Metabolic Syndrome and Diabetes: Evaluating CVD Risk and Strategies for CVD Risk Reduction

Nathan D. Wong, PhD, FACC, FAHA

Professor and Director

Heart Disease Prevention Program

Division of Cardiology

University of California, Irvine

**Immediate Past President, American Society for Preventive Cardiology**

Outline

- Review the epidemiological relation of metabolic syndrome, diabetes, and cardiovascular disease.

- Discuss strategies for CVD risk assessment in persons with metabolic syndrome and diabetes.

- Review the evidence and recommendations for risk factor management for prevention of CVD in persons with metabolic syndrome and diabetes.

The shape of things to come
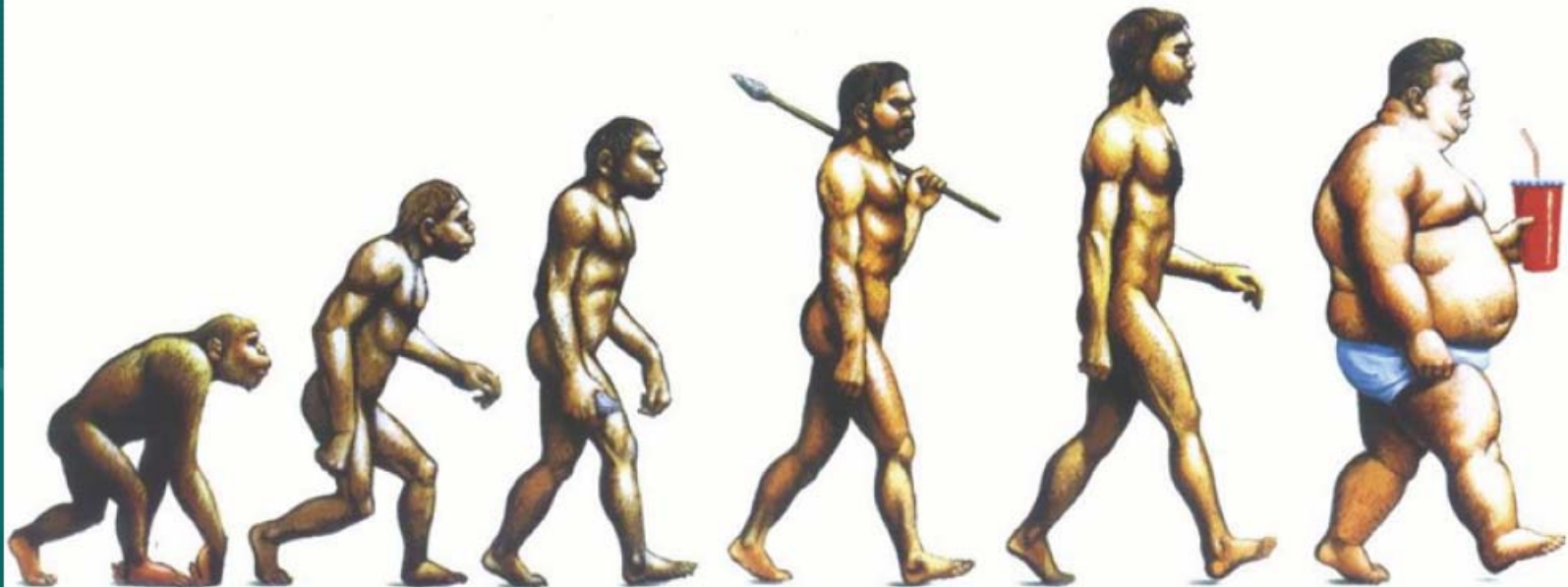
The cover of "The Economist", Dec. 13-19, 2003.

Figure 29 Ranking of 10 selected risk factors of cause of death (2).

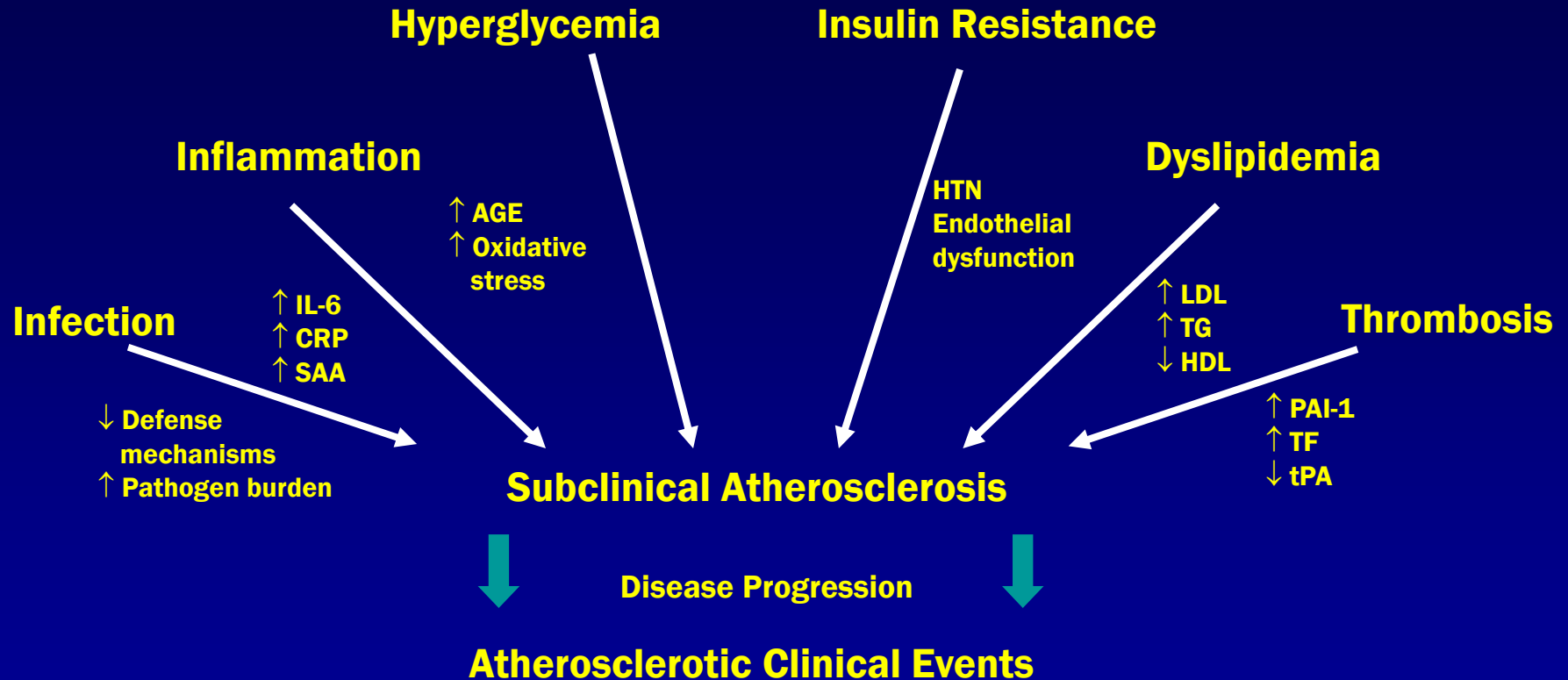Attributable deaths due to selected risk factors (in thousands)
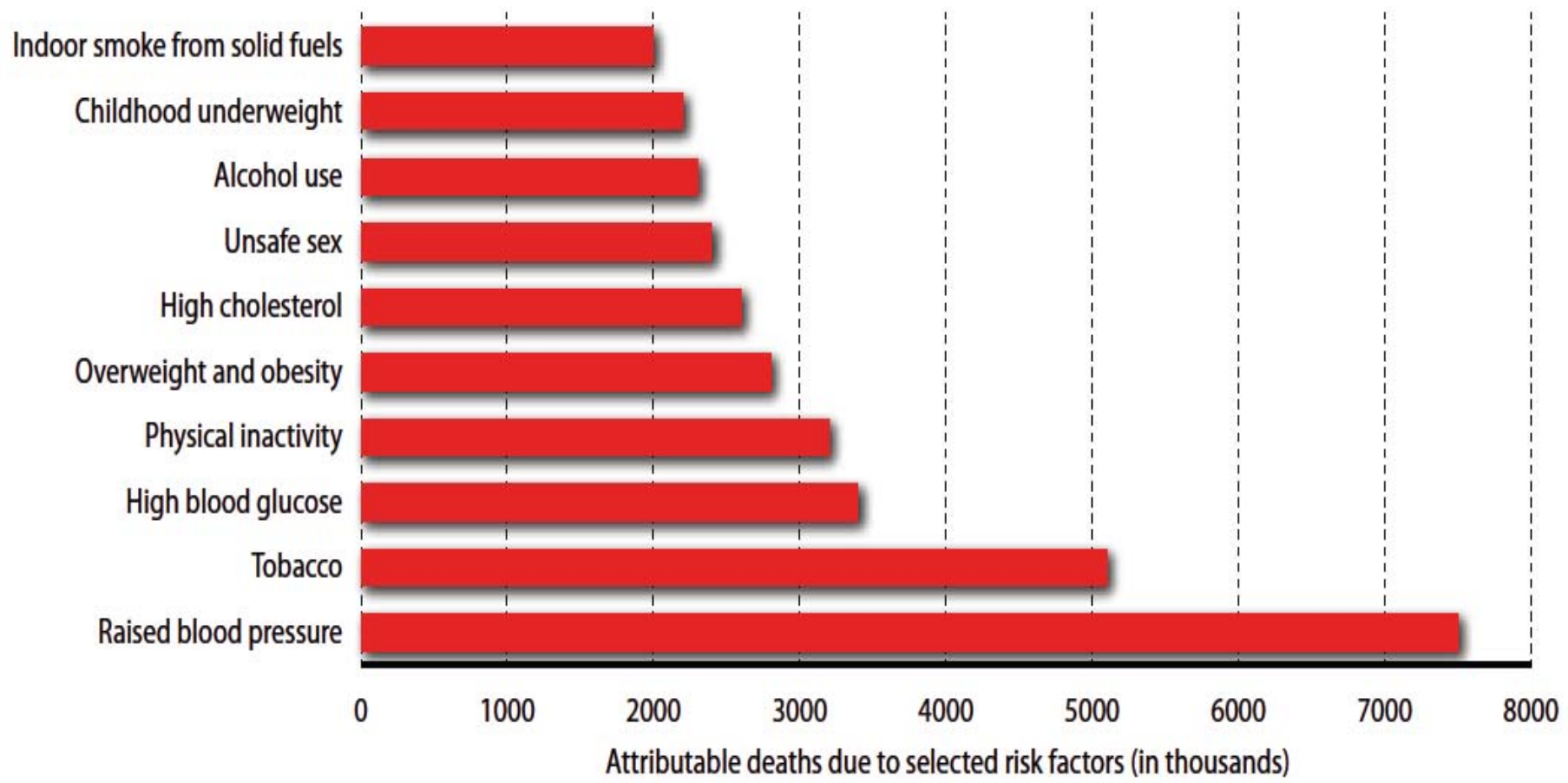
Six of the top 10 causes of death globally are cardiometabolic / behavioral risk factors

Diabetes and CVD

- Atherosclerotic complications responsible for
  - 80% of mortality among patients with diabetes
  - 75% of cases due to coronary artery disease (CAD)
  - Results in >75% of all hospitalizations for diabetic complications

- 50% of patients with type 2 diabetes have preexisting CAD. (This number may be less now that more younger people are diagnosed with diabetes.)

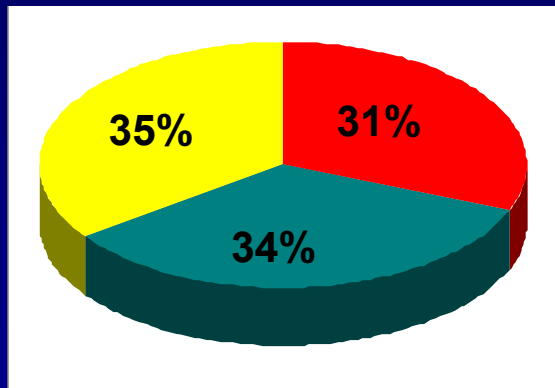- 1/3 of patients presenting with myocardial infarction have undiagnosed diabetes mellitus

Lewis GF. *Can J Cardiol.* 1995;11(suppl C):24C-28C
Norhammar A, et.al. *Lancet* 2002;359;2140-2144

Mechanisms by which Diabetes Mellitus Leads to Coronary Heart Disease

Hyperglycemia

Insulin Resistance

Inflammation

Dyslipidemia

↑ AGE
↑ Oxidative stress

HTN
Endothelial dysfunction

Infection

↑ IL-6
↑ CRP
↑ SAA

↑ LDL
↑ TG
↓ HDL

Thrombosis

↓ Defense mechanisms
↑ Pathogen burden

↑ PAI-1
↑ TF
↓ tPA

Subclinical Atherosclerosis

Disease Progression
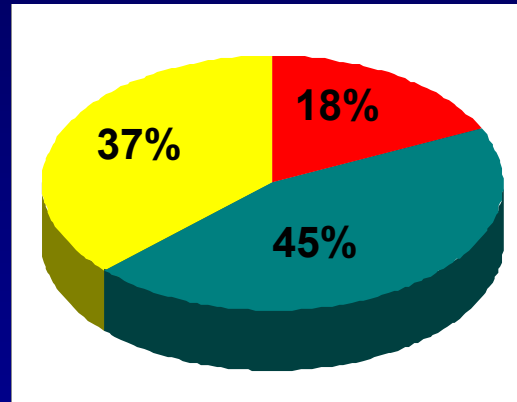
Atherosclerotic Clinical Events

AGE=Advanced glycation end products, CRP=C-reactive protein, CHD=Coronary heart disease HDL=High-density lipoprotein, HTN=Hypertension, IL-6=Interleukin-6, LDL=Low-density lipoprotein, PAI-1=Plasminogen activator inhibitor-1, SAA=Serum amyloid A protein, TF=Tissue factor, TG=Triglycerides, tPA=Tissue plasminogen activator

Biondi-Zoccai GGL et al. *JACC* 2003;41:1071-1077.

Most Cardiovascular Patients Have Abnormal Glucose Metabolism

GAMI
n = 164

EHS
n = 1920

CHS
n = 2263

GAMI: 31% Normoglycemia, 34% Type 2 Diabetes, 35% Prediabetes

EHS: 18% Normoglycemia, 45% Type 2 Diabetes, 37% Prediabetes

CHS: 27% Normoglycemia, 36% Type 2 Diabetes, 37% Prediabetes
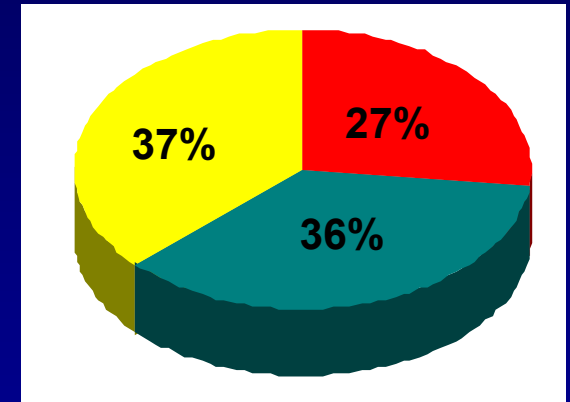
- Normoglycemia
- Prediabetes
- Type 2 Diabetes

GAMI = Glucose Tolerance in Patients with Acute Myocardial Infarction study;
EHS = Euro Heart Survey; CHS = China Heart Survey

Anselmino M, et al. *Rev Cardiovasc Med*. 2008;9:29-38.

Diagnostic Criteria for Metabolic Syndrome: Modified NCEP ATP III

≥3 Components Required for Diagnosis

Components	Defining Level
Increased waist circumference **Men** **Women**	**≥ 40 in** **≥ 35 in**
Elevated triglycerides	**≥150 mg/dL** **(or Medical Rx)**
Reduced HDL-C **Men** **Women**	**<40 mg/dL** **<50 mg/dL** **(or Medical Rx)**
Elevated blood pressure	**≥130 / ≥85 mm Hg** **(or Medical Rx)**
Elevated fasting glucose	**≥100 mg/dL** **(or Medical Rx)**

IDF Criteria: Abdominal Obesity and Waist Circumference Thresholds

|	Men	Women
Europid	≥ 94 cm (37.0 in)	≥ 80 cm (31.5 in)
South Asian	≥ 90 cm (35.4 in)	≥ 80 cm (31.5 in)
Chinese	≥ 90 cm (35.4 in)	≥ 80 cm (31.5 in)
Japanese	≥ 85 cm (33.5 in)	≥ 90 cm (35.4 in)

- AHA/NHLBI criteria: ≥ 102 cm (40 in) in men, ≥ 88 cm (35 in) in women

- Some US adults of non-Asian origin with marginal increases should benefit from lifestyle changes. Lower cutpoints (≥ 90 cm in men and ≥ 80 cm in women) for Asian Americans
  >90cm (male) and >80cm (female) recommended for persons of Central and South American ancestry (including US Hispanics)

Alberti KGMM et al. *Lancet* 2005;366:1059-1062. | Grundy SM et al. *Circulation* 2005;112:2735-2752.

Intra-abdominal (Visceral) Fat
The dangerous inner fat!

Front

Visceral AT

Subcutaneous AT

Back
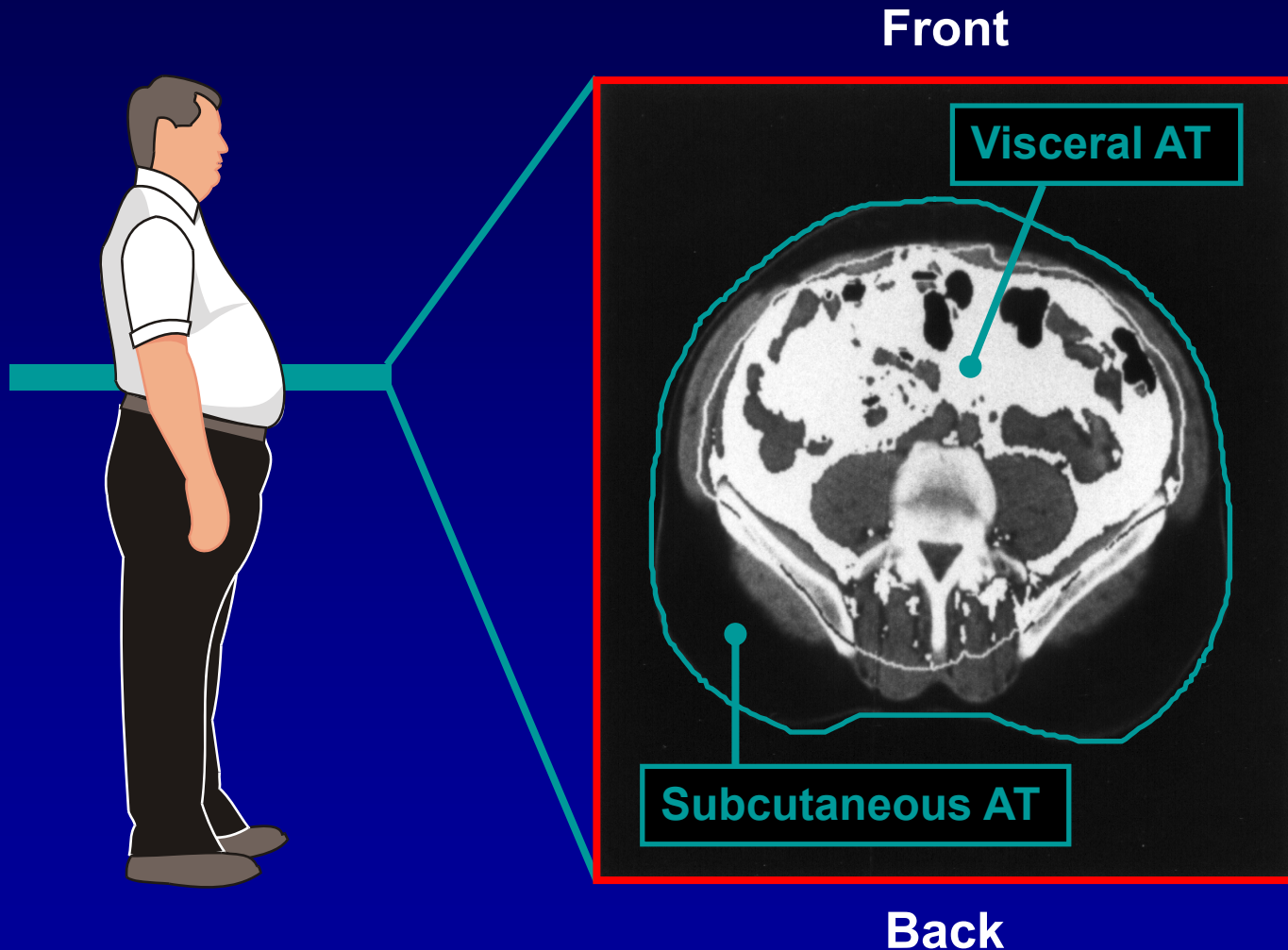
Abdominal Adiposity Is Associated With Increased Risk of Diabetes

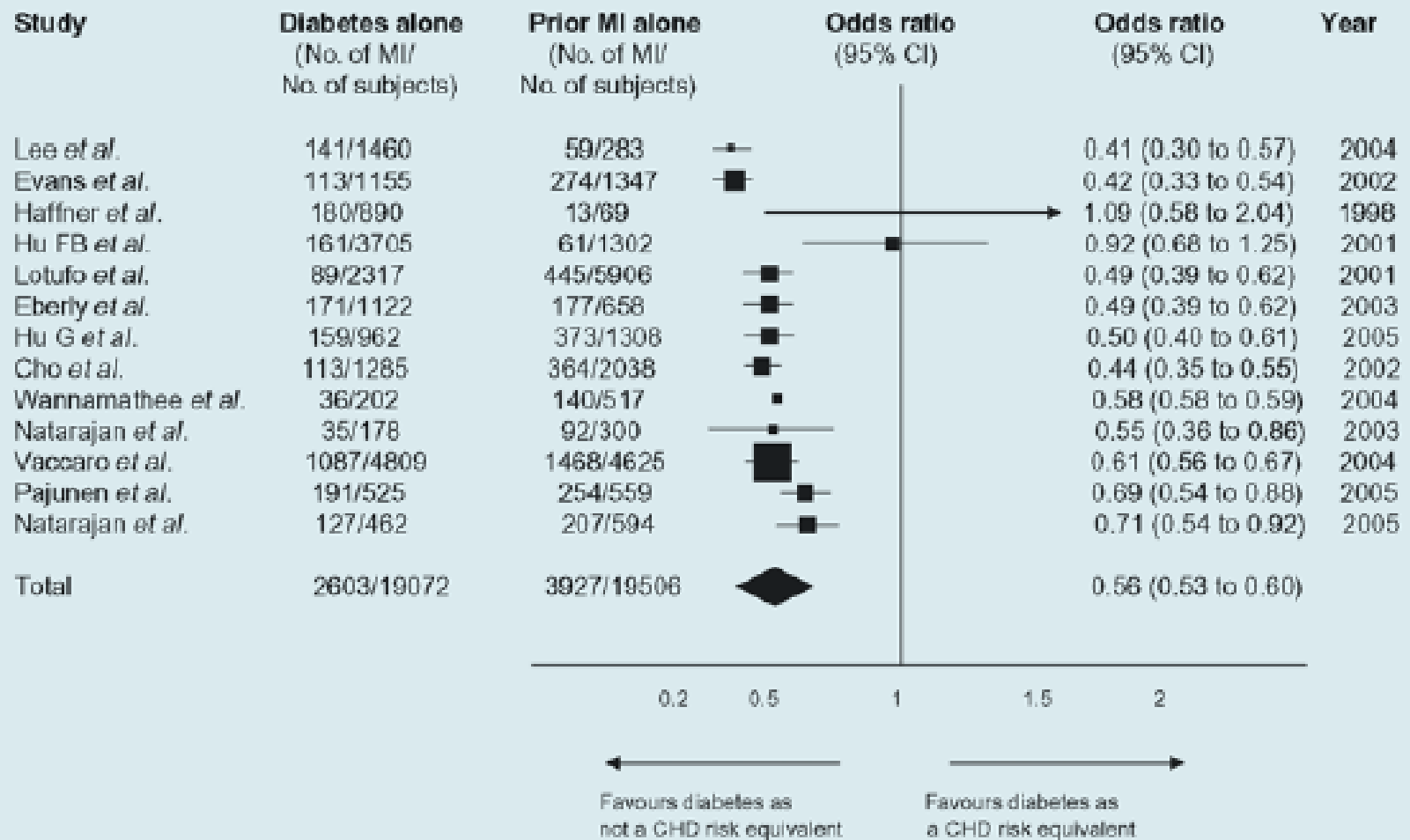Carey VJ, et al. Am J Epidemiol. 1997;145:614-619
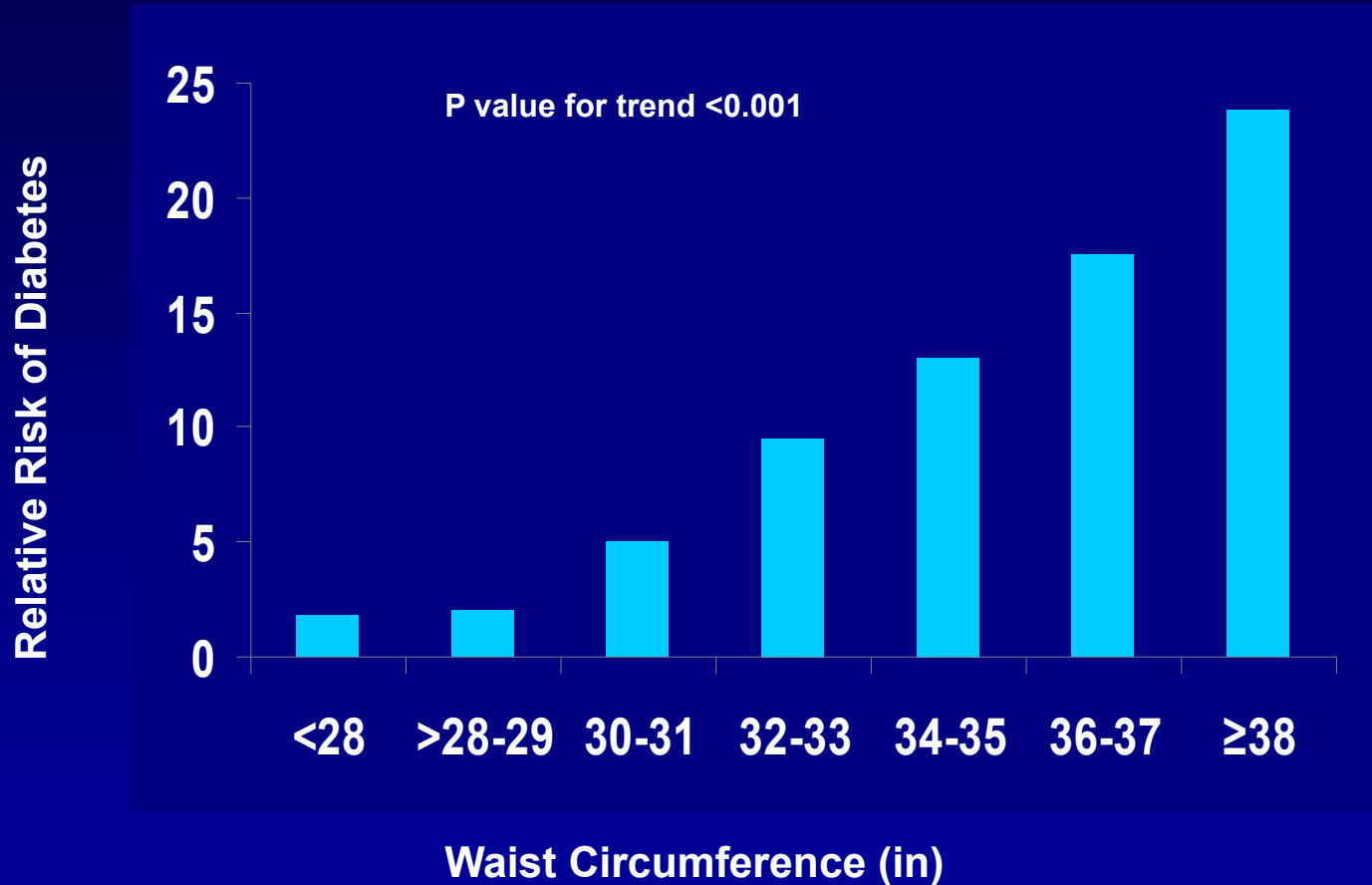
Metabolic Syndrome and Diabetes in Relation to CHD, CVD, and Total Mortality: U.S. Men and Women Ages 30-74

## (Risk-factor Adjusted Cox Regression) NHANES II Follow-up (n=6255)

Malik and Wong, et al., Circulation 2004.

* p<.05, ** p<.01, **** p<.0001 compared to none
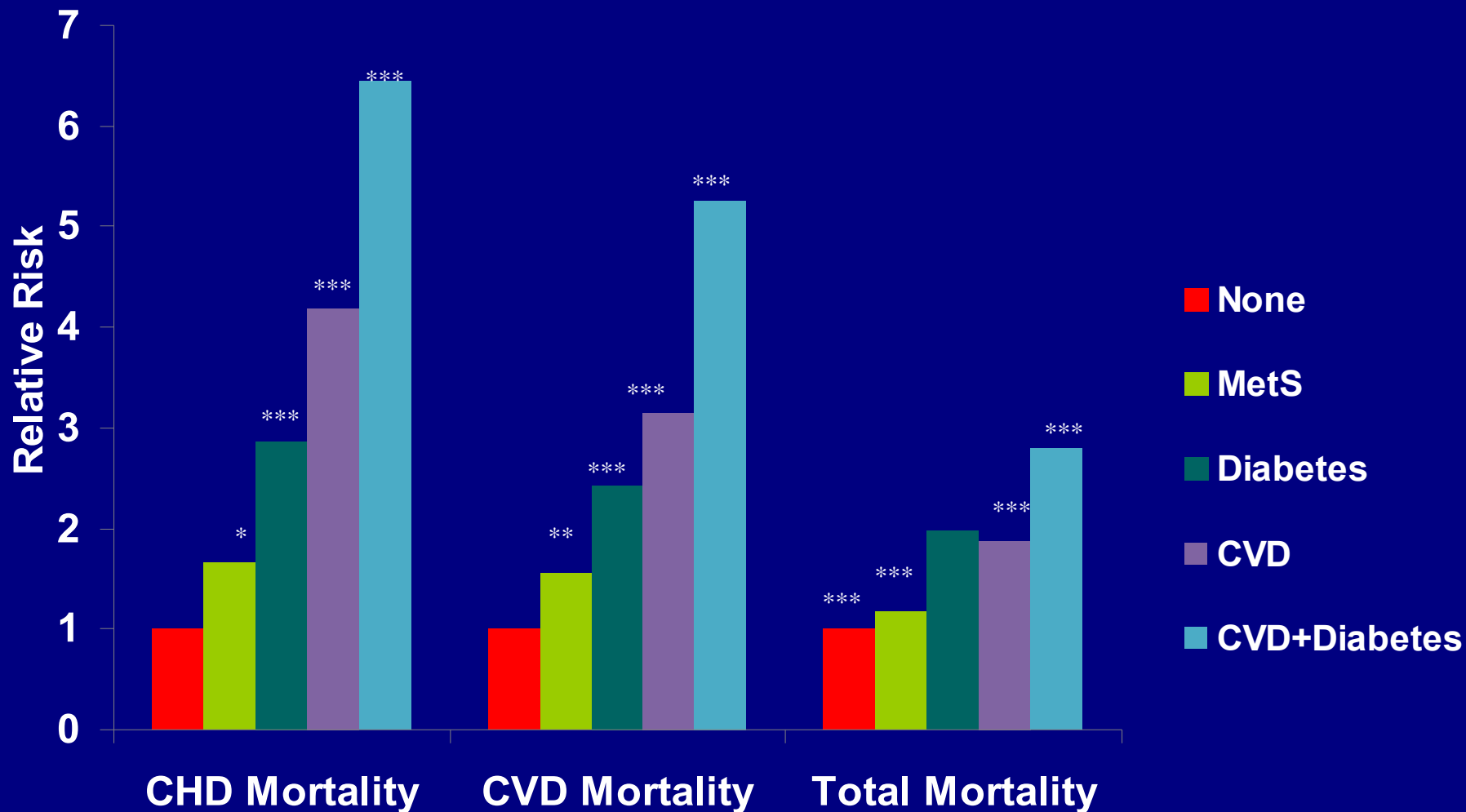
Is DM really a CHD Risk Equivalent?   Meta-Analysis of 38,578 subjects (Bulugahapitiya et al. Diabetic Med 2008)

Study	Diabetes alone (No. of MI/ No. of subjects)	Prior MI alone (No. of MI/ No. of subjects)	Odds ratio (95% CI)	Odds ratio (95% CI)	Year
Lee *et al.*	141/1460	59/283		0.41 (0.30 to 0.57)	2004
Evans *et al.*	113/1155	274/1347		0.42 (0.33 to 0.54)	2002
Haffner *et al.*	180/890	13/69		1.09 (0.58 to 2.04)	1998
Hu FB *et al.*	161/3705	61/1302		0.92 (0.68 to 1.25)	2001
Lotufo *et al.*	89/2317	445/5906		0.49 (0.39 to 0.62)	2001
Eberly *et al.*	171/1122	177/658		0.49 (0.39 to 0.62)	2003
Hu G *et al.*	159/962	373/1308		0.50 (0.40 to 0.61)	2005
Cho *et al.*	113/1285	364/2038		0.44 (0.35 to 0.55)	2002
Wannamathee *et al.*	36/202	140/517		0.58 (0.58 to 0.59)	2004
Natarajan *et al.*	35/178	92/300		0.55 (0.36 to 0.86)	2003
Vaccaro *et al.*	1087/4809	1468/4625		0.61 (0.56 to 0.67)	2004
Pajunen *et al.*	191/525	254/559		0.69 (0.54 to 0.88)	2005
Natarajan *et al.*	127/462	207/594		0.71 (0.54 to 0.92)	2005
Total	2603/19072	3927/19506		0.56 (0.53 to 0.60)	

0.2   0.5   1   1.5   2

Favours diabetes as not a CHD risk equivalent   Favours diabetes as a CHD risk equivalent

Random effects model	odds ratio = 0.56 (0.53, 0.60)
Fixed effects model	odds ratio = 0.56 (0.53, 0.60)
Test for heterogeneity	$I^2 = 75.0\%$

Annual CHD Event Rates (in %) by Calcium Score Events by CAC Categories in Subjects with DM, MetS, or Neither Disease (Malik and Wong et al., Diabetes Care 2011)

Coronary Heart Disease
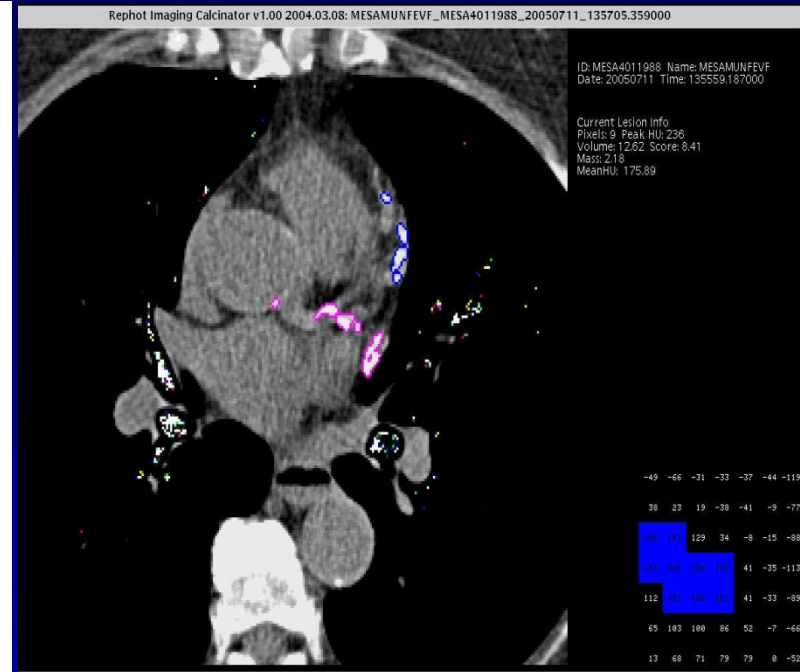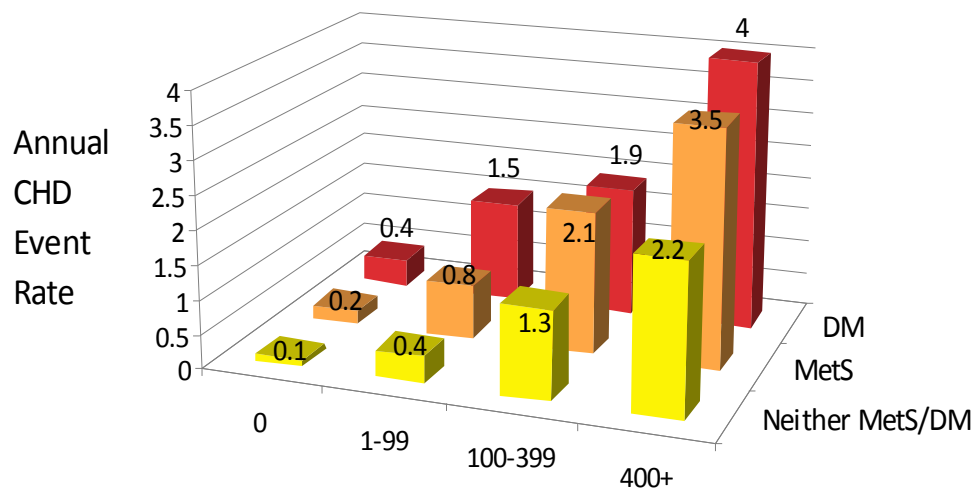
Coronary Artery Calcium Score

ACCF/AHA 2010 Guideline: CAC Scoring for CV risk assessment in asymptomatic adults aged 40 and over with diabetes (Class IIa-B)

Summary of Intervention Studies
Risk Reduction with Individual Treatments
Persons with Diabetes Mellitus

	Macrovascular Event Reduction
Blood pressure treatment	30-50%
Lipid treatment	25-55%
Glucose treatment per 1% HbA_{1c}	10-20%

Poor Control of Multiple Cardiovascular Risk Factors Among U.S. Adults with Type 2 Diabetes

- NHANES Survey 2003-2006, n=889 (14.3 million) or 6.6% of adults aged >/=18 years had type 2 diabetes
- 58.2% at HbA1c goal <7%
- 44.2% at BP goal <130/80 mmHg
- 56.4% at recommended HDL-C >/=40 (M), >/=50 (F)
- 25.8% at recommended triglycerides <150 mg/dl
- 13.9% at BMI<25 kg/m^2
- Overall, only 10.5% of men and 9.9% of women at goal for HbA1c, BP, and LDL-C simultaneously; only 0.3% at goal also including BMI.

Wong K, Wong ND et al . J Diab Complic 2012

Summary of Care:
ABC's for Providers

| A	A1c Target Aspirin Daily
B	Blood Pressure Control
C	Cholesterol Management Cigarette Smoking Cessation
D	Diabetes and Pre-Diabetes Management
E	Exercise
F	Food Choices

Diabetes Mellitus (Type II): Effect of Intensive Glycemic Control

United Kingdom Prospective Diabetes Study (UKPDS) 10-Year Follow-Up

Sulphonylurea vs. Conventional Therapy
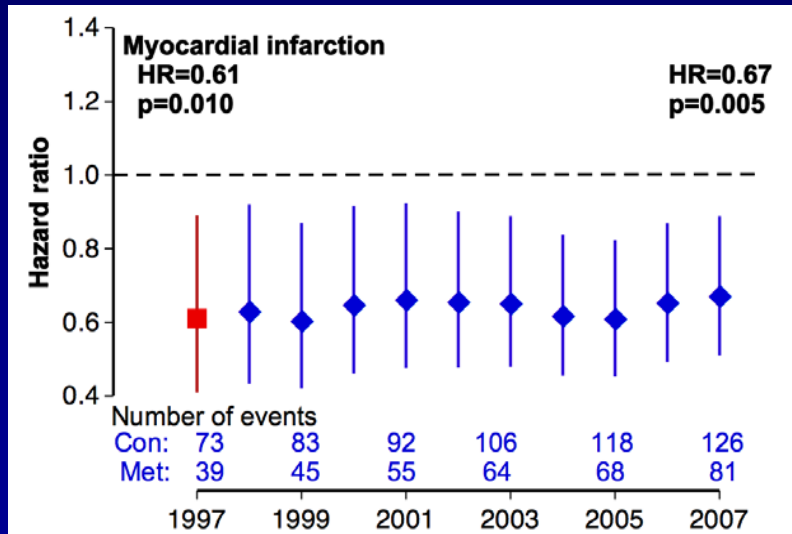
Insulin vs. Conventional Therapy
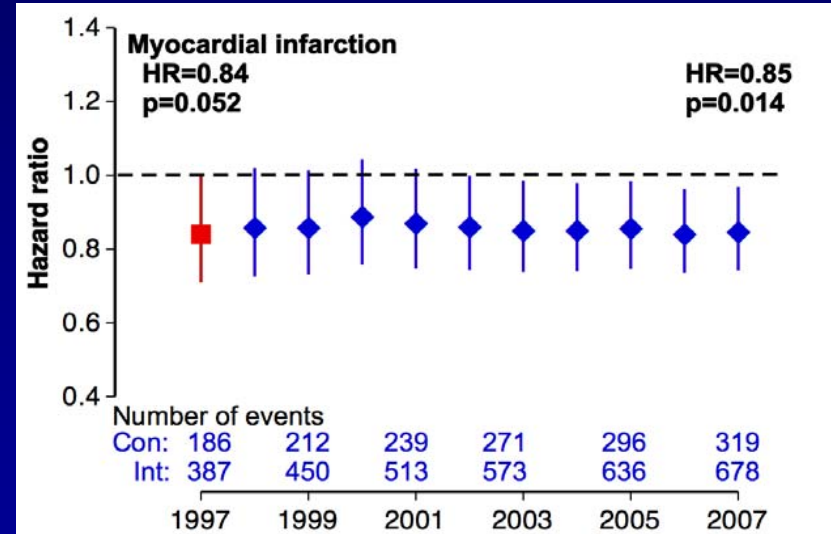
Intensive glycemic control in DM reduces the long-term risk of myocardial infarction

Holman RR et al. NEJM 2008;359:1577-89

Glycemic Legacy?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes

Rury R. Holman, F.R.C.P., Sanjoy K. Paul, Ph.D., M. Angelyn Bethel, M.D., David R. Matthews, F.R.C.P., and H. Andrew W. Neil, F.R.C.P.

CONCLUSIONS

Despite an early loss of glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during 10 years of post-trial follow-up. A continued benefit after metformin therapy was evident among overweight patients. (UKPDS 80; Current Controlled Trials number, ISRCTN75451837.)

Recent Trials Show No Reduction in CV Events with More Intensive Glycemic Control

ACCORD: Primary Outcome

Patients with events (%) vs Years

- Intensive therapy
- Standard therapy
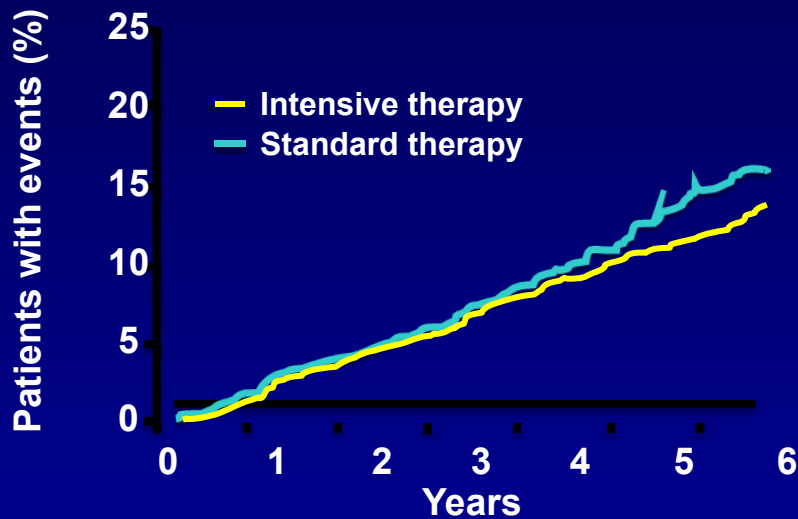
Number at Risk

Intensive	5128	4843	4390	2839	1337	475	448
Standard	5123	4827	4262	2702	1186	440	395

ADVANCE: Primary Outcome

Cumulative incidence (%) vs Months of follow-up

- Intensive therapy
- Standard therapy
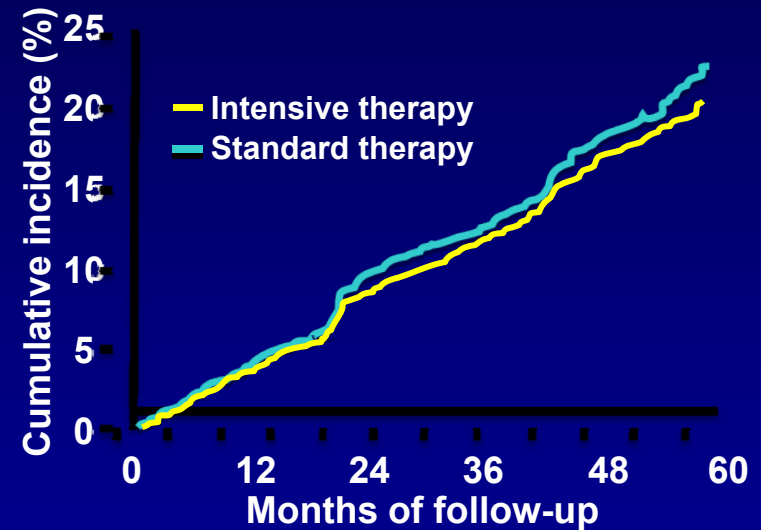
Number at Risk

Intensive	5570	5369	5100	4867	4599	1883
Standard	5569	5342	5065	4808	4545	1921

[1]ACCORD Study Group. *N Engl J Med.* 2008;358:2545-2559.
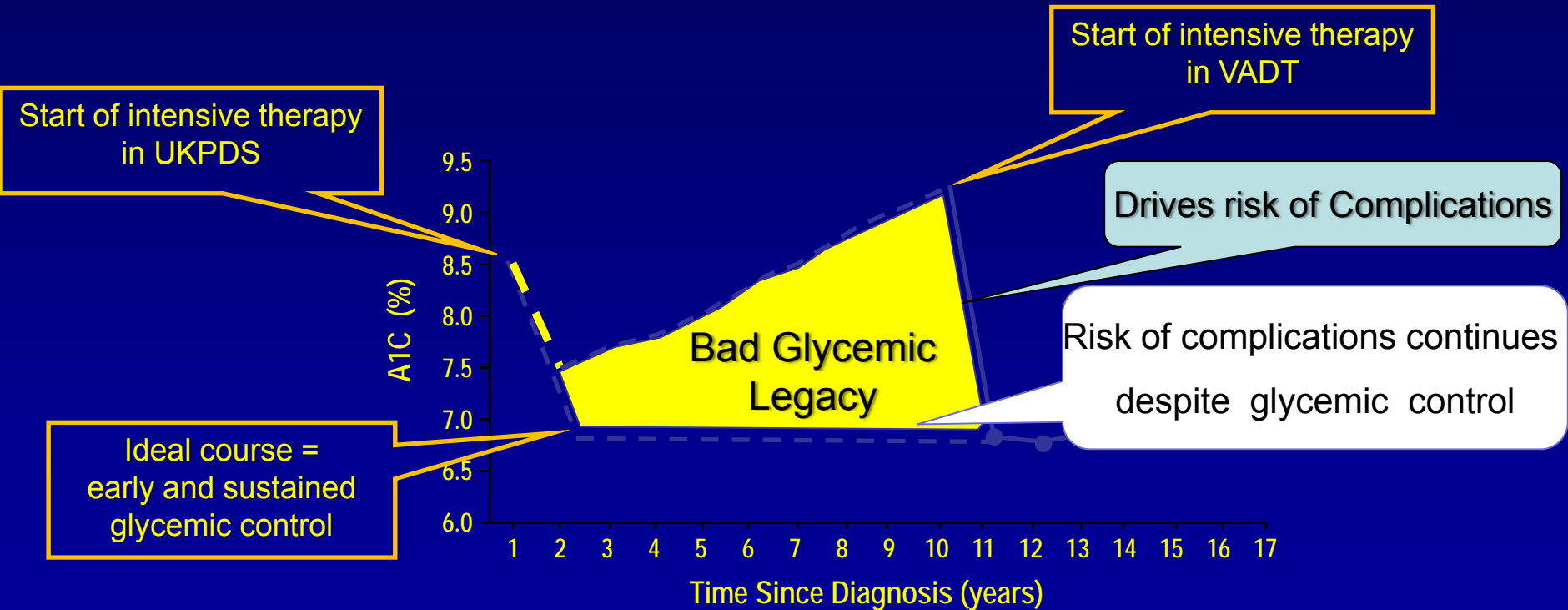[2]ADVANCE Collaborative Group. *N Engl J Med.* 2008;358:2560-2572.

Was Intensive Glycemic Control Harmful?
A closer look at ACCORD AND ADVANCE

- ACCORD was discontinued early due to increased total and CVD mortality in the intensive arm.

- VA Diabetes Trial showed severe hypoglycemia to be a powerful predictor of CVD events.

- A recent analysis of ACCORD (Diabetes Care, May 2010) showed deaths related to unsuccessful intensive therapy where A1c remained high.

- But in both ACCORD AND ADVANCE, those *without macrovascular disease at baseline had an actual benefit in the primary endpoint.*

Metabolic Memory and Glycemic Legacy

UKPDS vs. VADT

Start of intensive therapy in UKPDS

Start of intensive therapy in VADT

Drives risk of Complications

Risk of complications continues despite glycemic control

Bad Glycemic Legacy

Ideal course = early and sustained glycemic control

A1C (%)

Time Since Diagnosis (years)

Del Prato S. *Diabetalogia*. 2009;52:1219-1226.

American Diabetes Association 2012 Standards of Medical Care: HbA1c Goals

- **A reasonable A1C goal for many nonpregnant adults is <7%** due to efficacy in reducing microvascular complications.

- **Consider more stringent A1C goals (such as <6.5%)** for selected patients, if this can be achieved without significant hypoglycemia or other adverse effects of treatment.

- **Less stringent A1C goals (such as <8%)** may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, and extensive comorbid conditions and for those with longstanding diabetes in whom the general goal is difficult to attain.

# UKPDS: Effects of Tight vs. Less-Tight Blood Pressure Control
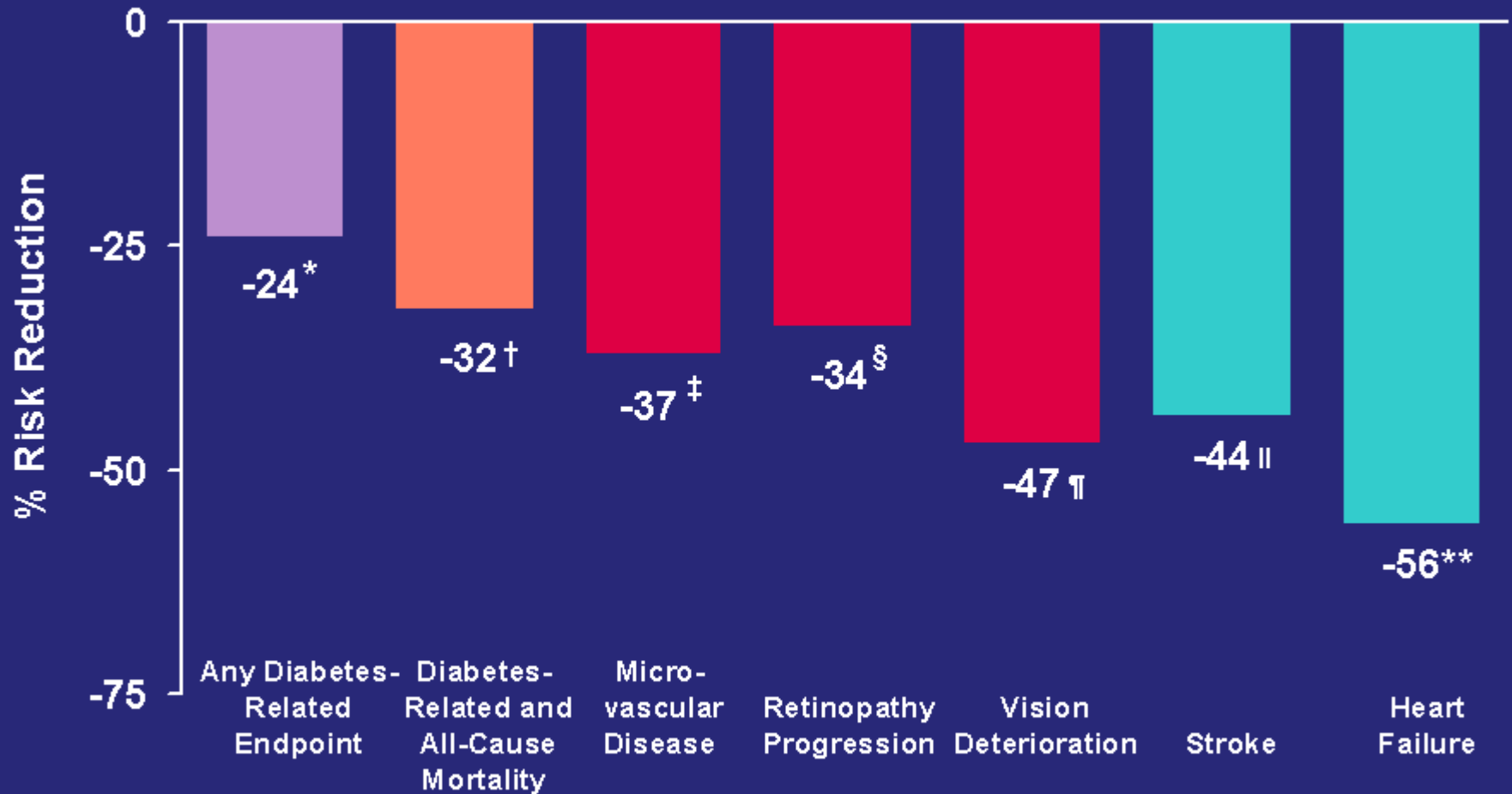
*P=0.0046; †P=0.019; ‡P=0.0092; §P=0.0038; ¶P=0.0036; ‖P=0.013; **P=0.0043

Diabetes Mellitus:
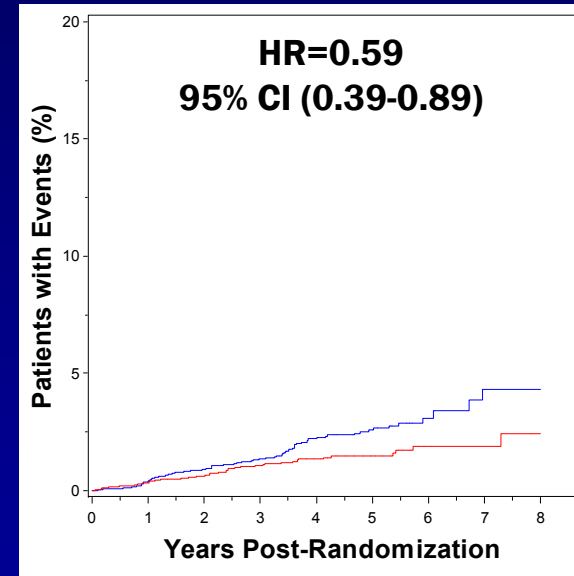# Effect of Blood Pressure Control

Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial

4,733 diabetic patients randomized to intensive BP control (target SBP <120 mm Hg) or standard BP control (target SBP <140 mm Hg) for 4.7 years
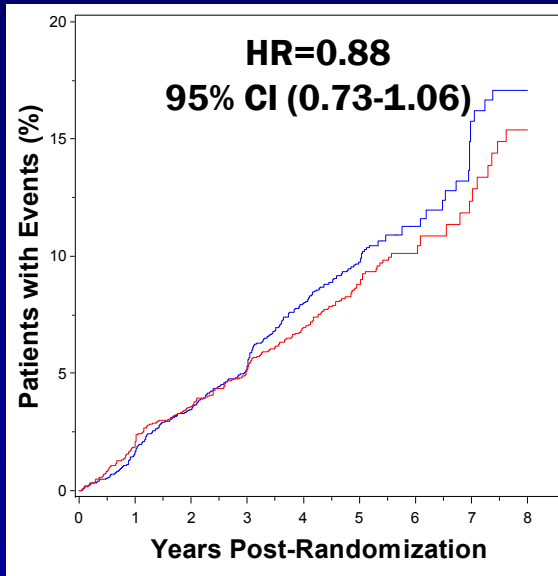
Intensive BP control in DM does not reduce a composite of adverse CV events, but does reduce the rate of stroke

BP=Blood pressure, DM=Diabetes mellitus, HR=Hazard ratio, SBP=Systolic blood pressure
ACCORD study group. NEJM 2010

Recommendations: Hypertension/Blood Pressure Control

Goals

- People with diabetes and hypertension should be treated to a systolic blood pressure goal of <140 mmHg (B)

- Lower systolic targets, such as <130 mmHg, may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden (C)

- Patients with diabetes should be treated to a diastolic blood pressure <80 mmHg (B)

Recommendations: Hypertension/Blood Pressure Control

Treatment (1)

- Patients with a blood pressure (BP) >120/80 mmHg should be advised on lifestyle changes to reduce BP (B)

- Patients with confirmed BP ≥140/80 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely subsequent titration of pharmacological therapy to achieve BP goals (B)

Recommendations: Hypertension/Blood Pressure Control

Treatment (2)

- Lifestyle therapy for elevated BP (B)
  - Weight loss if overweight
  - DASH-style dietary pattern including reducing sodium, increasing potassium intake
  - Moderation of alcohol intake
 - Increased physical activity

Recommendations: Hypertension/Blood Pressure Control

Treatment (3)

- Pharmacological therapy for patients with diabetes and hypertension (C)
  - A regimen that includes either an ACE inhibitor or angiotensin II receptor blocker; if one class is not tolerated, substitute the other
- Multiple drug therapy (two or more agents at maximal doses) generally required to achieve BP targets (B)
- Administer one or more antihypertensive medications at bedtime (A)

Diabetes Mellitus:
Effect of an HMG-CoA Reductase Inhibitor

Meta-analysis of 18,686 patients with DM randomized to treatment with a HMG-CoA Reductase Inhibitor
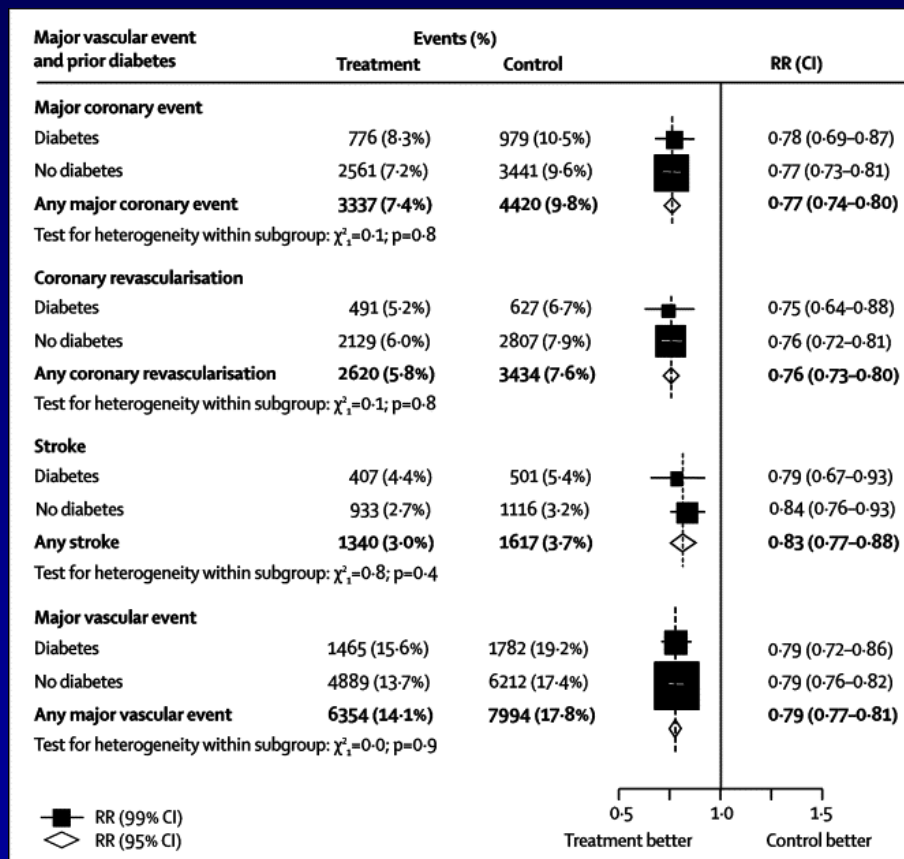
Statins reduce CV events 21% in diabetics (similar to non-diabetics)

Cholesterol Treatment Trialists' (CTT) Collaborators. Lancet 2008;37:117-25
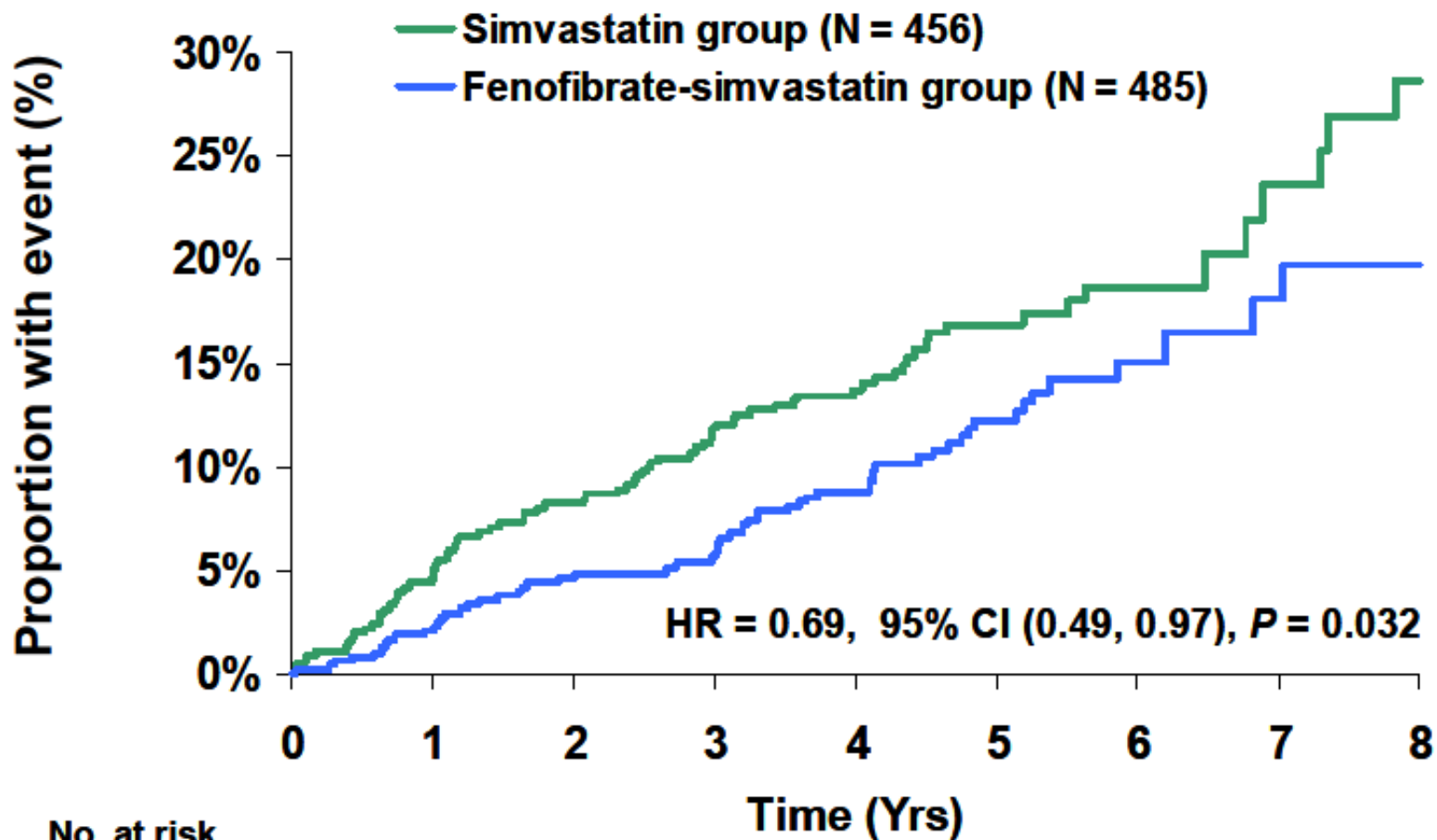
ACCORD Lipid Study Results (NEJM 2010; 362: 1563-74)

- 5518 patients with type 2 DM treated with open label simvastatin randomly assigned to fenofibrate or placebo and followed for 4.7 years.

- Annual rate of primary outcome of nonfatal MI, stroke or CVD death 2.2% in fenofibrate group vs. 1.6% in placebo group (HR=0.91, p=0.33).

- Pre-specified subgroup analyses showed possible benefit in men vs. women and those with high triglycerides and low HDL-C.

- Results support statin therapy alone to reduce CVD risk in high risk type 2 DM patients.

Figure 5. Coadministration Therapy Reduces Risk of CV Events in Prespecified Subgroup with Dysliplidemia in ACCORD Lipid

Simvastatin group (N = 456)
Fenofibrate-simvastatin group (N = 485)

HR = 0.69, 95% CI (0.49, 0.97), *P* = 0.032

Proportion with event (%)

Time (Yrs)

No. at risk					
Simvastatin	456	410	312	76	25
Fenofibrate-simvastatin	485	449	350	81	29

Figure 4. Fibrates Reduced CV Events in Patients with Elevated TG and Low HDL-C in 4 Fibrate Outcomes Trials Conducted Before ACCORD Lipid
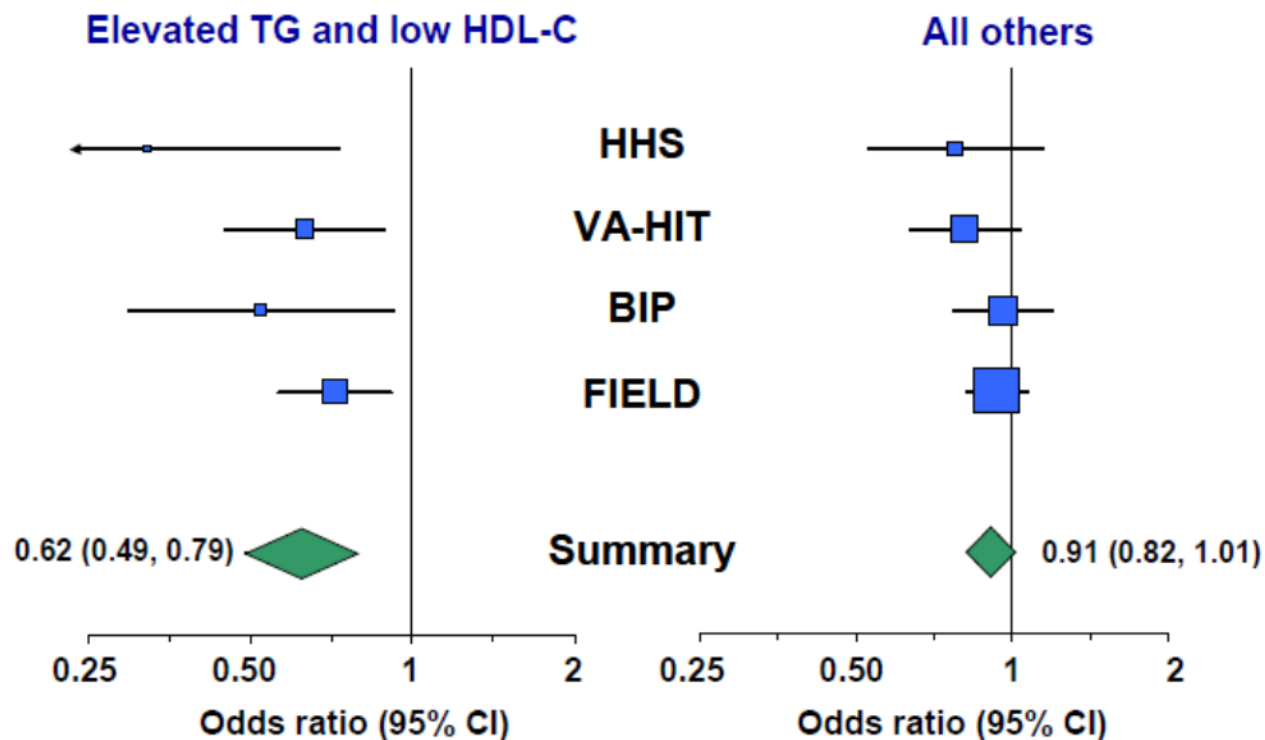
The odds ratio of 0.62 for patients with elevated TG and low HDL-C shows a significant 38% reduction in the risk of CV events with fibrate therapy, while the odds ratio of 0.91 in all other patients represents a nonsignificant 10% reduction in CV risk.

Recommendations: Dyslipidemia/Lipid Management (2)

Treatment recommendations and goals (1)

- To improve lipid profile in patients with diabetes, recommend lifestyle modification (A), focusing on
  - Reduction of saturated fat, *trans* fat, cholesterol intake
  - Increased n-3 fatty acids, viscous fiber, plant stanols/sterols
  - Weight loss (if indicated)
  - Increased physical activity

Recommendations: Dyslipidemia/Lipid Management (3)

Treatment recommendations and goals (2)

- Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels
  - with overt CVD (A)
  - without CVD >40 years of age who have one or more other CVD risk factors (A)
- For patients at lower risk (e.g., without overt CVD, <40 years of age) (C)
  - Consider statin therapy in addition to lifestyle therapy if LDL cholesterol remains >100 mg/dL
  - In those with multiple CVD risk factors

Recommendations: Dyslipidemia/Lipid Management (4)

Treatment recommendations and goals (3)

- In individuals without overt CVD
    - Primary goal is an LDL cholesterol <100 mg/dL (2.6 mmol/L) (B)
- In individuals with overt CVD
    - Lower LDL cholesterol goal of <70 mg/dL (1.8 mmol/L), using a high dose of a statin, is an option (B)

Recommendations: Dyslipidemia/Lipid Management (5)

Treatment recommendations and goals (4)

- If targets not reached on maximal tolerated statin therapy
  - Alternative therapeutic goal: reduce LDL cholesterol ~30–40% from baseline (B)
- Triglyceride levels <150 mg/dL (1.7 mmol/L), HDL cholesterol >40 mg/dL (1.0 mmol/L) in men and >50 mg/dL (1.3 mmol/L) in women, are desirable (C)
  - However, LDL cholesterol–targeted statin therapy remains the preferred strategy (A)

Weight Management Recommendations

Goals

BMI 18.5 to 24.9 kg/m^2

Women: <35 inches
Men: <40 inches

10% weight reduction within the 1st yr of Rx

*BMI is calculated as the weight in kilograms divided by the body surface area in meters^2

Recommendations

I IIa IIb III

B

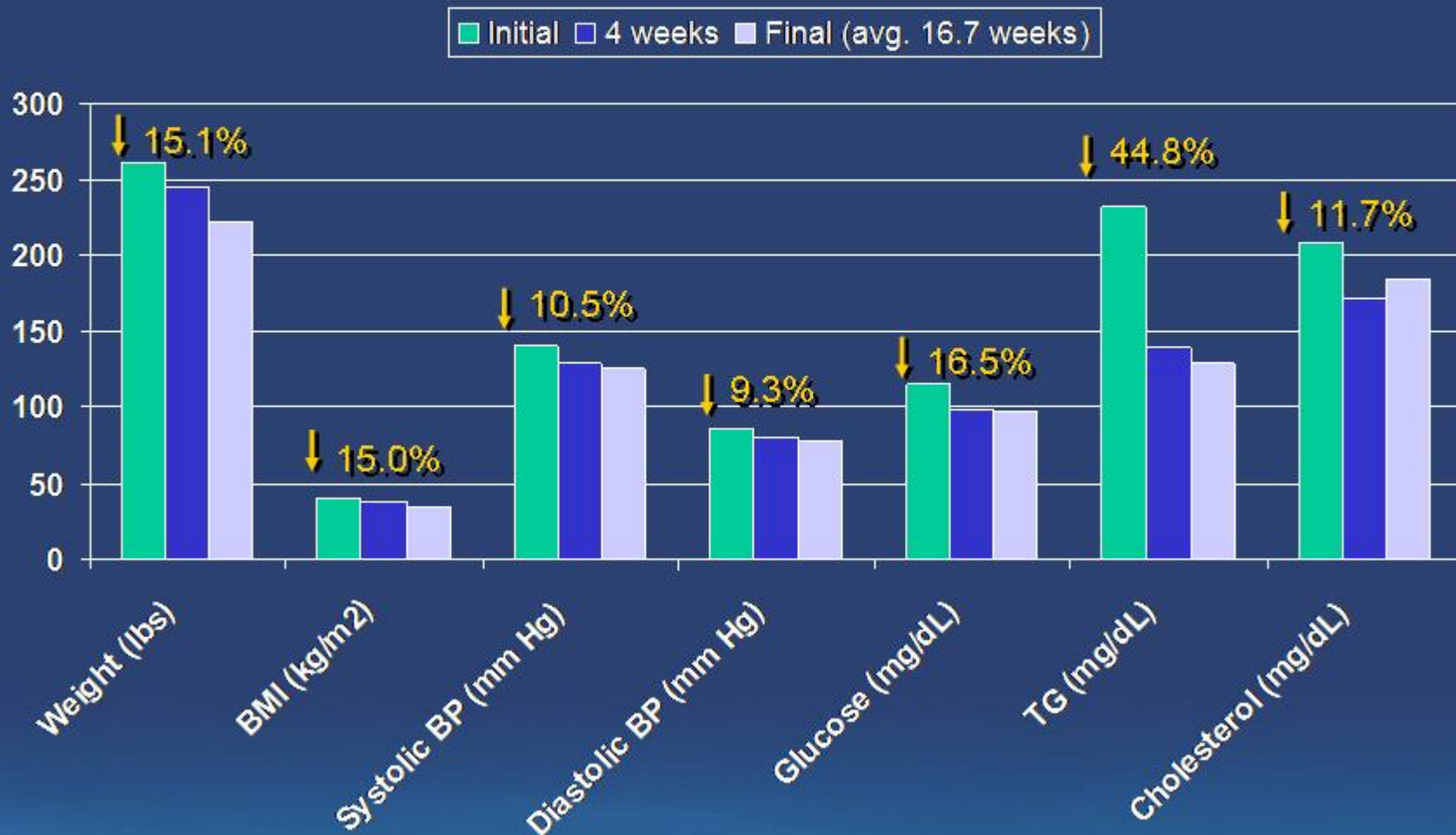Calculate BMI* and measure waist circumference

Monitor response to treatment

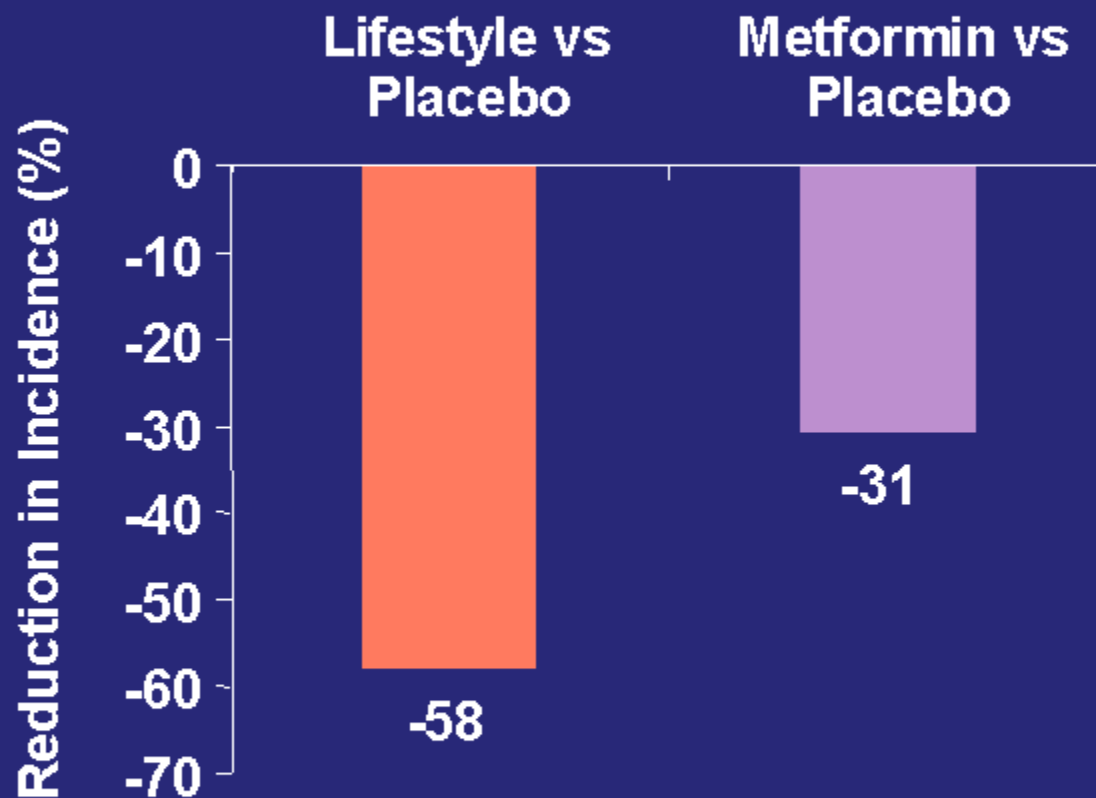Start weight management and physical activity as appropriate

If BMI and/or waist circumference is above goal, initiate caloric restriction and increase caloric expenditure

Cardiometabolic Risk

Effect of Moderate Weight Loss On Cardiometabolic Risk Factors

Legend: Initial ☐ 4 weeks ☐ Final (avg. 16.7 weeks)

- Weight (lbs): ↓ 15.1%
- BMI (kg/m2): ↓ 15.0%
- Systolic BP (mm Hg): ↓ 10.5%
- Diastolic BP (mm Hg): ↓ 9.3%
- Glucose (mg/dL): ↓ 16.5%
- TG (mg/dL): ↓ 44.8%
- Cholesterol (mg/dL): ↓ 11.7%

Case CC, et al. *Diabetes Obes Metab*. 2002;4:407-414.

Percent changes are initial visit to final visit.

Diabetes Prevention Program: Reduction in Diabetes Incidence

N=3,234
39% lower incidence of diabetes in the lifestyle vs. metformin group

Diabetes Prevention Program Research Group. *N Engl J Med*. 2002;346:393–403.

Look AHEAD (Action for Health in Diabetes): Trial Halted Early

- Intensive lifestyle intervention resulted in[1]
  - Average 8.6% weight loss
  - Significant reduction of A1C
  - Reduction in several CVD risk factors
- Benefits sustained at 4 years[2]
- However, trial halted after 11 years of follow-up because there was no significant difference in primary cardiovascular outcome between weight loss, standard care group

1, 2. Look AHEAD Research Group. *Diabetes Care*. 2007;30:1374-1383 and *Arch Intern Med*. 2010;170:1566–1575; http://www.nih.gov/news/health/oct2012/niddk-19.htm.

PREDIMED STUDY (n=7447): Primary Prevention of High Risk Pts with DM or 3+ Risk Factors Randomized to Mediterranean Diet with Extra Virgin Olive Oil or Nuts vs. AHA Diet

Results /primary end point

A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)

Med diet, EVOO: hazard ratio, 0.70 (95% CI, 0.53–0.91); P=0.009
Med diet, nuts: hazard ratio, 0.70 (95% CI, 0.53–0.94); P=0.02

No. at Risk

Control diet	2450	2268	2020	1583	1268	946
Med diet, EVOO	2543	2486	2320	1987	1687	1310
Med diet, nuts	2454	2343	2093	1657	1389	1031
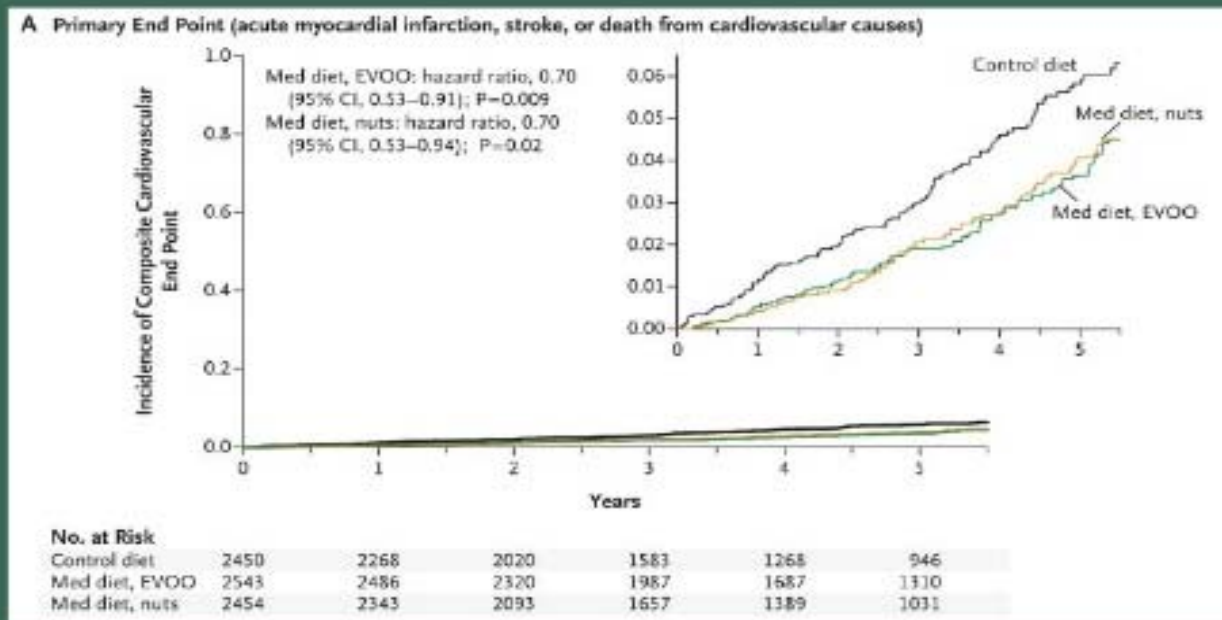
Risk of composite cardiovascular end point was reduced by 30 % in both Med Diet groups vs controls.

Pronutritionist

Recommendations:
Medical Nutrition Therapy (MNT)

- Individuals who have prediabetes or diabetes should receive individualized MNT as needed to achieve treatment goals, preferably provided by a registered dietitian familiar with the components of diabetes MNT (A)

- Because MNT can result in cost-savings and improved outcomes (B), MNT should be adequately covered by insurance and other payers (E)

THE REAL NIGHTMARE

Recommendations: Physical Activity

- Advise people with diabetes to perform at least 150 min/week of moderate-intensity aerobic physical activity (50–70% of maximum heart rate), spread over at least 3 days per week with no more than
2 consecutive days without exercise (A)

- In absence of contraindications, adults with type 2 diabetes should be encouraged to perform resistance training at least twice per week (A)

ADA. V. Diabetes Care. *Diabetes Care* 2013;36(suppl 1):S24.

RCT Trial Assessment of Pedometer Interventions

N=277; 8 Trials
Pedometer increased steps by 2500/day

Bravata, DM et al. JAMA 2007; 298:2296-2304
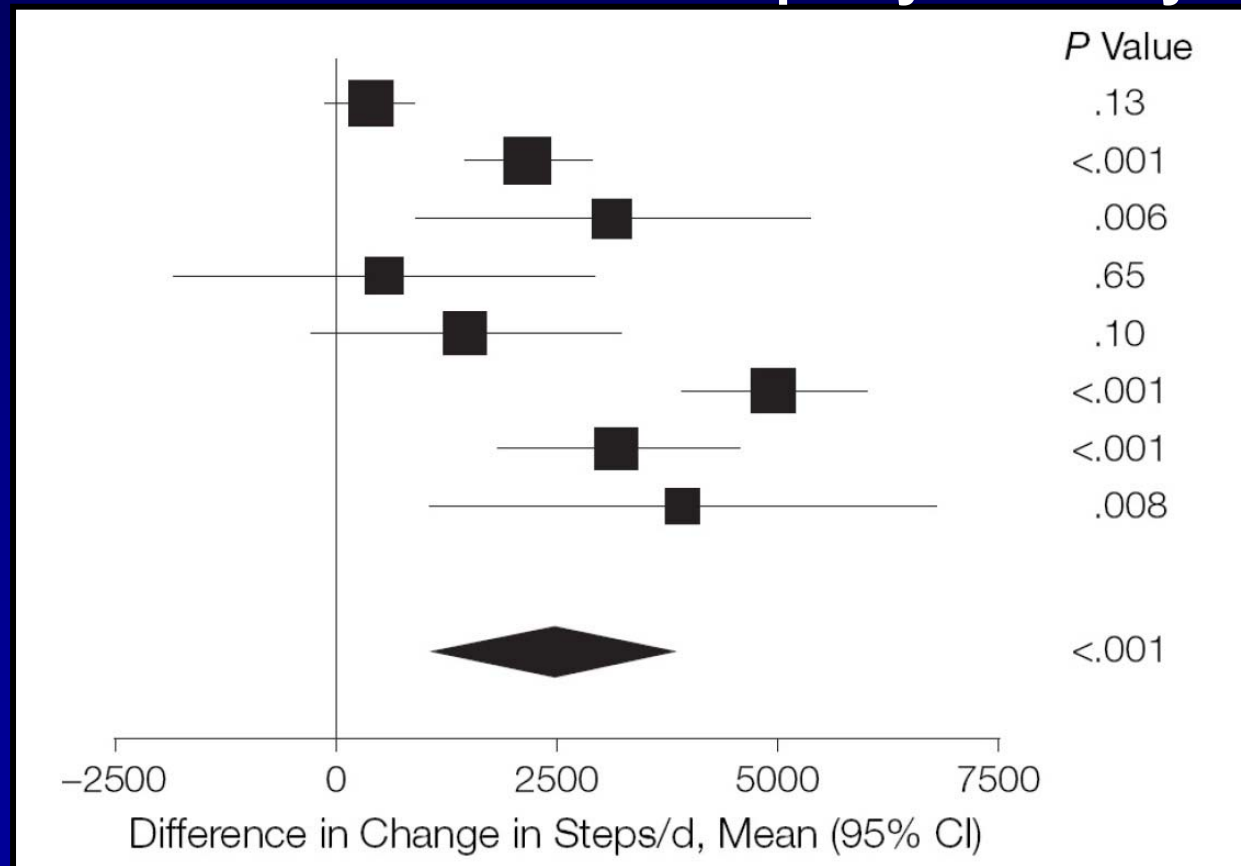
Benefit of Comprehensive, Intensive Management: STENO 2 Study

- Treatment Goals:
  - Intensive TLC
  - HgbA1c <6.5%
  - Cholesterol <175
  - Triglycerides <150
  - BP <130/80

Primary End Point=CV events (%)

— Conventional Therapy
— Intensive Therapy

n =80

n =80

Months of Follow Up
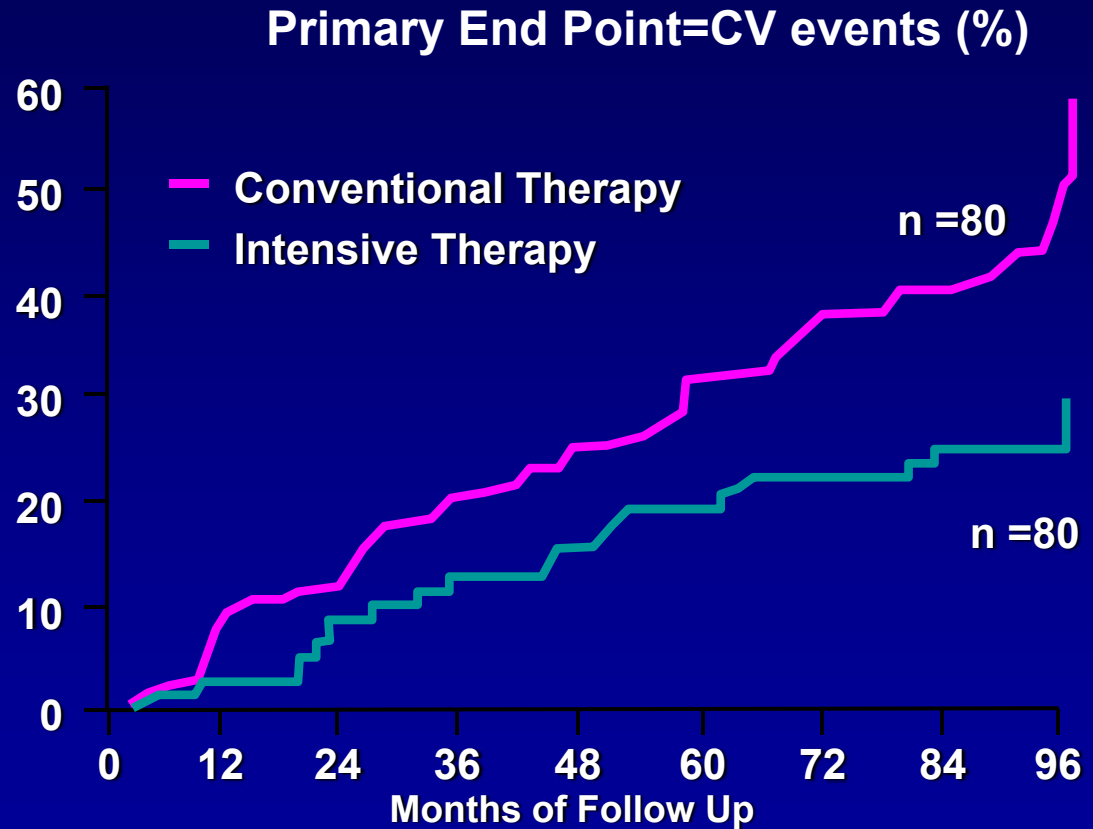
Percent of CHD Events Over 10 Years Prevented in US Adults with T2DM, According to Individual and Composite Risk Factor Control (Wong ND, et al., AHA 2012)
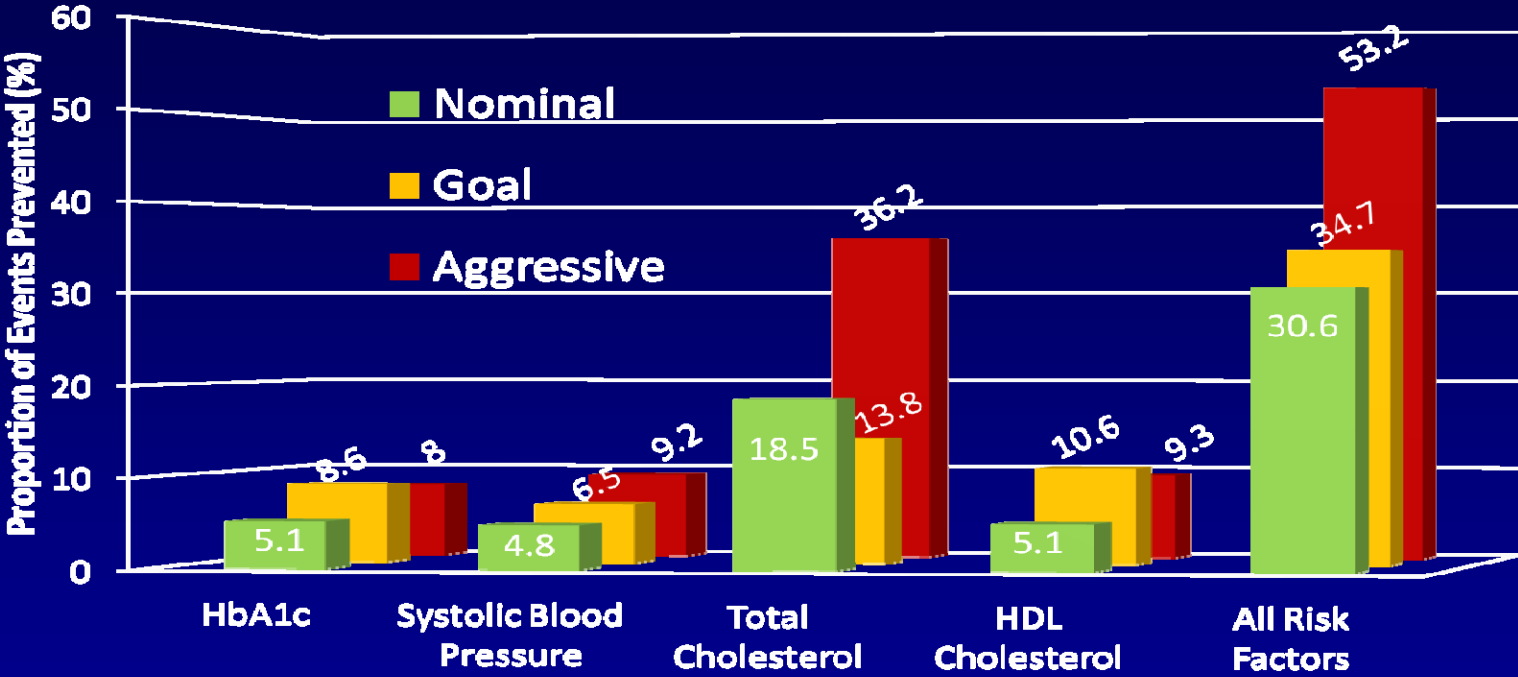

	Goal(ADA Guidelines)	Nominal	Aggressive
HbA1C*	7%	1% AR	2% AR
Systolic Blood Pressure	130mmHg	10% RR	20% RR
Total Cholesterol	170mg/dl (4.4mmol/L)	25% RR	50% RR
HDL-Cholesterol	40mg/dl(M), 50 mg/dl(F)	10% relative increase	20% relative increase
RR-Relative Reduction; AR- Absolute Reduction; HbA1C levels were not allowed to be reduced further than 6.5%			

SUMMARY

- MetS and DM confer increased risks for CVD complications
- The wide spectrum in CVD risks, however, warrants careful CVD risk assessment in such individuals
- Lifestyle modification remains the cornerstone of efforts to prevent and reduce progression of MetS and DM globally
- Glycemic, blood pressure, lipid, and antiplatelet therapy are key to reduce CVD risks associated with MetS and DM

Thank you!
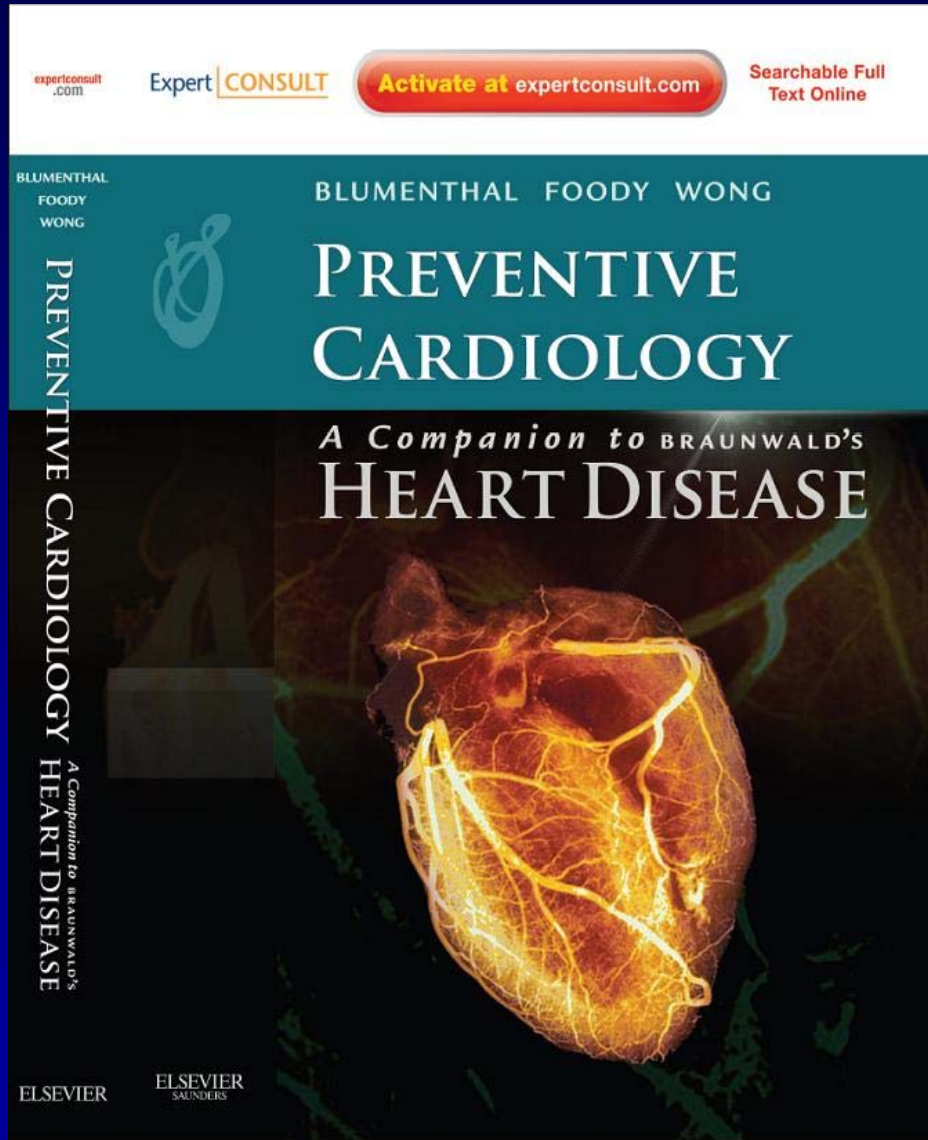
www.heart.uci.edu

Join the ASPC at
www.aspconline.org