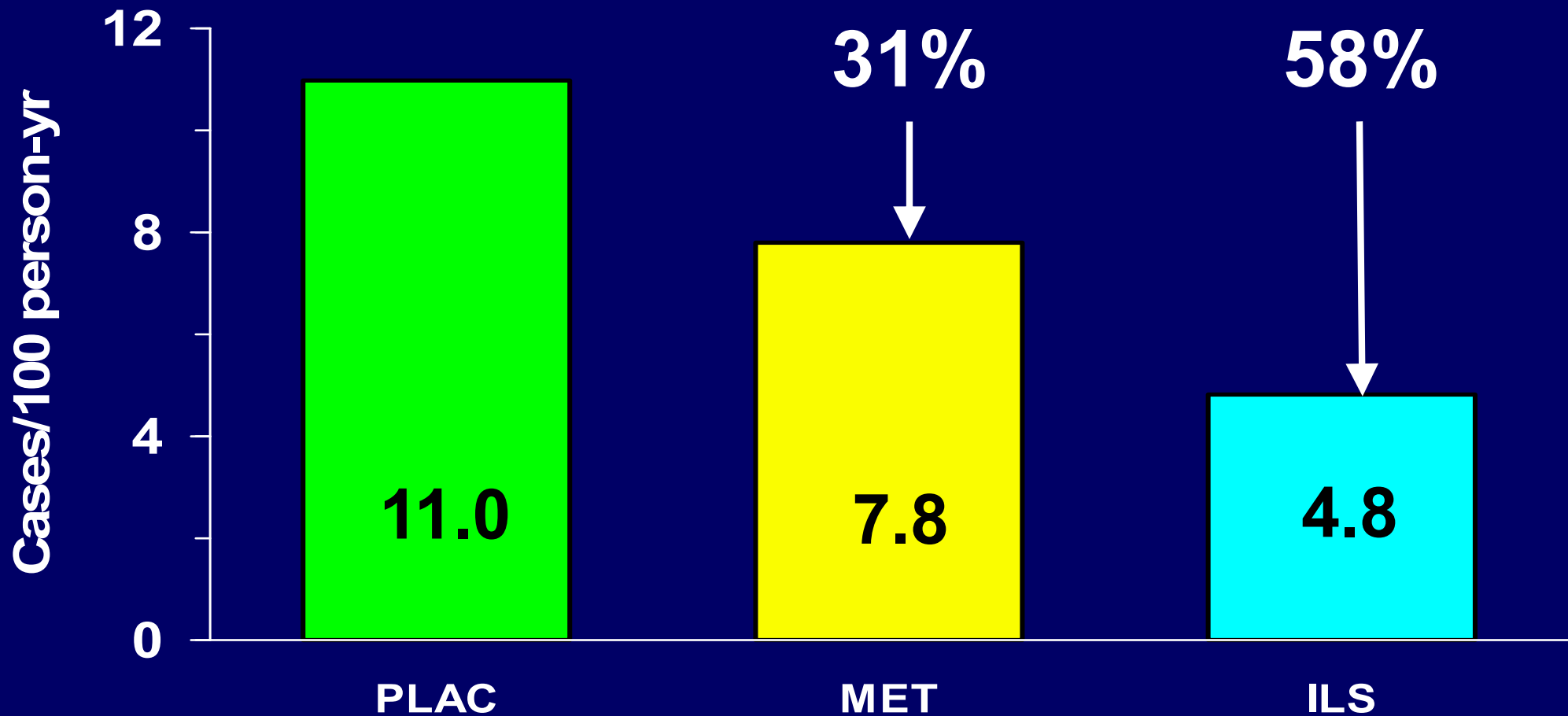
**31% by metformin**

**58% by lifestyle**

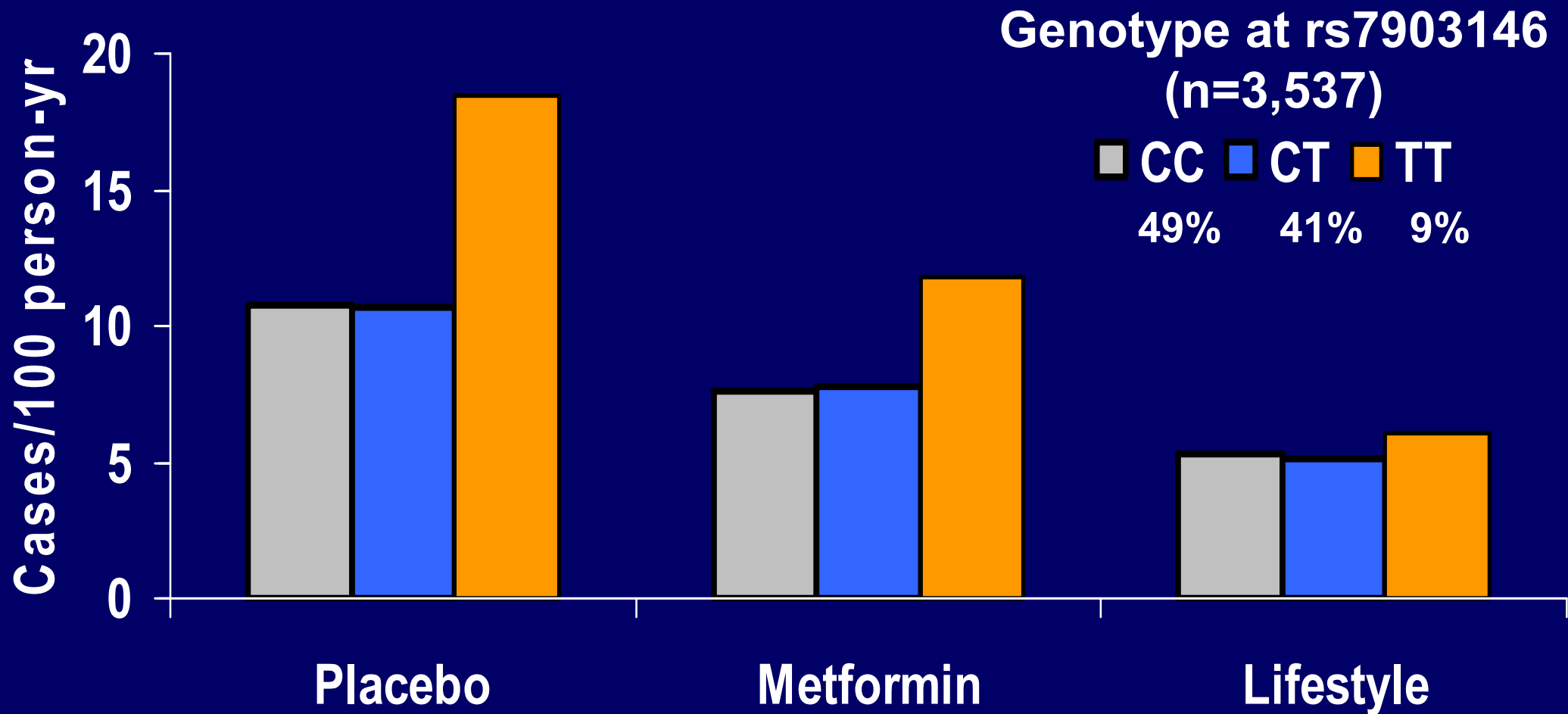




# Diabetes Incidence Rates in DPP



# TCF7L2 Genotype and Diabetes Incidence in the DPP



# **Other Benefits of DPP Lifestyle Intervention on CVD Risk Factors**

- **Lowered blood pressure**
- **Stopped development of new hypertension**
- **Lowered triglycerides**
- **Reduced development of new hyperlipidemia**
- **Lowered CRP and fibrinogen**
- **Reduced incidence of metabolic syndrome**
- **Too few CVD events to evaluate treatment effect**

**Diabetes Care 2005; Diabetes 2005; Ann Internal Med 2005**

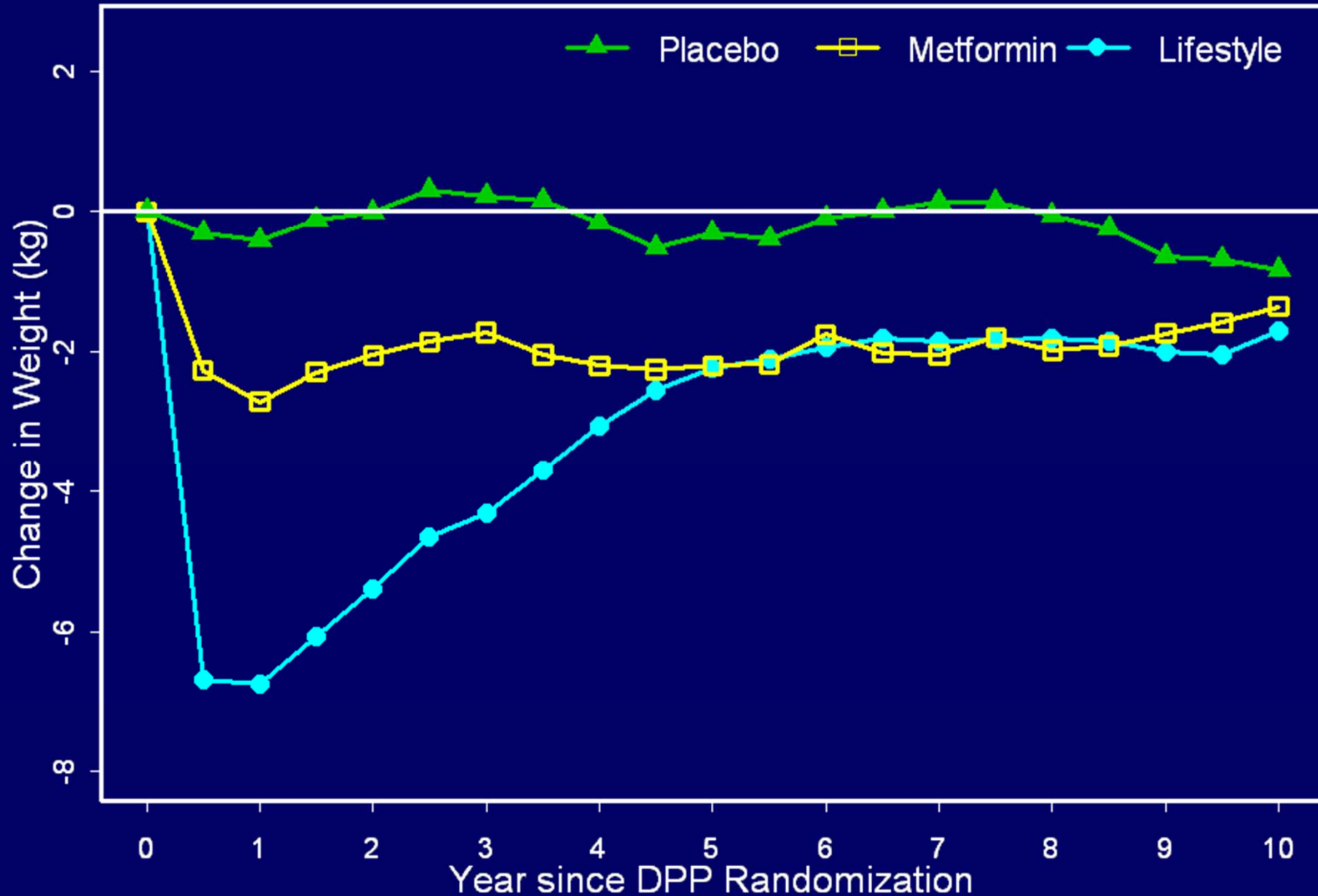
# **DPP Outcomes Study (DPPOS) 2002 – 2014**

**Masked phase ended, metformin continued,  
placebo discontinued, all offered lifestyle.**

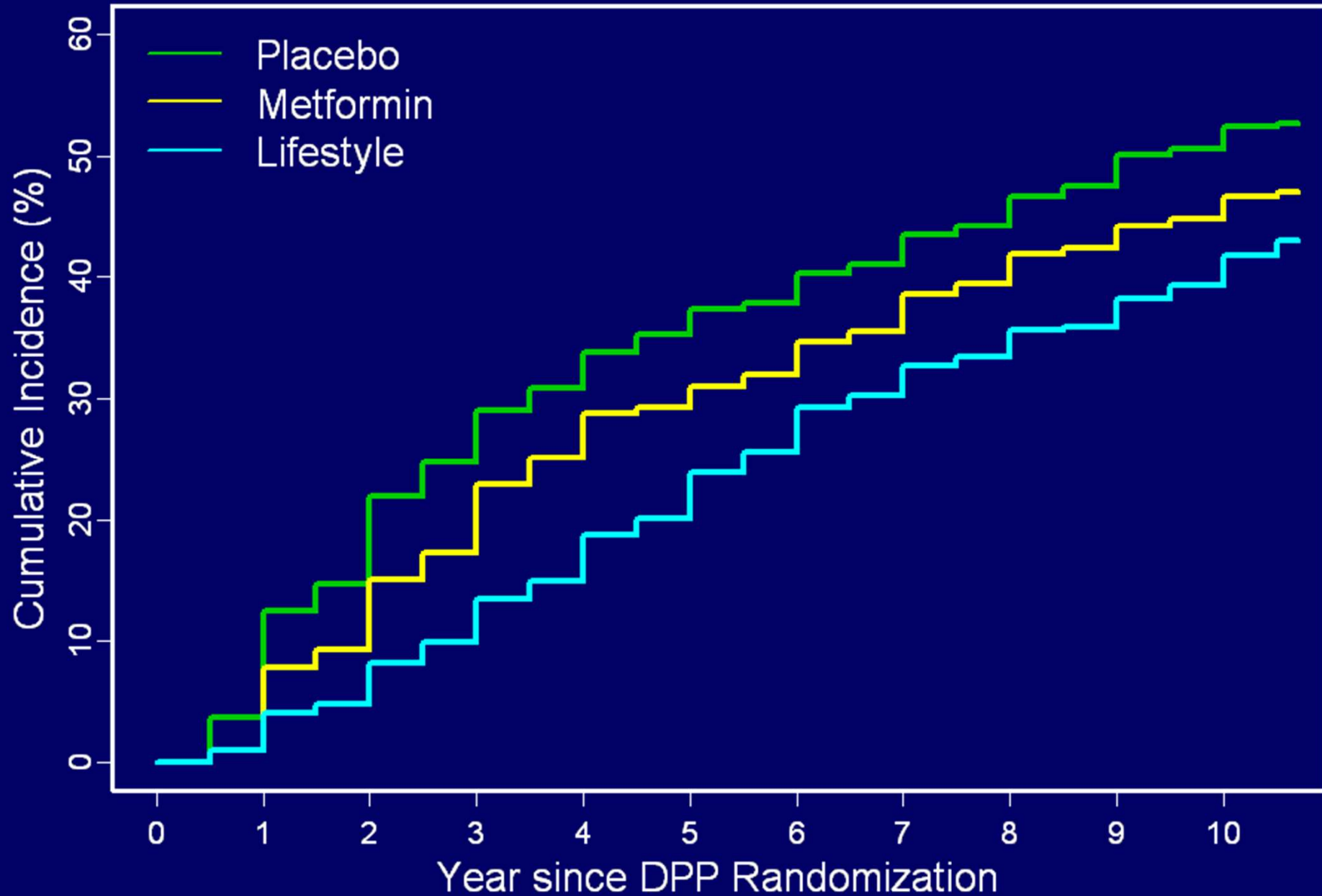
## **Long-term effects of DPP interventions on**

- Weight loss maintenance**
- Further diabetes incidence**
- Diabetes complications and death**

# 10-Year Weight Change: DPP + DPPOS

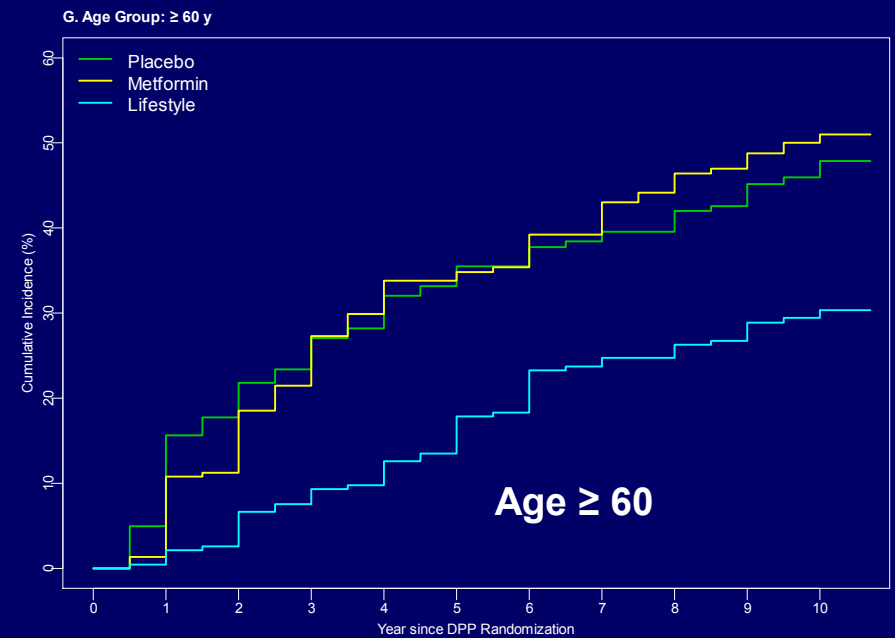
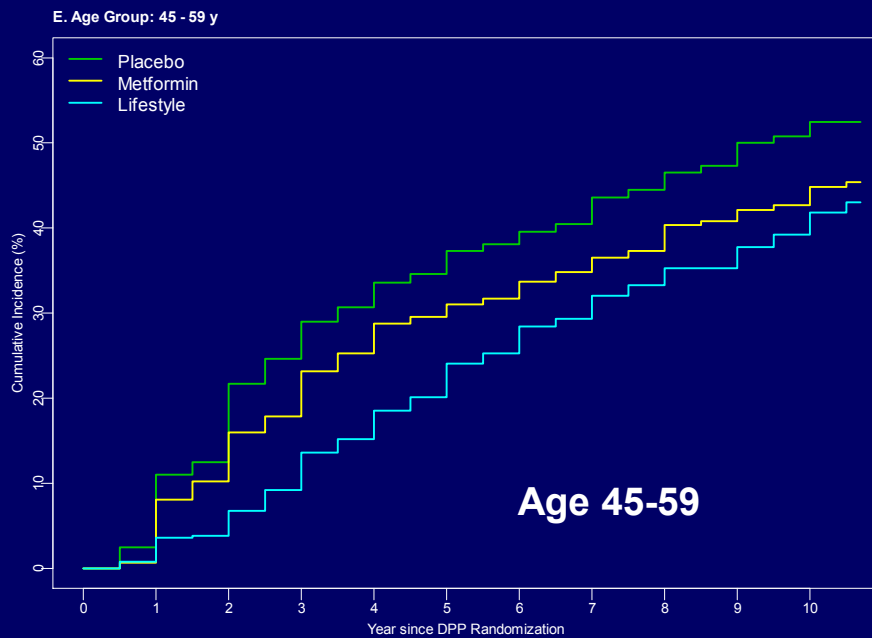
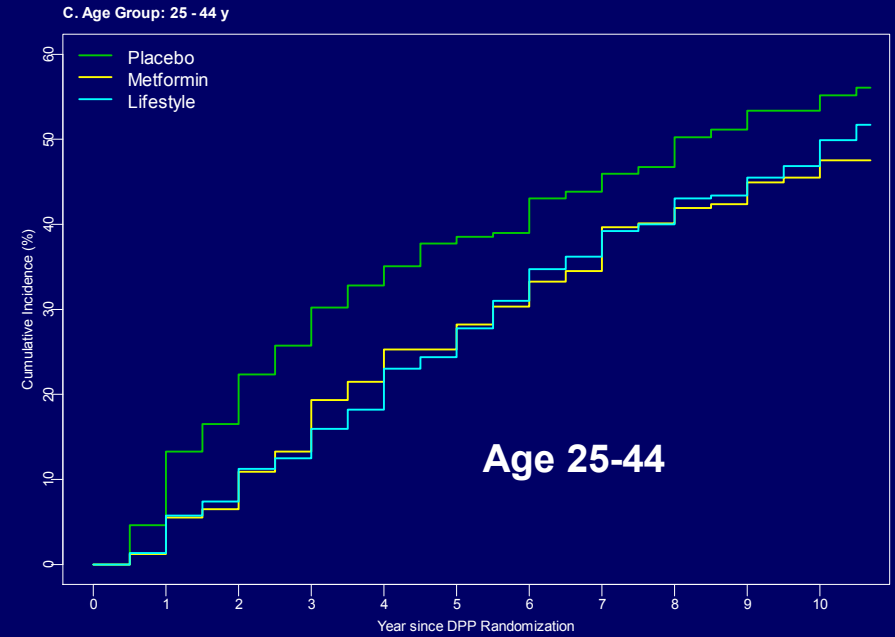
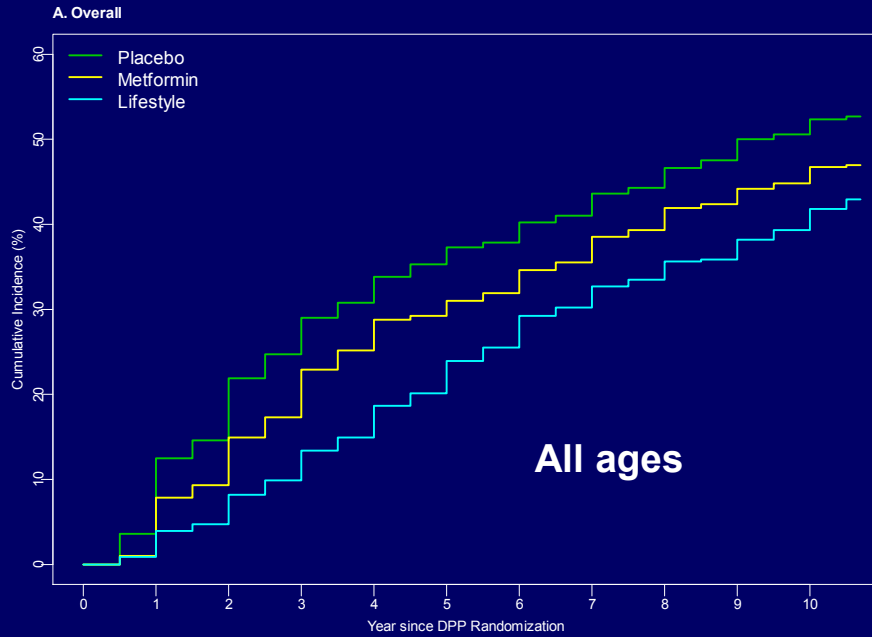


# Cumulative Incidence of Diabetes

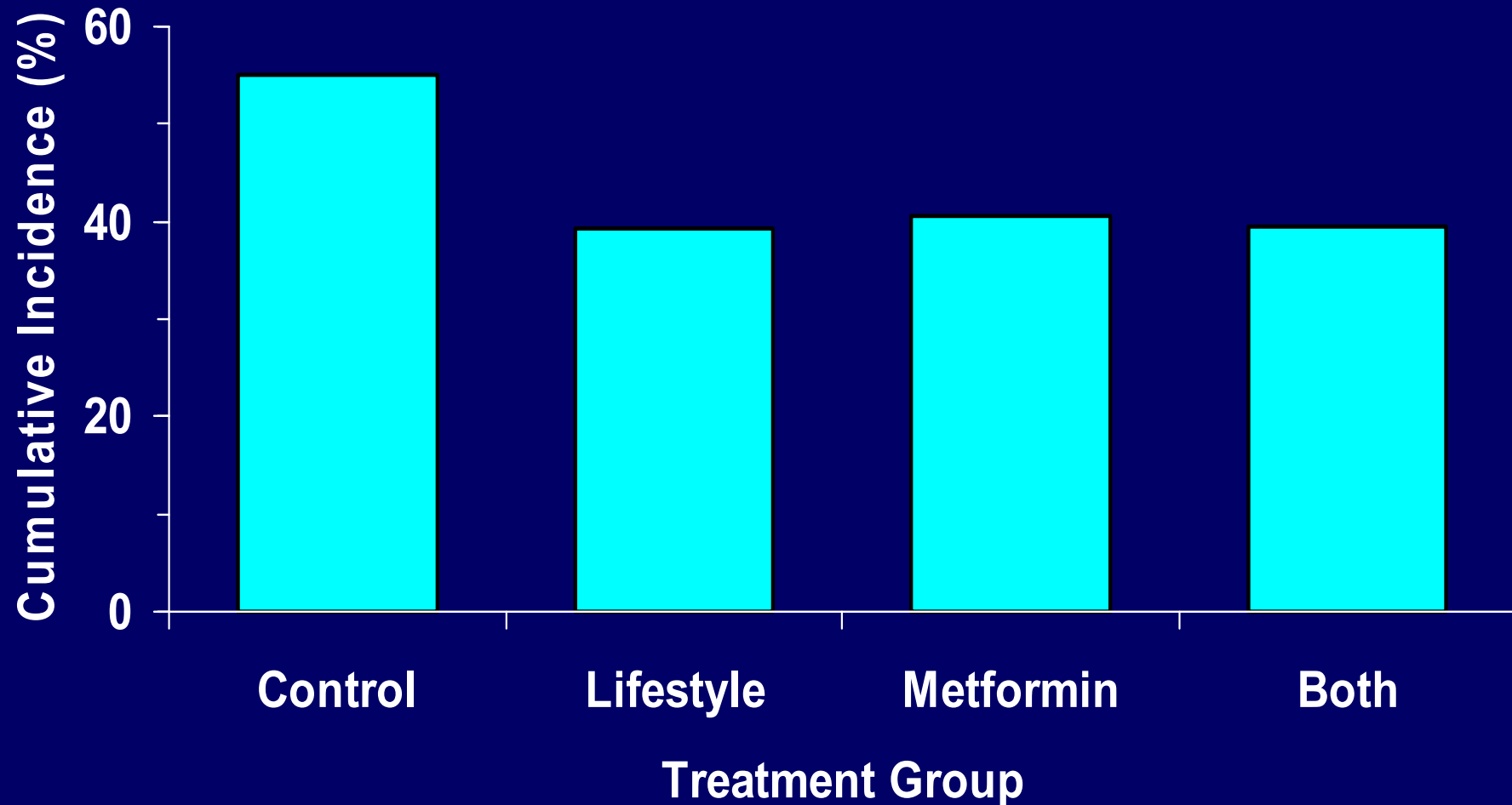


# Cumulative Incidence of Diabetes Since Randomization

▲ Placebo    □ Metformin    ● Lifestyle



# 3-Yr Diabetes Incidence in the Indian DPP (531 adults with IGT, Chennai, India)



Ramachandran: *Diabetologia* 49: 289-297, 2006



# **Rosiglitazone and Ramipril in IFG or IGT (DREAM)**

- **International, multicenter (n=5,269)**
- **IFG or IGT**
- **Randomized to rosiglitazone, ramipril, both, or placebo (2 x 2 factorial design)**
- **Primary outcome: Diabetes by OGTT**

# Rosiglitazone and Ramipril in IFG or IGT (DREAM)

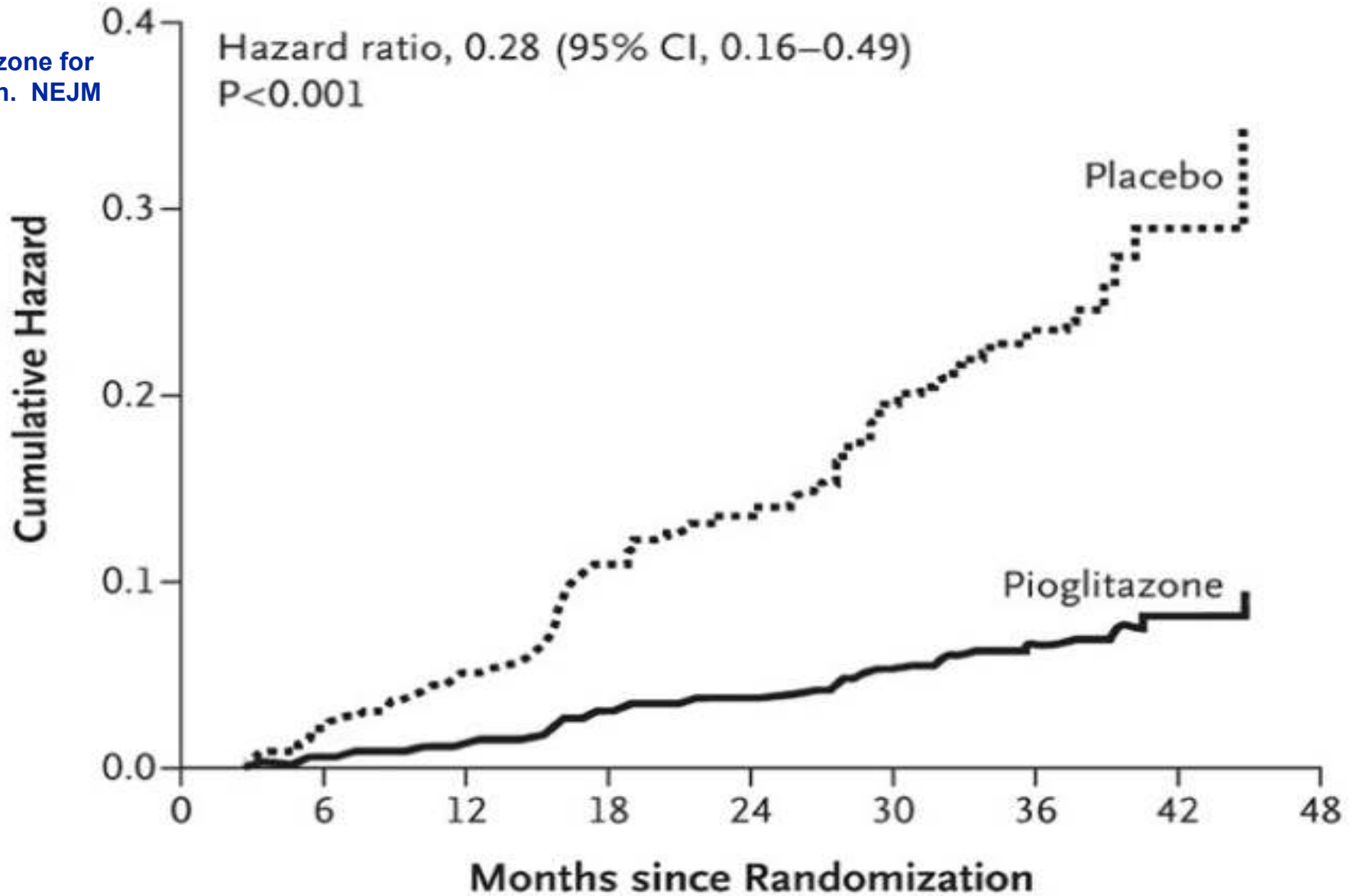
	Placebo	Ramipril
Placebo		
Rosi- glitazone		

*n*=5,269

# Rosiglitazone and Ramipril in IFG or IGT (DREAM)

	Placebo	Ramipril	HR (95%CI)
Placebo	?	?	1.0
Rosiglitazone	?	?	0.38 * (0.33 – 0.44)
HR (95%CI)	1.0	0.91 § (0.80 – 1.03)	n=5,269

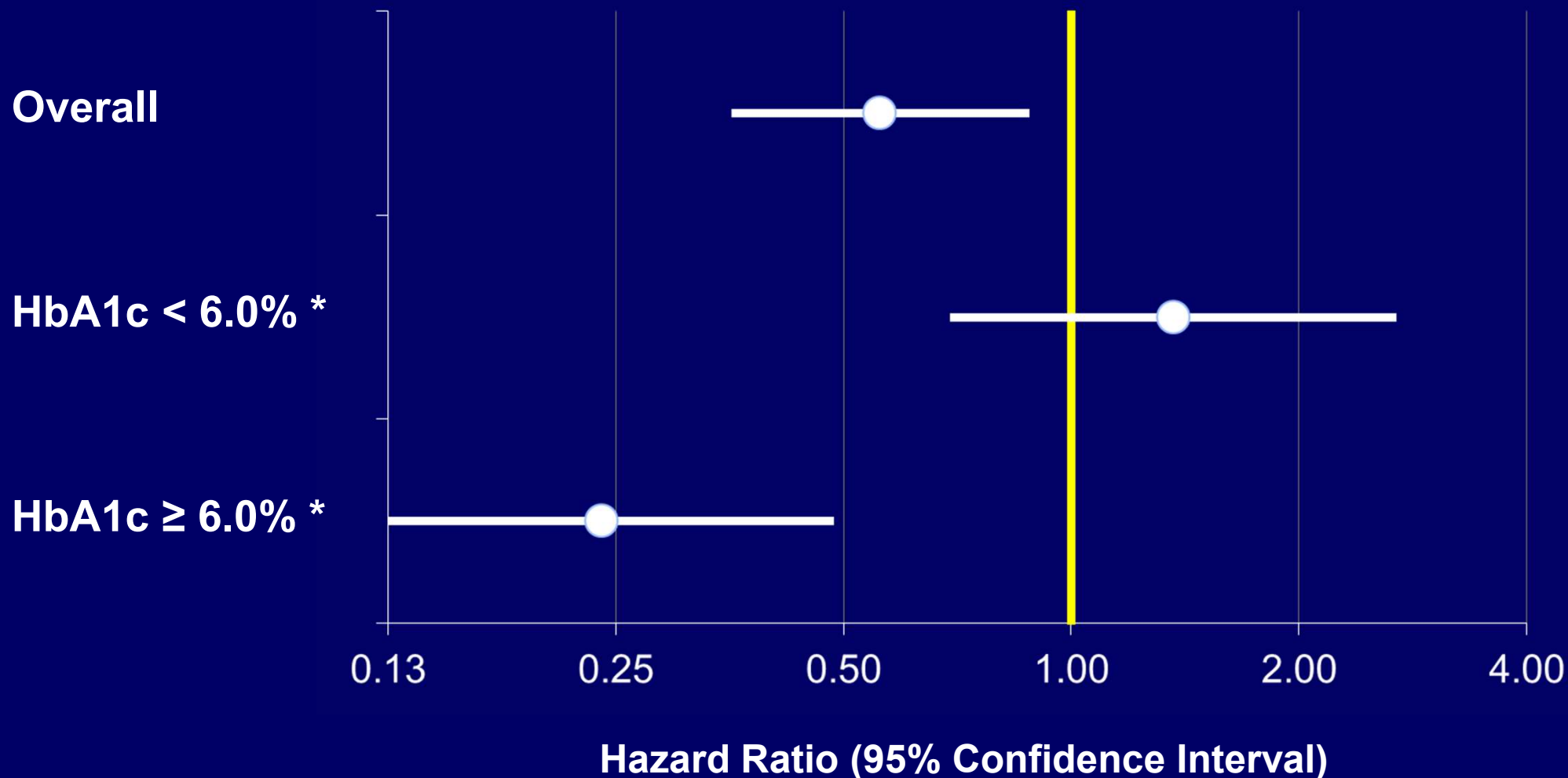
DeFronzo: Pioglitazone for diabetes prevention. NEJM 2011



**No. at Risk**

Placebo	299	259	228	204	191	134	83	17
Pioglitazone	303	262	244	228	218	140	87	24

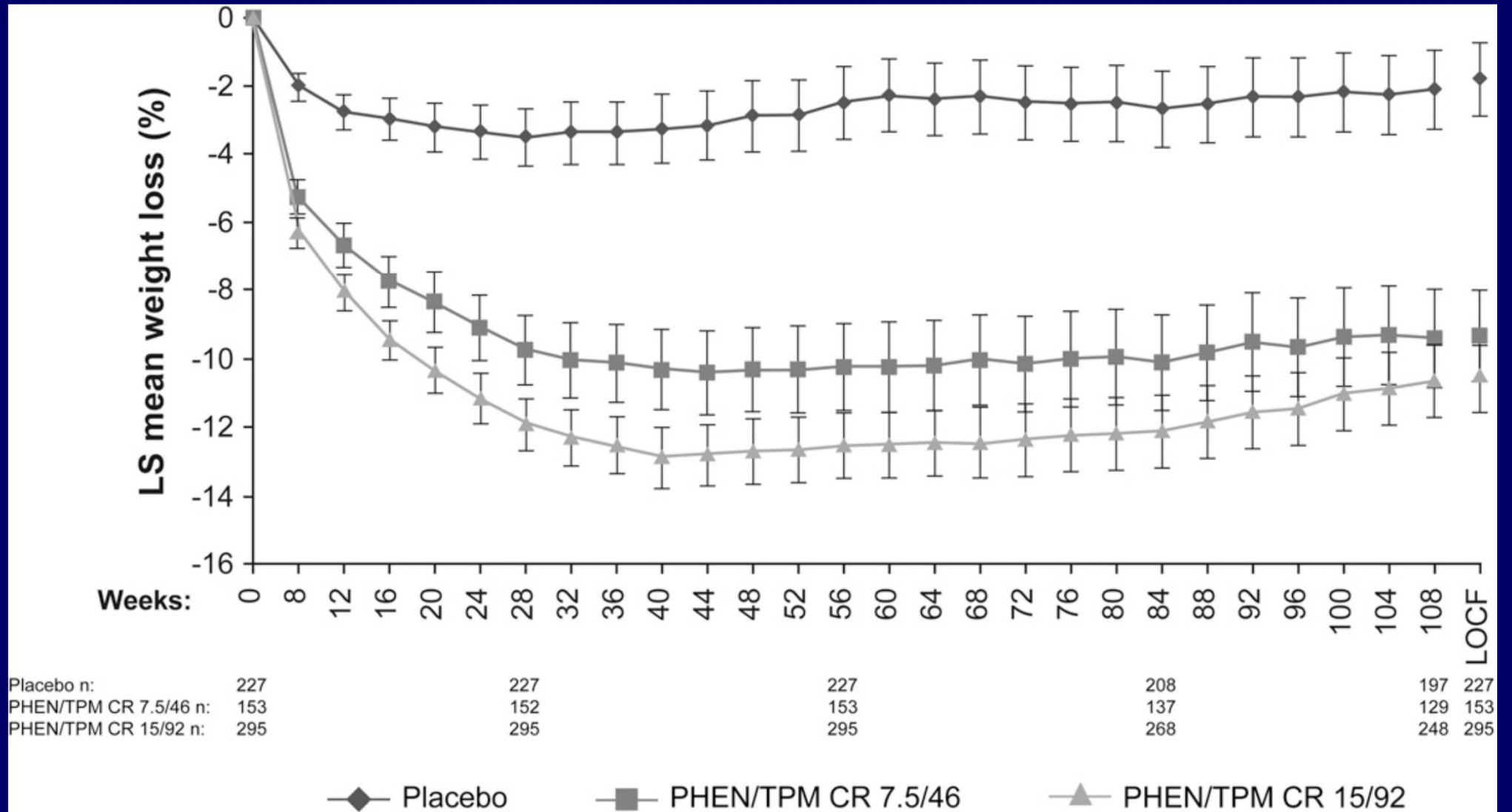
# Lifestyle Modification and Diabetes Incidence in Overweight Japanese Men with IFG



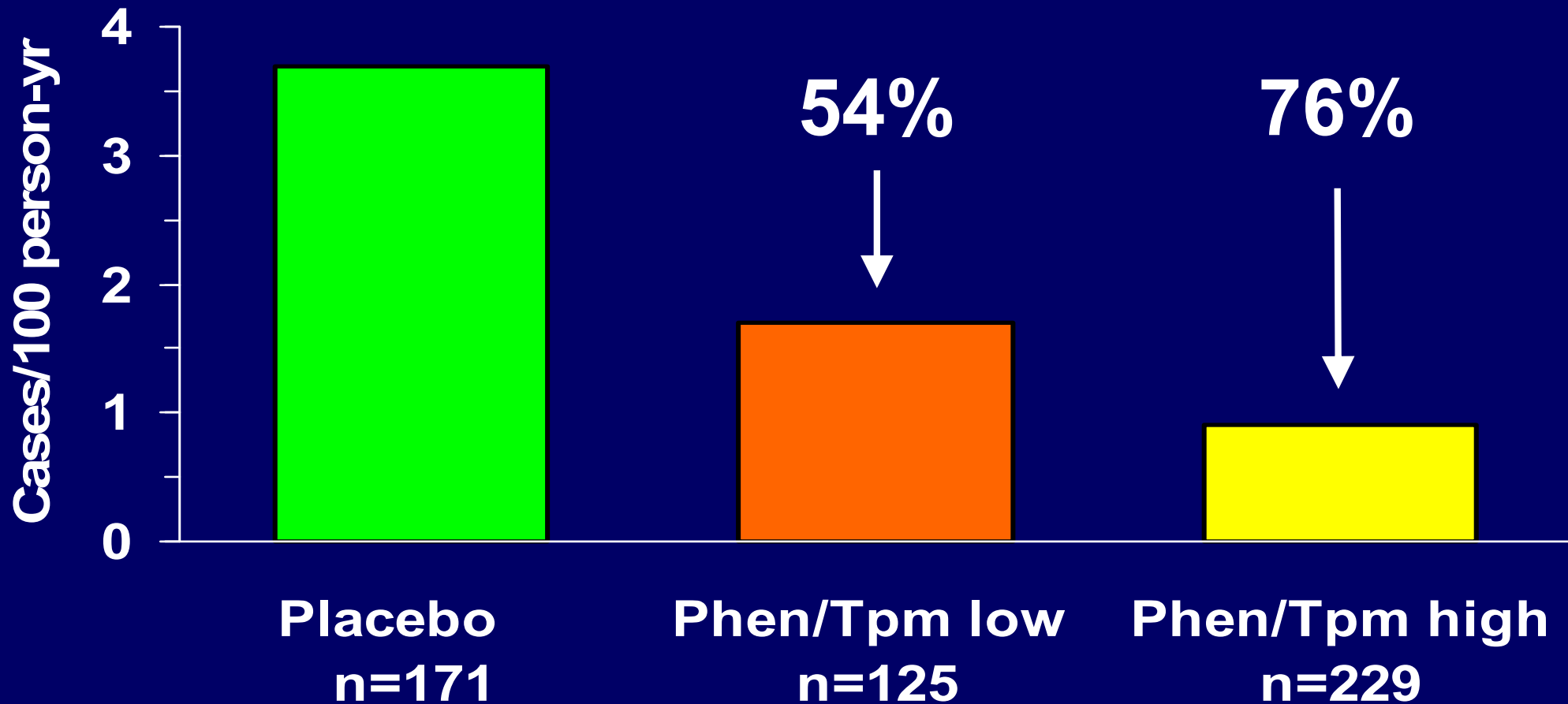
\* Approximate equivalent to NGSP

Saito. Arch Int Med 2011

# Mean Weight Loss with Phentermine + Topiramate



# Diabetes Incidence Rates with Phentermine + Topiramate

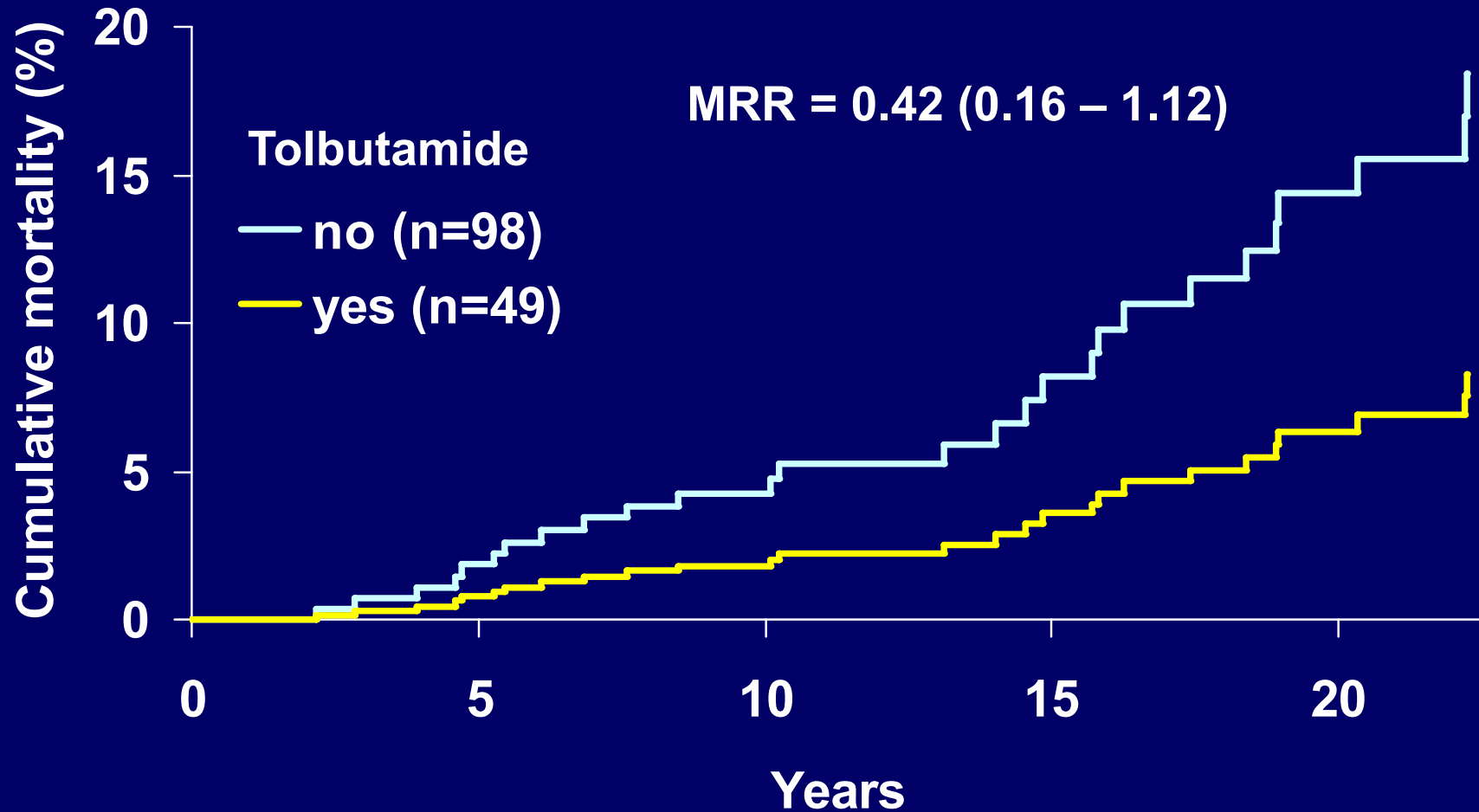


# **Beyond Glucose: From Predicting Diabetes to Predicting “Hard” Outcomes**

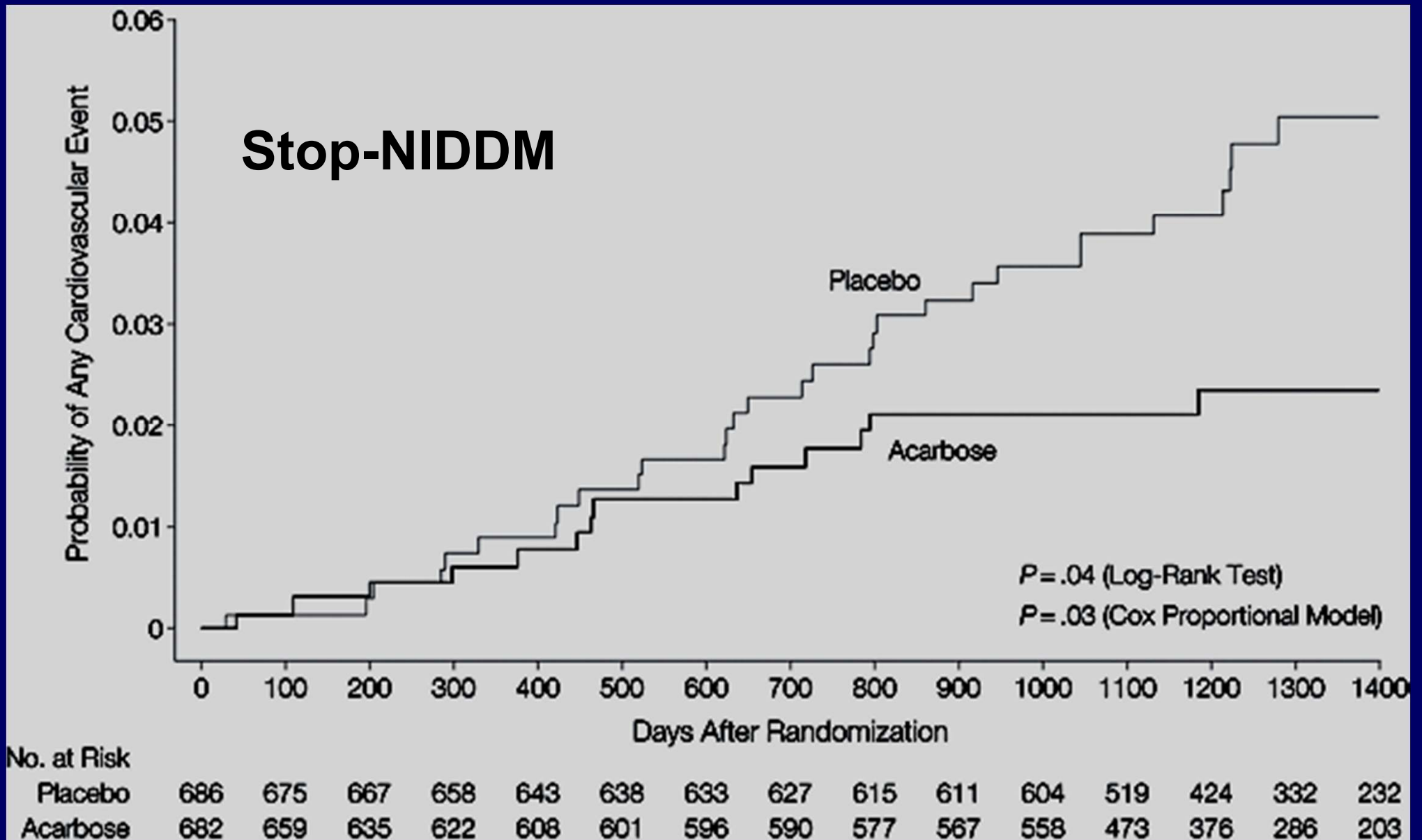
- **Will keeping glucose below diagnostic thresholds prevent complications and reduce mortality?**
- **If so, does it matter how it is done (lifestyle modification or drugs)?**



# Ischemic Heart Disease Mortality by Tolbutamide Malmöhus Prevention Trial

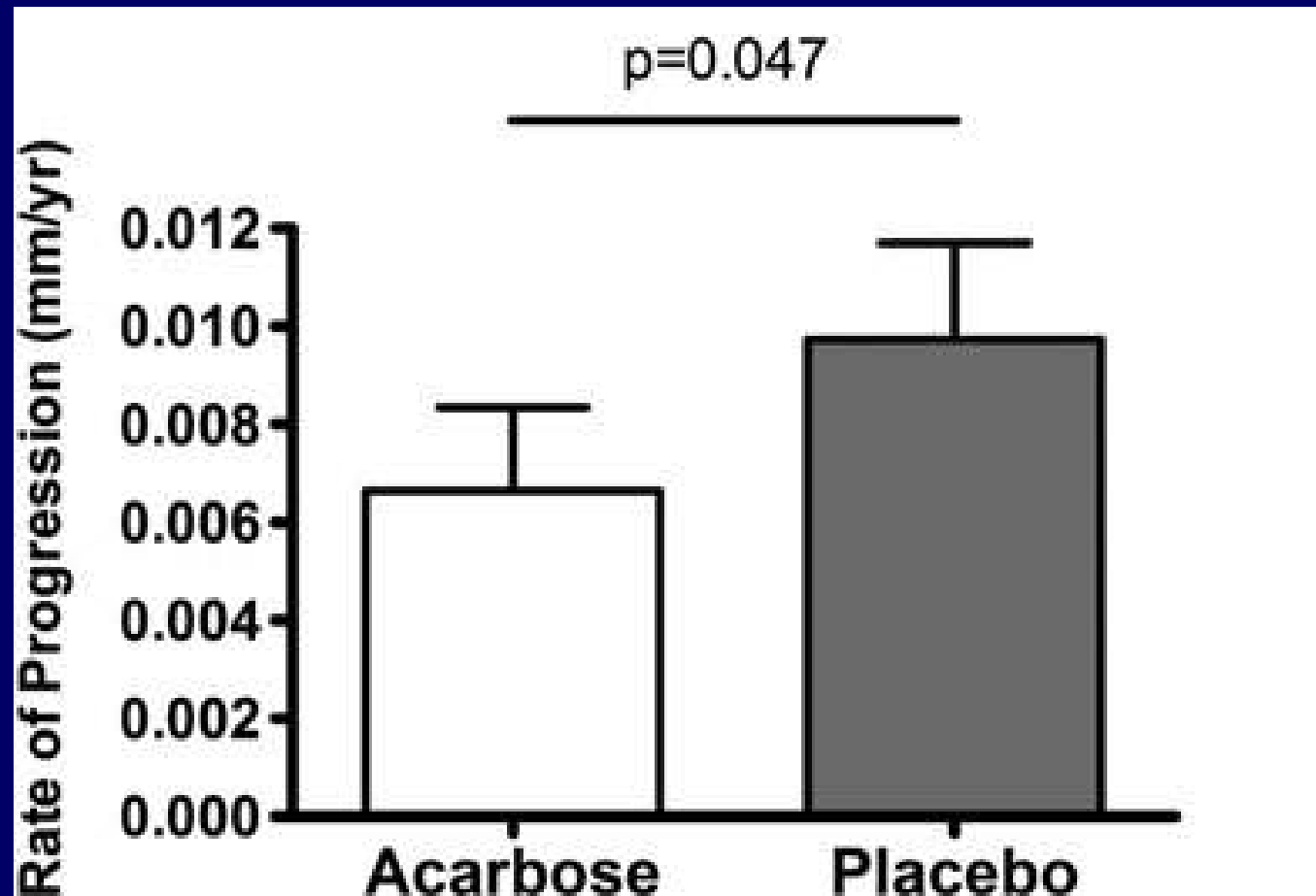


# Incidence of Cardiovascular Events by Acarbose



# Effects of Acarbose on Progression of Intima-Media Thickness

Early Diabetes Intervention Program, 2 yr follow-up



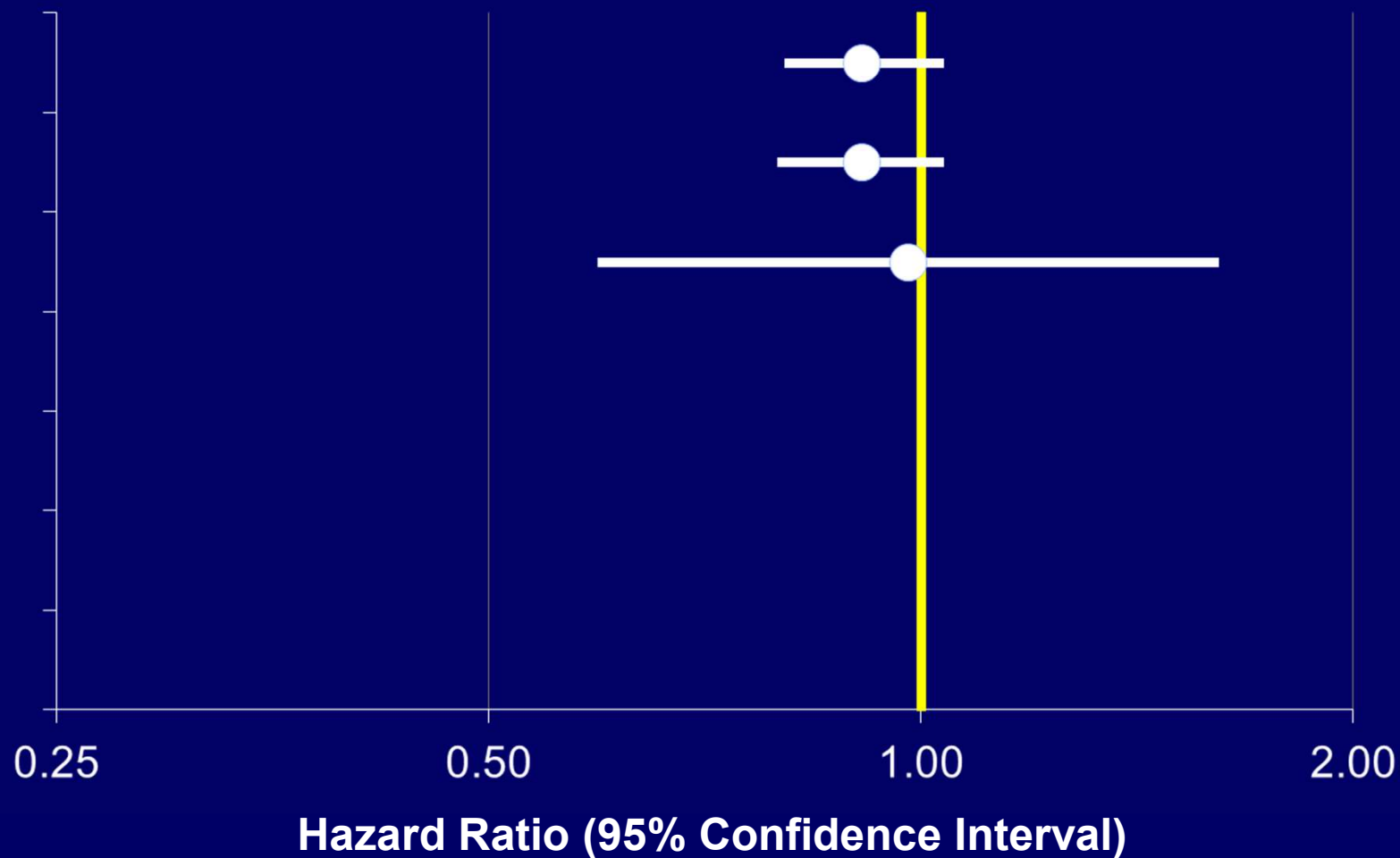
# Primary Outcome (Diabetes or Death) in DREAM: Ramipril

## Ramipril

Primary

Diabetes

Death



# Primary Outcome (Diabetes or Death) in DREAM: Ramipril and Rosiglitazone

## Ramipril

Primary

Diabetes

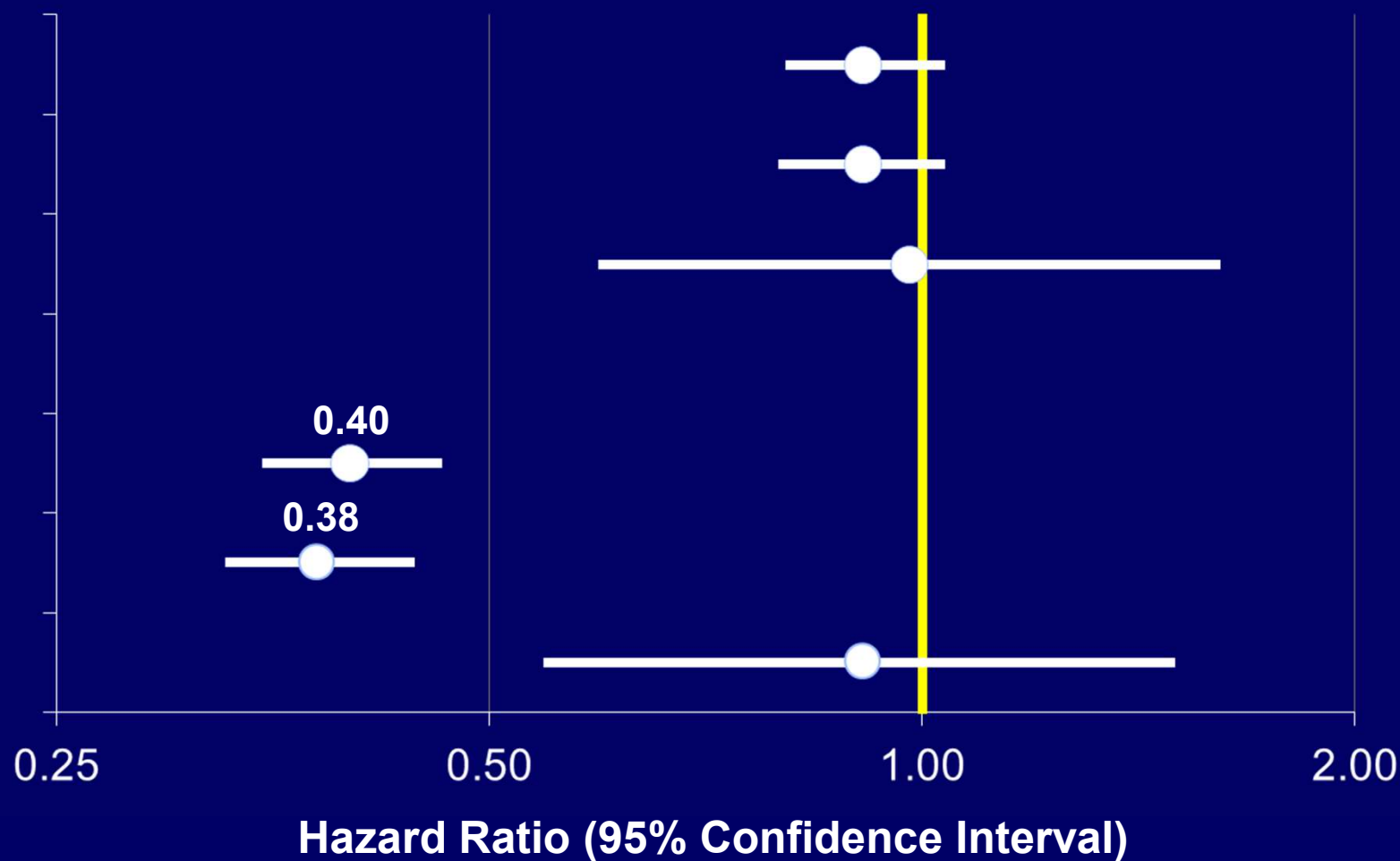
Death

## Rosiglitazone

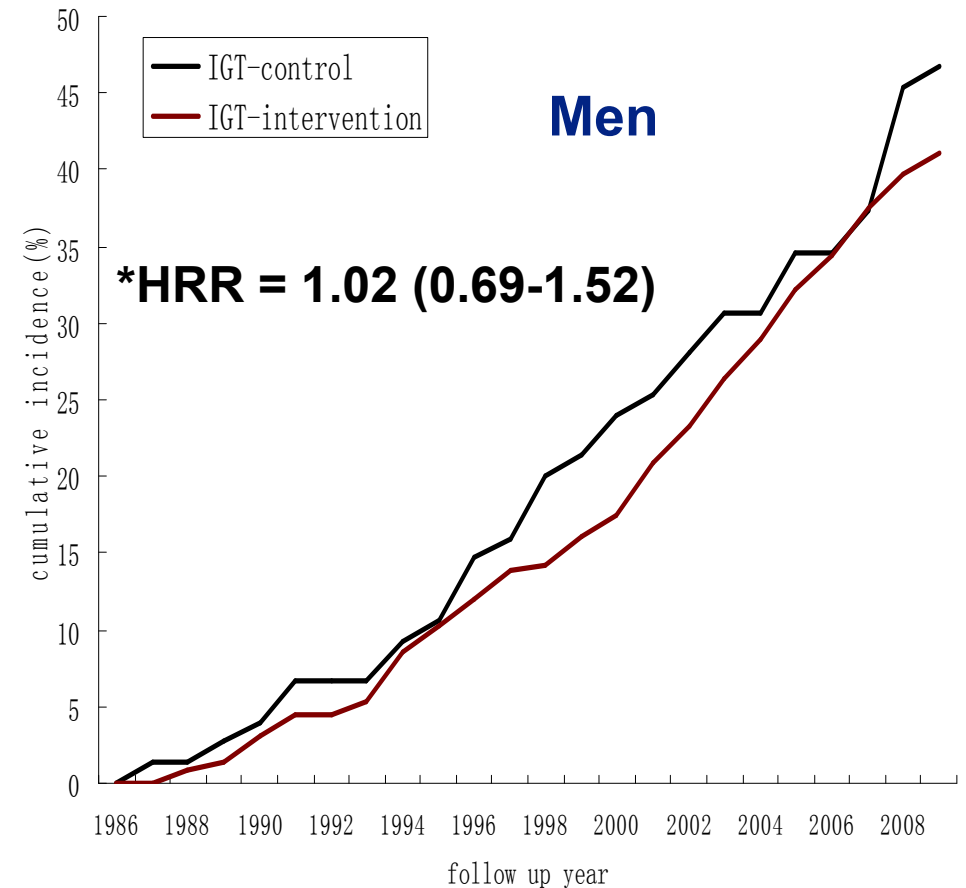
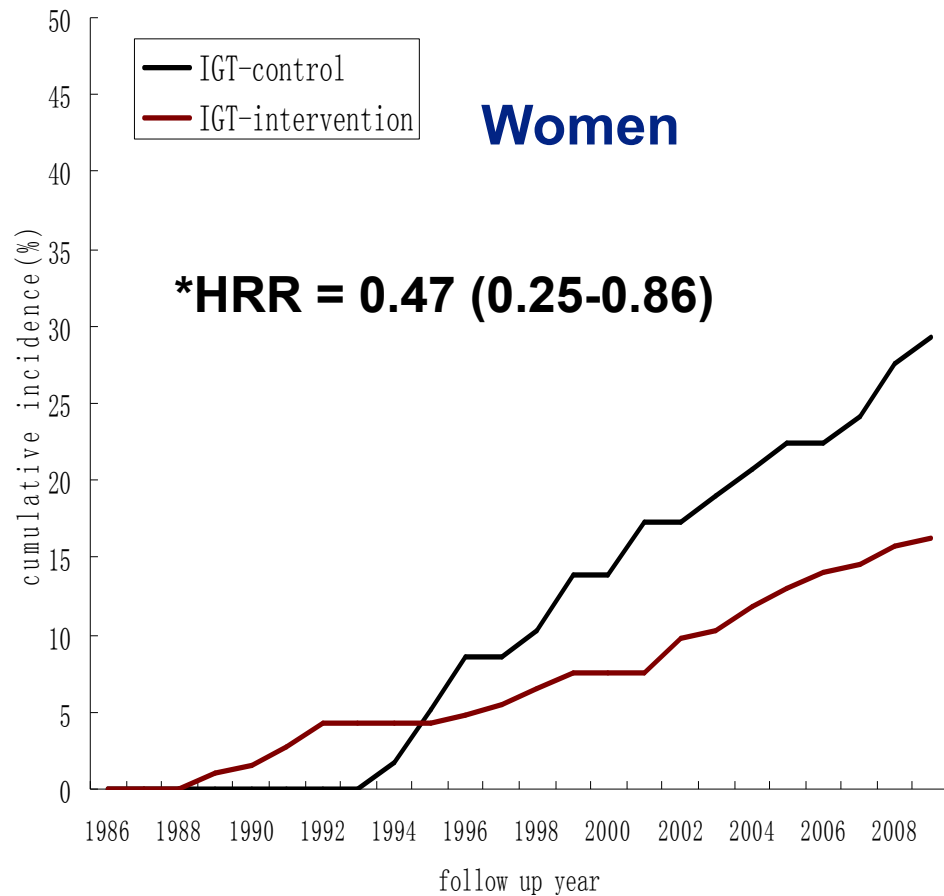
Primary

Diabetes

Death



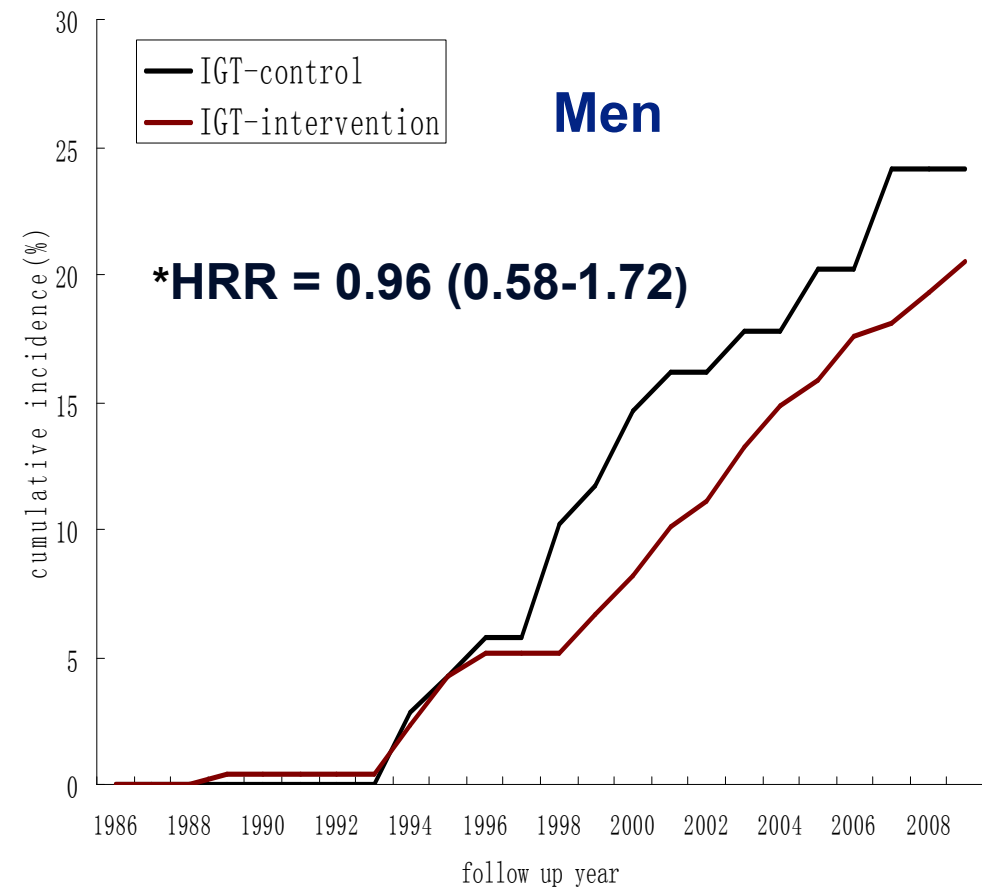
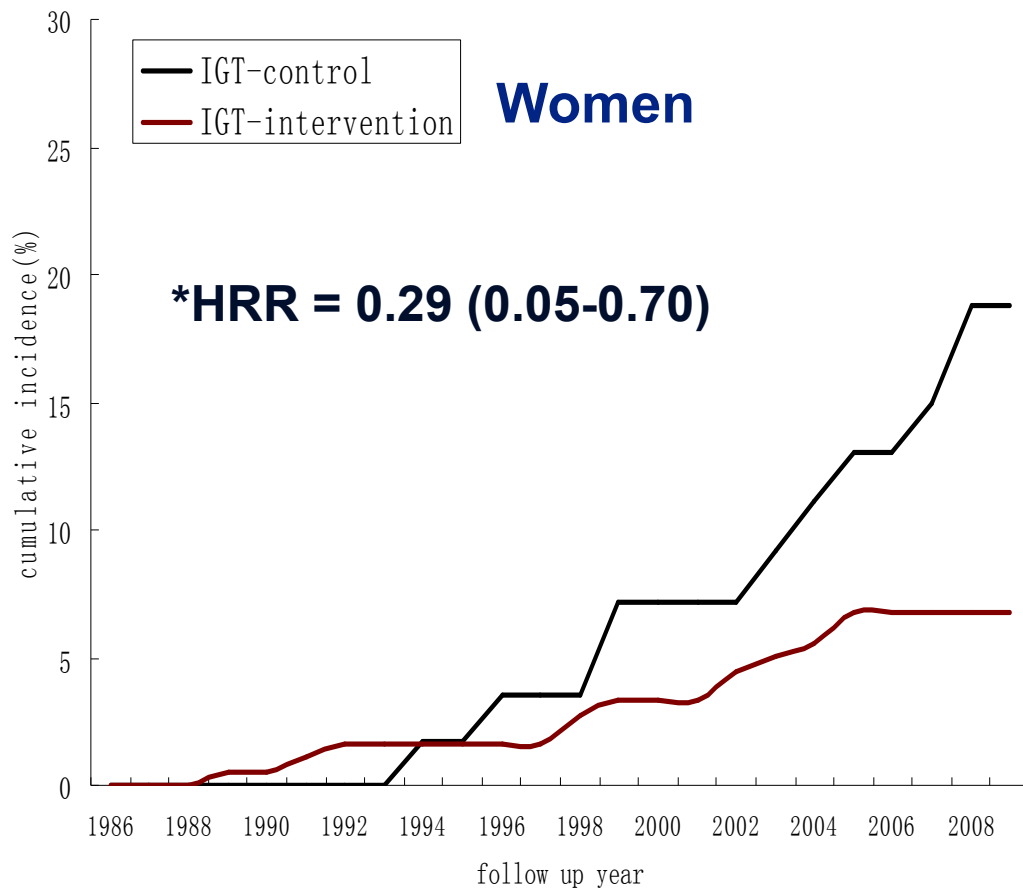
# Cumulative Incidence of All Cause Mortality in Da Qing Over the 23-year Follow-up (1986-2009)



\* HRR: age and cluster clinic adjusted

Li G: ADA presentation 2012

# Cumulative Incidence of CVD Mortality in Da Qing Over the 23-year Follow-up (1986-2009)



\* HRR: age and cluster clinic adjusted

Li G: ADA presentation 2012

# **Micro- and MacroVascular Outcomes in the DPP/DPPPOS?**

**Expected in 2014**



# When to diagnose and treat?

Allocate diabetes resources to

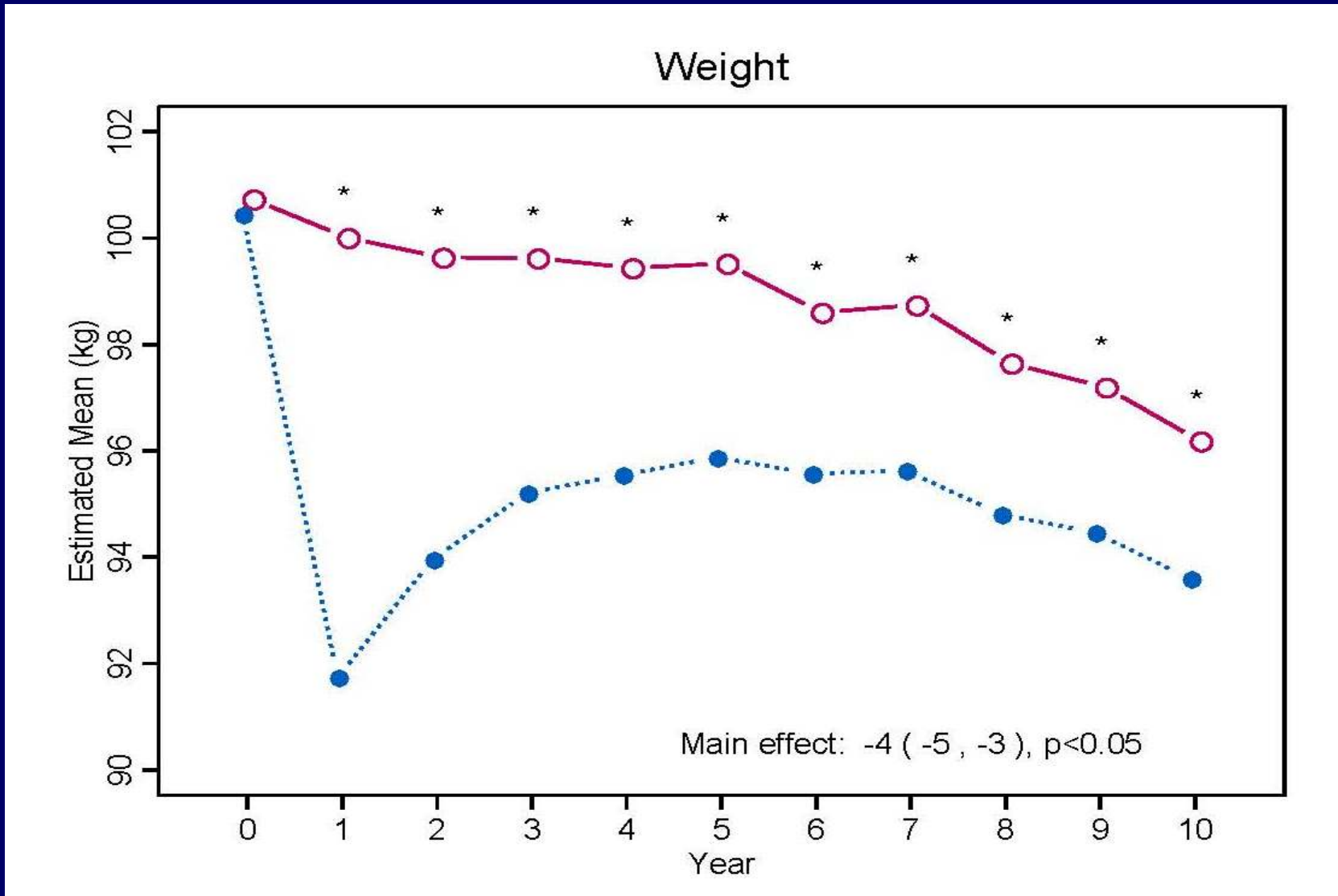
- Prevention ?
- Early detection and treatment ?

# **Look AHEAD**

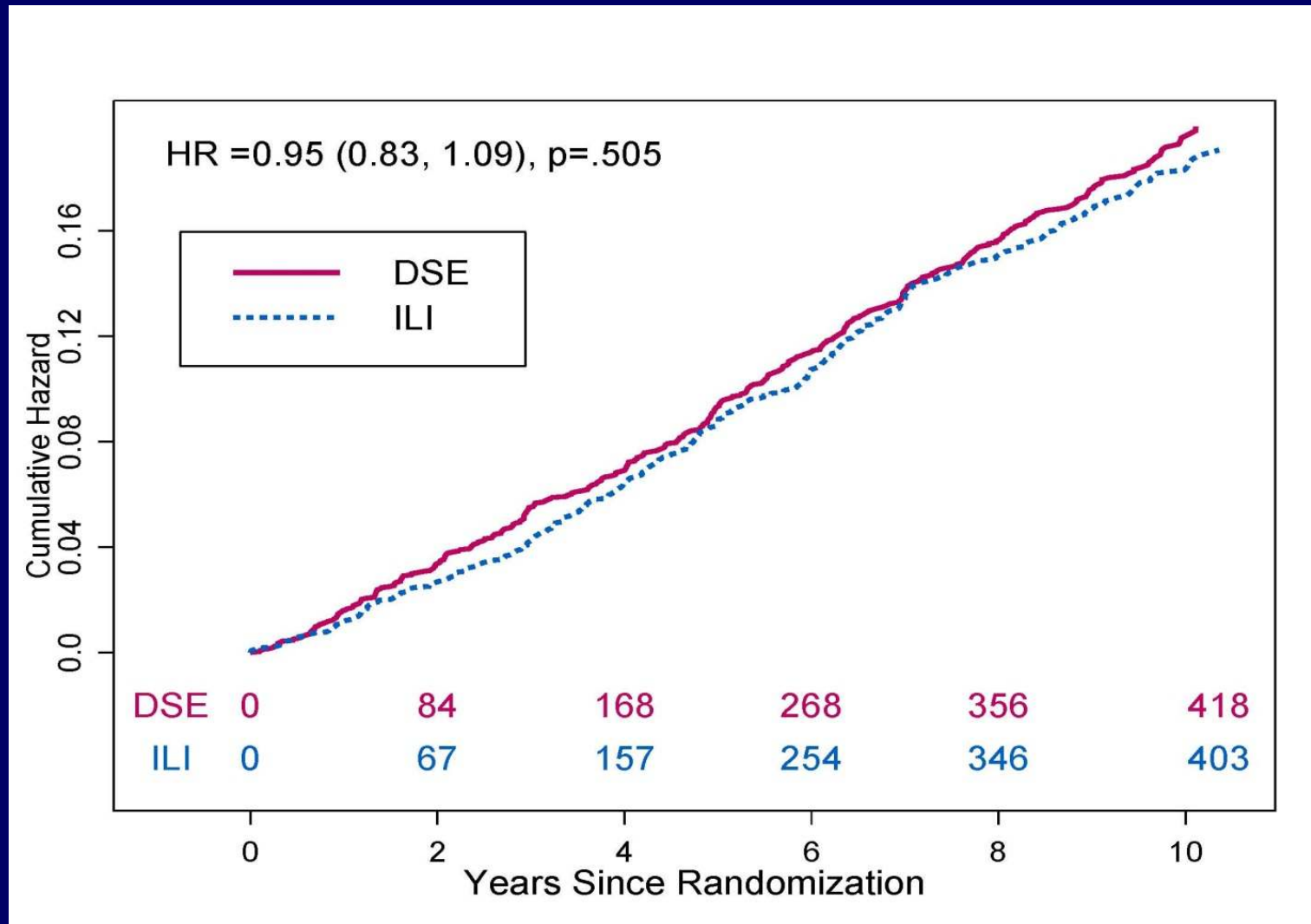
## **Randomized Clinical Trial of Weight Loss in Type 2 Diabetes**

**Does an intensive lifestyle intervention  
designed to produce weight loss decrease  
CVD morbidity and mortality in overweight  
and obese adults with type 2 diabetes?**

# Body Weight Change in Look AHEAD



# CVD Primary Outcome in Look AHEAD



# Conclusions

## What Can We Accomplish by Treating “Prediabetes”?

- Prevent or delay diabetes: **YES**
- Prevent complications of diabetes: ?
- Prevent cardiovascular disease: ?
- Reduce health care costs: ?
- Extend life: ?

