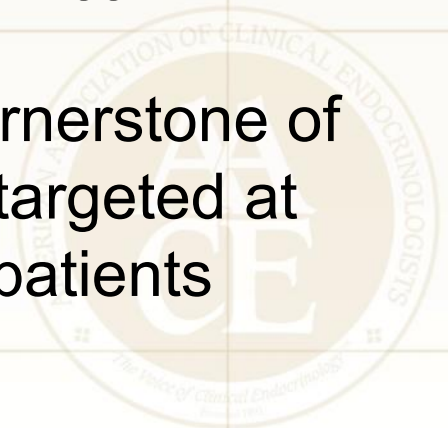


# Prediabetes Management



# 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



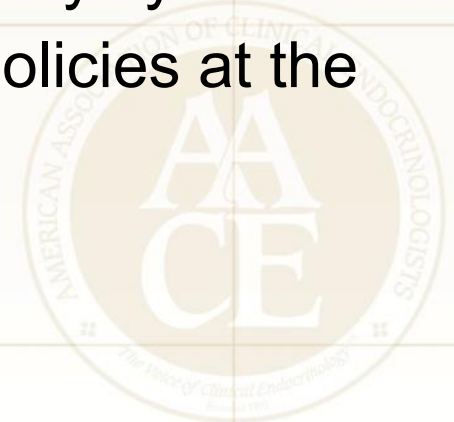
# Prediabetes

- 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



# Policy Paradigm Shifts Needed to Stem Global Tide of T2D

- Integrating primary and secondary prevention along a clinical continuum
- Early detection of prediabetes and undiagnosed diabetes
- Implementing cost-effective prevention and control by integrating community and clinical expertise and resources within affordable service delivery systems
- Sharing and adopting evidence-based policies at the global level





# Lifestyle Therapy

## RISK STRATIFICATION FOR DIABETES COMPLICATIONS



### INTENSITY STRATIFIED BY BURDEN OF OBESITY AND RELATED COMPLICATIONS

<b>Nutrition</b>	<ul style="list-style-type: none"> <li>Maintain optimal weight</li> <li>Calorie restriction (if BMI is increased)</li> <li>Plant-based diet; high polyunsaturated and monounsaturated fatty acids</li> </ul>	+	<ul style="list-style-type: none"> <li>Avoid <i>trans</i> fatty acids; limit saturated fatty acids</li> </ul>	+	<ul style="list-style-type: none"> <li>Structured counseling</li> <li>Meal replacement</li> </ul>
<b>Physical Activity</b>	<ul style="list-style-type: none"> <li>150 min/week moderate exertion (eg. walking, stair climbing)</li> <li>Strength training</li> <li>Increase as tolerated</li> </ul>	+	<ul style="list-style-type: none"> <li>Structured program</li> <li>Wearable technologies</li> </ul>	+	<ul style="list-style-type: none"> <li>Medical evaluation/clearance</li> <li>Medical supervision</li> </ul>
<b>Sleep</b>	<ul style="list-style-type: none"> <li>About 7 hours per night</li> <li>Basic sleep hygiene</li> </ul>	+	<ul style="list-style-type: none"> <li>Screen OSA</li> <li>Home sleep study</li> </ul>	+	<ul style="list-style-type: none"> <li>Referral to sleep lab</li> </ul>
<b>Behavioral Support</b>	<ul style="list-style-type: none"> <li>Community engagement</li> <li>Alcohol moderation</li> </ul>	+	<ul style="list-style-type: none"> <li>Discuss mood with HCP</li> </ul>	+	<ul style="list-style-type: none"> <li>Formal behavioral therapy</li> </ul>
<b>Smoking Cessation</b>	<ul style="list-style-type: none"> <li>No tobacco products</li> </ul>	+	<ul style="list-style-type: none"> <li>Nicotine replacement therapy</li> </ul>	+	<ul style="list-style-type: none"> <li>Referral to structured program</li> </ul>

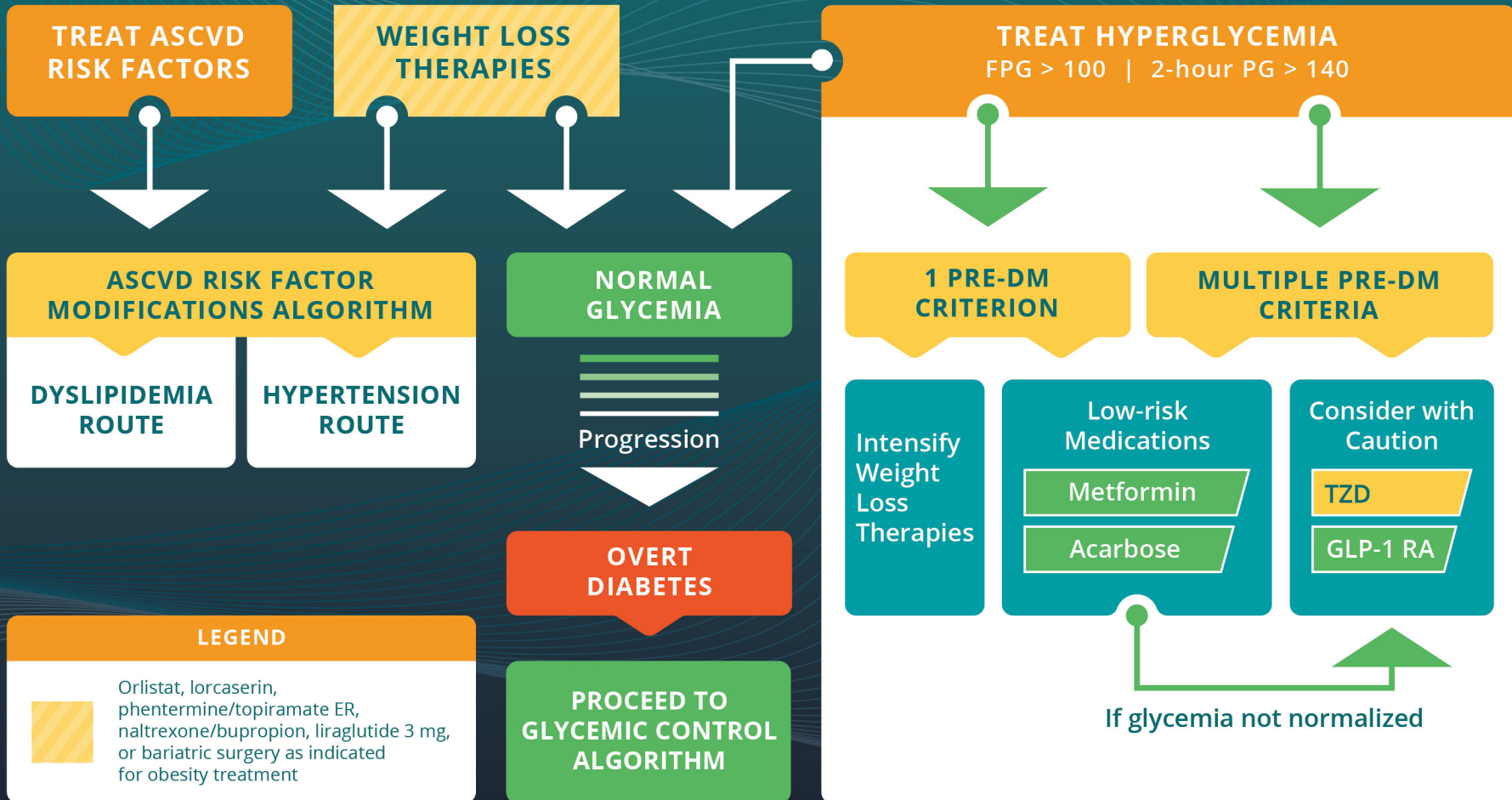
# Prediabetes Algorithm



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

## LIFESTYLE THERAPY

(Including Medically Assisted Weight Loss)



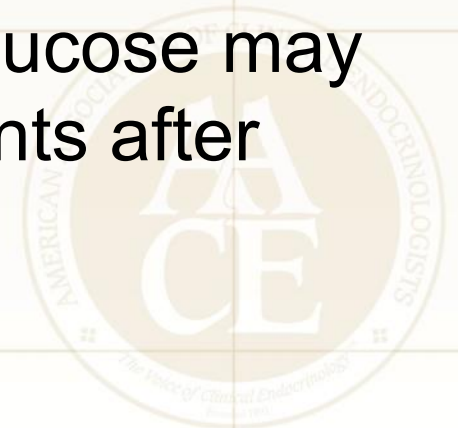
# Feasibility of Preventing Type 2 Diabetes

- 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



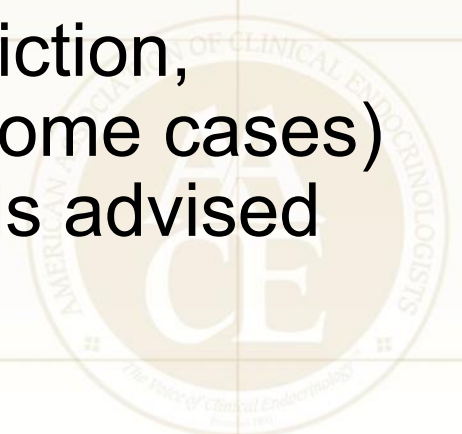
# Interventions to Reduce Risks Associated With Prediabetes

- 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



# Lifestyle Intervention in Prediabetes

- Persons with prediabetes should reduce weight by 5% to 10%, with long-term maintenance at this level
  - A program of regular moderate-intensity physical activity for 30-60 minutes daily, at least 5 days a week, is recommended
  - A diet that includes caloric restriction, increased fiber intake, and (in some cases) carbohydrate intake limitations is advised



# Primary Care-Based Counseling for T2D Prevention: ADAPT

## ADAPT System for Behavior-Change Counseling

### Behavior-Change Principles

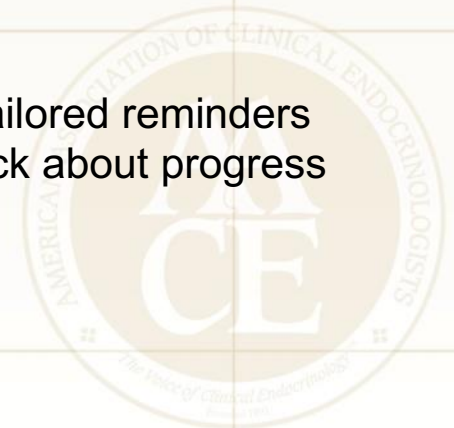
- Patient-selected behavior-change goals
- Behavior-change props
- Implementation-intentions exercise

### Persuasive Psychology

- Behavior-change prescription
- Social comparisons
- Behavior-change samples
- Testimonials

### Technology

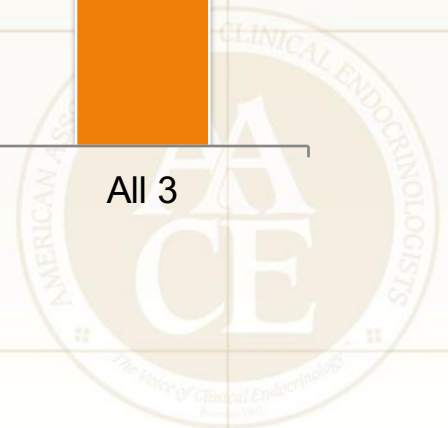
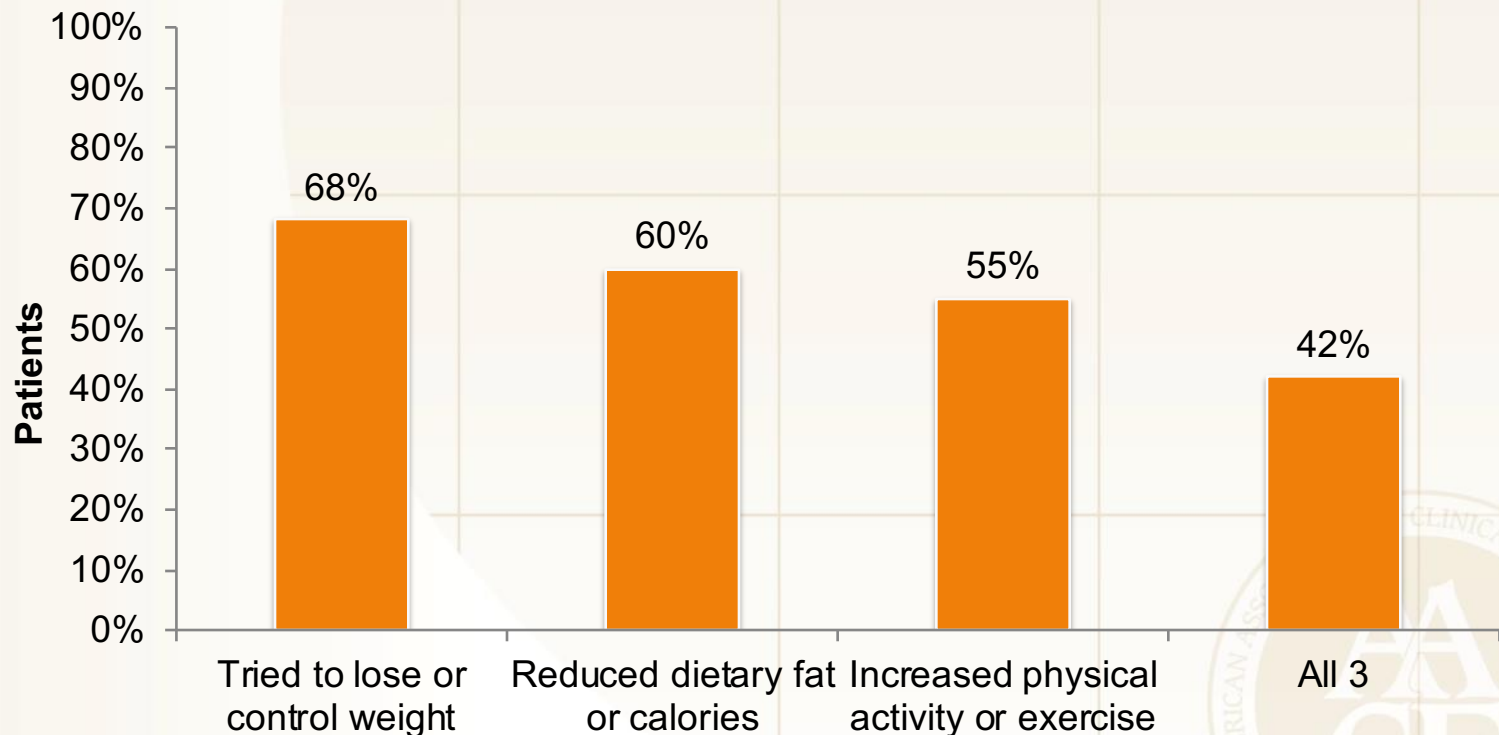
- Electronic record–based goal-setting tool with facilitated order entry and documentation
- Website-based tailored reminders
- Frequent feedback about progress via email





# Self-Reported Risk Reduction Activities in Patients With Prediabetes

## National Health and Nutrition Examination Survey



**Prediabetes Management**

# **PREVENTION OF DIABETES: LIFESTYLE STUDIES**





# Prevention of T2D: Selected Lifestyle Modification Trials

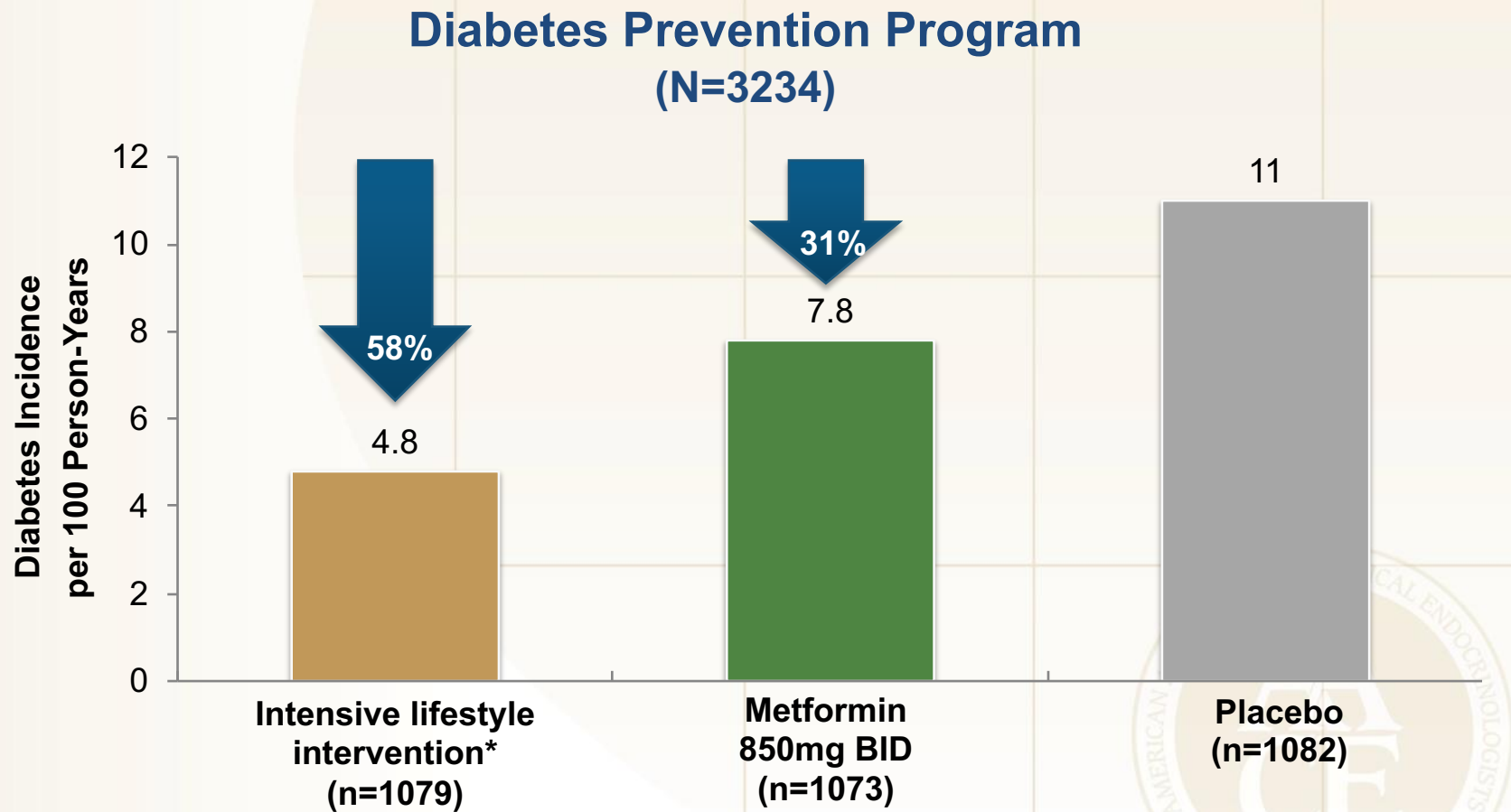
Study	Country	N	Baseline BMI (kg/m <sup>2</sup> )	Intervention period (years)	RRR (%)	NNT
Diabetes Prevention Program	USA	3234	34.0	2.8	58	21
Diabetes Prevention Study	Finland	523	31	4	39	22
Da Qing	China	577	25.8	6	51	30



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



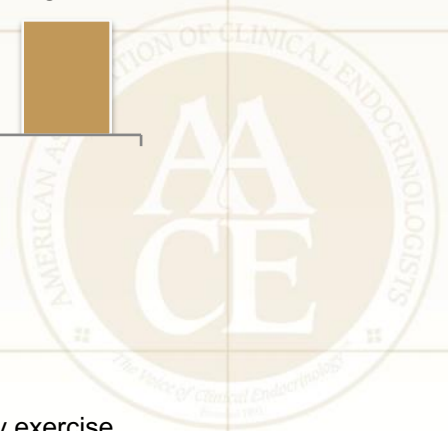
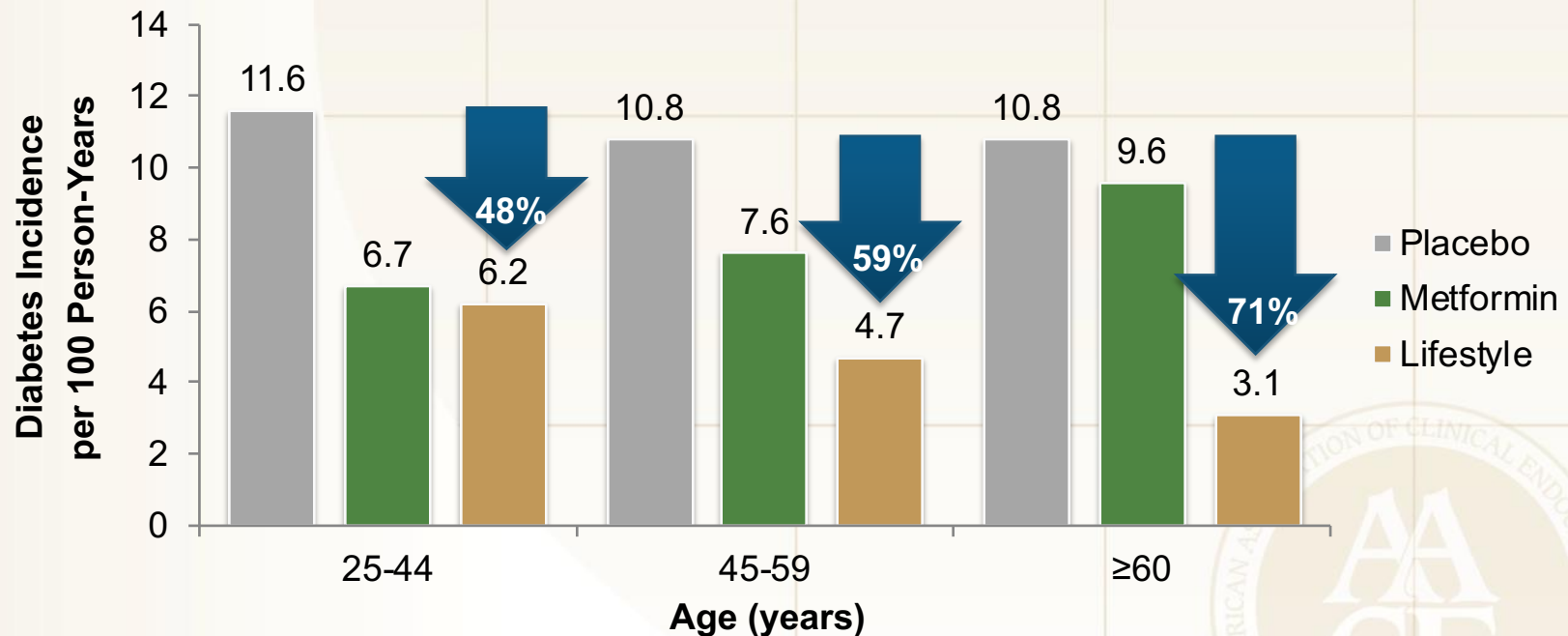
\*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and  $\geq 150$  min/week moderate intensity exercise .

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)

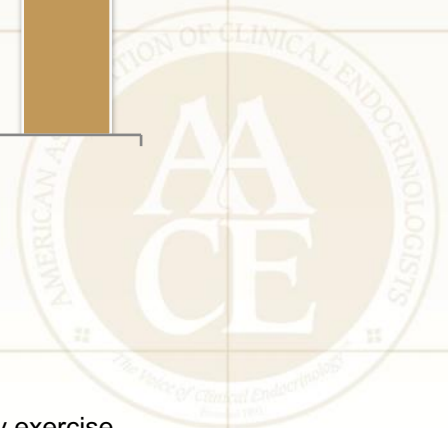
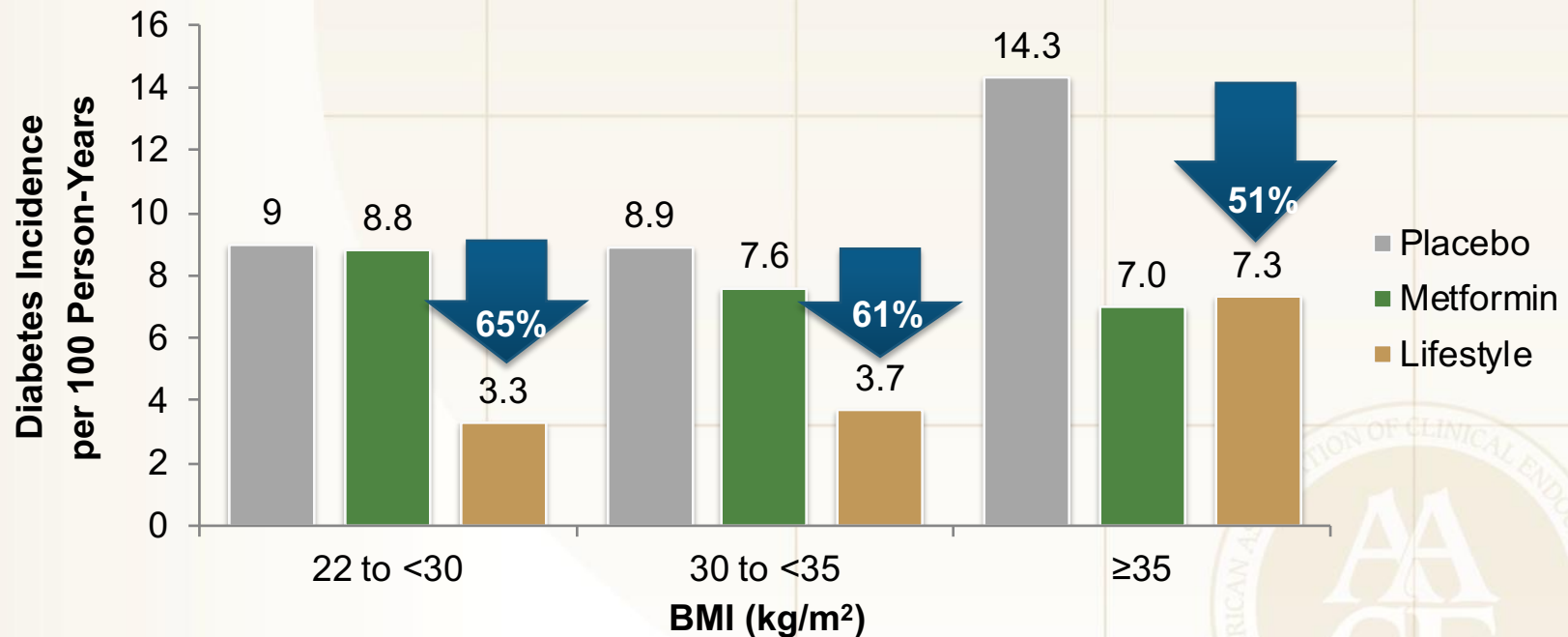


\*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise .

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)

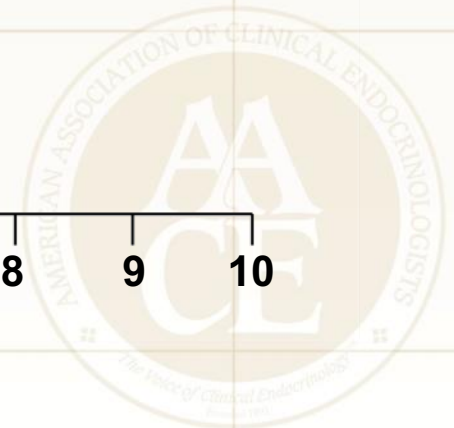
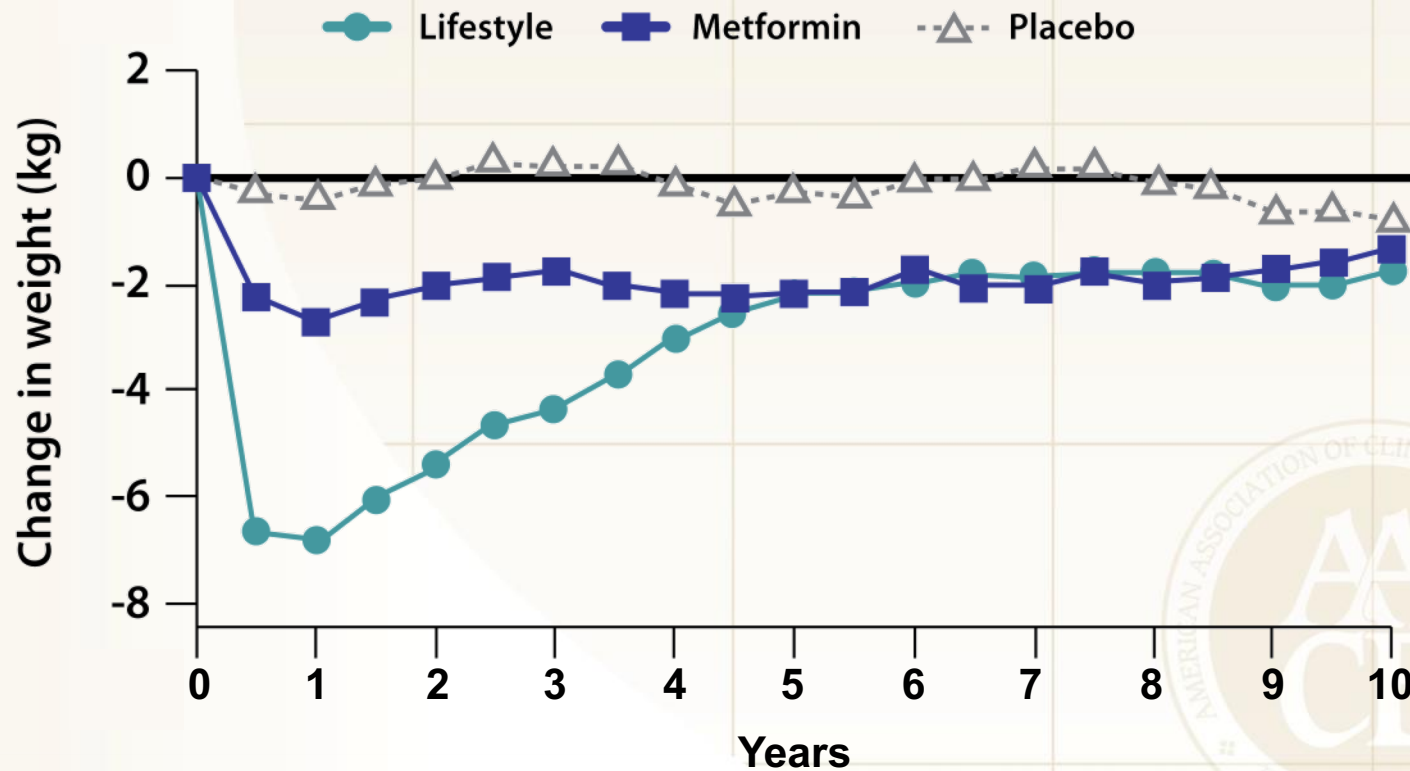


\*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥150 min/week moderate intensity exercise .

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

# Maintenance of Long-Term Weight Loss

DPP Outcomes Study  
(N=2766)

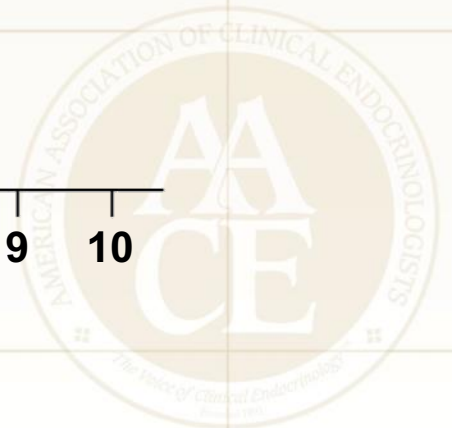
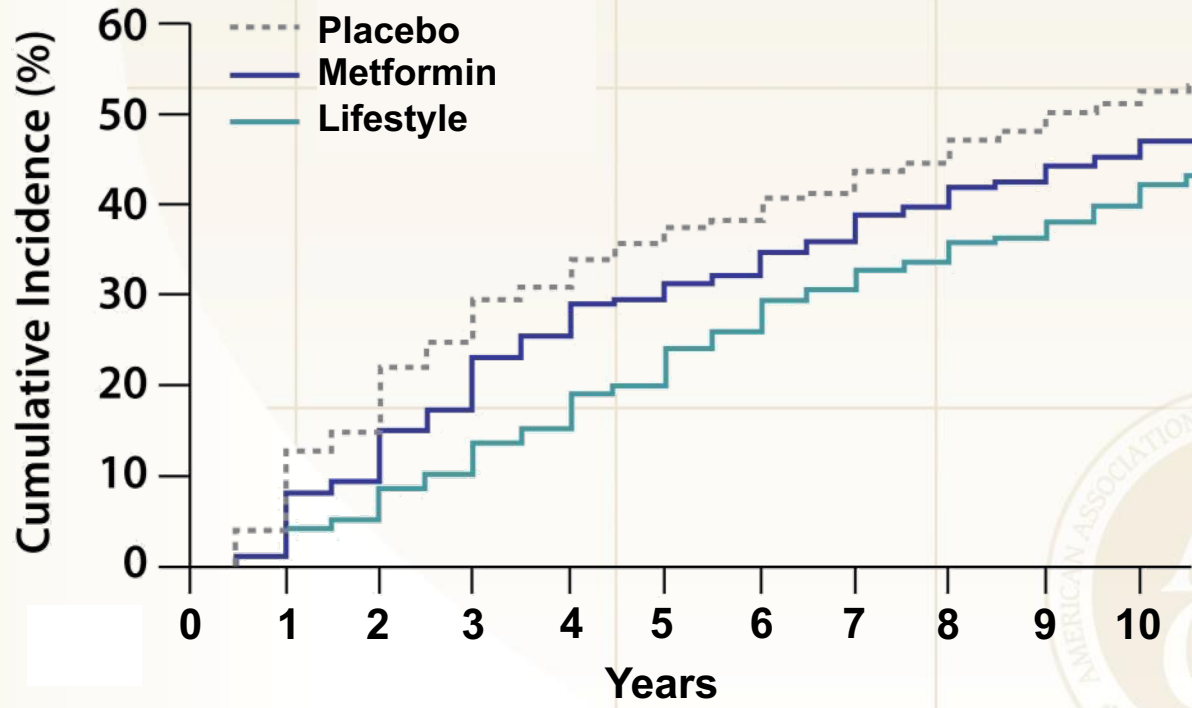


DPP, Diabetes Prevention Program; T2D, type 2 diabetes.

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

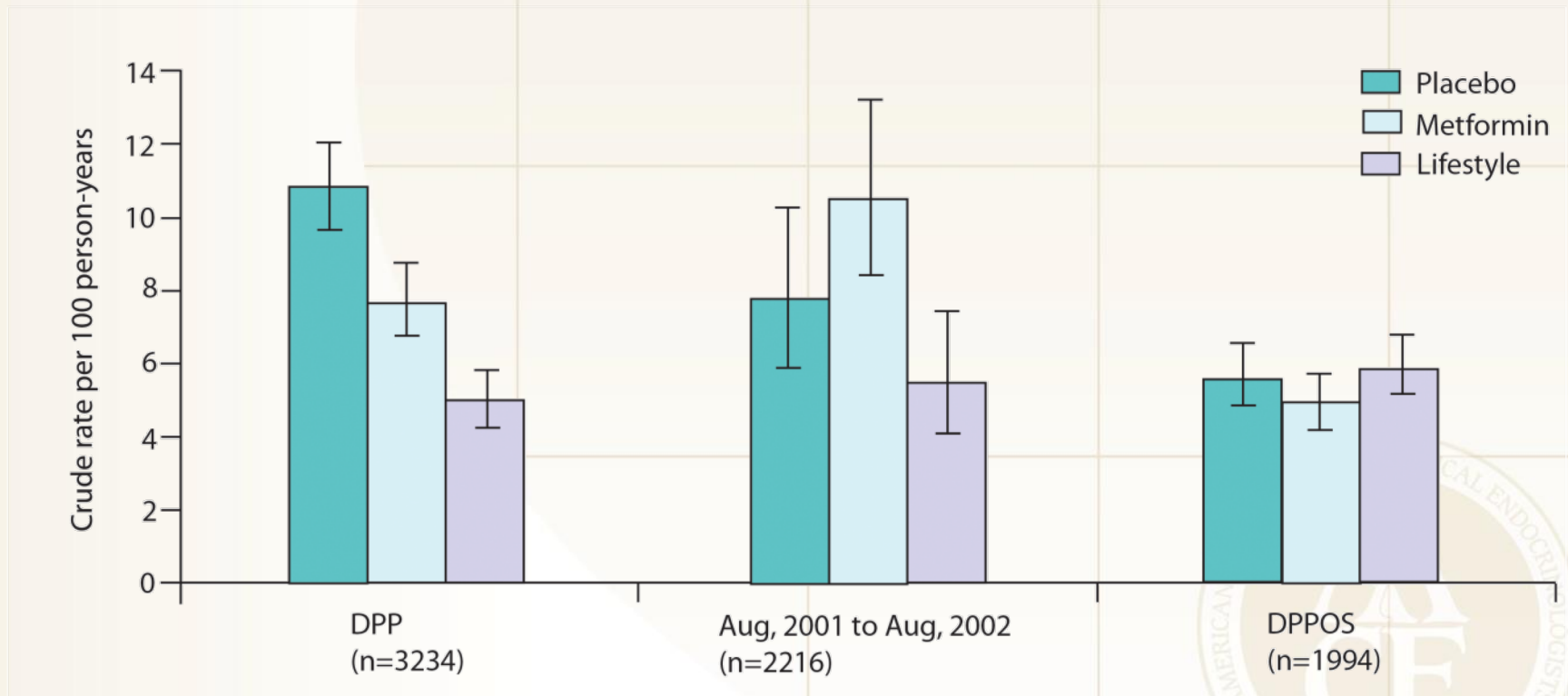
# 10-Year Incidence of T2D

## DPP Outcomes Study (N=2766)



# 10-Year Incidence of Type 2 Diabetes

## DPP Outcomes Study

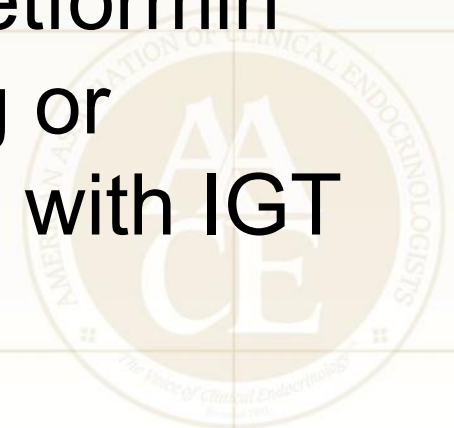


DPP, Diabetes Prevention Program; DPPOS, Diabetes Prevention Program Outcomes Study; T2D, type 2 diabetes.

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

# T2D Prevention in Women With a History of GDM

- Findings from the DPP
  - Progression to diabetes is more common in women with a history of GDM vs those without, despite equivalent degrees of IGT at baseline
- Both intensive lifestyle and metformin are highly effective in delaying or preventing diabetes in women with IGT and a history of GDM



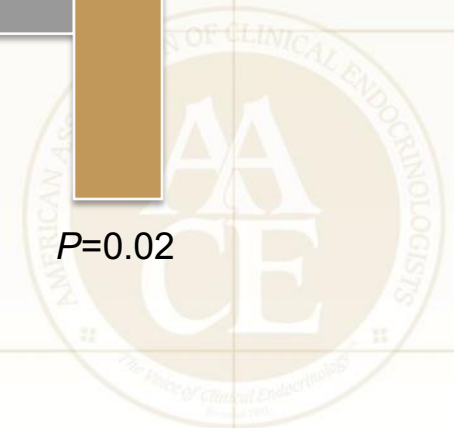
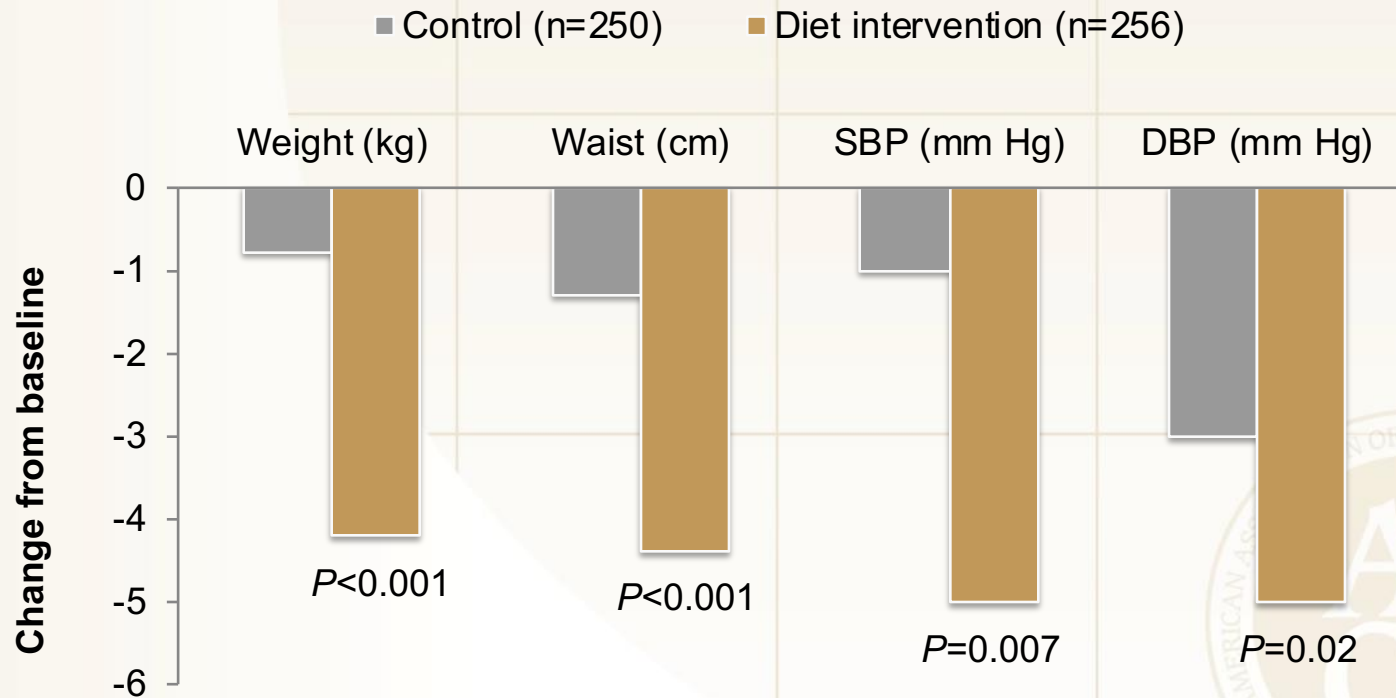
DPP, Diabetes Prevention Program; GDM, gestational diabetes mellitus; IGT, impaired glucose tolerance; T2D, type 2 diabetes.

Ratner RE, et al. *J Clin Endocrinol Metab.* 2008;93:4774-4779.



# Effect of Lifestyle Modification on Weight and Blood Pressure

## The Finnish Diabetes Prevention Study

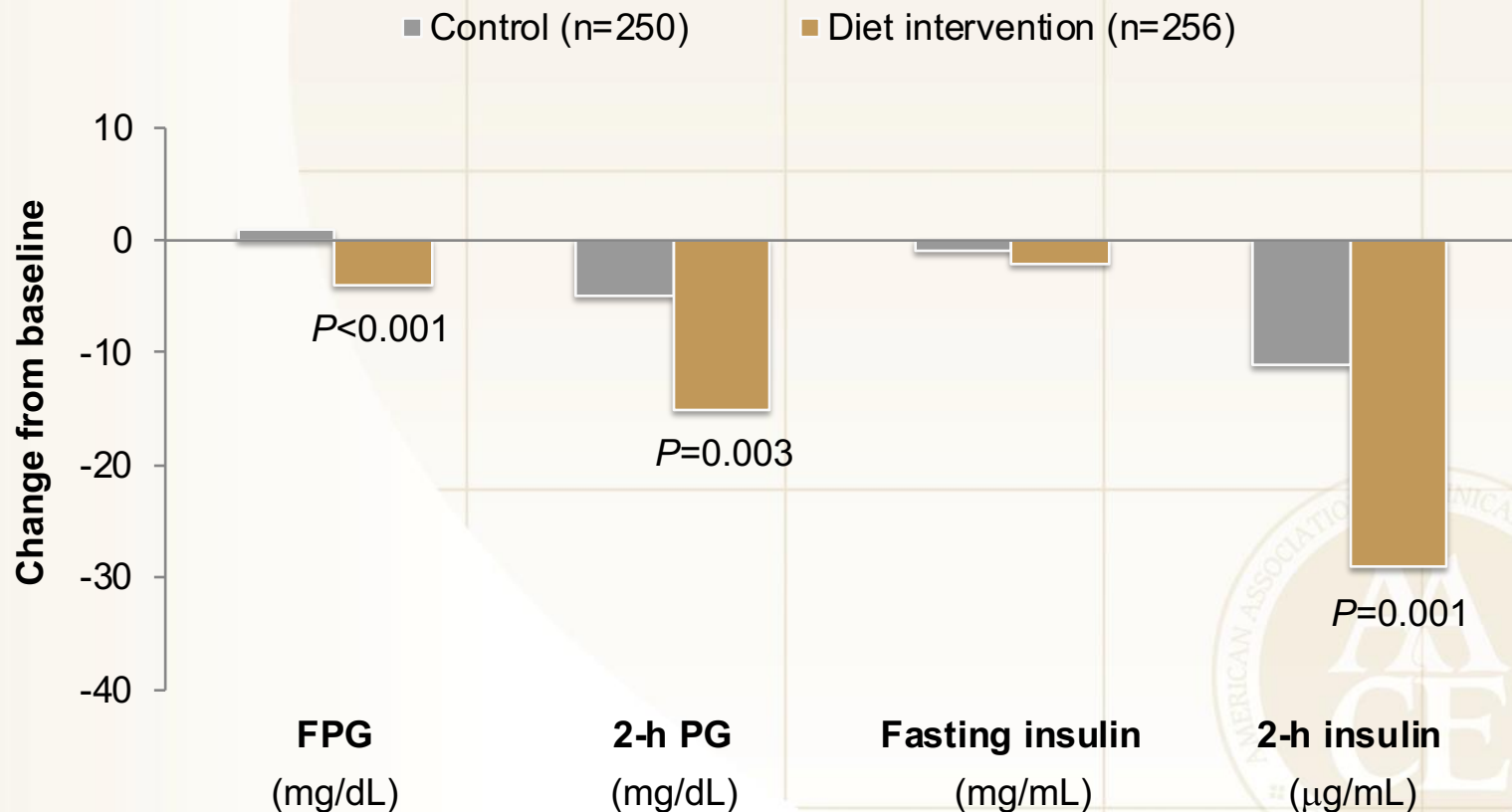


DBP, diastolic blood pressure; SBP, systolic blood pressure.

Tuomilehto J, et al. *N Engl J Med.* 2001;344:1343-1350.

# Effect of Lifestyle Modification on Glucose in Patients with IGT

## The Finnish Diabetes Prevention Study

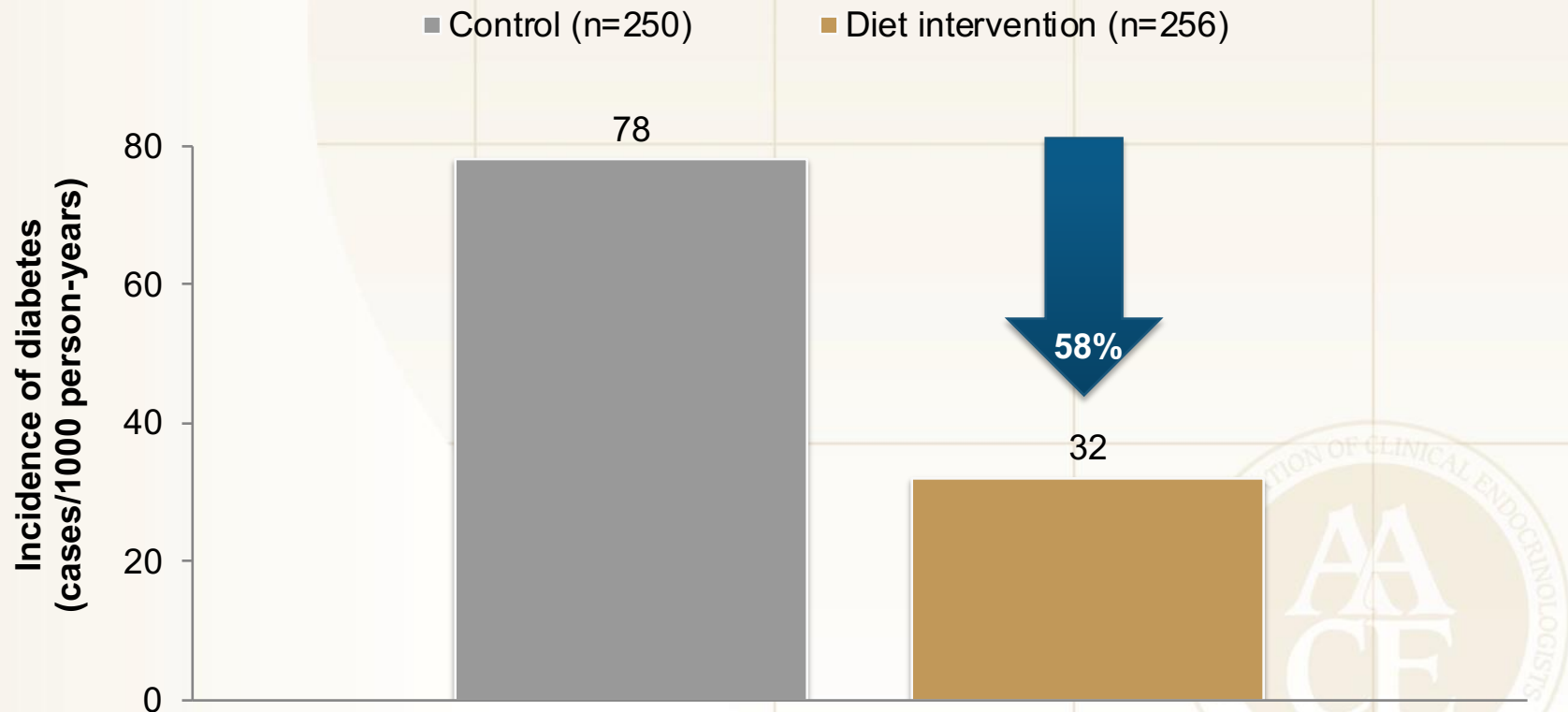


IGT, impaired glucose tolerance.

Tuomilehto J, et al. *N Engl J Med.* 2001;344:1343-1350.

# Cumulative Incidence of Diabetes Over 4 Years

## The Finnish Diabetes Prevention Study

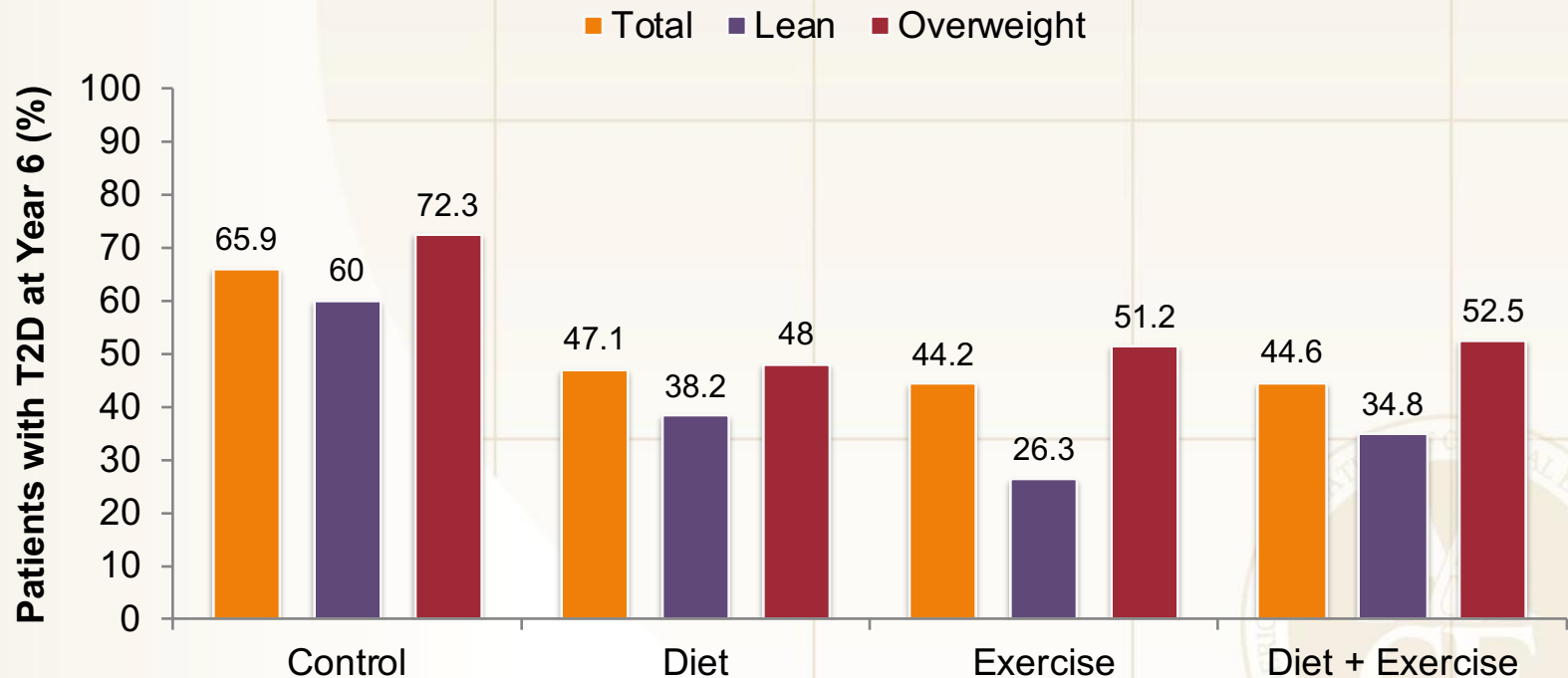


DBP, diastolic blood pressure; SBP, systolic blood pressure.

Tuomilehto J, et al. *N Engl J Med.* 2001;344:1343-1350.

# Cumulative Incidence of Diabetes in Asian Patients with IGT

## Da Qing Diabetes Prevention Study (N=577)

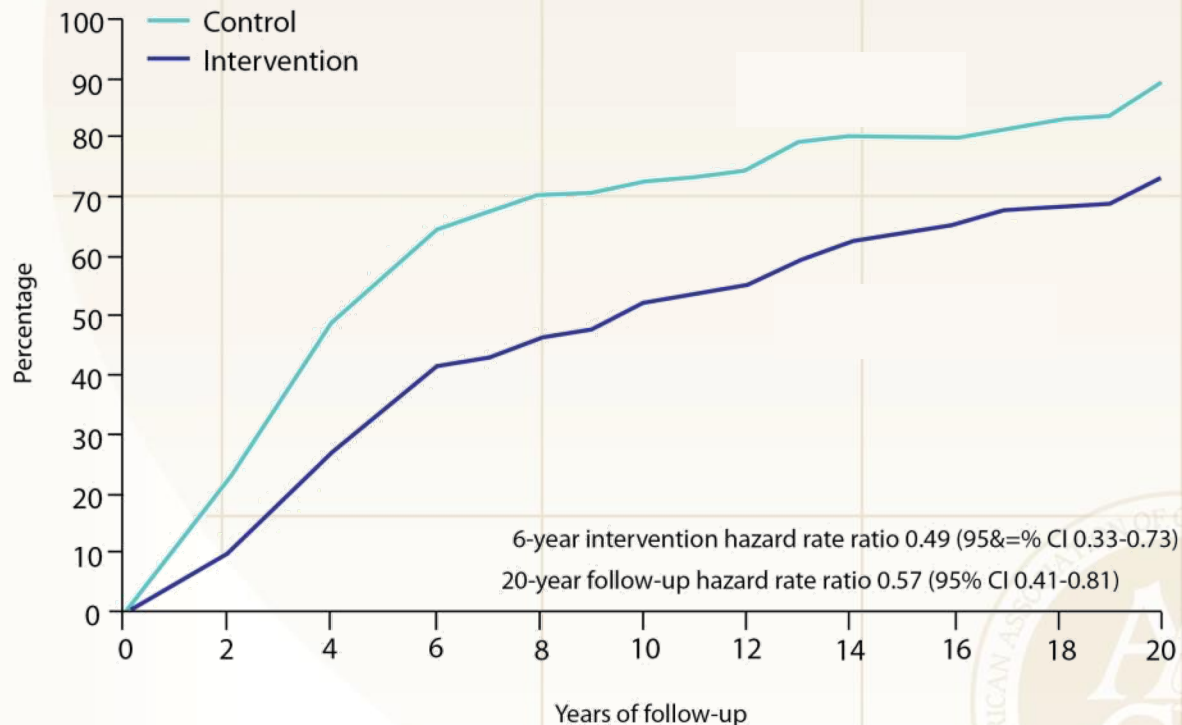


IGT, impaired glucose tolerance; T2D, type 2 diabetes.

Pan XR, et al. *Diabetes Care*. 1997;20:537-544.

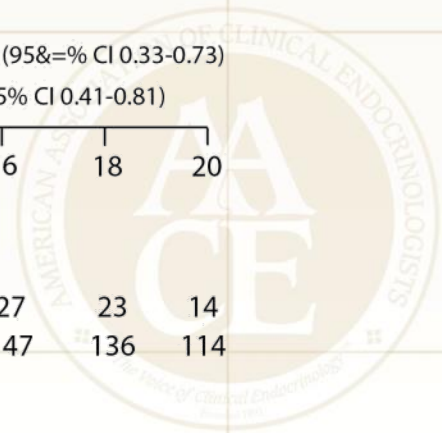
# 20-Year Cumulative T2D Incidence in Asian Patients with IGT

## Da Qing Diabetes Prevention Study



### Number at risk

Control	135	105	69	48	40	37	34	27	27	23	14
Intervention	428	387	314	250	230	206	192	161	147	136	114

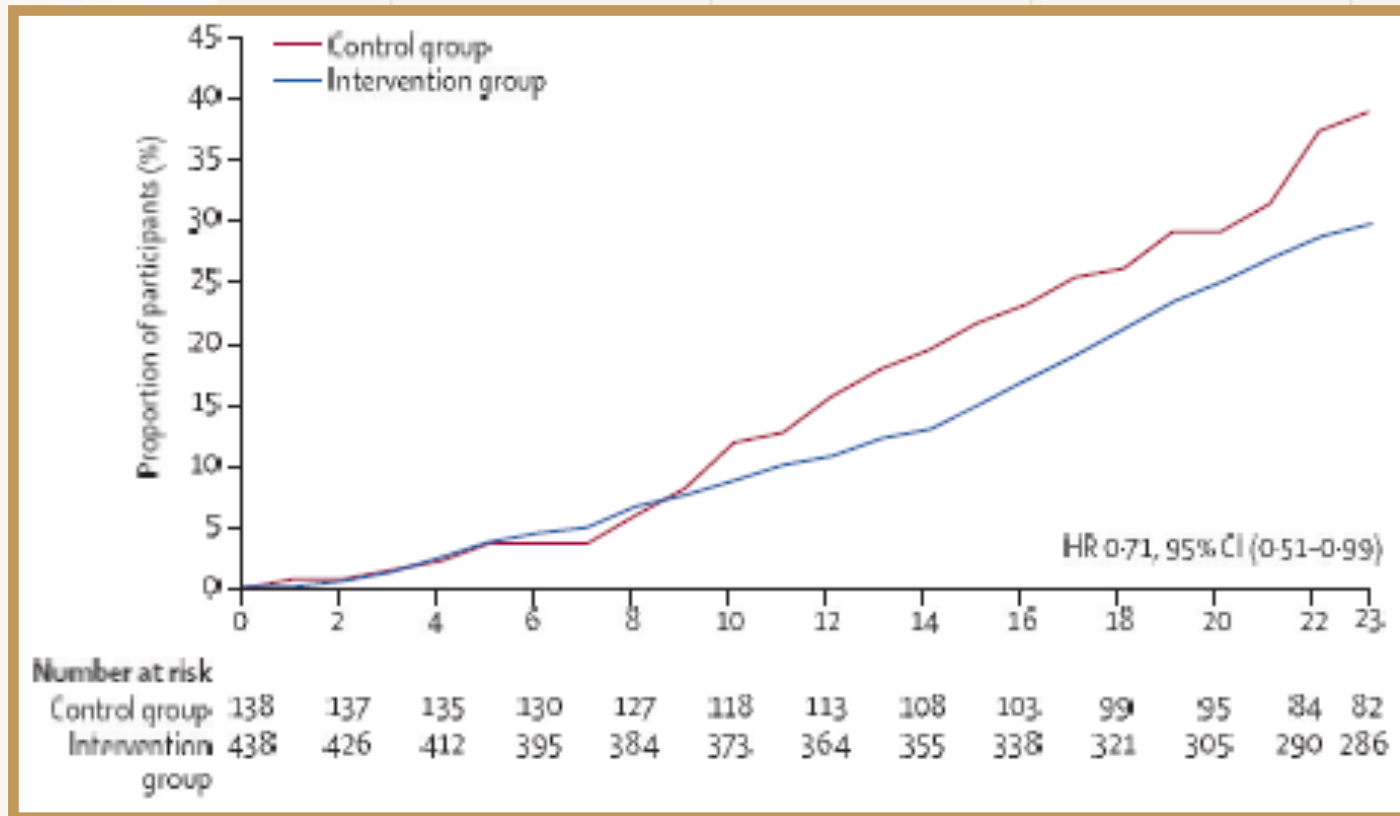


IGT, impaired glucose tolerance; T2D, type 2 diabetes.

Li G, et al. *Lancet*. 2008;371:1783-1789.

# 23-Year All-Cause Mortality in Asian Patients with IGT

## Da Qing Diabetes Prevention Study

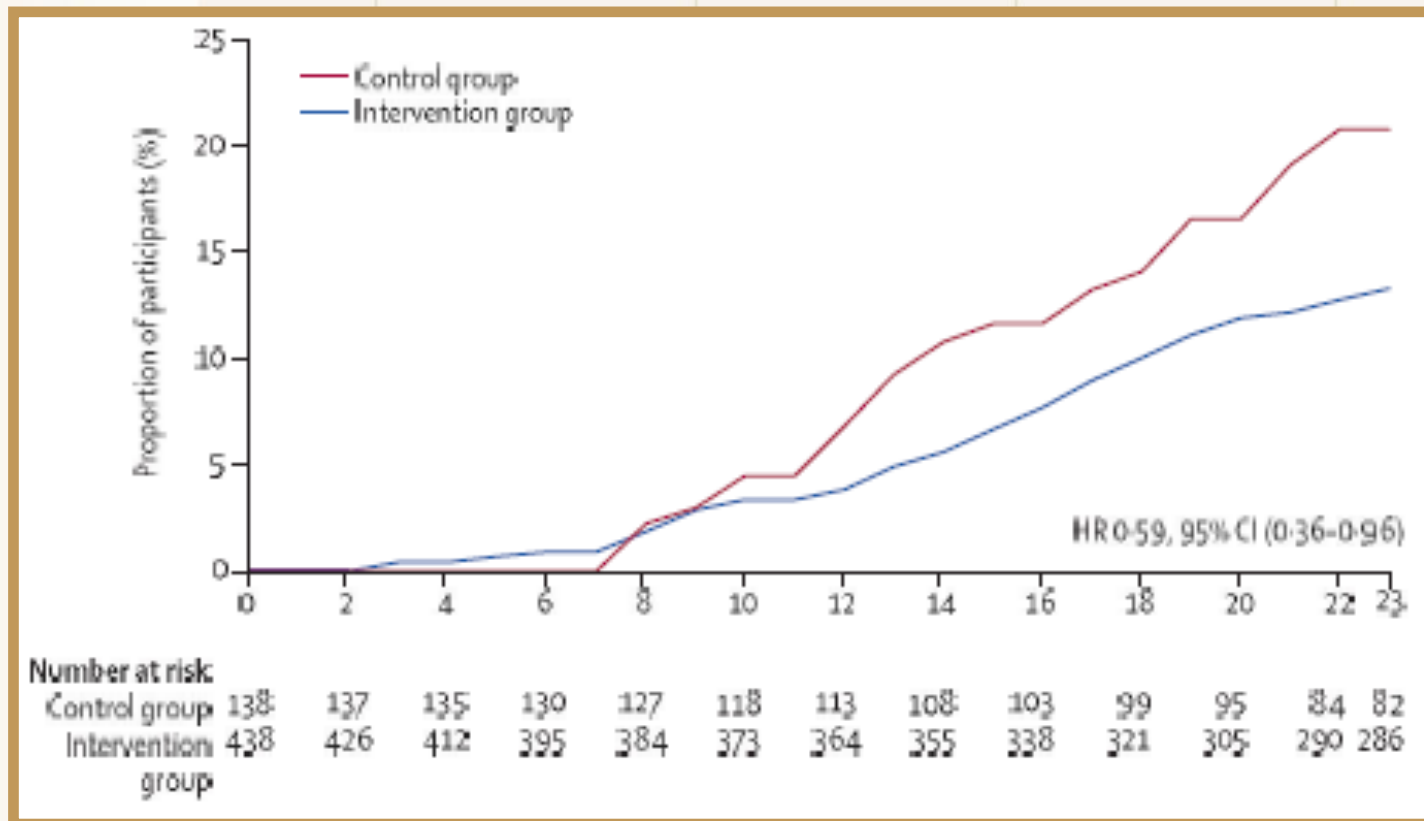


IGT, impaired glucose tolerance.

Li G, et al. *Lancet Diabetes Endocrinol.* 2014;2:474-478.

# 23-Year Cardiovascular Mortality in Asian Patients with IGT

## Da Qing Diabetes Prevention Study

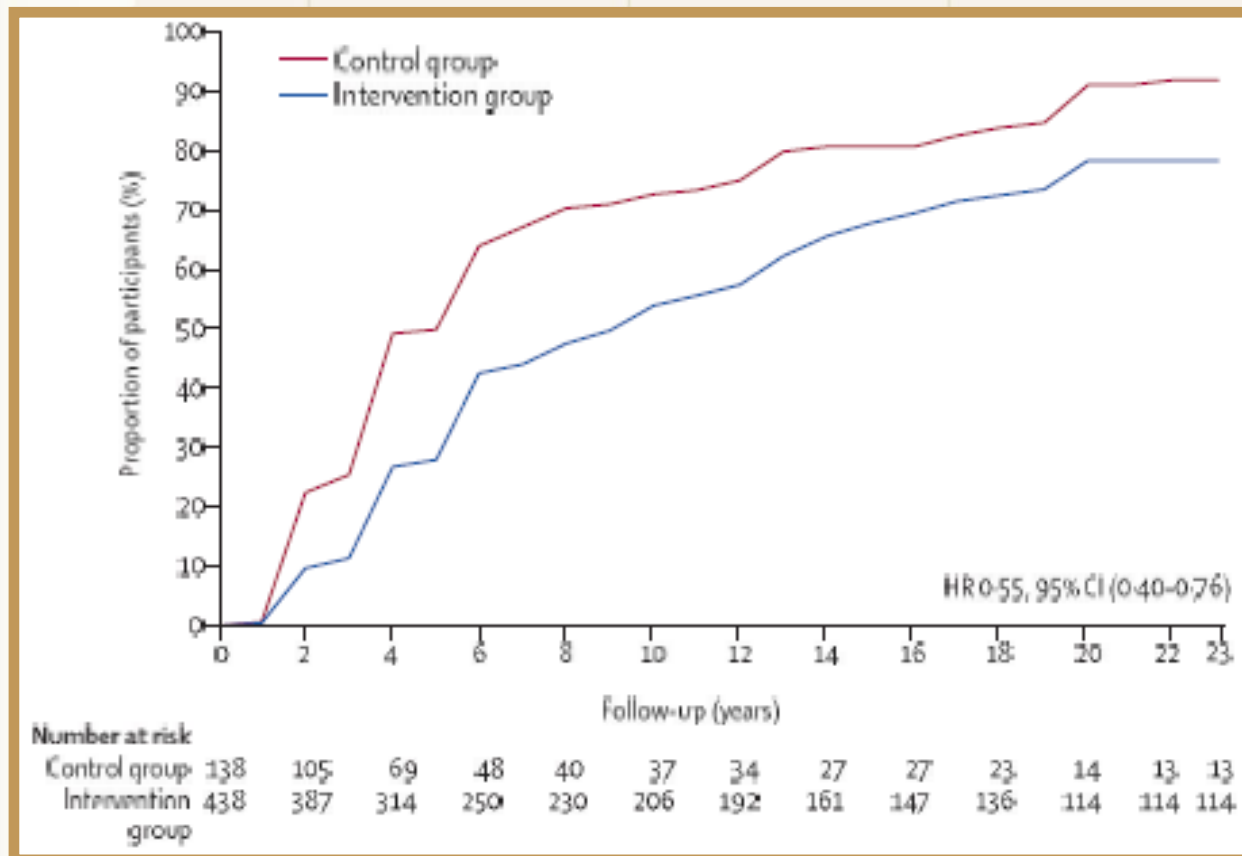


IGT, impaired glucose tolerance.

Li G, et al. *Lancet Diabetes Endocrinol.* 2014;2:474-478.

# 23-Year Incidence of T2D in Asian Patients with IGT

## Da Qing Diabetes Prevention Study



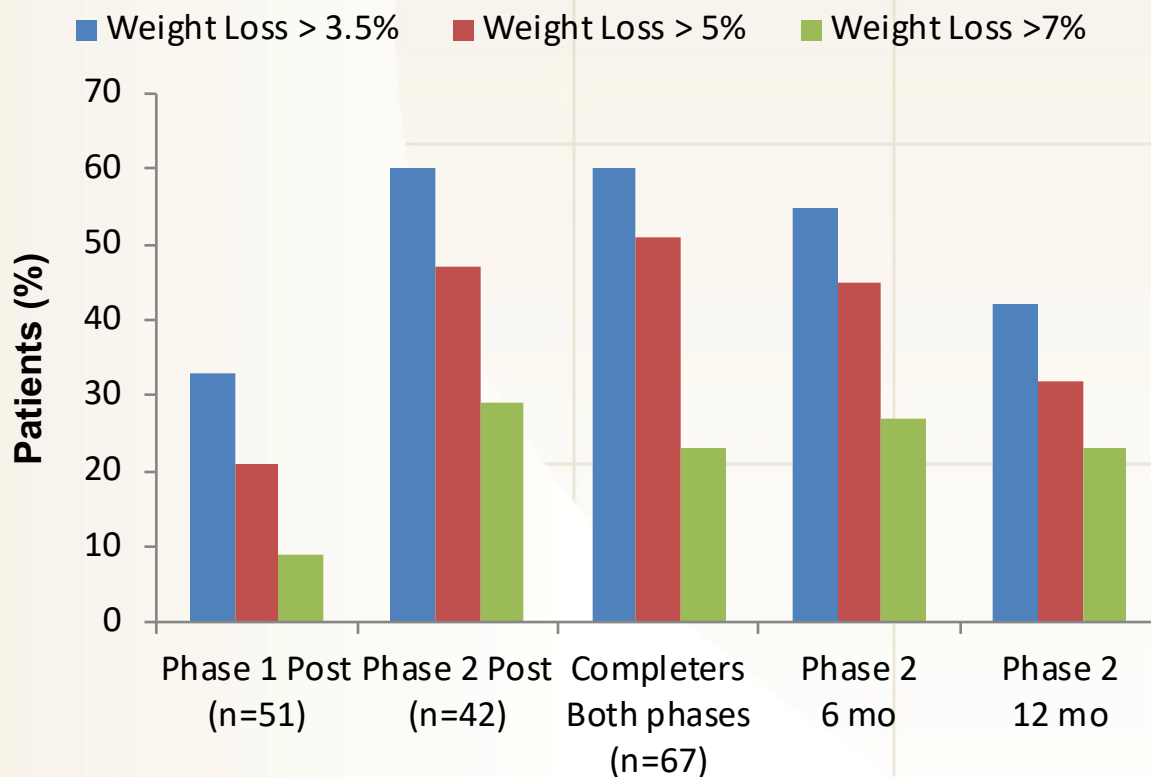
IGT, impaired glucose tolerance; T2D, type 2 diabetes.

Li G, et al. *Lancet Diabetes Endocrinol.* 2014;2:474-478.



# Group Lifestyle Balance Program Intervention

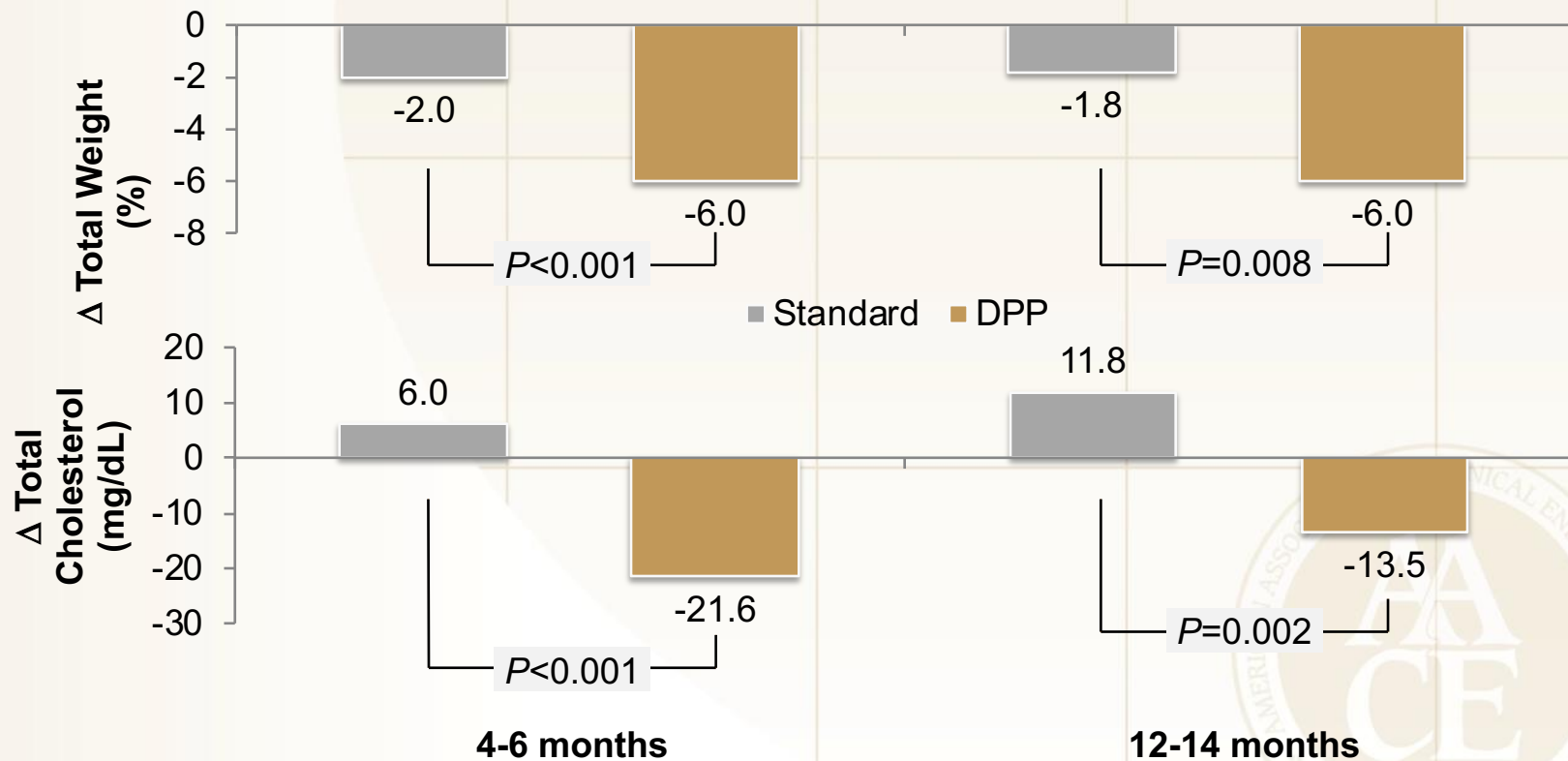
## University of Pittsburgh Primary Care Practice and Diabetes Prevention Support Center



- DPP lifestyle intervention adapted to a 12-session group-based program
- Implemented in a community setting in 2 phases using a nonrandomized prospective design
- Significant decreases in weight, waist circumference, and BMI noted in both phases vs baseline
- Average combined weight loss for both groups over the 3-month intervention
  - 7.4 pounds (3.5% relative loss,  $P < 0.001$ )

# Translating the DPP Into Community Intervention

## The DEPLOY Pilot Study (N=92)

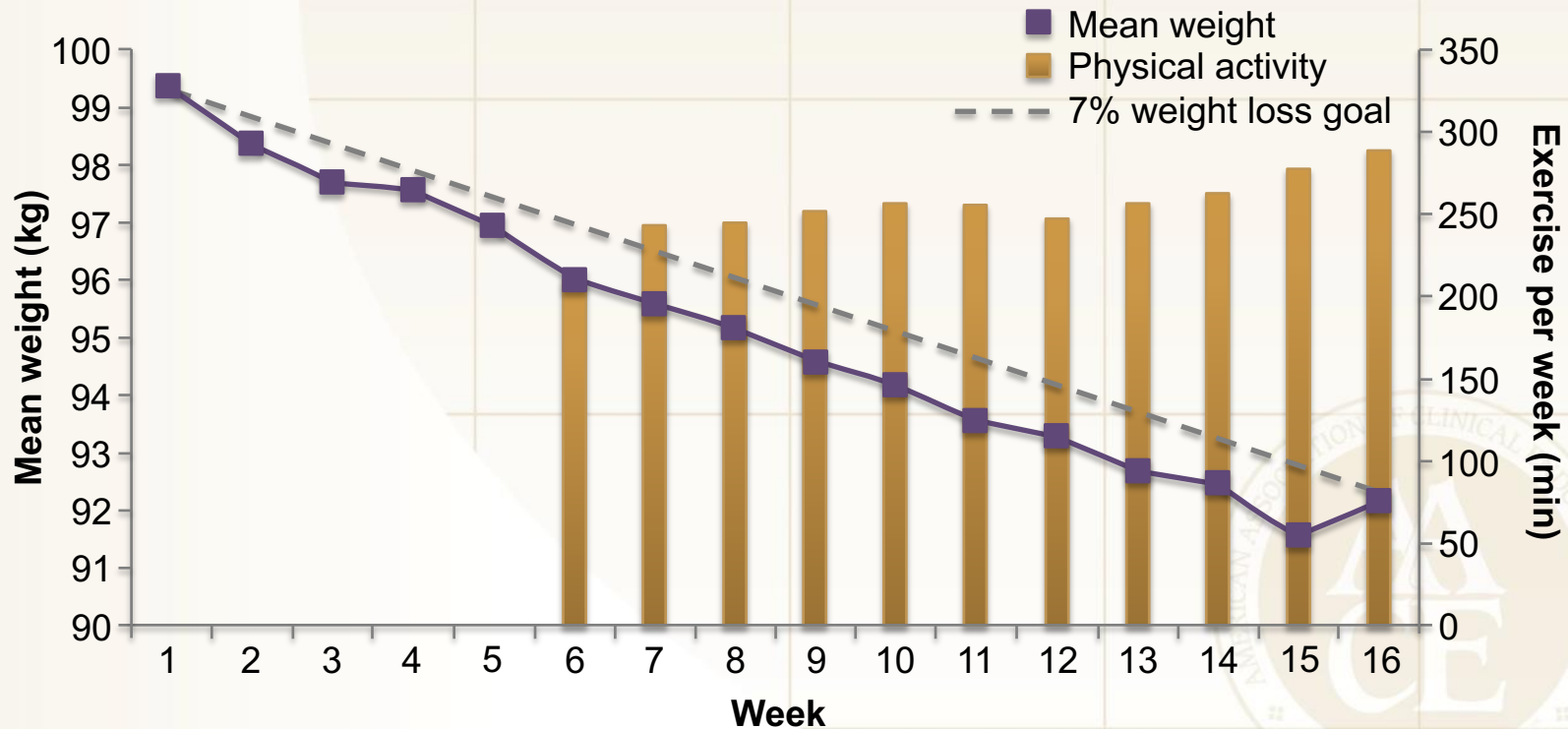


DEPLOY, Diabetes Education & Prevention with a Lifestyle Intervention Offered at the YMCA; DPP, Diabetes Prevention Program; YMCA, Young Men's Christian Association.

Ackermann RT, et al. *Am J Prev Med.* 2008;35:357-363.

# Structured Programs Foster Adherence

**Montana Diabetes Control Program**  
16-session program based on DPP-style intervention  
(N=355)



DPP, Diabetes Prevention Program.

Amundson HA, et al. *Diabetes Educ.* 2009;35:209-223.

**Prediabetes Management**

**PREVENTION OF DIABETES:  
PHARMACOTHERAPY AND  
SURGICAL STUDIES**



# Medical and Surgical Interventions Shown to Delay or Prevent T2D

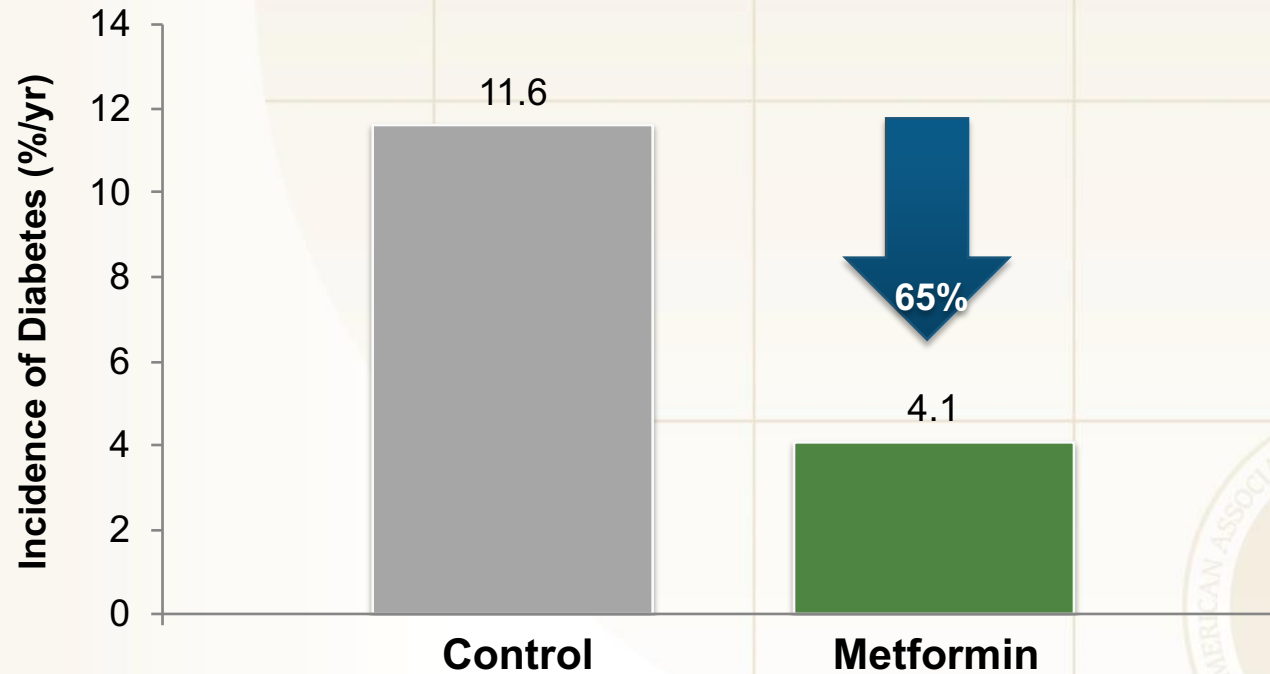
Intervention	Follow-up Period	Reduction in Risk of T2D (P value vs placebo)
Antihyperglycemic agents		
Metformin <sup>1</sup>	2.8 years	31% ( $P<0.001$ )
Acarbose <sup>2</sup>	3.3 years	25% ( $P=0.0015$ )
Pioglitazone <sup>3</sup>	2.4 years	72% ( $P<0.001$ )
Rosiglitazone <sup>4</sup>	3.0 years	60% ( $P<0.0001$ )
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

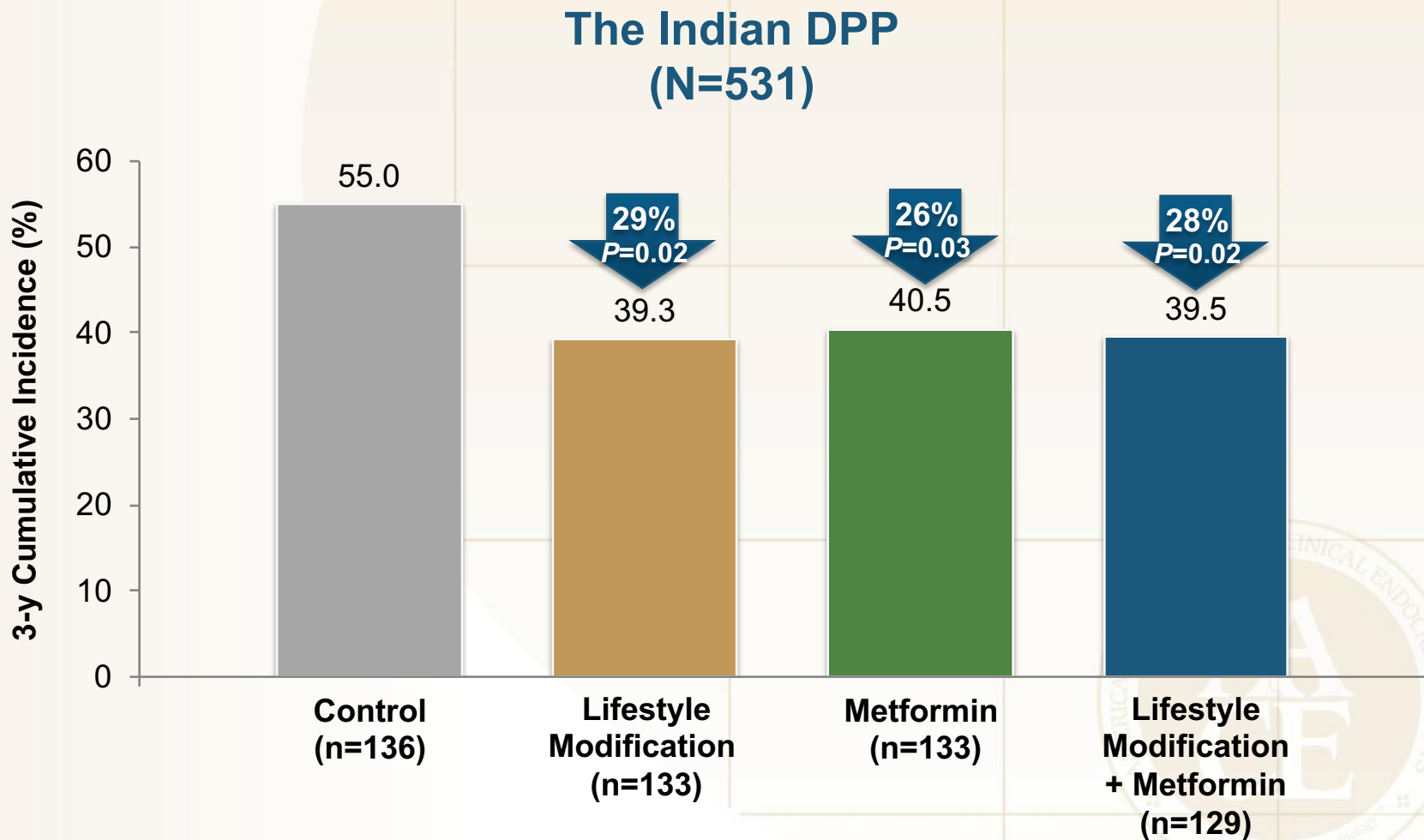
The Chinese Prevention Study  
(N=321)



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

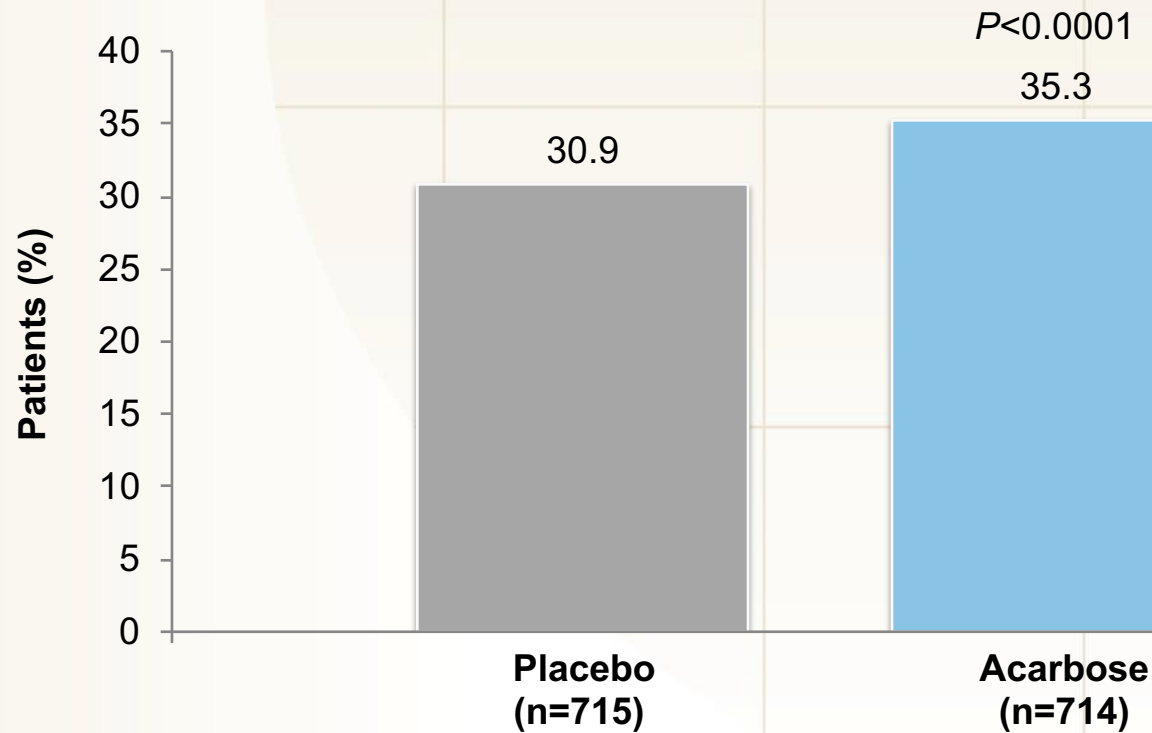


DPP, Diabetes Prevention Program; LSM, lifestyle modification; MET, metformin; RRR, relative risk reduction.

Ramachandran A, et al. *Diabetologia*. 2006;49:289-297.

# Effect of Acarbose on Reversion of IGT to NGT

## STOP-NIDDM



IGT, impaired glucose tolerance; NGT, normal glucose tolerance; STOP-NIDDM, Study to Prevent Non-Insulin Dependent Diabetes Mellitus.

Chiasson JL, et al. *Lancet*. 2002;359:2072-2077.



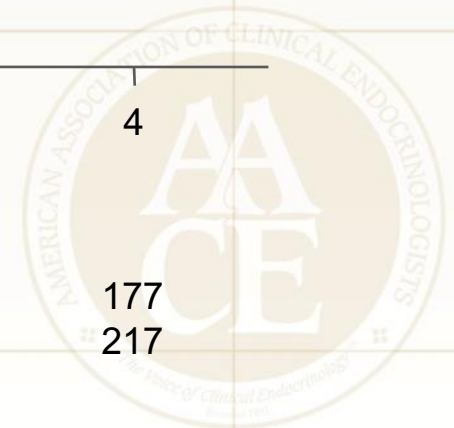
# Effect of Rosiglitazone on New-Onset Diabetes or Death in Patients with Prediabetes



No. at risk

Placebo	2634	2470	2150	1148
Rosiglitazone	2635	2538	2414	1310

177  
217



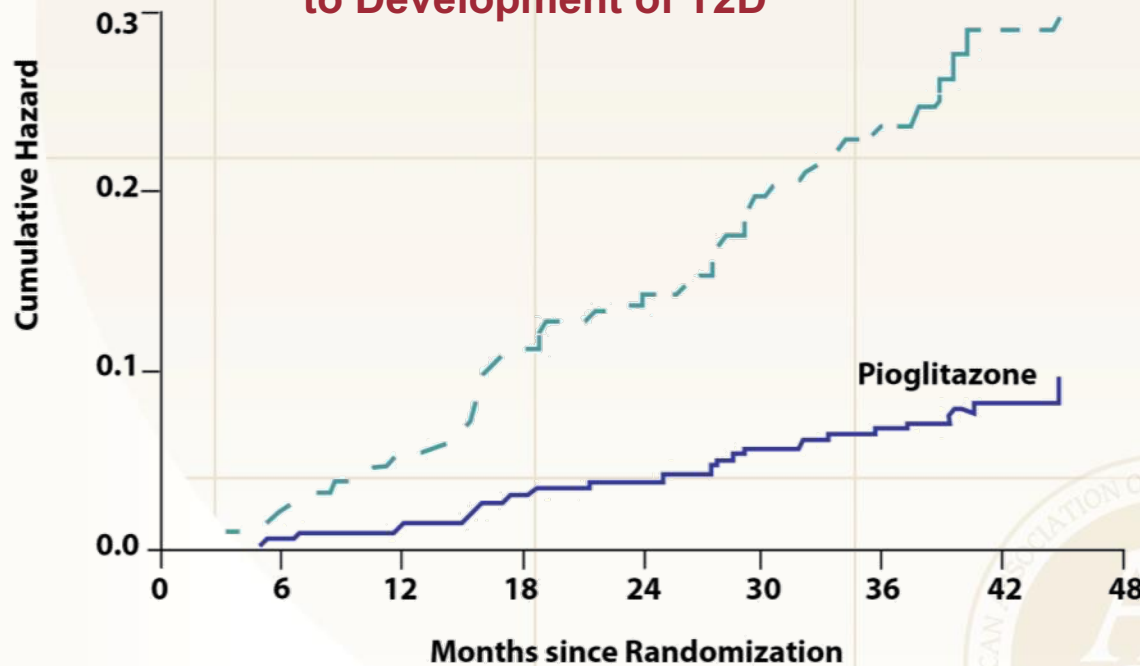
DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication.

DREAM Trial Investigators. *Lancet*. 2006;368:1096-1105.

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

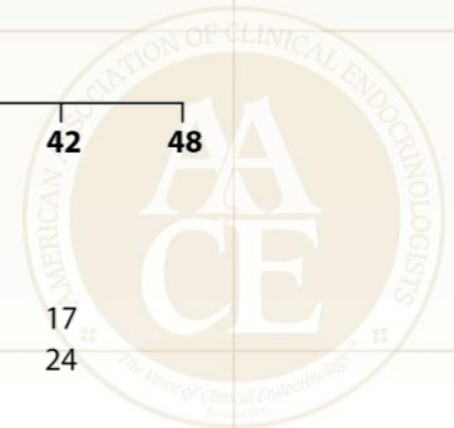
## ACT NOW

Kaplan-Meier plot of Hazard Ratios for Time to Development of T2D



### No. at Risk

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



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.

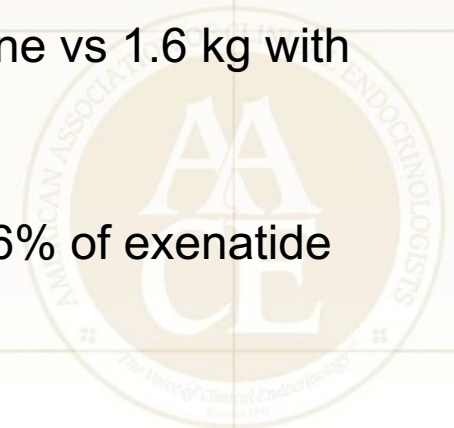
# Special Considerations for Thiazolidinedione Use in Patients With Prediabetes

- 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



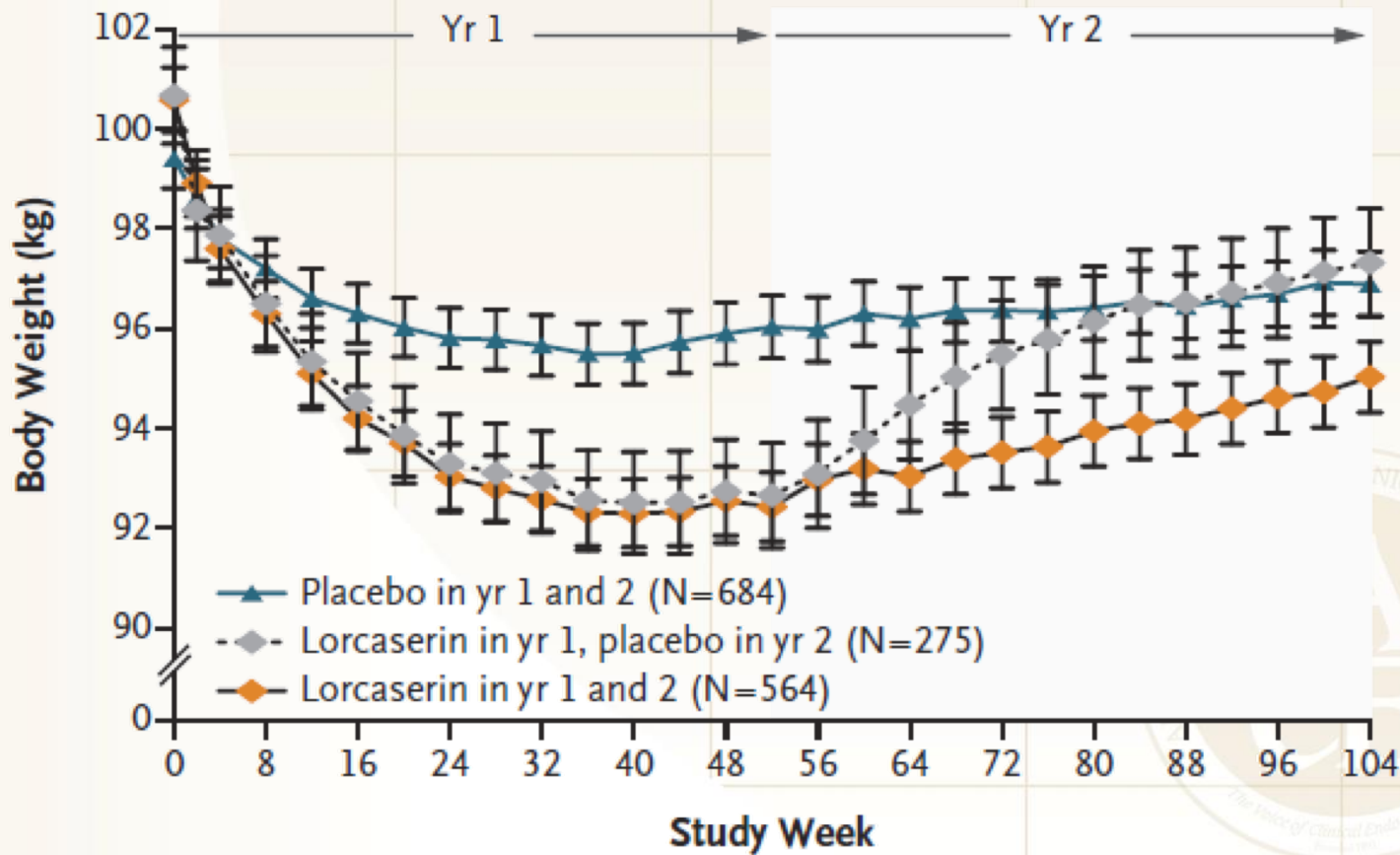
# Effects of Exenatide and Lifestyle Modification on Body Weight and Glucose Tolerance in Obese Patients With and Without Prediabetes

- 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



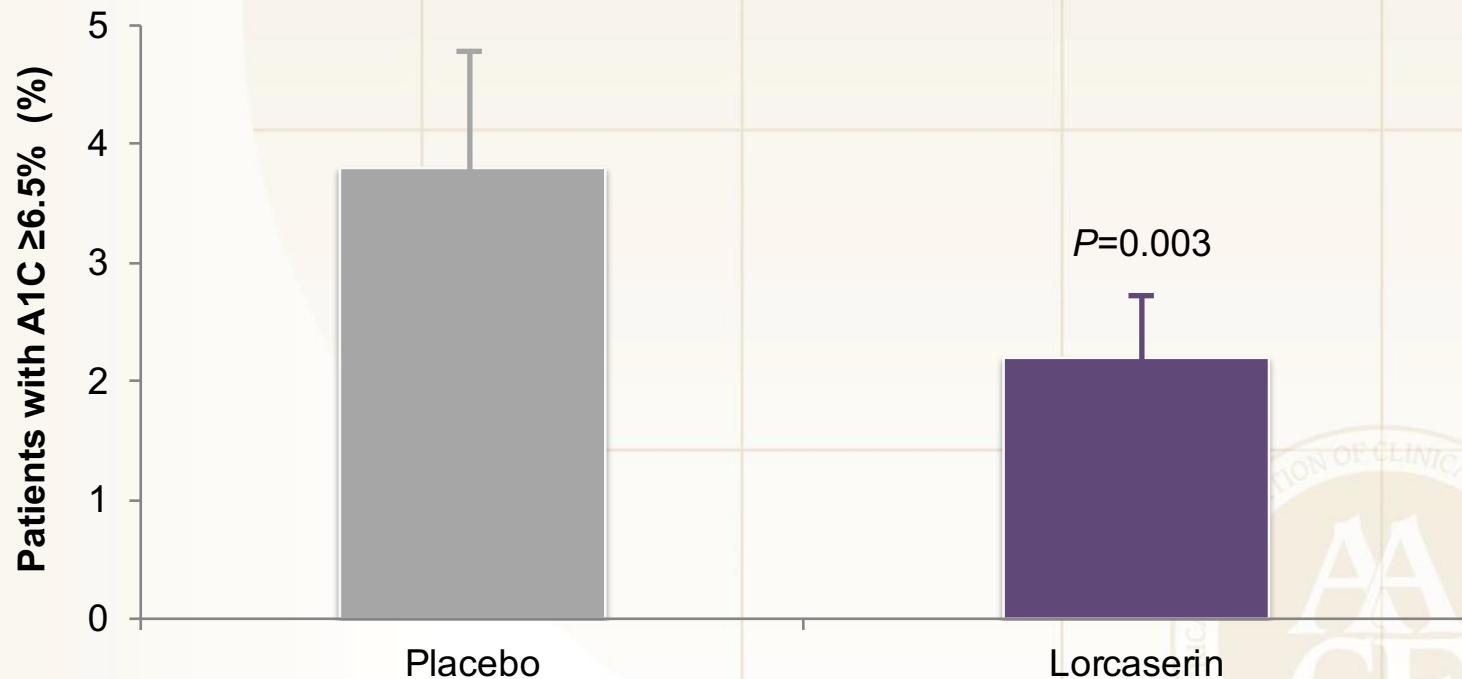
# Effect of Lorcaserin on Body Weight in Obese Adults Over 2 Years

## BLOOM Study



# Effect of Lorcaserin on Progression to T2D

Proportion of BLOOM and BLOSSOM Patients With Newly Diagnosed Diabetes After 52 Weeks of Treatment



T2D, type 2 diabetes.

Lorcaserin hydrochloride briefing document for FDA Advisory Committee. Woodcliff Lake, NJ: Eisai Inc.; 2012. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM303200.pdf>.

# Effect of Lorcaserin on Cardiometabolic Risk Markers

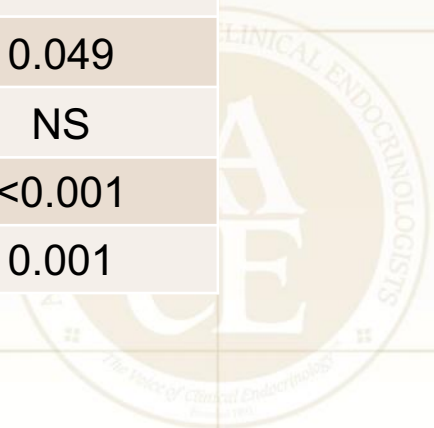
## BLOOM Study

Risk Factors (Mean % Weight Loss)	Lorcaserin 10 mg (5.8%)		P value*
Systolic BP, mmHg	↓	-1.4	0.04
Diastolic BP, mmHg	↓	-1.1	0.01
Triglycerides, %	↓	-6.15	<0.001
Total cholesterol, %	↓	-0.90	0.001
LDL-C, %	↑	2.87	0.049
HDL-C, %	↑	0.05	NS
hsCRP, mg/L	↓	-1.19	<0.001
Fibrinogen, mg/dL	↓	-21.5	0.001

\*P values represent comparisons to placebo.

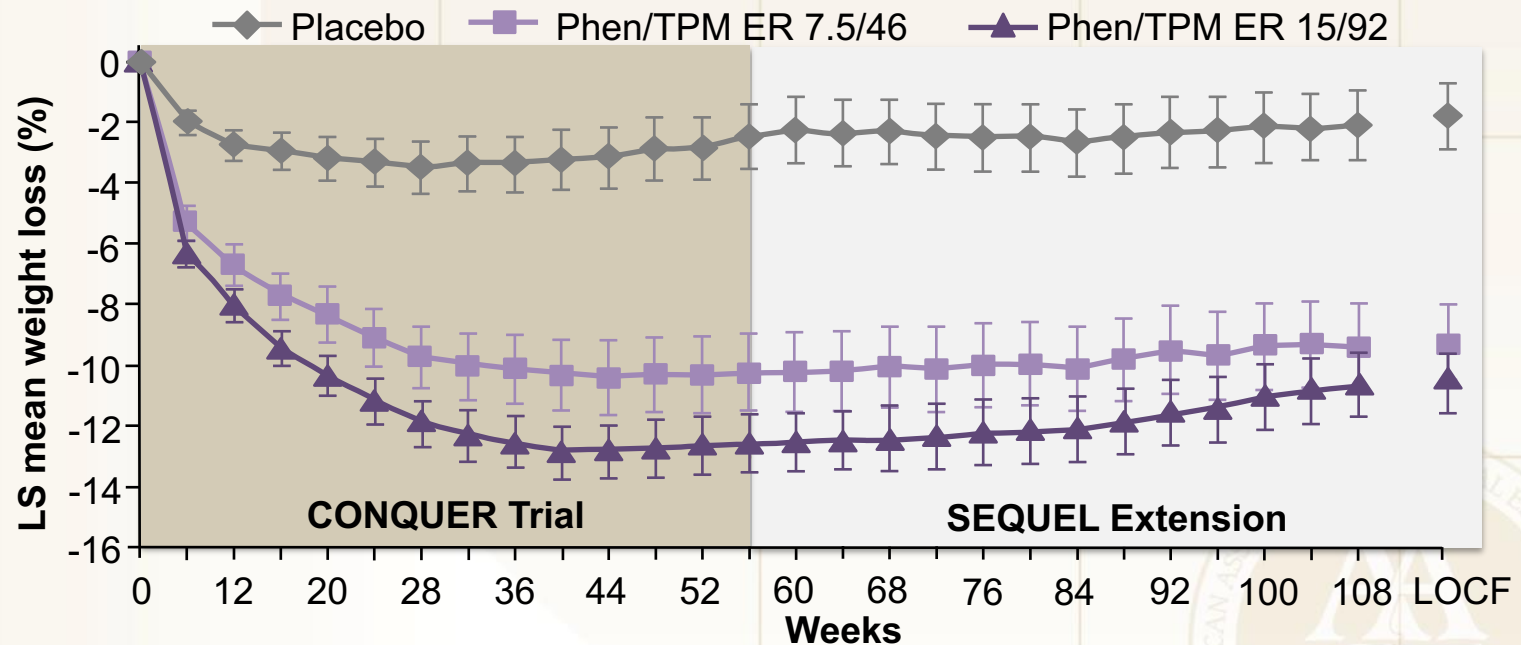
Intent to treat, last observation carried forward analysis for total study population.

Smith SR, et al. *N Engl J Med*. 2010;363:245-256.



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

## SEQUEL Study (Completer Analysis)



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.

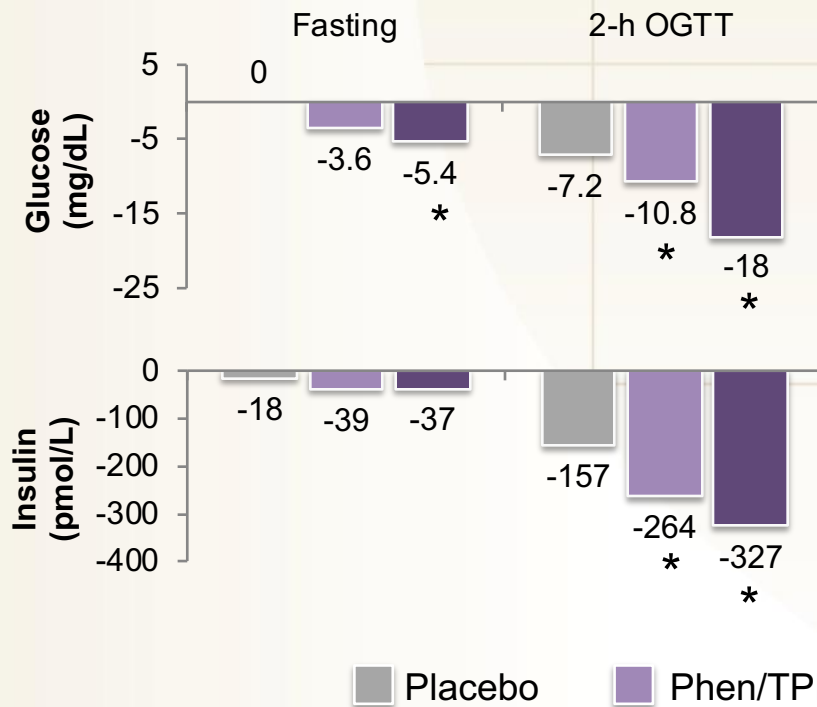
Garvey WT, et al. *Am J Clin Nutr.* 2012;95:297-308.



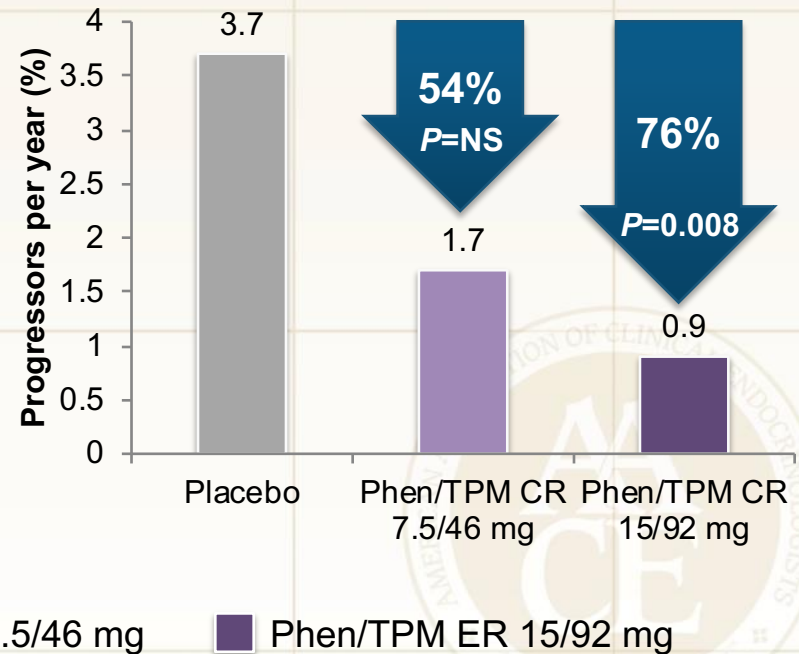
# Effects of Phentermine/Topiramate ER on Glucose, Insulin, and Progression to T2D

## SEQUEL Study (N=675)

### Glucose and Insulin



### Annualized Incidence of T2D



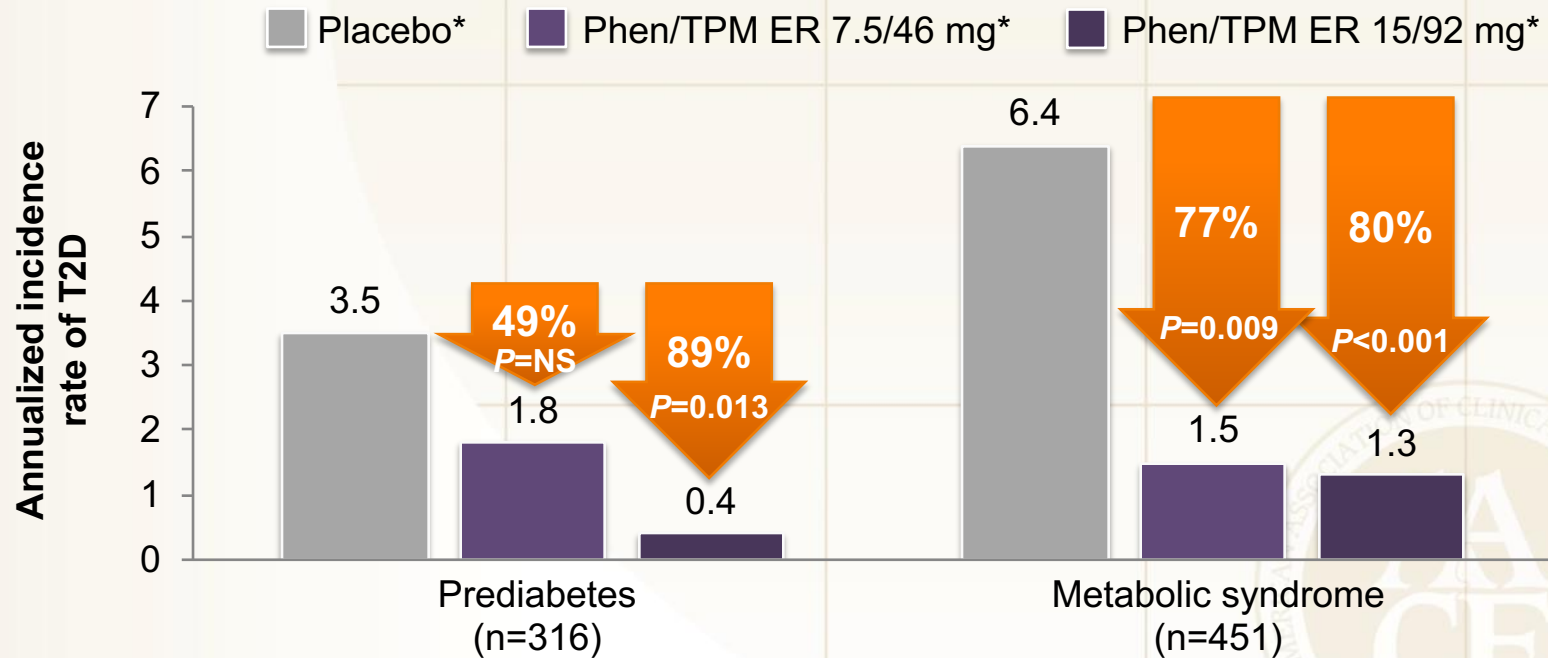
\*P<0.005 vs placebo.

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.

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

## SEQUEL Prediabetes/Metabolic Syndrome Cohort (N=475)



\*All groups had lifestyle intervention.

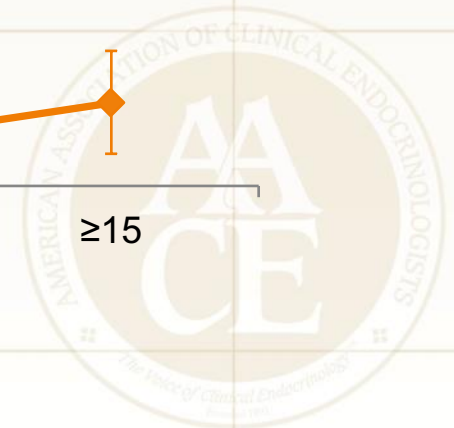
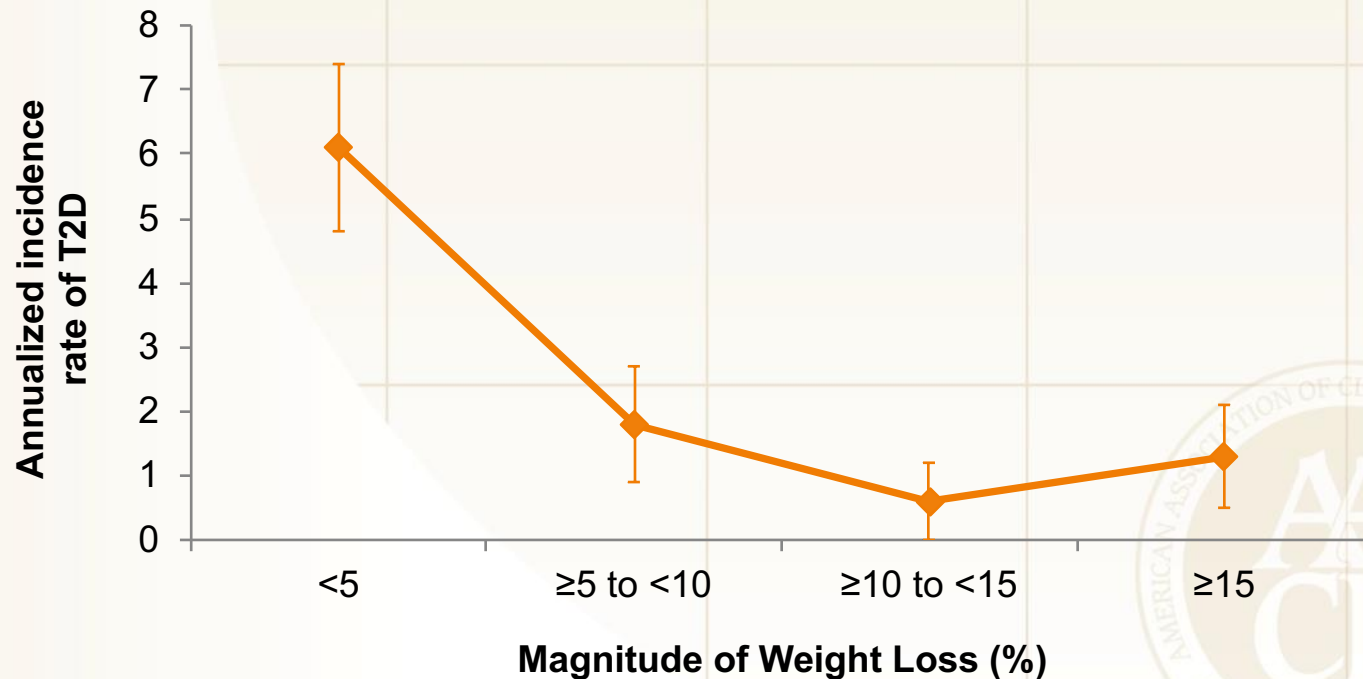
NS, not significant; Phen/TPM ER, phentermine/topiramate extended release; T2D, type 2 diabetes.

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

# Relationship Between Weight Loss and Prevention of Type 2 Diabetes

**SEQUEL Prediabetes/Metabolic Syndrome Cohort  
(N=475)**

**ITT-LOCF Analysis**



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

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

# Effect of Phentermine/Topiramate ER on Cardiometabolic Risk Markers

## CONQUER Study

Risk Factors (Mean % Weight Loss)	Phentermine/ Topiramate ER 7.5/46 mg (8.4%)	P value*	Phentermine/ Topiramate ER 15/92 mg (10.4%)	P value*
Systolic BP, mmHg	↓ -4.7	0.0008	↓ -5.6	<0.0001
Diastolic BP, mmHg	↓ -3.4	NS	↓ -3.8	0.0031
Triglycerides, %	↓ -8.6	<0.0001	↓ -10.6	<0.0001
Total cholesterol, %	↓ -4.9	0.0345	↓ -6.3	<0.0001
LDL-C, %	↓ -3.7	NS	↓ -6.9	0.0069
HDL-C, %	↑ 5.2	<0.0001	↑ 6.8	<0.0001
hsCRP, mg/L	↓ -2.49	<0.0001	↓ -2.49	<0.0001
Adiponectin, µg/mL	↑ 1.40	<0.0001	↑ 2.08	<0.0001

\*P values represent comparisons to placebo.

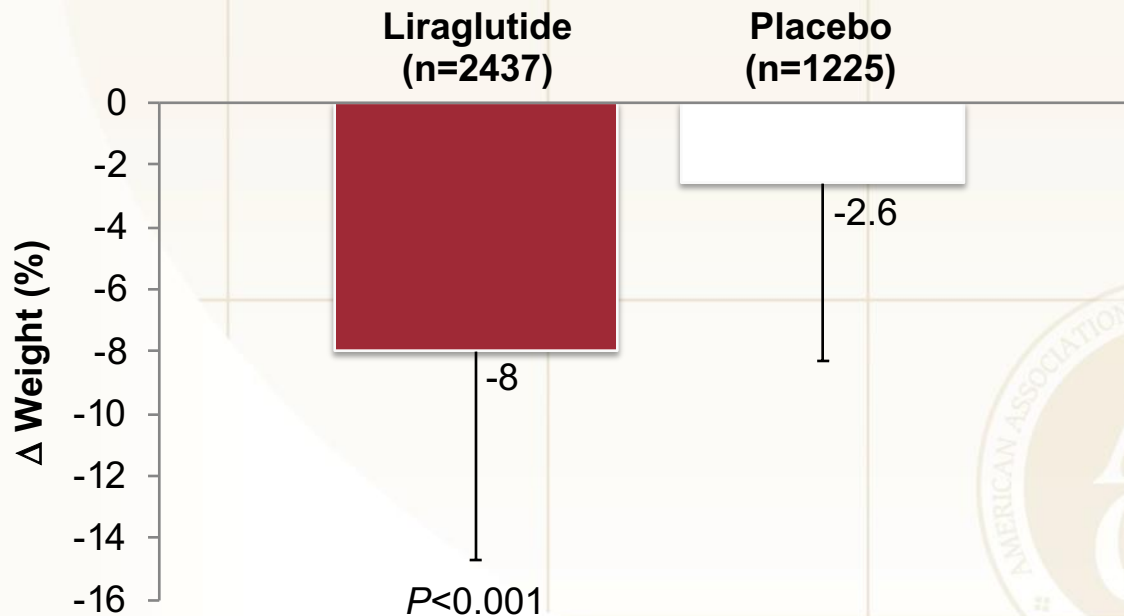
Intent to treat, last observation carried forward analysis for total study population.

Gadde KM, et al. *Lancet*. 2011;377:1341-1352.

# Effects of Liraglutide in Obese Patients

**SCALE Obesity  
(N=3731)**

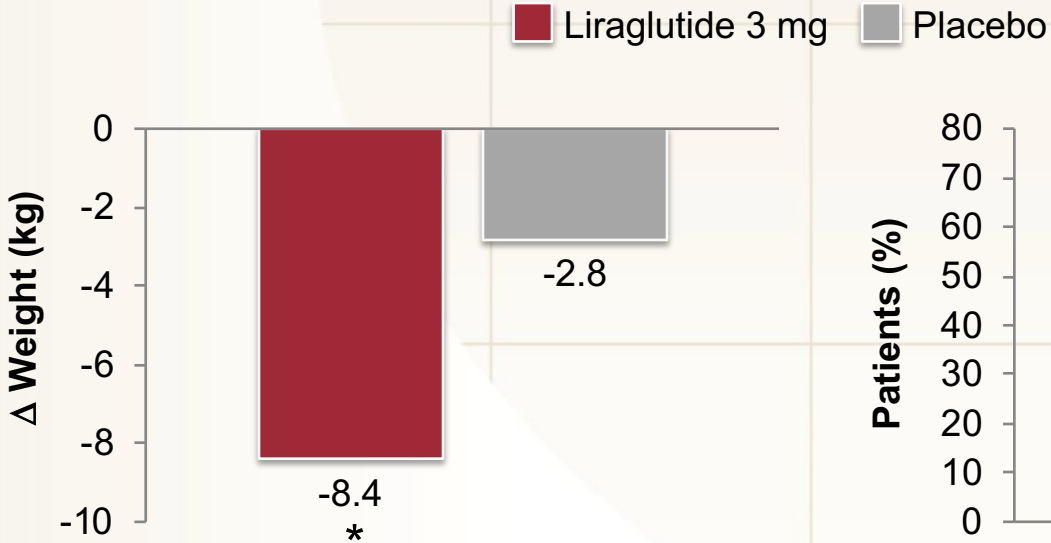
**Weight Change After 56 Weeks**



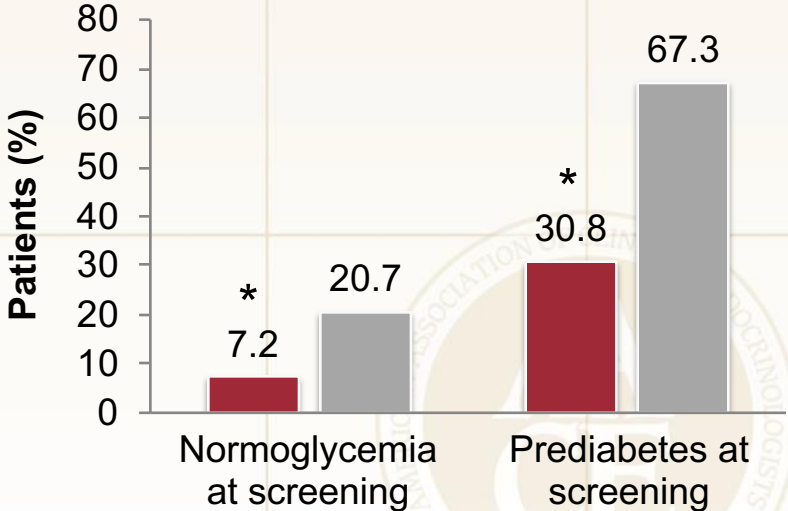
# Effects of Liraglutide in Obese Patients with Prediabetes

## SCALE Obesity and Prediabetes (N=3731)

### Weight Change After 56 Weeks



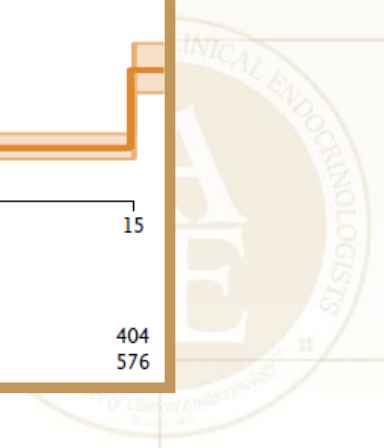
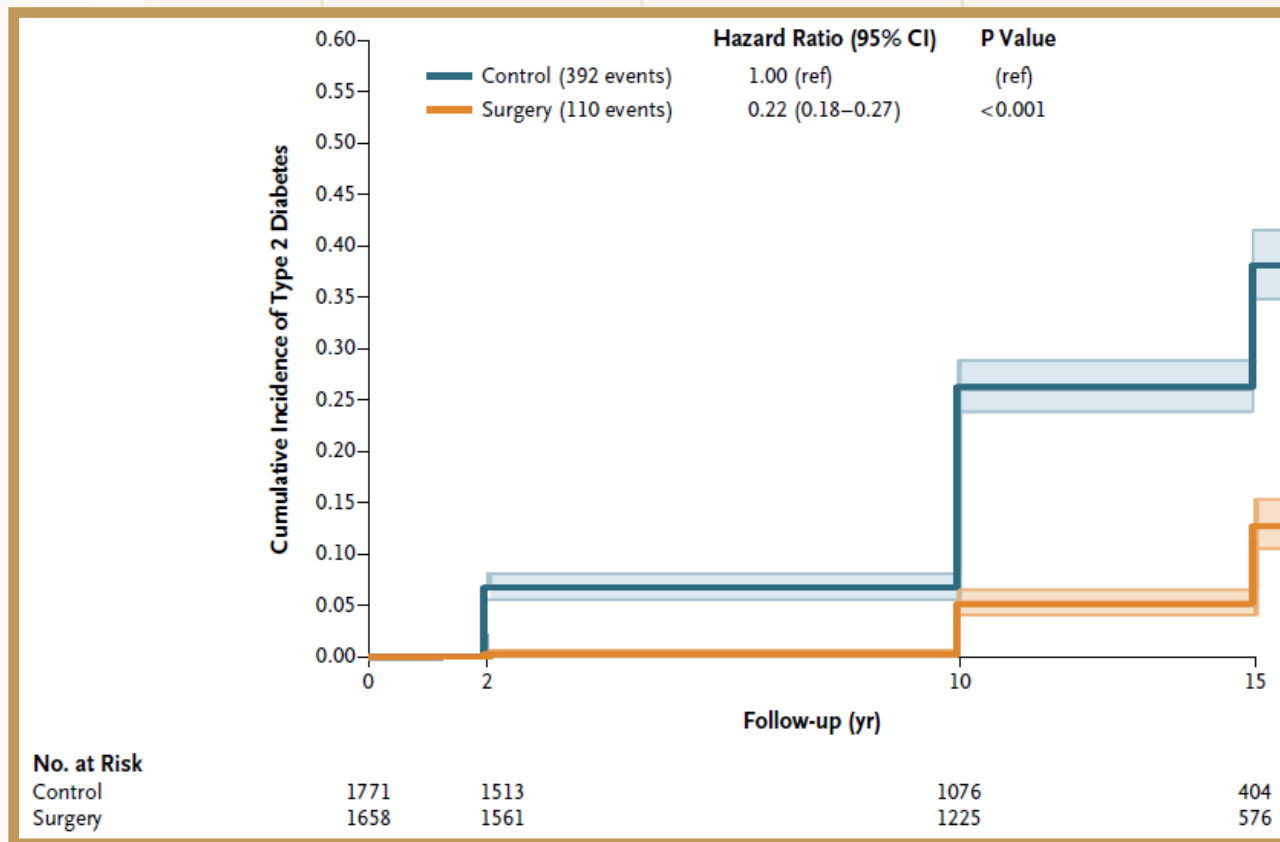
### Patients with Prediabetes After 56 Weeks



\*P<0.001 vs placebo.

# Effect of Bariatric Surgery on Incidence of Type 2 Diabetes

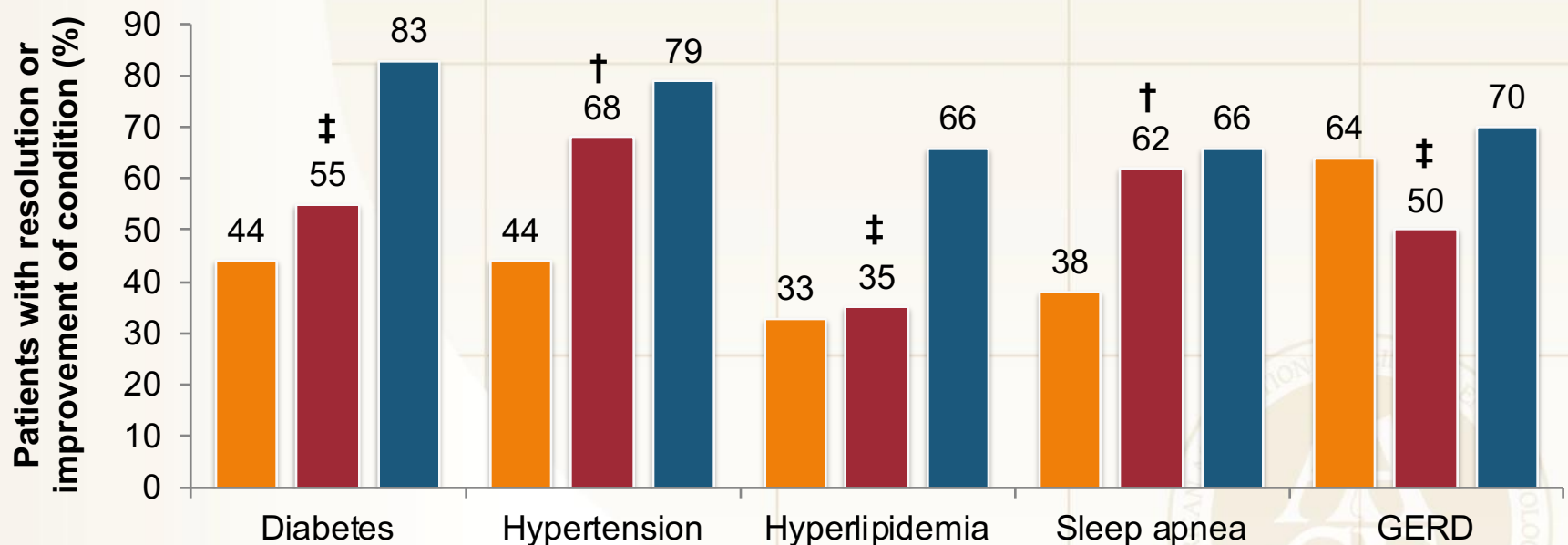
## Swedish Obesity Study



# Effect of Different Bariatric Surgeries on Weight-Related Comorbidities at 1 Year

## ACS Bariatric Surgery Center Network Prospective Observational Study (N=28,616)

LAGB LSG\* LRYGB



\*Small numbers of patients with 1 year of follow-up for all comorbidities (n≤38).

<sup>†</sup>P<0.05 vs LAGB; <sup>‡</sup>P<0.05 vs LRYGB.

ACS, American College of Surgeons; BMI, body mass index; GERD, gastroesophageal reflux disease; LAGB, laparoscopic adjustable gastric band; LSG, laparoscopic sleeve gastrectomy; LRYGB, laparoscopic Roux-en-Y gastric bypass.

Hutter MM, et al. *Ann Surg.* 2011;254:410-420.