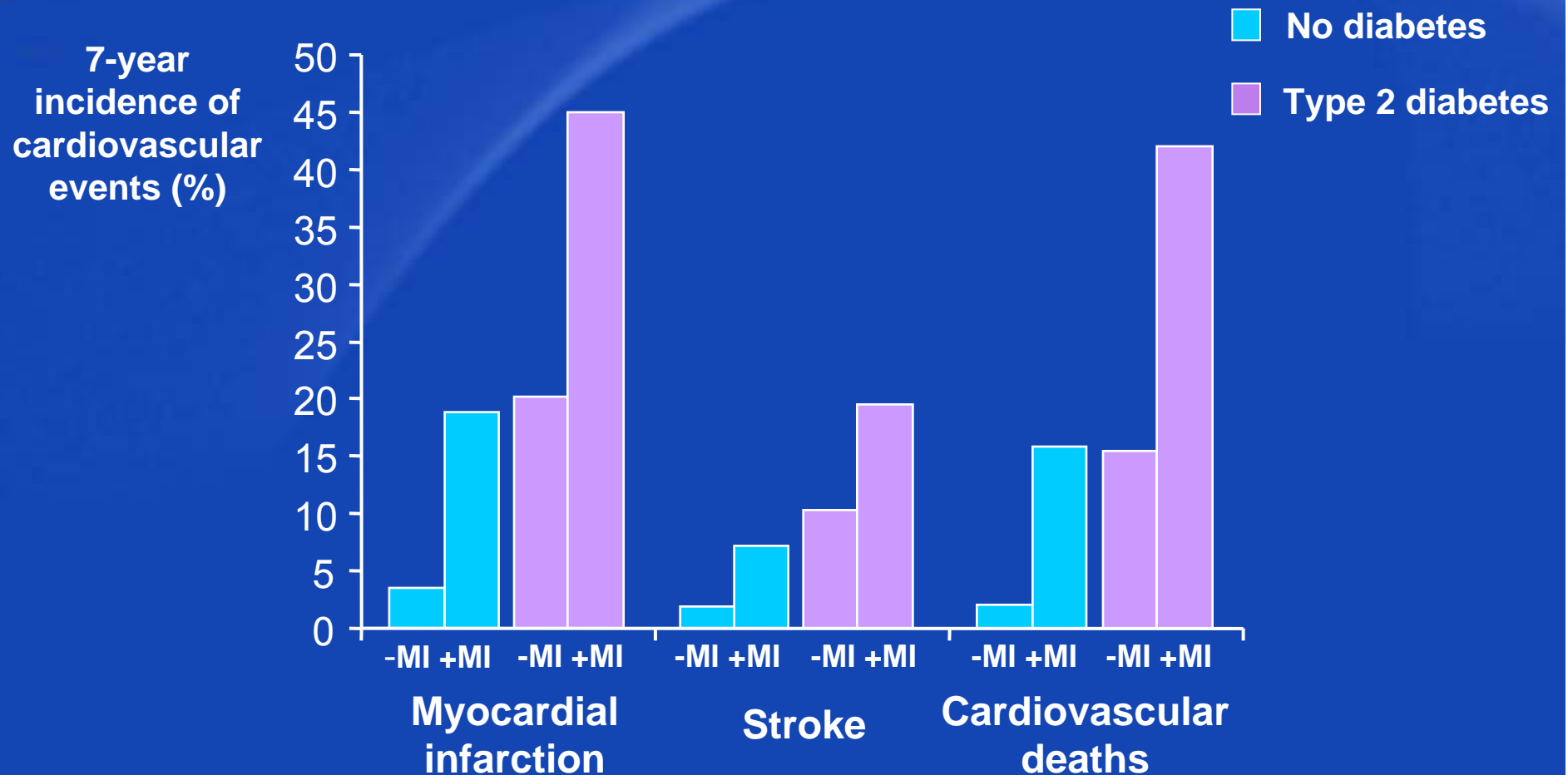


**Achieving comprehensive cardiovascular risk reduction through integrated management of diabetes, obesity, hypertension, and lipid disorders**

**Antonio Ceriello  
Warwick Medical School  
University of Warwick  
Coventry, UK**

# High risk of cardiovascular events in Type 2 diabetes



-MI=no prior myocardial infarction; +MI=prior myocardial infarction  
Grundy et al. *Circulation*. 2004; Haffner et al. *N Engl J Med*. 1998

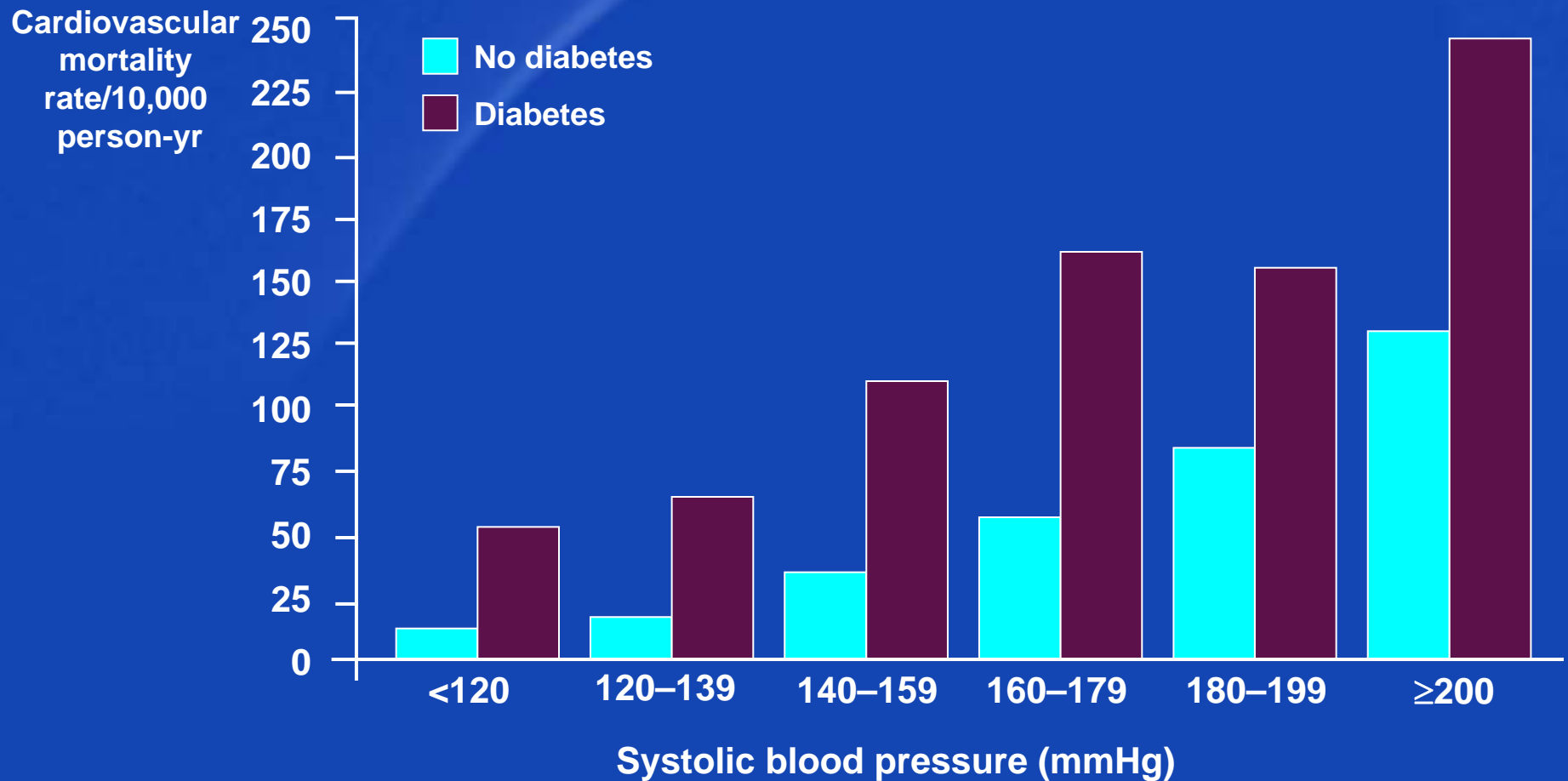
# Prevalence of cardiovascular risk factors in diabetes relative to no diabetes

Risk factor	Type 1	Type 2
Dyslipidaemia		
Hypertriglyceridaemia	+	++
Low HDL cholesterol	-	++
Small, dense LDL cholesterol	-	++
Increased apo B	-	++
Hypertension	+	++
Hyperinsulinaemia/insulin resistance	-	++
Central obesity	-	++
Family history of atherosclerosis	-	+
Cigarette smoking	-	-

+ = moderately increased compared with nondiabetic population; ++ = markedly increased compared with nondiabetic population ; - = not different compared with nondiabetic population;  
 HDL=high-density lipoprotein; LDL=low-density lipoprotein

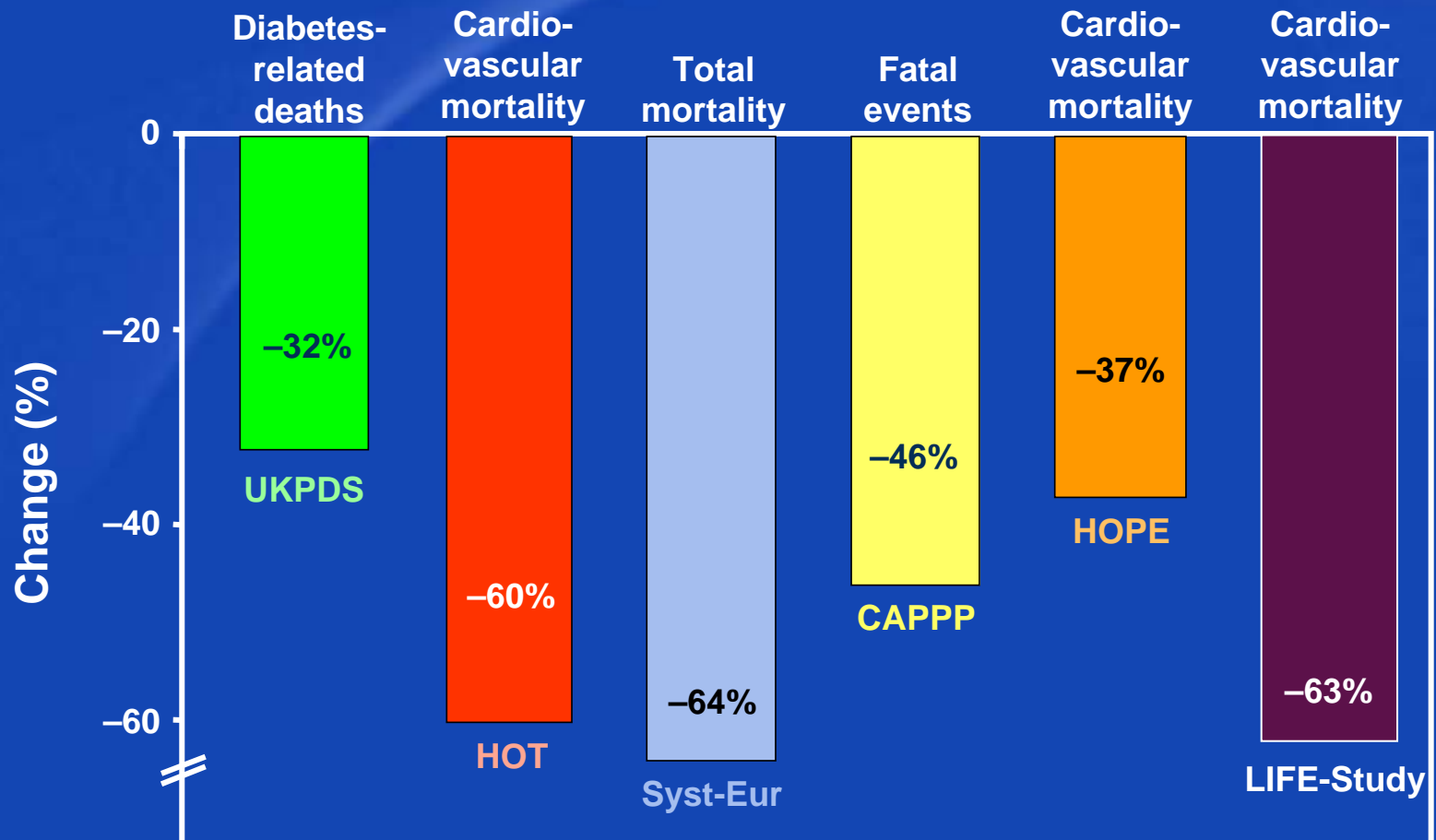
Chait, Bierman. In: *Joslin's Diabetes Mellitus*. Lea & Febiger; 1994

# Association of systolic blood pressure and cardiovascular death in Type 2 diabetes



Stamler et al. *Diabetes Care*. 1993

# Effect of lowering blood pressure in diabetes



BP-lowering (mmHg)

Intervention group

Control group

Δ (Difference)

-16/-12

-30/-24

-22.1/-6.9

-13/-10

-2/-3

-31/-17

-6/-7

-26/-20

-13.5/-2.9

-13/-10

1/-2

-29/-17

-10/-5

-4/-4

8.6/-4.0

0/0

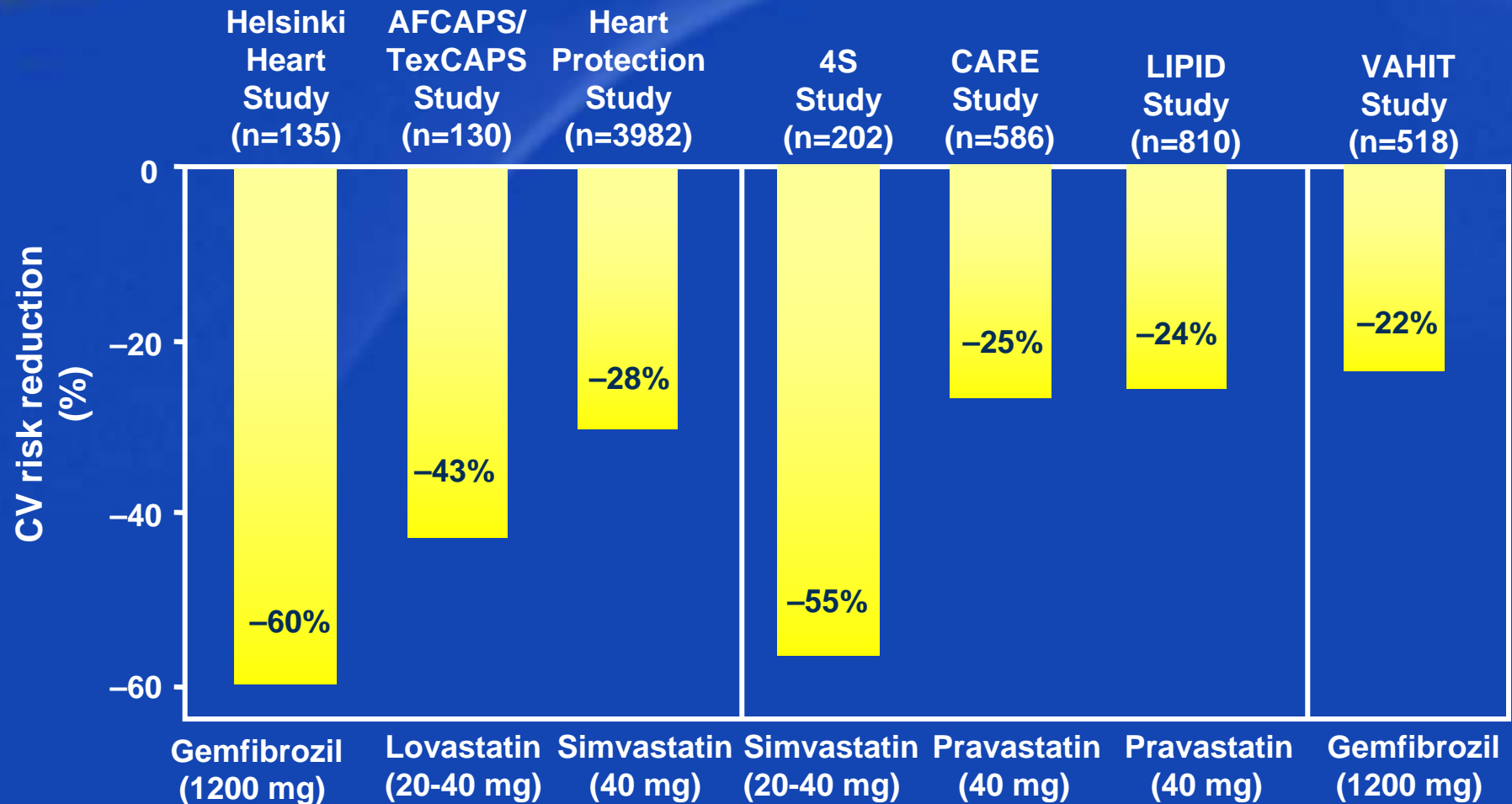
3/1

2/0

# Lipid treatment in diabetes and CV risk reduction

## Primary prevention

## Secondary prevention



CV=cardiovascular



## FIELD study: conclusions

- Effect of fenofibrate on the primary outcome, coronary heart disease death or nonfatal MI, did not achieve statistical significance
- However, fenofibrate significantly reduced total CVD events, particularly due to reductions in nonfatal MI and coronary revascularisations
- Fenofibrate also conferred beneficial microvascular-associated effects on renal and retinal disease

# CARDS endpoints

## Primary Efficacy Parameters

- Acute coronary heart disease death
- Non-fatal MI including silent MI
- Hospitalised unstable angina
- Resuscitated cardiac arrest
- Coronary revascularisation
- Stroke





*Major coronary events*

## Secondary Efficacy Parameters

- Total mortality
- Any cardiovascular endpoint
- Lipid and lipoproteins

CARDS=Collaborative Atorvastatin Diabetes Study  
Colhoun et al. *Lancet*. 2004

# CARDS: treatment effect on the primary endpoint

Event	Placebo*	Atorva- statin*	Hazard ratio	Risk reduction (CI)
Primary endpoint	127 (9.0%)	83 (5.8%)		37% (17-52) P=0.001
Acute coronary events	77 (5.5%)	51 (3.6%)		36% (9-55)
Coronary revascularisation	34 (2.4%)	24 (1.7%)		31% (-16-59)
Stroke	39 (2.8%)	21 (1.5%)		48% (11-69)


.2 .4 .6 .8 1 1.2

\* N (% randomized)

Colhoun et al. *Lancet*. 2004

Favours Atorvastatin

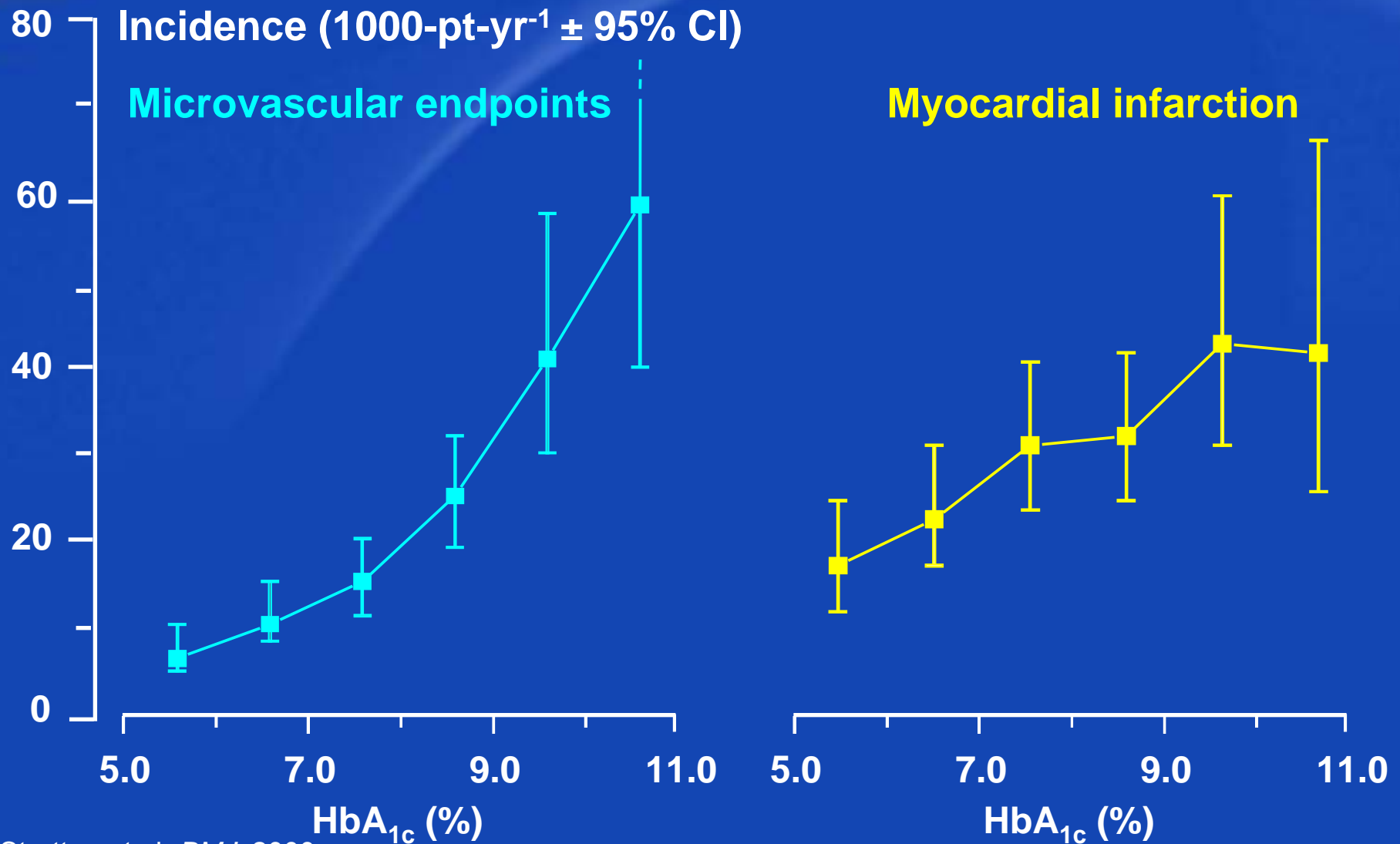
Favours Placebo



# Association of glycaemia with macrovascular and microvascular complications of Type 2 diabetes

UKPDS 35:  
Prospective  
Observational Study

# Relationship of endpoints and HbA<sub>1c</sub> in the UKPDS





## **What is already known on this topic**

- The risk of developing complications of diabetes increases with increasing concentrations of hyperglycaemia
- Reduction of hyperglycaemia in these individuals reduces the risk of complications

## **What this study adds**

- There is a direct relation between the risk of complications of diabetes and glycaemia over time
- No threshold of glycaemia was observed for a substantive change in risk for any of the clinical outcomes examined
- The lower the glycaemia, the lower the risk of complications
- The rate of increase of risk of microvascular disease with hyperglycaemia is greater than that for macrovascular disease

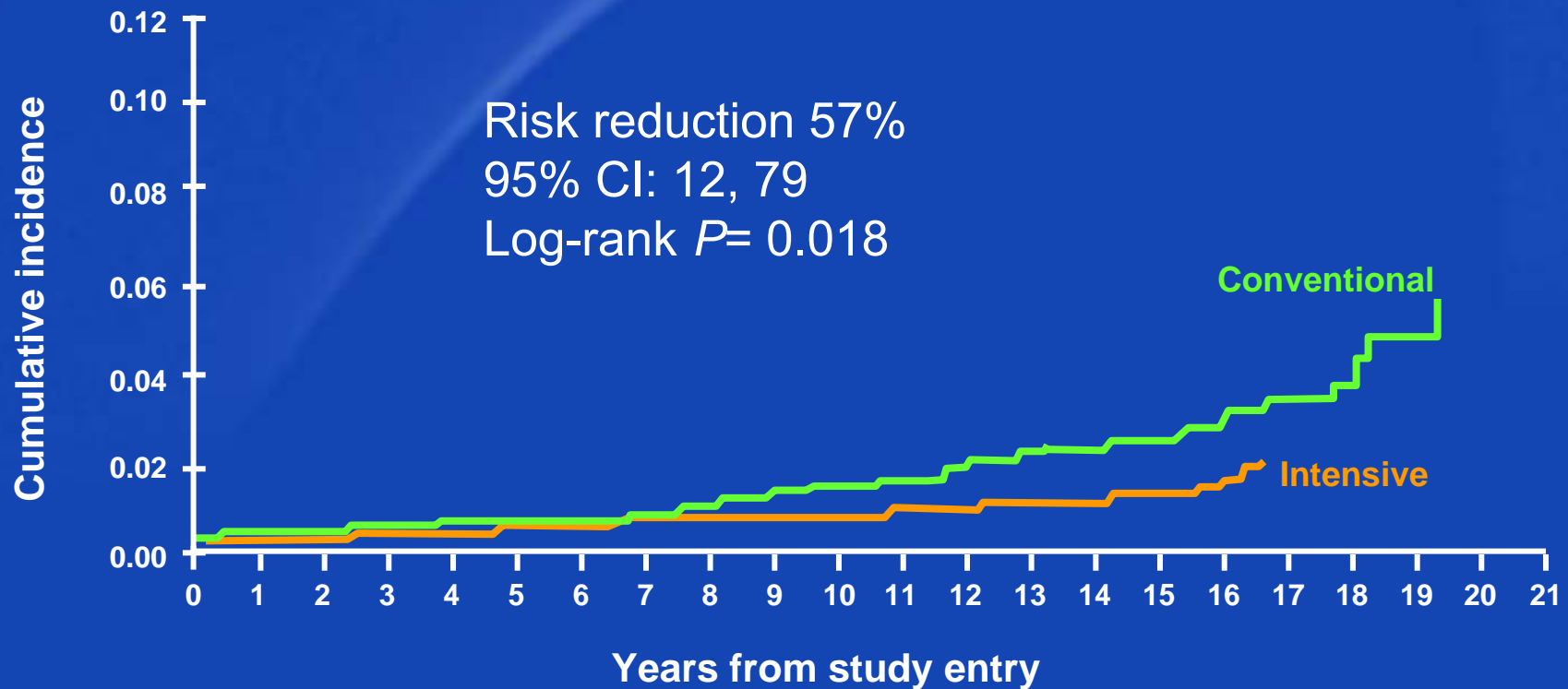


# **Intensive diabetes treatment and cardiovascular disease in patients with Type 1 diabetes**

**DCCT/EDIC Study Research Group**

# Cardiovascular events

Non-fatal myocardial infarction, stroke, or CVD death

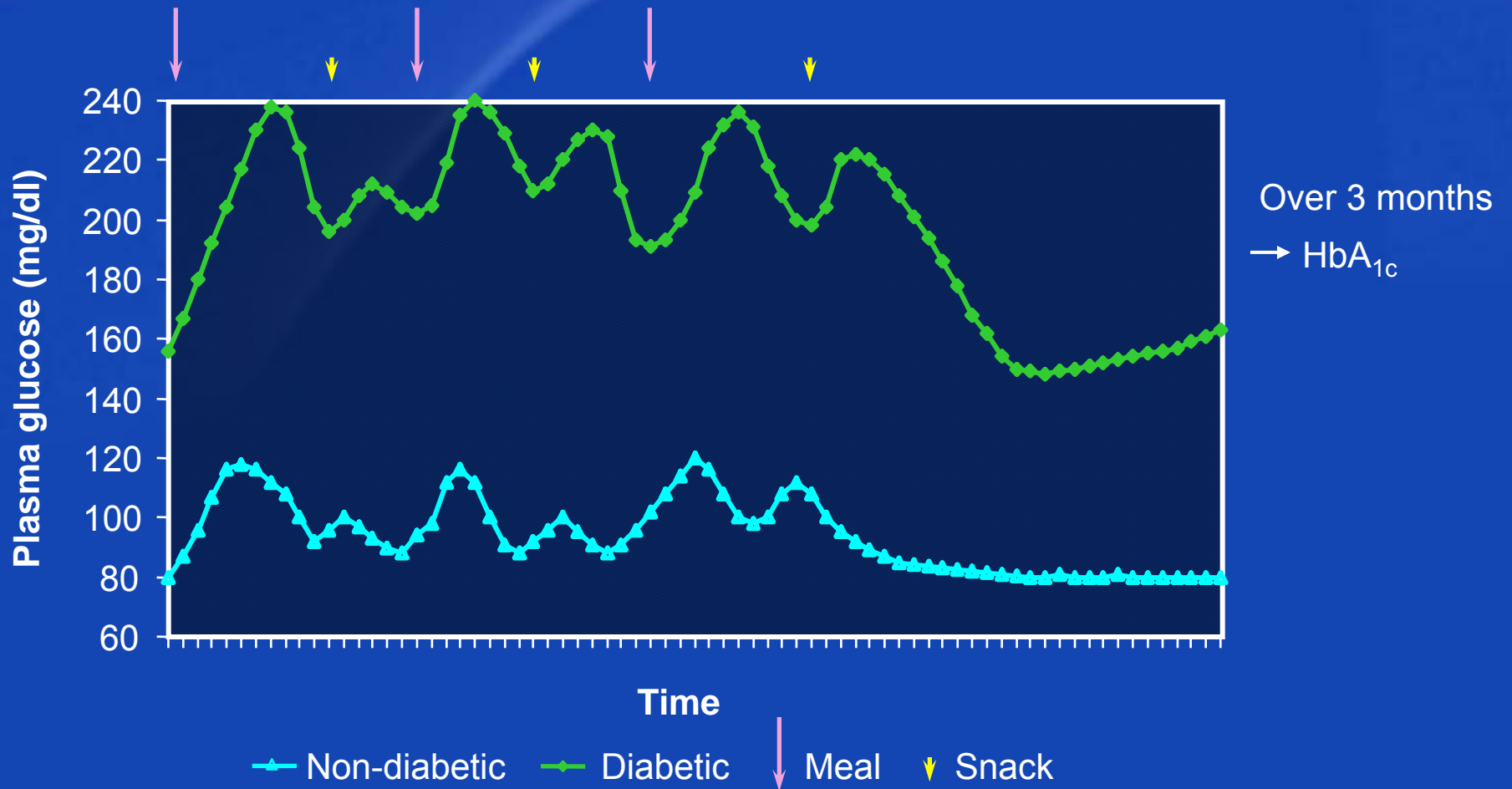


## Number at Risk

Intensive	705	686	640	118
Conventional	721	694	637	96

# Blood glucose levels over 24 hours

## Meal-related plasma glucose excursions



# Evidence associates mealtime glucose spikes with risk of CVD and mortality

DECODE, 1999<sup>1</sup>

- ➔ High 2-hour post-load blood glucose is associated with increased risk of death, independent of FPG

Pacific and Indian Ocean, 1999<sup>2</sup>

- ➔ Isolated 2-hour hyperglycaemia doubles the risk of mortality

Funagata Diabetes Study, 1999<sup>3</sup>

- ➔ IGT, but not IFG, is a risk factor for CVD

Whitehall, Paris, Helsinki Study, 1998<sup>4</sup>

- ➔ Men in upper 2.5% of 2-hour post-meal glucose distribution had significantly higher coronary heart disease mortality

The Rancho-Bernardo Study, 1998<sup>5</sup>

- ➔ 2-hour post-challenge hyperglycaemia more than doubles the risk of fatal CVD and heart disease in older adults

Diabetes Intervention Study, 1996<sup>6</sup>

- ➔ Post-meal, but not fasting glucose, is associated with coronary heart disease

1. DECODE Study Group. *Lancet*. 1999


2. Shaw et al. *Diabetologia*. 1999

3. Tominaga et al. *Diabetes Care*. 1999

4. Balkau et al. *Diabetes Care*. 1998

5. Barrett-Connor et al. *Diabetes Care*. 1998

6. Hanefeld et al. *Diabetologia*. 1996



**Postprandial blood glucose  
is a stronger predictor  
of cardiovascular events than fasting  
blood glucose in Type 2 diabetes  
mellitus, particularly in women**

**San Luigi Gonzaga Diabetes Study**

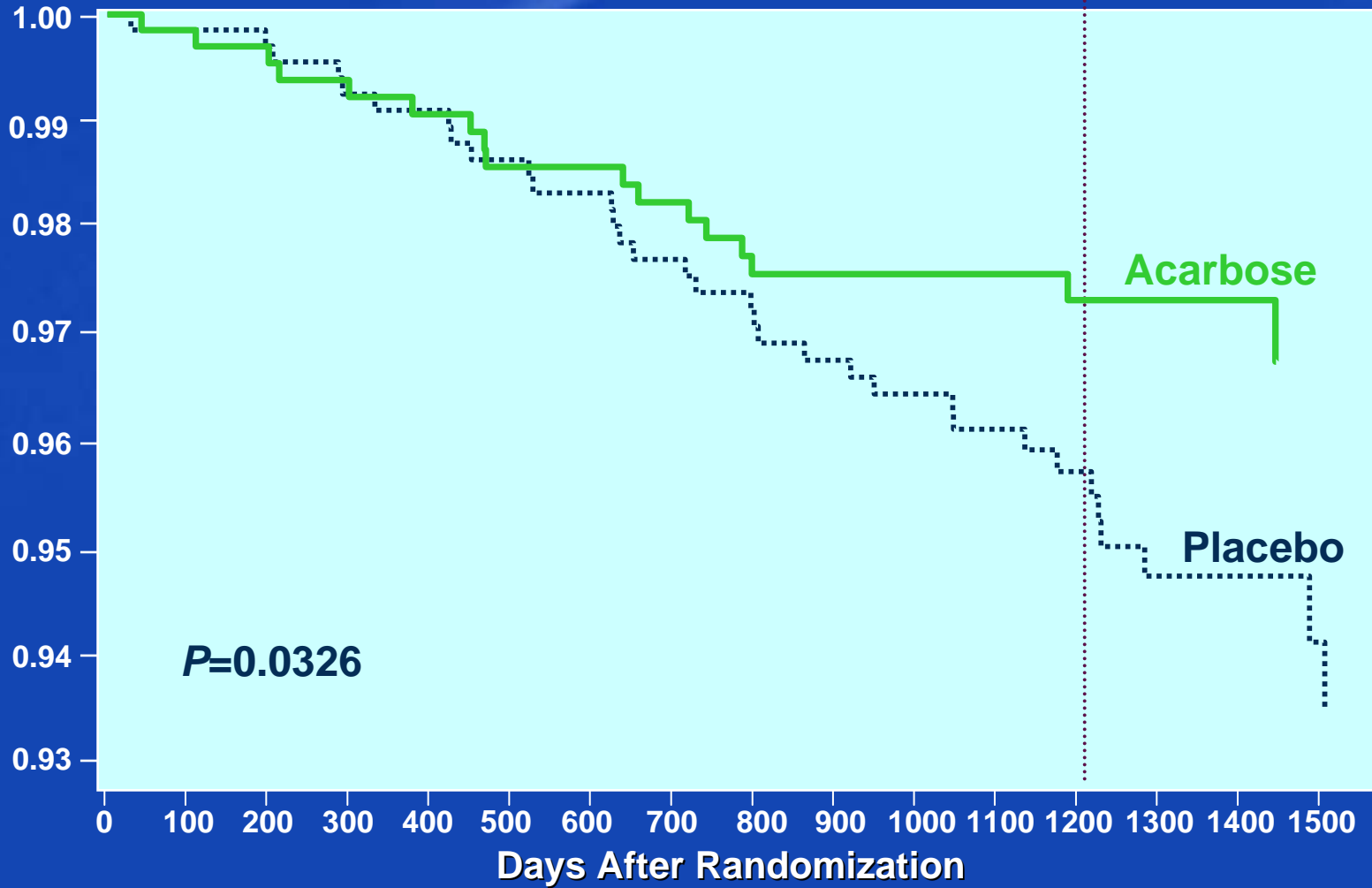



# Time to any cardiovascular event (first event only)

ITT

Survival Distribution Function

Mean Treatment Duration





# Cardiovascular risk factors in people with diabetes

- Dyslipidaemia<sup>1</sup>
- Hypertension<sup>2,3</sup>
- Hyperinsulinaemia / insulin resistance<sup>4,5</sup>
- Central obesity<sup>6-8</sup>
- Cigarette smoking<sup>2,9,10</sup>
- Hyperglycaemia<sup>11,12</sup>
- Postprandial hyperglycaemia<sup>13</sup>

1. Grundy. *Circulation*. 1997

2. Grundy et al. *Circulation*. 1999

3. Chobanian et al. *Hypertension*. 2003

4. Reaven. *Diabetes*. 1988

5. Reaven. *Physiol Rev*. 1995

6. Laakso. *Diabetes Rev*. 1995

7. Stunkard. *Am J Med*. 1996

8. Despres. *Baillieres Clin Endocrinol Metab*. 1994

9. Neaton, Wentworth. *Arch Intern Med*. 1992

10. Heitzer et al. *Circulation*. 1996

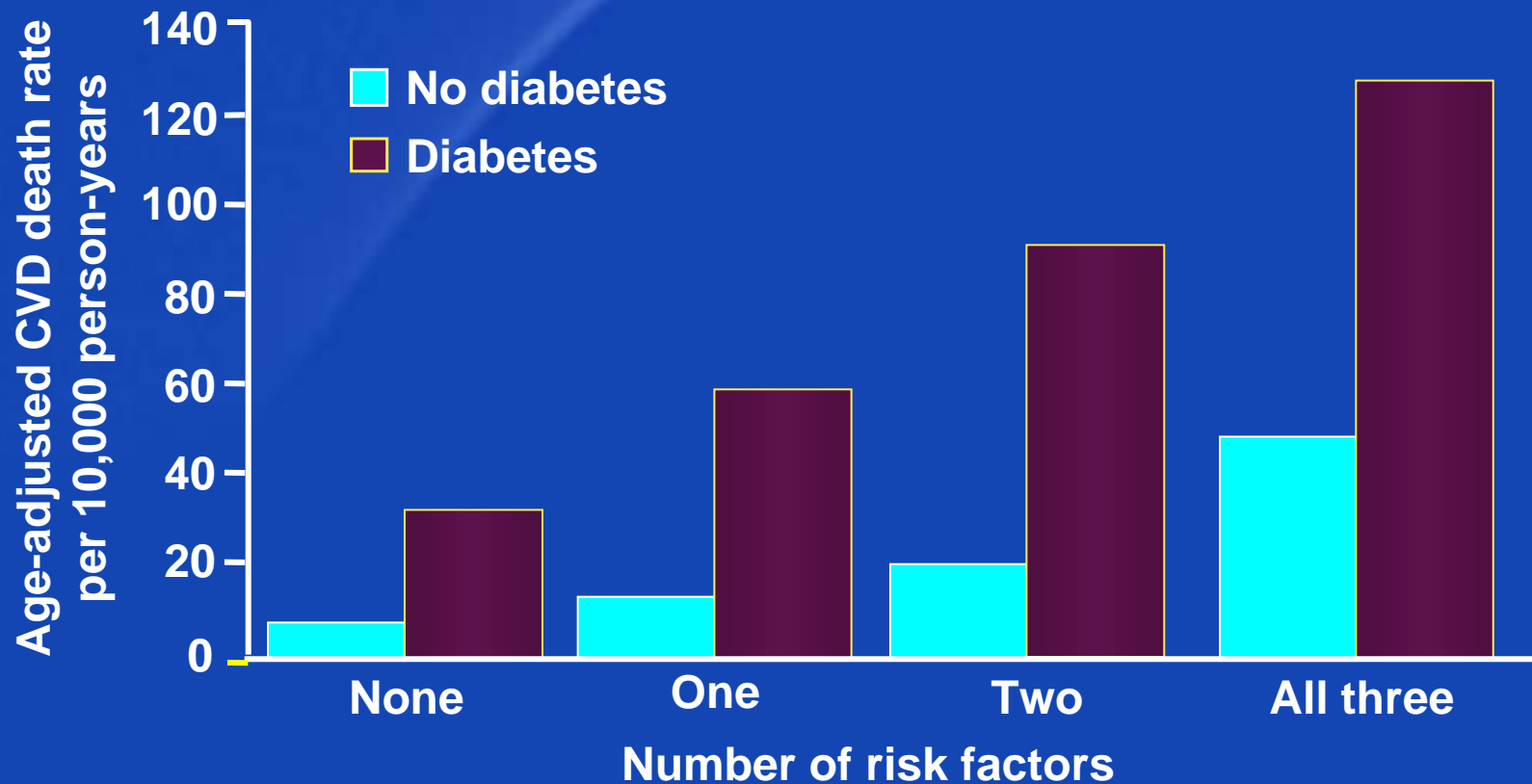
11. Haffner. *Diabetes Care*. 1998

12. Cohen. *Circulation*. 1993

13. Ceriello et al. *Nutr Metab Cardiovasc Dis*. 2006

# MRFIT

Additive effects of hypertension, hypercholesterolaemia, and smoking



CVD=cardiovascular disease; MRFIT=Multiple Risk Factor Intervention Trial  
Stamler et al. *Diabetes Care*. 1993

# Steno-2

## The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

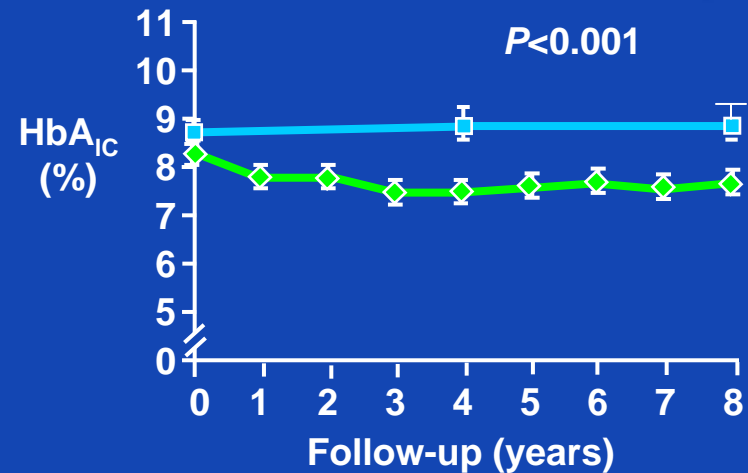
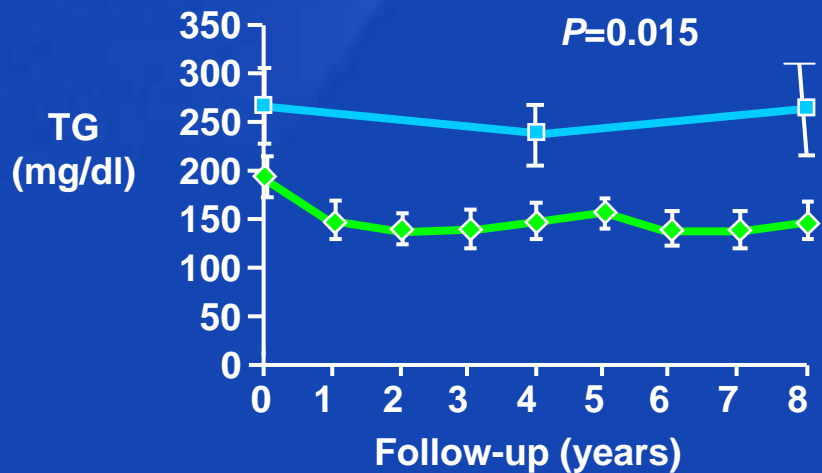
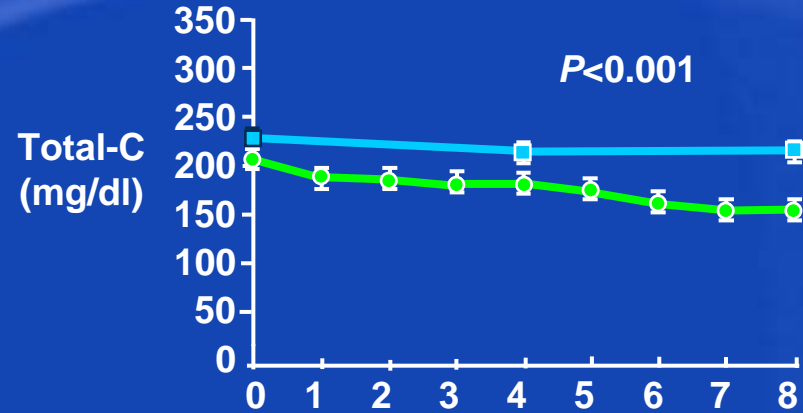
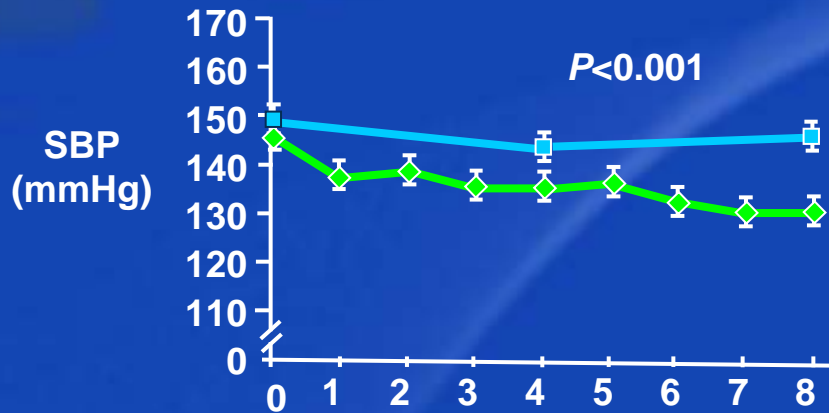
JANUARY 30, 2003

VOL. 348 NO. 5

### Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes

Peter Gæde, M.D., Pernille Vedel, M.D., Ph.D., Nicolai Larsen, M.D., Ph.D., Gunnar V.H. Jensen, M.D., Ph.D.,  
Hans-Henrik Parving, M.D., D.M.Sc., and Oluf Pedersen, M.D., D.M.Sc.

# Steno-2: better risk factor control with intensive therapy



■ Conventional therapy (n=80)

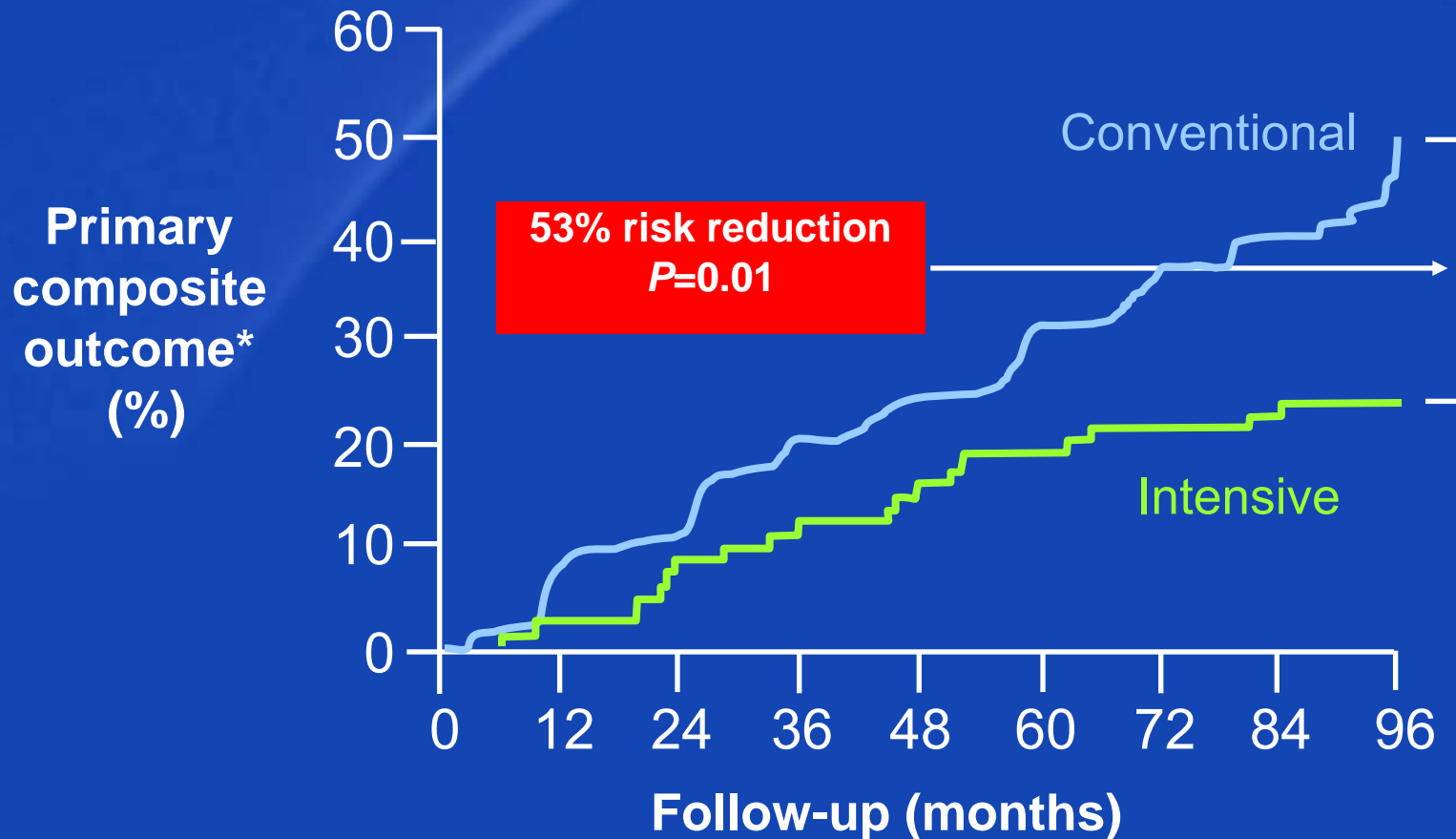
◆ Intensive therapy (n=80)

SBP=systolic blood pressure; TG=triglycerides; Total-C=total cholesterol

Gaede et al. *N Engl J Med.* 2003

# Steno-2: effects of multifactorial intervention on cardiovascular outcomes

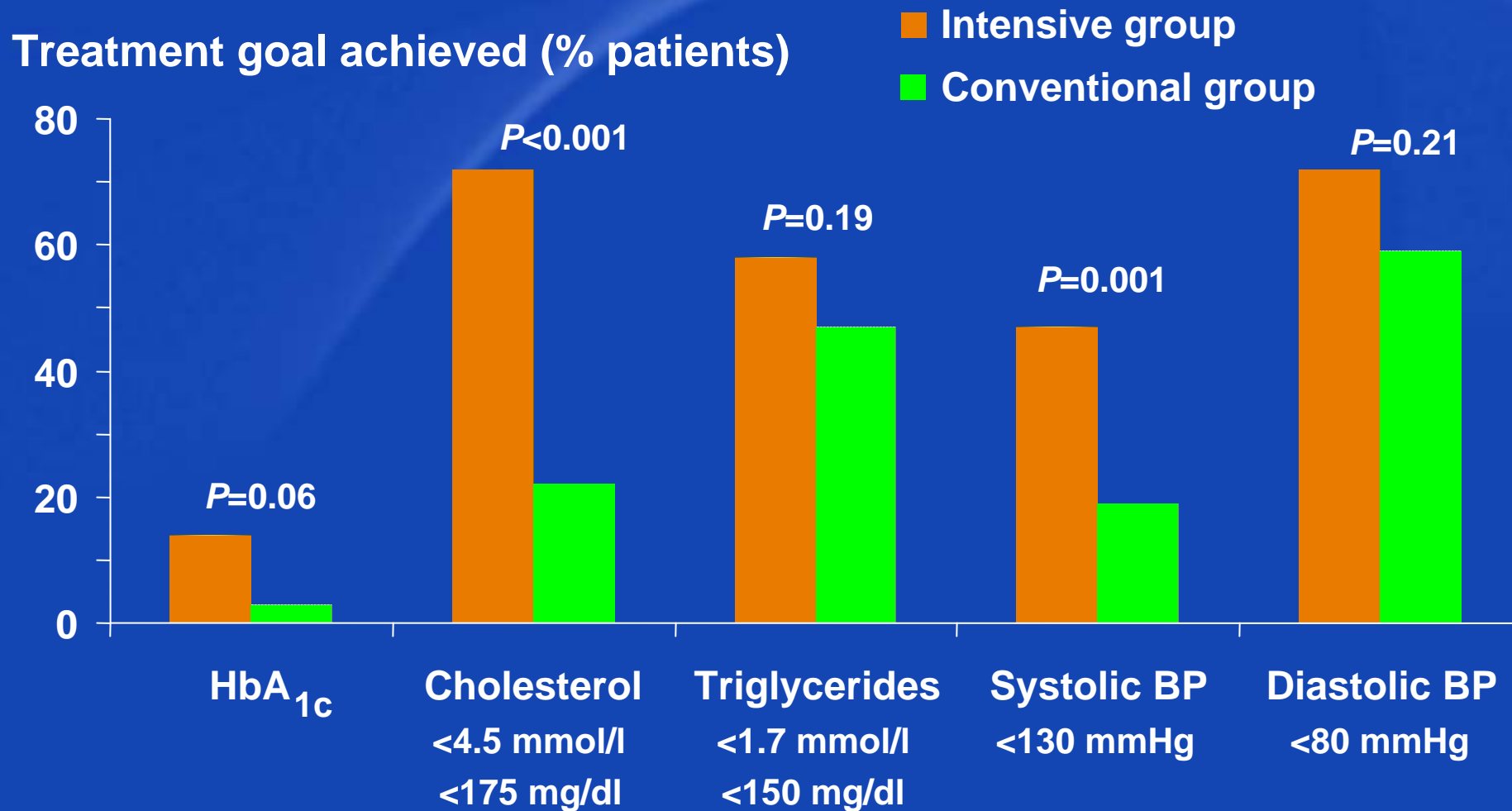
N=160 with Type 2 diabetes and microalbuminuria



\*Cardiovascular death, MI, stroke, revascularisation, amputation

Gaede et al. *N Engl J Med.* 2003

# Achievement of treatment goals in different biomedical modalities of the Steno-2 study



# Rimonabant in obesity (RIO) program

RIO-Europe	RIO-Lipids	RIO-NA	RIO-Diabetes
N=1507 BMI $\geq 30$ kg/m <sup>2</sup> or >27 kg/m <sup>2</sup> with comorbidity*	N=1033 BMI 27–40 kg/m <sup>2</sup> and dyslipidaemia	N=3045 BMI $\geq 30$ kg/m <sup>2</sup> or >27 kg/m <sup>2</sup> with comorbidity*	N=1045 BMI 27–40 kg/m <sup>2</sup> and Type 2 diabetes
1 year	1 year	2 years	1 year
<ul style="list-style-type: none"> <li>• Randomized, double-blind, placebo-controlled evaluations of rimonabant 5 mg or 20 mg QD added to hypocaloric diet (600 kcal/day deficit)<sup>†</sup></li> <li>• Weight, waist circumference, metabolic syndrome, and cardiometabolic risk factors assessed</li> <li>• Potential central nervous system effects assessed via Hospital Anxiety and Depression scale (HAD)</li> </ul>			

\*Hypertension and/or dyslipidaemia

<sup>†</sup>RIO-NA: rimonabant patients re-randomized at 1 year to placebo or continued rimonabant

BMI=body mass index

Després et al. *N Engl J Med.* 2005; Pi-Sunyer et al. *JAMA.* 2006;

Gelfand et al. *J Am Coll Cardiol.* 2006

# RIO clinical trial program: efficacy overview

RIO-Europe, RIO-Lipids, RIO-NA; Placebo-corrected change from baseline at 1 year

	Rimonabant 5 mg (range)	Rimonabant 20 mg (range)
Weight (lb)	↓2.9–3.6*	↓10.4–12.0*
Waist (in)	↓0.2–0.6	↓1.4–1.9*
HDL cholesterol (%)	↑2.3–3.2	↑7.2–8.7*
Triglycerides (%)	↓4.2–↑1.4	↓12.4–13.2*
Insulin resistance (%) (RIO-Europe and NA only)	↓0.4–0.6	↓0.7–0.8*
CRP (mg/l) (RIO-Lipids only)	↑0.2	↓0.5†
Adiponectin (μg/ml) (RIO-Lipids only)	↑0.3	↑1.5*

\* $P \leq 0.002$  vs placebo; † $P = 0.02$  vs placebo

CRP=C-reactive protein

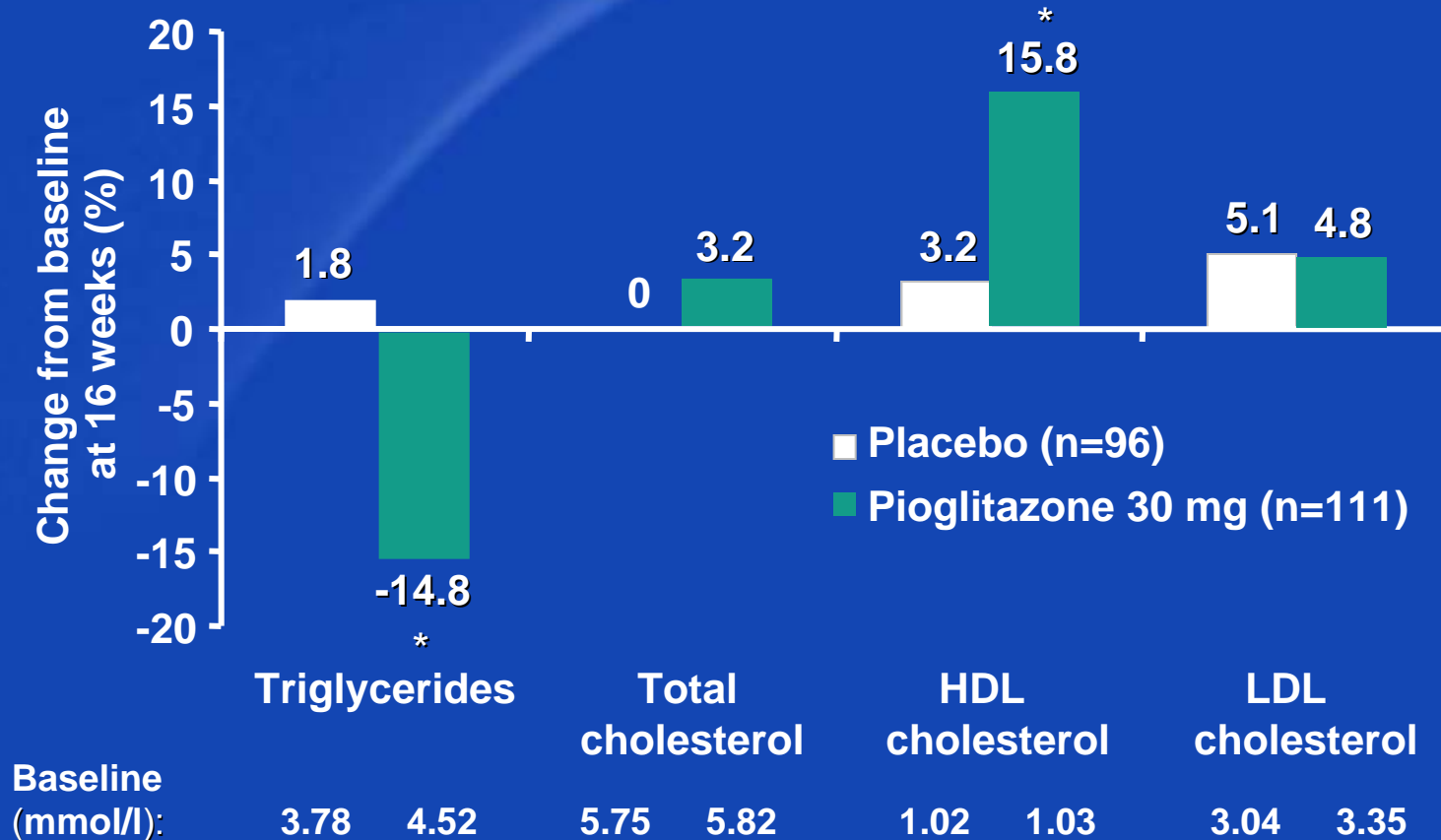
Van Gaal et al. *Lancet*. 2005; Després et al. *N Engl J Med*. 2005; Pi-Sunyer et al. *JAMA*. 2006



## RIO-diabetes: conclusions

- Rimonabant is the first selective CB<sub>1</sub> blocker studied for the treatment of Type 2 diabetes and related disorders
- Rimonabant achieved clinically significant improvements in HbA<sub>1c</sub> lipids and blood pressure with a concomitant substantial reduction in body weight
- Rimonabant offers a new approach to the management of Type 2 diabetes addressing multiple cardiometabolic risk factors commonly observed in Type 2 diabetes

# Pioglitazone monotherapy: change in lipid profile at endpoint



\* $P < 0.05$  vs placebo

Schneider et al. *Diabetes*. 1999



## Rosiglitazone: other than hypoglycaemic effects

- Decreases diastolic blood pressure<sup>1</sup>
- Improves lipid profile
  - Increases HDL<sub>2</sub> levels<sup>2</sup>
  - Shifts LDL from small dense to large buoyant<sup>2</sup>
  - Decreases triglycerides by 15% (4–8 mg, 26 weeks)
- Reduces urinary AER (8 mg, 52 weeks)<sup>3</sup>
- Diminishes PAI-1 activity (8 mg)<sup>4</sup>
- Decreases CRP and IL-6 (26 weeks)<sup>5</sup>

AER=albumin excretion rate; IL-6=interleukin-6

1. Bakris et al. *Diabetes*. 2000

2. Brunzell. *Diabetes*. 2001

3. Bakris et al. *Diabetologia*. 1999

4. Freed. *Diabetologia*. 2000

5. Fuell. *Diabetes*. 2001



# Conclusions

- Simultaneous treatment of all cardiovascular risk factors can reduce the impact of CVD in diabetes
- Hyperglycaemia must be considered a risk factor for CVD in diabetes
- Treatment goal is to near-normalize the level of each risk factor
- New compounds, producing multiple therapeutic effects on cardiovascular risk factors, may be useful