Why Do We Treat Obesity?

Metabolic Complications

AACE OBESITY RESOURCE CENTER

AACE ONLINE ENDOCRINE ACADEMY
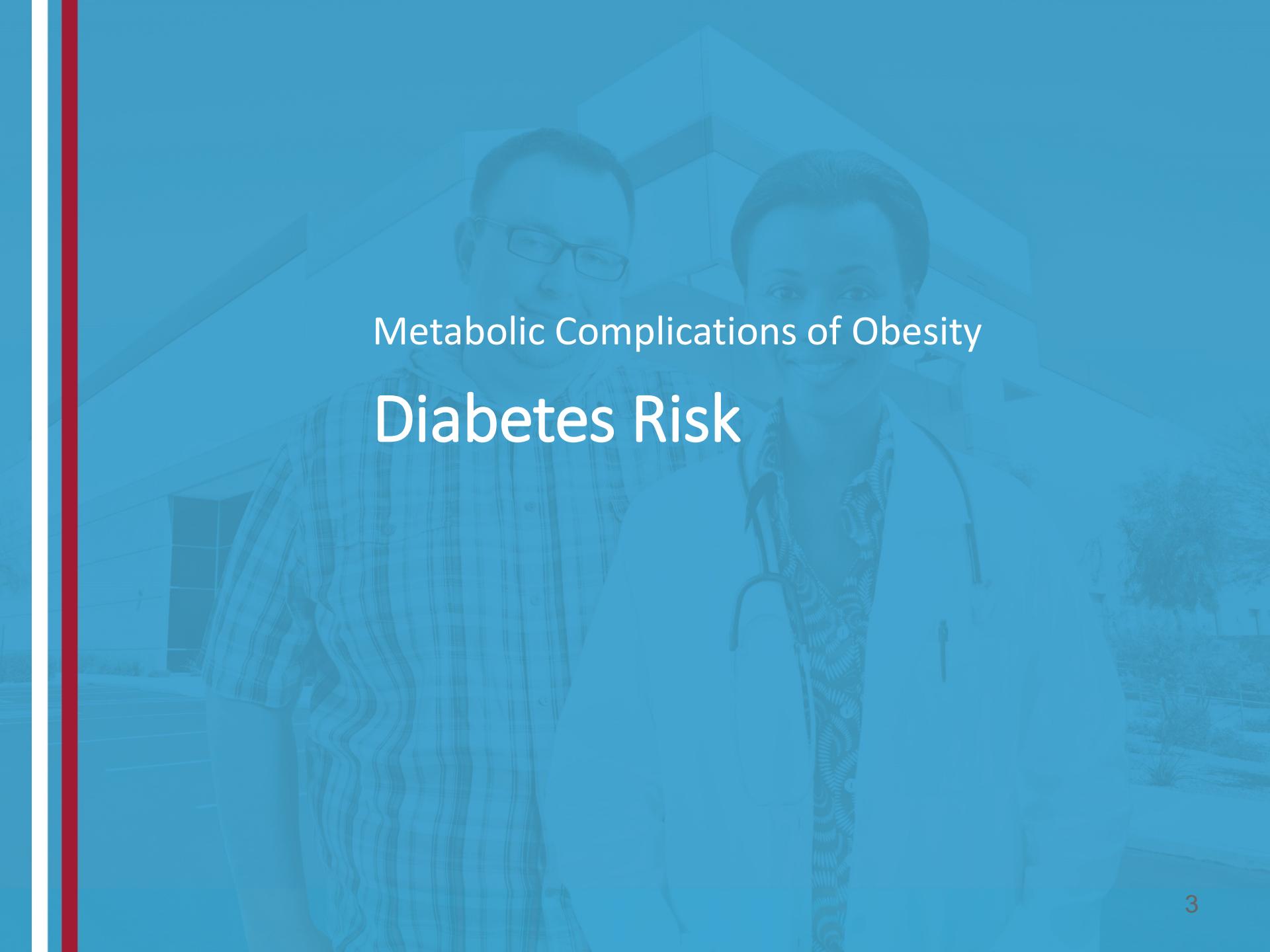
3. Treatment Based on Clinical Judgment

TREATMENT GOALS BASED ON DIAGNOSIS IN THE MEDICAL MANAGEMENT OF PATIENTS WITH OBESITY

		DIAGNOSIS		TREATMENT GOALS	
	Anthropometric Component	Clinical Component		Intervention/ Weight-Loss Goal	Clinical Goals
TERTIARY PREVENTION					
Overweight or Obesity	BMI ≥25 (≥23 in certain ethnicities)	Metabolic syndrome		10%	Prevention of T2D
		Prediabetes		10%	Prevention of T2D
		T2D		5% to ≥15%	• Reduction in A1C • Reduction in number and/or doses of glucose lowering medications • Diabetes remission especially when diabetes duration is short
		Nonalcoholic fatty liver disease	Steatosis	5% or more	Reduction in intrahepatocellular lipid
			Steatohepatitis	10% to 40%	Reduction in inflammation and fibrosis

Metabolic Complications of Obesity

Diabetes Risk

Criteria for Diagnosis of the Metabolic Syndrome

Characteristic	Cut Point
Waist circumference	Population or country-specific definitions United States: Men: ≥102 cm (40.2 in) Women: ≥88 cm (34.6 in)
Triglycerides	≥150 mg/dL or drug therapy* for hypertriglyceridemia
HDL-C	Men: <40 mg/dL Women: <50 mg/dL or drug therapy* for low HDL-C
Blood pressure	Systolic: ≥130 mmHg Diastolic: ≥85 mmHg or antihypertensive drug therapy/history of hypertension
Fasting glucose	≥100 mg/dL or drug therapy for hyperglycemia

*Fibrates or nicotinic acid.
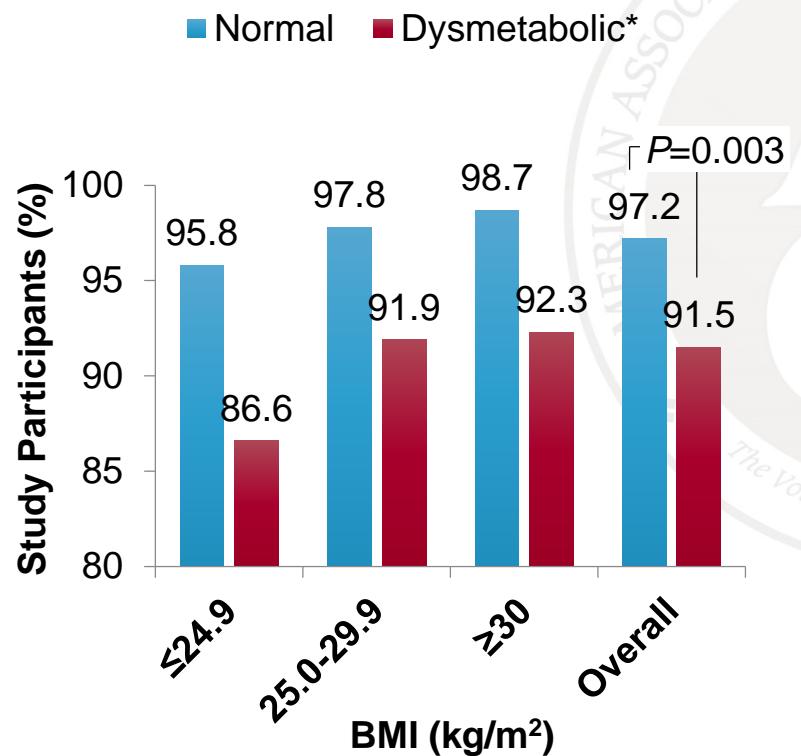
HDL-C = high-density lipoprotein cholesterol.
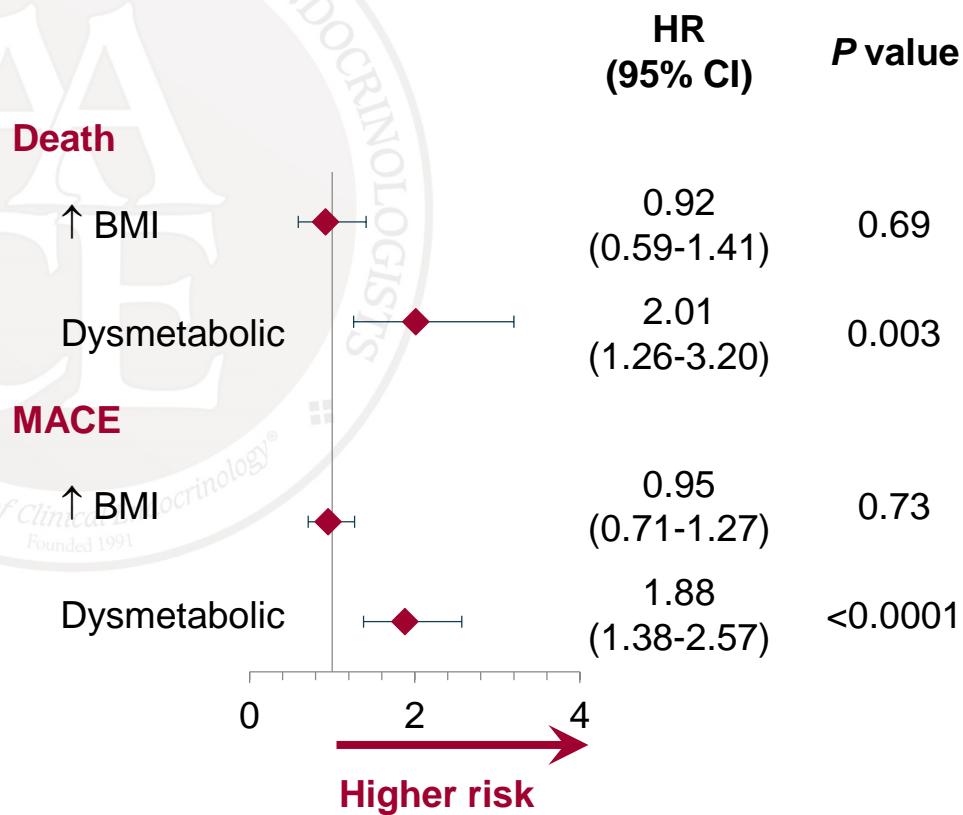
Metabolic Syndrome Is More Important Than Obesity in Terms of Cardiovascular Risk

Women's Ischemia Syndrome Evaluation (WISE) Study

3-Year Survival

■ Normal ■ Dysmetabolic*

P=0.003

Study Participants (%)

BMI (kg/m²)	Normal	Dysmetabolic*
≤24.9	95.8	86.6
25.0-29.9	97.8	91.9
≥30	98.7	92.3
Overall	97.2	91.5

3-Year Risk of Death or MACE

|	HR (95% CI)	P value
Death		
↑ BMI	0.92 (0.59-1.41)	0.69
Dysmetabolic	2.01 (1.26-3.20)	0.003
MACE		
↑ BMI	0.95 (0.71-1.27)	0.73
Dysmetabolic	1.88 (1.38-2.57)	<0.0001

0   2   4

Higher risk
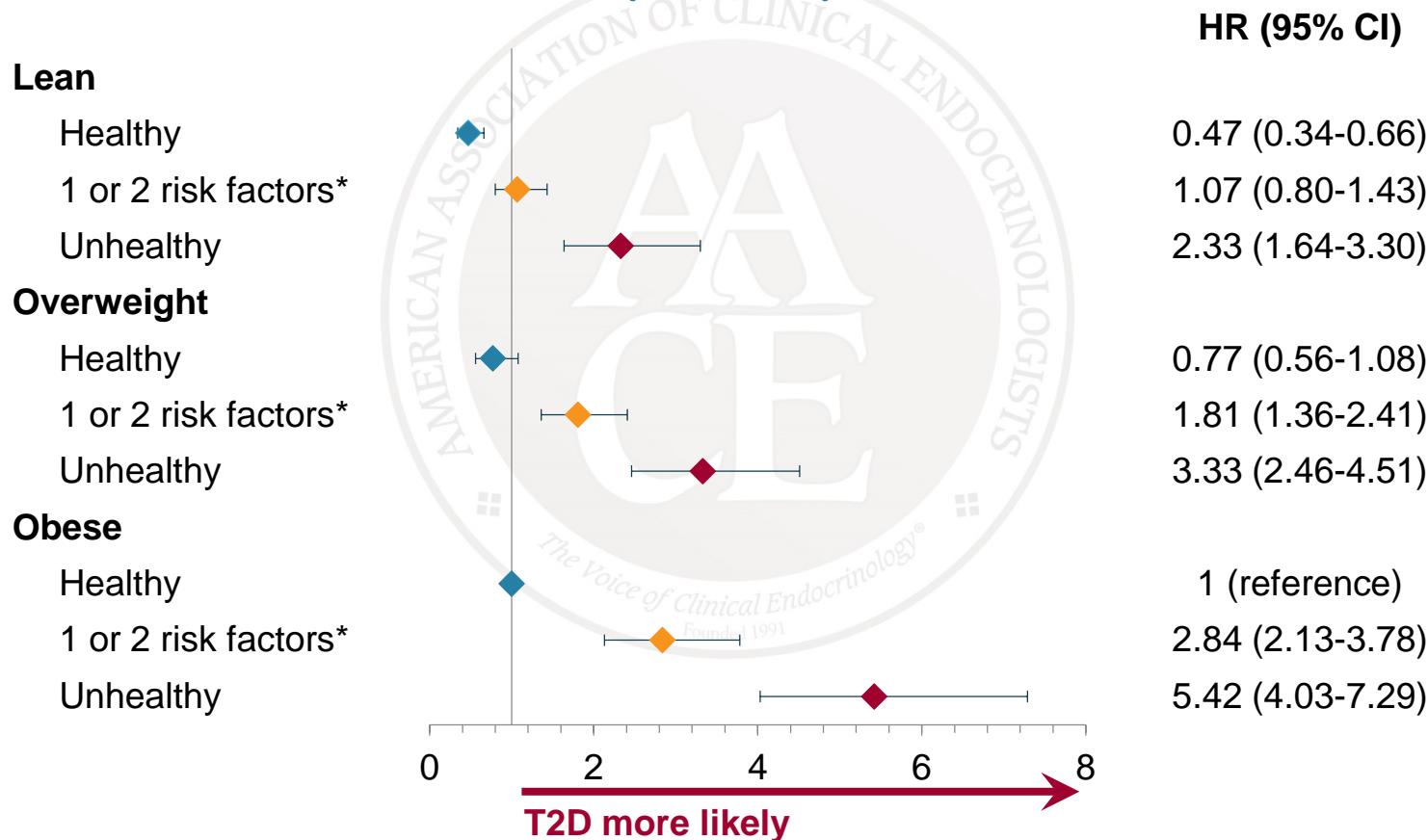
*Metabolic syndrome or diabetes.

MACE = major adverse cardiac event (death, nonfatal myocardial infarction, stroke, congestive heart failure).

Kip KE et al. *Circulation.* 2004;109:706-713.

5

Risk of Developing T2D in Metabolically Healthy vs Unhealthy Individuals

Atherosclerosis Risk in Communities Study
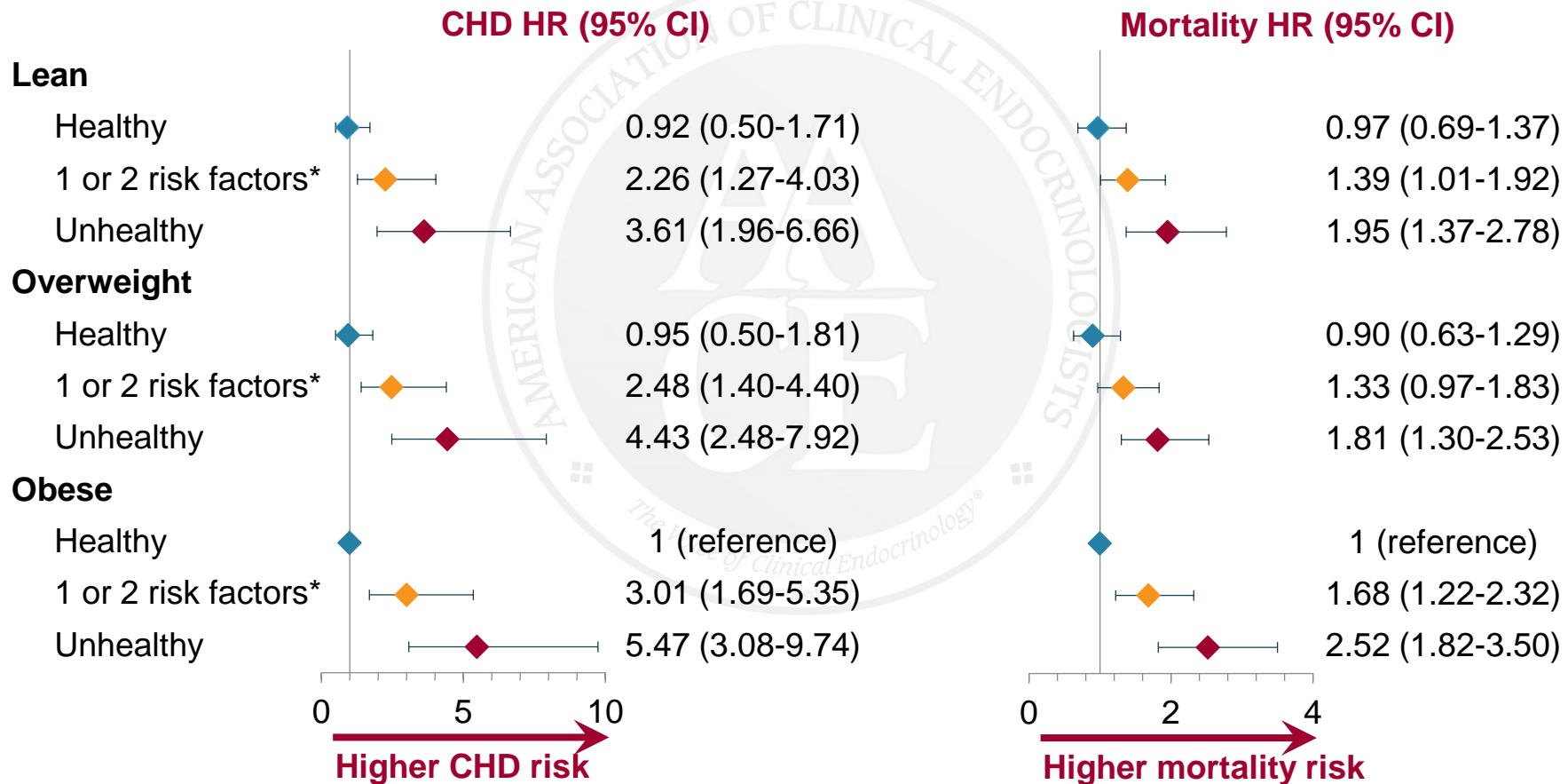
(N=14,685)

HR (95% CI)

Lean

Healthy — 0.47 (0.34-0.66)

1 or 2 risk factors* — 1.07 (0.80-1.43)

Unhealthy — 2.33 (1.64-3.30)

Overweight

Healthy — 0.77 (0.56-1.08)

1 or 2 risk factors* — 1.81 (1.36-2.41)

Unhealthy — 3.33 (2.46-4.51)

Obese

Healthy — 1 (reference)

1 or 2 risk factors* — 2.84 (2.13-3.78)

Unhealthy — 5.42 (4.03-7.29)

0   2   4   6   8

T2D more likely

*Untreated values: BP ≥130/85, fasting glucose ≥100 mg/dL, A1C ≥5.7%, TC ≥240, and/or HDL-C <40 in men or <50 in women.

BP = blood pressure; HDL-C = high density lipoprotein cholesterol; HR = hazard ratio; T2D = type 2 diabetes; TC = total cholesterol.

Guo F, Garvey WT. *Obesity.* 2016;24:516-525.

Risk of CHD or Death in Metabolically Healthy vs Unhealthy

Atherosclerosis Risk in Communities Study (N=14,685)
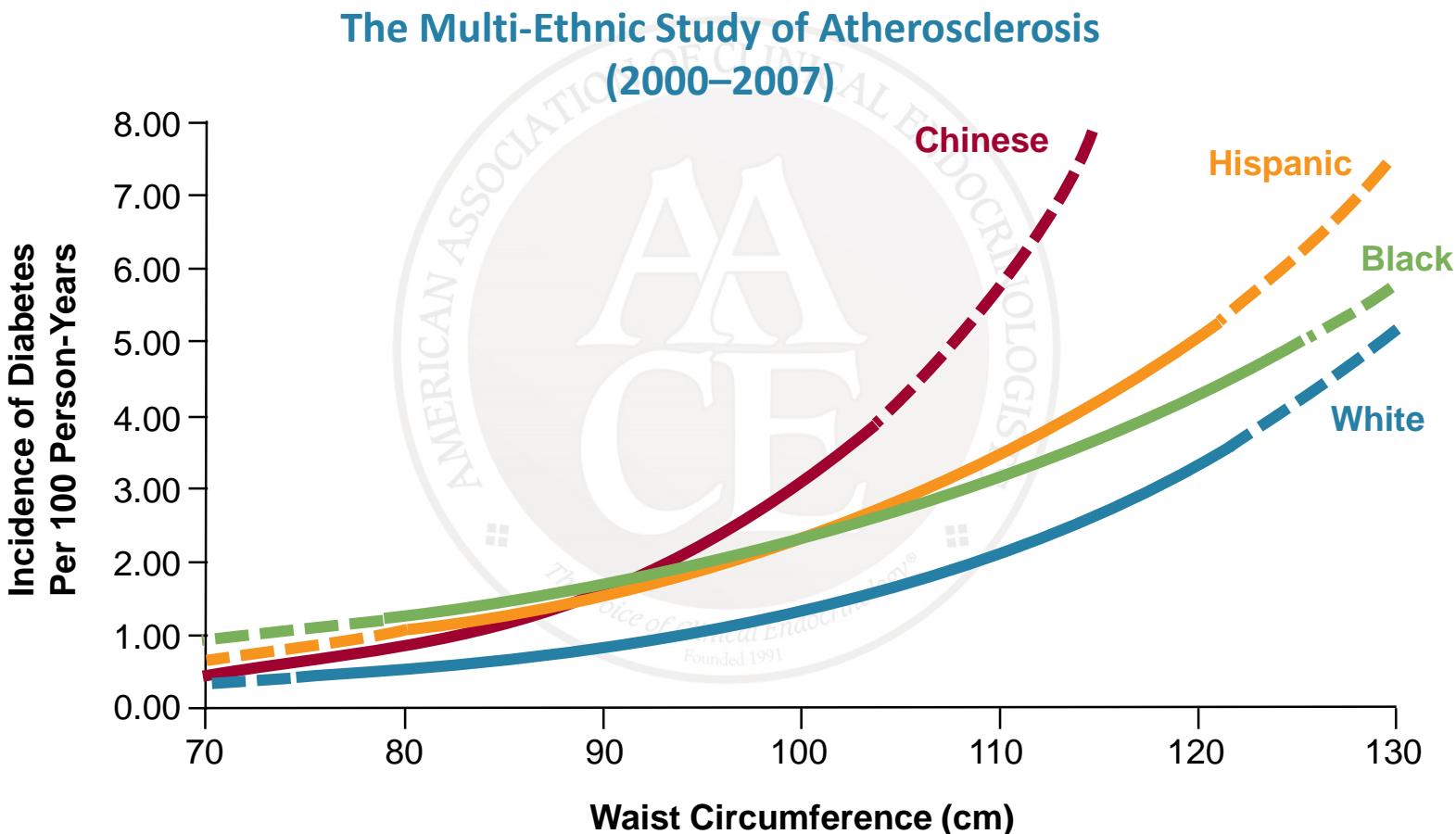
	CHD HR (95% CI)	Mortality HR (95% CI)
Lean		
Healthy	0.92 (0.50-1.71)	0.97 (0.69-1.37)
1 or 2 risk factors*	2.26 (1.27-4.03)	1.39 (1.01-1.92)
Unhealthy	3.61 (1.96-6.66)	1.95 (1.37-2.78)
Overweight		
Healthy	0.95 (0.50-1.81)	0.90 (0.63-1.29)
1 or 2 risk factors*	2.48 (1.40-4.40)	1.33 (0.97-1.83)
Unhealthy	4.43 (2.48-7.92)	1.81 (1.30-2.53)
Obese		
Healthy	1 (reference)	1 (reference)
1 or 2 risk factors*	3.01 (1.69-5.35)	1.68 (1.22-2.32)
Unhealthy	5.47 (3.08-9.74)	2.52 (1.82-3.50)

Higher CHD risk

Higher mortality risk

*Untreated values: BP ≥130/85, fasting glucose ≥100 mg/dL, A1C ≥5.7%, TC ≥240, and/or HDL-C <40 in men or <50 in women.

BP = blood pressure; CHD = coronary heart disease; HDL-C = high density lipoprotein cholesterol; HR = hazard ratio; TC = total cholesterol.

Guo F, Garvey WT. *Obesity.* 2016;24:516-525.

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Incidence Rates of Diabetes by Waist Circumference and Race/Ethnicity

**The Multi-Ethnic Study of Atherosclerosis (2000–2007)**
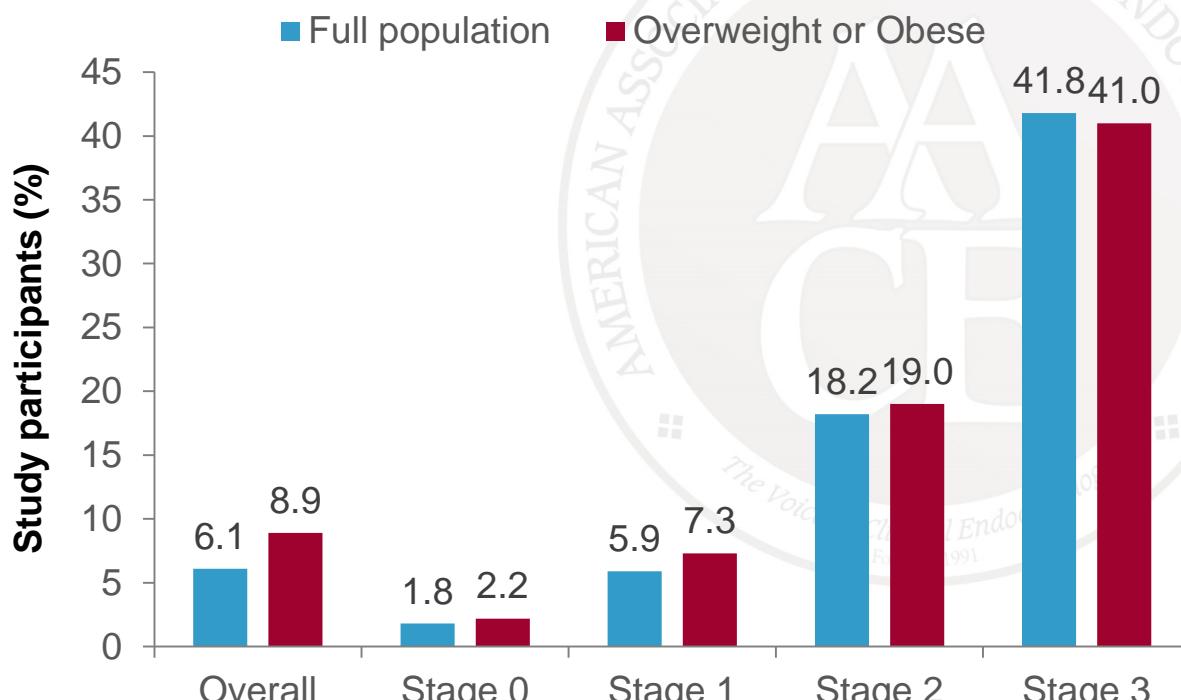
Solid lines pertain to values between the race-specific 5th and 95th percentiles of waist circumference. Dotted lines are extrapolated values outside the aforementioned race-specific ranges. Adjusted for age, sex, education, and income.

Lutsey PL, et al. *Am J Epidemiol.* 2010;172:197-204.

10-Year Incidence of T2D as a Function of Increasing CMDS Risk Stage

CARDIA Study Cohort (N=3315)

Bar chart legend: ■ Full population ■ Overweight or Obese

Y-axis: Study participants (%)

Category	Full population	Overweight or Obese
Overall	6.1	8.9
Stage 0	1.8	2.2
Stage 1	5.9	7.3
Stage 2	18.2	19.0
Stage 3	41.8	41.0

Stage	Criteria
0	**No risk factors**
1	**1 or 2 risk factors** Waist circumference, blood pressure, triglycerides, HDL-C
2	**Metabolic syndrome or prediabetes** Metabolic syndrome alone, or IFG, or IGT
3	**Metabolic syndrome plus prediabetes** 2 or more out of 3: metabolic syndrome, IFG, IGT
4	**End-stage cardiometabolic disease** T2D and/or CVD

CARDIA = Coronary Artery Risk Development in Young Adults; CMDS = cardiometabolic disease staging; CVD = cardiovascular disease; HDL-C = high density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; T2D = type 2 diabetes.
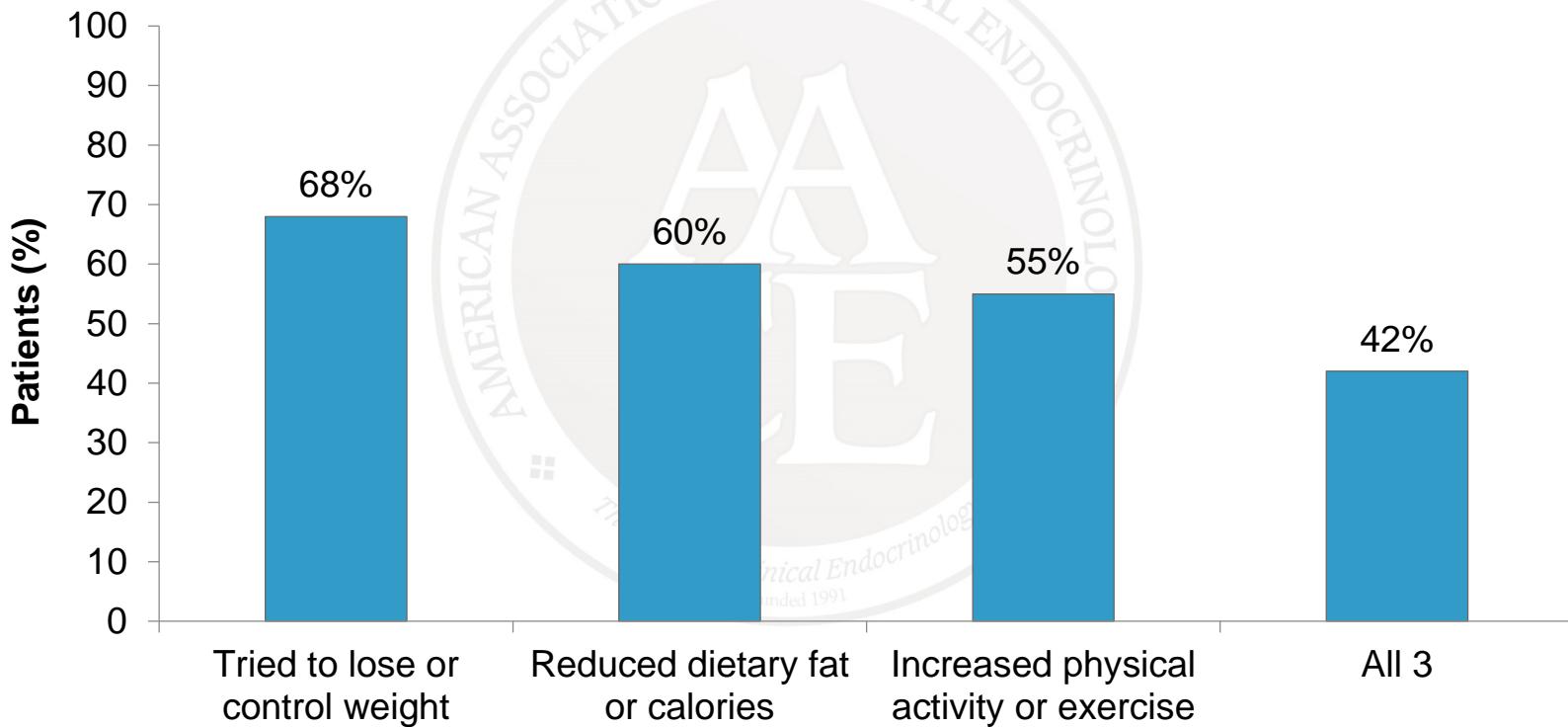
Guo F, et al. *Obesity*. 2014;22:110-118.

Metabolic Complications of Obesity

Prevention of Diabetes: Lifestyle Studies

Self-Reported Risk Reduction Activities in Patients With Prediabetes

National Health and Nutrition Examination Survey

Bar chart showing Patients (%) on the y-axis (0 to 100):
- Tried to lose or control weight: 68%
- Reduced dietary fat or calories: 60%
- Increased physical activity or exercise: 55%
- All 3: 42%

CDC. *MMWR Morb Mortal Wkly Rep*. 2008;57:1203-1205.

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

Garber AJ, et al. *Endocr Pract.* 2008;14:933-946.
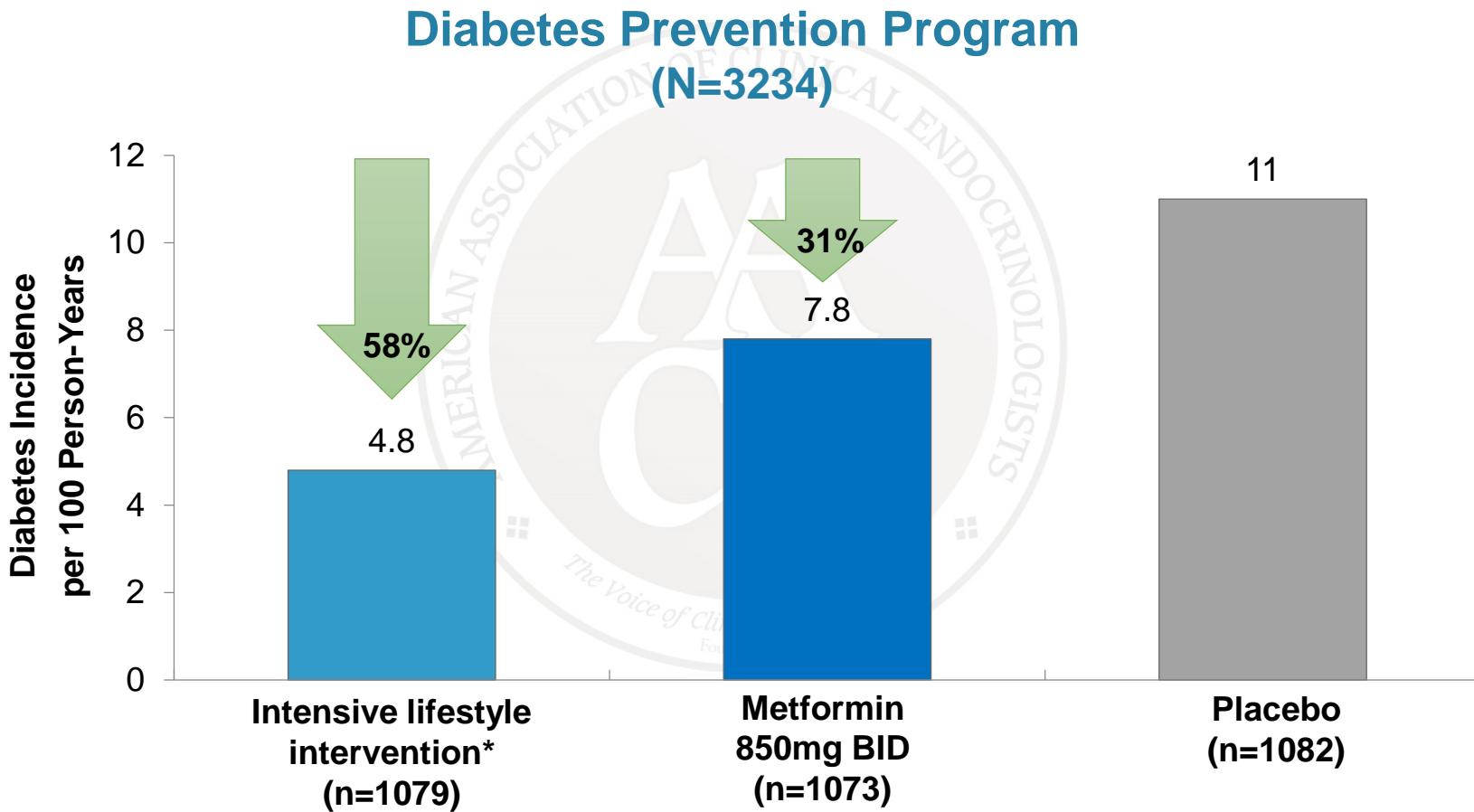
Prevention of T2D:
Selected Lifestyle Modification Trials

Study	Country	N	Baseline BMI (kg/m²)	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
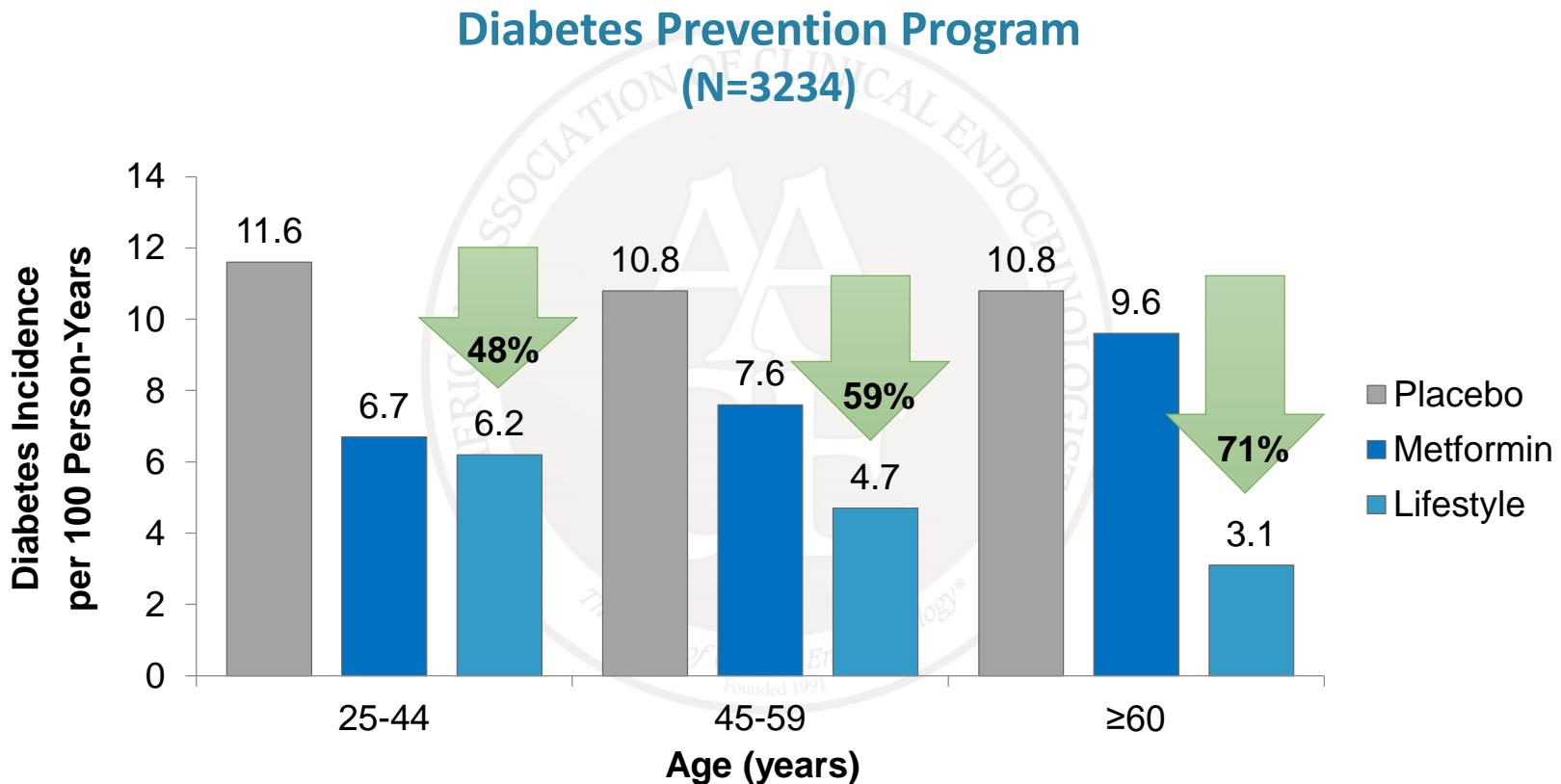
Diabetes Prevention Program
(N=3234)

*Goal: 7% reduction in baseline body weight through low-calorie, low-fat diet and ≥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.

14
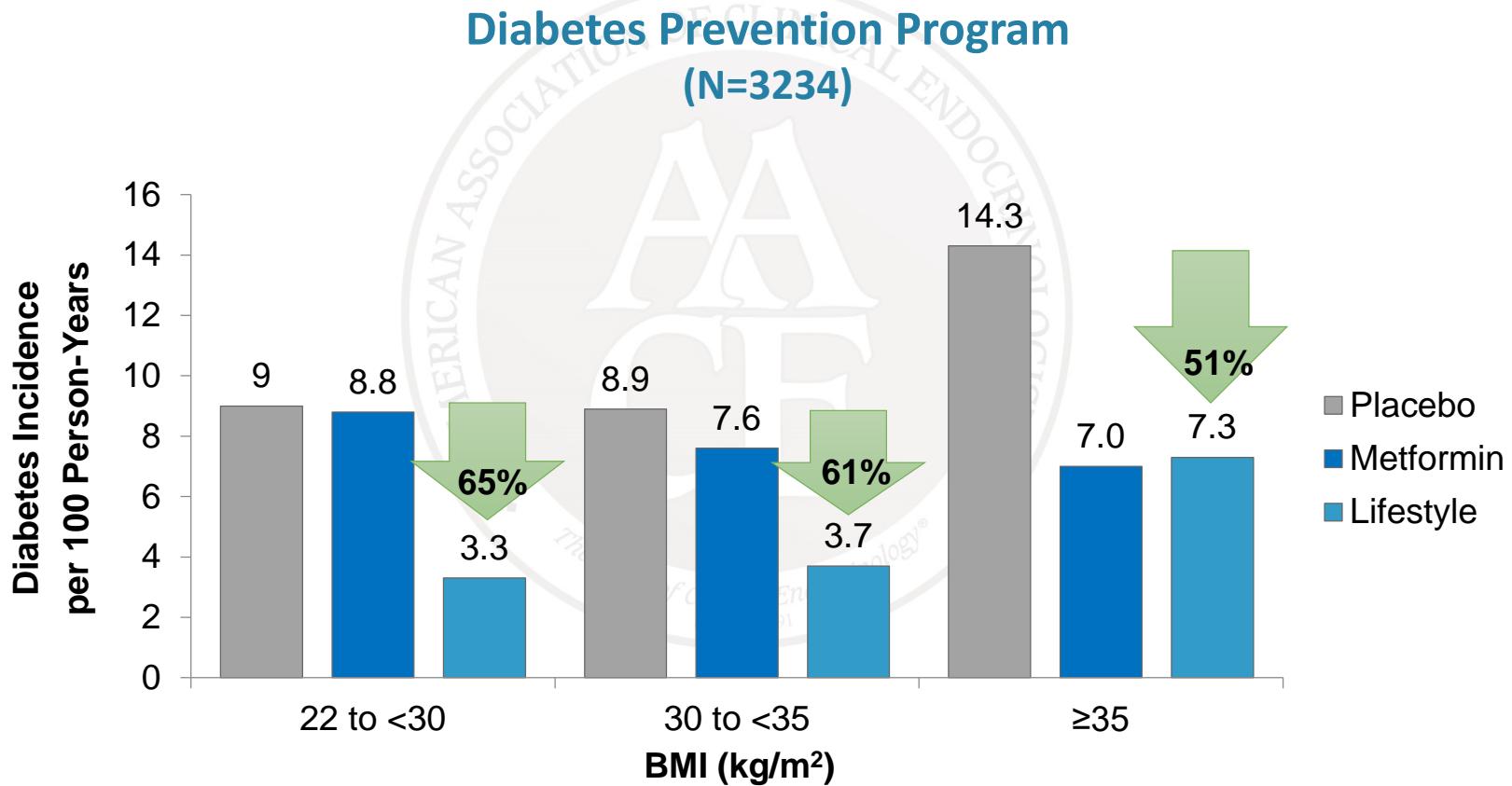
Lifestyle Intervention More Effectively Prevents Diabetes as Populations Age

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
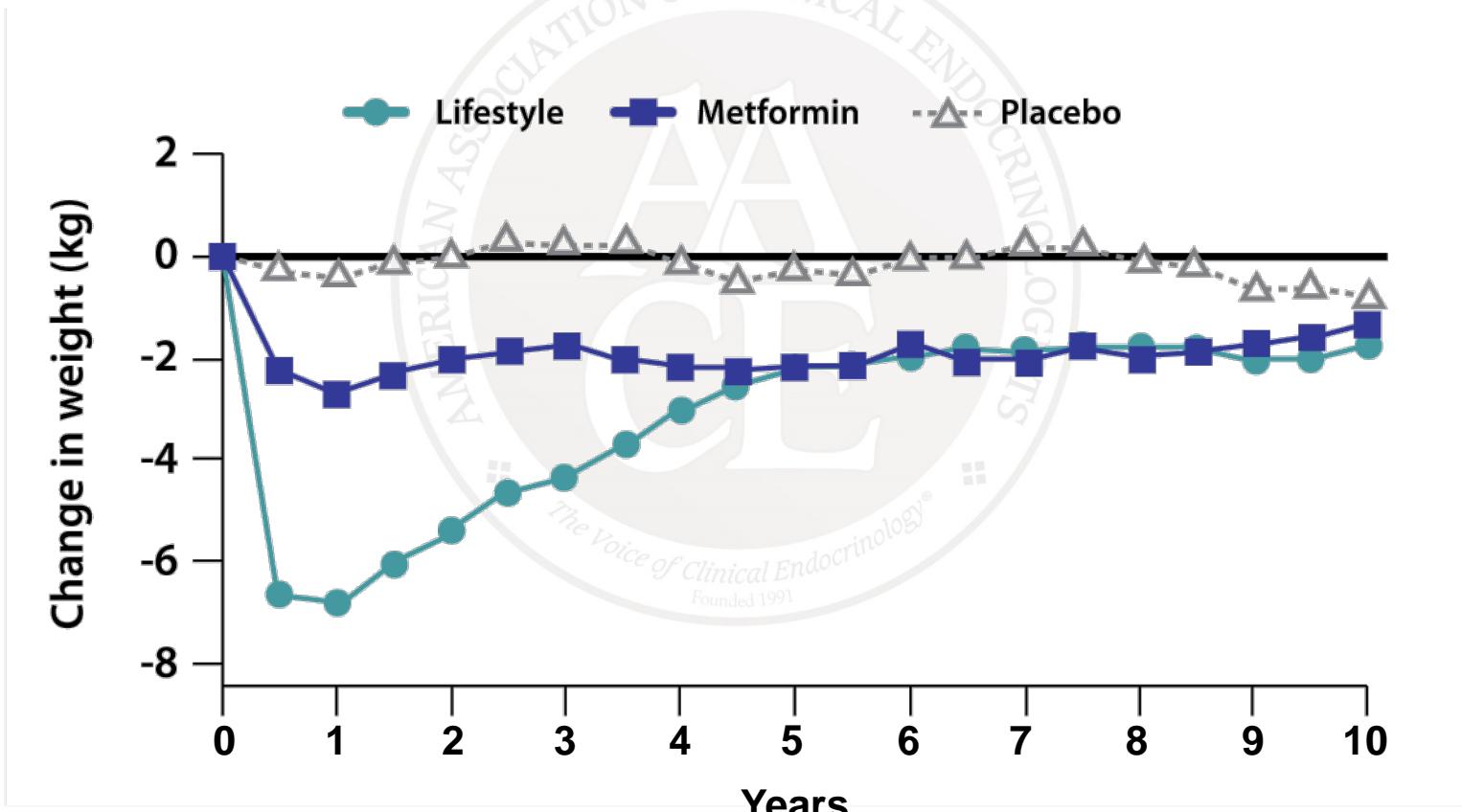
Diabetes Prevention Program
(N=3234)

*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
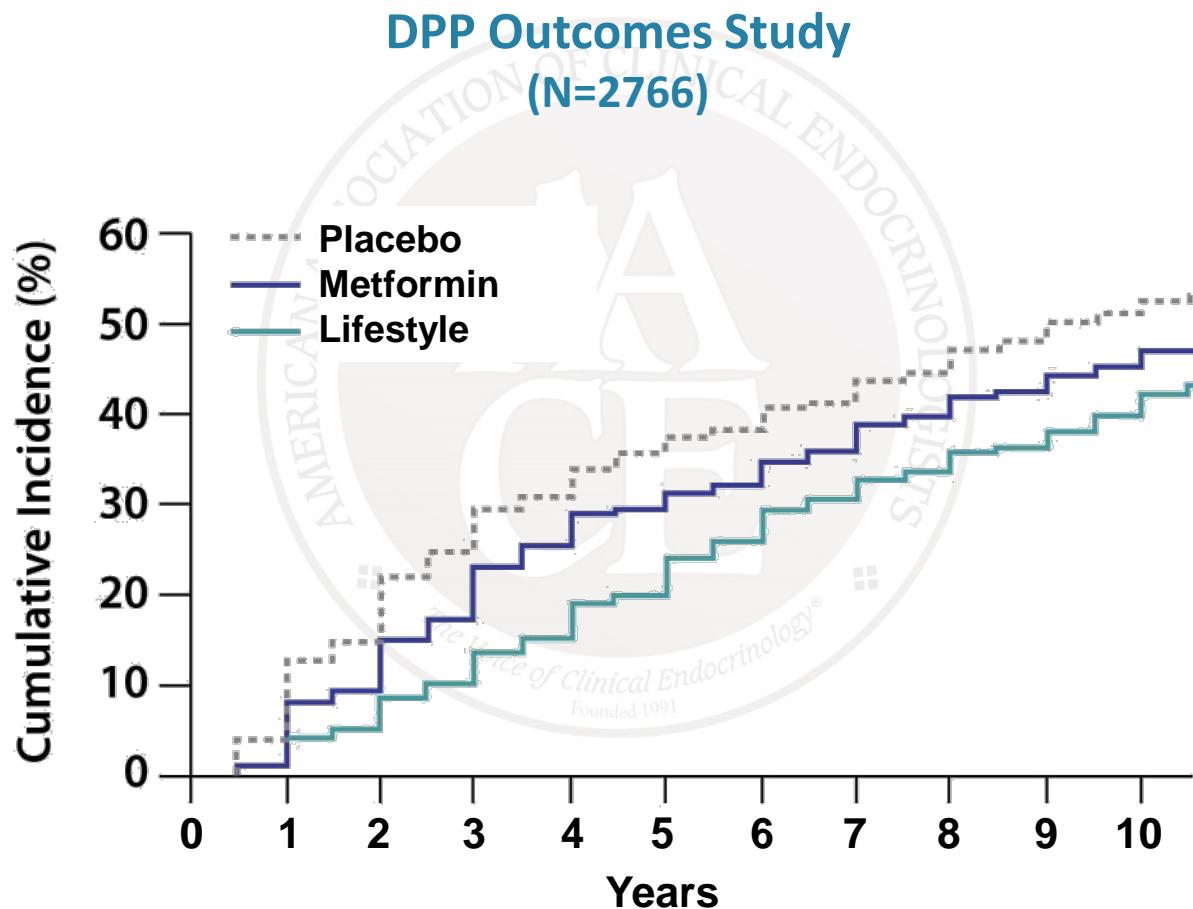
DPP Outcomes Study
(N=2766)

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

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

10-Year Incidence of T2D
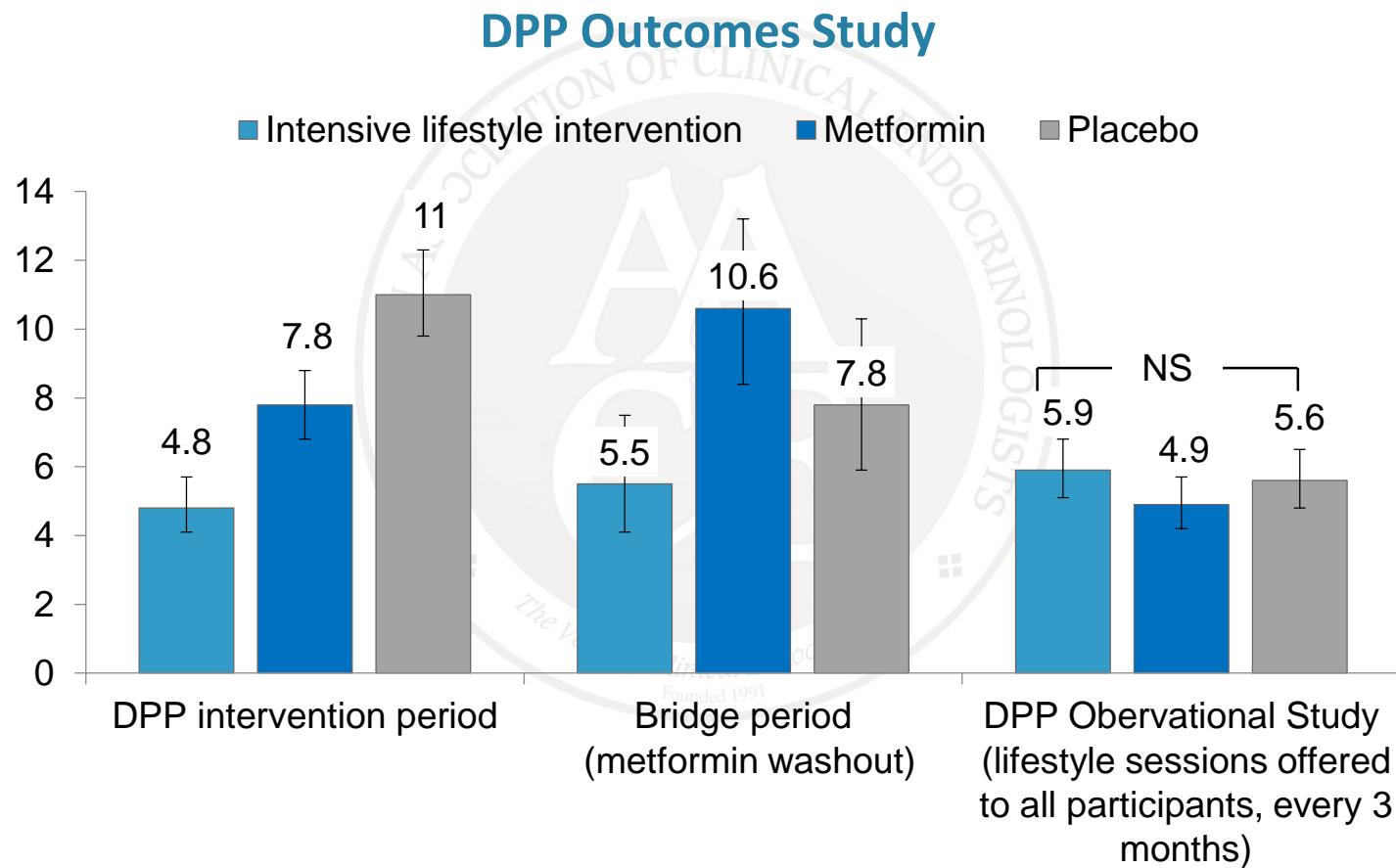
DPP Outcomes Study
(N=2766)

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

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

Incidence of T2D

DPP Outcomes Study

■ Intensive lifestyle intervention   ■ Metformin   ■ Placebo

DPP intervention period: 4.8, 7.8, 11
Bridge period (metformin washout): 5.5, 10.6, 7.8
DPP Obervational Study (lifestyle sessions offered to all participants, every 3 months): 5.9, 4.9, 5.6 — NS
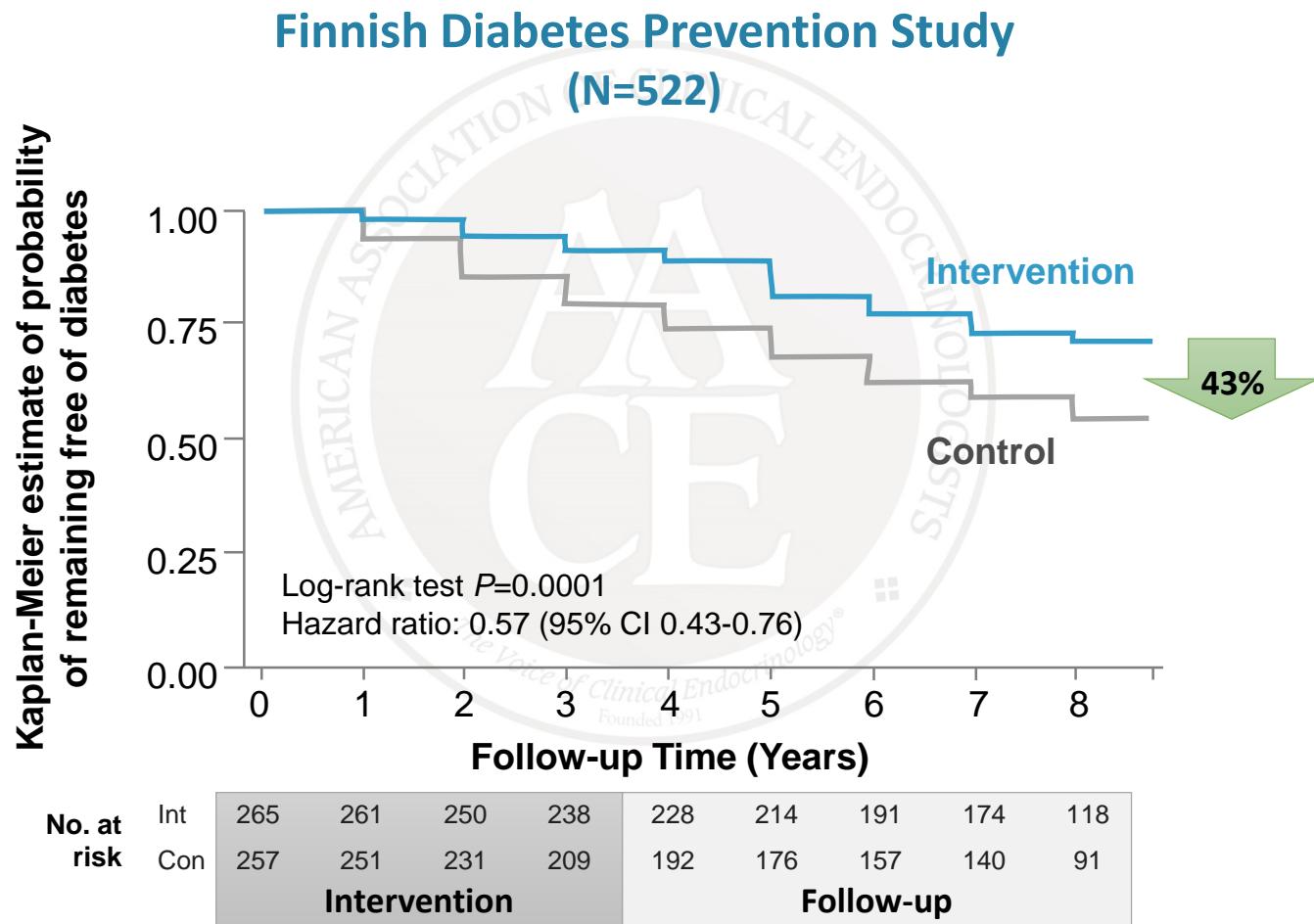
DPP = Diabetes Prevention Program; DPPOS = Diabetes Prevention Program Outcomes Study; NS = not significant; T2D = type 2 diabetes.

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

Early Weight Loss Reduces Long-term Incidence of Type 2 Diabetes

Finnish Diabetes Prevention Study (N=522)

Kaplan-Meier estimate of probability of remaining free of diabetes

Intervention

Control

43%

Log-rank test *P*=0.0001
Hazard ratio: 0.57 (95% CI 0.43-0.76)

Follow-up Time (Years)

No. at risk		0	1	2	3	4	5	6	7	8
	Int	265	261	250	238	228	214	191	174	118
	Con	257	251	231	209	192	176	157	140	91

Intervention	**Follow-up**
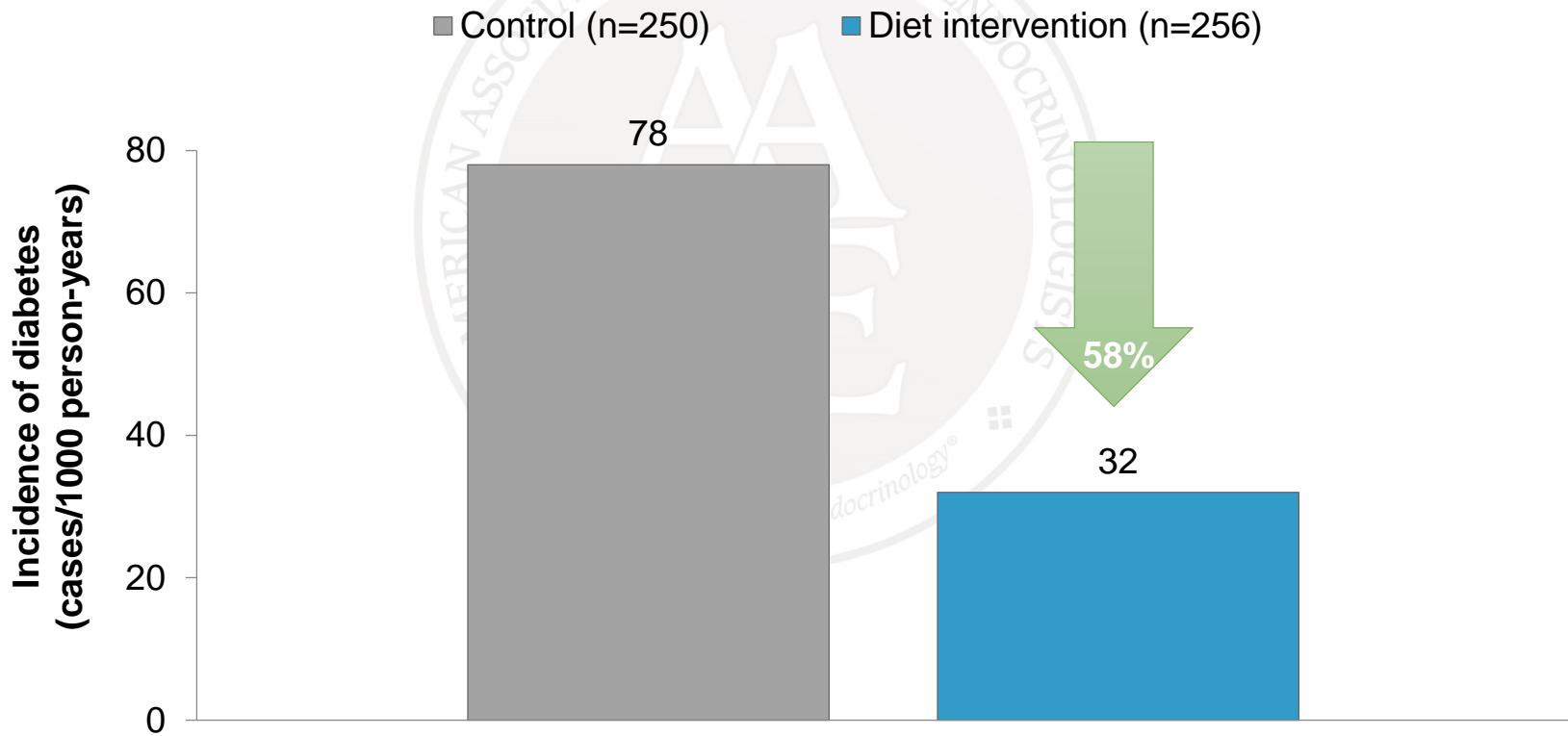
Intensive lifestyle intervention goal: 5% reduction in body weight with moderate-intensity exercise for ≥30 minutes/day plus diet consisting of <30% calories from fat, <10% calories from saturated fat, and ≥15 mg fiber.

Lindstrom J, et al. *Lancet*. 2006;368:1673-1679.
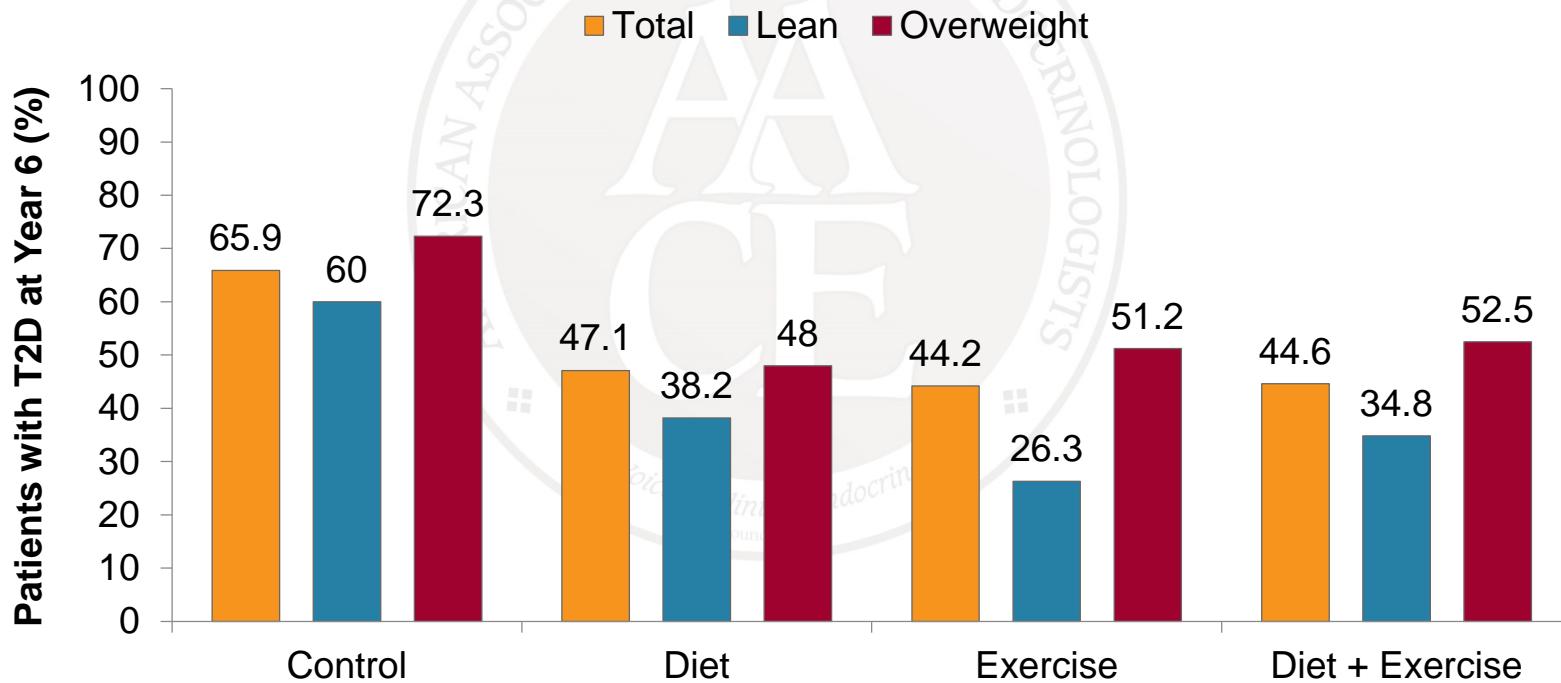
Cumulative Incidence of Diabetes Over 4 Years

The Finnish Diabetes Prevention Study

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)
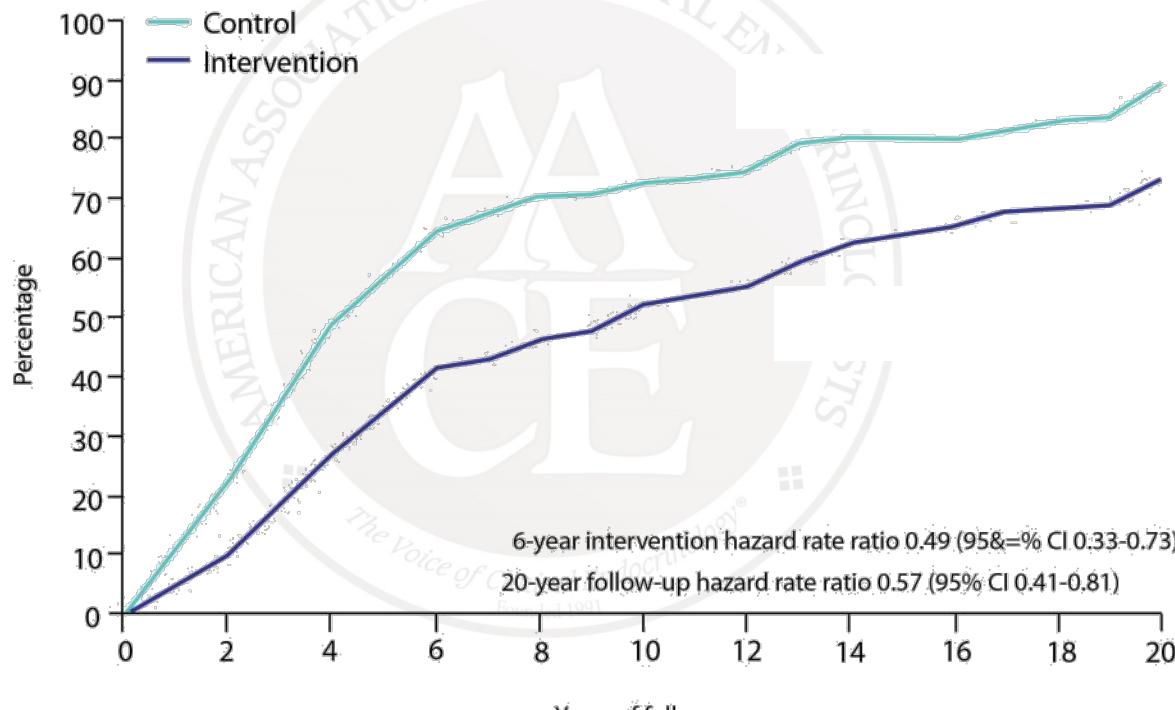
IGT = impaired glucose tolerance; T2D = type 2 diabetes.

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

20-Year Cumulative T2D Incidence in Asian Patients with IGT
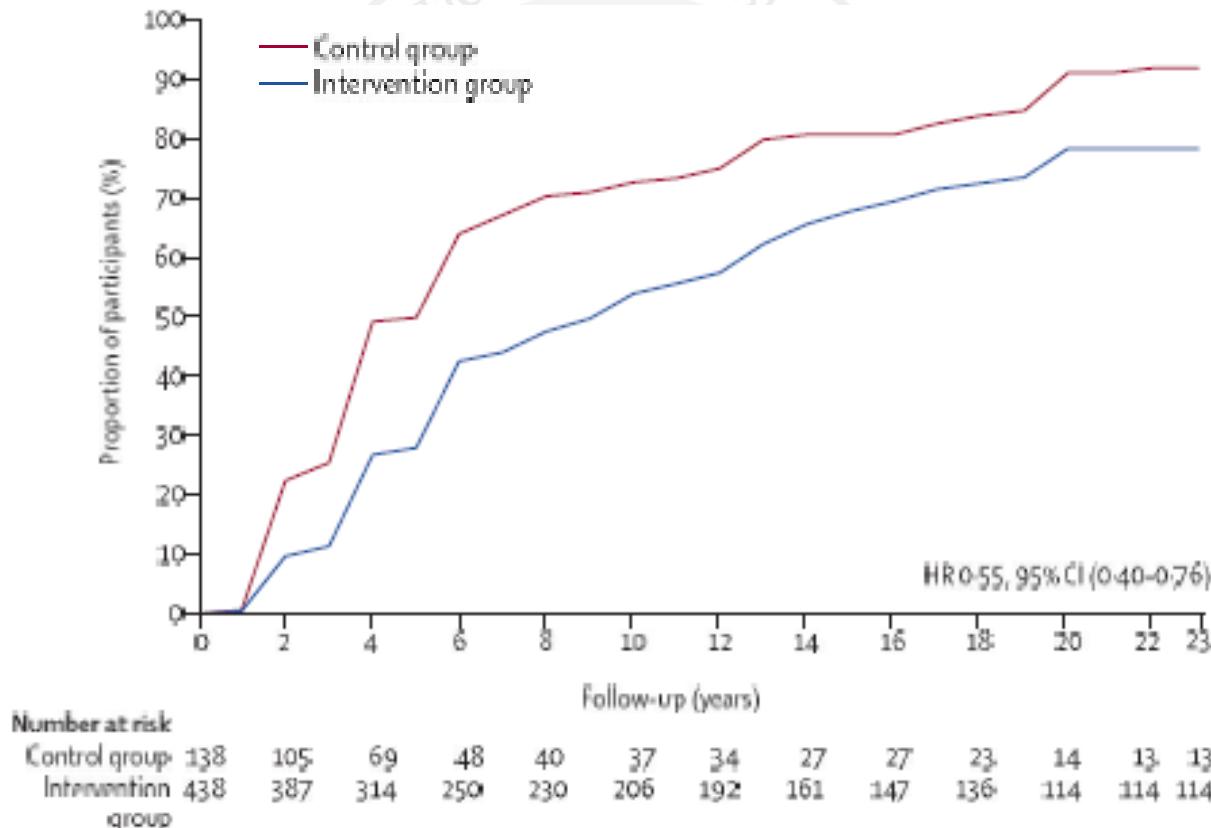

Da Qing Diabetes Prevention Study

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

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

23-Year Incidence of T2D in Asian Patients with IGT

Da Qing Diabetes Prevention Study
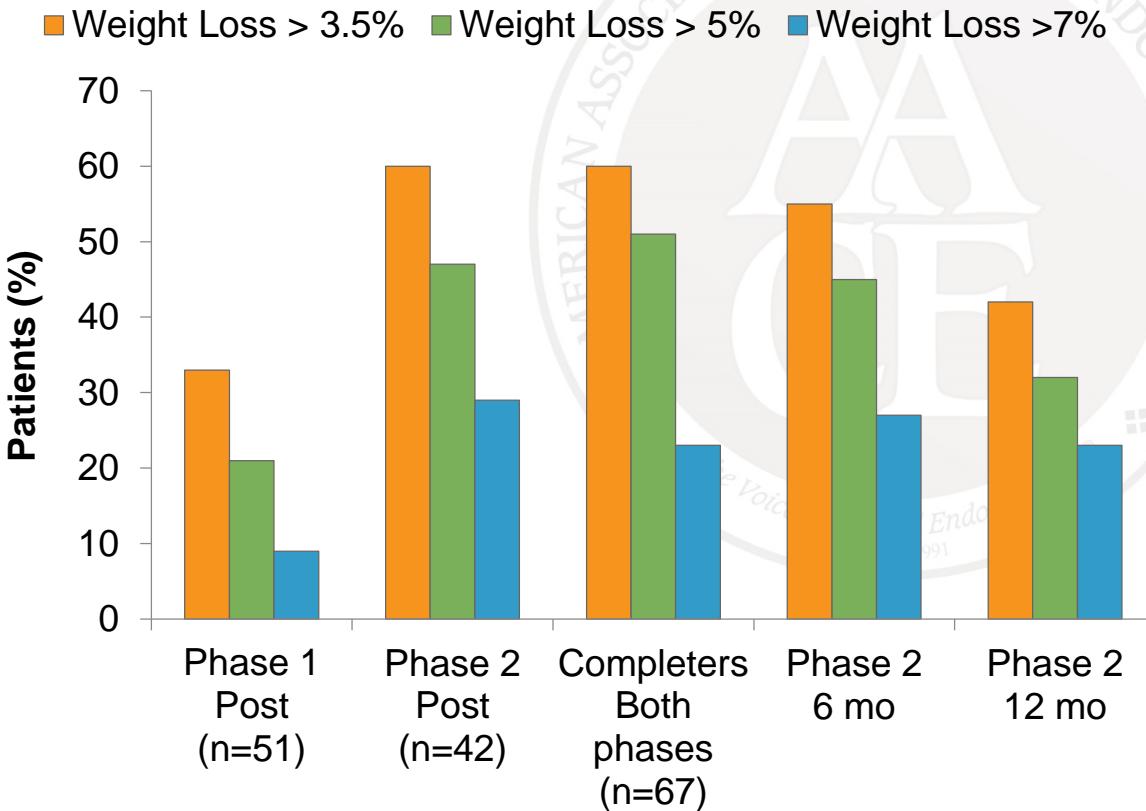
IGT = impaired glucose tolerance; T2D = type 2 diabetes.

Li G, et al. *Lancet Diabetes Endocrinol*. 2014;2:474-480.

Group Lifestyle Balance Program Intervention

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

Legend:
- Weight Loss > 3.5% (orange)
- Weight Loss > 5% (green)
- Weight Loss >7% (blue)

Chart: Patients (%) vs intervention phases

Category	Weight Loss > 3.5%	Weight Loss > 5%	Weight Loss >7%
Phase 1 Post (n=51)	33	21	9
Phase 2 Post (n=42)	60	47	29
Completers Both phases (n=67)	60	51	23
Phase 2 6 mo	55	45	27
Phase 2 12 mo	42	32	23
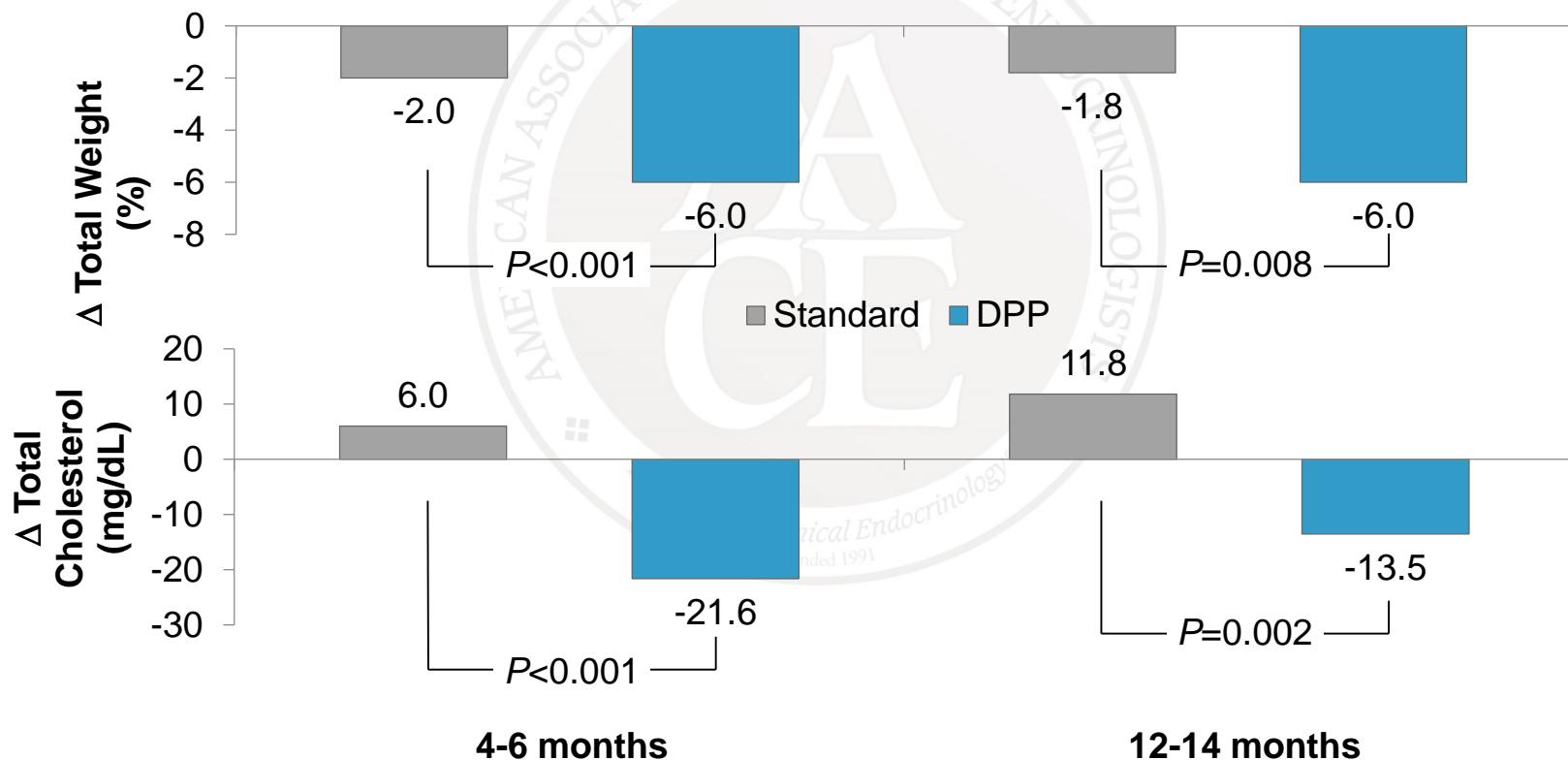
- DPP lifestyle intervention adapted to a 12-session group-based program

- 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, $P<0.001$)

DPP = Diabetes Prevention Program.

Kramer MK, et al. *Am J Prev Med*. 2009;37:505-511.

Translating the DPP Into Community Intervention

The DEPLOY Pilot Study
(N=92)
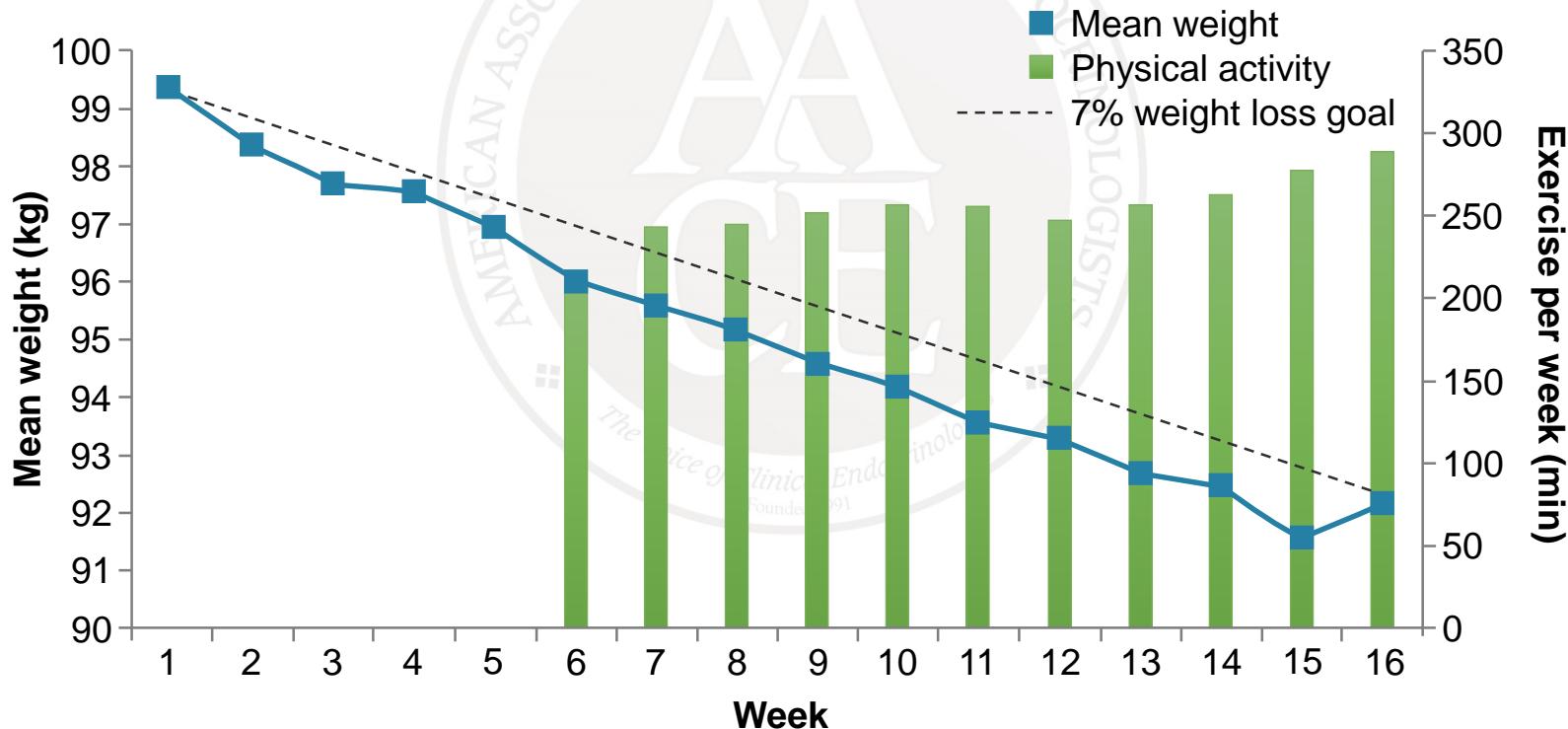
DEPLOY = Diabetes Education & Prevention with a Lifestyle Intervention Offered at the YMCA; DPP = Diabetes Prevention Program; YMCA = Young Men's Christian Association.

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.
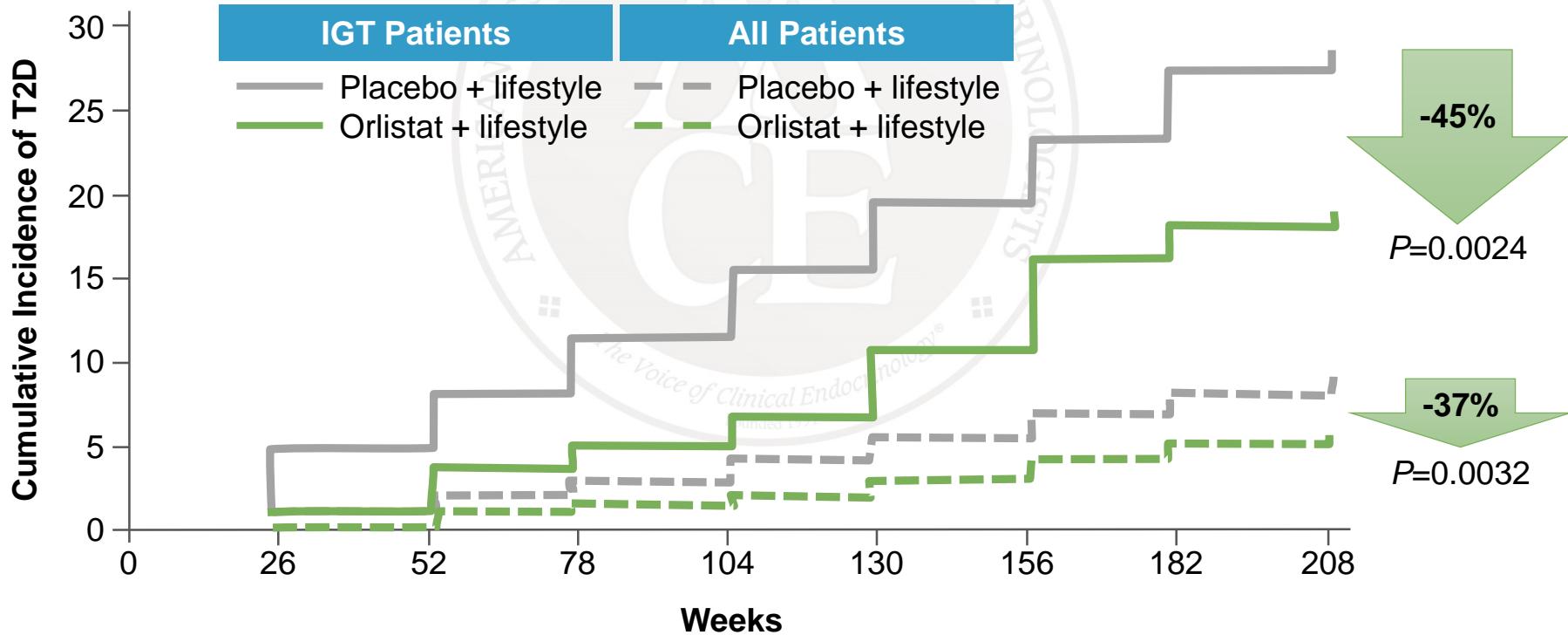
Metabolic Complications of Obesity

Prevention of Diabetes: Pharmacotherapy and Surgical Studies

Effect of Orlistat on Incidence of Diabetes in Obese Patients with Normal and Impaired Glucose Tolerance
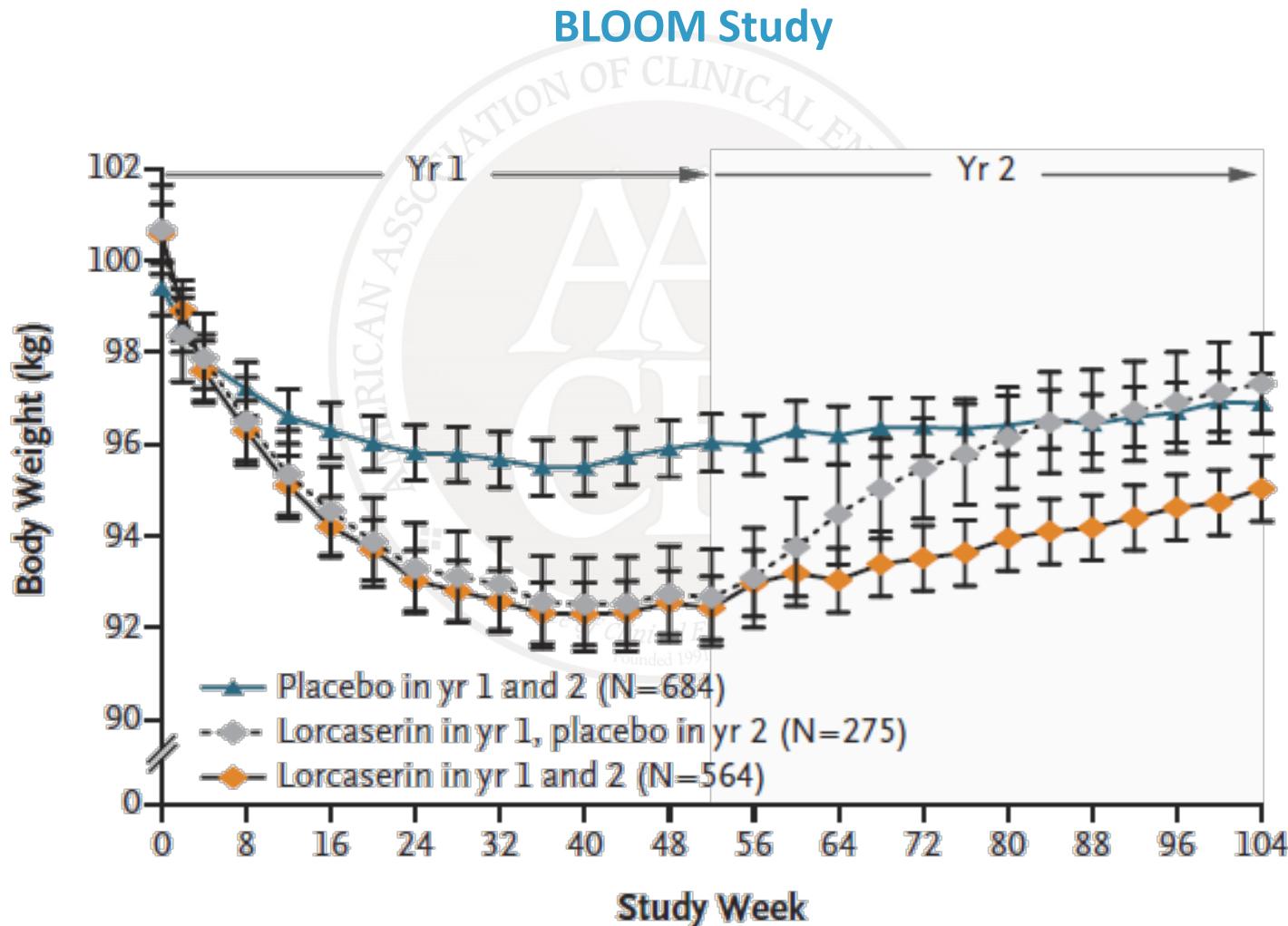

XENDOS Study (N=3305)
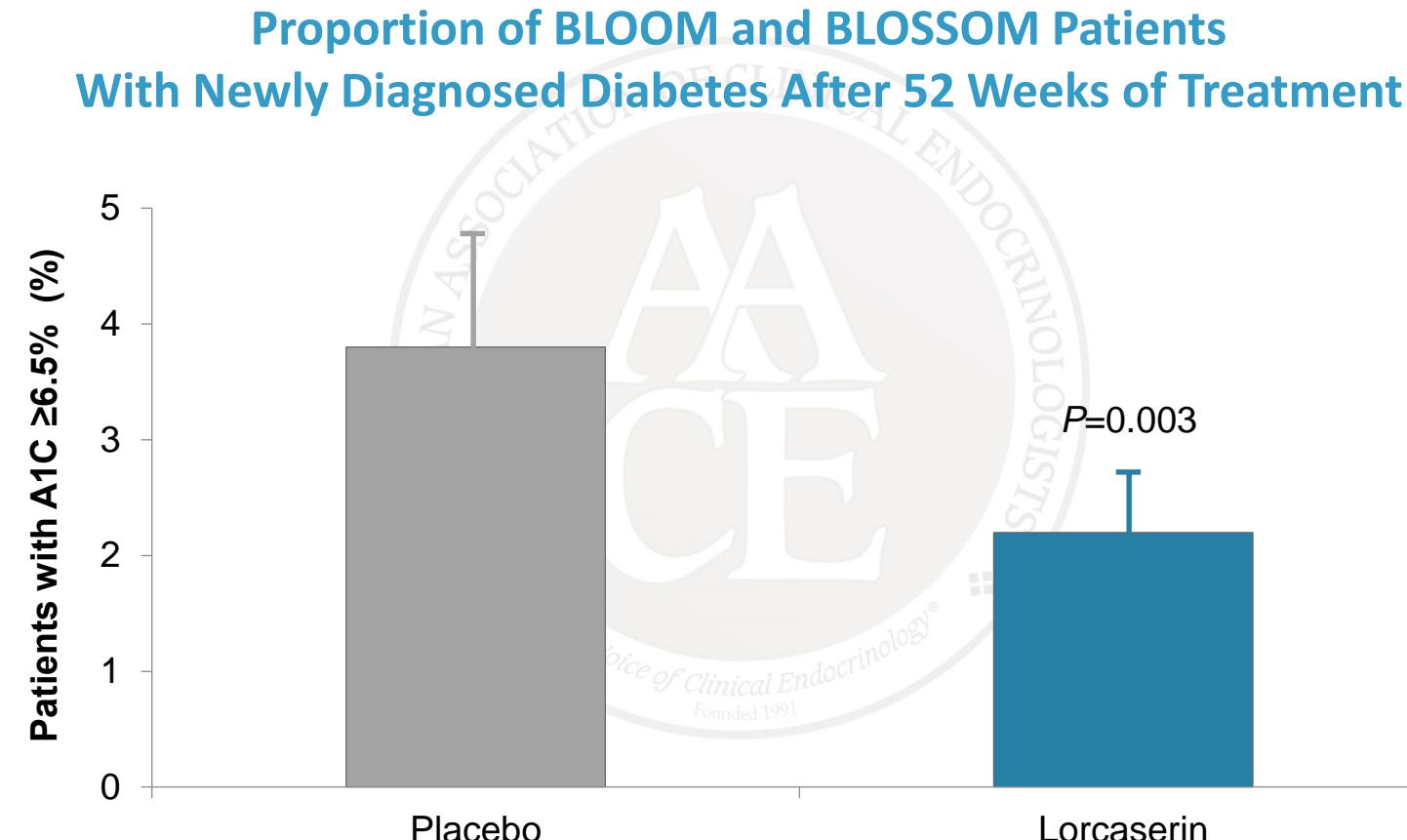
IGT = impaired glucose tolerance; XENDOS = Xenical in the prevention of Diabetes in Obese Subjects.

Torgerson JS, et al. *Diabetes Care.* 2004;27:155-161.

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

BLOOM Study

Smith SR, et al. *N Engl J Med.* 2010;363:245-256.
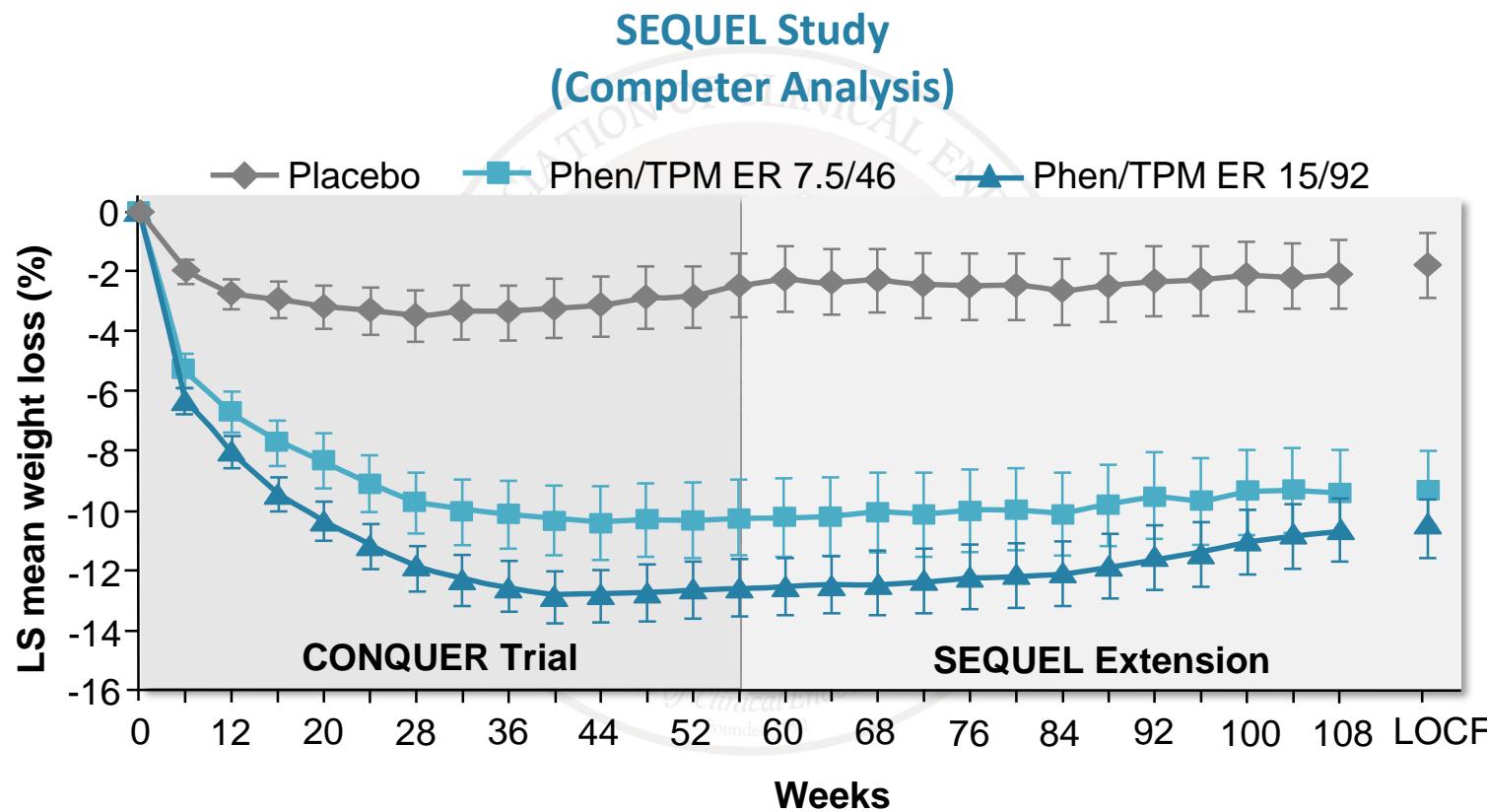
# Effect of Lorcaserin on Progression to T2D

**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/EndocrinologicandMetabolicDrugsAdvis
oryCommittee/UCM303200.pdf.

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).
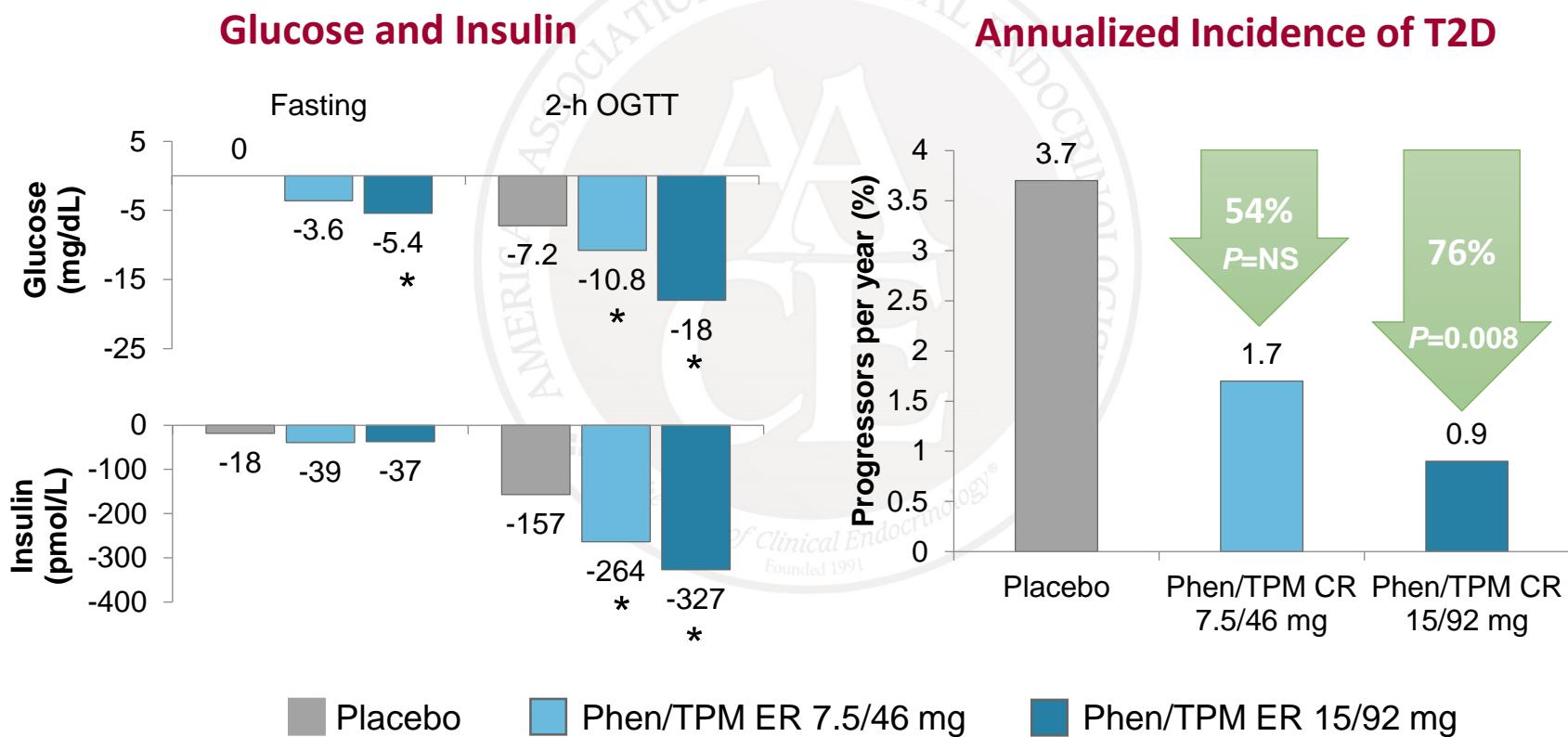
Phen/TPM ER = phentermine/topiramate extended release.

Garvey WT, et al. *Am J Clin Nutr*. 2012;95(2):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
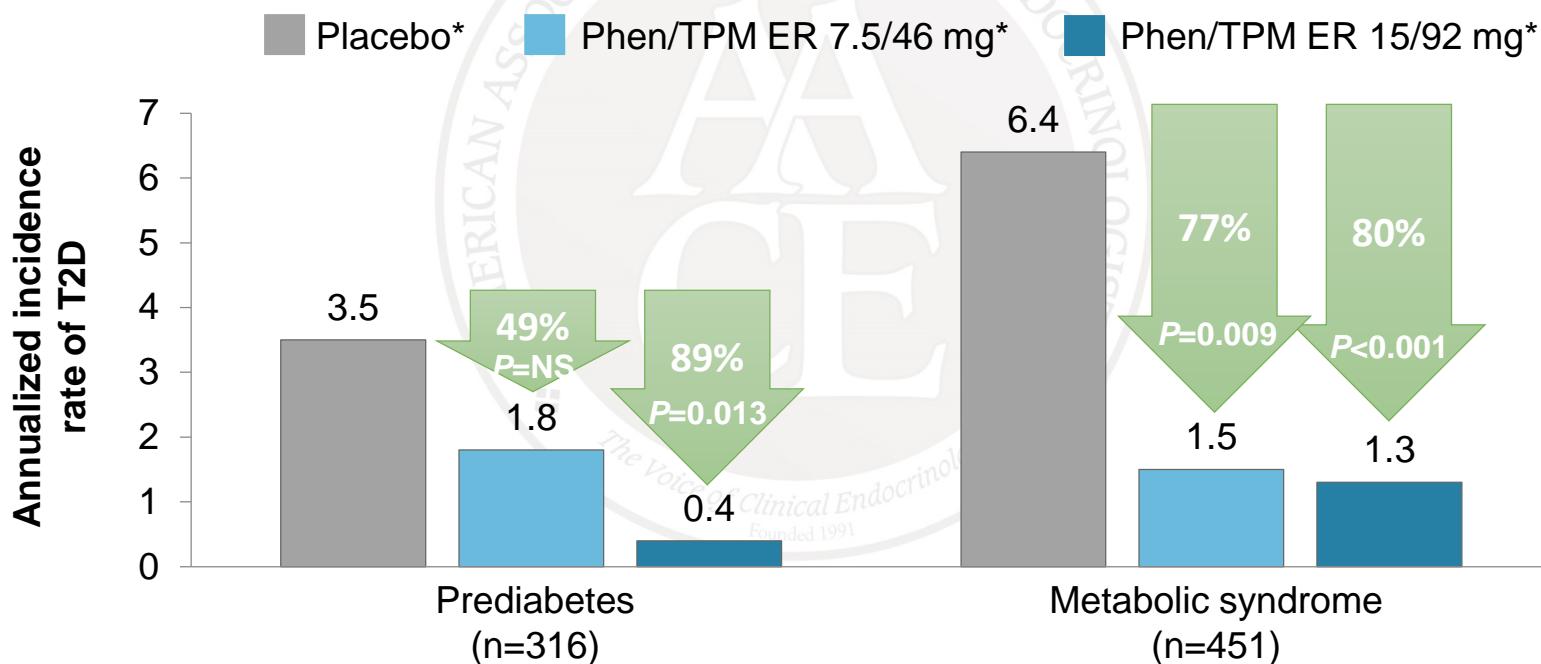
*P≤0.005 vs placebo.

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.

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

SEQUEL Prediabetes/Metabolic Syndrome Cohort (N=475)
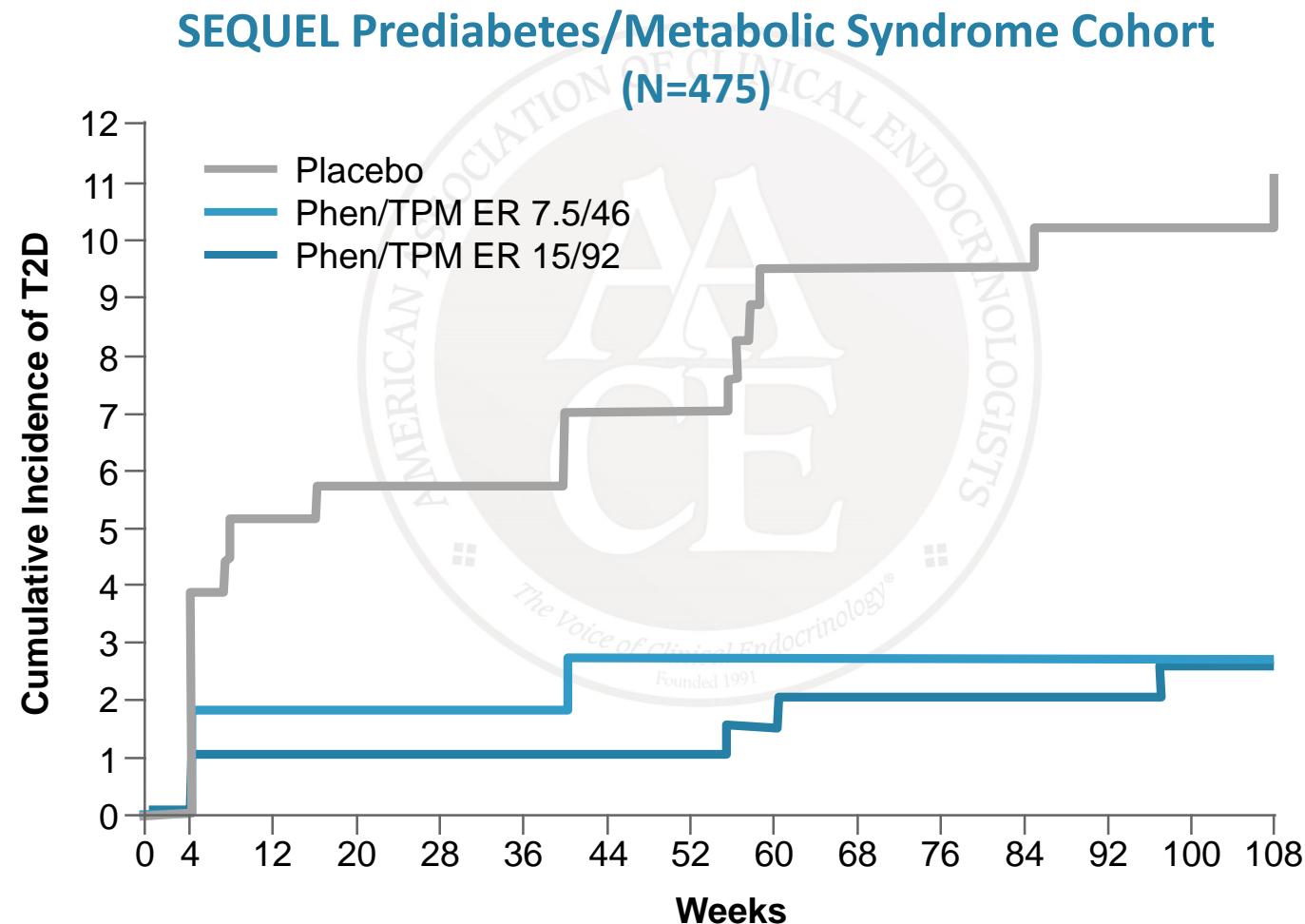

*All groups had lifestyle intervention.

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

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

# Effect of Phentermine/Topiramate ER on Incidence of Diabetes
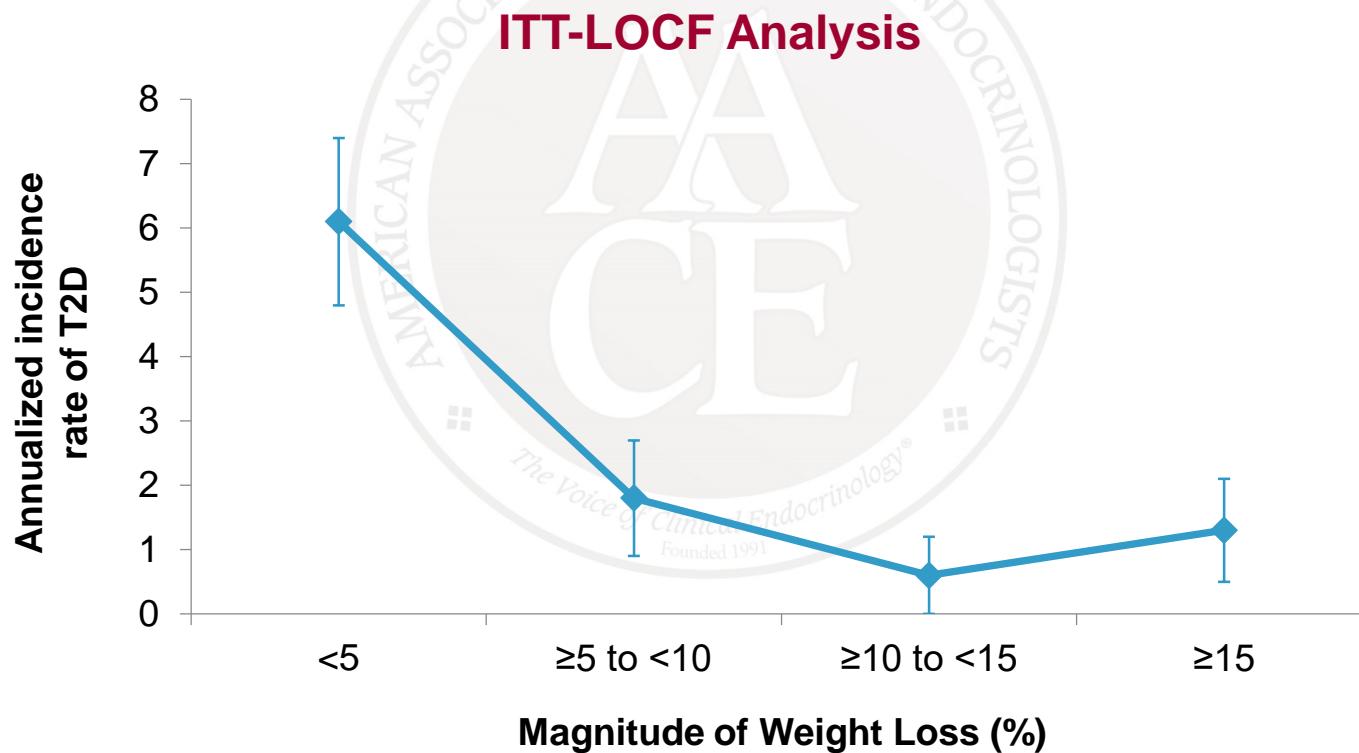
SEQUEL Prediabetes/Metabolic Syndrome Cohort (N=475)

- Placebo
- Phen/TPM ER 7.5/46
- Phen/TPM ER 15/92

x-axis: Weeks (0, 4, 12, 20, 28, 36, 44, 52, 60, 68, 76, 84, 92, 100, 108)

y-axis: Cumulative Incidence of T2D (0–12)

Phen/TPM ER = phentermine/topiramate extended release; T2D = type 2 diabetes.

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

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Relationship Between Weight Loss and Prevention of Type 2 Diabetes

SEQUEL Prediabetes/Metabolic Syndrome Cohort (N=475)

ITT-LOCF Analysis

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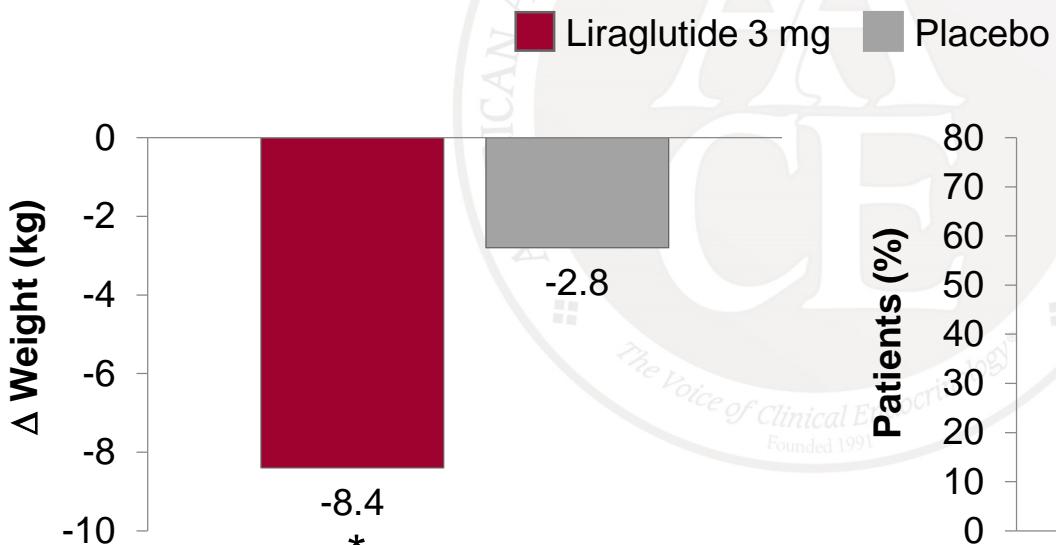
Intent to treat, last observation carried forward analysis for total study population.

Gadde KM, et al. *Lancet*. 2011;377:1341-1352.
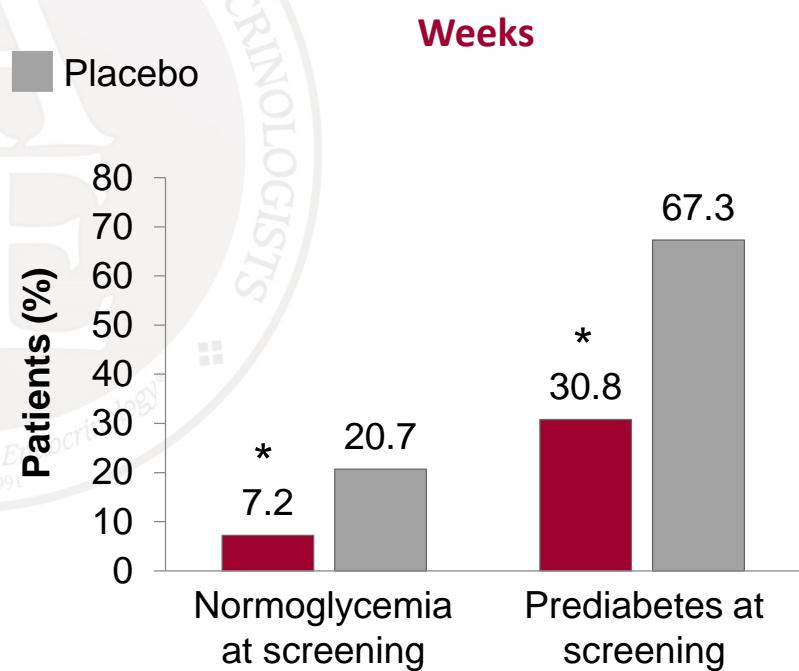
Effects of Liraglutide in Obese Patients with Prediabetes

SCALE Obesity and Prediabetes (N=3731)

Weight Change After 56 Weeks

Liraglutide 3 mg   **Placebo**

Δ Weight (kg)

- Liraglutide 3 mg: -8.4 *
- Placebo: -2.8

Patients with Prediabetes After 56 Weeks
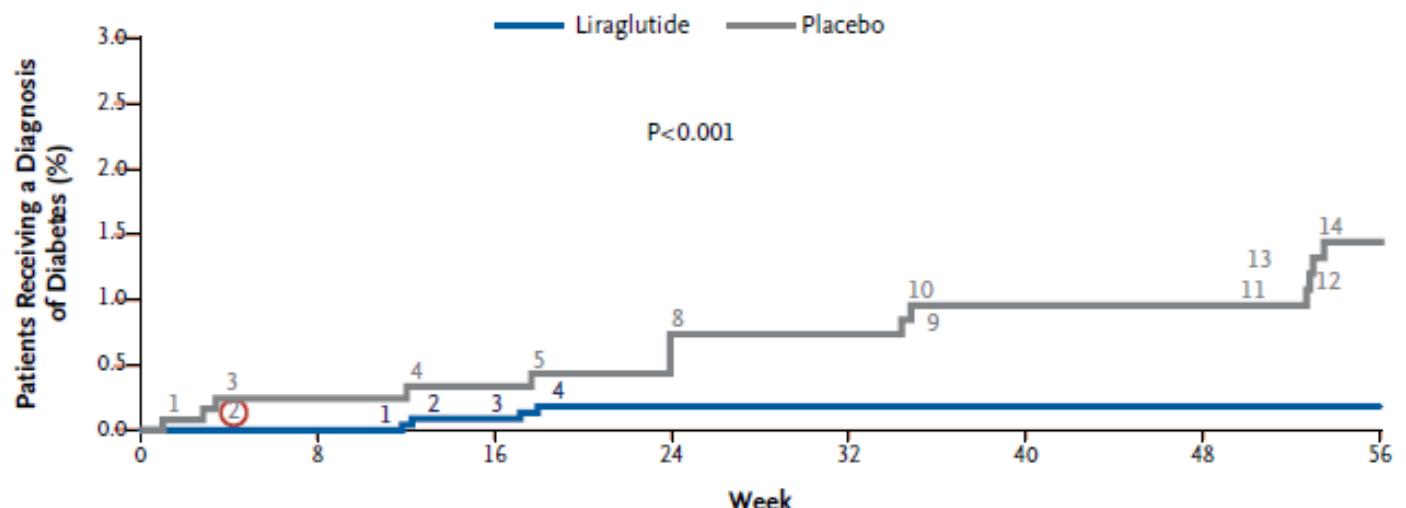
Patients (%)

Normoglycemia at screening
- Liraglutide 3 mg: 7.2 *
- Placebo: 20.7

Prediabetes at screening
- Liraglutide 3 mg: 30.8 *
- Placebo: 67.3

*P<0.001 vs placebo.

Pi-Sunyer X, et al. *N Engl J Med.* 2015;373:11-22.

Effects of Liraglutide in Obese Patients with Prediabetes

SCALE Obesity and Prediabetes (N=3731)

Cumulative Incidence of Type 2 Diabetes

Pi-Sunyer X, et al. *N Engl J Med*. 2015;373:11-22.
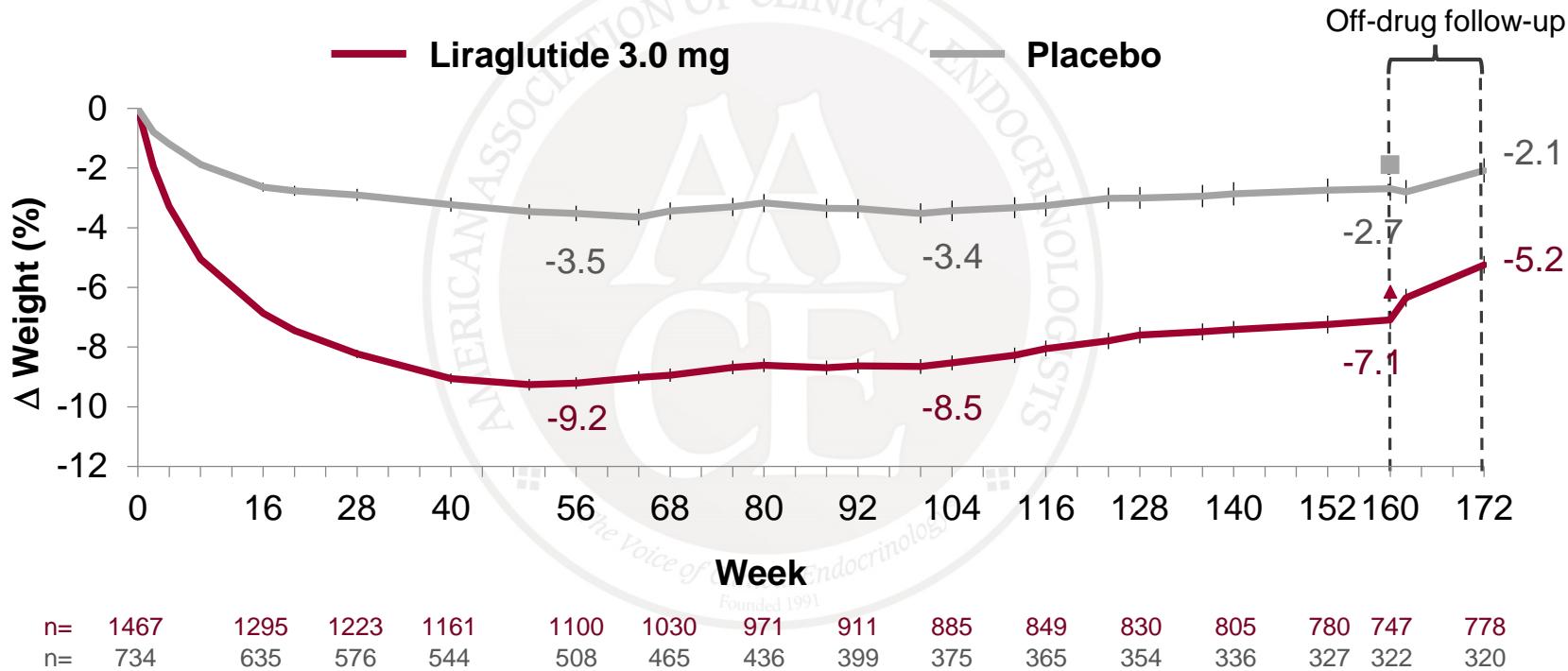
# Effects of Liraglutide on Body Weight Over 3 Years
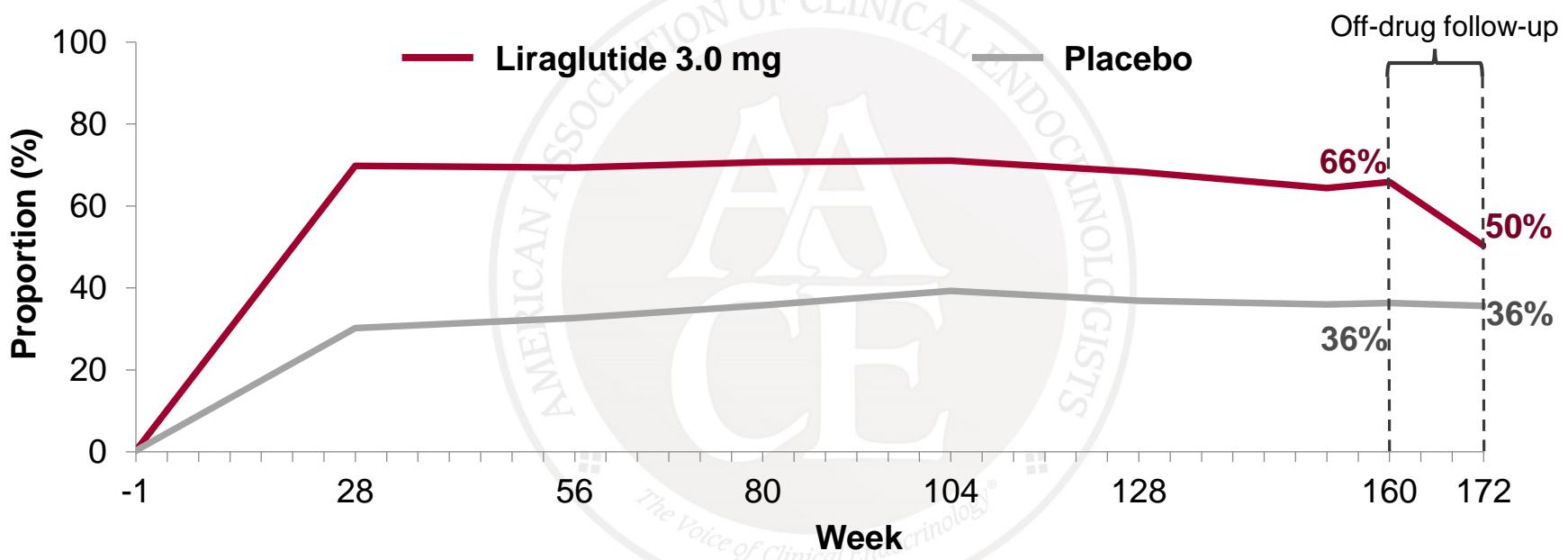
All arms included lifestyle intervention: −500 kcal/day hypocaloric diet + 150 min/week increased physical activity.

Full analysis set, fasting visit data only. Line graphs are observed means (±SE). Points (sqaure, triangle) are observed means with last observation carried forward (LOCF).

Fujioka K, et al. ENDO 2016, April 1-4, 2016; Abstract 24365.

Regression to Normoglycemia Among Patients with Prediabetes Treated With Liraglutide Over 3 Years

Likelihood of normoglycemia >3X higher with liraglutide 3 mg
OR = 3.6 (95% CI, 3.0 to 4.4); *P*<0.0001; NNT = ~3

All arms included lifestyle intervention: −500 kcal/day hypocaloric diet + 150 min./week increased physical activity.
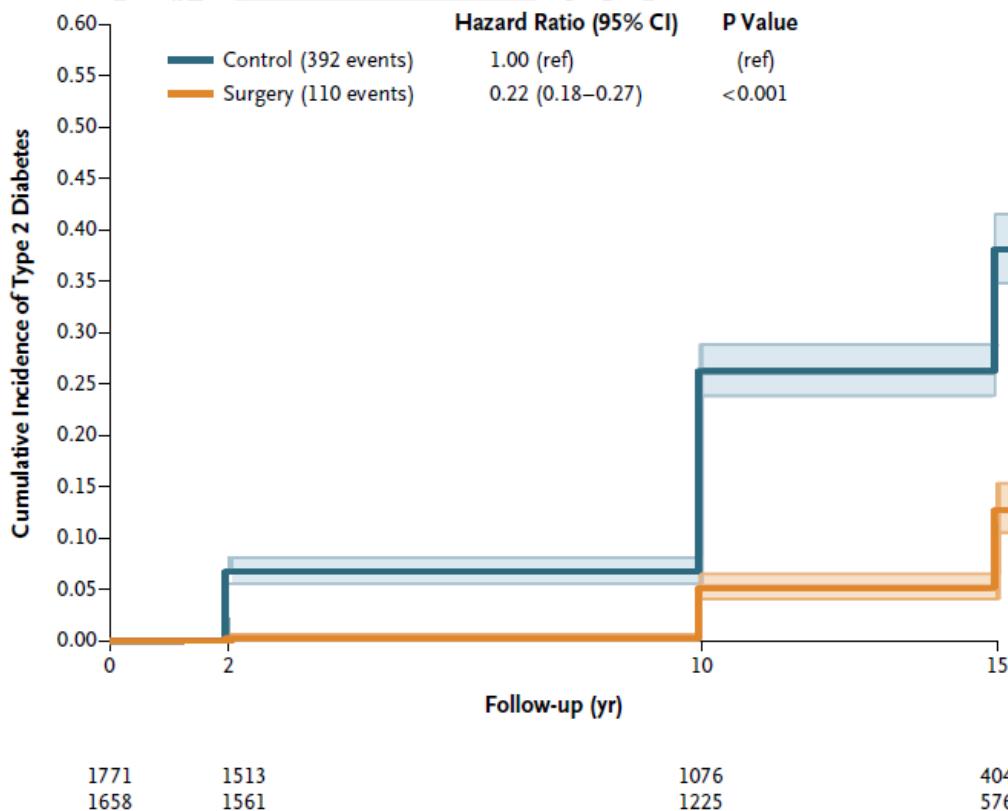
Full analysis set. Statistical analysis is logistic regression.

CI = confidence interval; NNT = number needed to treat; OR = odds ratio.

Fujioka K, et al. ENDO 2016, April 1-4, 2016; Abstract 24365.
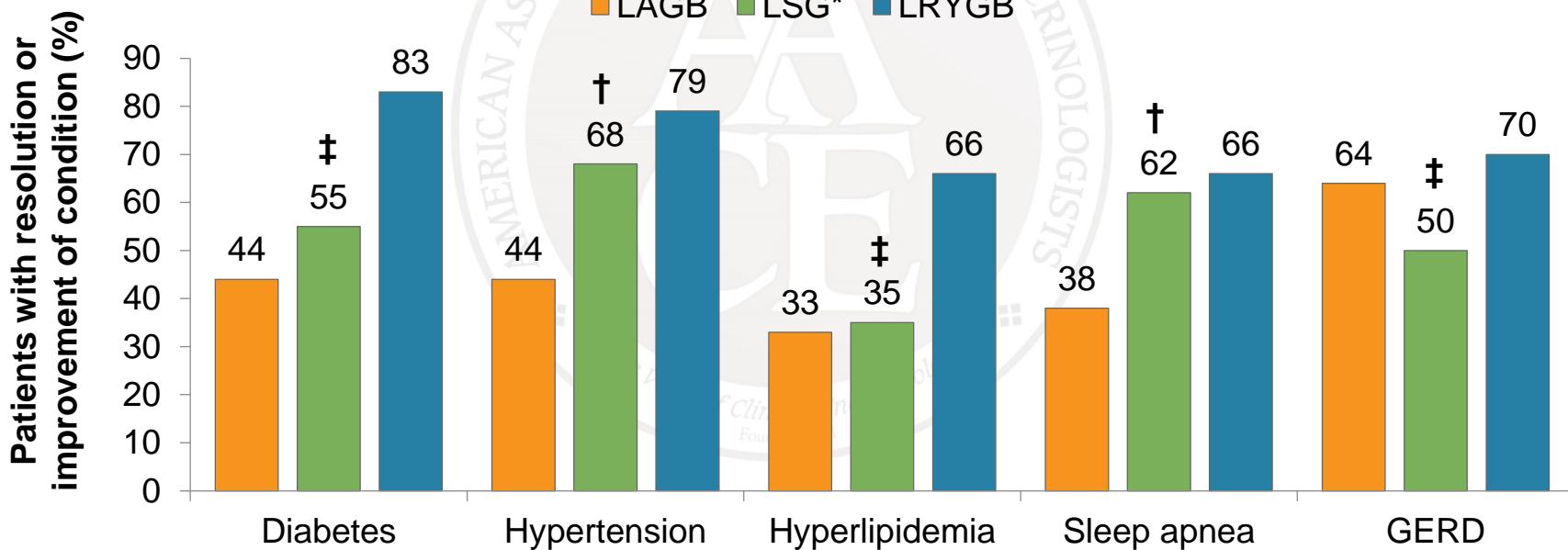
Effect of Bariatric Surgery on Incidence of Type 2 Diabetes

Swedish Obesity Study

Carlsson LM, et al. *N Engl J Med*. 2012;367:695-704.

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

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

Legend: LAGB, LSG*, LRYGB

Y-axis: Patients with resolution or improvement of condition (%), 0 to 90

Diabetes: LAGB 44, LSG 55 ‡, LRYGB 83
Hypertension: LAGB 44, LSG 68 †, LRYGB 79
Hyperlipidemia: LAGB 33, LSG 35 ‡, LRYGB 66
Sleep apnea: LAGB 38, LSG 62 †, LRYGB 66
GERD: LAGB 64, LSG 50 ‡, LRYGB 70
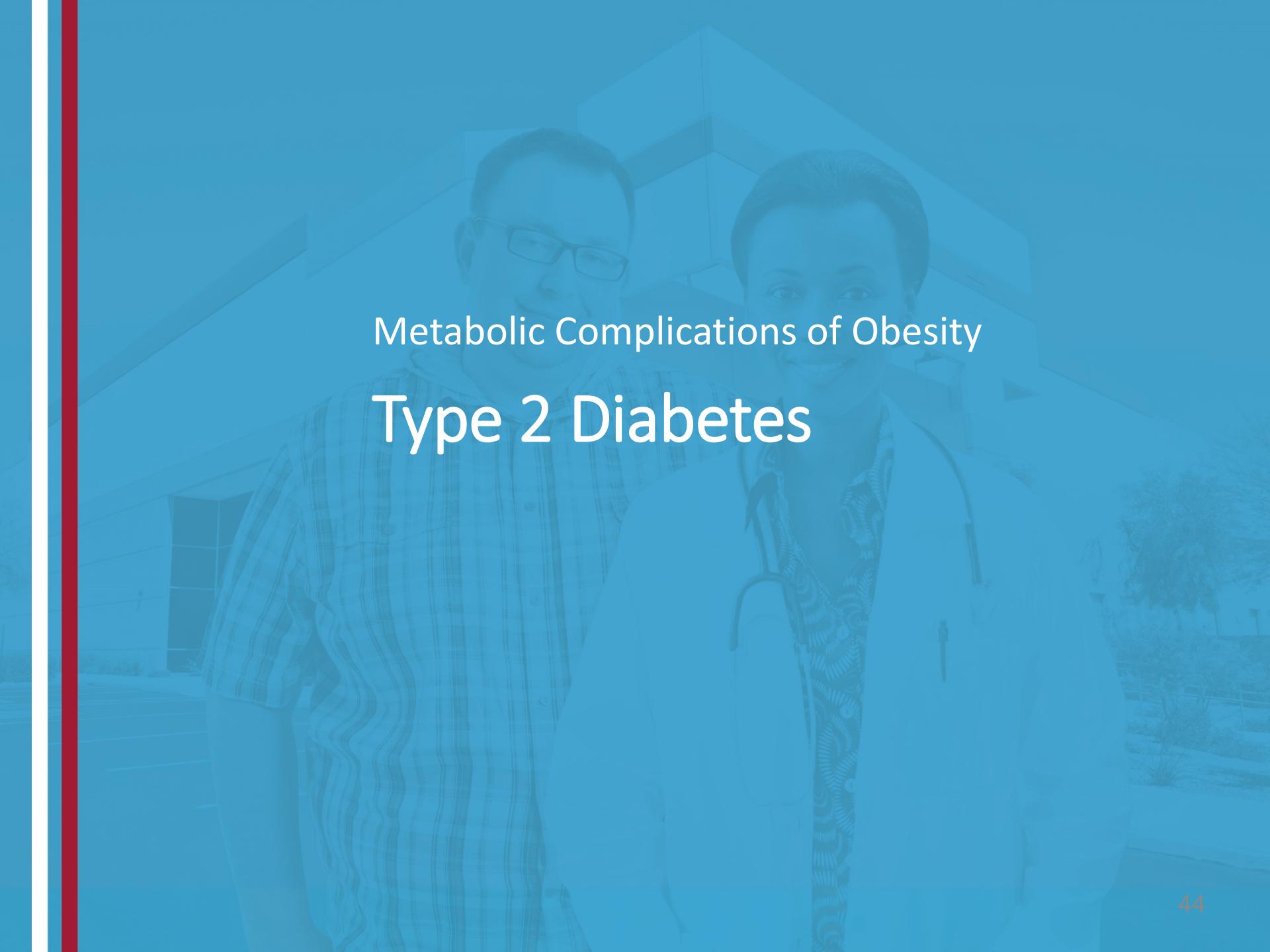
*Small numbers of patients with 1 year of follow-up for all comorbidities (n≤38).

†$P<0.05$ vs LAGB; ‡$P<0.05$ 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.
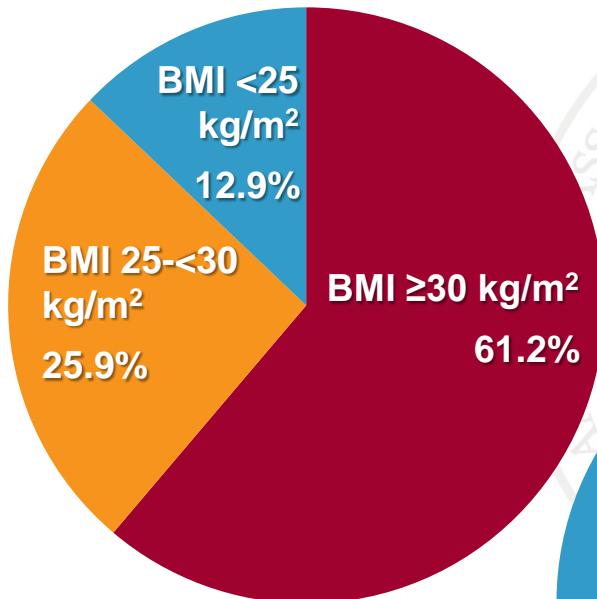
Metabolic Complications of Obesity
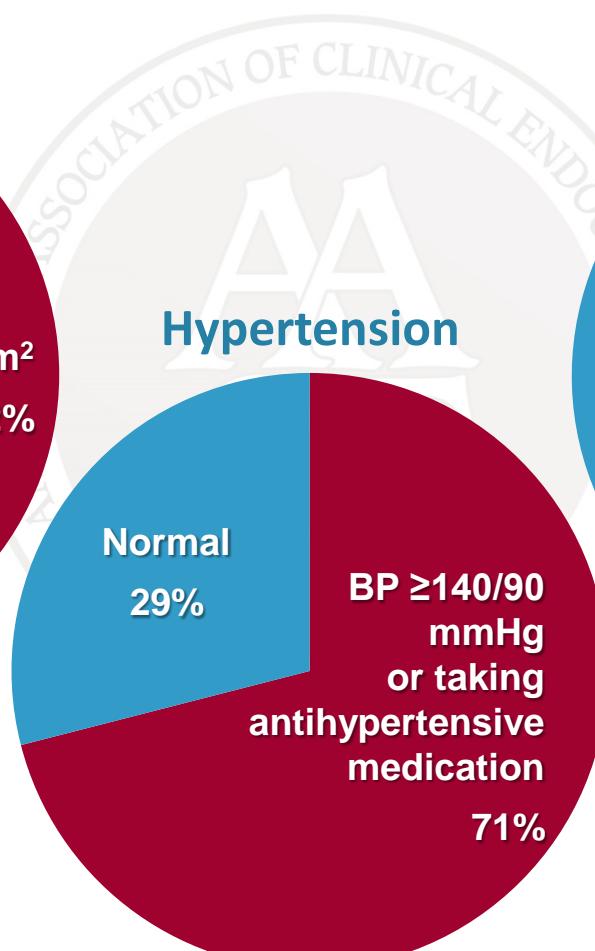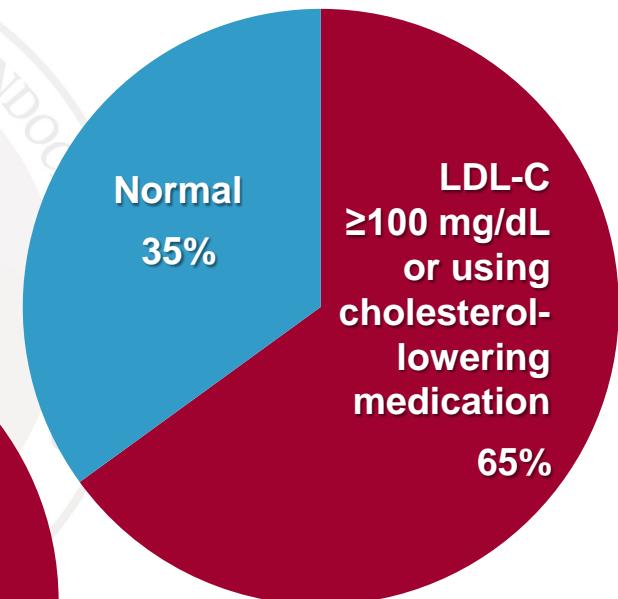
Type 2 Diabetes

Prevalence of CV Risk Factors in Diabetes

Overweight / Obese

- BMI <25 kg/m^2 — 12.9%
- BMI 25–<30 kg/m^2 — 25.9%
- BMI ≥30 kg/m^2 — 61.2%

Hypertension

- Normal — 29%
- BP ≥140/90 mmHg or taking antihypertensive medication — 71%

Hyperlipidemia

- Normal — 35%
- LDL-C ≥100 mg/dL or using cholesterol-lowering medication — 65%

BMI = body mass index.

Selvin S, et al. *Ann Intern Med*. 2014;160:517-525. CDC. National diabetes statistics report, 2014. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, 2014.

Consequences of Obesity in Diabetes

- Increases risk of cardiovascular comorbidities
  - Hypertension
  - Dyslipidemia
  - Atherosclerosis
- May limit ability to engage in physical activity
- Increases insulin resistance
  - Worsens glucose tolerance
  - Necessitates higher exogenous insulin doses
- Changes neuroendocrine signaling and metabolism
- Reduces quality of life

Goal: 5% to 10% weight loss

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

Weight Gain/Loss Potential with Antidiabetic Agents
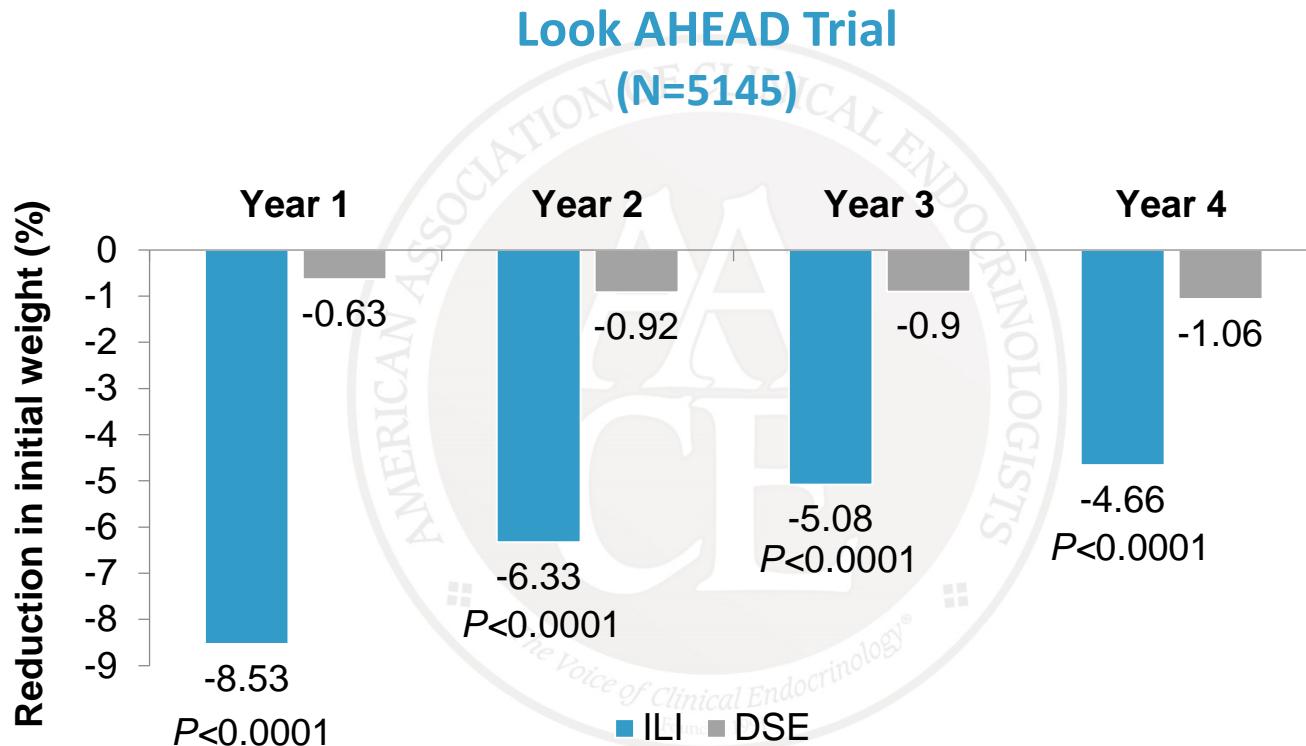
Class	Agent(s)	Weight Effect
Amylin analogs	Pramlintide	↓
Biguanides	Metformin	↓
GLP-1 receptor agonists	Albiglutide, dulaglutide, exenatide, exenatide XR, liraglutide	↓↓
SGLT-2 inhibitors	Canagliflozin, dapagliflozin, empagliflozin	↓
α-Glucosidase inhibitors	Acarbose, miglitol	↔
Bile acid sequestrants	Colesevelam	↔
DPP-4 inhibitors	Alogliptin, linagliptin, saxagliptin, sitagliptin	↔
Dopamine-2 agonists	Bromocriptine	↔
Glinides	Nateglinide, repaglinide	↑
Sulfonylureas	Glimepiride, glipizide, glyburide	↑
Insulins	Aspart, degludec, detemir, glargine, glulisine, lispro, inhaled, NPH, regular	↑↑
Thiazolidinediones	Pioglitazone, rosiglitazone	↑↑

Garber AJ, et al. *Endocr Pract*. 2016;22:84-113.

Metabolic Complications of Obesity

Effects of Lifestyle Change in Type 2 Diabetes
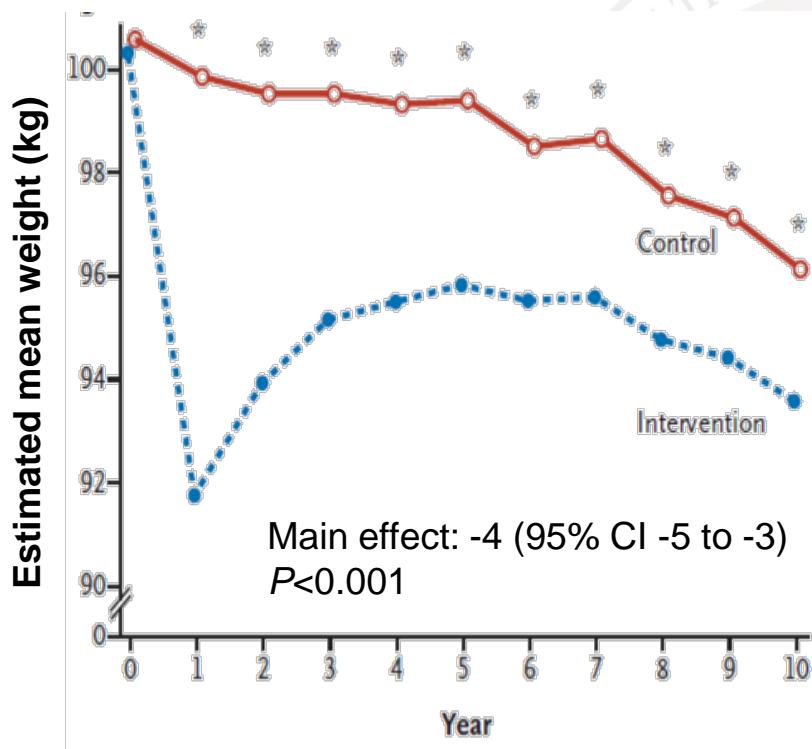
Intensive Intervention Reduces Significantly More Weight than Standard Approaches in T2D

Look AHEAD Trial
(N=5145)

Reduction in initial weight (%)

	Year 1	Year 2	Year 3	Year 4
ILI	-8.53 $P<0.0001$	-6.33 $P<0.0001$	-5.08 $P<0.0001$	-4.66 $P<0.0001$
DSE	-0.63	-0.92	-0.9	-1.06

■ ILI ■ DSE

DSE = diabetes support and education; ILI = intensive lifestyle intervention; T2D = type 2 diabetes.

Look AHEAD Research Group. *Arch Intern Med.* 2010;170:1566-1575.

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Long-term Limitations of Weight Loss Benefits in T2D

Main effect: -4 (95% CI -5 to -3)
P<0.001

Main effect:
-0.22 (95% CI -0.28 to -0.16)
P<0.001
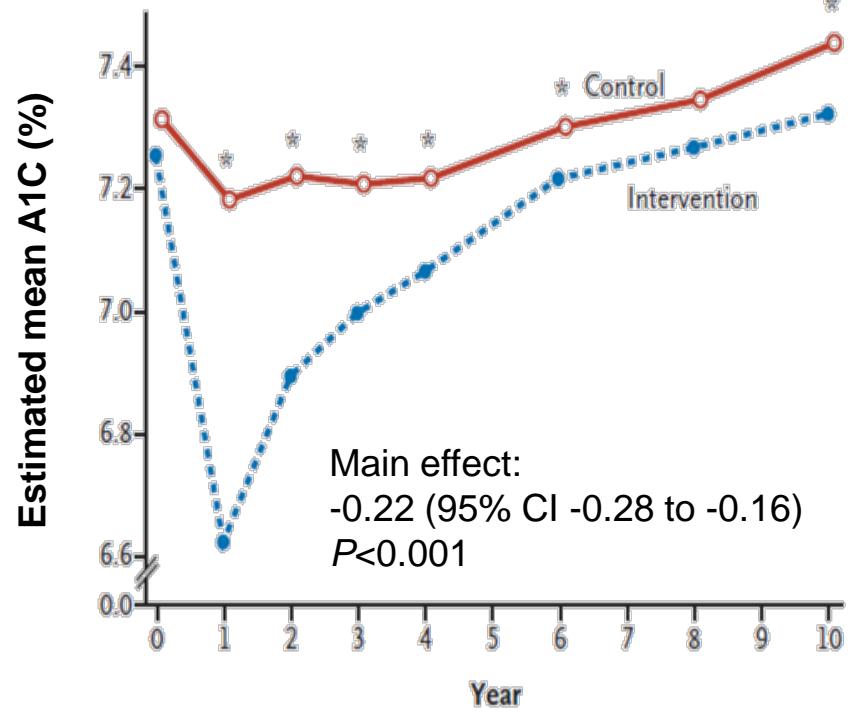
*P<0.05 for between-group comparison.

Main effect is the average of post-baseline differences.

CI = confidence interval; T2D = type 2 diabetes.
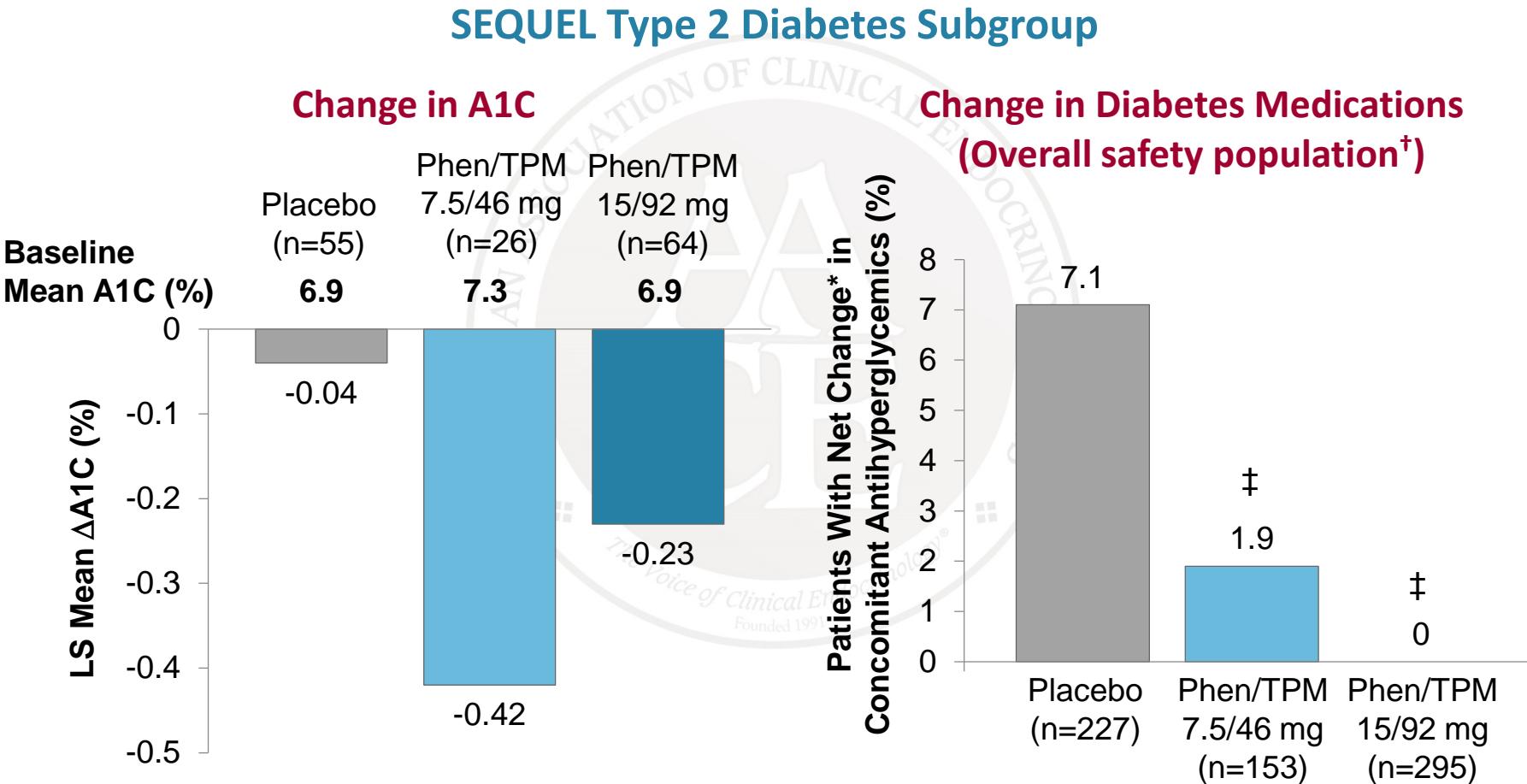
Look AHEAD Research Group. *N Engl J Med.* 2013;369:145-154.

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Metabolic Complications of Obesity

Effects of Weight Loss Medications in Type 2 Diabetes

Effect of Phentermine/Topiramate ER on A1C and Number of Diabetes Medications

SEQUEL Type 2 Diabetes Subgroup

Change in A1C

	Placebo (n=55)	Phen/TPM 7.5/46 mg (n=26)	Phen/TPM 15/92 mg (n=64)
Baseline Mean A1C (%)	**6.9**	**7.3**	**6.9**

LS Mean ΔA1C (%):
- Placebo: -0.04
- Phen/TPM 7.5/46 mg: -0.42
- Phen/TPM 15/92 mg: -0.23

Change in Diabetes Medications (Overall safety population[†])

Patients With Net Change* in Concomitant Antihyperglycemics (%):
- Placebo (n=227): 7.1
- Phen/TPM 7.5/46 mg (n=153): 1.9 ‡
- Phen/TPM 15/92 mg (n=295): 0 ‡
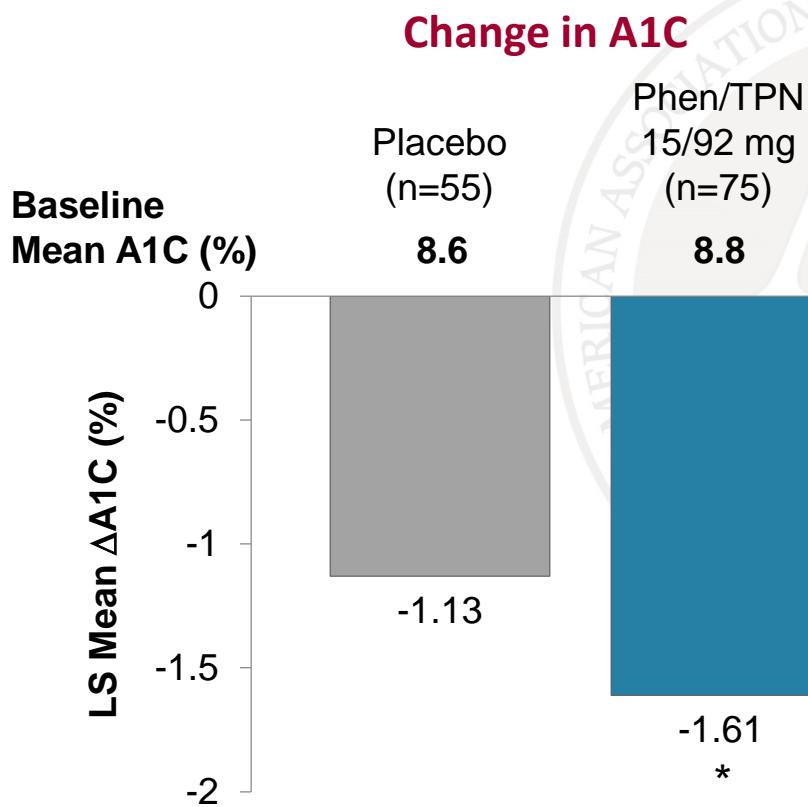
*Percent increase minus percent decrease. [†] The safety population was defined as all subjects who received at least 1 dose of study drug. ‡ P=0.013 for between-group differences.

LS = least squares; Phen/TPM = phentermine/topiramate.

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

Effects of Phentermine/Topiramate ER on Glucose Control in Advanced T2D

Poorly Controlled Type 2 Diabetes

Change in A1C

Change in Diabetes Medications[†]
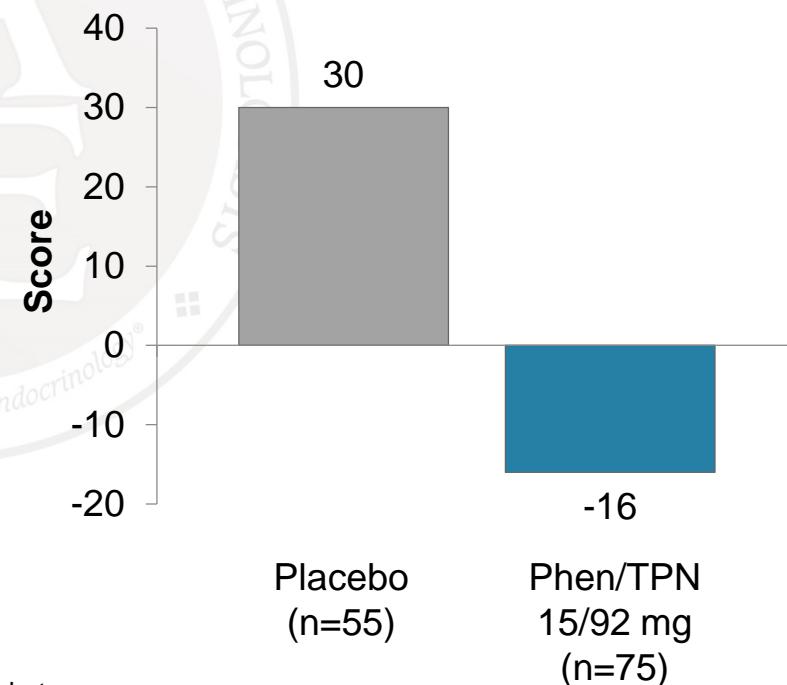
*P=0.038 vs placebo.

LS = least squares; Phen/TPM = phentermine/topiramate; T2D = type 2 diabetes.

[†]Net score reflecting change in medication number and change in dose level of diabetes medications.
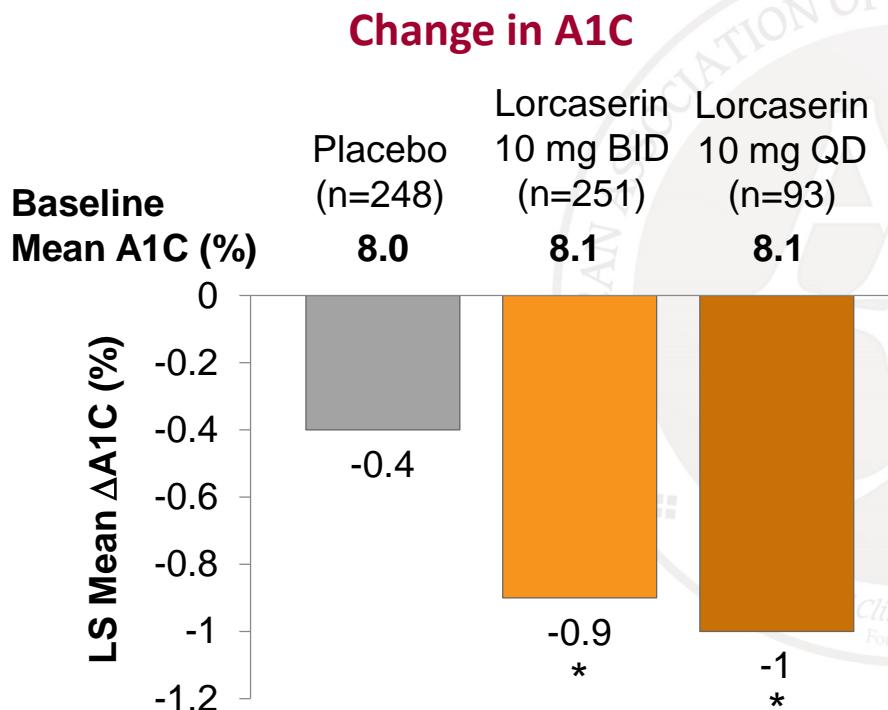
Garvey WT, et al. *Diabetes*. 2009;58(suppl 2): Abstr. 361-OR.

Effect of Lorcaserin on Glycemia in Type 2 Diabetes

BLOOM-DM Study

Change in A1C

Change in Diabetes Medications

Baseline Mean A1C (%)

	Placebo (n=248)	Lorcaserin 10 mg BID (n=251)	Lorcaserin 10 mg QD (n=93)
	8.0	8.1	8.1

LS Mean ΔA1C (%)

- Placebo: -0.4
- Lorcaserin 10 mg BID: -0.9 *
- Lorcaserin 10 mg QD: -1 *
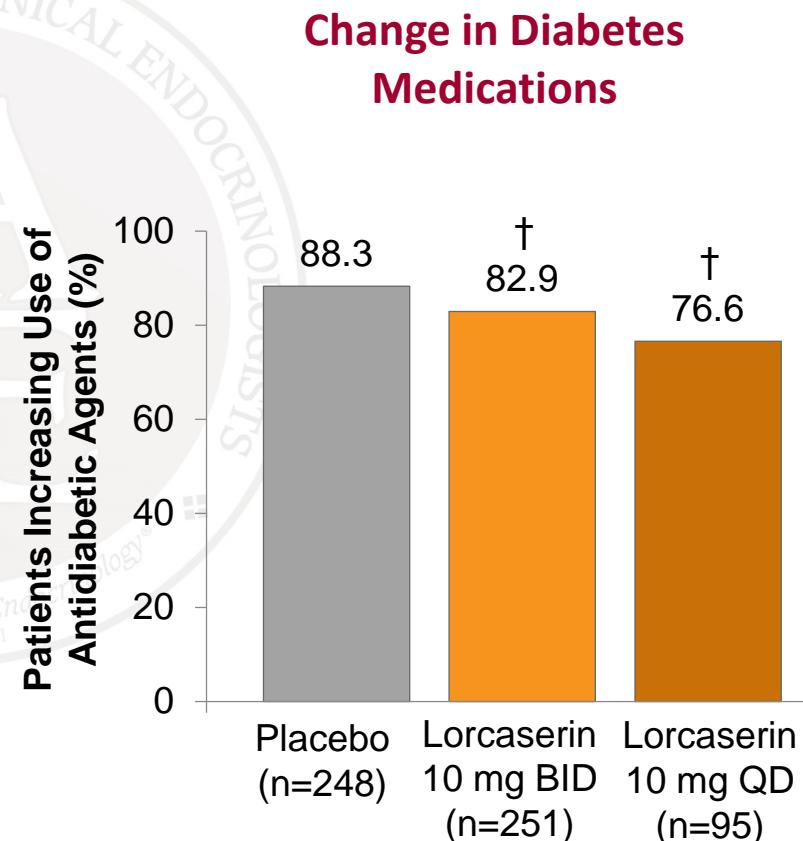
NNT = 4.4
To achieve a 1.0% reduction in A1C

Patients Increasing Use of Antidiabetic Agents (%)

- Placebo (n=248): 88.3
- Lorcaserin 10 mg BID (n=251): 82.9 †
- Lorcaserin 10 mg QD (n=95): 76.6 †

*$P<0.001$ vs placebo. †$P=0.087$ vs placebo.
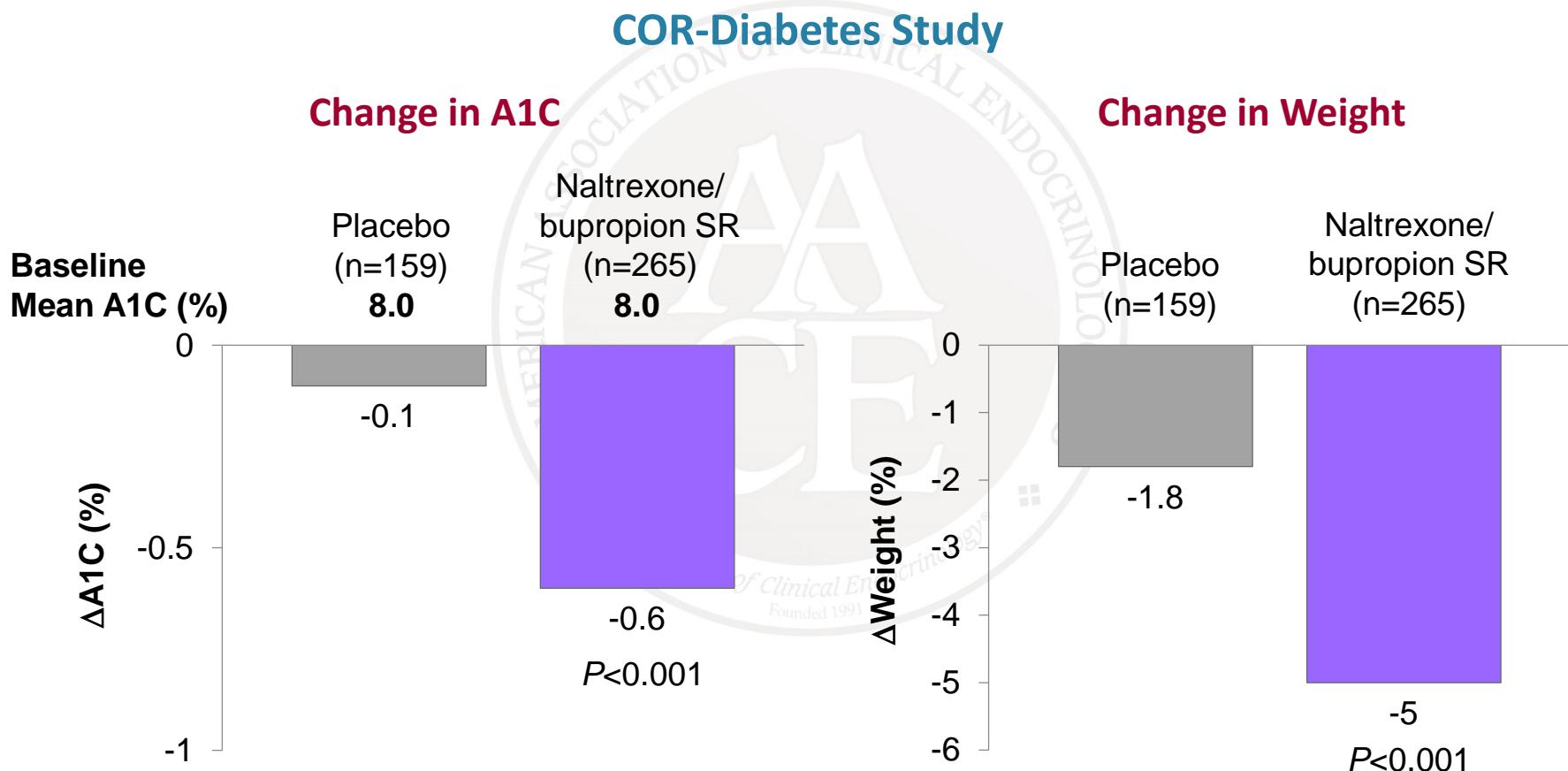
BLOOM-DM = Behavioral Modification and Lorcaserin for Obesity and Overweight Management in Diabetes Mellitus.

O'Neil PM, et al. *Obesity*. 2012;20:1426-1436.

Handelsman Y, et al. Presented at The Obesity Society, November 2-7, 2014. Boston, MA. Abstr. # T-2576-P.

Effect of Naltrexone/Bupropion SR on Glycemia in Type 2 Diabetes

COR-Diabetes Study
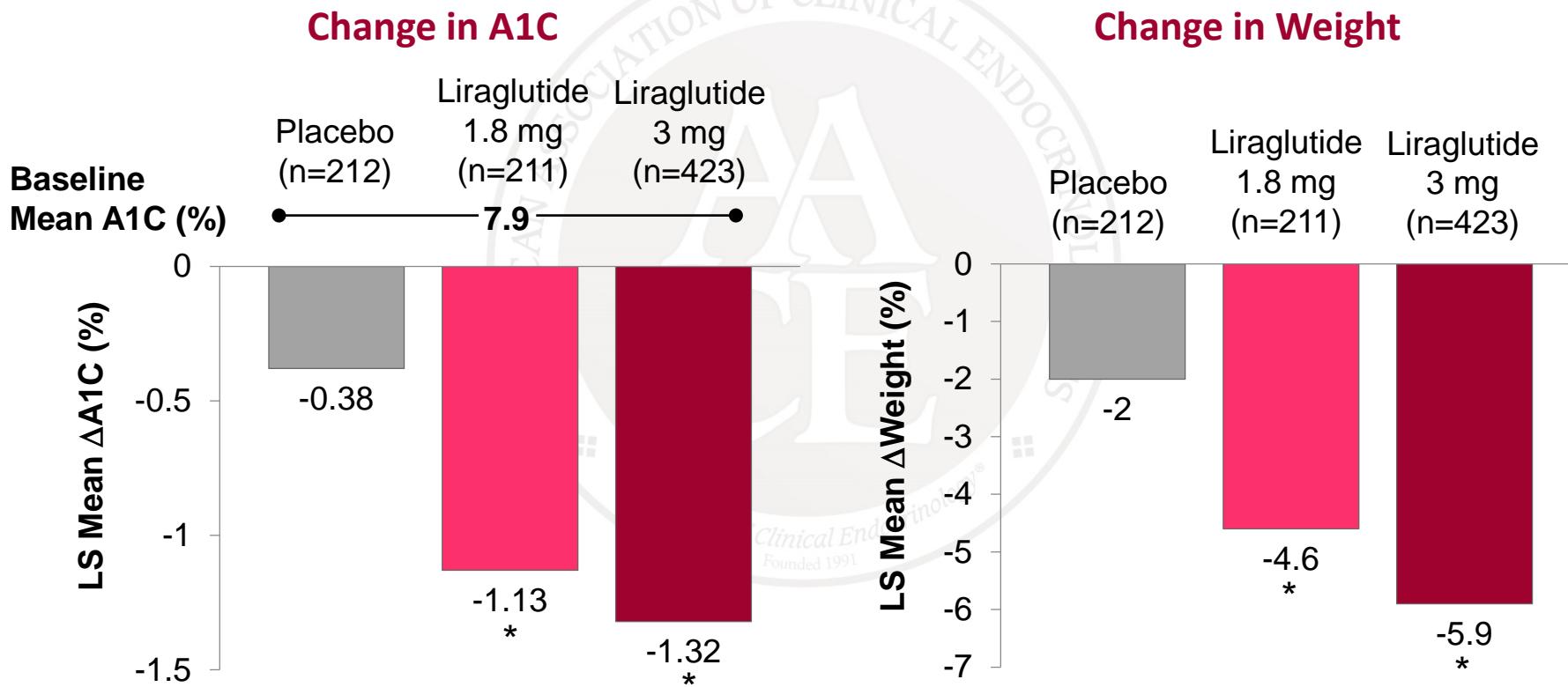
COR = CONTRAVE Obesity Research; LOCF = last observation carried forward; MITT = modified intent to treat; SR, sustained release.
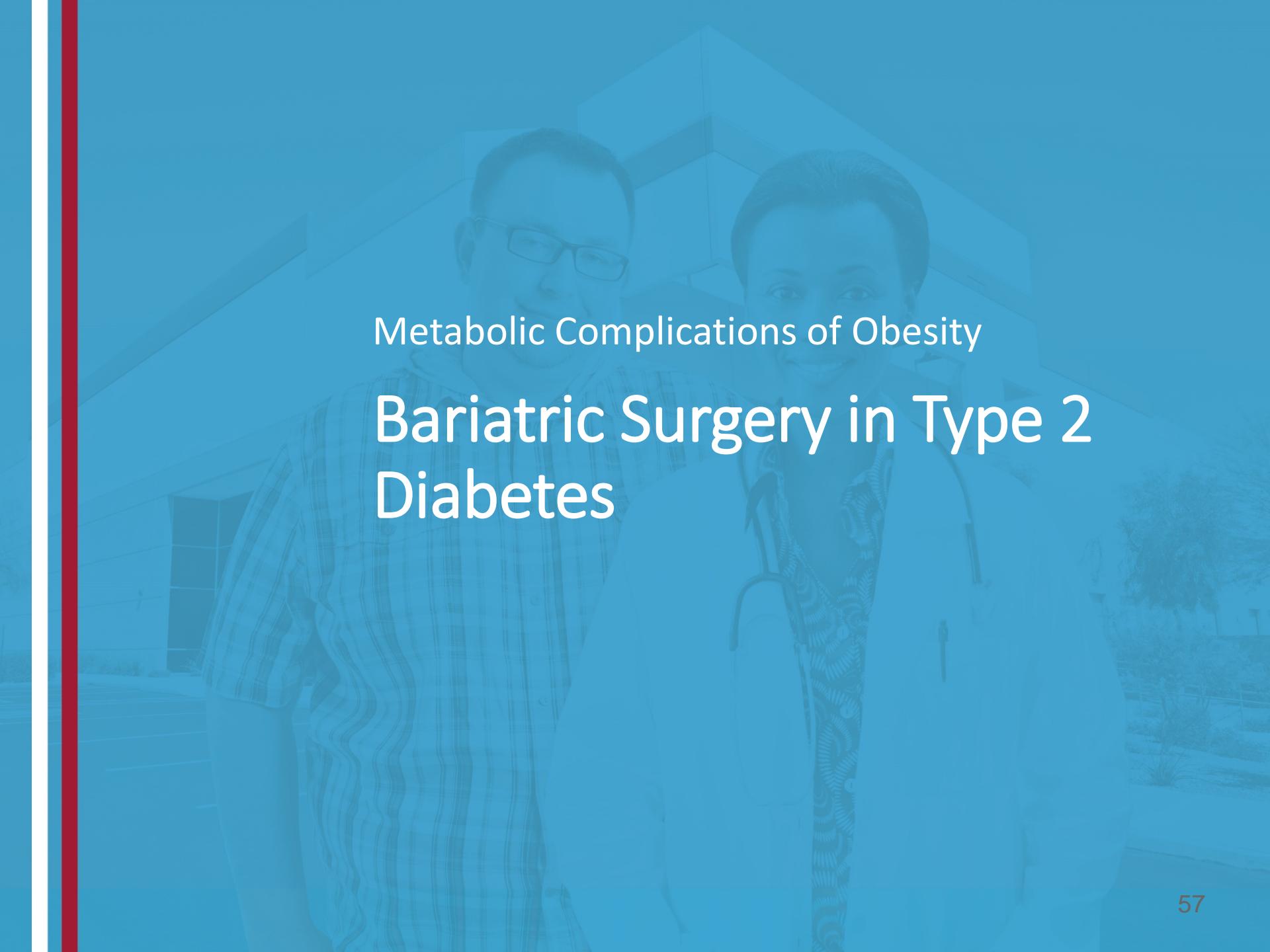
Hollander P, et al. *Diabetes Care*. 2013;36:4022-4029.

Effects of High- and Low-Dose Liraglutide in Type 2 Diabetes

SCALE Diabetes Study
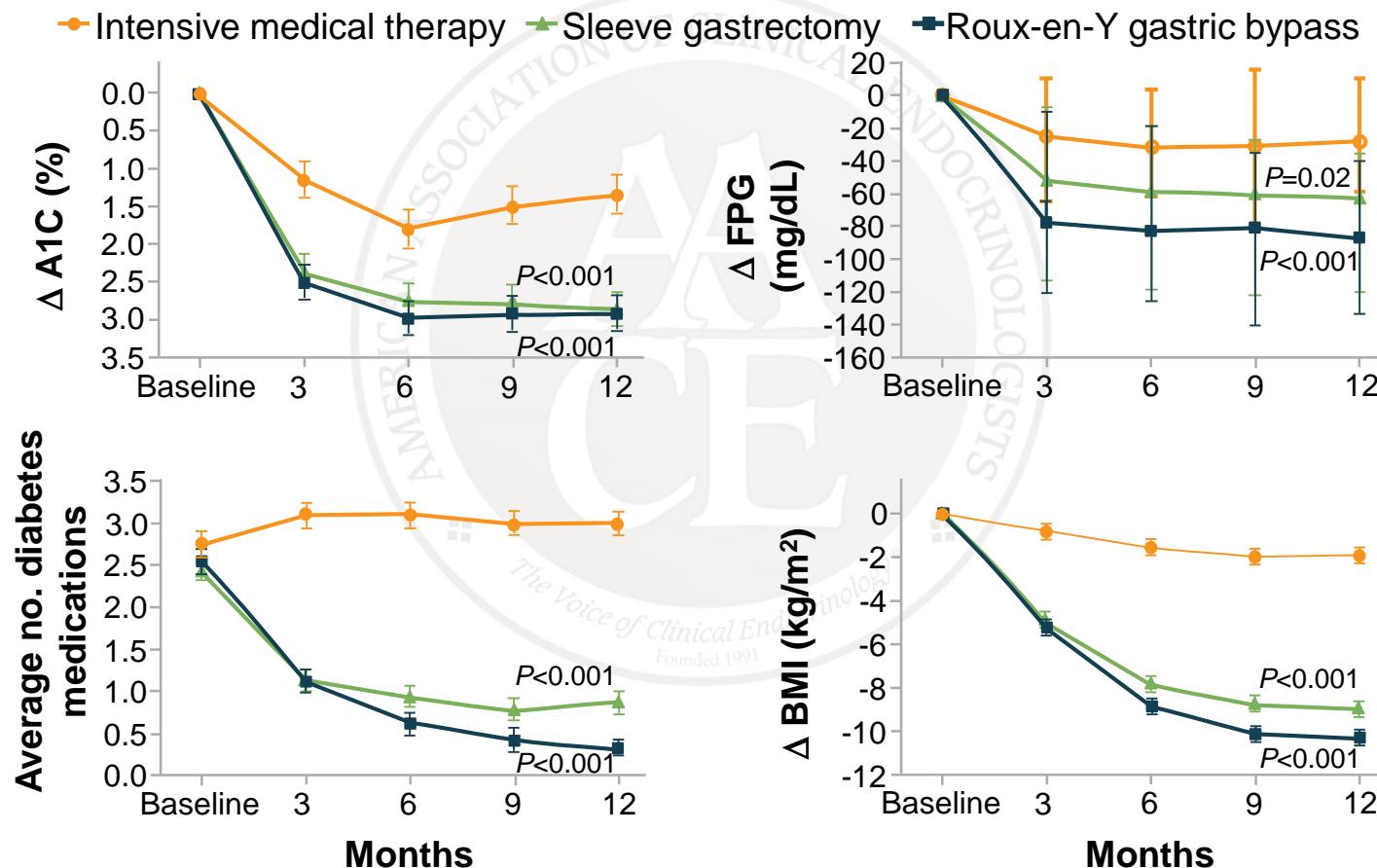
Change in A1C

Change in Weight

*P<0.0001 vs placebo.

Davies M, et al. *Diabetes*. 2014;63(suppl 1):A26, Abstr. 97-OR.

Metabolic Complications of Obesity

Bariatric Surgery in Type 2 Diabetes

Surgical Intervention in Type 2 Diabetes
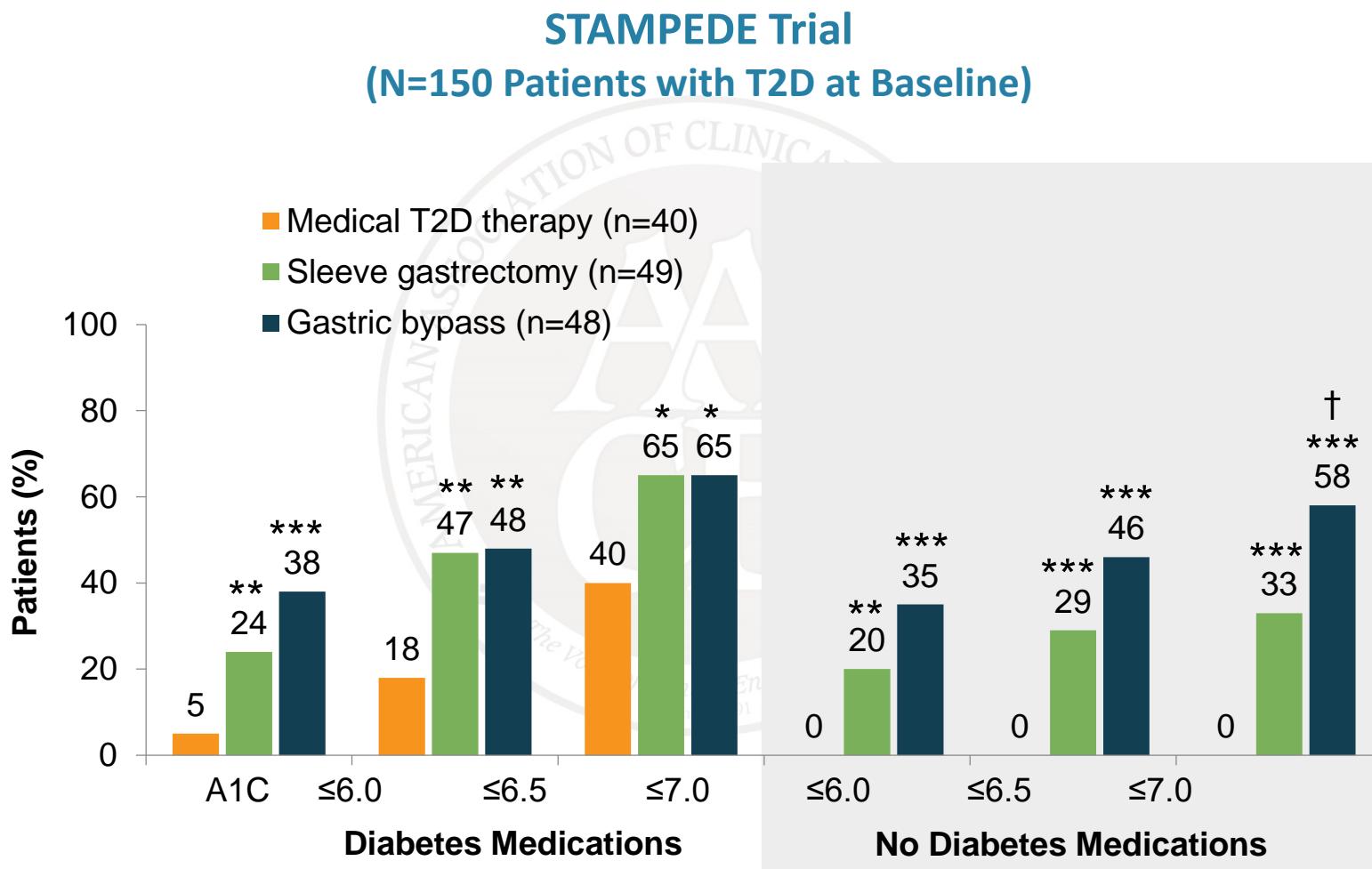
STAMPEDE Trial
(n=150)

FPG = fasting plasma glucose; STAMPEDE = Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently.

Schauer PR, et al. *N Engl J Med.* 2012;366:1567-1576.

Resolution of Type 2 Diabetes After 3 Years

STAMPEDE Trial
(N=150 Patients with T2D at Baseline)

Legend:
- Medical T2D therapy (n=40)
- Sleeve gastrectomy (n=49)
- Gastric bypass (n=48)

Diabetes Medications:
- A1C ≤6.0: 5, 24 (**), 38 (***)
- ≤6.5: 18, 47 (**), 48 (**)
- ≤7.0: 40, 65 (*), 65 (*)

No Diabetes Medications:
- ≤6.0: 0, 20 (**), 35 (***)
- ≤6.5: 0, 29 (***), 46 (***)
- ≤7.0: 0, 33 (***), 58 (†, ***)

Y-axis: Patients (%)
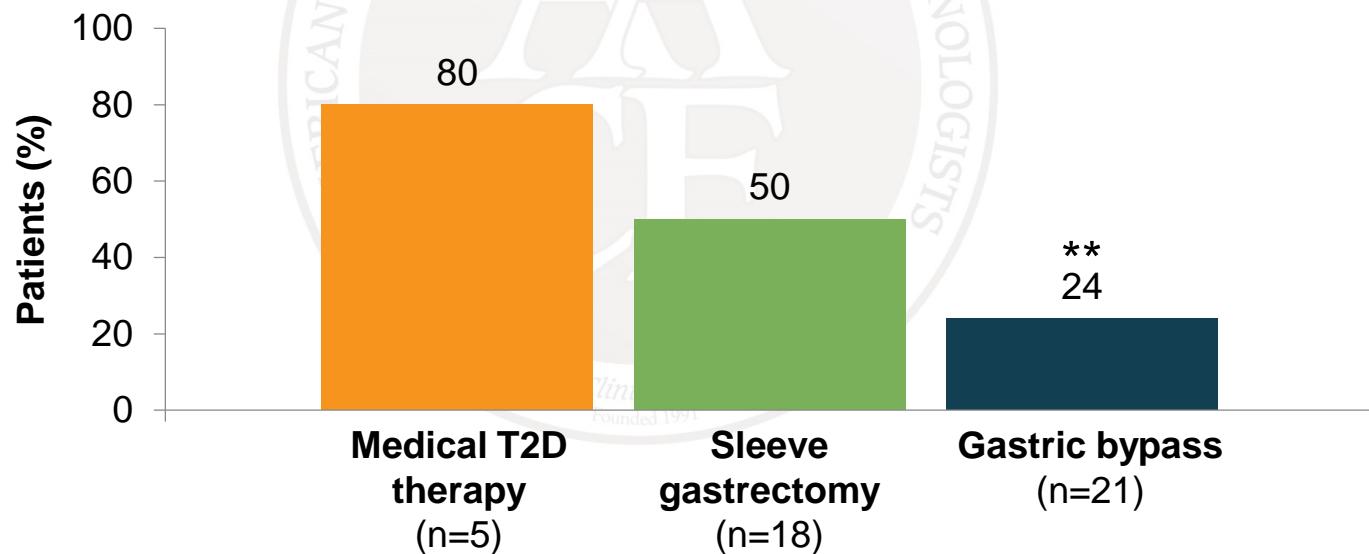
*P<0.05, **P≤0.01, ***P<0.001 vs medical therapy. †P=0.01 vs sleeve gastrectomy.

STAMPEDE = Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently; T2D = type 2 diabetes.

Schauer PR, et al. *N Engl J Med*. 2014;370:2002-2013.

Loss of Glycemic Control After 3 Years

STAMPEDE Trial
(N=150 Patients with T2D at Baseline)


*Defined as failure to maintain A1C ≤6.0%.
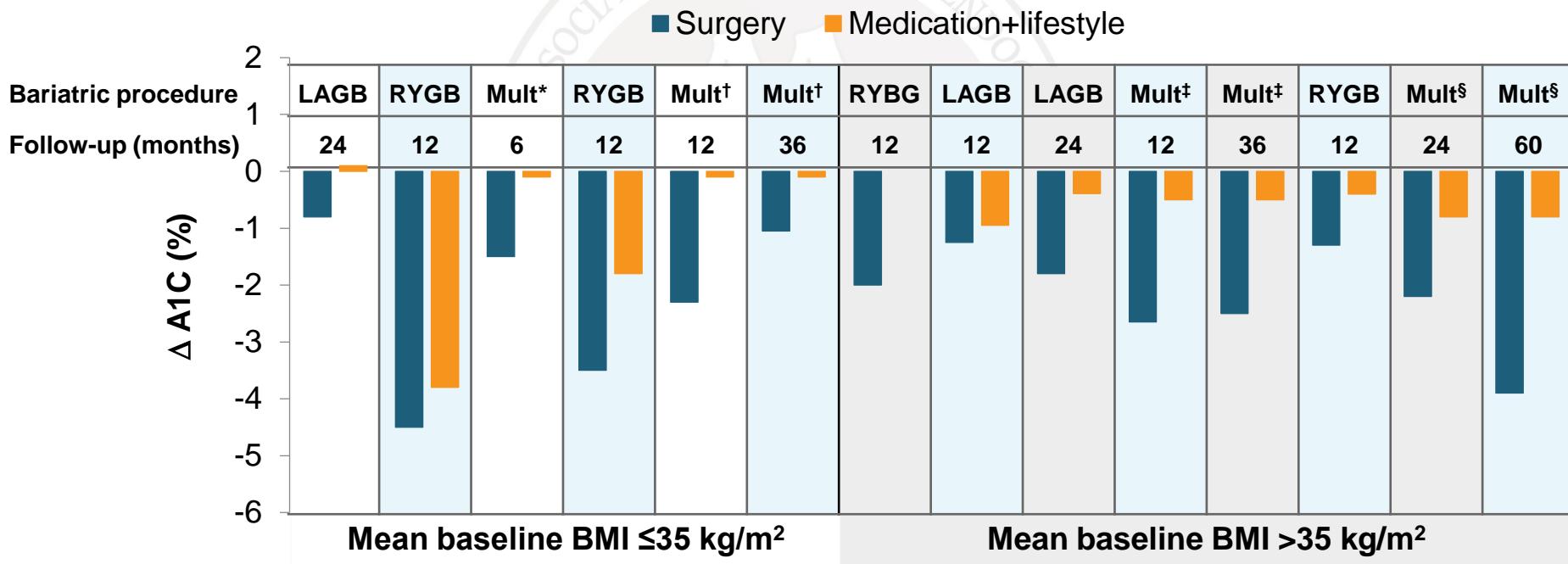
**P=0.03 vs medical therapy.

 T2D = type 2 diabetes.

Schauer PR, et al. *N Engl J Med.* 2014;370:2002-2013.

Effect of Bariatric Surgery vs Medication plus Lifestyle Therapy on A1C in T2D

Second Diabetes Surgery Summit
(Systematic Review; N=11 RCTs)

■ Surgery ■ Medication+lifestyle

Bariatric procedure	LAGB	RYGB	Mult*	RYGB	Mult†	Mult†	RYBG	LAGB	LAGB	Mult‡	Mult‡	RYGB	Mult§	Mult§
Follow-up (months)	24	12	6	12	12	36	12	12	24	12	36	12	24	60

Y-axis: Δ A1C (%), from 2 to -6

Left section: **Mean baseline BMI ≤35 kg/m²**
Right section: **Mean baseline BMI >35 kg/m²**
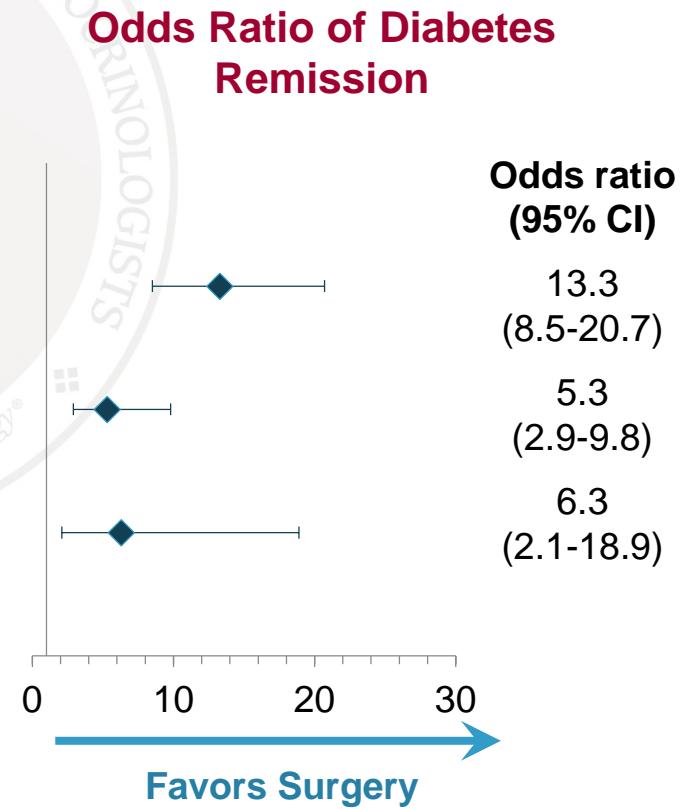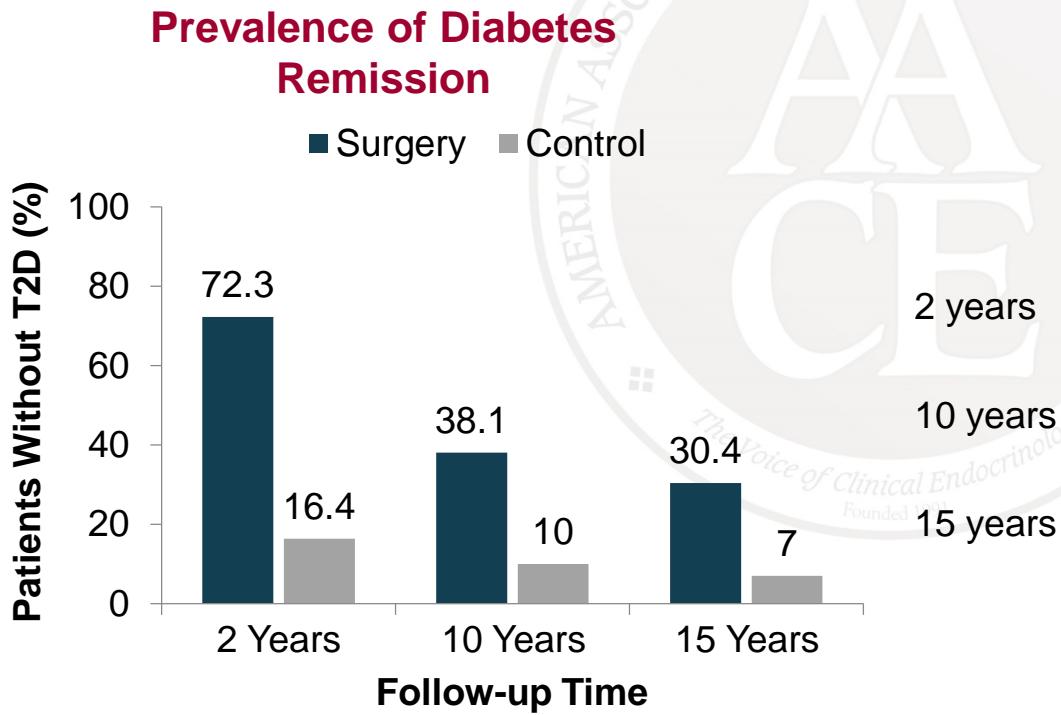
*RYGB, LAGB, or SG. †RYGB or LAGB. ‡SYGB or SG. §RYGB or BPD.

BPD = biliopancreatic diversion; BMI = body mass index; LAGB = laparoscopic adjustable gastric band; Mult = multiple treatment arms; RCT = randomized controlled trial; RYGB = Roux en Y gastric bypass; SG = sleeve gastrectomy; T2D = type 2 diabetes.

Rubino F, et al. *Diabetes Care*. 2016;39:861-877.

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Long-Term Diabetes Remission After Bariatric Surgery

Swedish Obese Subjects Study
**(N=603 Patients with T2D at Baseline)**

Prevalence of Diabetes Remission

■ Surgery ■ Control

Patients Without T2D (%)

Follow-up Time	Surgery	Control
2 Years	72.3	16.4
10 Years	38.1	10
15 Years	30.4	7

Follow-up Time

Odds Ratio of Diabetes Remission

	Odds ratio (95% CI)
2 years	13.3 (8.5-20.7)
10 years	5.3 (2.9-9.8)
15 years	6.3 (2.1-18.9)

Favors Surgery

T2D = type 2 diabetes.
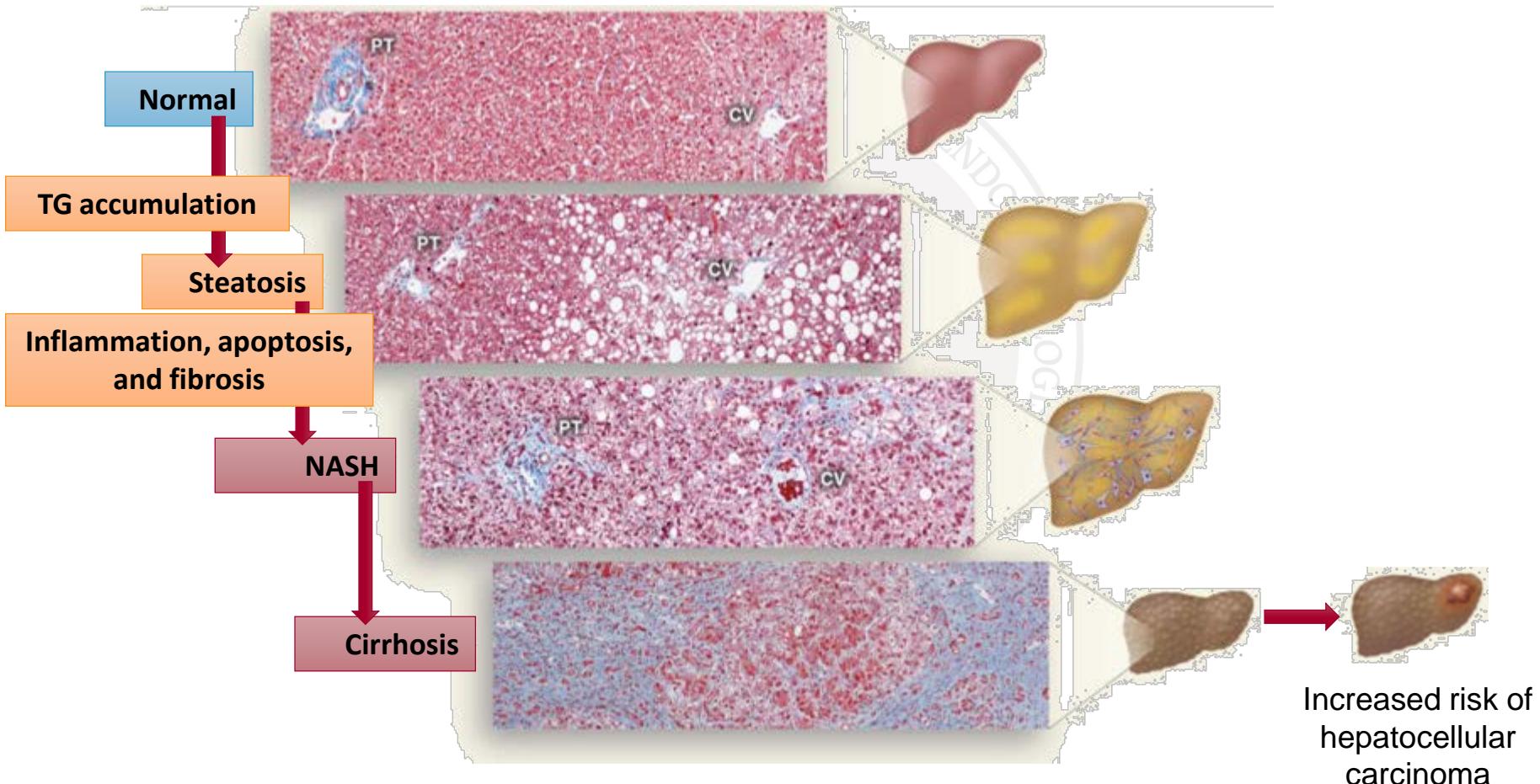
Sjostrom L, et al. *JAMA*. 2014;311:2297-2304.

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Metabolic Complications of Obesity

Liver Disease

Progression of NAFLD

Normal

TG accumulation

Steatosis

Inflammation, apoptosis, and fibrosis

NASH

Cirrhosis

Increased risk of hepatocellular carcinoma
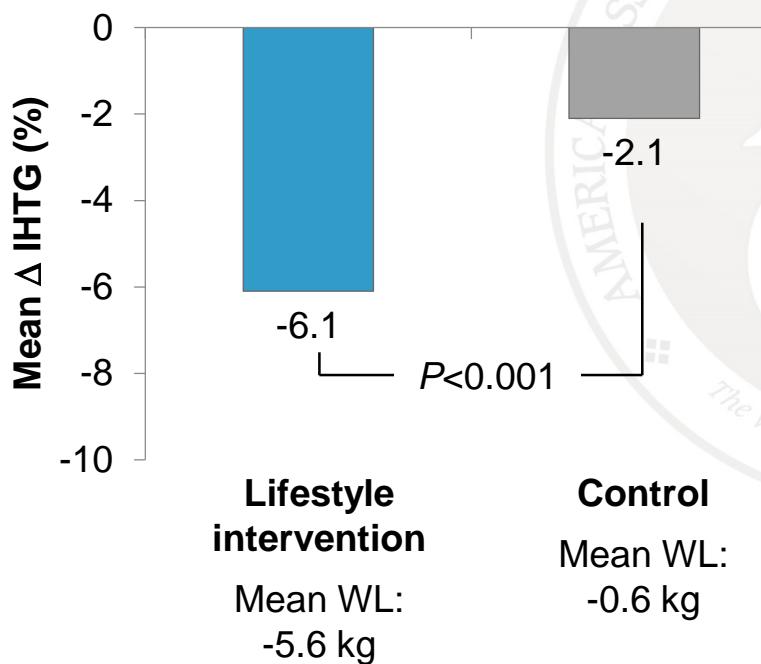
CV = central vein; NAFLD = nonalcoholic fatty liver disease; NASH = nonalchoholic steatohepatitis; PT = portal triad; TG = triglyceride.

Cohen JC, et al. *Science*. 2011;332:1519-1523.
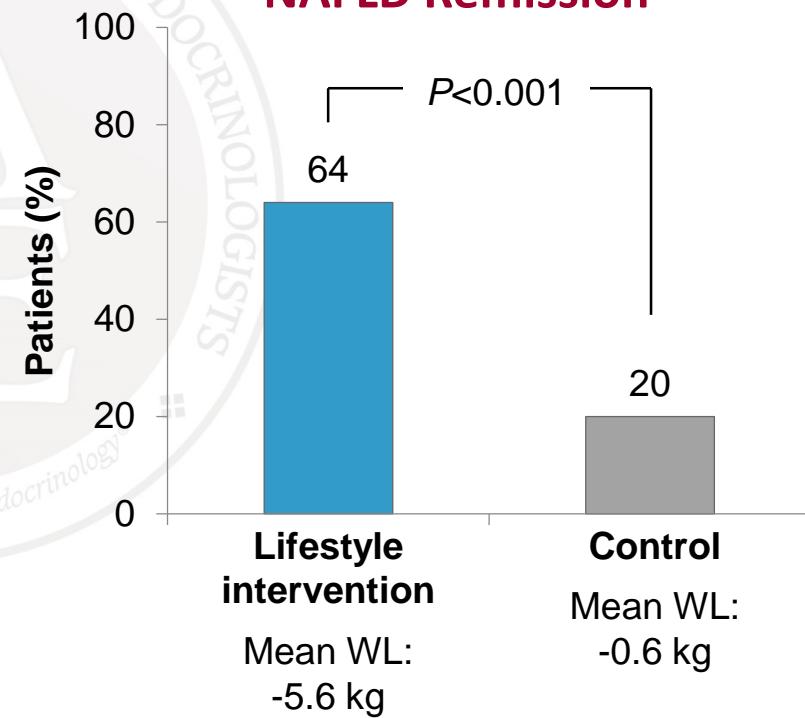
Effect of Weight Loss on NAFLD

Community Intervention Program
(N=154)

Intrahepatic Triglycerides After 12 Months

Mean Δ IHTG (%)

- Lifestyle intervention: -6.1
  - Mean WL: -5.6 kg
- Control: -2.1
  - Mean WL: -0.6 kg

P<0.001

Patients Achieving NAFLD Remission*

Patients (%)

- Lifestyle intervention: 64
  - Mean WL: -5.6 kg
- Control: 20
  - Mean WL: -0.6 kg

P<0.001

*At month 12, defined as IHTG <5% by proton-magnetic resonance spectroscopy.

IHTG = intrahepatic triglyceride content; WL = weight loss.

Wong VW, et al. *J Hepatol.* 2013;59:536-542.

Summary

- Obesity is associated with higher risks of prediabetes and type 2 diabetes

- Weight loss with lifestyle therapy, pharmacotherapy, or bariatric surgery
  - Reduces the risk of progression to type 2 diabetes
  - Improves glycemic control in patients with type 2 diabetes