

# DISCLOSURES

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CONSULTANT:

NOVO NORDISK

# DIABETES PREVENTION

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COLORADO SCHOOL OF PUBLIC HEALTH



# PREVENTING DIABETES IN PEOPLE AT HIGHEST RISK

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Cardiovascular and Metabolic Risk

**ORIGINAL ARTICLE**

## **Diabetes Risk Calculator**

A simple tool for detecting undiagnosed diabetes and pre-diabetes

KENNETH E. HEIKES, PHD<sup>1</sup>  
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BHAKTI ARONDEKAR, MBA, PHD<sup>2</sup>  
LEONARD SCHLESSINGER, PHD<sup>1</sup>

defined as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Pre-diabetes implies an increased risk of devel-

# CDC STATEMENT

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January 26, 2011

“An estimated 79 million Americans - 35% of the population over 20 years of age - currently has pre-diabetes.”

**Global burden may be as high as 840 million**

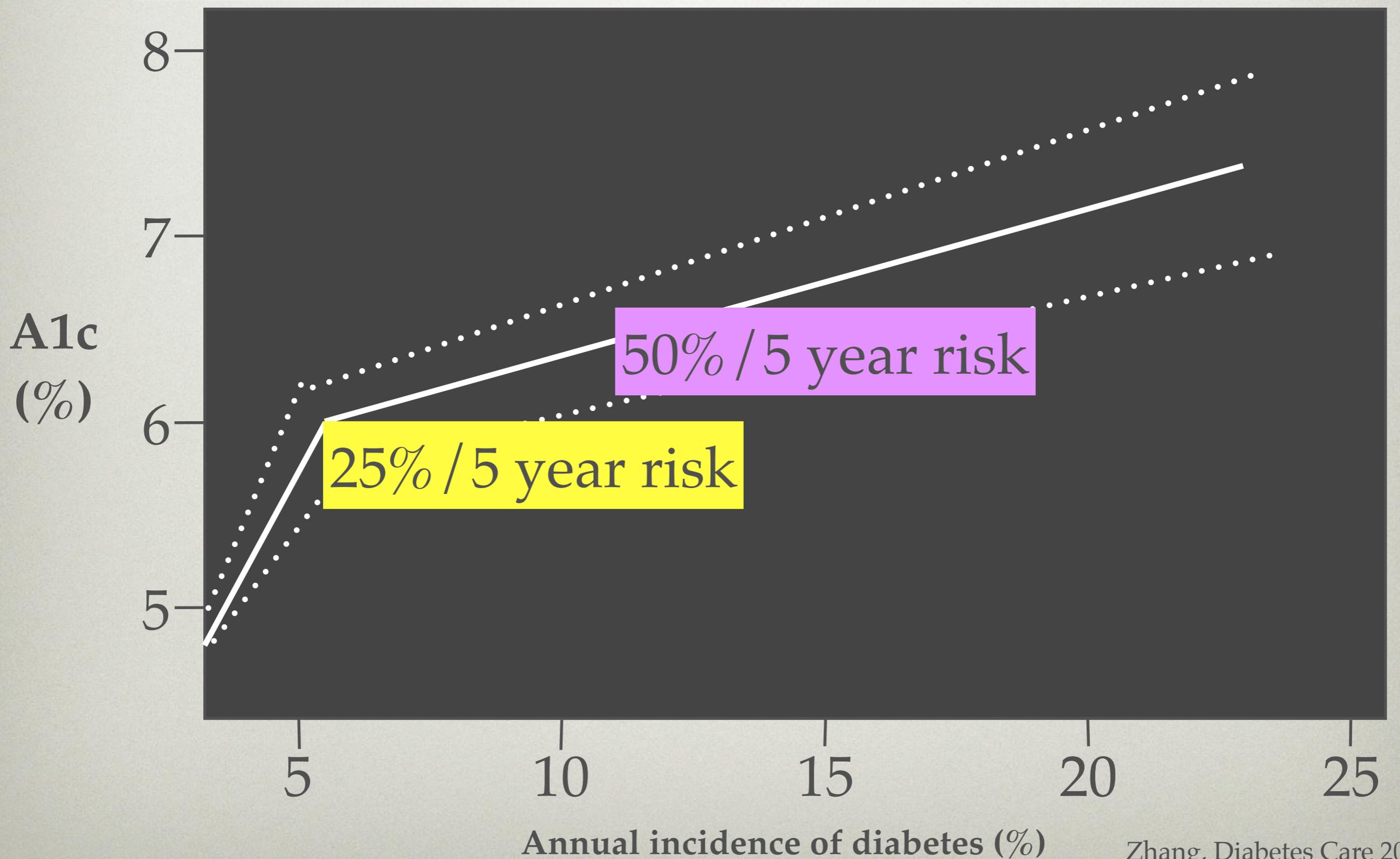
# AMERICAN DIABETES ASSOCIATION: GLUCOSE CRITERIA FOR PRE-DIABETES

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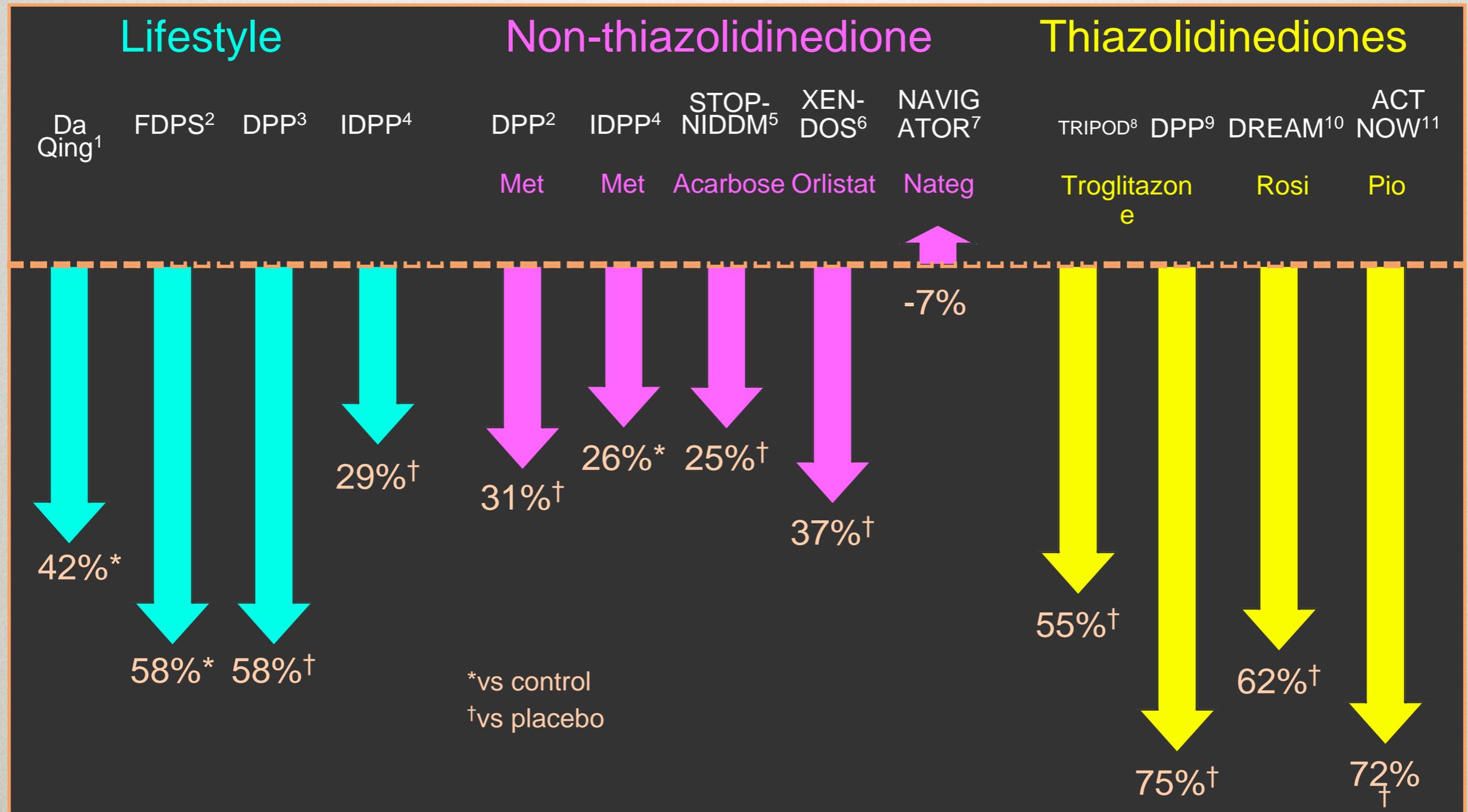
		Fasting glucose (mg/dl)	
		<100	100-125
2h glucose (mg/dl)	<140	<b>NGT</b>	<b>IFG</b>
	140-199	<b>IGT</b>	<b>IFG/IGT</b>

A1c = 5.7-6.4%

# RISK OF DIABETES FOR THOSE WITH PRE-DIABETES

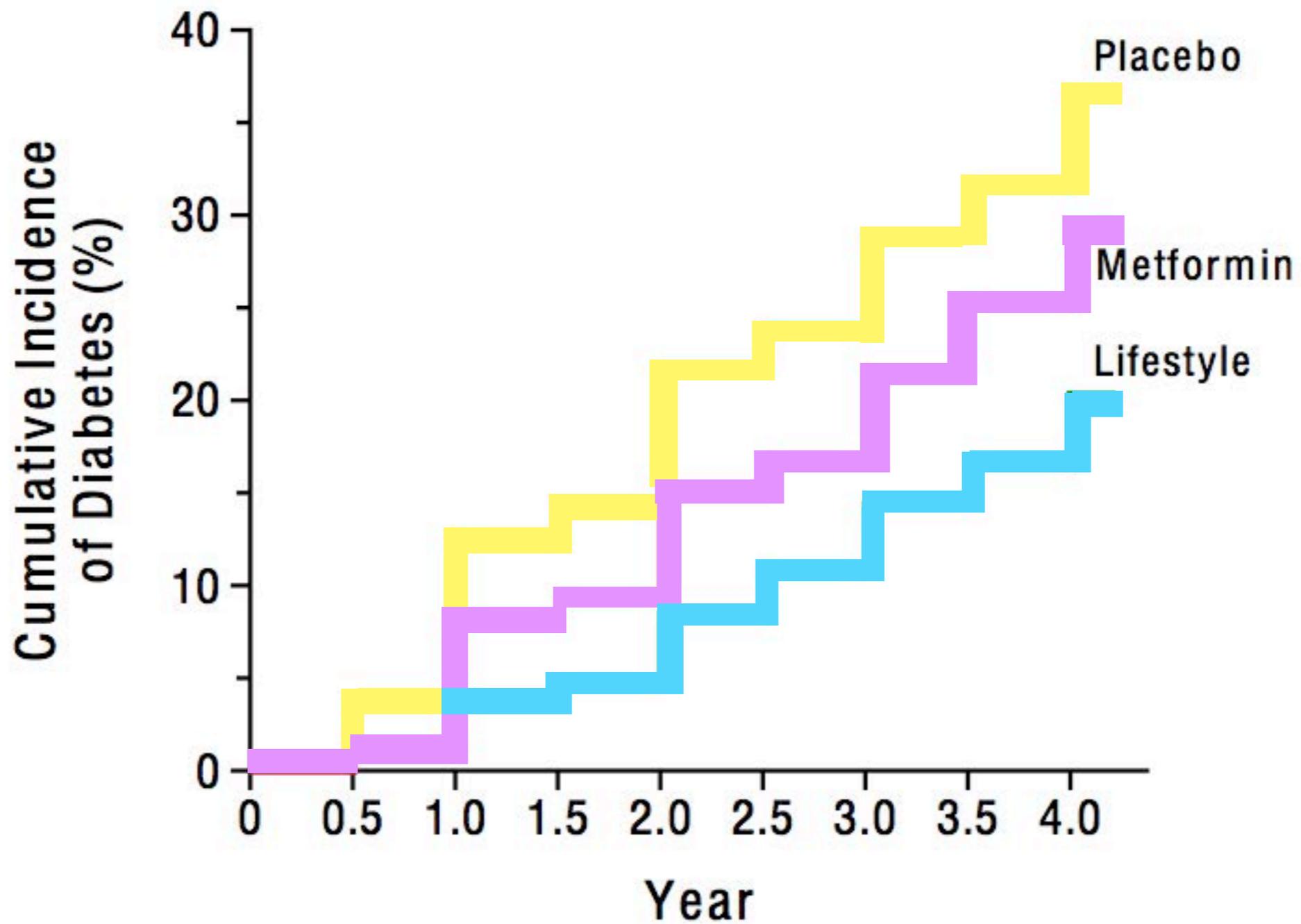


# INTERVENTION TRIALS TO REDUCE PROGRESSION OF IGT TO TYPE 2 DIABETES



<sup>1</sup>Pan XR et al: Diabetes Care 20:537-544; 1997. <sup>2</sup>Tuomilehto J et al: N Engl J Med 344:1343-1350; 2001. <sup>3</sup>DPP Research Group: N Engl J Med 346:393-403; 2002. <sup>4</sup>Ramachandran A et al: Diabetologia 49:289-297; 2006. <sup>5</sup>Chiasson JL et al: Lancet 359:2072-2207; 2002. <sup>6</sup>Torgerson JS et al: Diabetes Care 27: 155-161; 2004. <sup>7</sup>Holman RR et al: N Engl J Med 362:1463-1476; 2010. <sup>8</sup>Buchanan TA et al: Diabetes 51:2796-2803; 2002. <sup>9</sup>DPP Research Group: Diabetes 54:1150-1156; 2005. <sup>10</sup>DREAM Trial Investigators: Lancet 368:1096-1105; 2006. <sup>11</sup>DeFronzo RA et al: N Engl J Med 364:1104-1115; 2011.

# DIABETES PREVENTION PROGRAM (DPP)



**-31%**

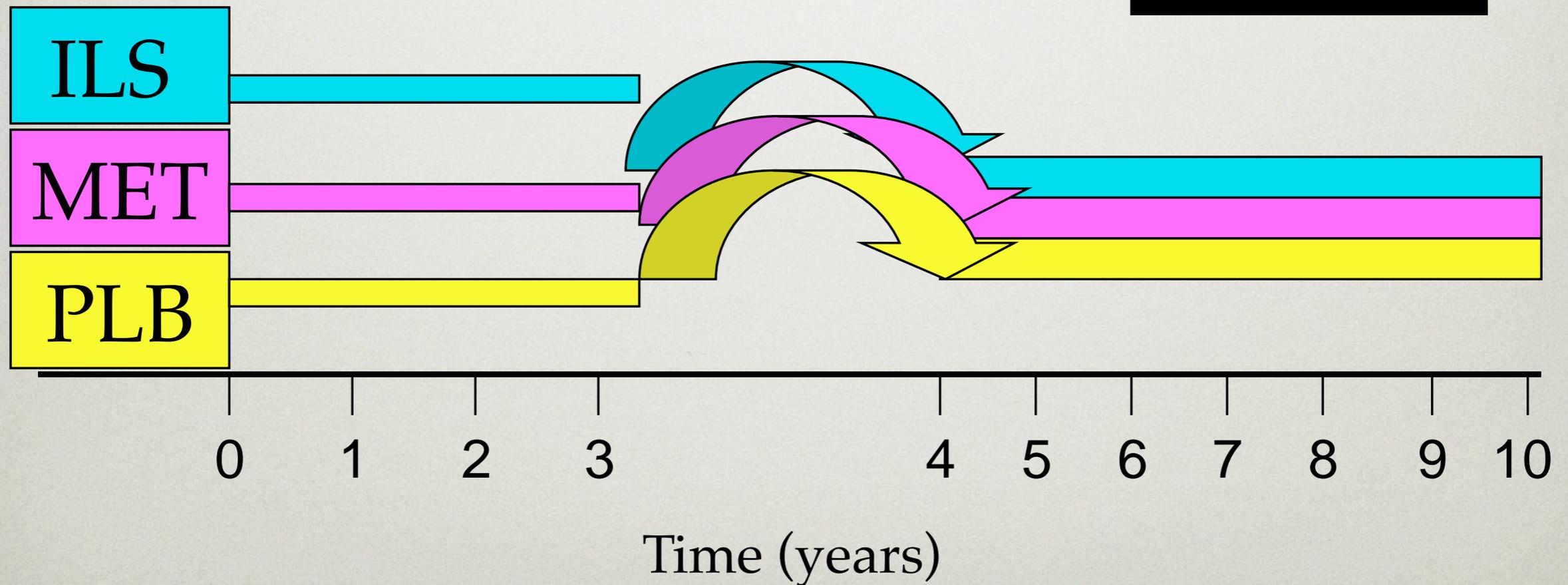
**-58%**

# BRIDGING DPP AND INTO DPPOS

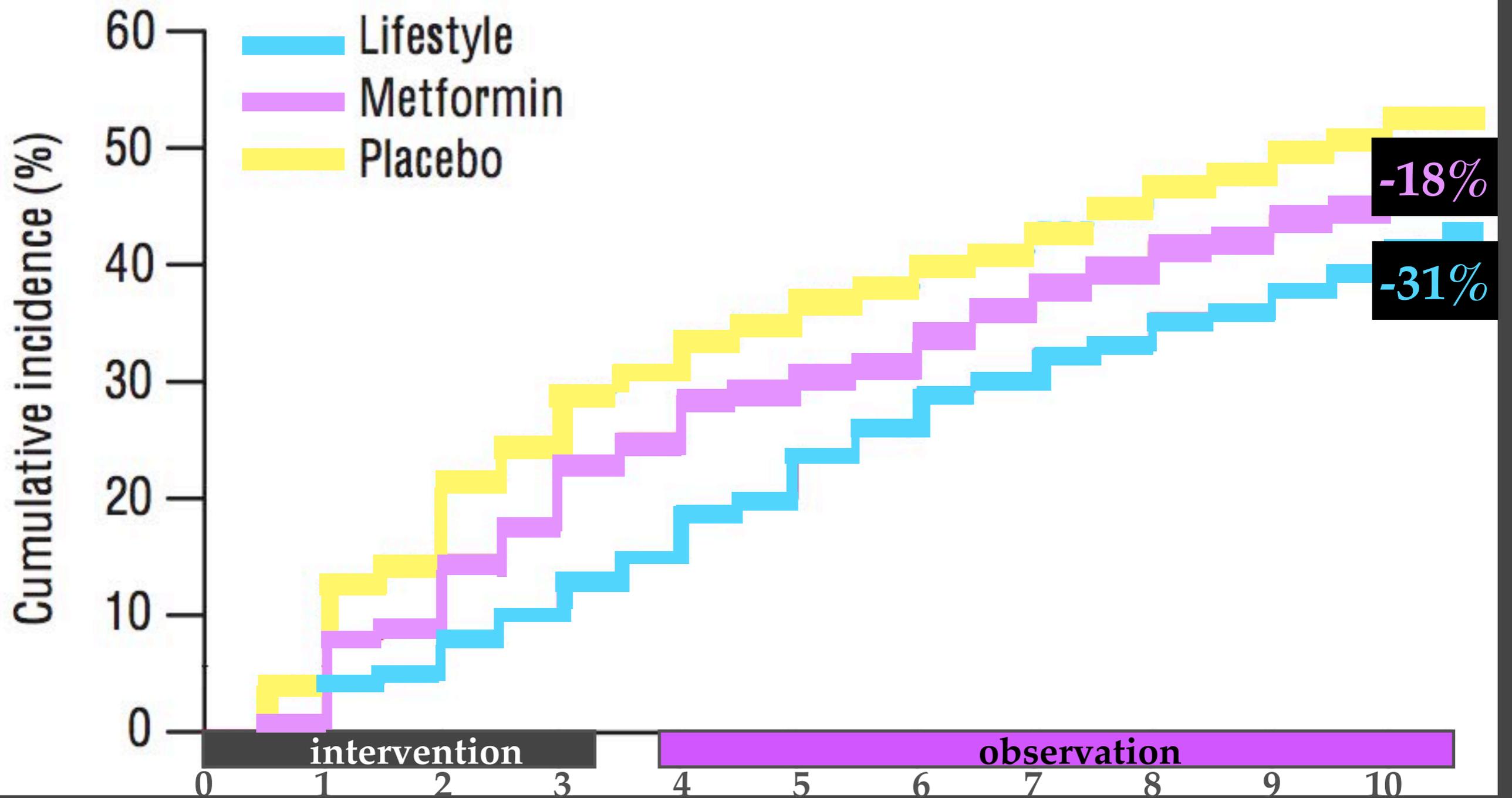
DPP:  
randomized  
intervention

Bridge:  
group lifestyle

DPPOS:  
post-  
intervention  
observation



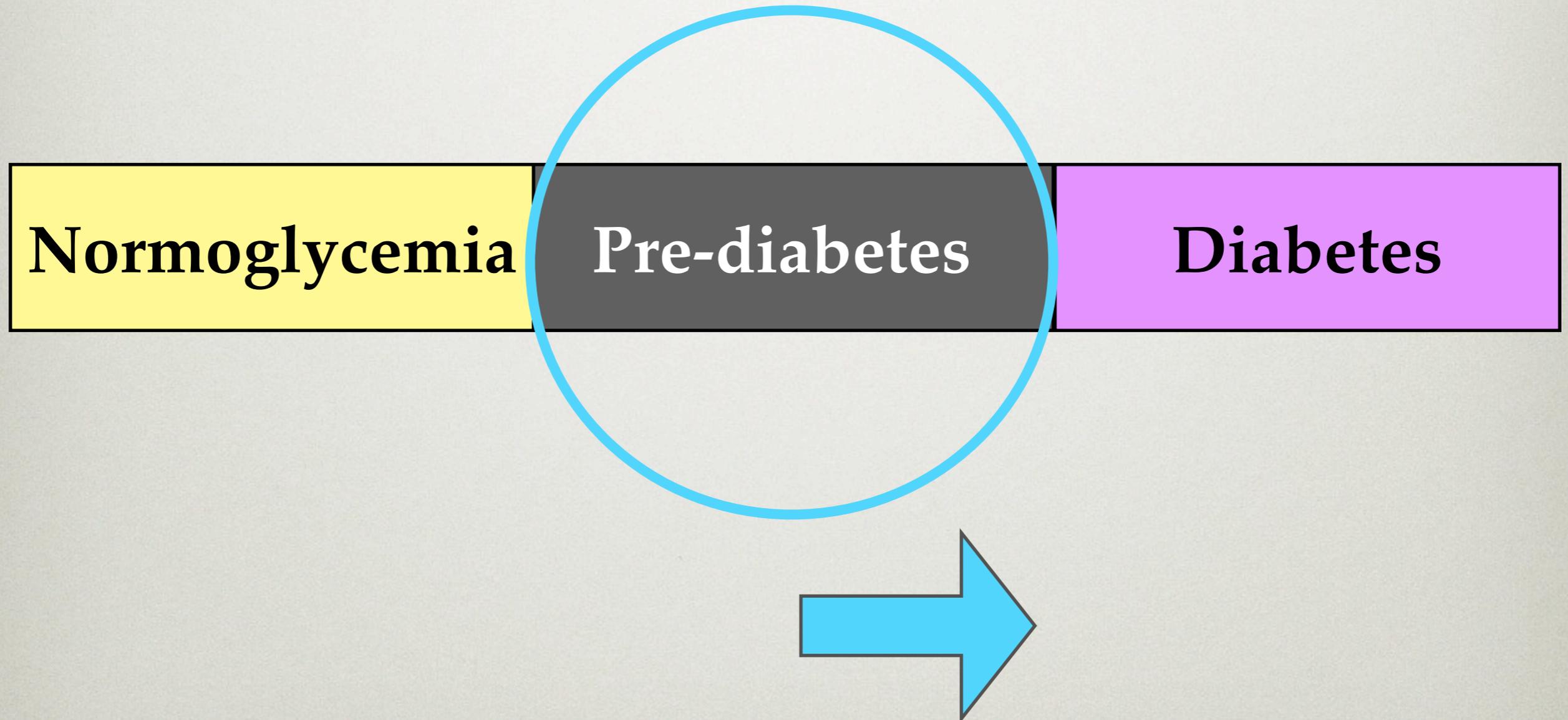
# DIABETES PREVENTION PROGRAM OUTCOMES STUDY (DPPOS)



Year since DPP randomisation

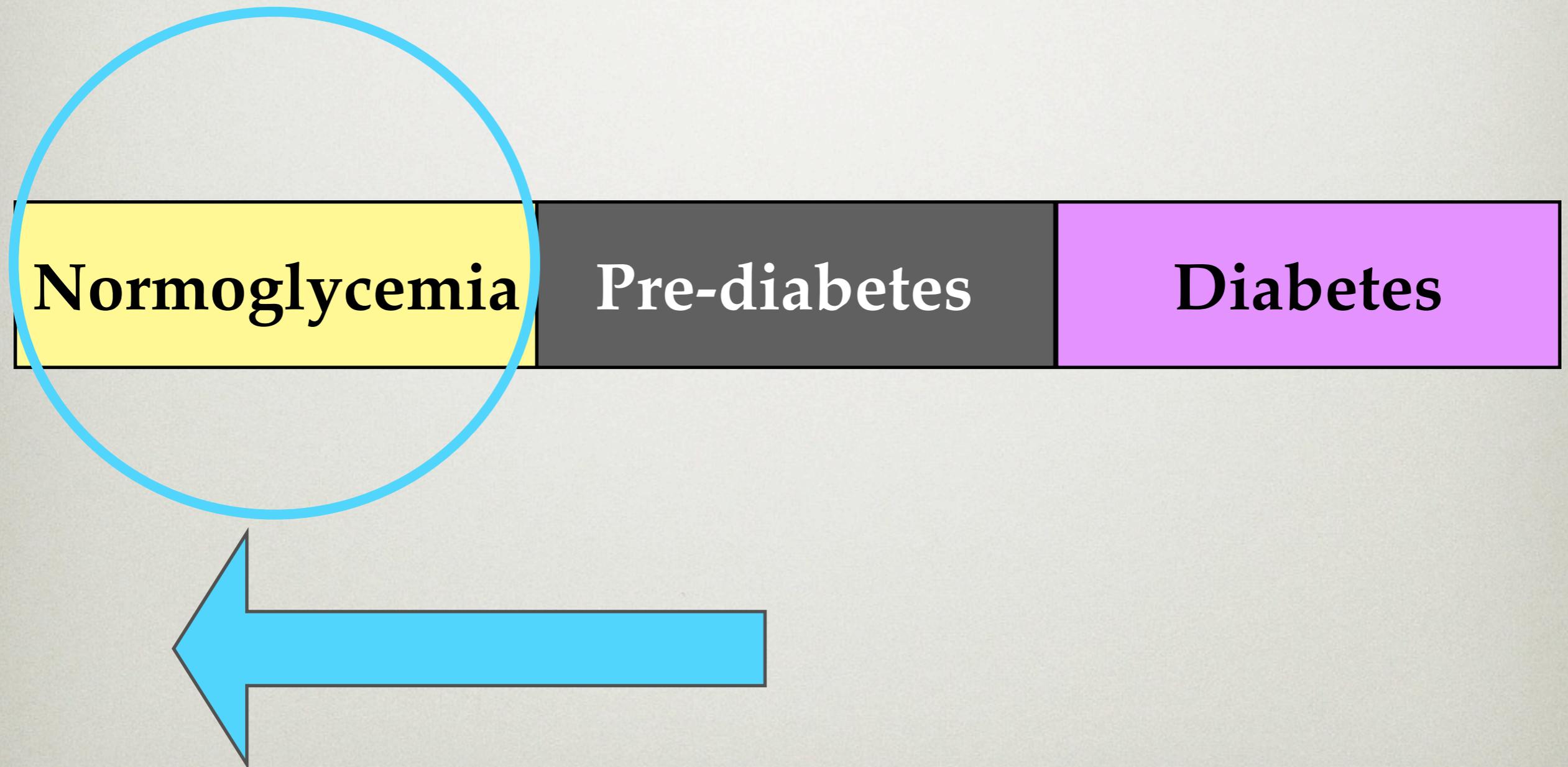
# THE ALTERNATE EXPLANATION: PRE-SPECIFIED ENDPOINT

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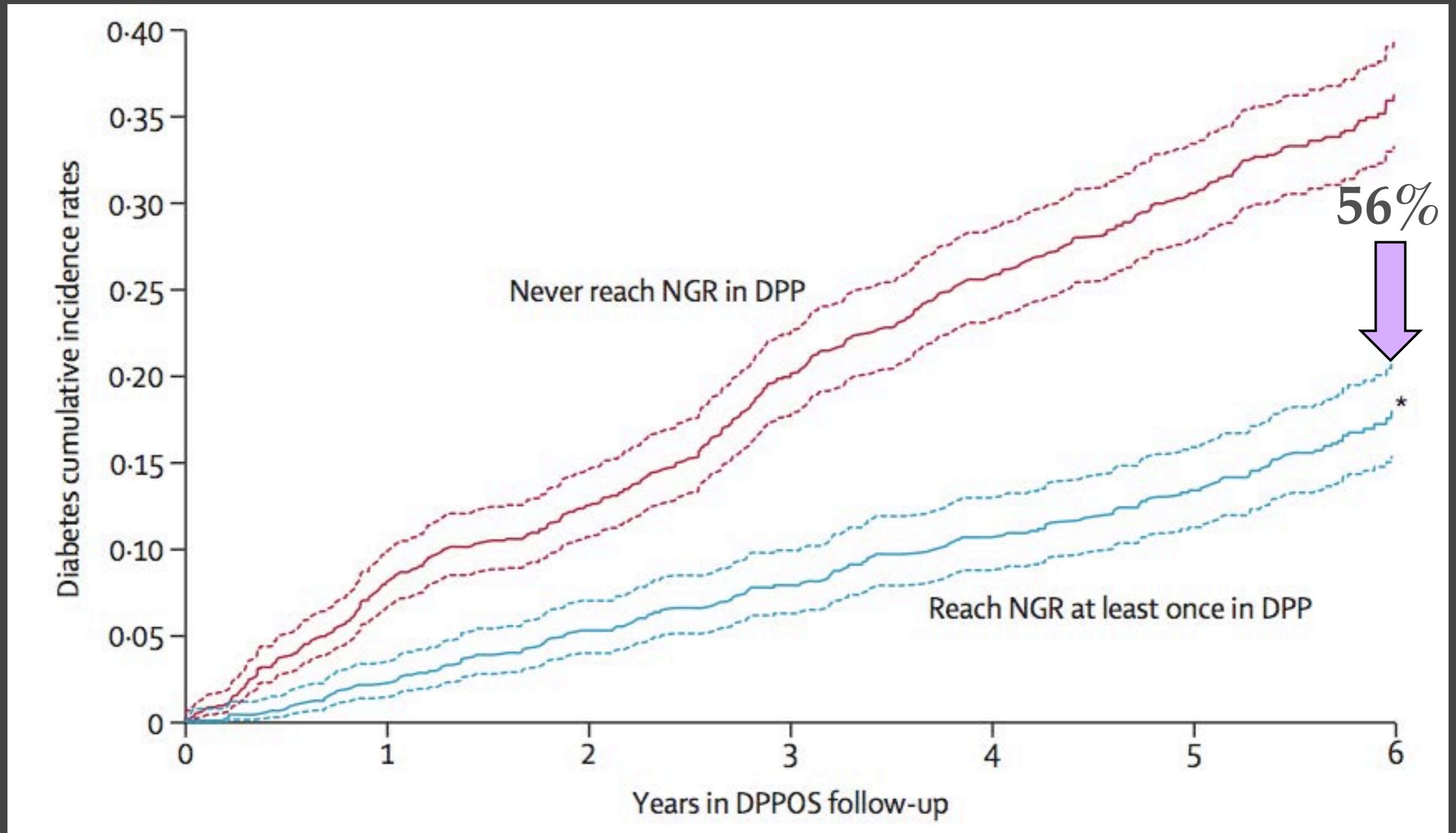


# THE ALTERNATE EXPLANATION: PRE-SPECIFIED ENDPOINT

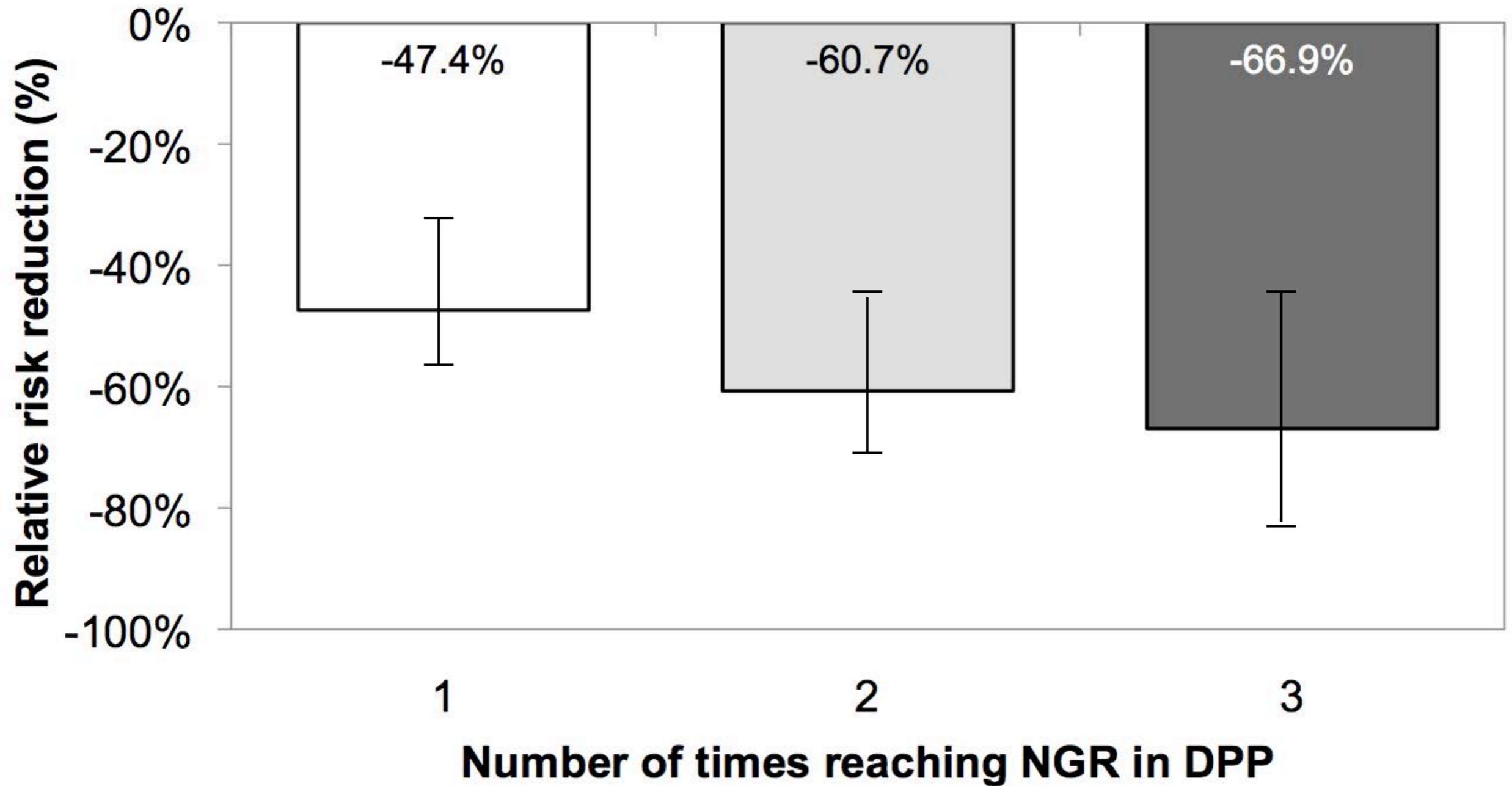
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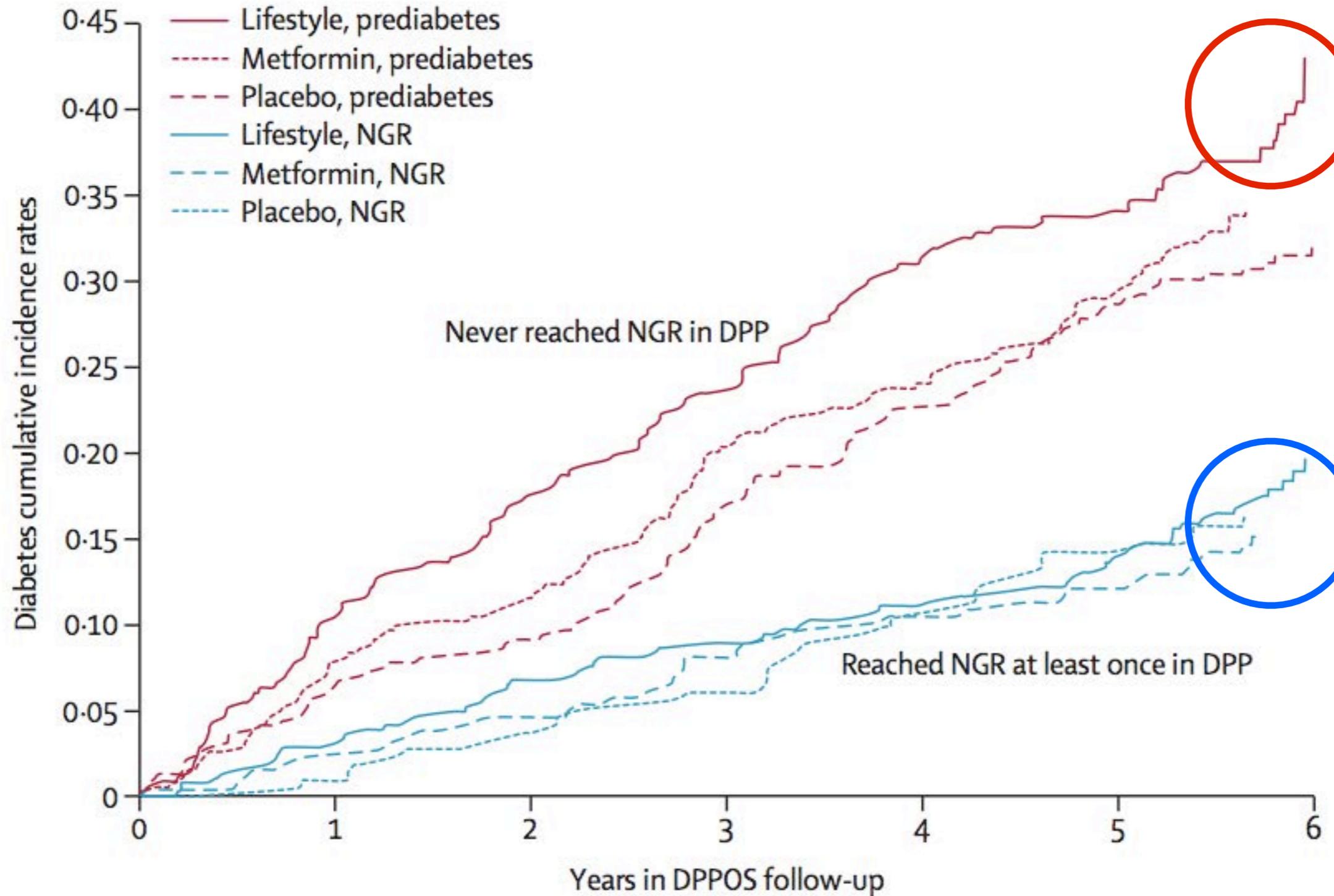
# ACHIEVING NORMAL GLUCOSE REGULATION PREVENTS DIABETES OVER THE LONG-TERM



# BENEFIT OF MAINTAINING NGR



# DOES TREATMENT MODALITY MATTER?



# Regression From Pre-Diabetes to Normal Glucose Regulation in the Diabetes Prevention Program

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THE DIABETES PREVENTION PROGRAM  
RESEARCH GROUP\*

70% of whom may develop diabetes in their lifetime (2–4). Consequently, a number of clinical trials (2,4–9) have examined the feasibility and efficacy of life-

- Lower baseline fasting and / or 2h glucose
- Younger age
- Higher insulin response
- Greater weight loss
- ILS

# Effect of regression from prediabetes to normal glucose regulation on long-term reduction in diabetes risk: results from the Diabetes Prevention Program Outcomes Study



Leigh Perreault, Qing P

ORIGINAL CONTRIBUTION

DIABETES

## Normal glucose regulation should be the goal for patients with prediabetes

Lawrence S. Phillips and David G. Klapper

Type 2 diabetes mellitus is a leading cause of morbidity and mortality. However, few clinicians manage hyperglycemia in patients with prediabetes. Normalization of glucose levels in these patients may reduce the risk of developing T2DM.

Phillips, L. S. & Olson, D. G. *Diabetes Care* 2013;36:1038-1044. doi:10.1038/nrendo.2013.103

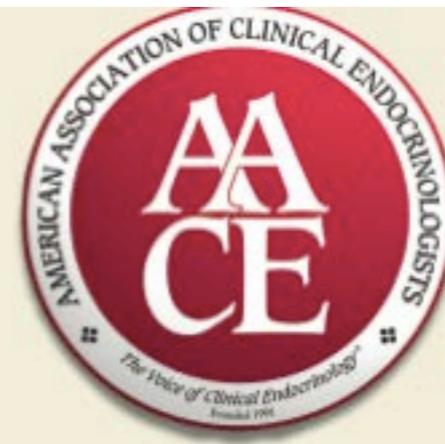
## Association of Normal Glucose Regulation With Long-Term Reduction in Diabetes Risk

Edward W. Gregg, Haiying Chen, Lynne E. Wagenknecht, Jeanne M. Clark, Linda M. Delamater, John Bantle, Henry J. Powell, and R. Sherwin

## Year in Diabetes

R. Sherwin and

Department of Internal Medicine, Division of Pediatric Endocrinology (R.M.S.), Yale University School of Medicine, New Haven, Connecticut 06520



# AACE COMPREHENSIVE DIABETES MANAGEMENT ALGORITHM 2013

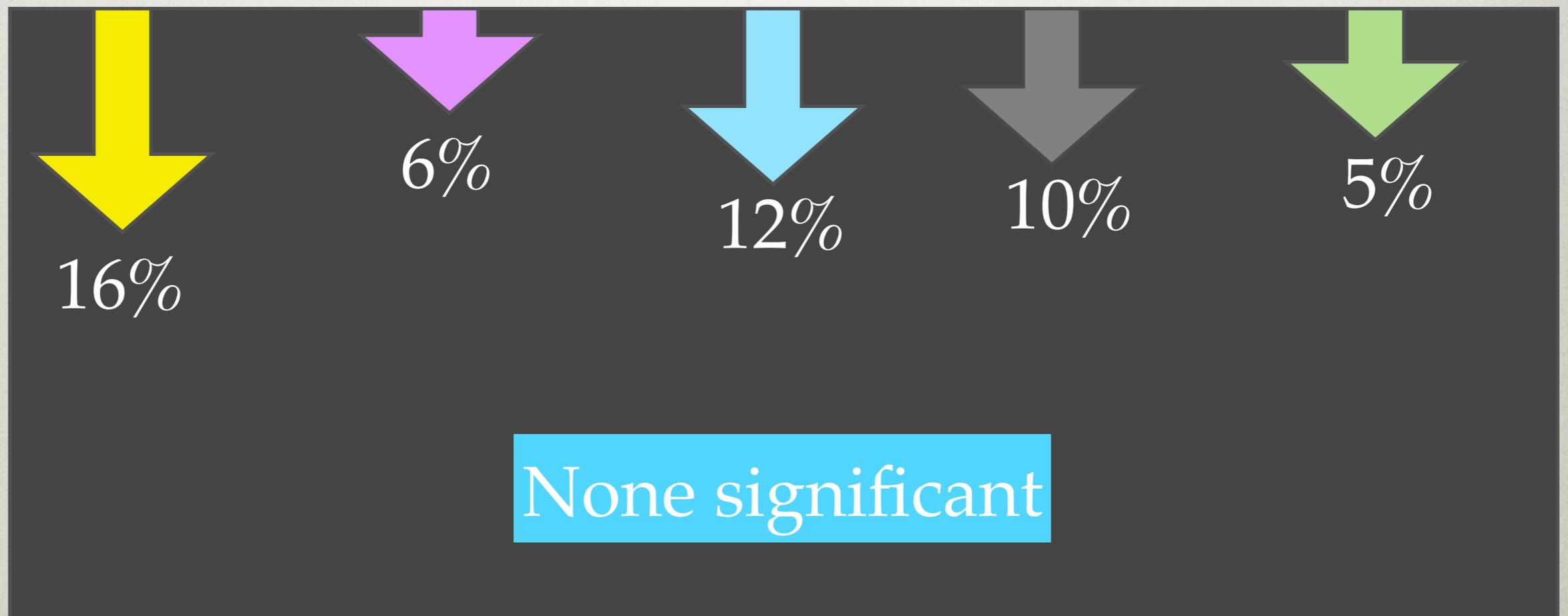
**WILL ACHIEVEMENT OF  
NORMOGLYCEMIA IMPROVE OUTCOMES  
IN PRE-DIABETES?**

# CAN GLUCOSE LOWERING IN PRE-DIABETES PREVENT MACROVASCULAR COMPLICATIONS?

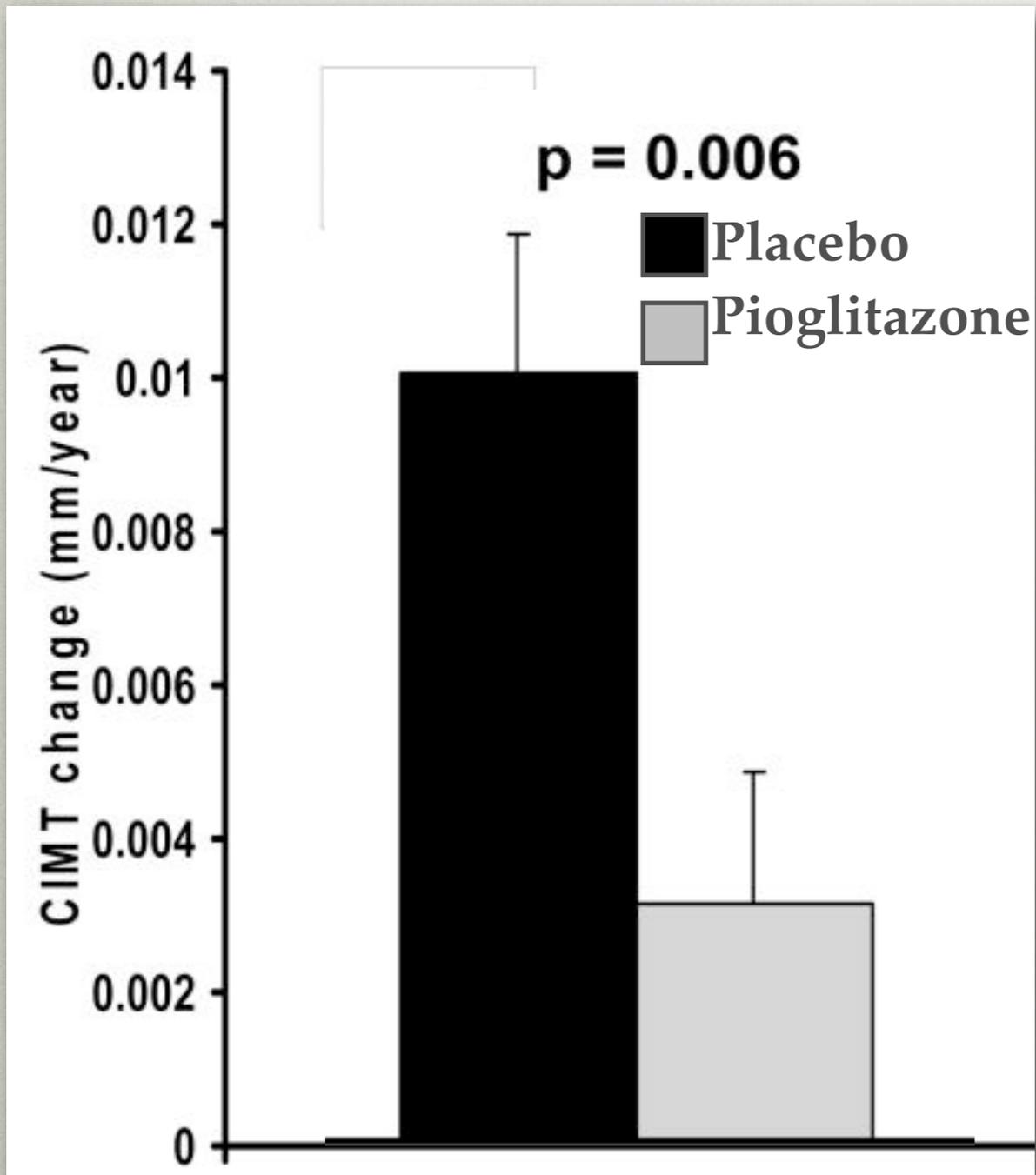
Data from trials in type 2 diabetes

% reduction in composite macrovascular disease

UKPDS    ADVANCE    VA-DT    ACCORD    LOOK AHEAD

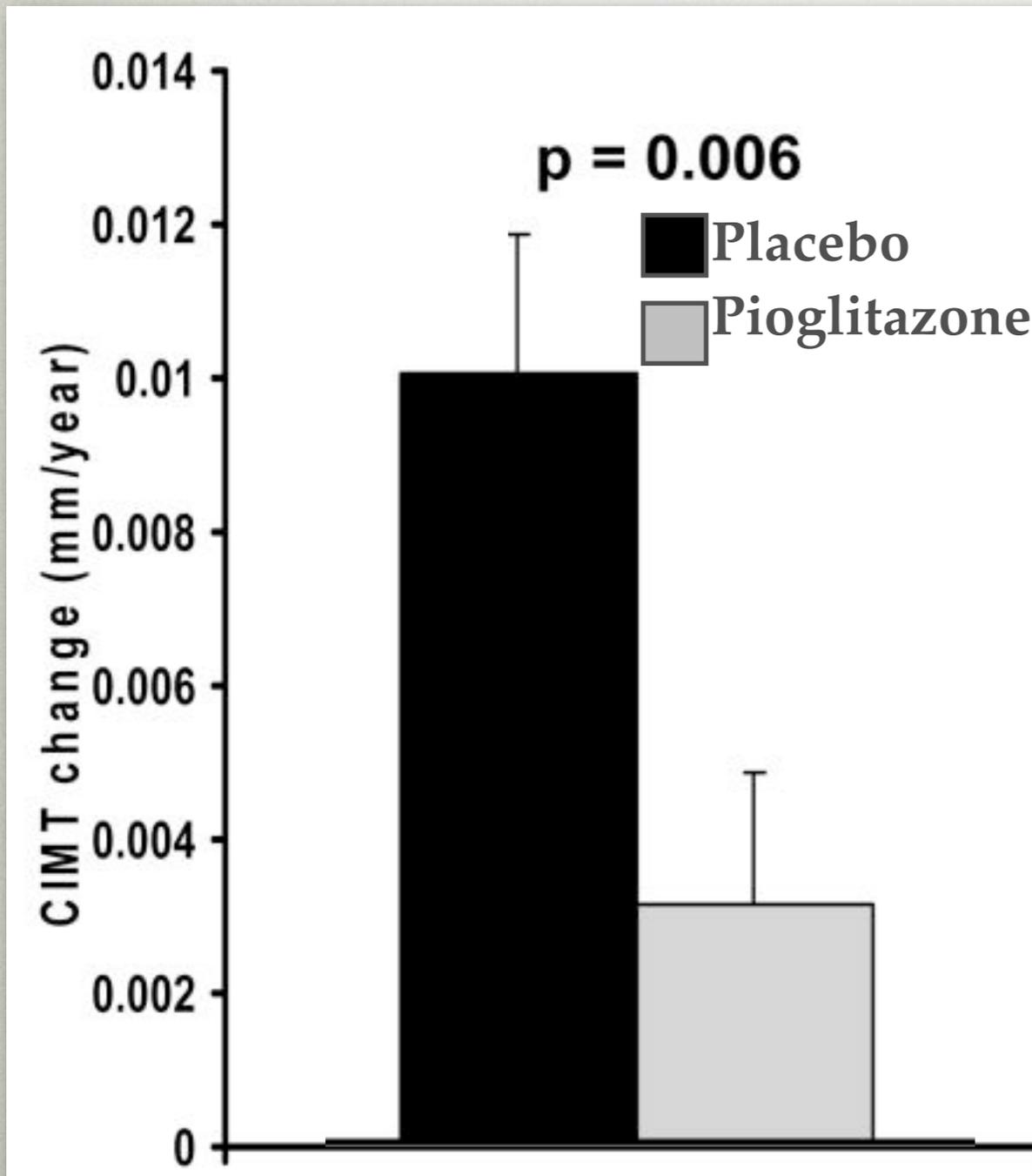


# GLUCOSE LOWERING DECREASES CAROTID INTIMA MEDIA THICKNESS IN PRE-DIABETES

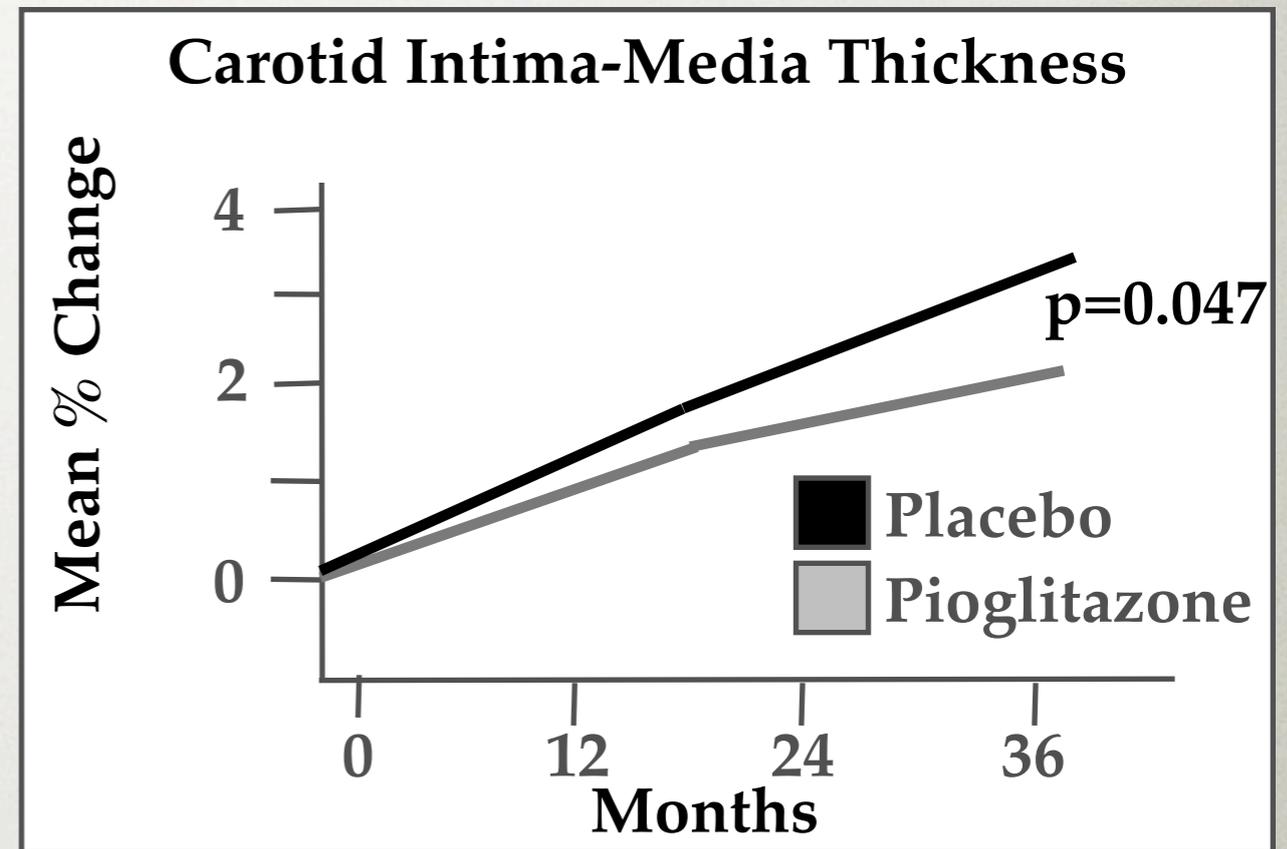


Xiang, Athero 2008

# GLUCOSE LOWERING DECREASES CAROTID INTIMA MEDIA THICKNESS IN PRE-DIABETES

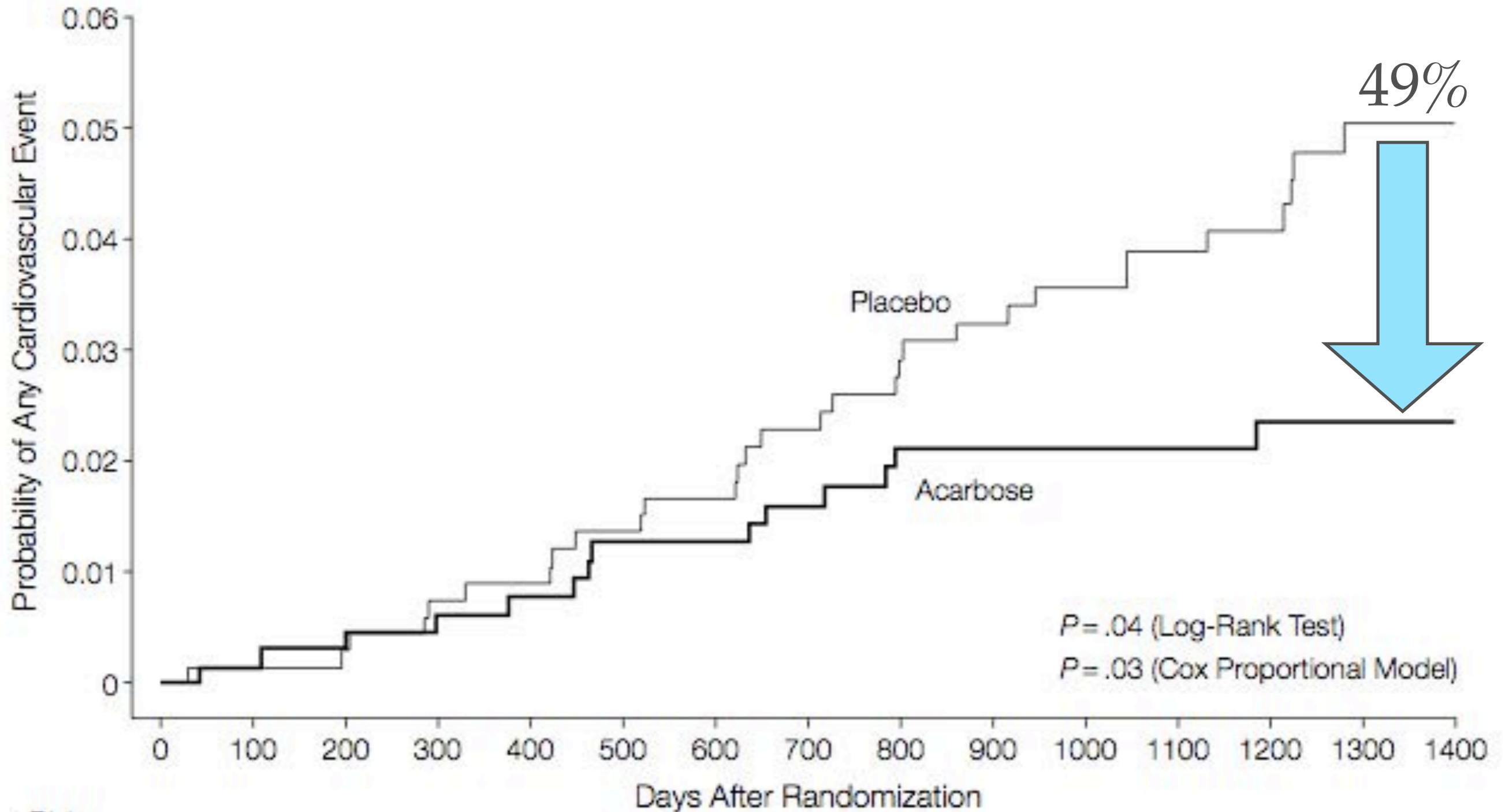


Xiang, Athero 2008



DeFronzo, NEJM 2011

# GLUCOSE LOWERING DECREASES CVD IN PRE-DIABETES



**SHOULD WE EXPAND OUR FOCUS ON  
CVD PREVENTION TO THOSE WITH  
PRE-DIABETES?**

**DIAGNOSIS AND MANAGEMENT OF PREDIABETES IN THE CONTINUUM OF HYPERGLYCEMIA—WHEN DO THE RISKS OF DIABETES BEGIN? A CONSENSUS STATEMENT FROM THE AMERICAN COLLEGE OF ENDOCRINOLOGY AND THE AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS\***

*Alan J. Garber, MD, PhD, FACE, Yehuda Handelsman, MD, FACP, FACE,  
Daniel Einhorn, MD, FACP, FACE, Donald A. Bergman, MD, FACE,  
Zachary T. Bloomgarden, MD, FACE, Vivian Fonseca, MD, FACE, W. Timothy Garvey, MD,  
James R. Gavin III, MD, PhD, George Grunberger, MD, FACP, FACE, Edward S. Horton, MD, FACE,  
Paul S. Jellinger, MD, MACE, Kenneth L. Jones, MD, Harold Lebovitz, MD, FACE,*

**Et Assessment and Treatment of Cardiovascular Risk in Prediabetes:  
Impaired Glucose Tolerance and Impaired Fasting Glucose**

Ralph A. DeFronzo, MD,\* and Muhammad Abdul-Ghani, MD, PhD

Individuals with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) are at high risk, not only to develop diabetes mellitus, but also to experience an adverse cardiovascular (CV) event (myocardial infarction, stroke, CV death) later in life. The underlying pathophysiologic disturbances (insulin resistance and impaired  $\beta$ -cell function) responsible for the development of type 2 diabetes are maximally/near maximally expressed in subjects with IGT/IFG. These individuals with so-called prediabetes manifest all of the same CV risk factors (dysglycemia, dyslipidemia, hypertension, obesity, physical inactivity, insulin resistance, procoagulant state, endothelial dysfunction, inflammation) that place patients with type 2 diabetes at high risk for macrovascular complications. The treatment of these CV risk factors should follow the same guidelines established for patients with type 2 diabetes, and should be aggressively followed to reduce future CV events. © 2011 Elsevier Inc. All rights reserved. (Am J Cardiol 2011;108[suppl]:3B–24B)

# AACE PRE-DIABETES ALGORITHM 2013

IFG (100-125 MG/DL) IGT (140-199 MG/DL) METABOLIC SYNDROME (NCEP 2005)

**Lifestyle Modification** (including medically assisted weight loss)

**CVD RFs**

**Anti-Obesity  
Therapies**

**Anti-Hyperglycemic  
Therapies**

**CVD RF  
modification**

**NGR**

**IFG or IGT**

**IFG & IGT**

**Lipids**

**BP**

**↓  
Wt**

**Metformin  
Acarbose**

**TZD  
GLP-1a**

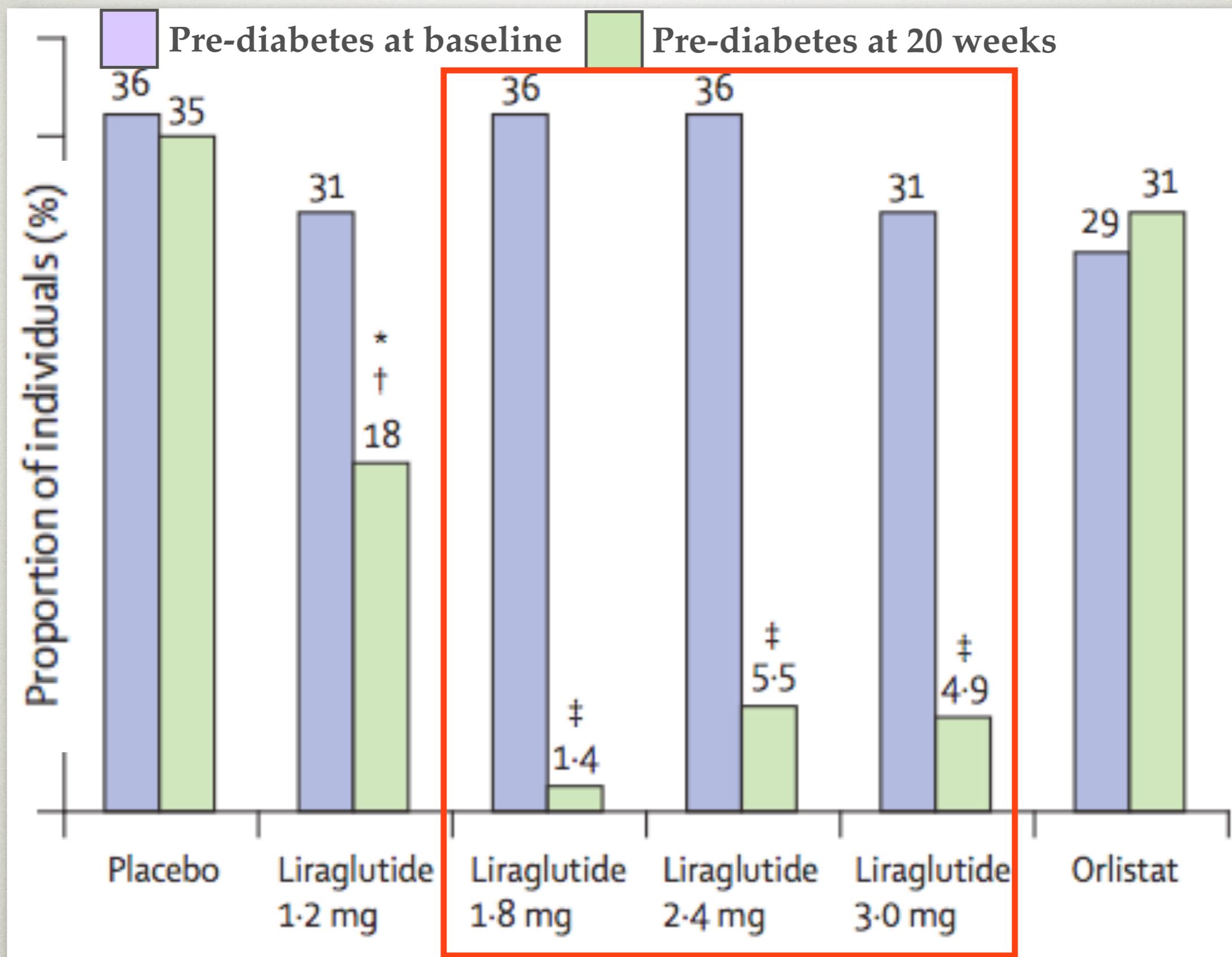
If DM, go to  
hyperglycemia  
algorithm

	N	Population	Length (years)	Regression in controls (%)	Active treatment	Risk of regression* (95% CI)
DPP <sup>2†</sup>	2528	IFG+IGT	3	NA	Lifestyle	2.05 (1.66–2.53)
					Metformin	1.25 (0.99–1.58)
Indian DPP-1 <sup>3</sup>	531	IGT	2.5	24.1%	Lifestyle	1.48 (0.99–2.22)
					Metformin	1.27 (0.85–1.89)
					Lifestyle+metformin	1.31 (0.87–1.95)
Indian DPP-2 <sup>4</sup>	407	IGT	3	32.3%	Lifestyle+pioglitazone	1.27 (0.98–1.65)
ACT NOW <sup>5†</sup>	602	IGT	2.4	28%	Pioglitazone	1.71 (1.33–2.19)
DREAM <sup>6,7†</sup>	5269	IFG+/-IGT	3	30.3%	Rosiglitazone	1.71 (1.57–1.87)‡
				38.2%	Ramipril	1.16 (1.07–1.27)‡
CANOE <sup>8†</sup>	207	IGT	3.9	53.1%	Rosiglitazone+metformin	1.50 (1.21–1.86)
Kawamori et al <sup>9†</sup>	1780	IGT	0.9	51.5%	Voglibose	1.54 (1.36–1.75)‡
STOP-NIDDM <sup>10</sup>	1429	IFG+IGT	3.3	31%	Acarbose	1.14 (0.98–1.33)

NA=not available. \*Unless otherwise noted, relative risk of regression to normoglycaemia was calculated from reported proportions of patients achieving normoglycaemia in treatment groups. †Normoglycaemia was defined on basis of oral glucose tolerance test; fasting plasma glucose cutoffs varied between studies. ‡Hazard ratio of regression to normoglycaemia was provided in publication.

**Table: Risk of regression to normoglycaemia in people with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or both**

# THE SCALE STUDY: LIRAGLUTIDE IN PRE-DIABETES



# AACE PRE-DIABETES ALGORITHM 2013

IFG (100-125 MG/DL) IGT (140-199 MG/DL) METABOLIC SYNDROME (NCEP 2005)

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**Lipids**

**BP**

**↓  
Wt**

**Metformin  
Acarbose**

**TZD  
GLP-1a**

If DM, go to  
hyperglycemia  
algorithm

# CVD EVENT OR RISK REDUCTION IN DPPOS?

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Cardiovascular and Metabolic Risk

**ORIGINAL ARTICLE**

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## **Effect of Progression From Impaired Glucose Tolerance to Diabetes on Cardiovascular Risk Factors and Its Amelioration by Lifestyle and Metformin Intervention**

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The Diabetes Prevention Program randomized trial by the Diabetes Prevention Program Research Group\*

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RONALD B. GOLDBERG, MD  
MARINELLA TEMPROSA, MS  
STEVEN HAFFNER, MD  
TREVOR J. ORCHARD, MD  
ROBERT E. RATNER, MD  
SARAH E. FOWLER, PHD

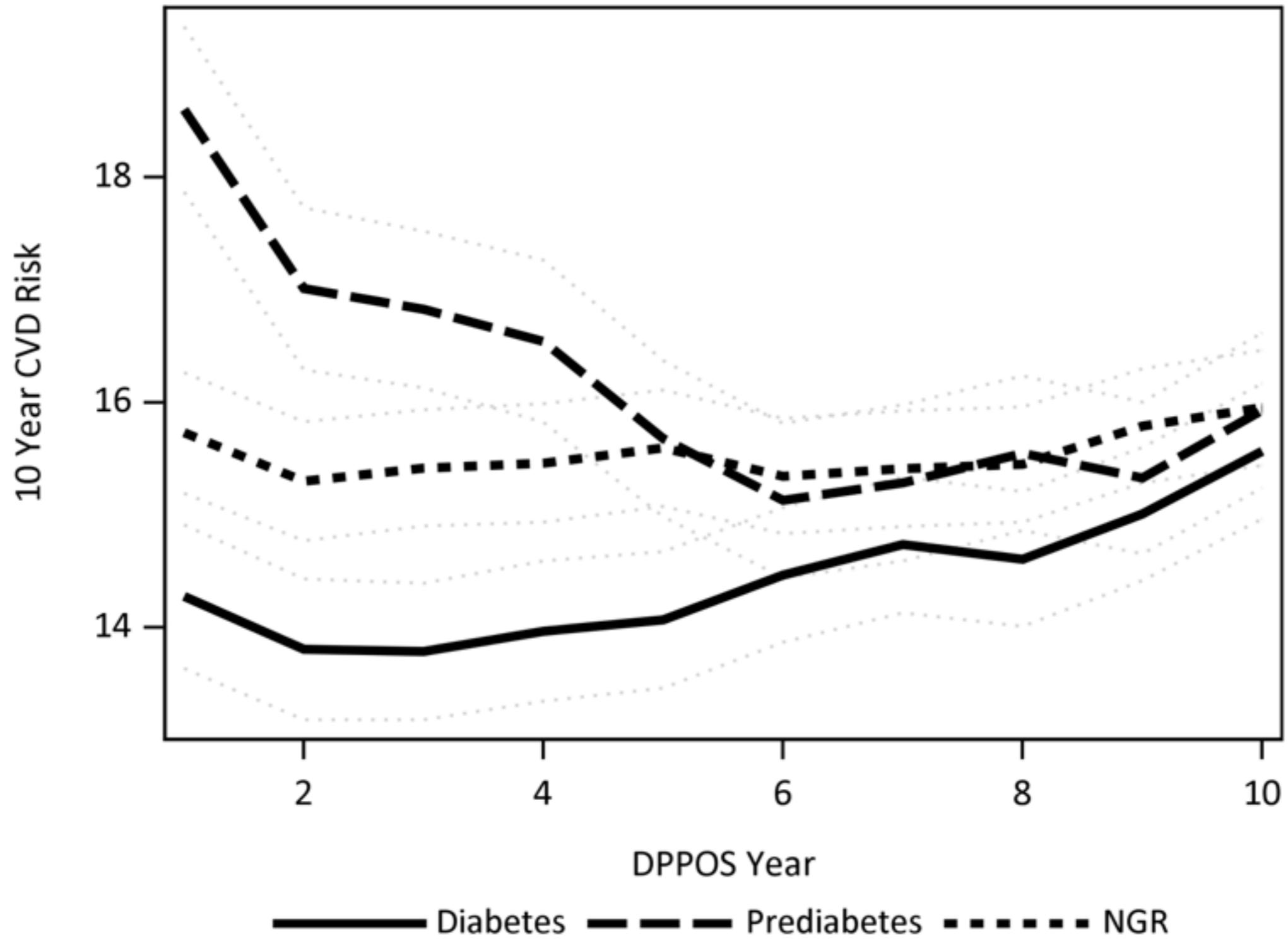
KIEREN MATHER, MD  
SANTICA MARCOVINA, PHD  
CHRIS SAUDEK, MD  
MARGARET J. MATULIK, MS  
DAVID PRICE, MD

**C**ardiovascular disease (CVD) is the major cause of morbidity and mortality in diabetes (1). Although the excess risk for CVD in diabetes has been linked to a clustering of risk factors that include blood pressure and lipoprotein

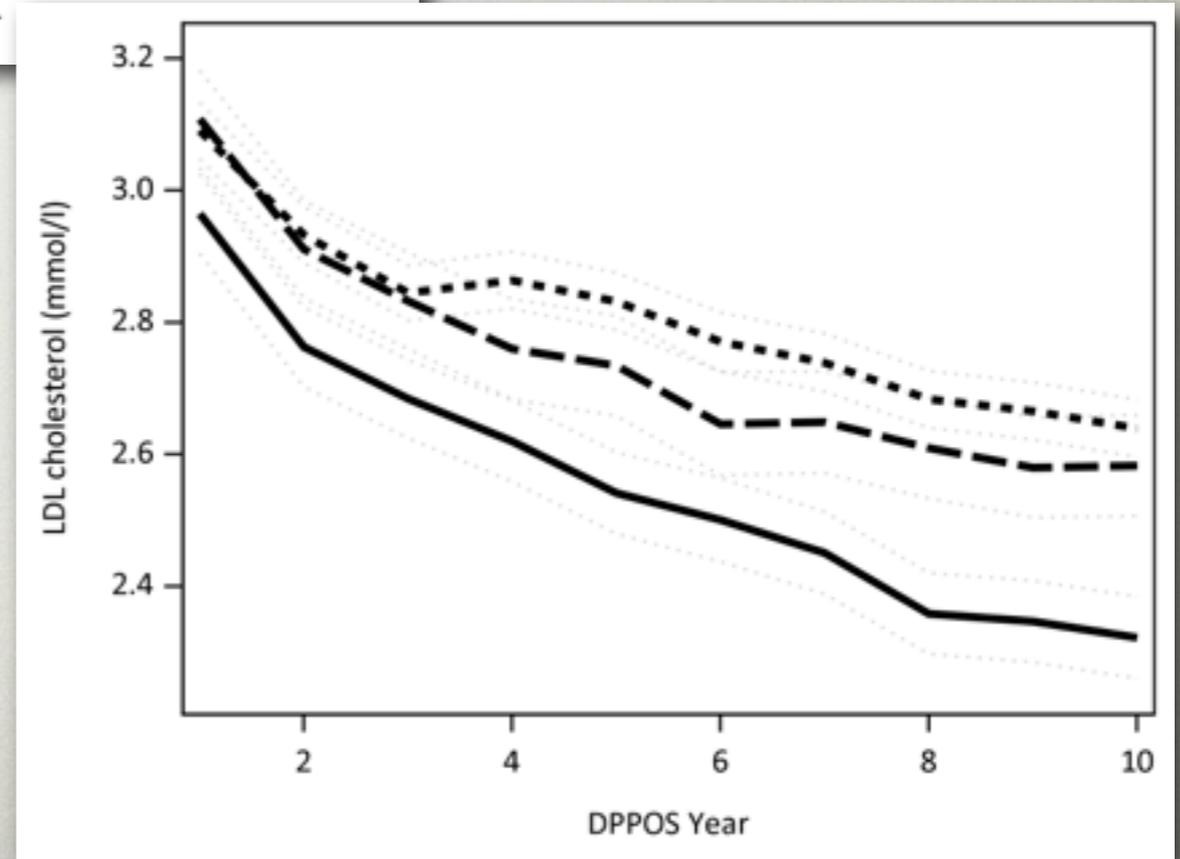
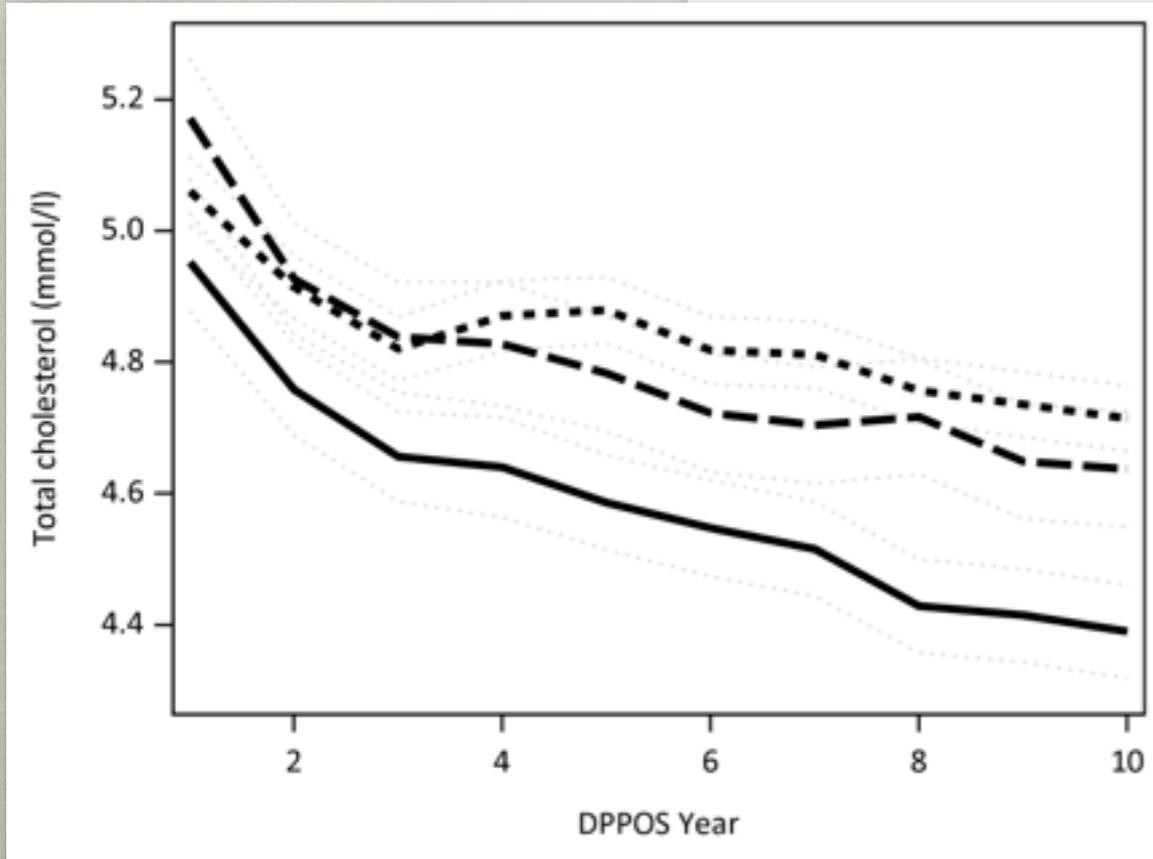
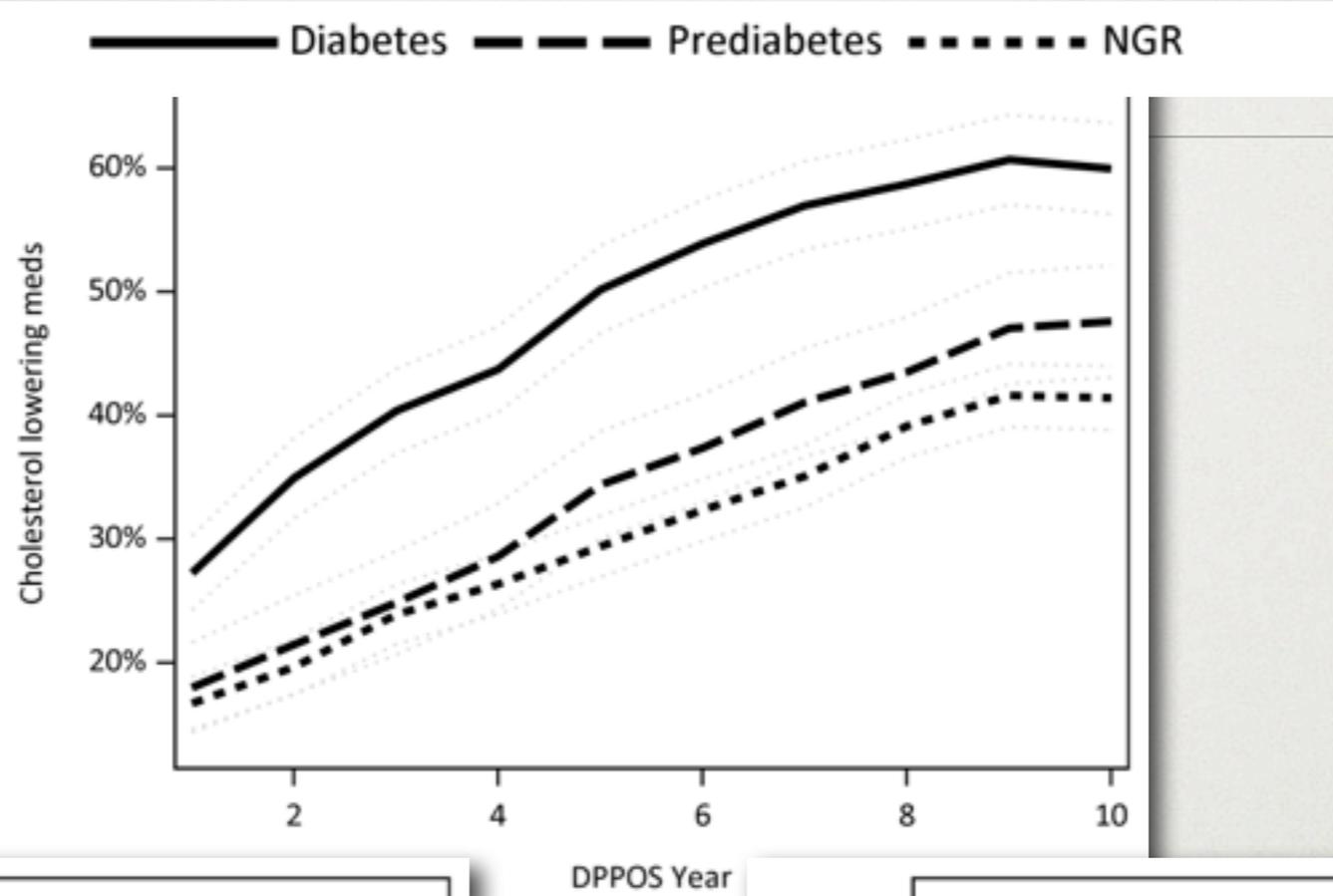
# COMPARISON OF SELECTED 10-YEAR CVD RISK ESTIMATORS

Risk Engine	Input	Output	Study Population (year of final outcome assessment)	Absolute Event Rate (women – men)
SCORE	Age, sex, TC, SBP, smoker, country	Fatal CVD	12 European studies (2000)	1.7-6.4
DECODE	Age, sex, TC, SBP, smoker, G0, G120, DM, BMI, country	Fatal CVD	14 European studies (1995)	1.8-3.8%
UKPDS	Age, sex, TC, SBP, smoker, A1c, DM, a. fib	Fatal and non-fatal CHD	UKPDS study (1998)	7.4-7.9%
ARIC	Sex, SBP/DBP/Rx, G0, HDL, TG, waist circumference	Fatal and non-fatal CHD	ARIC (1999)	3.1-10.3%
PROCAM	Age, SBP, smoker, HDL, LDL, TG, DM, +FHx	Fatal and non-fatal acute CHD	PROCAM (1995)	6.0% (men only)
Framingham 1991	Age, sex, SBP, smoker, LDL, HDL, VLDL, TG, G0	Fatal and non-fatal CHD	Framingham (1986)	3.2 -9.4%
Framingham 2008	Age, sex, TC, SBP/Rx, smoker, DM, HDL	Fatal and non-fatal CVD	Framingham (1999)	10.1-18.1%

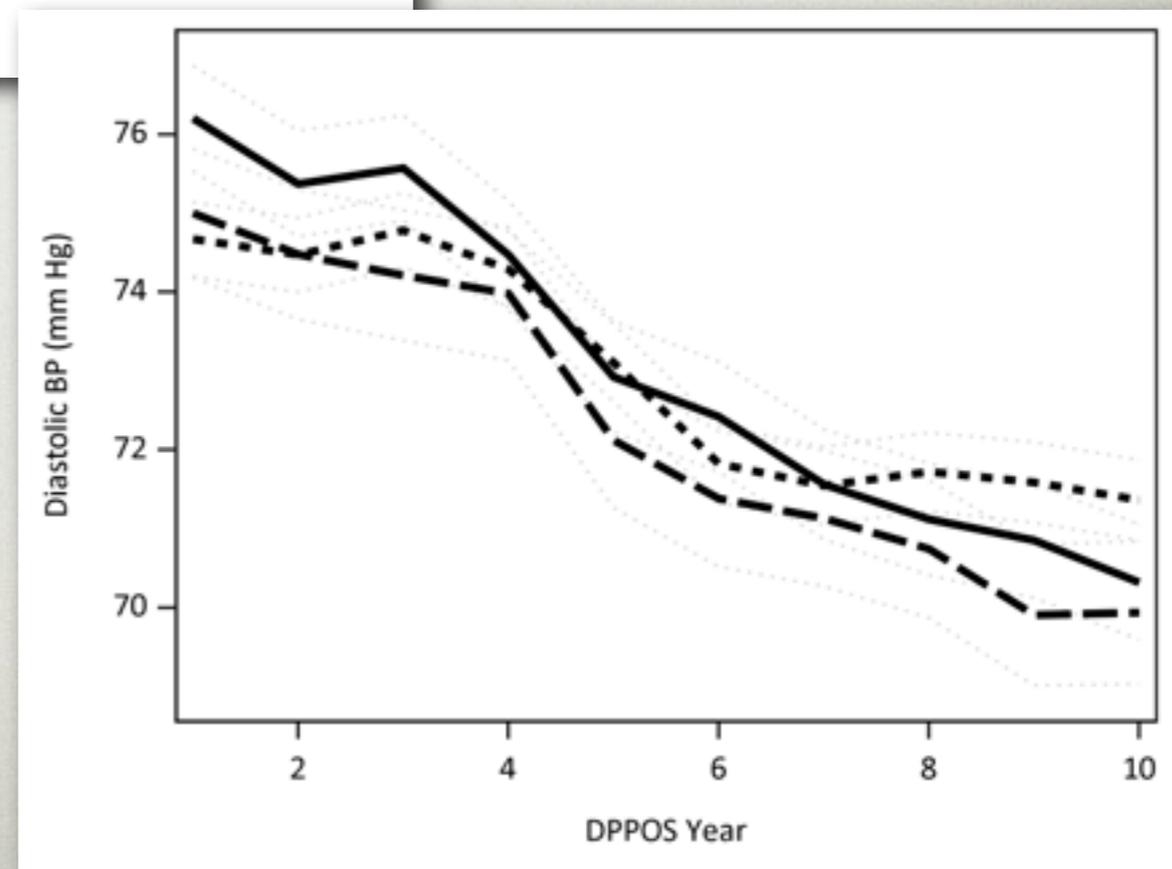
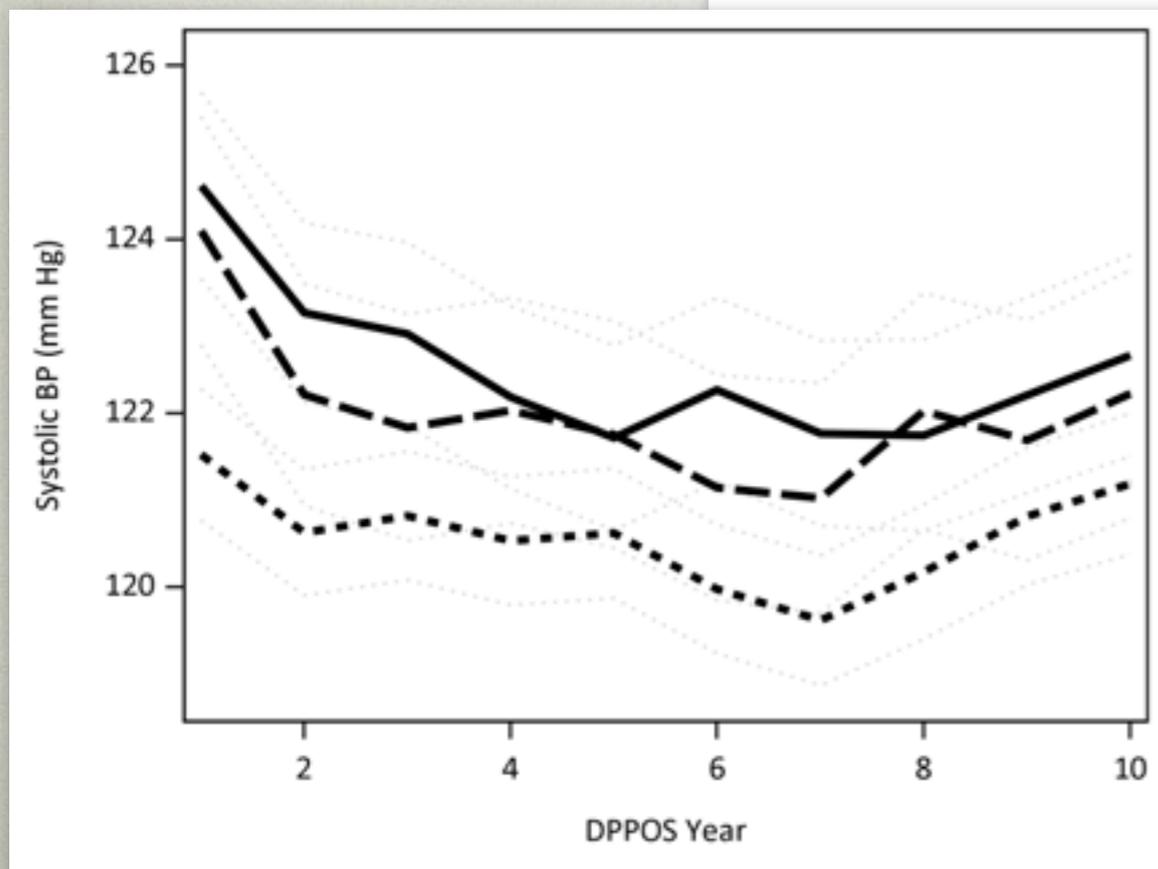
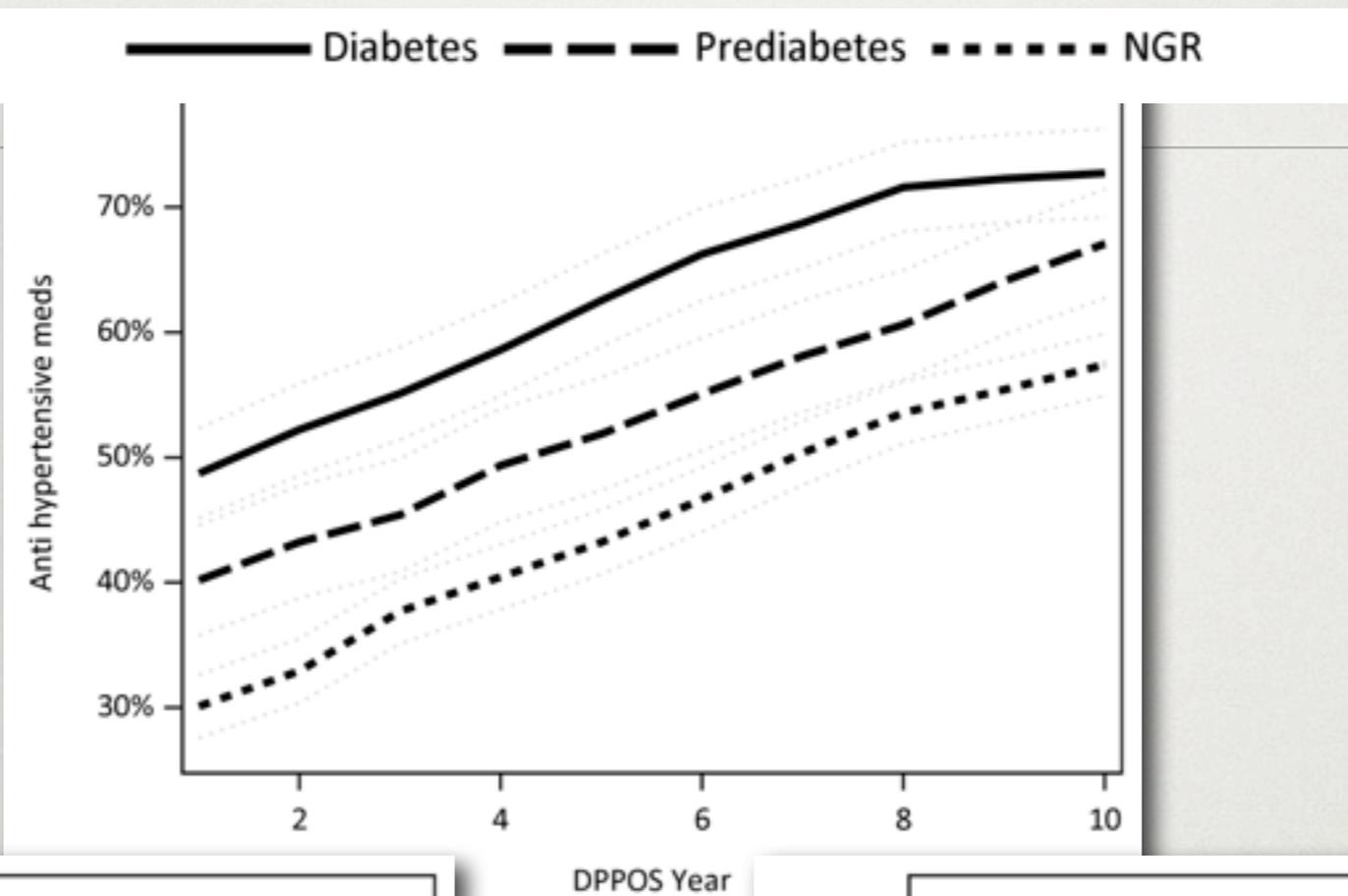
# FRAMINGHAM ESTIMATE OF 10-YEAR CVD RISK

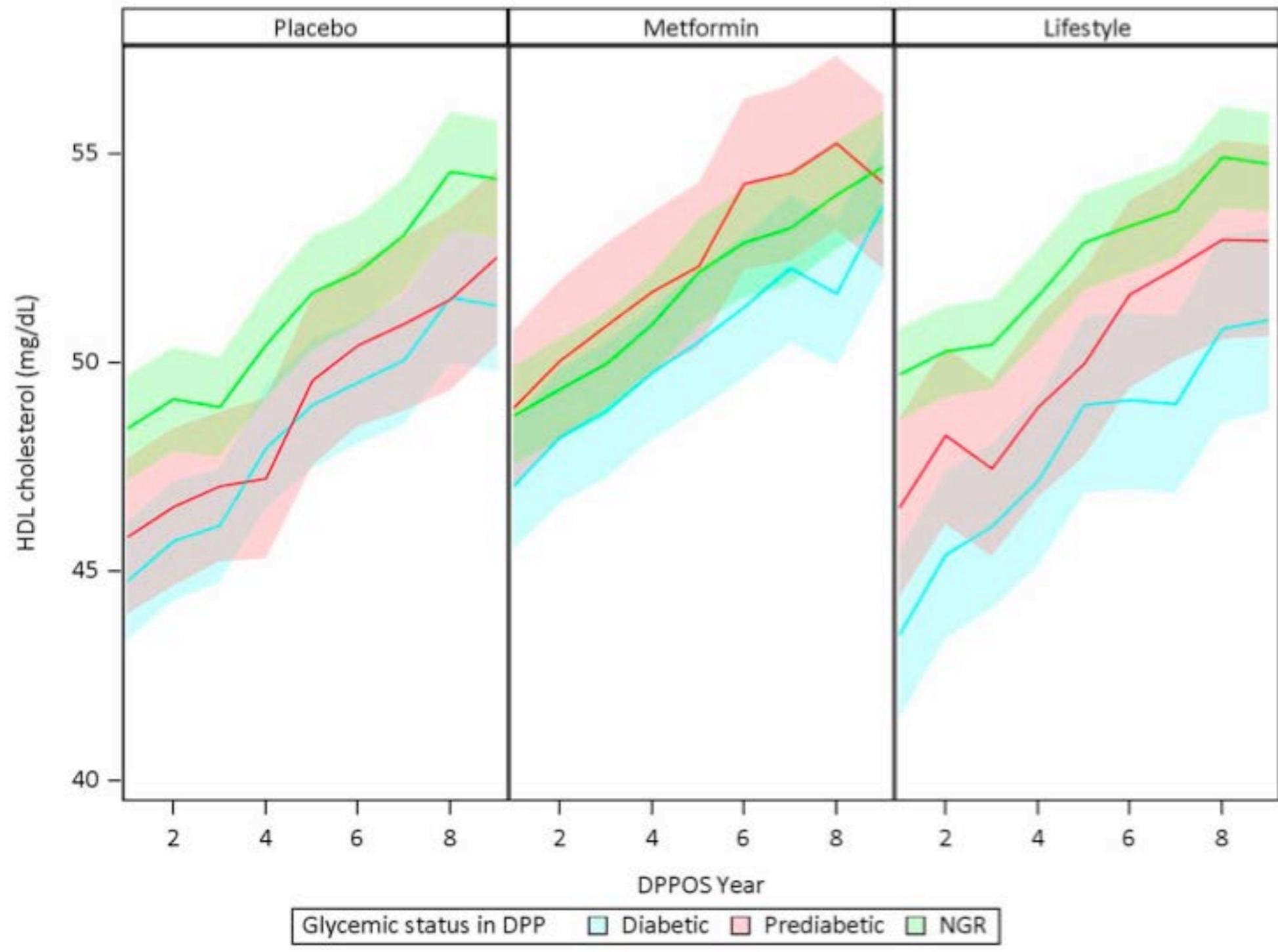


# LIPID-LOWERING MEDICATION USE AND LIPIDS



# BLOOD PRESSURE-LOWERING MEDICATION USE AND BLOOD PRESSURE





# CONCLUSIONS

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- Pre-diabetes represents a very high-risk state for diabetes and carries a higher incidence of related complications in and of itself.
- Prevention of diabetes - particularly when NGR can be attained - is key to lower risk.
- Additional risk can also be decreased through CVD risk stratification, but goals for lipids and BP in pre-diabetes are lacking.



**Thank you!**

Richard Hamman, MD, DrPH  
Diabetes Prevention Program Outcomes Study  
National Institutes of Health (5U01-DK048375-12)  
American Diabetes Association (1-09-CD-11)  
Clinical Translational Research Center

