Why Do We Treat Obesity?

Cardiovascular Complications

AACE OBESITY RESOURCE CENTER

AACE ONLINE ENDOCRINE ACADEMY

Prevalence of Weight-Related Comorbidities in the U.S.

NHANES 2007-2010
U.S. Adults Age ≥18 Years (N=12,175)

Legend: ■ Normal weight ■ Overweight ■ Obese

Hypertension
SBP ≥140 mmHg,
DBP ≥90 mmHg,
or using anti-HT drug

Normal weight: 19.8, Overweight: 26.4, Obese: 35.6

Dyslipidemia
Non-HDL-C ≥160 mg/dL
or using cholesterol-lowering drug

Normal weight: 28.6, Overweight: 44.2, Obese: 49.7

Diabetes
FPG ≥126 mg/dL,
A1C ≥6.5%,
or DM diagnosis

Normal weight: 5.4, Overweight: 8.2, Obese: 18.5

Y-axis: Patients (%), 0 to 60
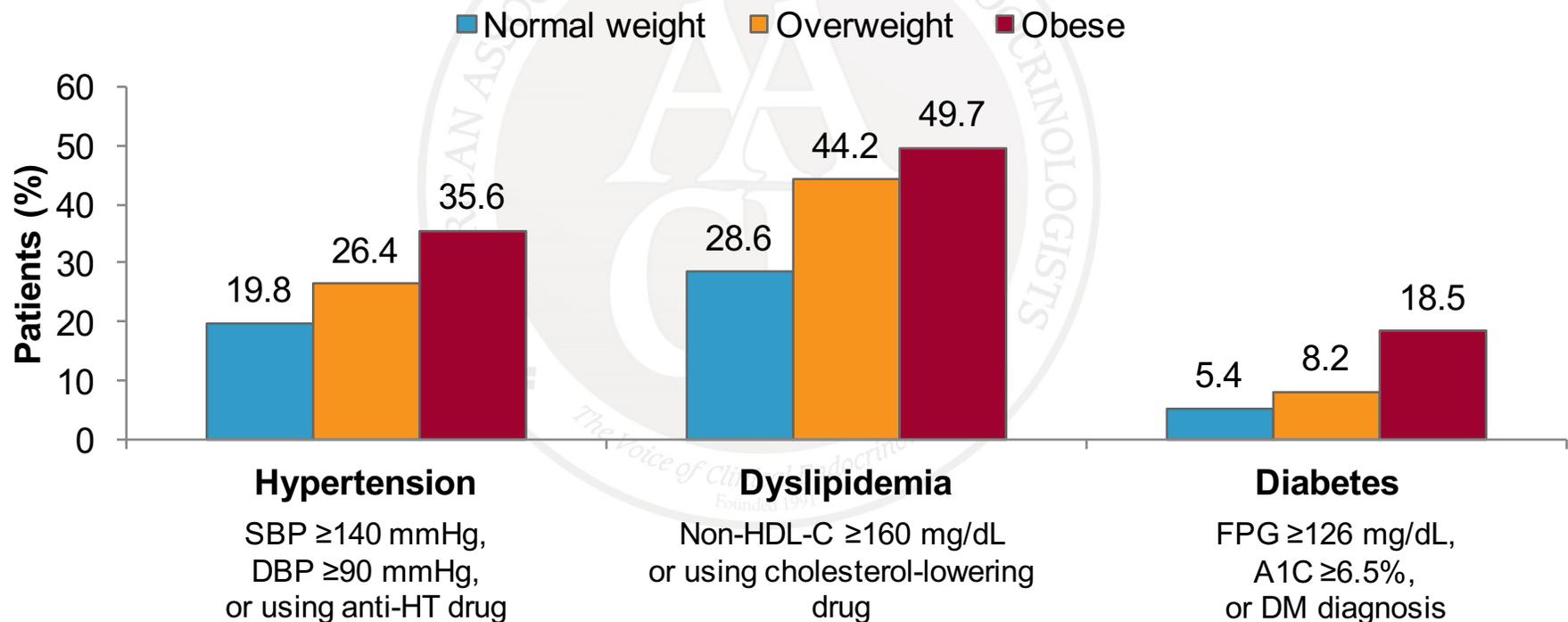
Normal weight = BMI 18 to <25 kg/m^2; overweight = BMI 25 to <30 kg/m^2; obese = BMI ≥30 kg/m^2

BMI = body mass index; DM = diabetes mellitus; DBP = diastolic blood pressure; HDL-C = high density lipoprotein cholesterol; HT = hypertension; SBP = systolic blood pressure.

Saydah S, et al. *Obesity (Silver Spring).* 2014;22:1888-1895.

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)	Dyslipidemia	5% to ≥15%	• Lower triglycerides • Raise HDL-c • Lower non-HDL-c
		Hypertension	5% to ≥15%	• Lower systolic and diastolic BP • Reductions in number and/or doses of antihypertensive medications
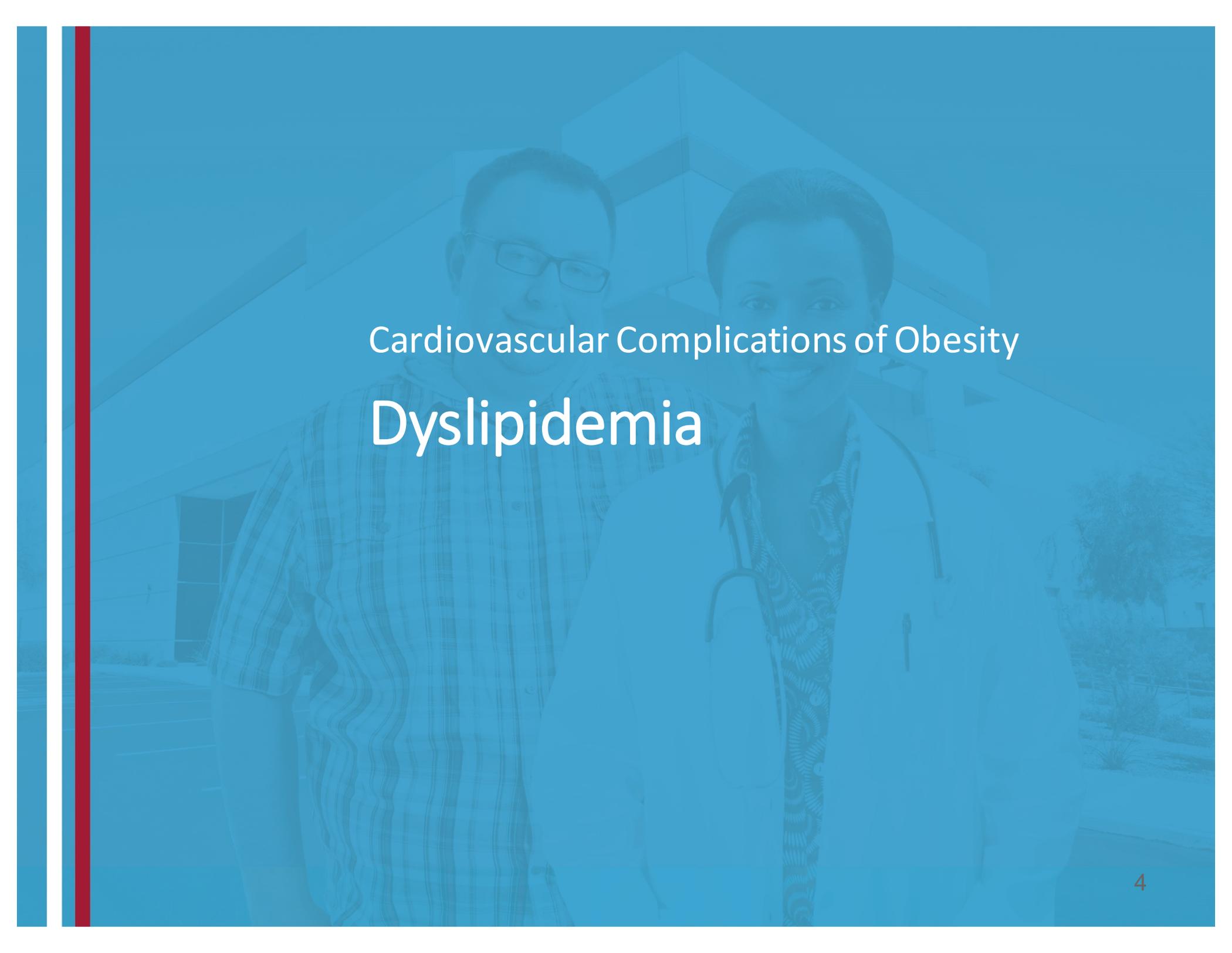
Cardiovascular Complications of Obesity

Dyslipidemia

Atherogenic Dyslipidemia

- Common in T2D and the metabolic syndrome

- Features
  - Elevated triglycerides
  - Decreased HDL-C
  - Increased small, dense LDL particles
 - Postprandial increase in triglyceride-rich lipoproteins

Fatty Acid Metabolism and Development of Atherogenic Dyslipidemia
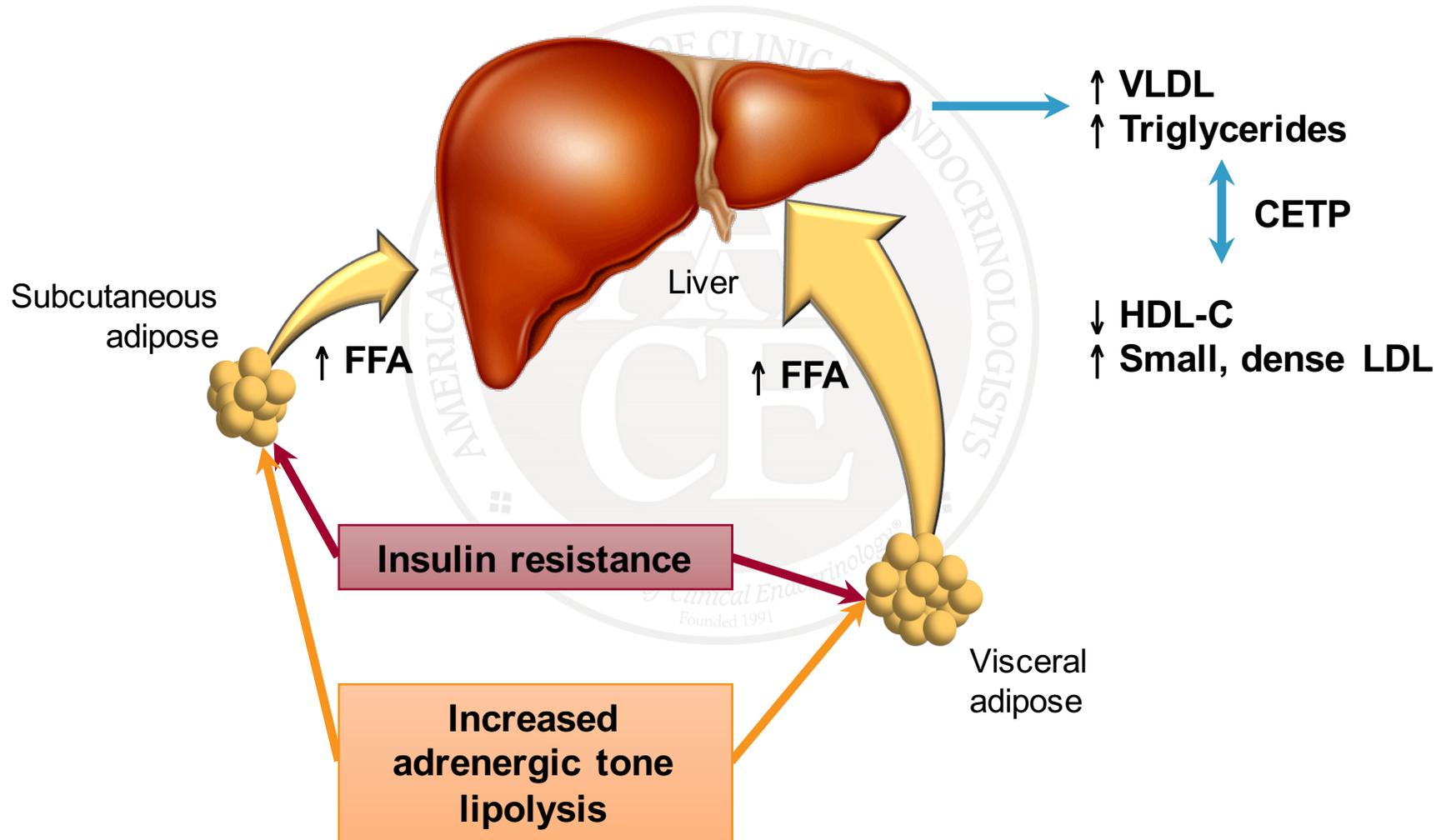
FFA = free fatty acid; HDL-C = high-density lipoprotein cholesterol; LDL = low-density lipoprotein; VLDL = very low density lipoprotein.

Intensive Lifestyle Intervention Reduces Dyslipidemia After 3 Years

Diabetes Prevention Program
(N=3234)

Legend: Placebo, Metformin, Intensive lifestyle intervention

Y-axis: Patients with dyslipidemia (%)
X-axis: Baseline, Year 1, Year 2, Year 3
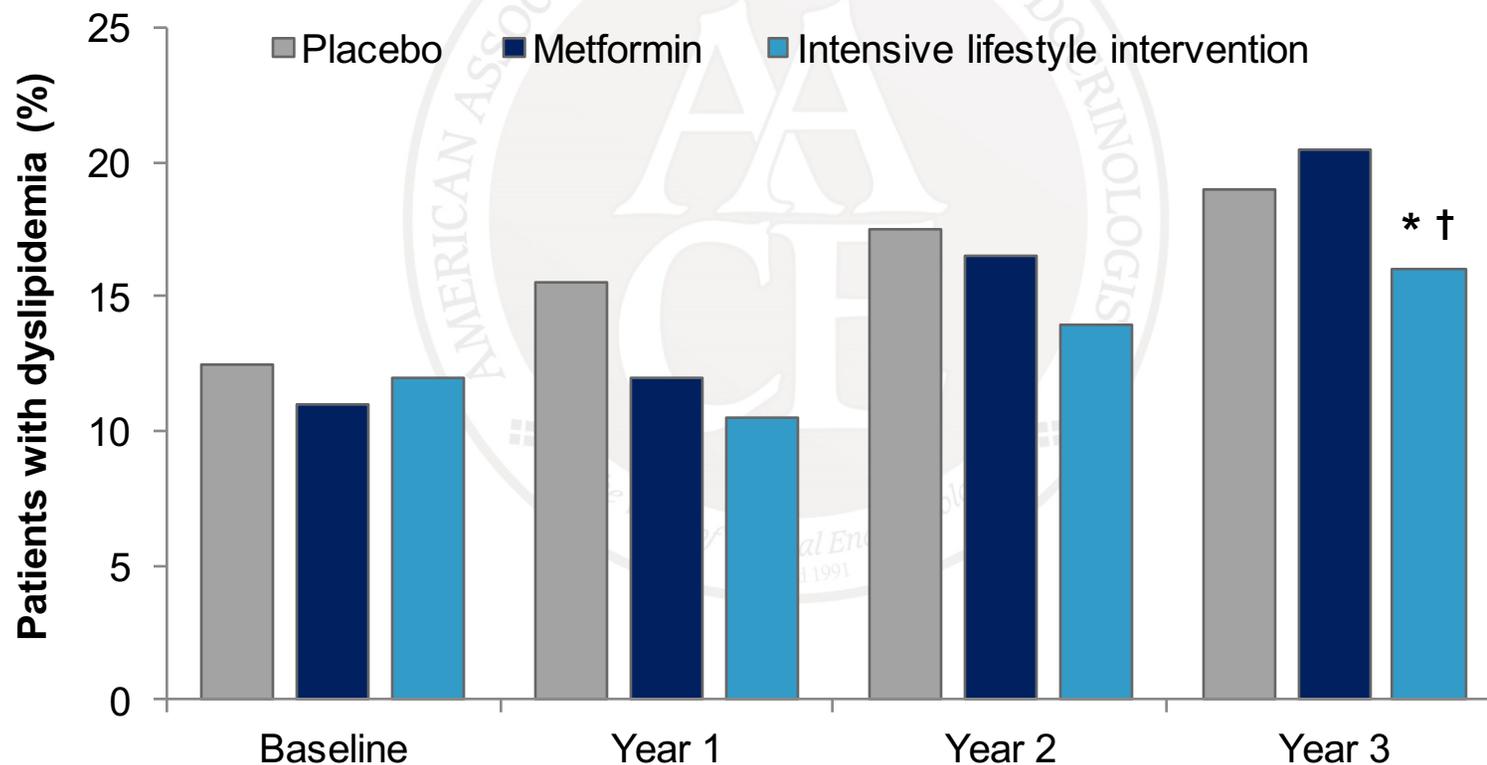
*P<0.001 vs placebo.

†P=0.015 vs metformin.

DPP Research Group. *Diabetes Care*. 2005;28:888-894.

# Weight Loss Leads to Less Atherogenic LDL

Weight Loss at 16 Weeks
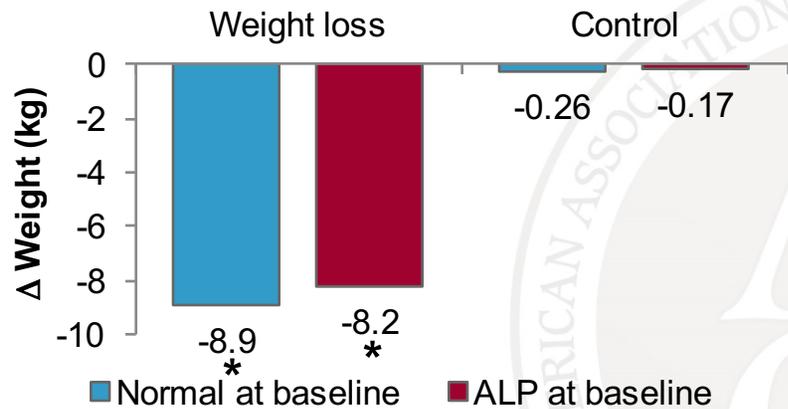
**Conversion from/to Atherogenic Lipoprotein Phenotype**
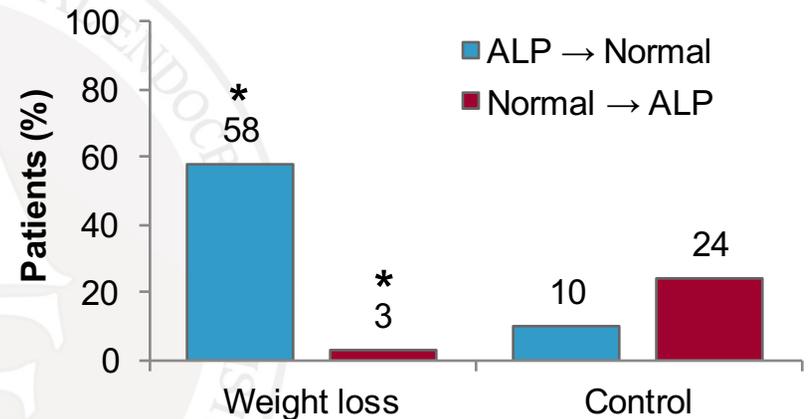
LDL Diameter
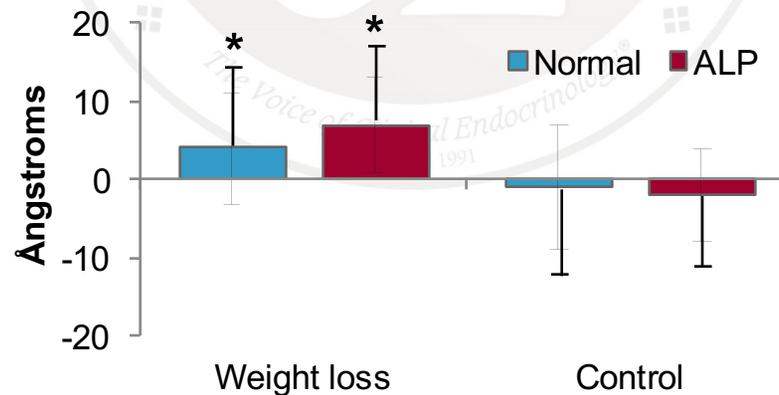
*P<0.0001 for weight loss vs control.

ALP = atherogenic lipoprotein phenotype, characterized by small, dense LDL particles; LDL = low density lipoprotein.

Siri-Tarino P, et al. *Obesity (Silver Spring).* 2009;17:1768-1775.

Weight Loss Improves LDL Subclass Patterns

## Patients with Atherogenic Lipoprotein Phenotype (n=80)
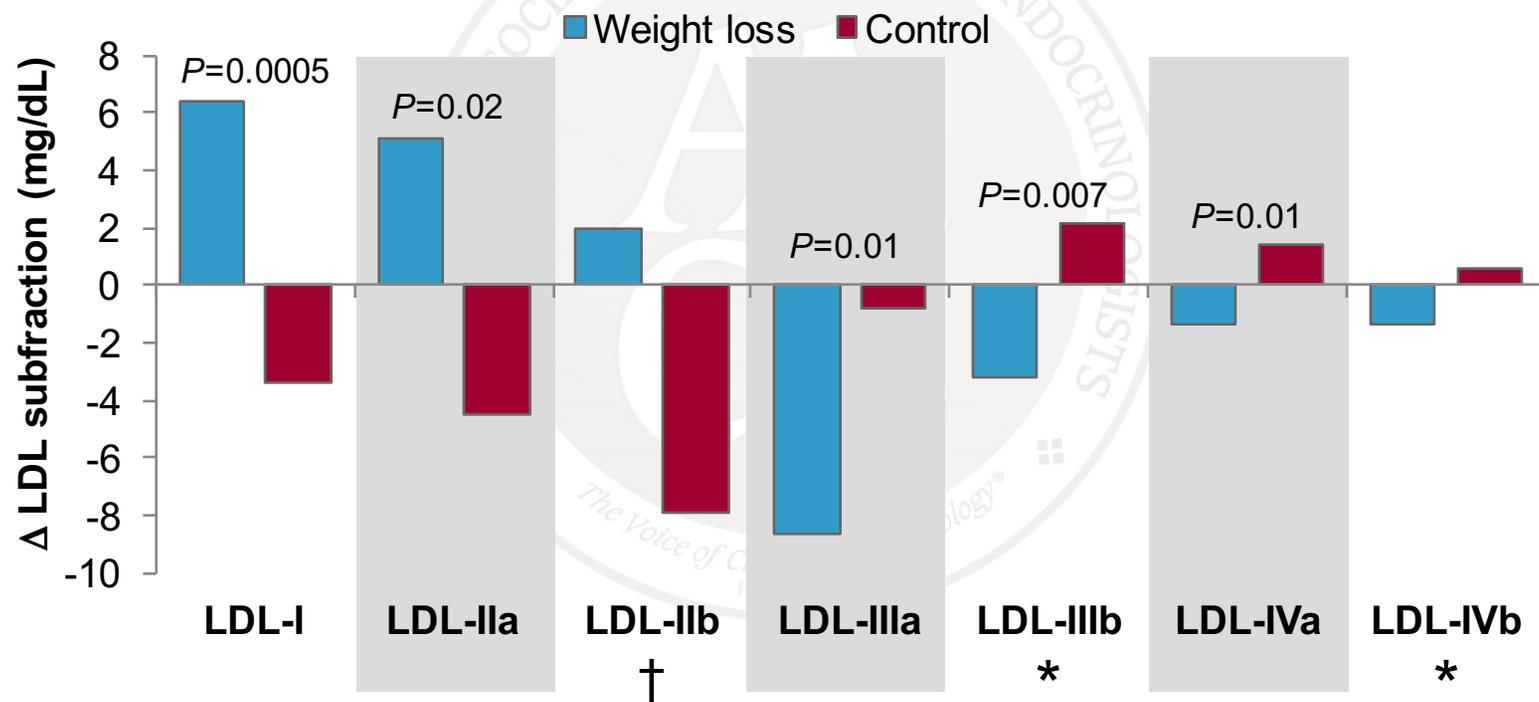
*Pro-atherogenic; †possibly anti-atherogenic.

ALP = atherogenic lipoprotein phenotype characterized by small, dense LDL particles; LDL = low density lipoprotein.

Siri-Tarino P, et al. *Obesity (Silver Spring).* 2009;17:1768-1775. Williams PT, et al. *Arterioscler Thromb Vasc Biol.* 2003;23:314-321.

Effect of Weight Loss in T2D on Lipids

Look AHEAD Trial
(N=5145)
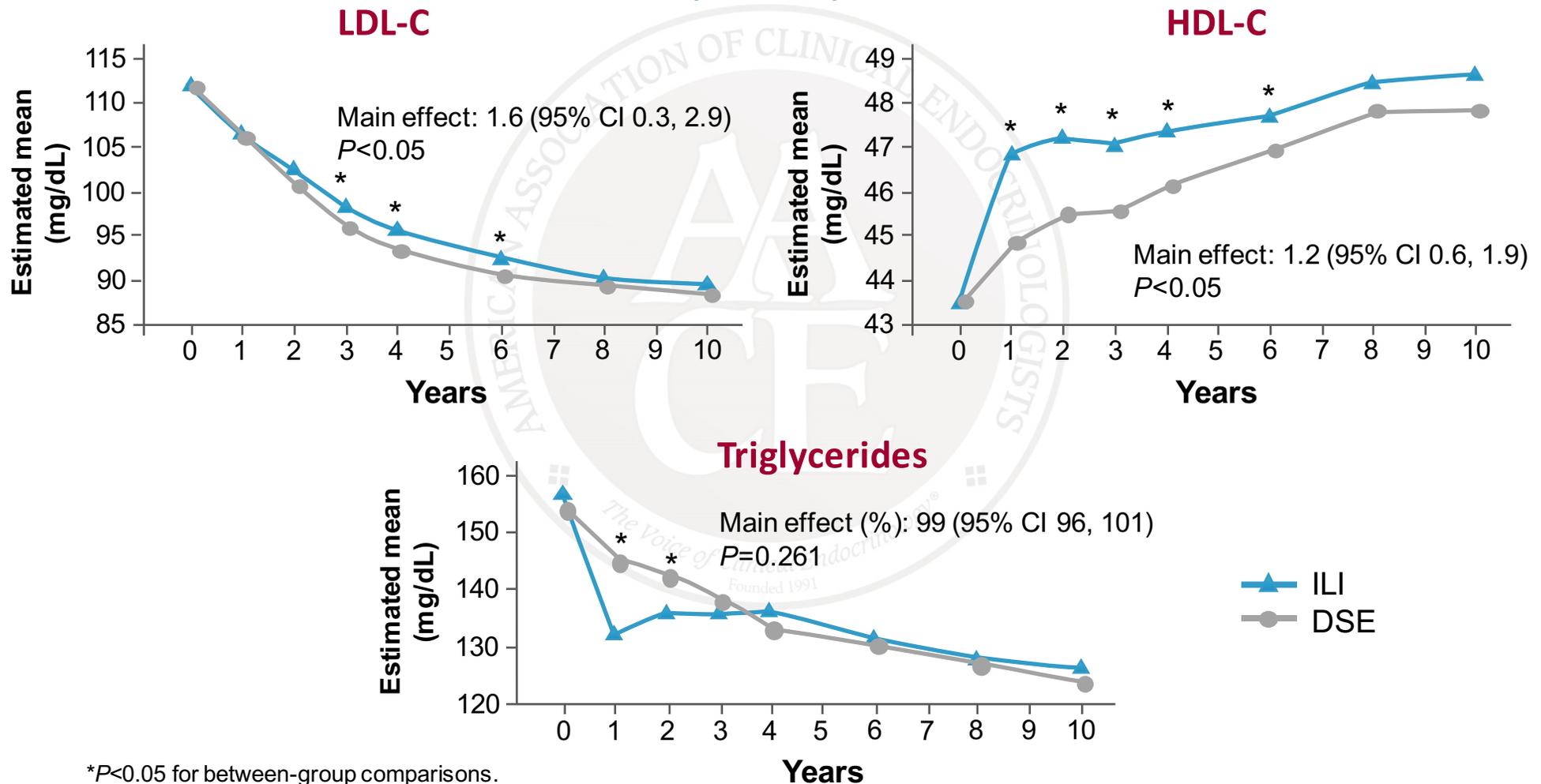
LDL-C

Main effect: 1.6 (95% CI 0.3, 2.9)
P<0.05

HDL-C

Main effect: 1.2 (95% CI 0.6, 1.9)
P<0.05

Triglycerides

Main effect (%): 99 (95% CI 96, 101)
P=0.261

— ▲ — ILI
— ● — DSE

*P<0.05 for between-group comparisons.

Main effect is the average of post-baseline differences.
CI = confidence interval; DSE = diabetes support and education; ILI = intensive lifestyle intervention; T2D = type 2 diabetes.

Look AHEAD Research Group. *N Engl J Med.* 2013;369:145-154.
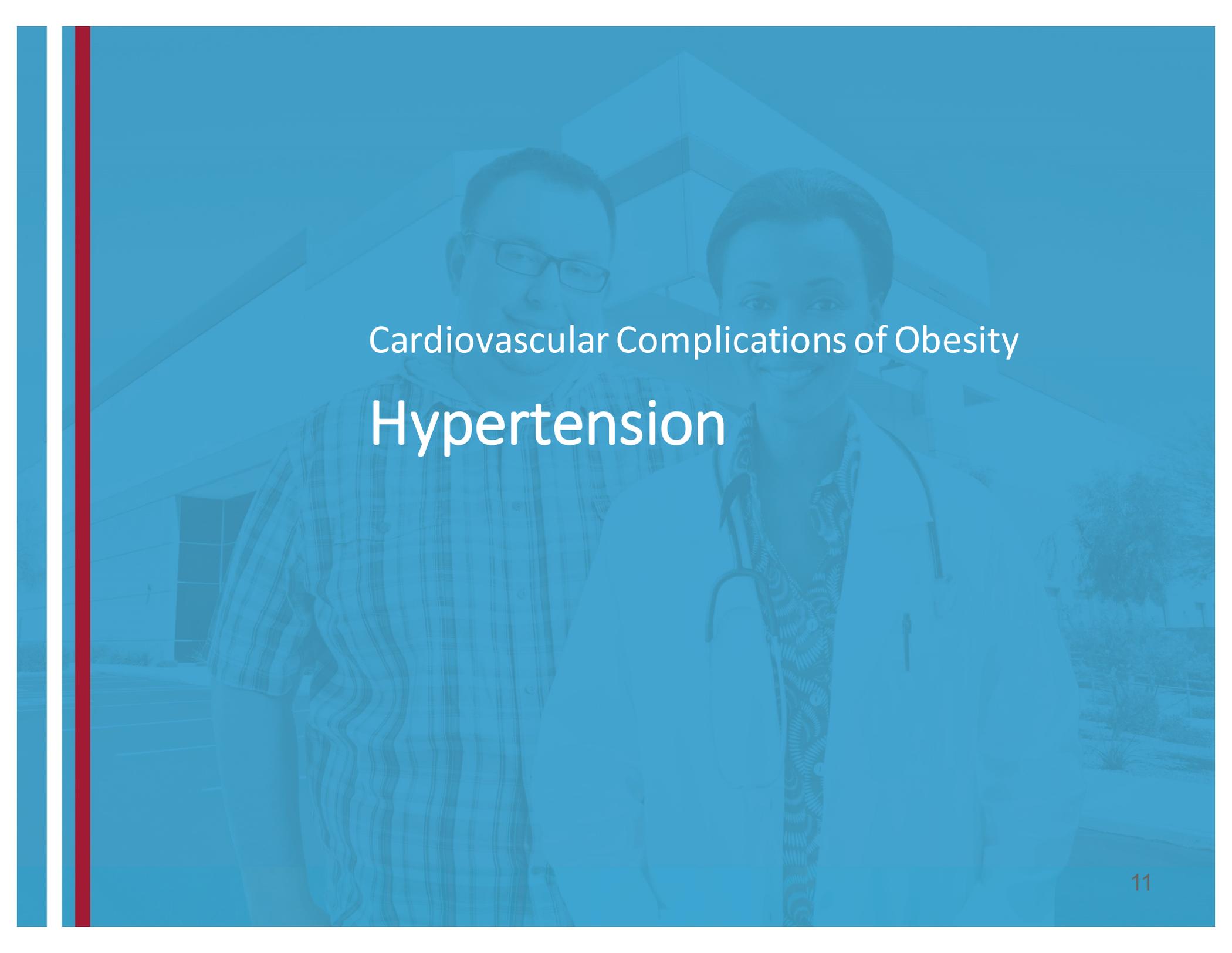
Cardiovascular Complications of Obesity

Hypertension

Intensive Lifestyle Intervention Reduces Blood Pressure

Diabetes Prevention Program
(N=3234)

Blood Pressure Change

- Placebo
- Metformin
- Intensive lifestyle intervention

P<0.001

Hypertension Prevalence

- Placebo
- Metformin
- Intensive lifestyle intervention
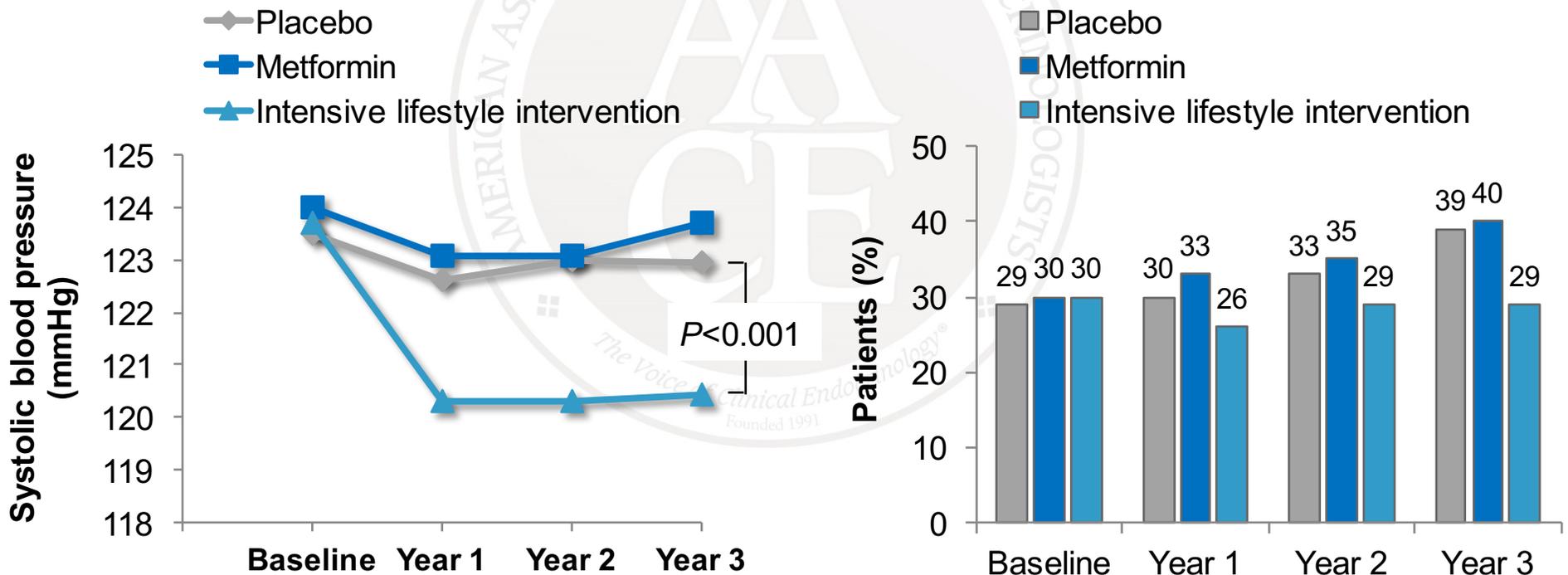
DPP = Diabetes Prevention Program; T2D = type 2 diabetes.

DPP Research Group. *Diabetes Care*. 2005;28:888-894.

Effect of Lifestyle Modification on Weight and Blood Pressure

The Finnish Diabetes Prevention Study
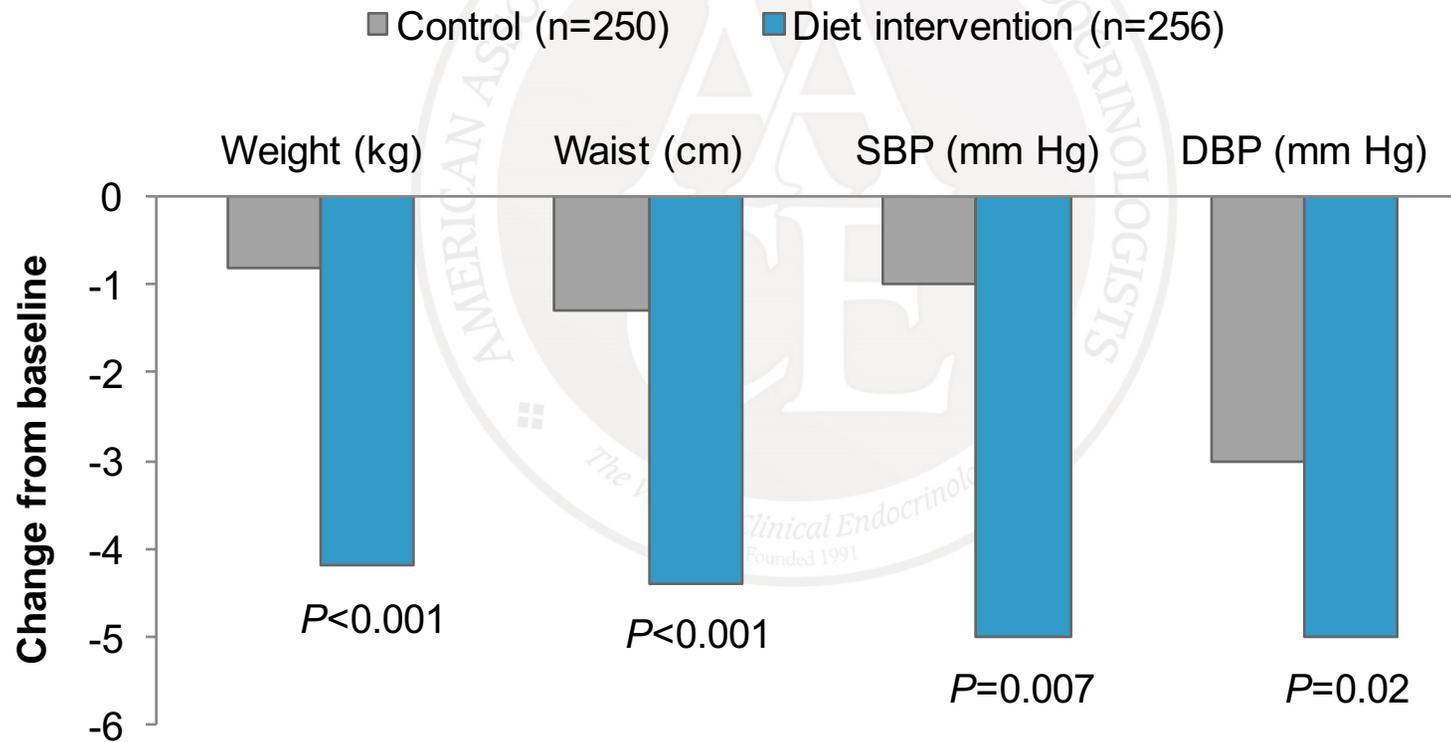
DBP = diastolic blood pressure; SBP = systolic blood pressure.

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

Effect of Weight Loss on Blood Pressure in Type 2 Diabetes

Look AHEAD Trial
(N=5145)
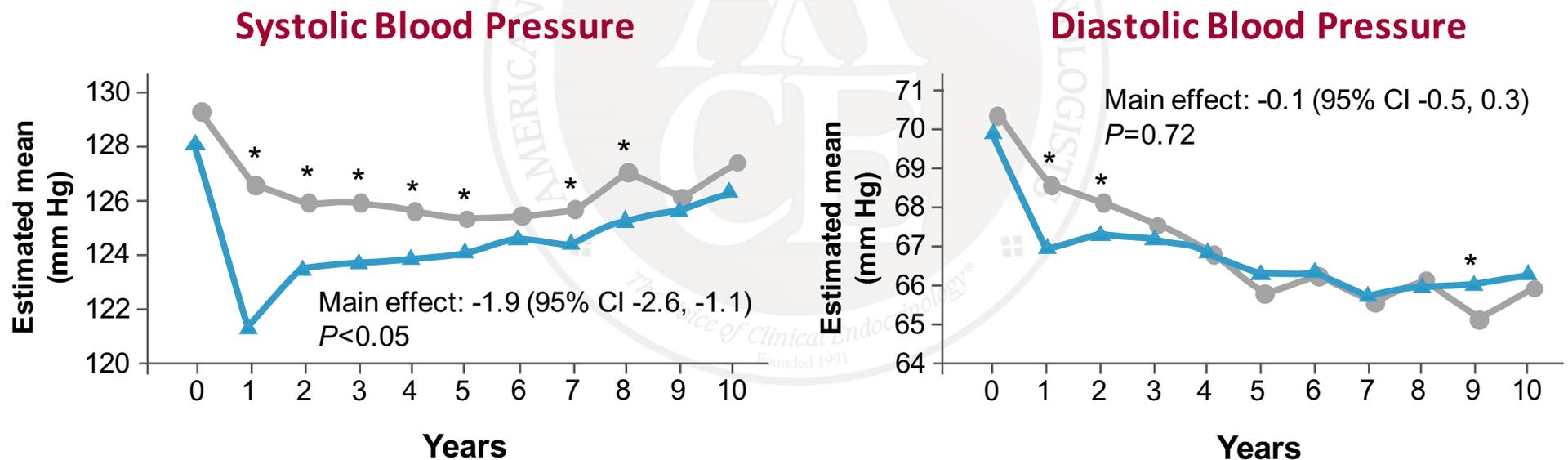
*P<0.05 for between-group comparisons.

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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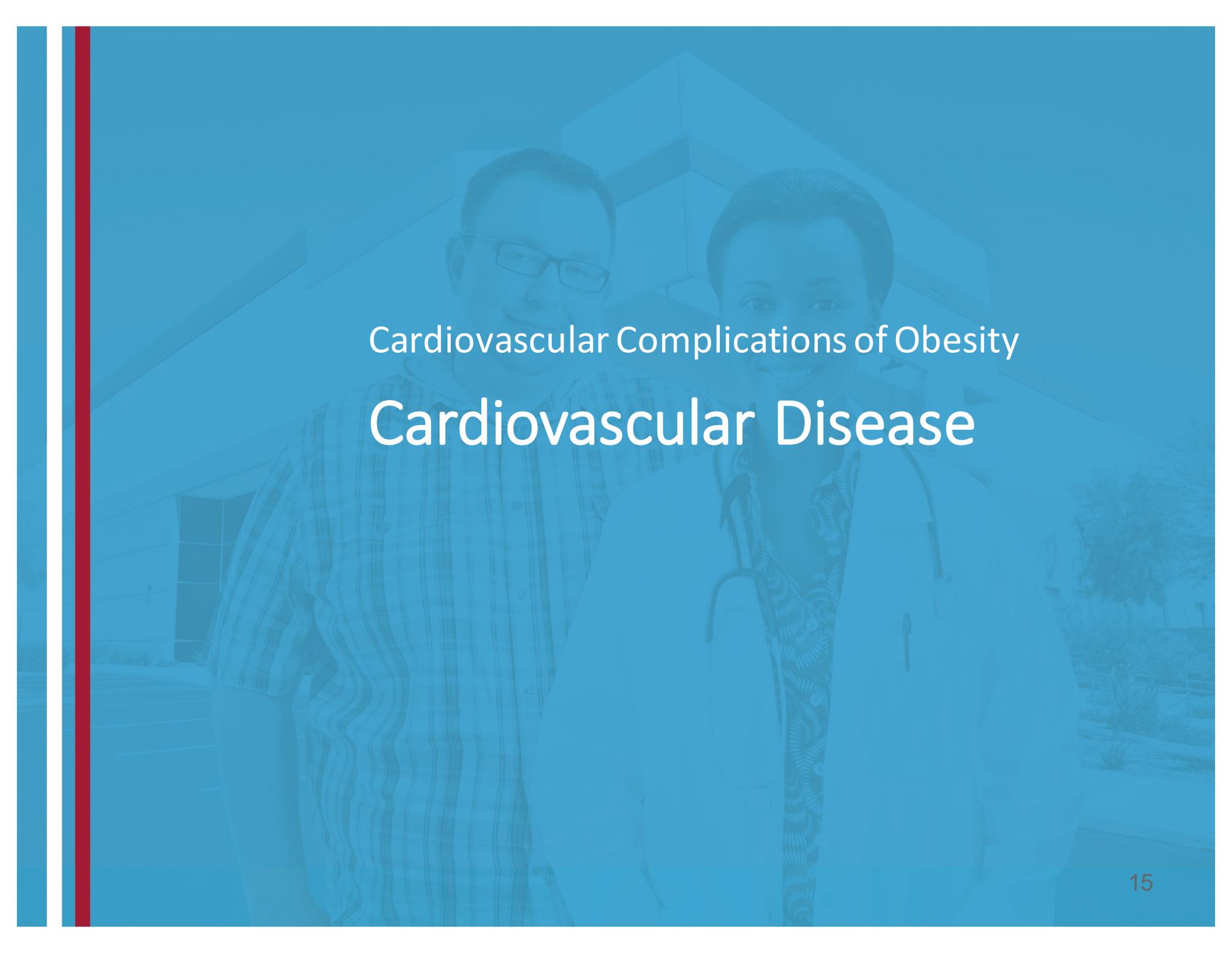
Cardiovascular Complications of Obesity
Cardiovascular Disease

Cardiovascular Disease Risk Factors

Major	Additional	Nontraditional

• Advancing age
• Features of dyslipidemia
   • High total serum cholesterol level
   • High non–HDL-C
   • High LDL-C
   • Low HDL-C
• Diabetes mellitus
• Hypertension
• Cigarette smoking
• Family history of CAD
	• Obesity or abdominal obesity
	• PCOS
	• Family history of hyperlipidemia
	• Features of dyslipidemia
	   • Small, dense LDL-C
	   • Increased Apo B
	   • Increased LDL particle number
	   • Fasting/postprandial hypertriglyceridemia
	   • Dyslipidemic triad*
		• Elevated clotting factors
		• Inflammation markers (hsCRP; Lp-PLA$_2$)
		• Hyperhomocysteinemia
		• Elevated uric acid
		• Features of dyslipidemia
		   • Apo E4 isoform
		   • Elevated lipoprotein (a)

*Hypertriglyceridemia; low HDL-C; and small, dense LDL-C.

Apo = apolipoprotein; CAD = coronary artery disease; HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; Lp-PLA$_2$ = lipoprotein-associated phospholipase A$_2$; PCOS = polycystic ovary syndrome.

Jellinger PS, et al. *Endocr Pract*. 2012;18(suppl 1):1-78.

Coronary Artery Disease Risk Categories

Risk Category	Risk Determinant
Very high	Established or recent hospitalization for coronary, carotid, and peripheral vascular disease – or – Diabetes plus 1 or more additional risk factor(s)

High	≥2 risk factors and 10-year risk* >20%
	– or –
	CHD risk equivalent
	• Diabetes ± other risk factors
	• Noncoronary atherosclerotic disease
	    • Peripheral arterial disease
	    • Abdominal aortic aneurysm
	    • Carotid artery disease

Moderately high	≥2 risk factors and 10-year risk 10% to 20%
Moderate	≥2 risk factors and 10-year risk <10%
Low	≤1 risk factor

*Framingham Risk Score

CHD = coronary heart disease.

Jellinger PS, et al. *Endocr Pract*. 2012;18(suppl 1):1-78.

Abdominal Obesity and Increased Risk of Cardiovascular Events

The HOPE Study

Waist Circumference (cm)		
	Men	**Women**
Tertile 1	<95	<87
Tertile 2	95-103	87-98
Tertile 3	>103	>98
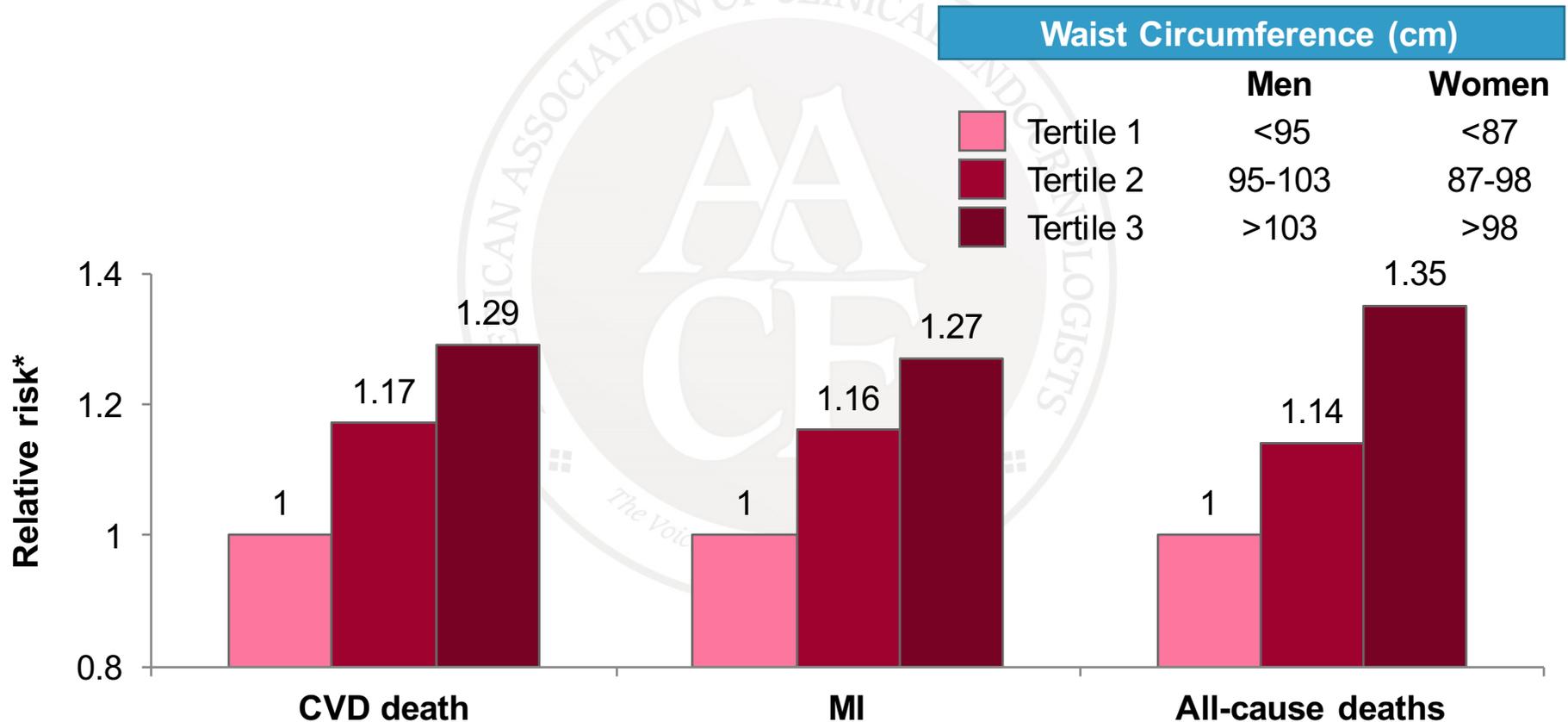
*Adjusted for BMI, age, smoking, sex, CVD, diabetes, HDL-C, and total cholesterol.

BMI = body mass index; CVD = cardiovascular disease; HDL-C = high density lipoprotein cholesterol; MI = myocardial infarction.

Dagenais GR, et al. *Am Heart J*. 2005;149:54-60.

Cumulative Diabetes Incidence as a Function of Increasing CMDS Risk Stage

CARDIA Study Cohort

Legend:
- Stage 0, Metabolically healthy
- Stage 1
- Stage 2
- Stage 3

Y-axis: Cumulative diabetes incidence (%)
X-axis: Follow-up time (years)

| 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.

Survival Probability as a Function of Increasing CMDS Risk Stage

NHANES


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

CMDS = cardiometabolic disease staging; CVD = cardiovascular disease; HDL-C = high density lipoprotein cholesterol; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; NHANES = National Health and Nutrition Examination Survey; T2D = type 2 diabetes.

Guo F, et al. *Obesity*. 2014;22:110-118.

CVD Risk Factors: AACE Targets

Risk Factor	Recommended Goal
Weight	Reduce by 5% to 10%; avoid weight gain
Lipids	
LDL-C, mg/dL	<70 very high risk; <100 all other risk categories
Non-HDL-C, mg/dL	<100 very high risk; <130 all other risk categories
Triglycerides, mg/dL	<150
TC/HDL-C ratio	<3.0 very high risk; <3.5 all other risk categories
ApoB, mg/dL	<80 very high risk; <90 high risk
LDL particles	<1000 very high risk; <1200 high risk
Blood pressure	
Systolic, mm Hg	~130
Diastolic, mm Hg	~80
Blood glucose	
FPG, mg/dL	<100
2-hour OGTT, mg/dL	<140
Anticoagulant therapy	Use aspirin for primary and secondary prevention of CVD events

FPG = fasting plasma glucose; OGTT = oral glucose tolerance test.

Garber AJ, et al. *Endocr Pract*. 2008;14:933-946; Handelsman Y, et al. *Endocr Pract*. 2015;21(suppl 1):1-87; Jellinger PS, et al. *Endocr Pract*. 2012;18(suppl 1):1-78.

Small Amounts of Weight Gain or Loss Have Important Effects on CHD Risk

Framingham Offspring Study 16-year Follow-up*

■ Loss ≥2.25 kg   ■ Gain ≥2.25 kg

Change in Risk Factor Sum (%)

Men: -48 **, 20 **

Women: -40 **, 37 **
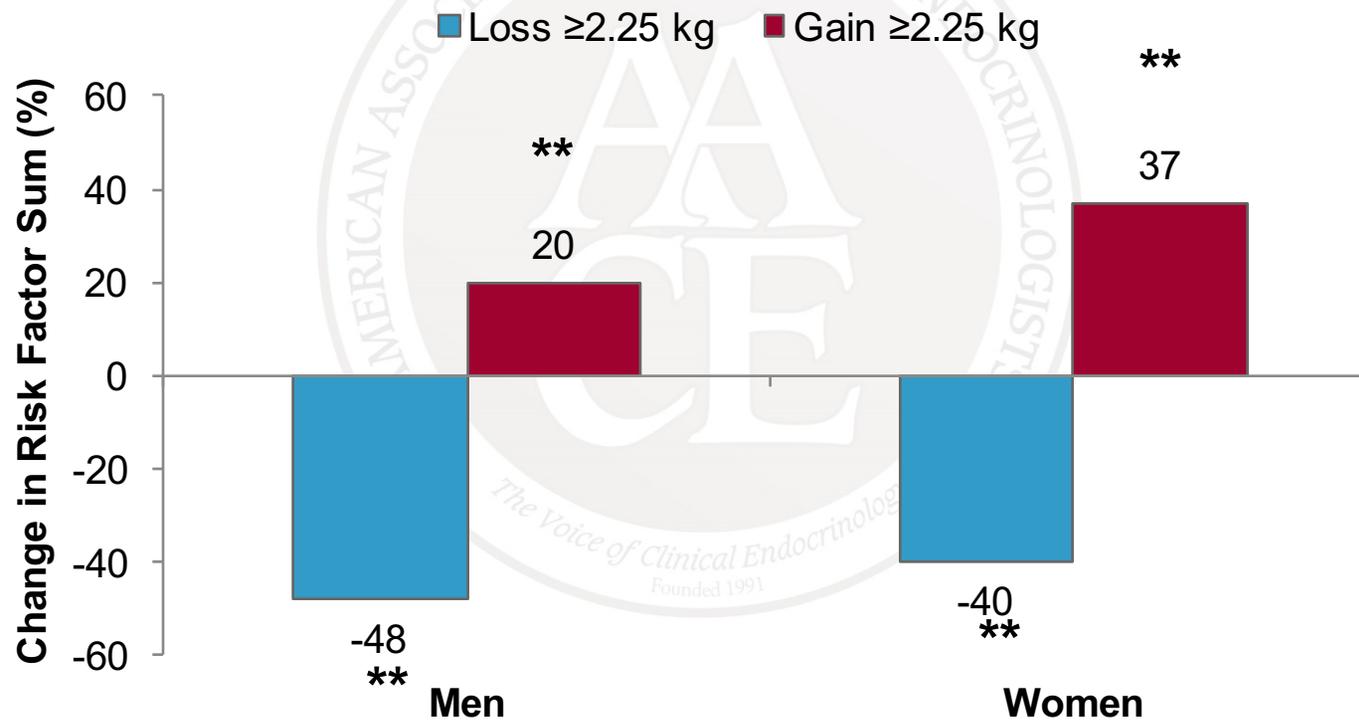
*Patients with Low HDL-C, high cholesterol, high BMI, high systolic BP, high triglyceride, high glucose.

**P <0.002 vs baseline.

BMI = body mass index; BP = blood pressure; CHD = coronary heart disease; HDL-C = high density lipoprotein cholesterol.

Wilson PW, et al. *Arch Intern Med*. 1999;159:1104-1109.

Effect of Weight Loss in T2D on CV Risk Factors and Diabetes Measures

Look AHEAD Trial
(N=5145)

	1 Year		4 Years	
	DSE	**ILI**	**DSE**	**ILI**
Weight loss (%)	-0.7	-8.6	-0.88	-6.15*
A1C (%)	-0.14	-0.64*	-0.09	-0.36*
FPG (mg/dL)	-7.2	-21.5*	—	—
% on diabetes medications	2.2	-7.8*	—	—
Systolic BP (mm Hg)	-2.8	-6.8*	-2.97	-5.33*
Diastolic BP (mm Hg)	-1.8	-3.0*	-2.48	-2.92†
LDL-C (mg/dL)	-5.7	-5.2	-12.84	-11.27
HDL-C (mg/dL)	1.4	3.4*	1.97	3.67*
TG (mg/dL)	-14.6	-30.3*	-19.75	-25.56*

*$P \leq 0.001$, †$P=0.01$ vs customary support.

BP = blood pressure; CV = cardiovascular; DSE = diabetes support and education; ILI = intensive lifestyle intervention; T2D = type 2 diabetes.

Look AHEAD Research Group. *Diabetes Care*. 2007;30:1374-1383. Look AHEAD Research Group. *Arch Intern Med*. 2010;170:1566-1575.

Long-Term Effects of Lifestyle Change on Cardiovascular Risk in T2D

Look AHEAD Trial

Patients experiencing death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for angina (%)

HR 0.95 (95% CI, 0.80 to 1.09)
P=0.51

No. at Risk						
Control	2575	2425	2296	2156	2019	688
Intervention	2570	2447	2326	2192	2049	505

Years
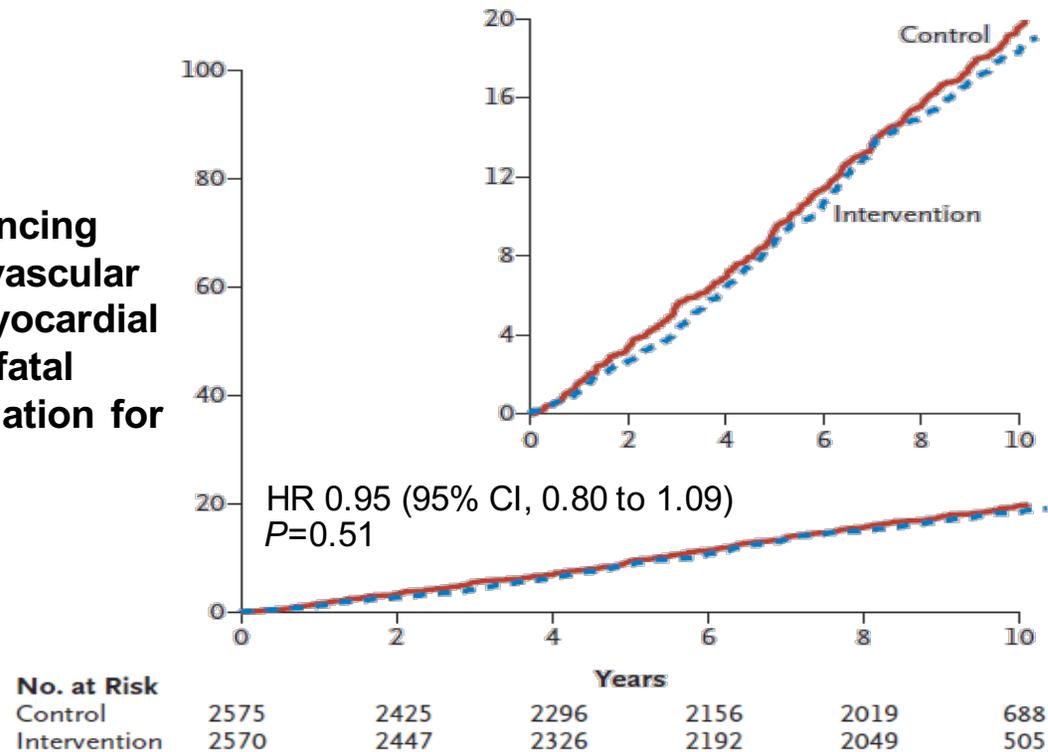
Lack of difference between treatment groups may be due to:
- Educational sessions in control group, contributing to weight loss
- Increased use of statins in control group
- Intensification of CV risk control in routine clinical care

T2D = type 2 diabetes.

Look AHEAD Research Group. *N Engl J Med.* 2013;369:145-154.

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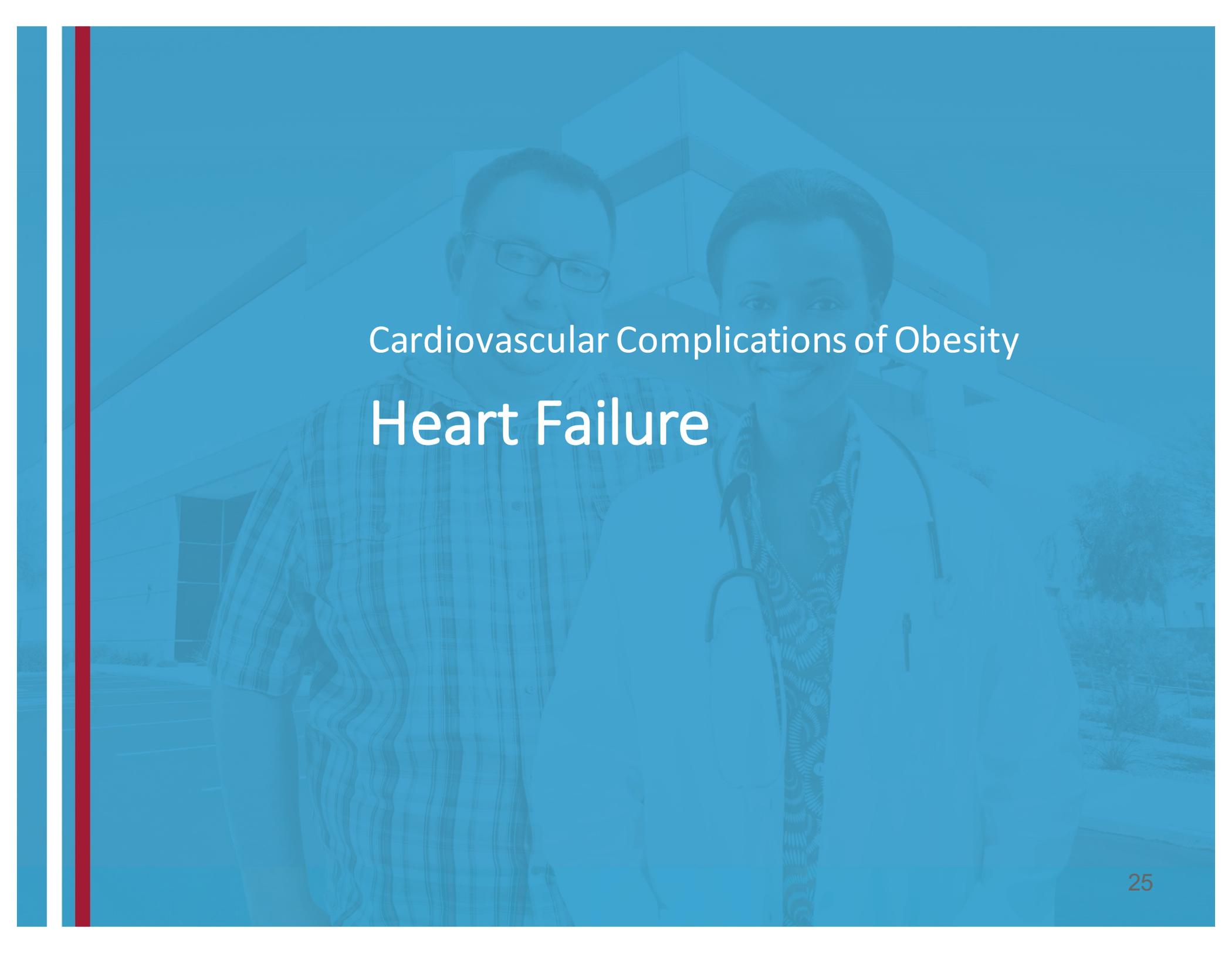
Cardiovascular Complications of Obesity

Heart Failure

Considerations for Patients with Congestive Heart Failure

The HF Mortality Obesity Paradox
Acute Decompensated Heart Failure Registry Study
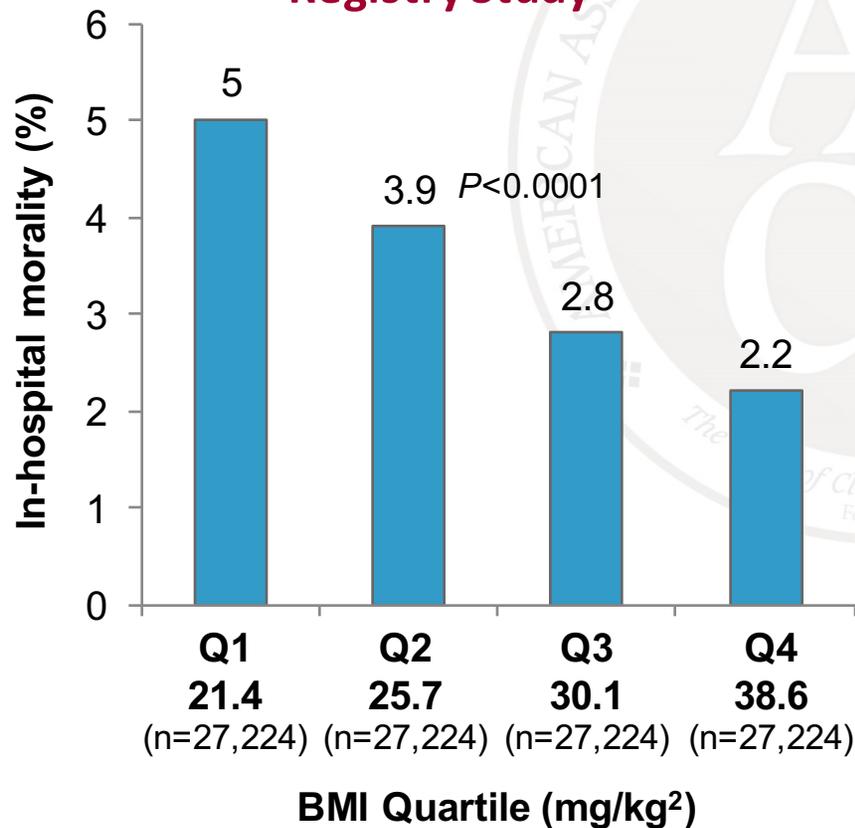
Weight Loss May Improve HF Functional Capacity
Mayo Clinic Retrospective Study

Fonarow GC, et al. *Am Heart J*. 2007;153:74-81. Miranda WR, et al. *Obes Surg*. 2013;23:1011-1015.
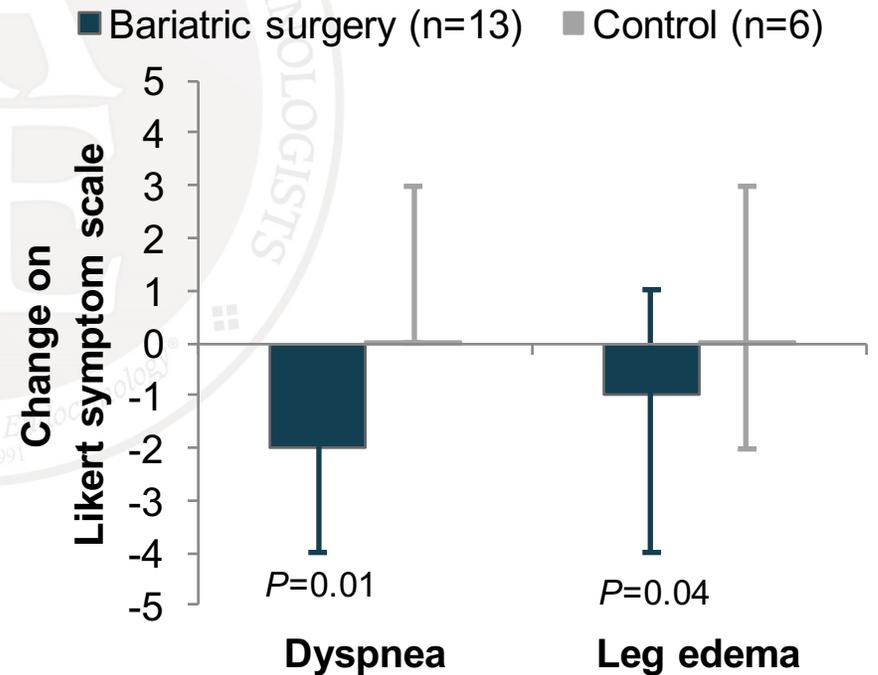
Predictors of 12-Year Mortality in Elderly Patients With and Without CHF

12-Year Longitudinal Observational Study
(N=1268 Patients ≥65 Years)

Patients With CHF (n=125)			Patients Without CHF (n=1143)		
	Hazard ratio (95% CI)	*P* value		Hazard ratio (95% CI)	*P* value
Age	1.02 (0.95-1.11)	0.57		1.17 (1.14-1.21)	0.001
Female	0.54 (0.18-1.60)	0.27		**0.48 (0.35-0.65)**	**0.001**
BMI	0.94 (0.94-1.01)	0.23		**0.94 (0.90-0.98)**	**0.001**
WC	**1.05 (1.01-1.08)**	**0.001**		**1.02 (1.01-1.04)**	**0.001**

Protective ← → Harmful

Protective ← → Harmful

Testa G, et al. *J Am Geriatr Soc*. 2010;58:1433-1440.
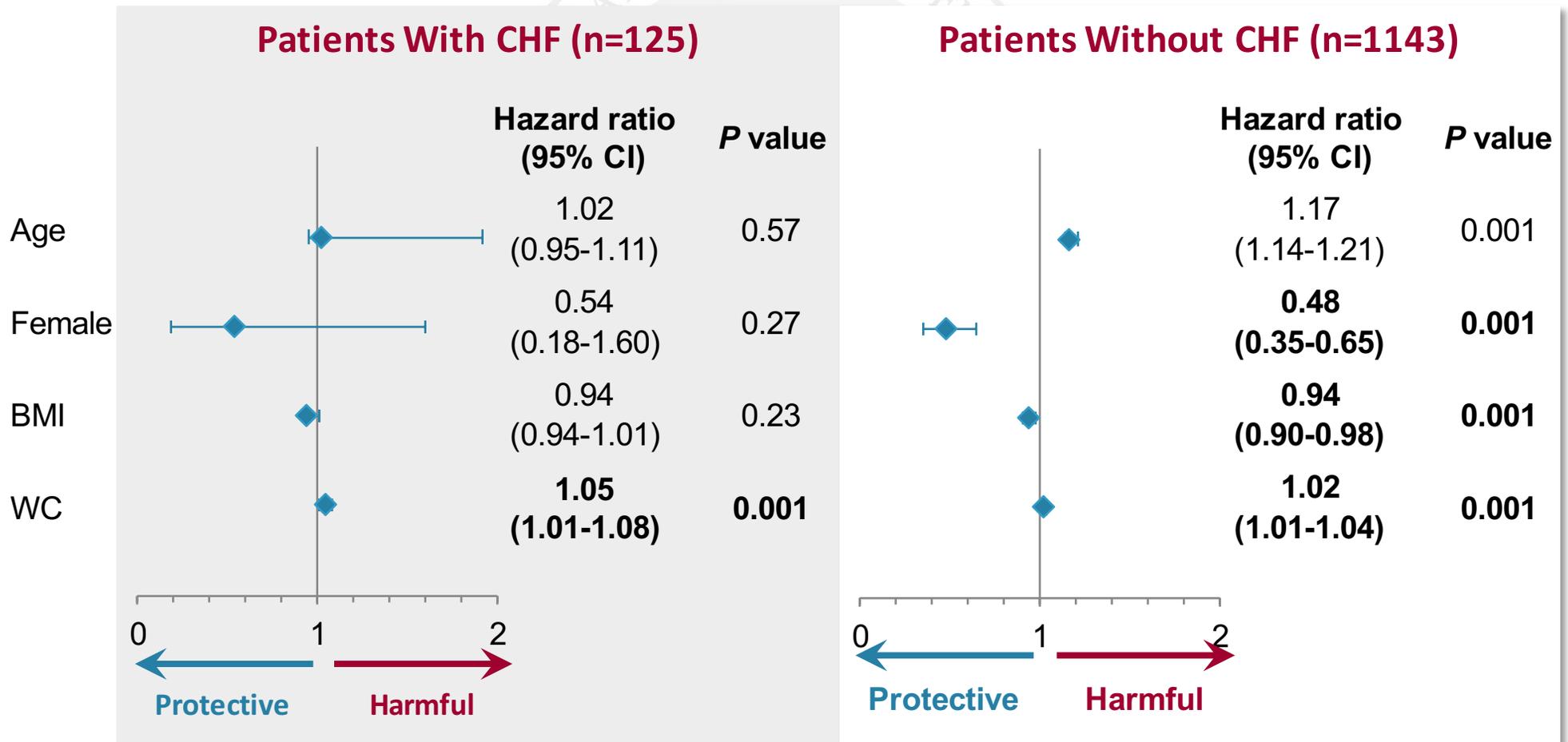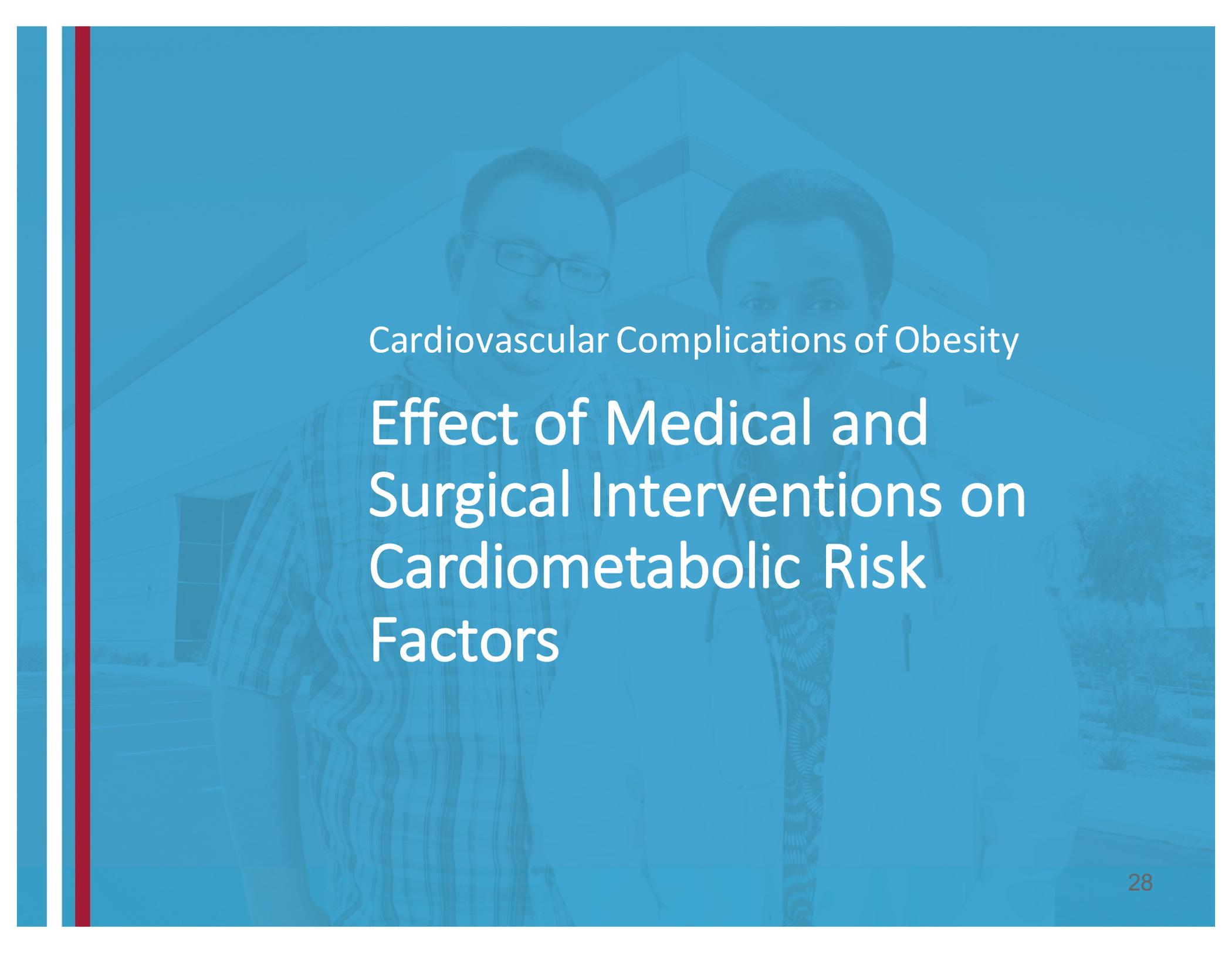
Cardiovascular Complications of Obesity

Effect of Medical and Surgical Interventions on Cardiometabolic Risk Factors

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 Lorcaserin on Hypertension

BLOSSOM Study

Blood Pressure

Systolic: Placebo -1.2, Lorcaserin 10 mg BID -1.9
Diastolic: Placebo -1.4, Lorcaserin 10 mg BID -1.9
Δ Mean BP (mmHg)

Antihypertensive Use

Decrease: Placebo 3.1, Lorcaserin 10 mg BID 4
Patients (%)

Placebo   Lorcaserin 10 mg BID
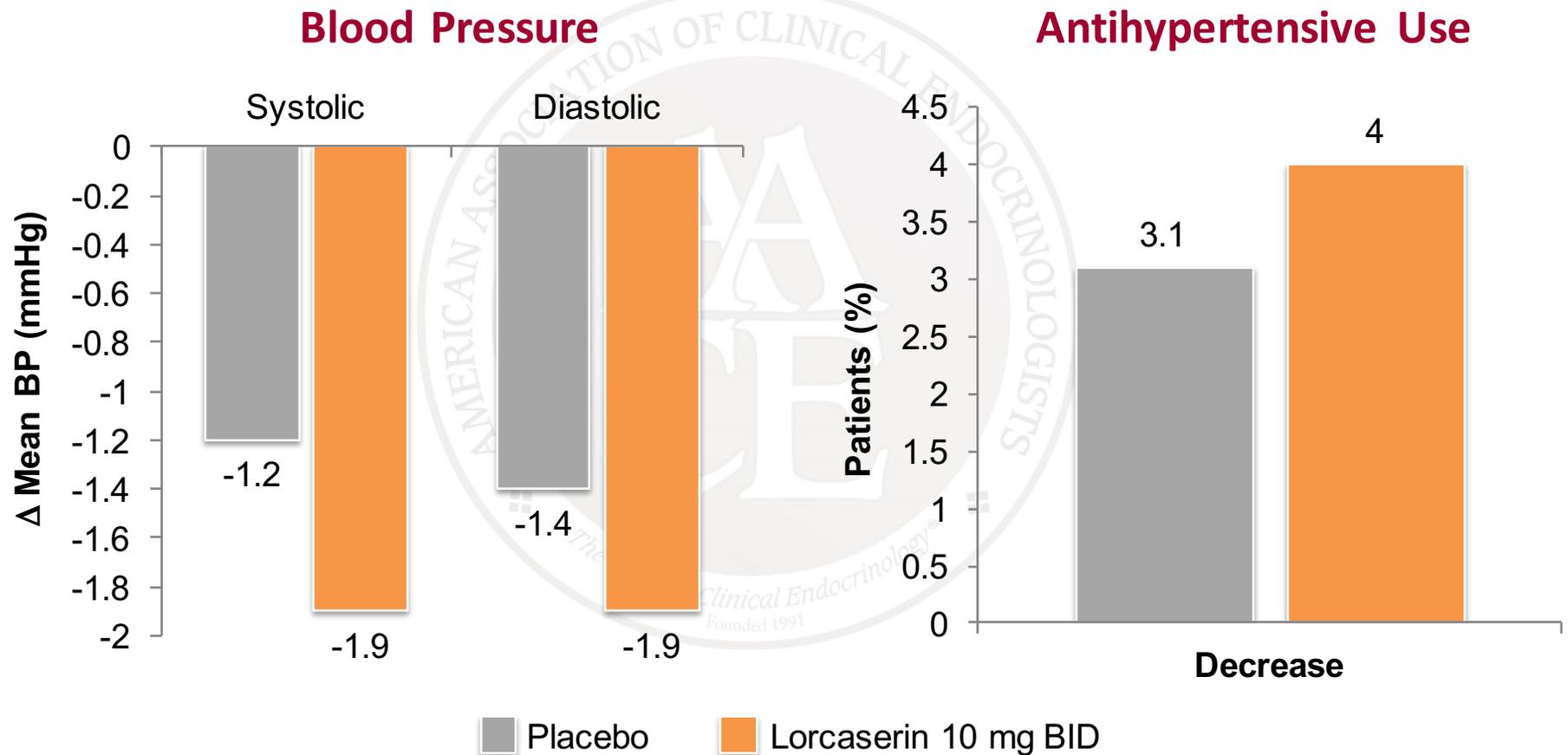
BID = twice daily; BLOSSOM = Behavioral Modification and Lorcaserin Second Study for Obesity Management; LS = least squares.

Fidler MC, et al. *J Clin Endocrinol Metab.* 2011;96:3067-3077.

Effect of Lorcaserin on Dyslipidemia

BLOSSOM Study

Lipids

Lipid Medication Use

- Triglycerides: Placebo -0.9, Lorcaserin -4.3, *P*=0.02
- HDL-C: Placebo 1.3, Lorcaserin 3.7, *P*<0.001
- LDL-C: Placebo 1.7, Lorcaserin 0.3
- ApoB: Placebo 1.4, Lorcaserin -2.9, *P*<0.001
- Increase: Placebo 5, Lorcaserin 4
- Decrease: Placebo 1.4, Lorcaserin 2.6

Legend: Placebo (gray), Lorcaserin 10 mg BID (orange)

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Effect of Phentermine/Topiramate ER on Cardiometabolic Risk Markers

| 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.

Effect of Phentermine/Topiramate ER on Hypertension

SEQUEL Study

Blood Pressure

**Antihypertensive Use**
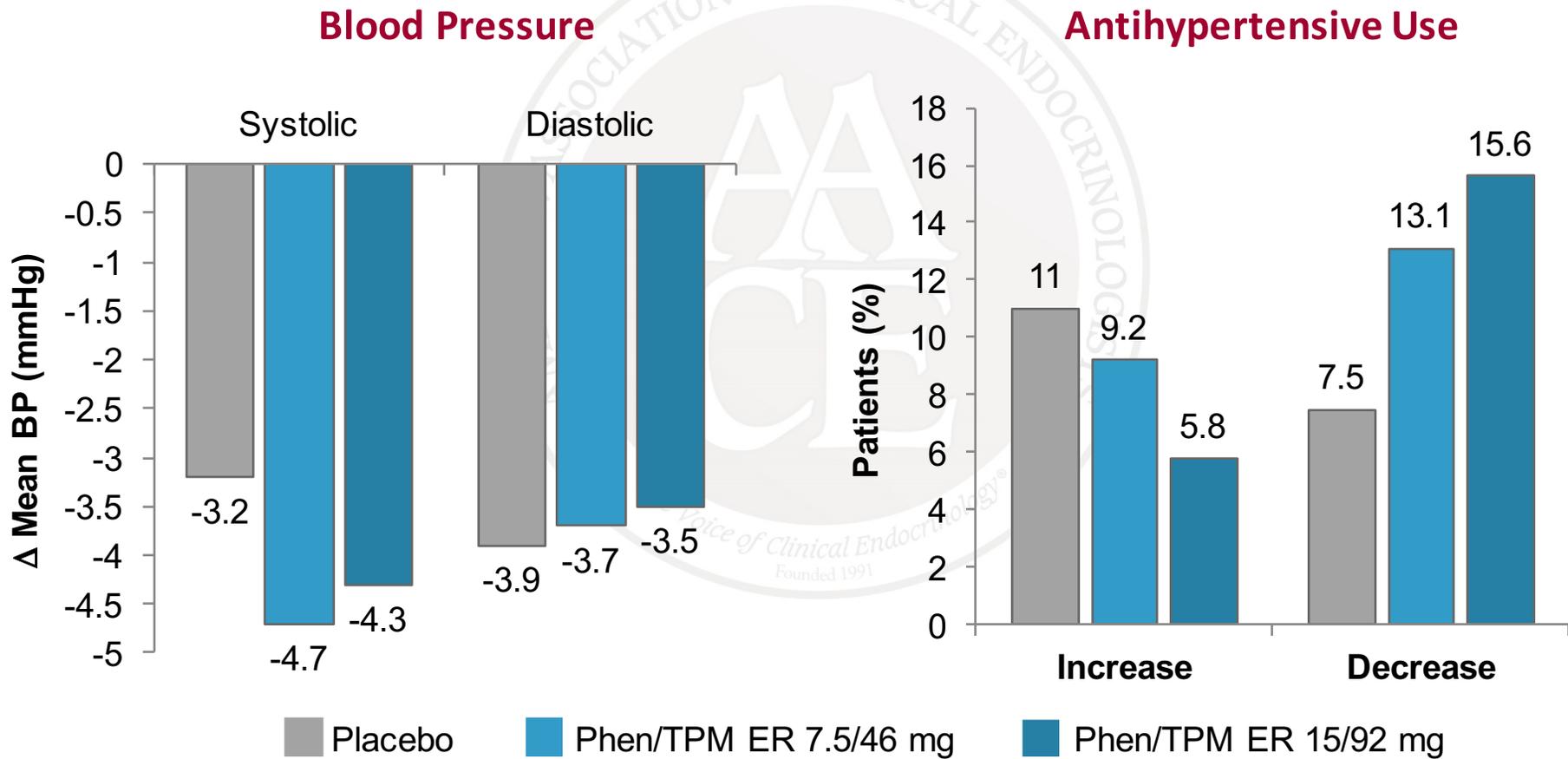
BP = blood pressure; Phen/TPM ER = phentermine/topiramate extended release.

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

Effect of Phentermine/Topiramate on Blood Pressure at 56 Weeks in Patients with T2D

Poorly Controlled Type 2 Diabetes
(ITT-LOCF Analysis)
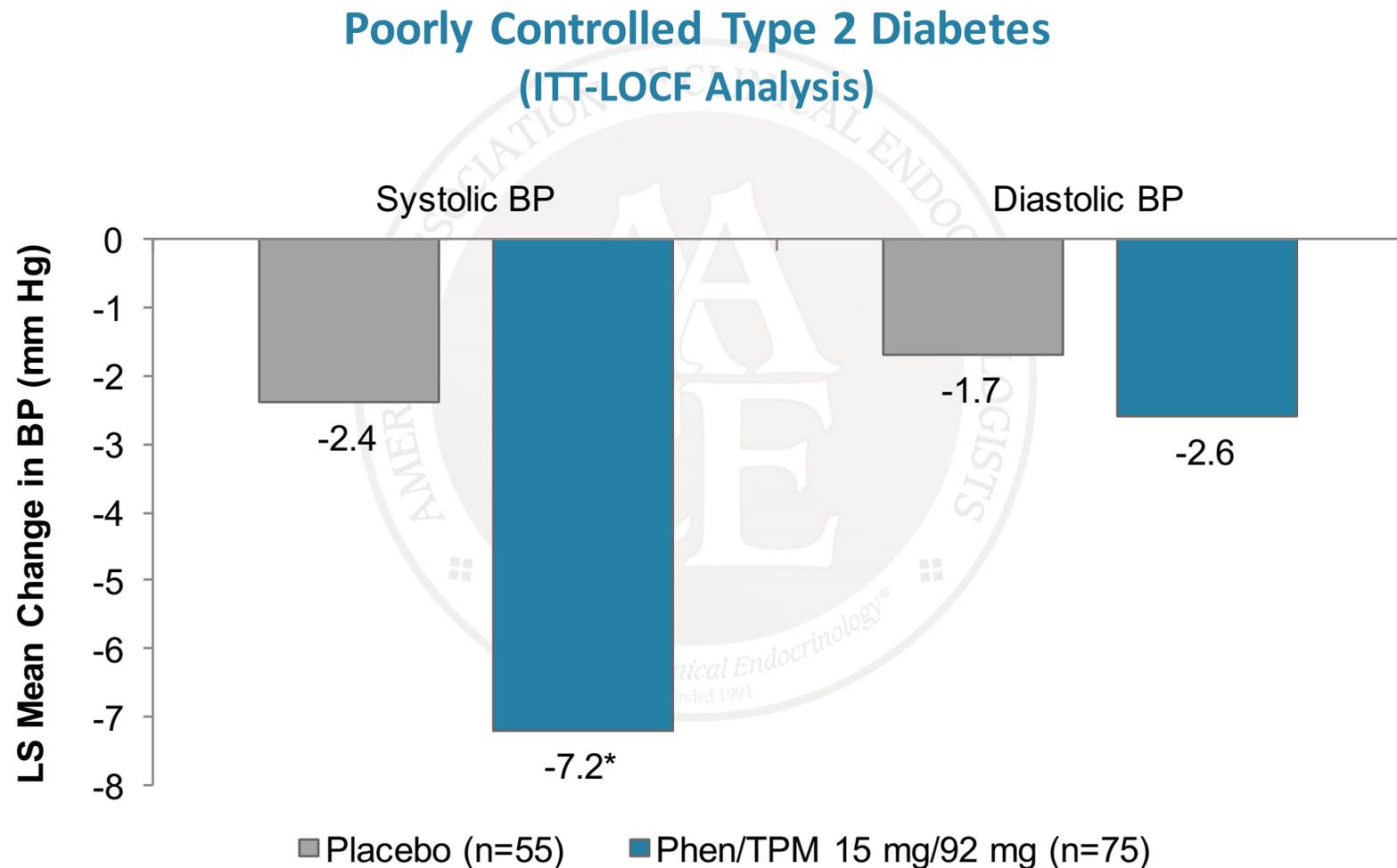
*$P<0.05$ vs placebo.

BP = blood pressure; Phen/TPM = phentermine/topiramate, T2D = type 2 diabetes.

Rueger MM, et al. Poster presented at AADE 37th Annual Meeting, San Antonio, TX, August 4-7, 2010; Abstr. 181580.

Effect of Naltrexone/Bupropion SR on Cardiometabolic Risk Markers

Risk Factors (Mean % Weight Loss)	Naltrexone/ Bupropion SR (6.4%)		P value*
Systolic BP, mmHg	↑	0.6	0.039
Diastolic BP, mmHg	↑	0.4	NS
Triglycerides, %	↓	-9.8	<0.001
LDL-C, %	↓	-6.2	0.008
HDL-C, %	↑	3.6	<0.001
hsCRP, mg/L	↓	-28.8	<0.001
FBG, mg/dL	↓	-2.8	NS

*P value vs placebo.

BP, blood pressure; COR II, CONTRAVE Obesity Research II; FBG, fasting blood glucose; SR, sustained release.

Apovian C, et al. *Obesity (Silver Spring)*. 2013;21:935-943.

Effect of Liraglutide 3 mg on Cardiometabolic Risk Markers

SCALE Study

| Risk Factors (Mean % Weight Loss)	Liraglutide 3 mg* (4.4%)		P value
Systolic BP, mmHg	↓	-2.8	<0.0001
Diastolic BP, mmHg	↓	-0.6	NS
Triglycerides, %	↓	-6.0	0.0003
Total cholesterol, %	↓	-2.0	0.03
LDL-C, %	↓	-0.9	NS
HDL-C, %	↑	0.9	NS
VLDL-C, %	↓	-6.0	0.0002
FFAs, %	↓	-5.0	0.03
Waist circumference, cm	↓	-3.5	<0.0001

*Placebo-adjusted values; *P* values represent comparisons to placebo (ANCOVA).

Full analysis set of 3-year data.

Fujioka et al. ENDO 2016, 1–4 April 2016, Abstract 24365.

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 (%)

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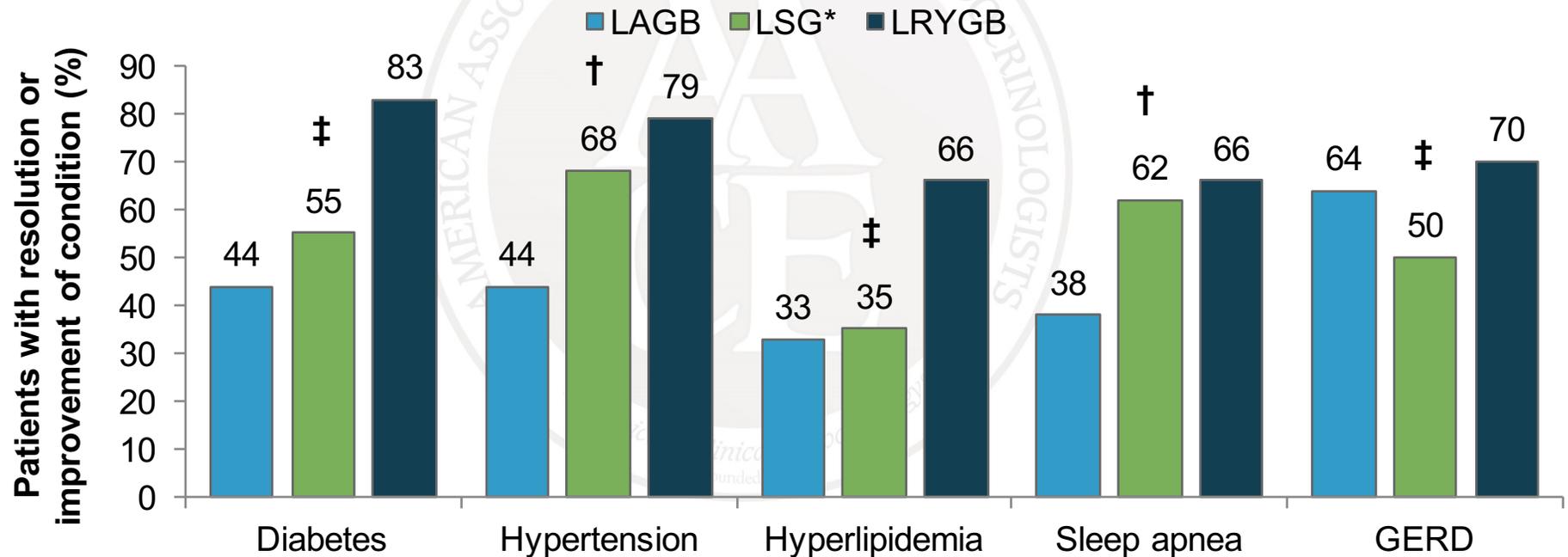
*Small numbers of patients with 1 year of follow-up for all comorbidities (n≤38).

†$P<0.05$ 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.

Summary

- Obesity is strongly associated with increased cardiovascular risk

- Weight loss by means of lifestyle therapy, pharmacotherapy, or bariatric surgery positively affects cardiovascular risk markers