Type 2 Diabetes and Cardiovascular Risk

: A Multi-factorial Approach

Cheol-Young Park

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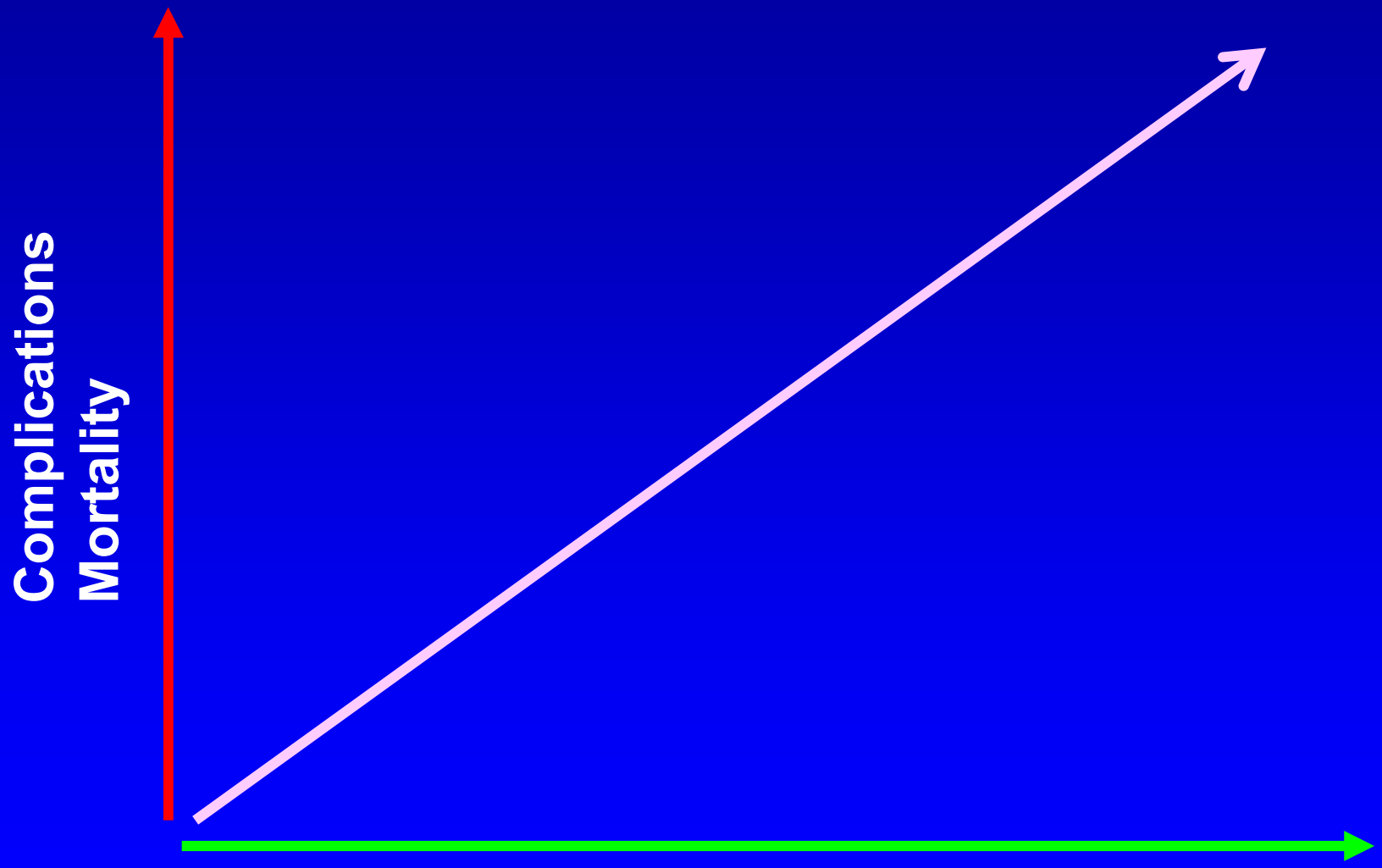
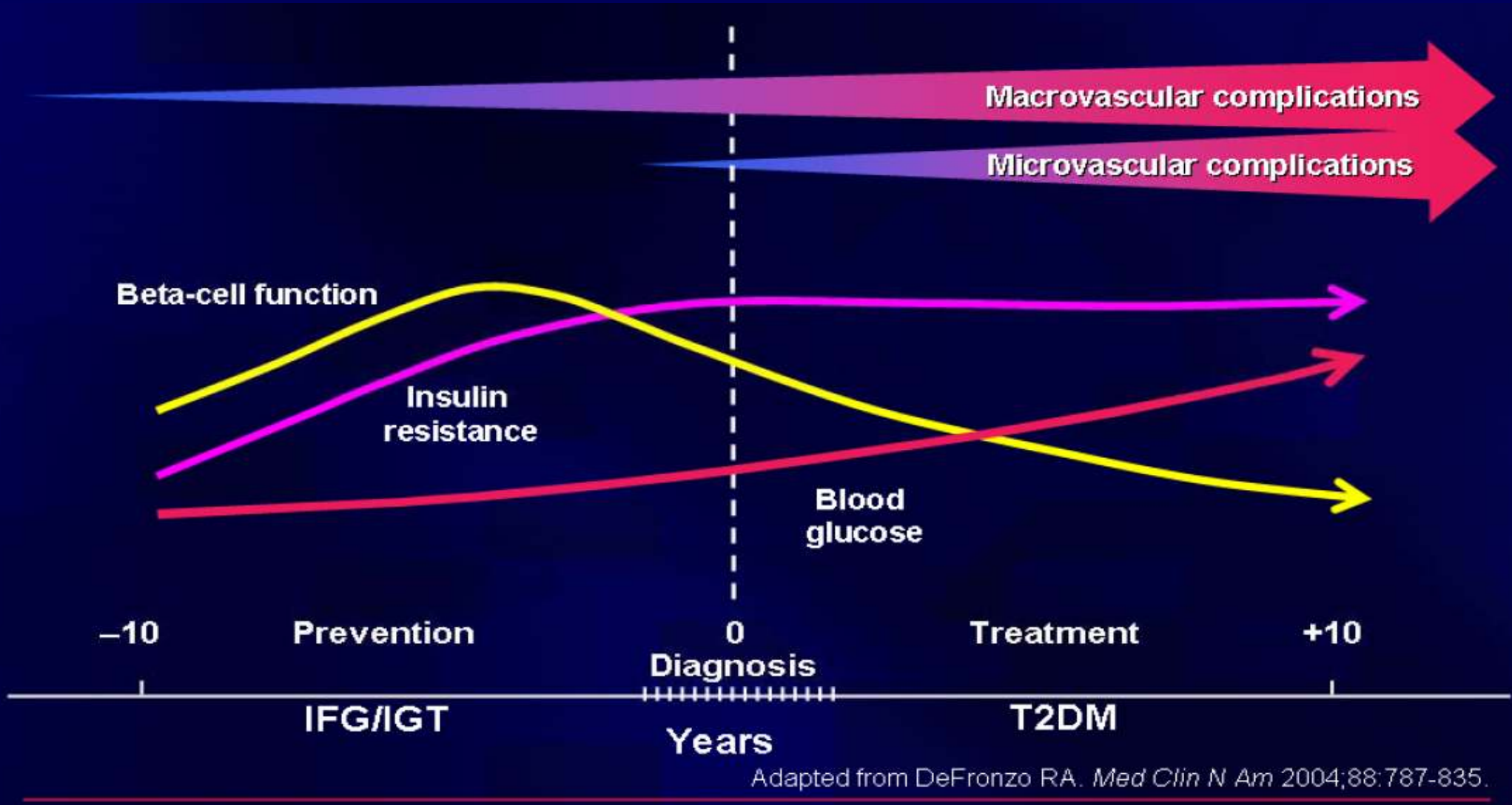
Is lowering blood glucose good for preventing complications

Question ?

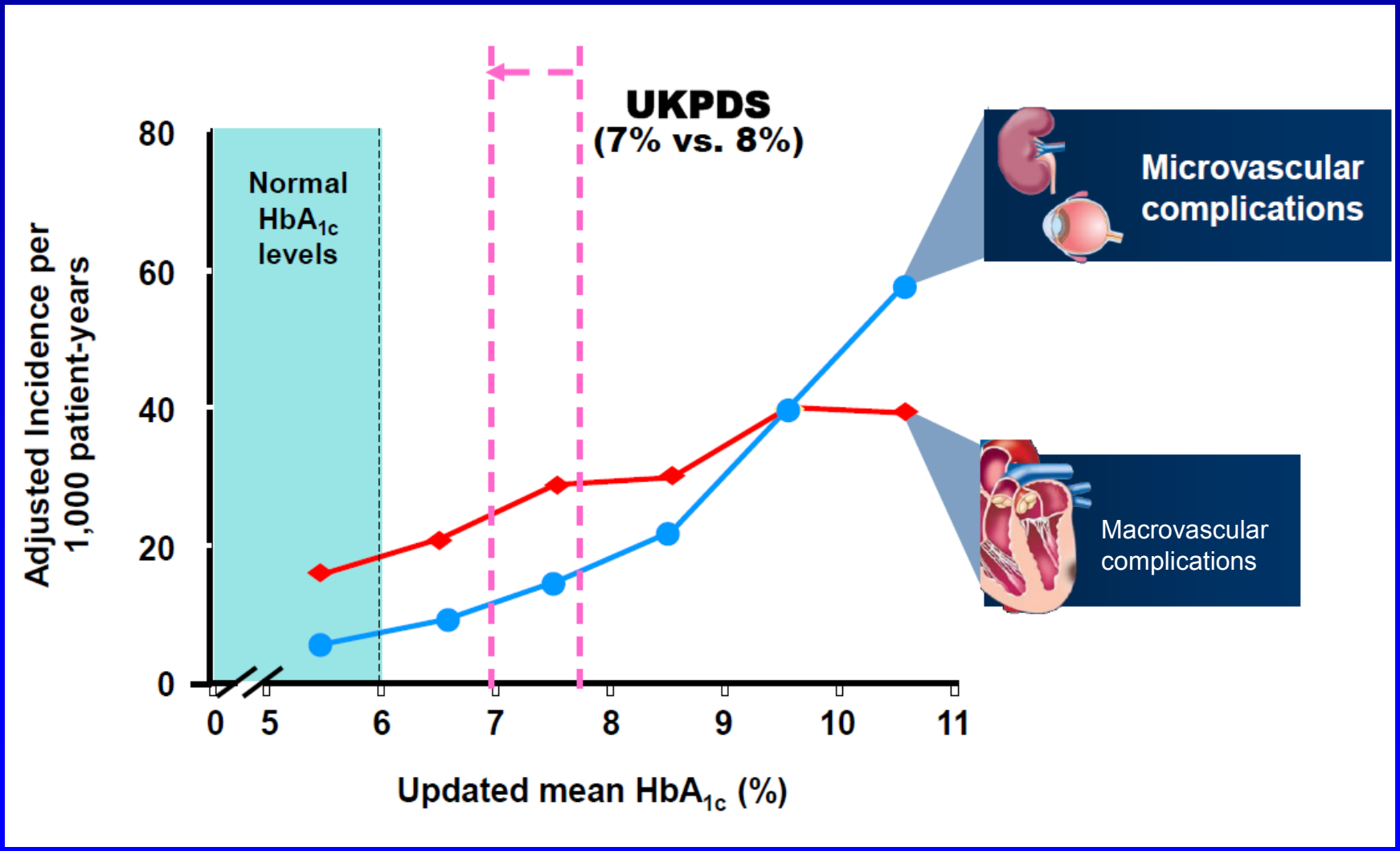


T2DM is a progressive disease: Do microvasular and macrovascular complications begin at different times?



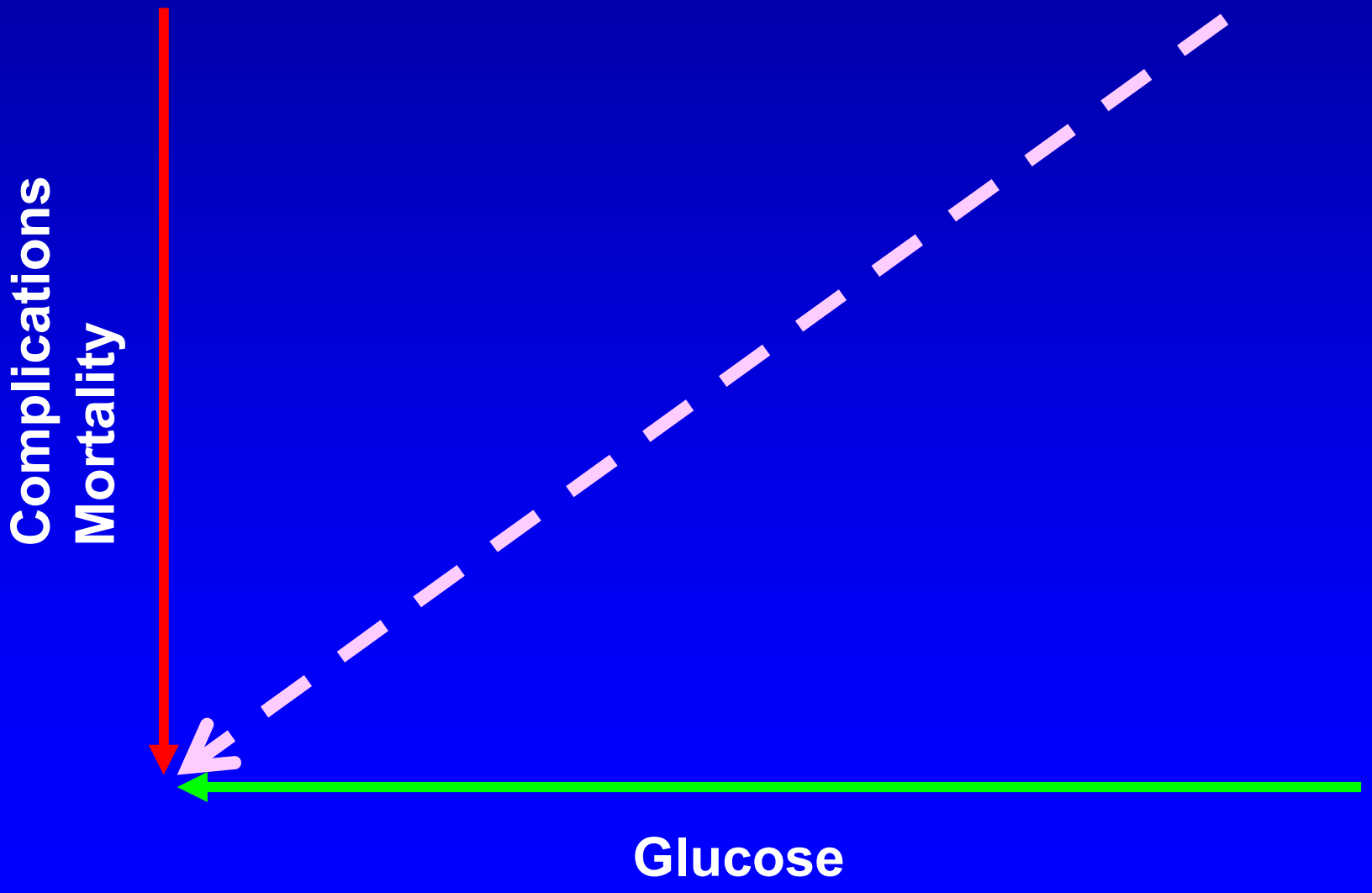
Adapted from DeFronzo RA. *Med Clin N Am* 2004;88:787-835.

Risk of complications decreases as HbA1c decreases in Type 2 Diabetes

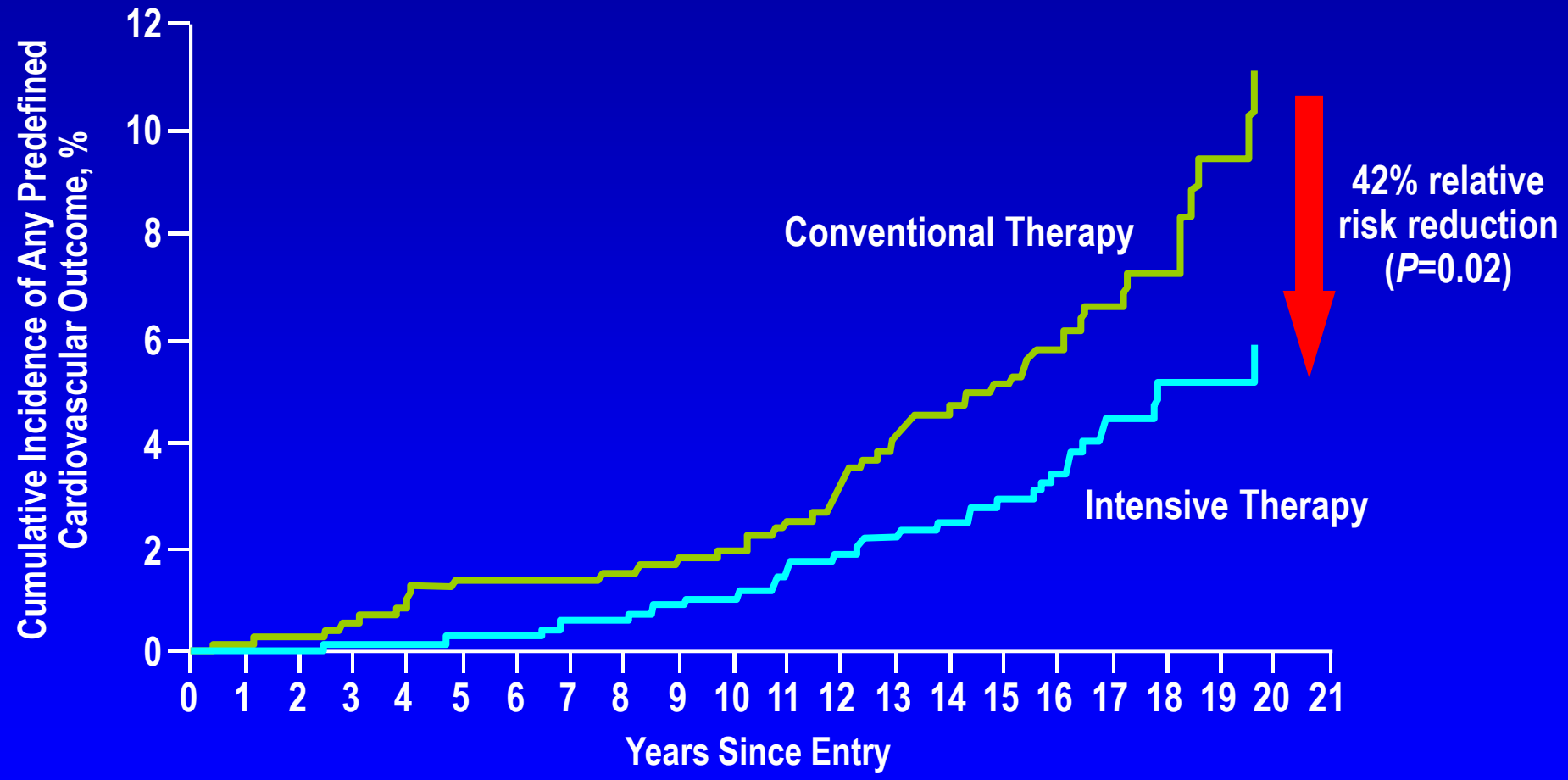


Stratton IM, *et al*. *BMJ* 2000; 321:405–412.

Question ?



Intensive Therapy Reduced Predefined Cardiovascular Events : DCCT/EDIC(12-year follow-up)



DCCT=Diabetes Control and Complications Trial; EDIC=Epidemiology of Diabetes Interventions and Complications.

1. Nathan DM et al. *N Engl J Med*. 2005;353(25):2643–2653.

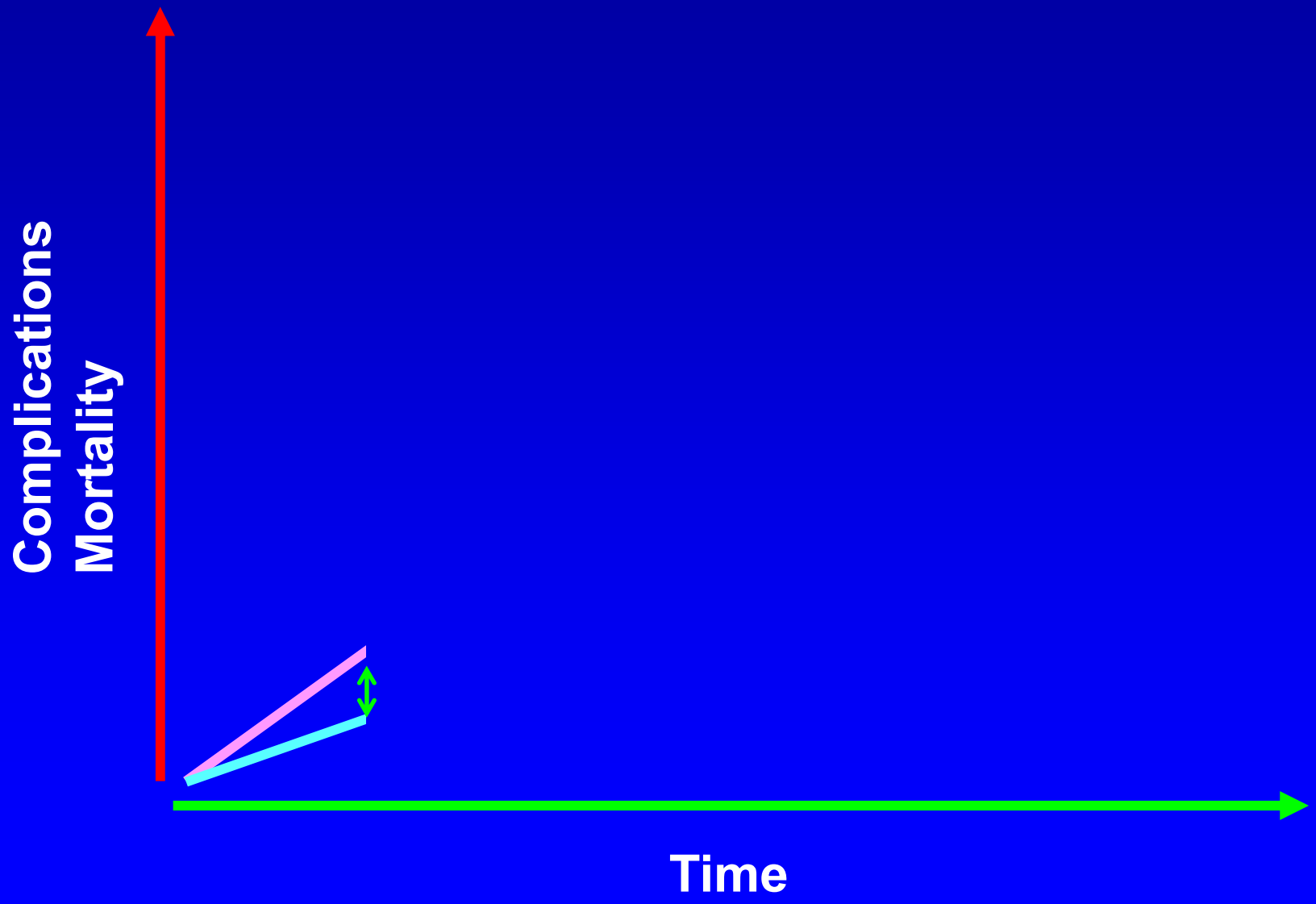
The Benefits of Starting Early with Intensive Treatment : Legacy Effects UKPDS (10-year follow-up)

- After median 8.8 years post-trial follow-up

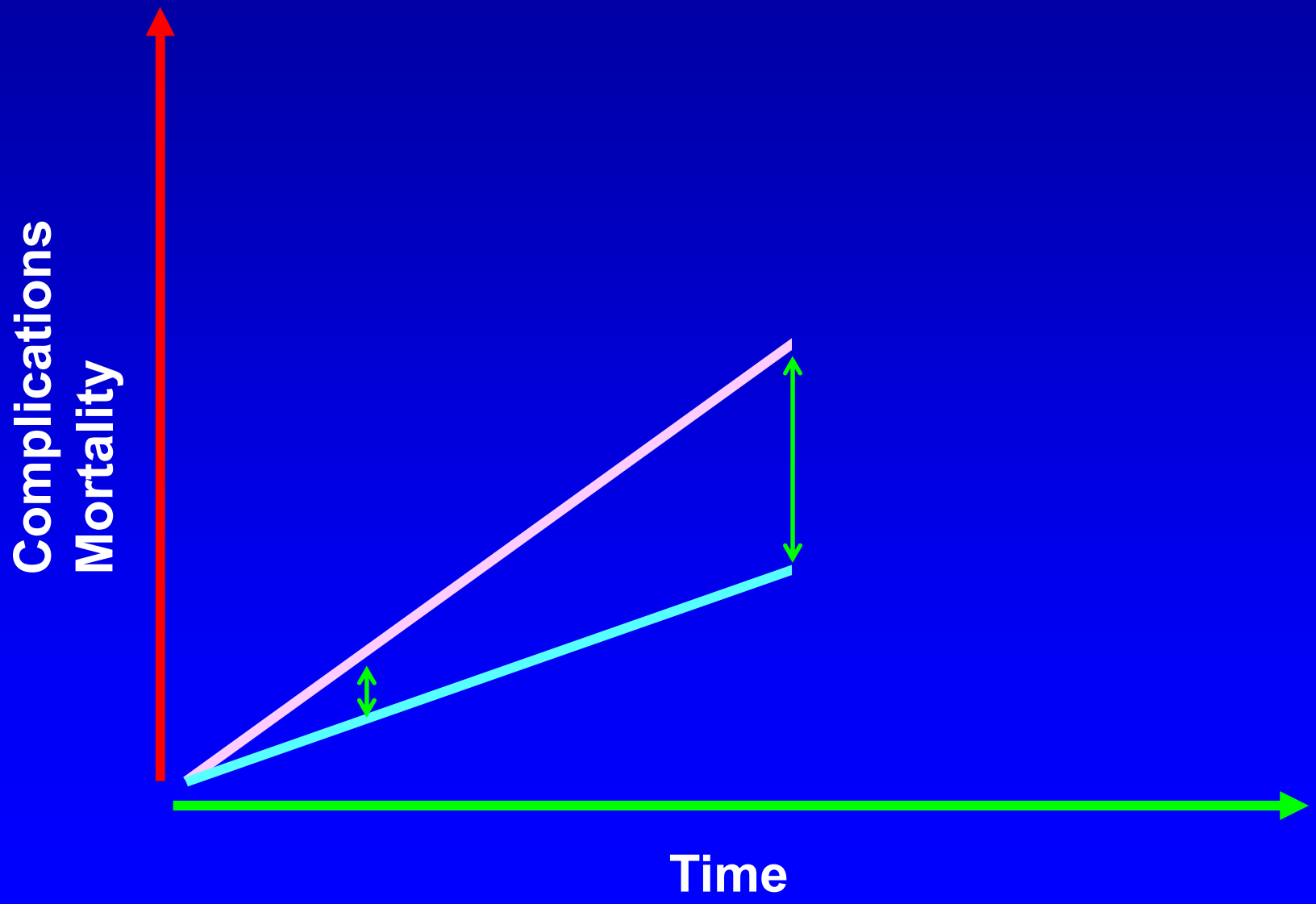
Aggregate Endpoint (Relative Risk Reduction)	1997
Any diabetes related endpoint	12% (p=0.029)
Microvascular disease	25% (p=0.009)
Myocardial infarction	16% (p=0.052)
All-cause mortality	6% (p=0.44)

Holman RR et l. New England Journal of Medicine 2008; 359:1577-1589

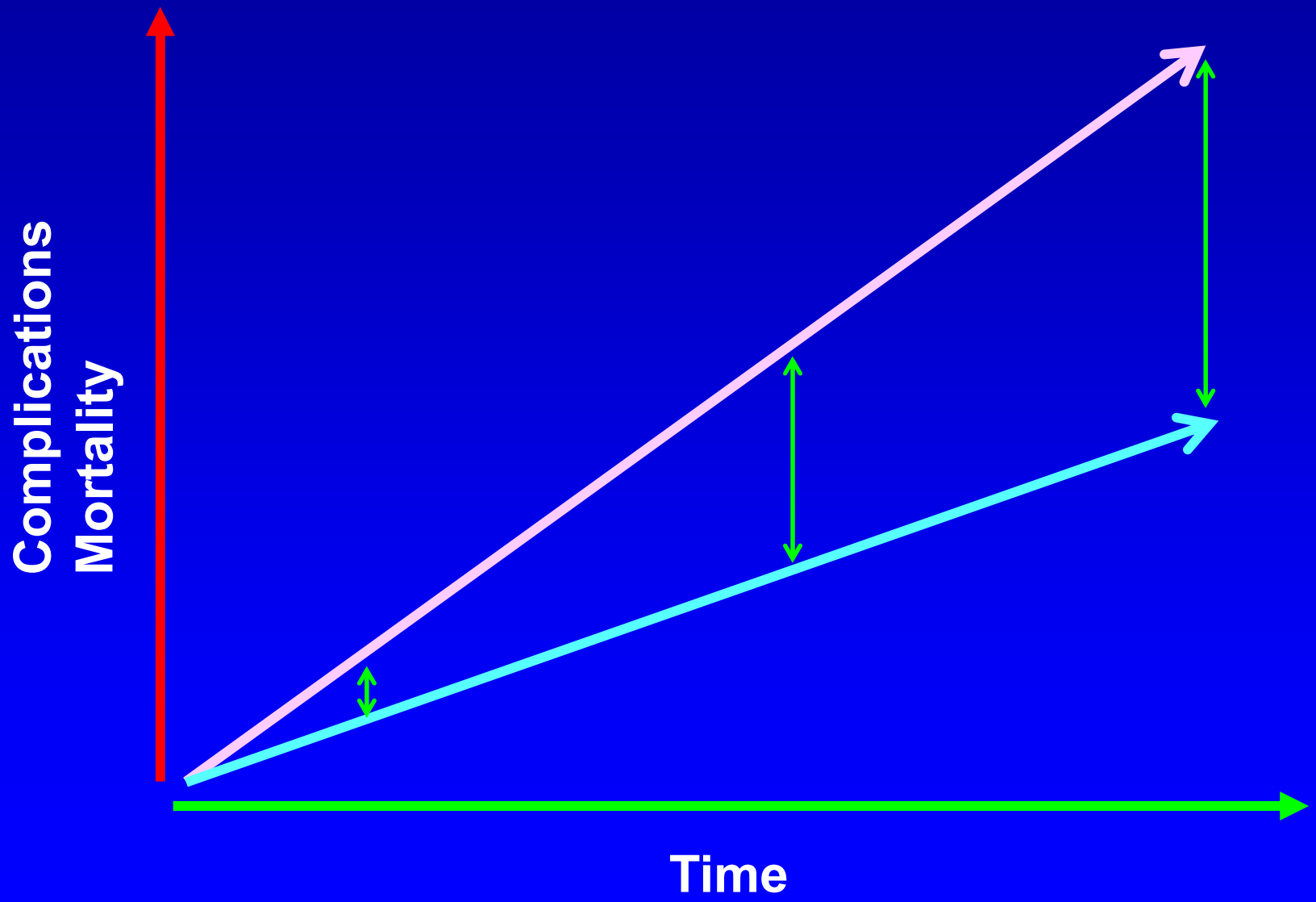
As Time Goes By…….



As Time Goes By…….



As Time Goes By…….

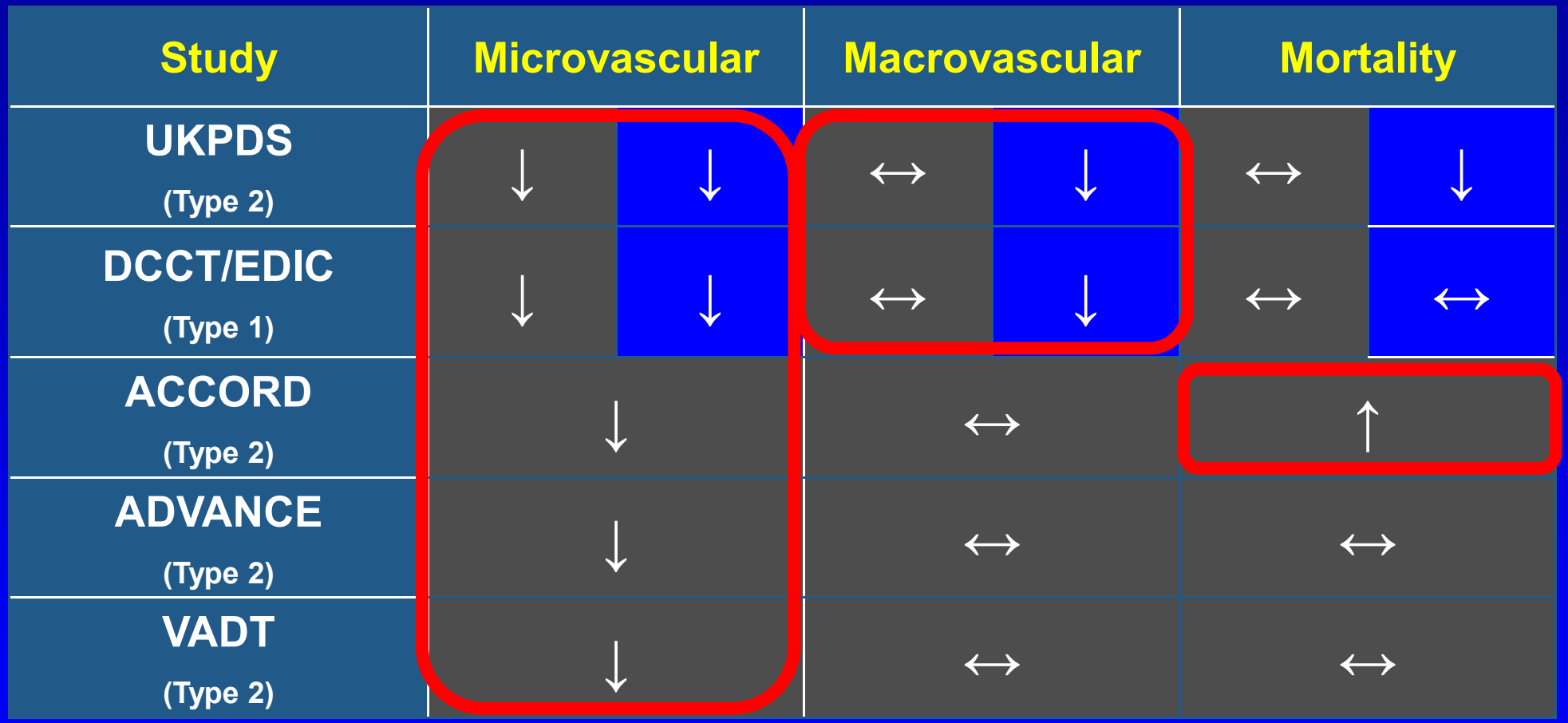


Comparison of Recent Glycemia Trials
ACCORD, ADVANCE and VADT

Characteristic	ACCORD	ADVANCE	VADT
N	10,251	11,140	1,791
Mean Age	62	66	60.4
Duration of T2DM	10 yr	8 yr	11.5 yr
History of CVD	35%	32%	40%
BMI	32	28	31
Baseline A1C	8.3%	7.5%	9.4%
A1C Achieved	**6.4% vs. 7.5%**	**6.5% vs. 7.3%**	**6.9% vs. 8.4%**
RRR CVD Events	**0.90** (0.78 – 1.04)	**0.94** (0.84 – 1.06)	**0.88** (0.74 – 1.05)
RRR Mortality	**1.22** (1.01 – 1.46)*	**0.93** (0.83 – 1.06)	**1.07** (0.80 – 1.42)

ACCORD Study Group. *N Engl J Med* 2008;358:2545-59.
ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560-72.
Duckworth W *et al*. *N Engl J Med* 2009;360:129-39.

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials



UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854-65. Holman RR. *N Engl J Med* 2008;9;359(15):1577-89. DCCT Research Group. *N Engl J Med* 1993;329;977-86. Nathan DM *et al. N Engl J Med* 2005;353:2643-53. Gerstein HC *et al. N Engl J Med* 2008;358:2545-59. Patel A *et al. N Engl J Med* 2008;358:2560-72. Duckworth W *et al. N Engl J Med* 2009;360:129-39.

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.

ABSTRACT

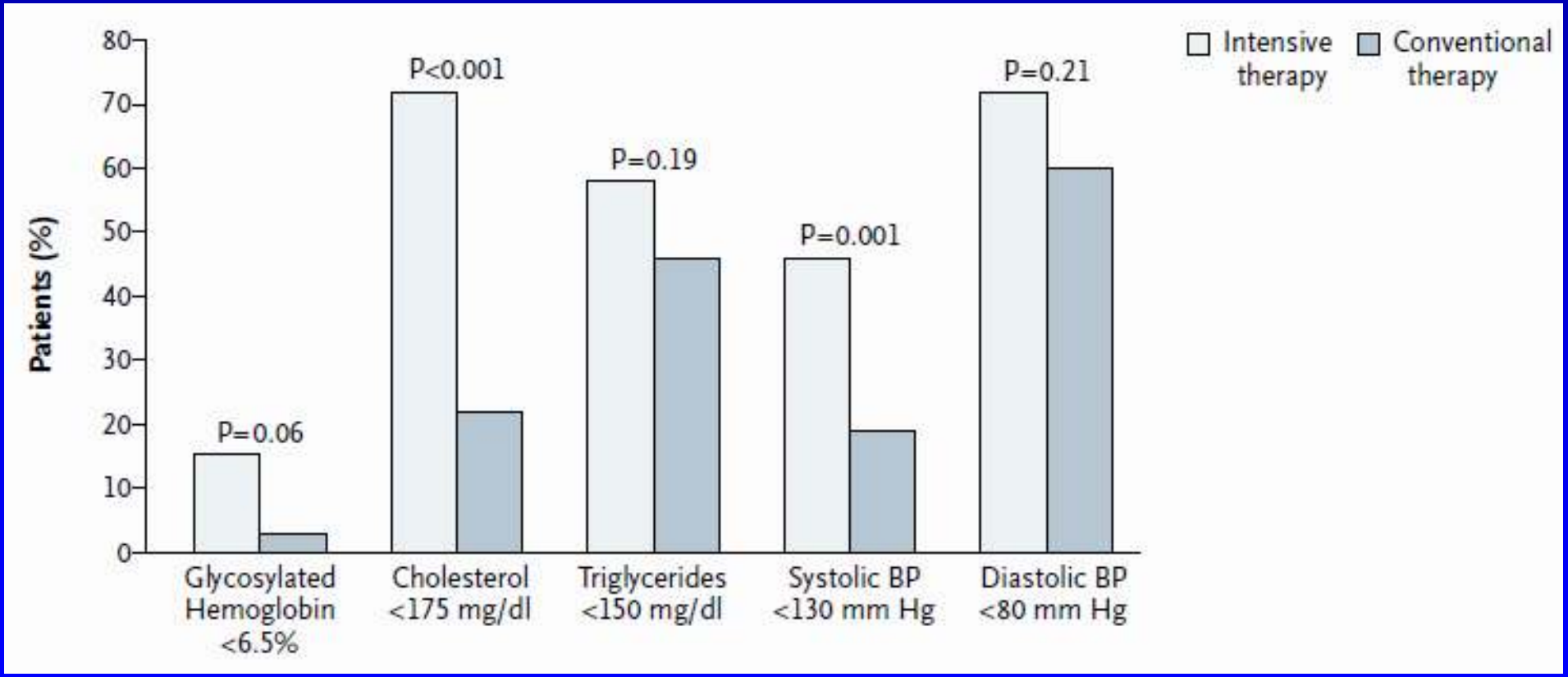
BACKGROUND

Cardiovascular morbidity is a major burden in patients with type 2 diabetes. In the Steno-2 Study, we compared the effect of a targeted, intensified, multifactorial intervention with that of conventional treatment on modifiable risk factors for cardiovascular disease in patients with type 2 diabetes and microalbuminuria.

From the Steno Diabetes Center, Copenhagen (P.G., P.V., N.L., H.-H.P., O.P.); Herlev County Hospital, Herlev (N.L.); Amtssygehuset Roskilde, Roskilde (G.V.H.J.); and the Faculty of Health Science, Aarhus Uni-

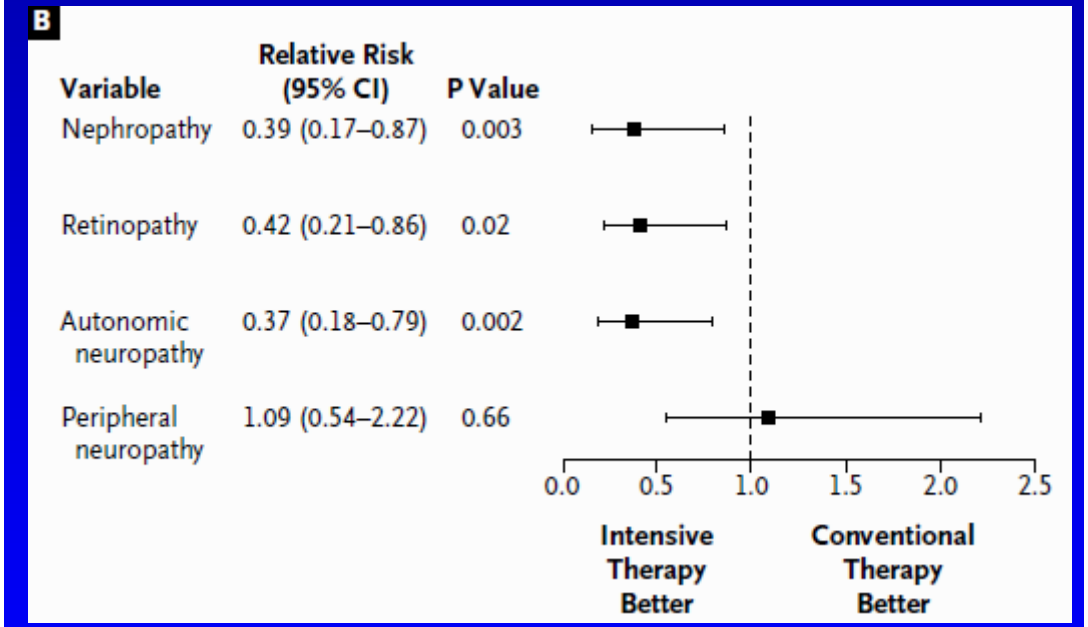
Gaede P et al. NEJM 2003

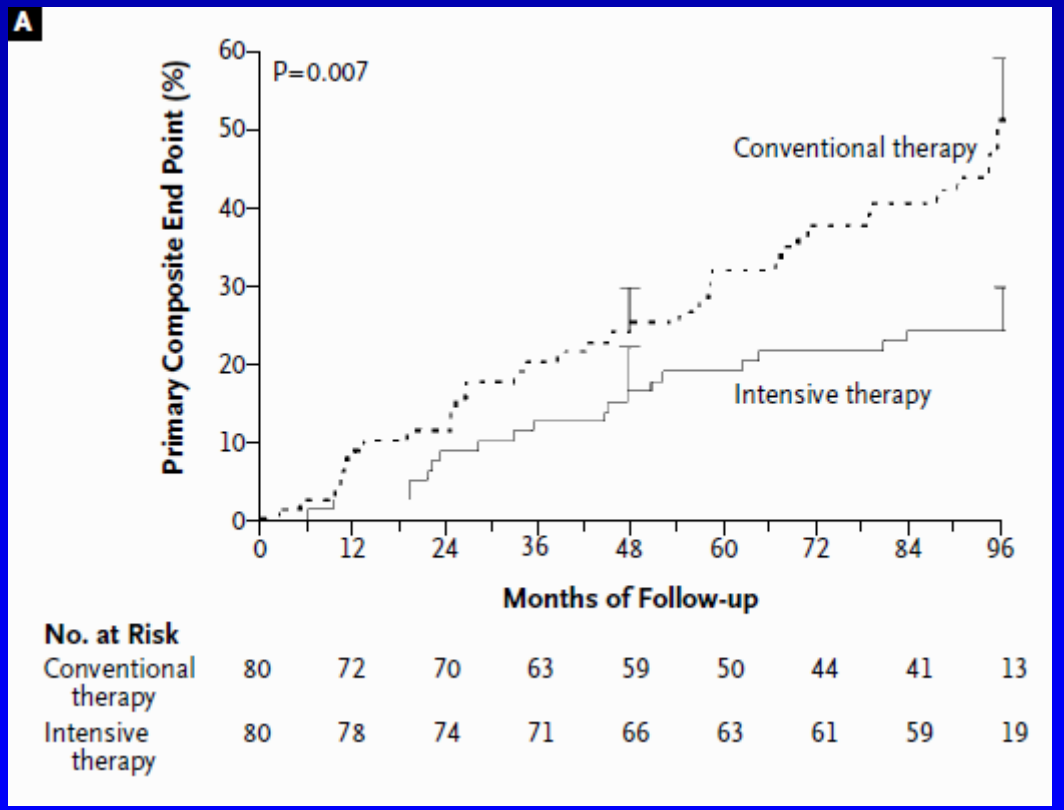
Multifactorial Intervention and Cardiovascular Disease in T2DM



Gaede P et al. NEJM 2003

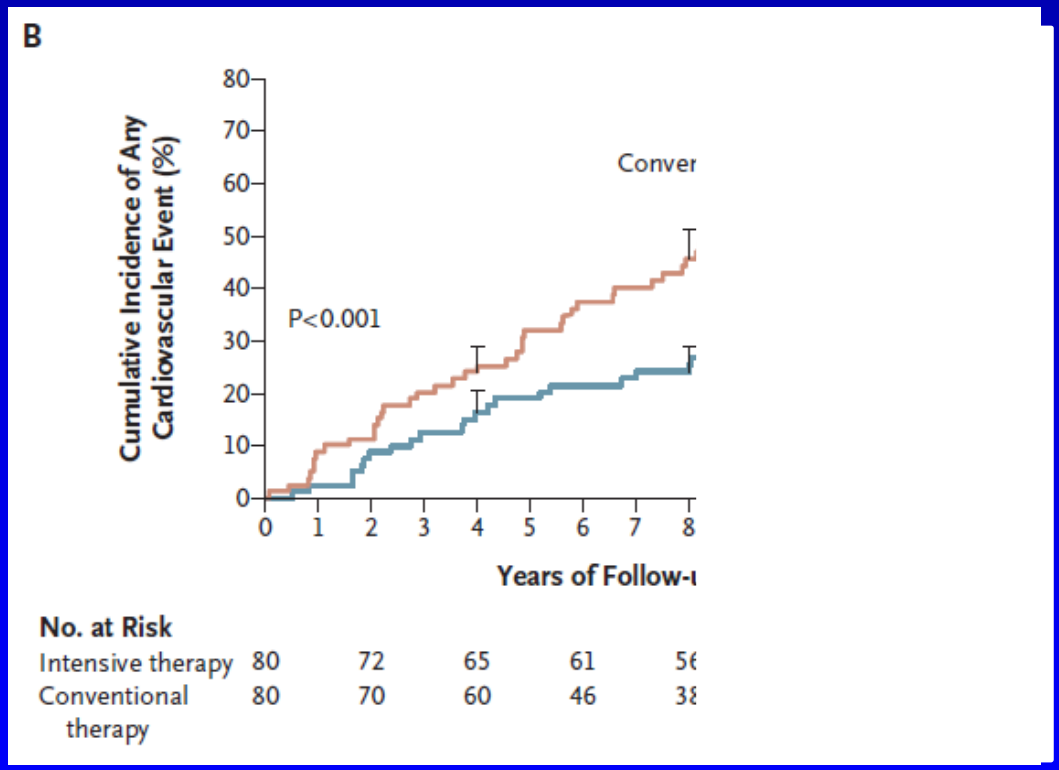
Results

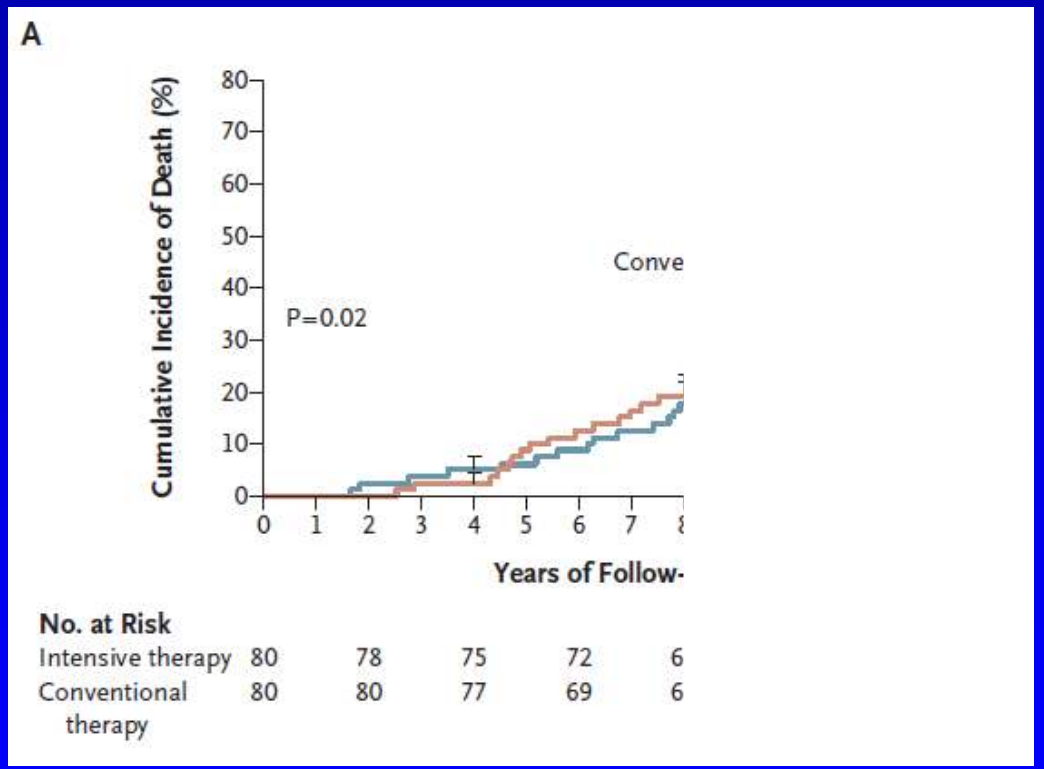




Gaede P et al. NEJM 2003

Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes





Gaede P et al. NEJM 2008

The NEW ENGLAND JOURNAL of MEDICINE

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

RESULTS

Data were combined by means of a fixed-effects model. In the 42 trials, the mean age of the subjects was approximately 56 years, and the mean baseline glycated hemoglobin level was approximately 8.2%. In the rosiglitazone group, as compared with the control group, the odds ratio for myocardial infarction was 1.43 (95% confidence interval [CI], 1.03 to 1.98; P=0.03), and the odds ratio for death from cardiovascular causes was 1.64 (95% CI, 0.98 to 2.74; P=0.06).

Nissen SE. N Engl J Med 2007;356(24):2457-71.

FDA Cardiovascular Guidance

: Evaluating CV risk in new therapies to treat T2DM

- July 2008 FDA Advisory Committee
  - In the absence of data concerning CV safety signal…should there be a requirement to conduct a long-term CV trial or to provide equivalent evidence to rule out an unacceptable CV risk?
    - Advisory committee vote: 14-2 in favor
    - However, this approach 'should not cause undue delay in approval
- Key components of guidance
  - Glycemic control *remains* cornerstone of approval
  - Must demonstrate that any new treatment does not unacceptably increase the already high baseline CV risk in diabetes
  - Standardized reporting and statistical analysis

Reviews/Consensus Reports/ADA Statements
POSITION STATEMENT

Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

Silvio E. Inzucchi, MD[1]
Richard M. Bergenstal, MD[2]
John B. Buse, MD, PHD[3]
Michaela Diamant, MD, PHD[4]
Ele Ferrannini, MD[5]
Michael Nauck, MD[6]
Anne L. Peters, MD[7]
Apostolos Tsapas, MD, PHD[8]
Richard Wender, MD[9]
David R. Matthews, MD, DPHIL[10,11,12]

Glycemic management in type 2 diabetes mellitus has become increasingly complex and, to some extent, controversial, with a widening array of pharmacological agents now available (1–5), information on the benefits/risks of glycemic control, recent evidence concerning efficacy and safety of several new drug classes (16,17), the withdrawal/restriction of others, and increasing calls for a move toward more

These recommendations should be considered within the context of the needs, preferences, and tolerances of each patient; individualization of treatment is the cornerstone of success. Our recommendations are less prescriptive than and not as algorithmic as prior guidelines. This follows from the general lack of comparative-effectiveness research in this area. Our intent is therefore to encourage an appreciation of the variable and progressive nature of type 2 diabetes, the specific role

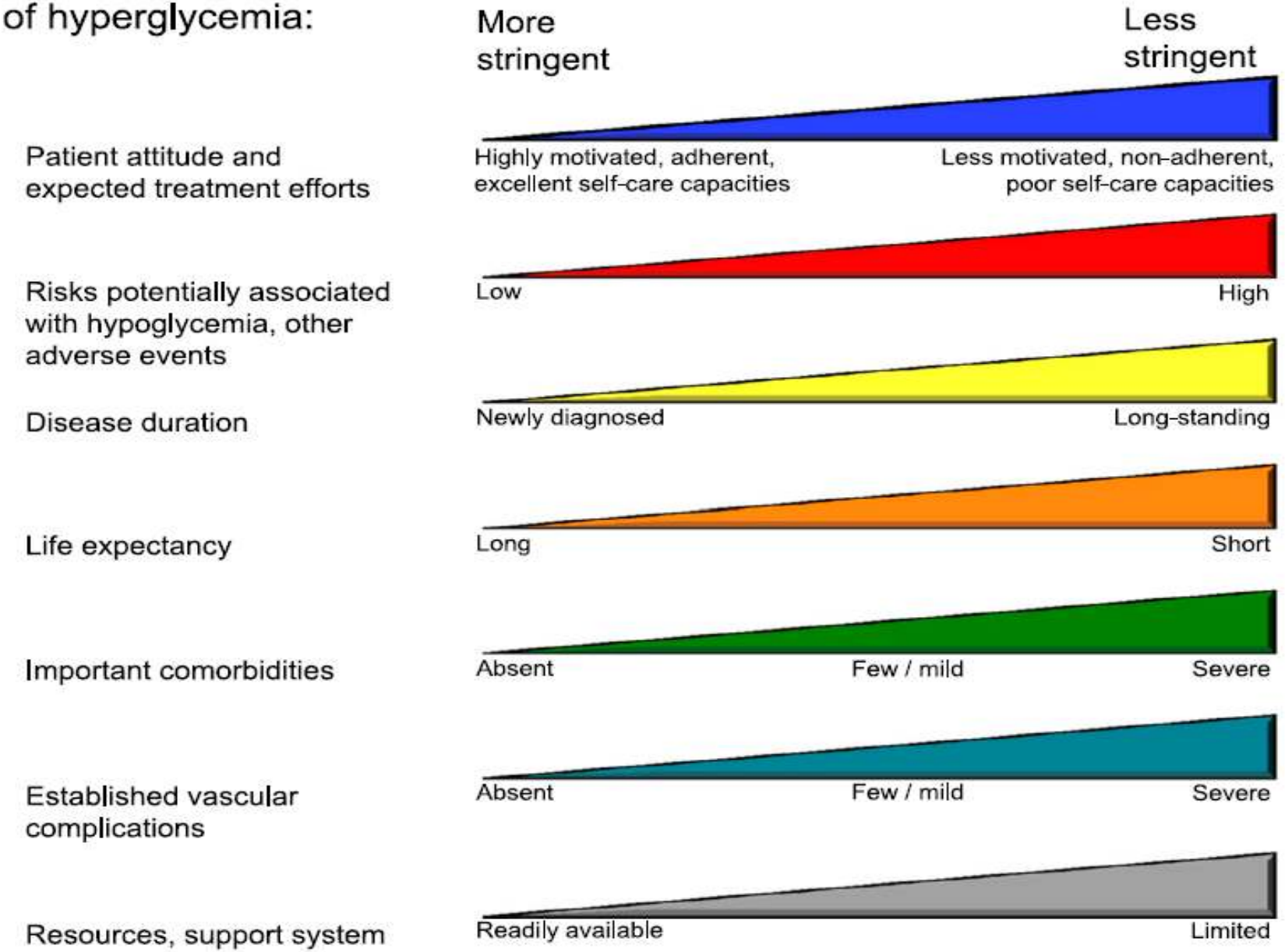
Inzucchi SE et al. Diabetes care. 2012

Key Points

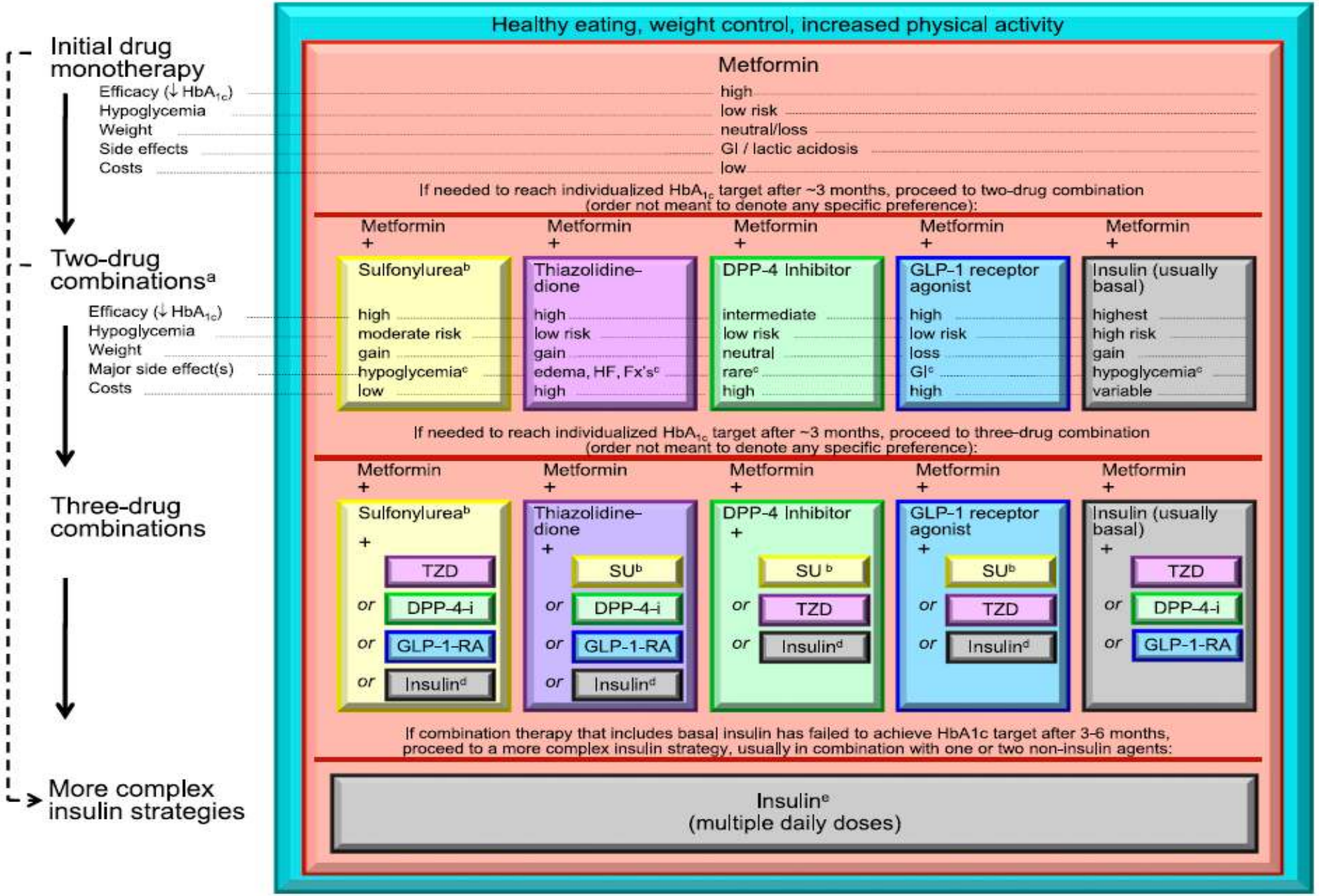
- Glycemic targets and glucose-lowering therapies must be individualized.
- Diet, exercise, and education remain the foundation of any type 2 diabetes treatment program.
- Unless there are prevalent contraindications, metformin is the optimal first-line drug.
- After metformin, there are limited data to guide us. Combination therapy with an additional 1–2 oral or injectable agents is reasonable, aiming to minimize side effects where possible.
- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain glucose control.
- All treatment decisions, where possible, should be made in conjunction with the patient, focusing on his/her preferences, needs, and values.
- Comprehensive cardiovascular risk reduction must be a major focus of therapy.

Inzucchi SE et al. Diabetes care. 2012

Approach to management of hyperglycemia:



Inzucchi SE et al. Diabetes care. 2012



Inzucchi SE et al. Diabetes care. 2012

Risk & Benefit & Individualization

Treatment goals

- Glycemic control
- Prevention of diabetes complications

Balancing efficacy and side effects when managing type 2 diabetes

Treatment complications and challenges

- Hypoglycemia
- Weight gain
- GI side effects
- Cardiovascular risks
- Injections

Adapted from Hollander PA et al. Postgrad Med 2010;122(3):71–80

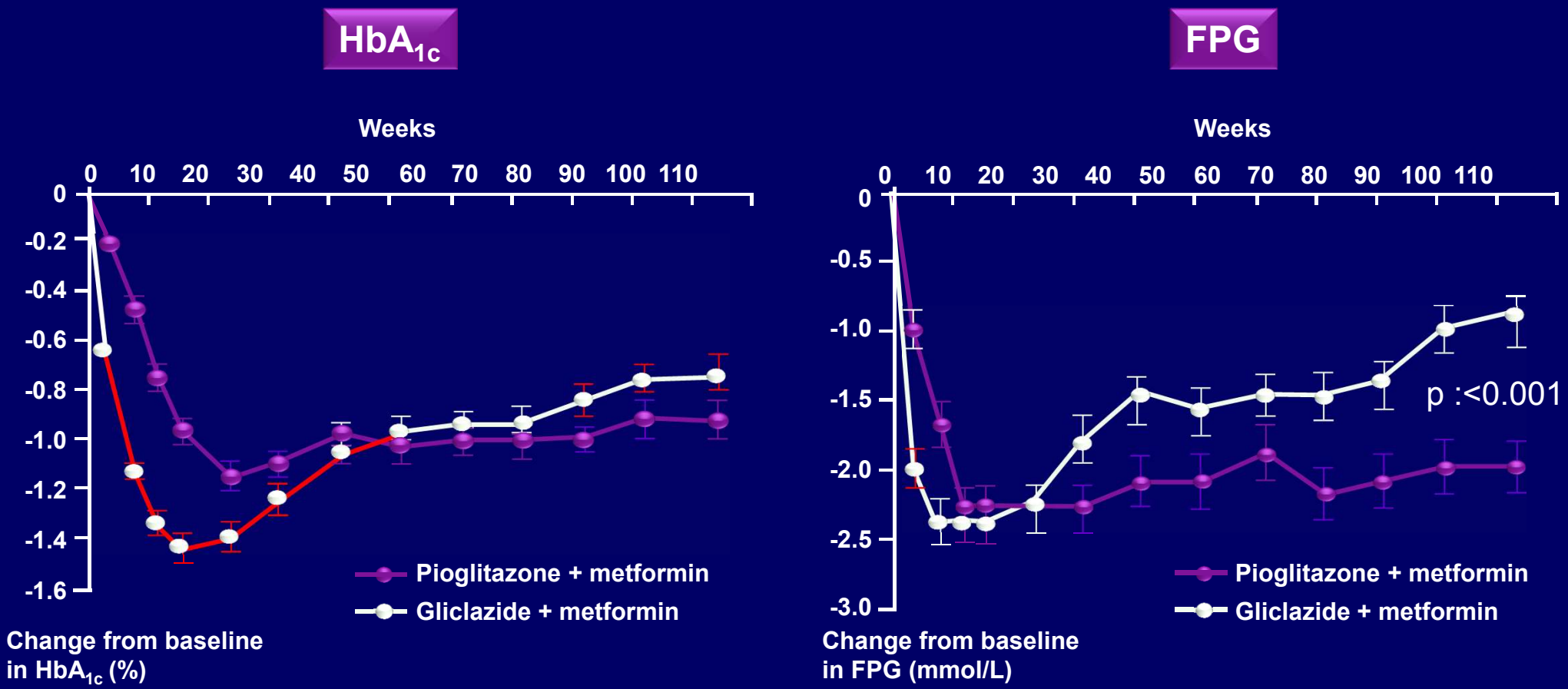
Use of Pioglitazone

- To date, over 10 years and >4 million patient years exposure in Europe and >20 million patient years globally

- Results from 2011 GPRD drug utilisation study showed use in line with licensed indications

- Pioglitazone is often used later in the disease process after other oral antidiabetics
  - Between 60% and 80% in combination with metformin
  - Use with insulin is under 10%

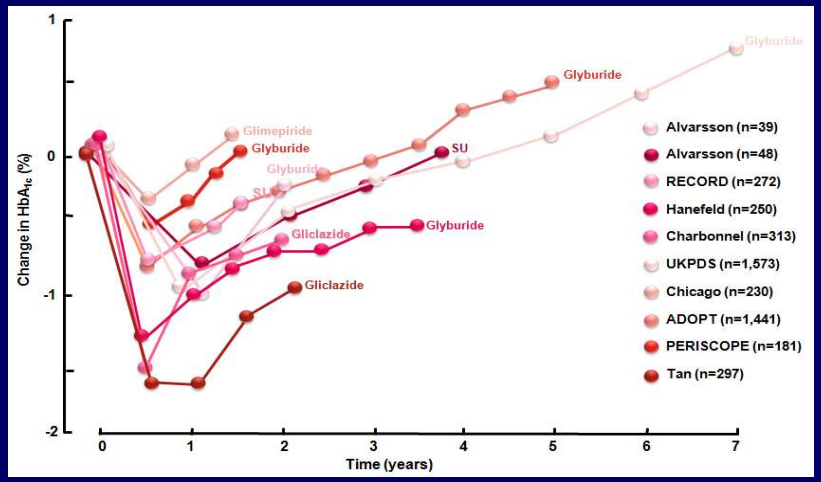
Pioglitazone vs Gliclazide as Add-on to Metformin: HbA_{1c} Results



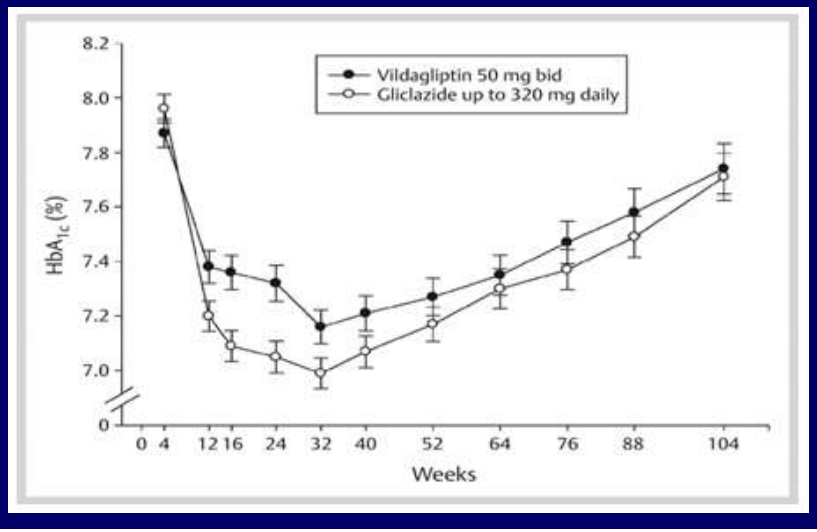
Charbonnel B et al. Diabetologia 2005;48:1093–1104

Durability of Glycemic Control TZDs vs. Other OADs

SU

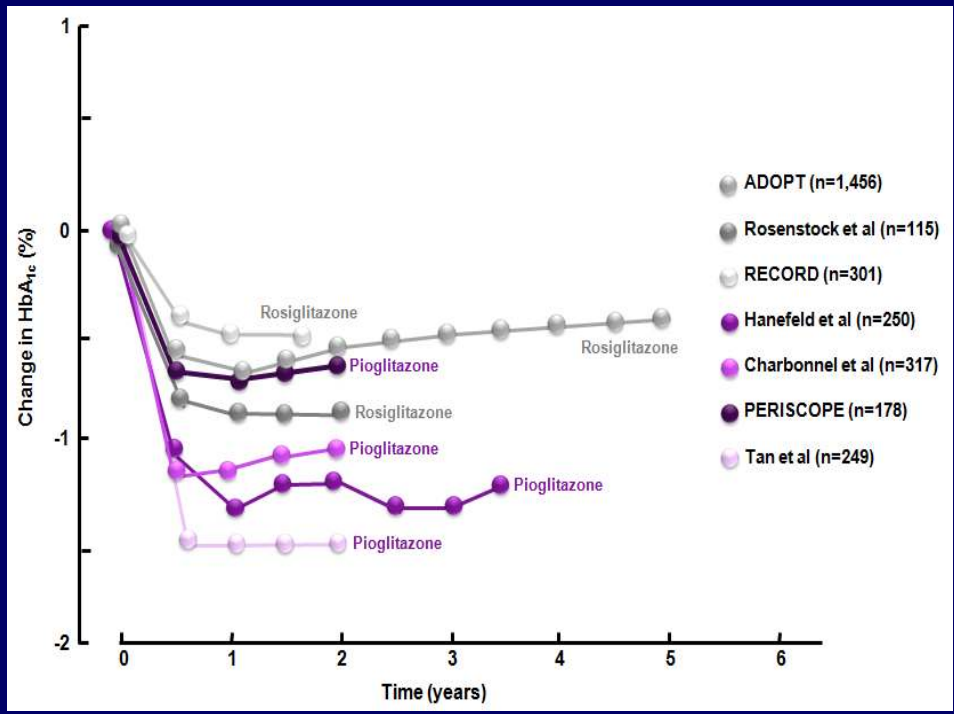


DPP-4 inhibitor



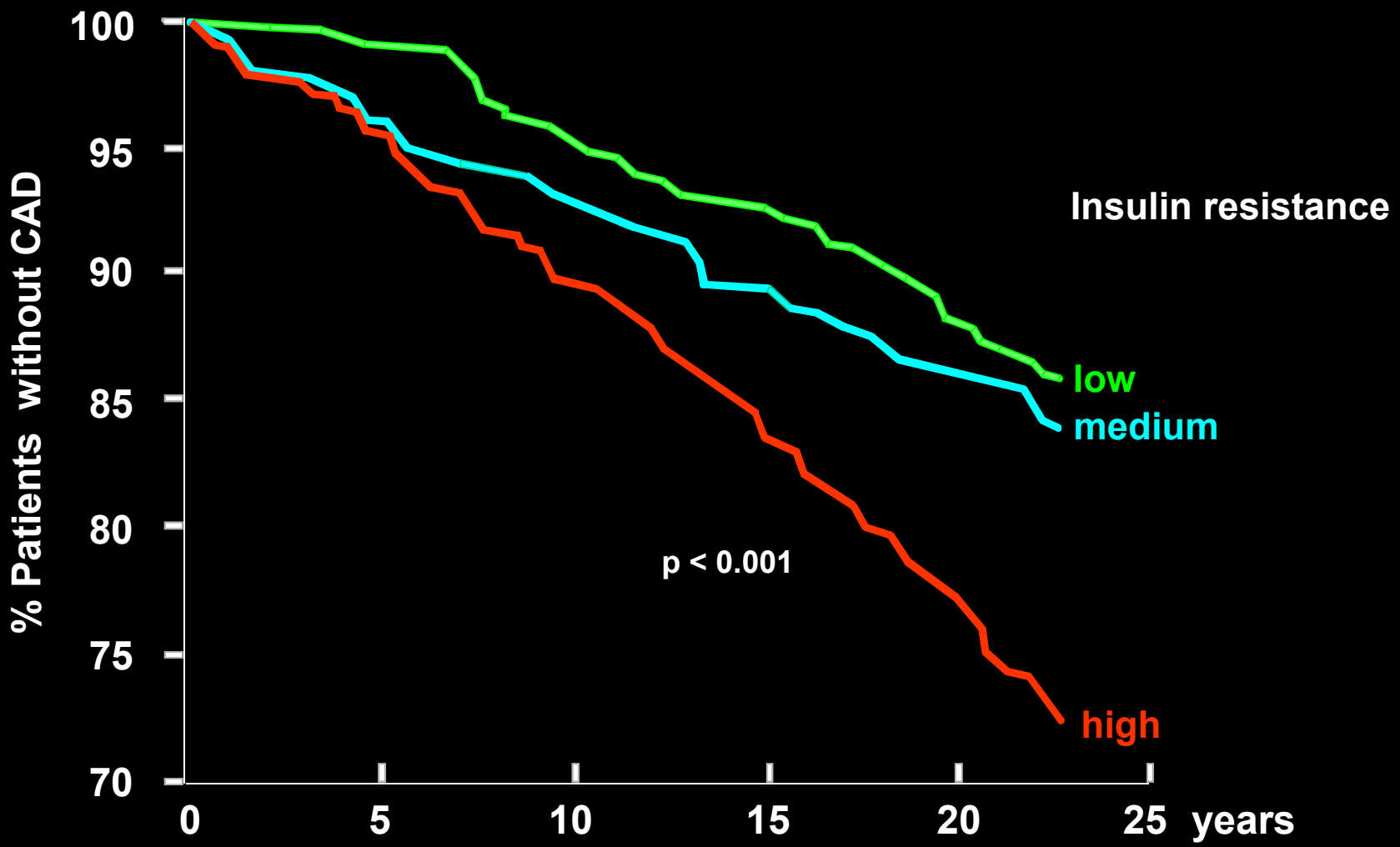
VS

TZD



RA DeFronzo. Diabetes 2009;58:773-795.

Insulin resistance and cardiovascular risk



Helsinki Policemen Study

Pyörälä et al, *ATVB* 2000; 20:538

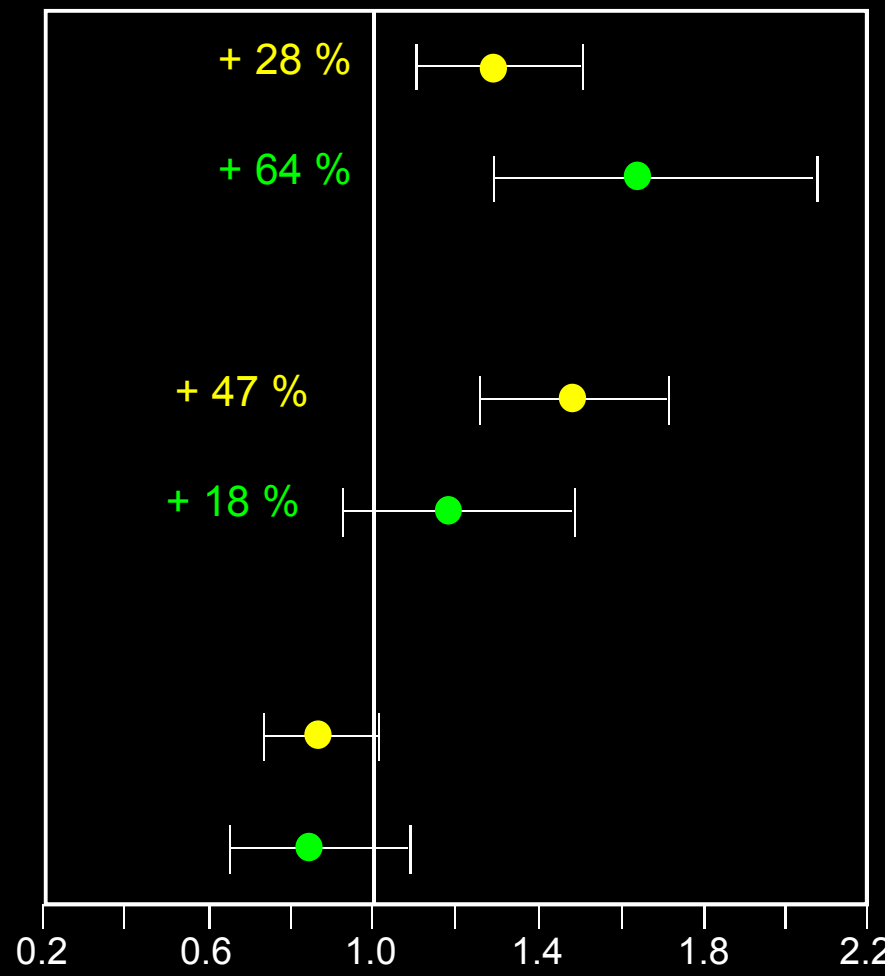
RISK FACTORS FOR CORONARY HEART DISEASE & STROKE

Helsinki Policemen Study, 22-year follow-up, 970 healthy men, CHD (n=164), Stroke (n=70), factor analysis, multivariate Cox models

INSULIN RESISTANCE FACTOR (BMI, Subscapular Skinfold, $AUC_{Insulin}$, $AUC_{Glucose}$, VO_{2max}, BP, Triglycerides

LIPID FACTOR
(Cholesterol, Triglycerides)

LIFESTYLE FACTOR
(Physical Activity, Smoking)

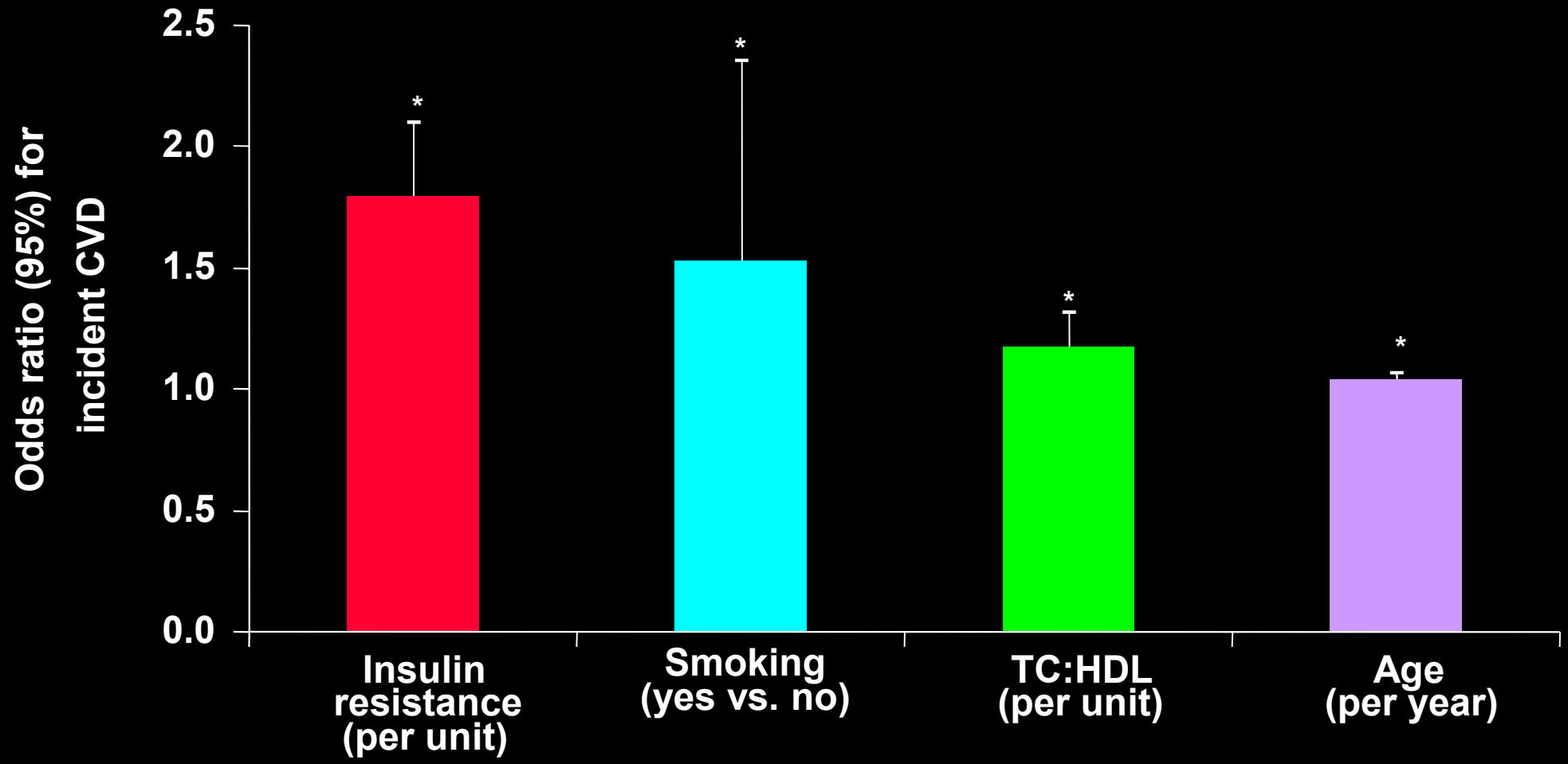


CHD: Coronary Heart Disease

Pyörala et al. ATVB 20:538-544, 2000

Insulin resistance is an independent predictor of CVD in type 2 diabetes

The Verona Diabetes Complications Study



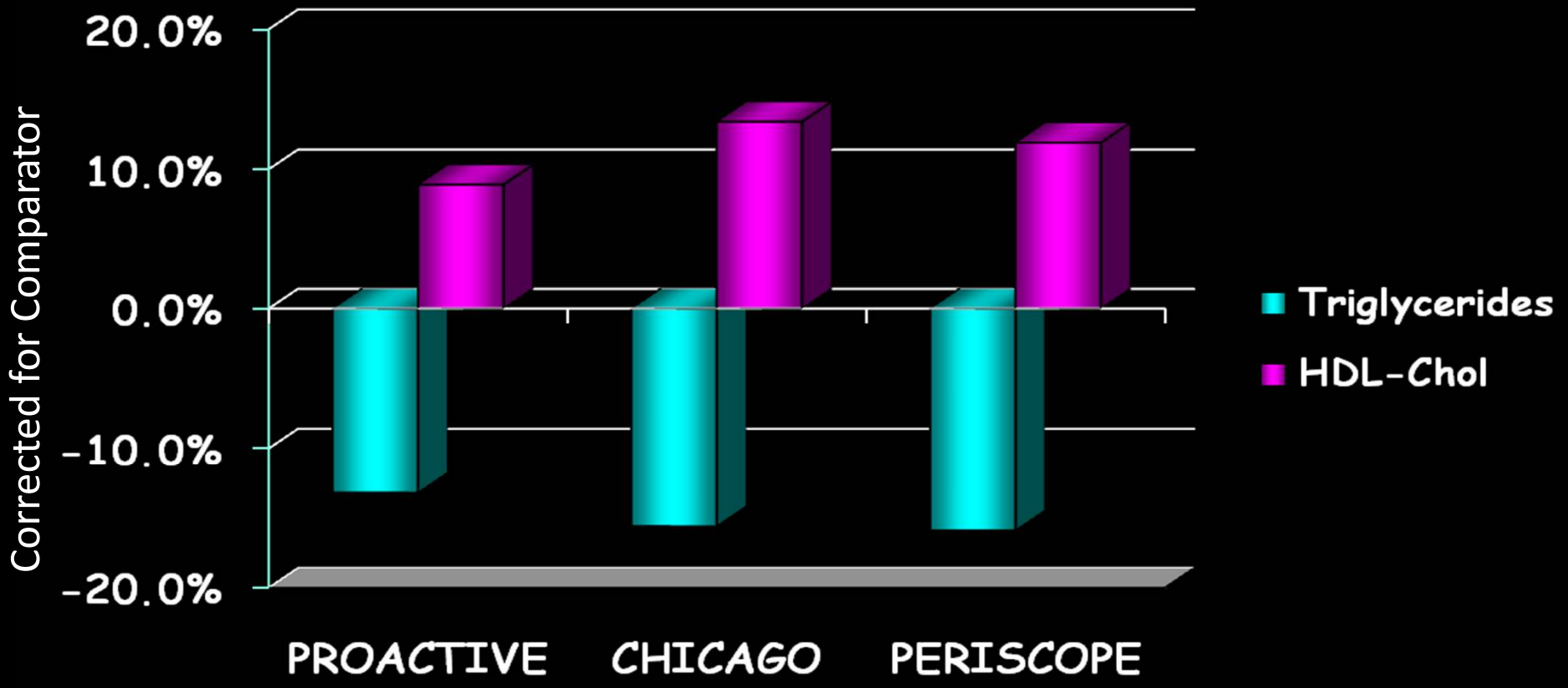
*P < 0.001; n = 627

Error bars = 95% CI

Bonora E, *et al. Diabetes Care* 2002; 25:1135.

Benefits of Pioglitazone: Lipid Metabolism

- Pioglitazone improves diabetic dyslipidaemia
  - Decreases triglyceride levels
  - Increases high-density lipoprotein (HDL) cholesterol levels



Dormandy JA et al., Lancet 2005;366:1279- Mazzone T et al., JAMA 2006; 296: 2572 Nicholls et al., J Am Coll Cardiol 2008; 52:255-62.

CHICAGO

A Study Evaluating Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone

Mazzone T et al. JAMA. 2006

Effect of TZD on CIMT in Patients with T2DM

Study	Population	Treatment	CIMT Δ
Koshiyama et al *JCEM* 2001	N=106 Japan	PIO *vs.* PLB 6 months	PIO: –0.084 mm PLB: +0.022 mm p<0.001
Langenfeld et al *Circulation* 2005	N=173 Germany SBP: 148 mmHg >90% Caucasian LDL-C 136 mg/dL	PIO *vs.* GLM 6 months	PIO: –0.054 mm GLM: –0.011 mm p<0.0001
Hodis et al *Diabetes Care* 2006	N=299 66% women 90% Hispanic	TROG *vs.* PLB 2 years	TRO: +0.003 mm/yr PLB: +0.007 mm/yr p=0.17

Study Objective and Design

Objective

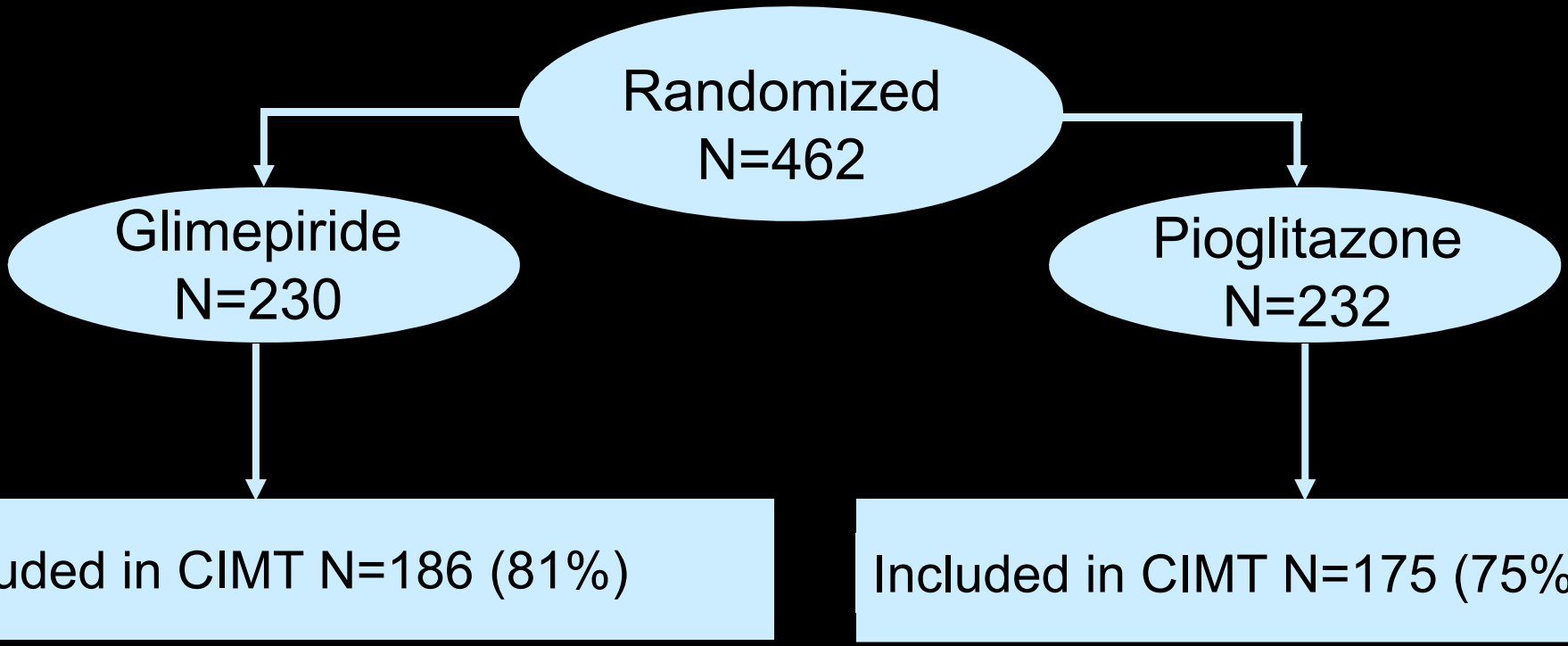
- To compare the effect of treatment with **PIO *vs* Glimepiride (GLM)** on absolute change in CIMT from baseline to final visit in subjects with T2DM

Study Design

- A 72-week, multicenter, randomized, double-blind, 2-arm study
- 15-45 mg PIO *vs.* 1-4 mg GLM (titrated to HbA1c target)
- 462 subjects
- Sulfonylurea treatment was discontinued at randomization, if applicable
- CIMT measured at Weeks 0, 24, 48, and 72 or Final Visit (LOCF)

Mazzone T et al. JAMA. 2006

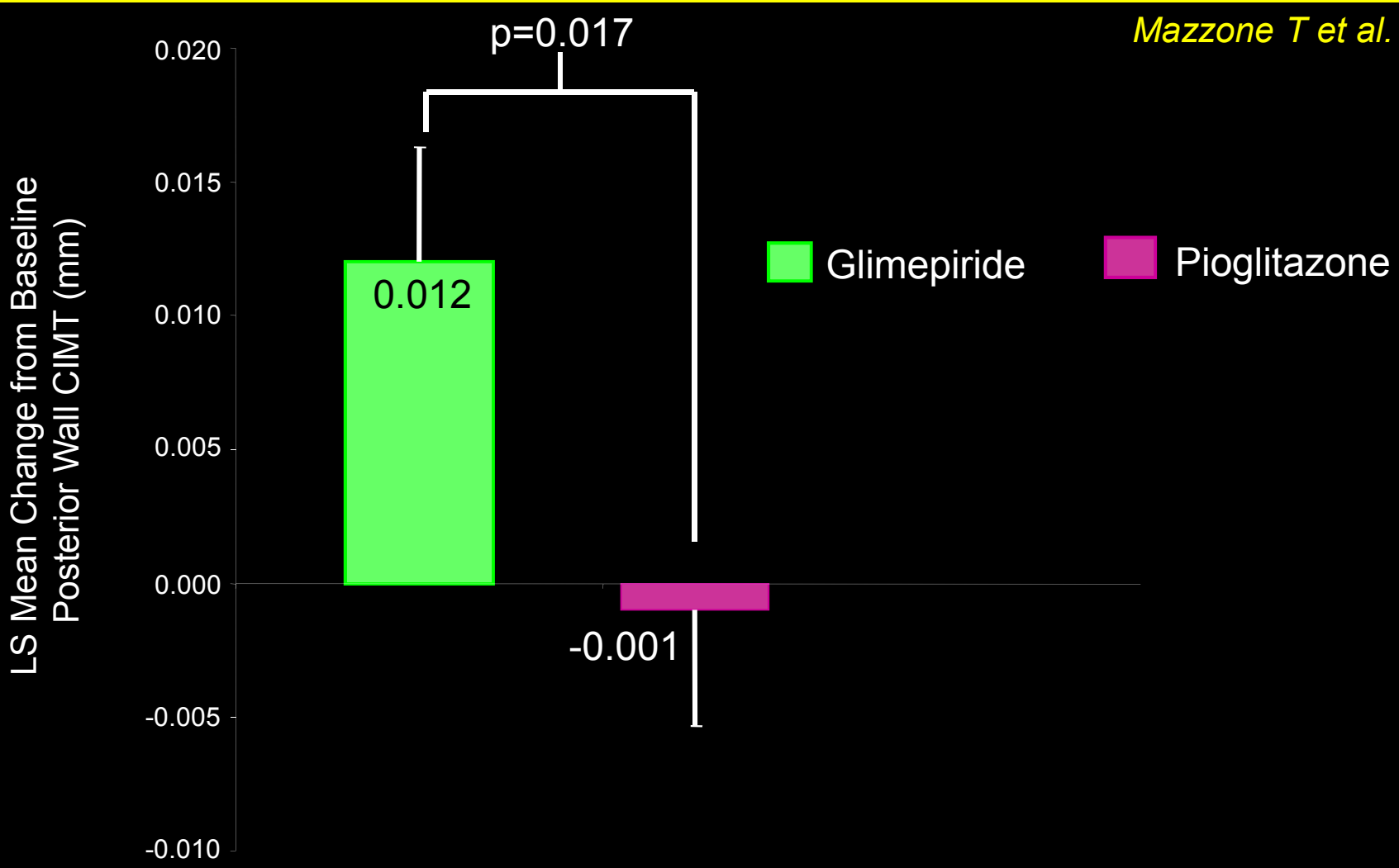
Subject Disposition



Mazzone T et al. JAMA. 2006

Mean Change in CIMT

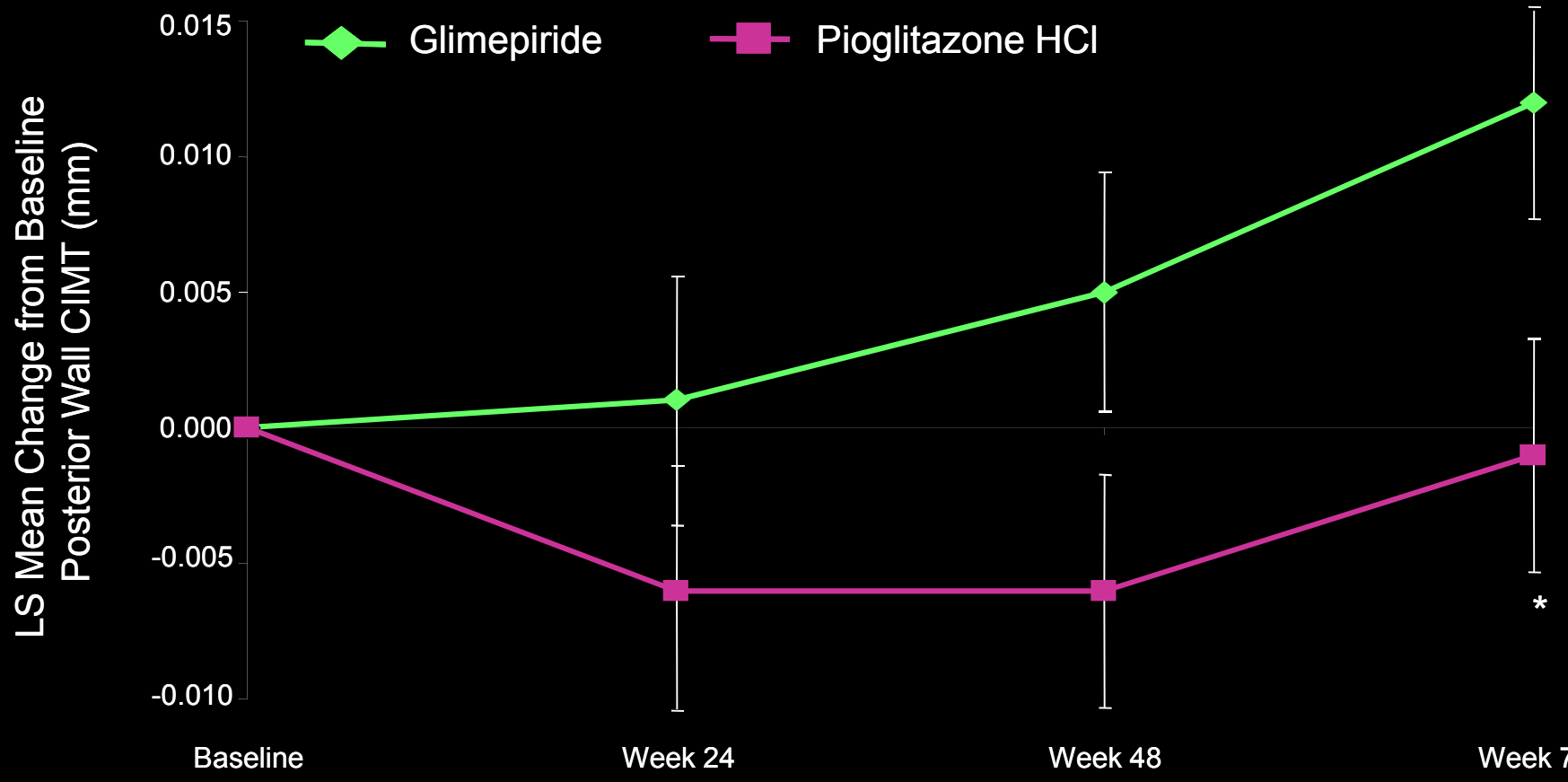
Mazzone T et al. JAMA. 2006



Baseline CIMT LS Mean (SE)	GLM (N=186)	PIO (N=175)	Treatment group difference, Final Visit
	0.779 (0.0085) mm	0.771 (0.0085) mm	-0.013 (95% CI: -0.024,-0.002)

Mean Change in Average CIMT

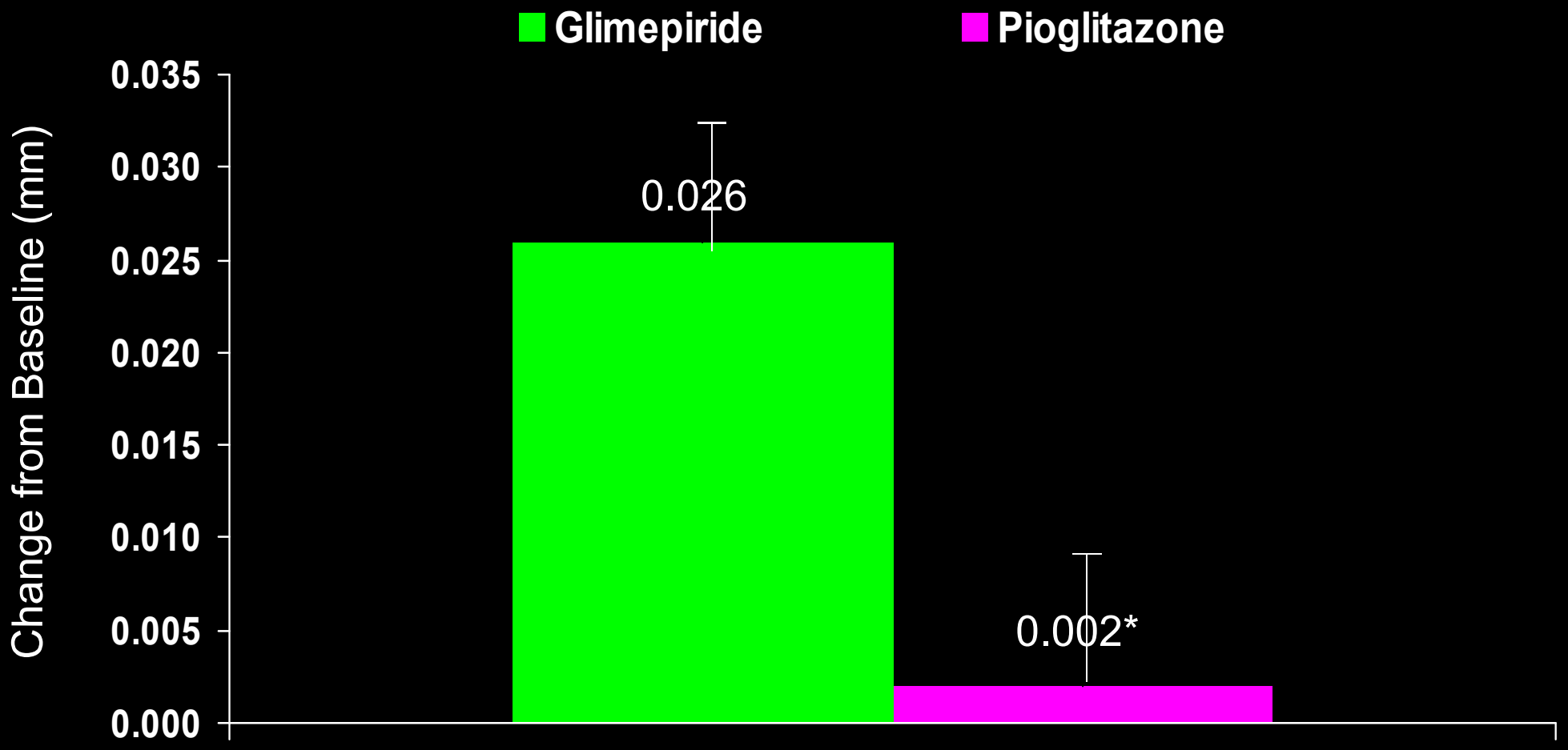
Mazzone T et al. JAMA. 2006



*P=0.017

Baseline CIMT (mm)	GLM (N=186)	PIO (N=175)	Treatment group difference, Final Visit
LS mean (SE)	0.779 (0.008)	0.771 (0.008)	-0.013 (95% CI: -0.024,-0.002)

Change from Baseline in Far Wall CIMT Max Value at Week 72 (LOCF)



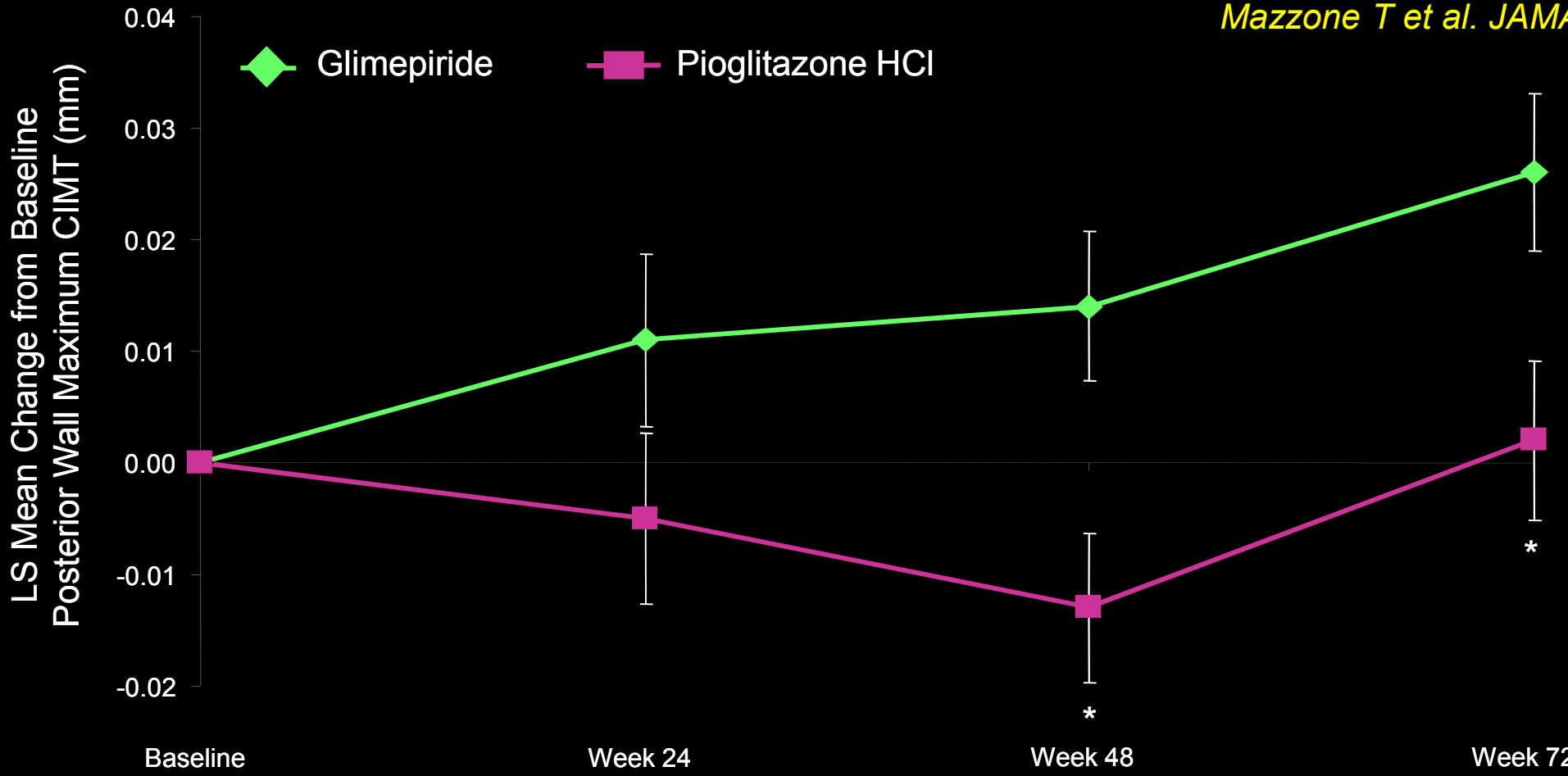
Difference from Glimepiride -0.024 (-0.042, -0.006)

* P-Value = 0.008 for comparing to Glimepiride

Mazzone T et al. JAMA. 2006

Mean Change in Maximal CIMT

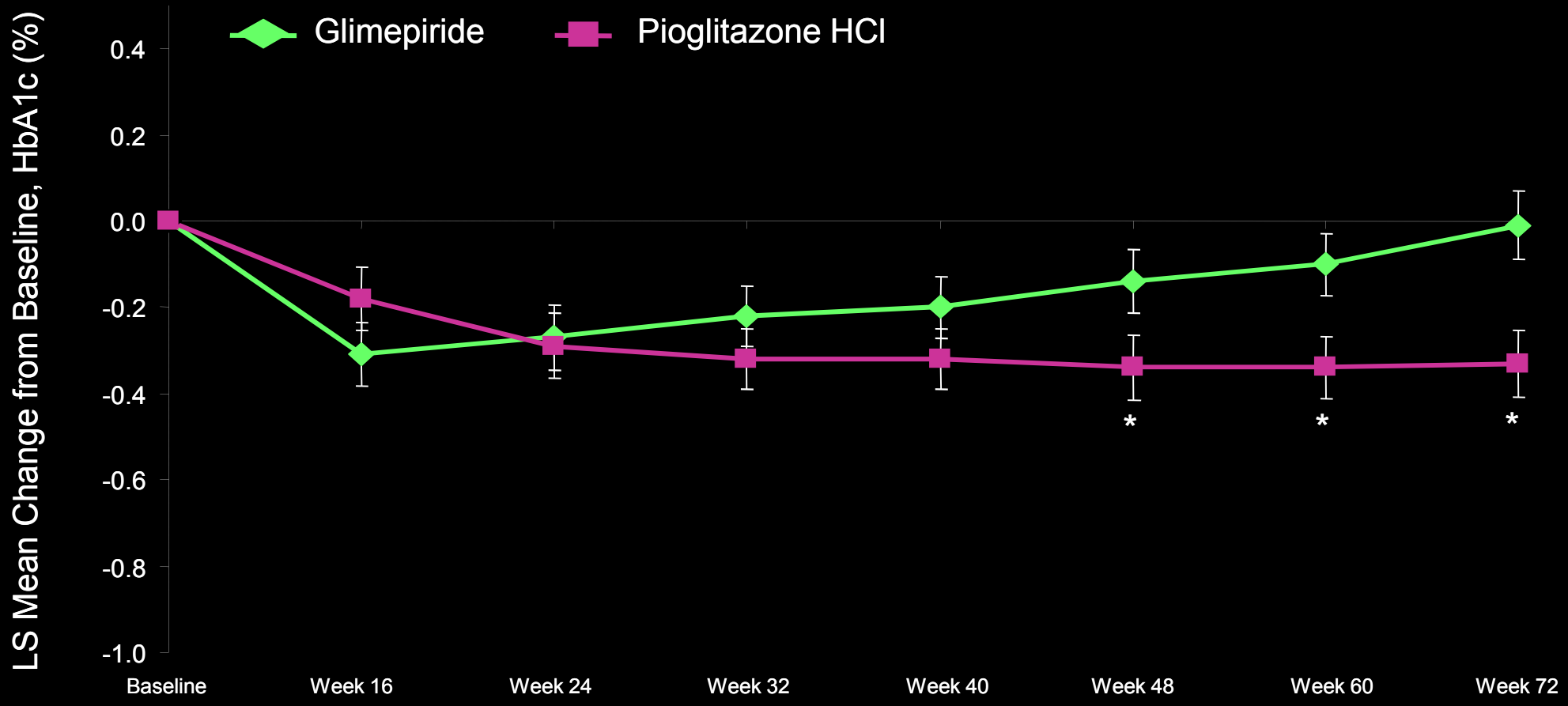
Mazzone T et al. JAMA. 2006



*P≤0.01

Baseline CIMT (mm)	GLM (N=186)	PIO (N=175)	Treatment group difference at Final Visit
LS Mean (SE)	1.042 (0.010)	1.038 (0.010)	-0.024 (95% CI: -0.042, -0.006)

Glycemic Effects

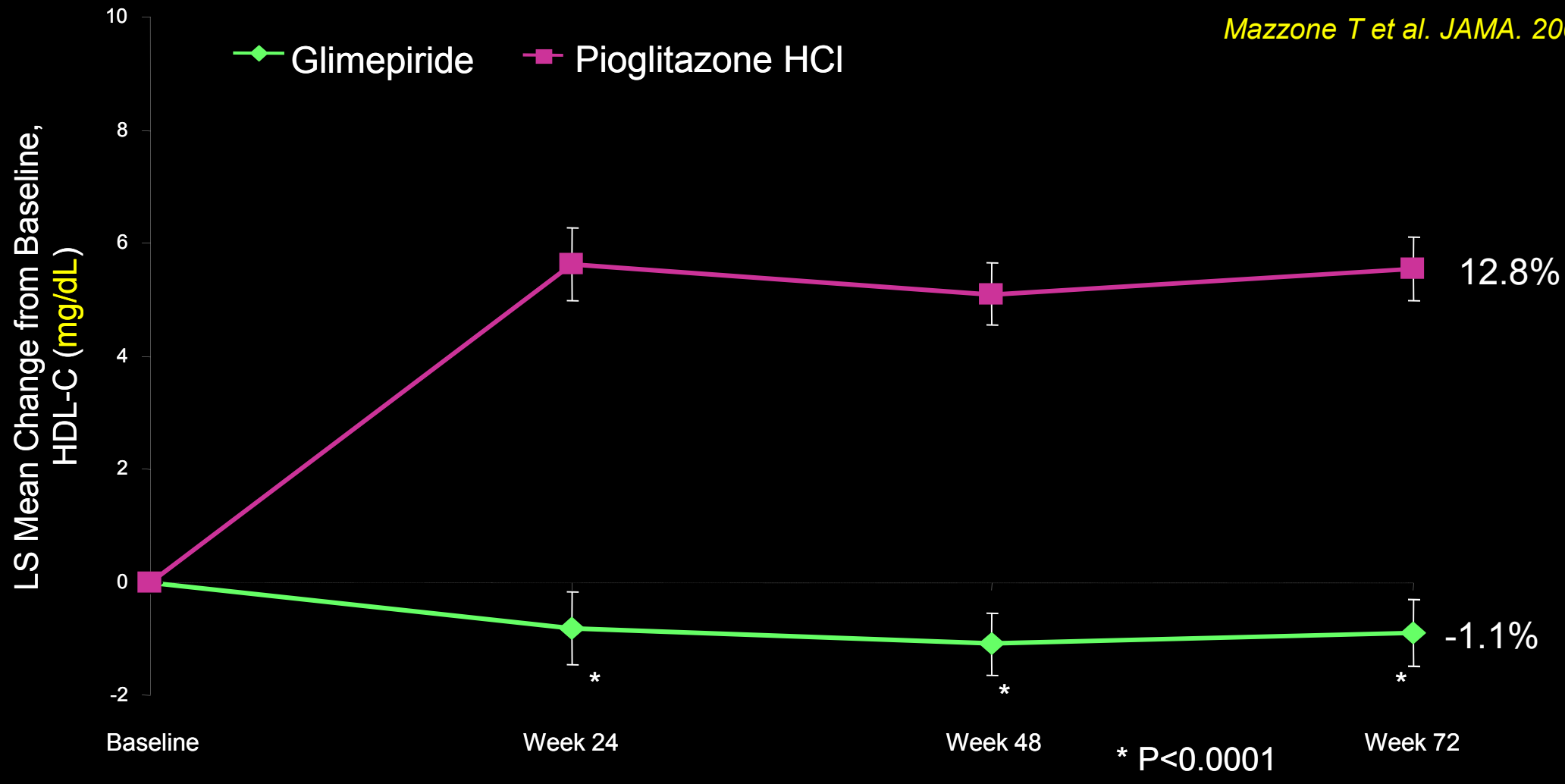


* P≤ 0.05

Baseline HbA1c (%)	GLM (N=206)	PIO (N=203)	Treatment group difference, Final Visit
LS mean (SE)	7.36 (0.075)	7.42 (0.074)	-0.32 (95% CI: -0.522, -0.124)

Mazzone T et al. JAMA. 2006

HDL-Cholesterol Changes



Baseline HDL-C (mg/dL)	GLM (N=206)	PIO (N=201)	Treatment group difference, Final Visit
LS mean (SE)	47.6 (0.91)	47.1 (0.90)	6.45 (95% CI: 4.97, 7.93)

Conclusion

- Diabetes is increasing in prevalence and is a major risk factor for CV disease; whereas lipid and blood pressure management have powerful benefits on such risk, new approaches are needed for patients with T2DM.

- Although additional data are needed, our results demonstrating the beneficial effect of pioglitazone compared to glimepiride on CIMT, a validated surrogate marker for CV risk, suggest a novel approach to managing such risk.

Mazzone T et al. JAMA. 2006

PERISCOPE

Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation Study

Nissen SE et al. JAMA. 2008

Comparison of Pioglitazone vs Glimepiride on Progression of Coronary Atherosclerosis in Patients With Type 2 Diabetes

The PERISCOPE Randomized Controlled Trial

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Context No antidiabetic regimen has demonstrated the ability to reduce progression of coronary atherosclerosis. Commonly used oral glucose-lowering agents include sulfonylureas, which are insulin secretagogues, and thiazolidinediones, which are insulin sensitizers.

Objective To compare the effects of an insulin sensitizer, pioglitazone, with an insulin secretagogue, glimepiride, on the progression of coronary atherosclerosis in patients with type 2 diabetes.

Design, Setting, and Participants Double-blind, randomized, multicenter trial at 97 academic and community hospitals in North and South America (enrollment August 2003-March 2006) in 543 patients with coronary disease and type 2 diabetes.

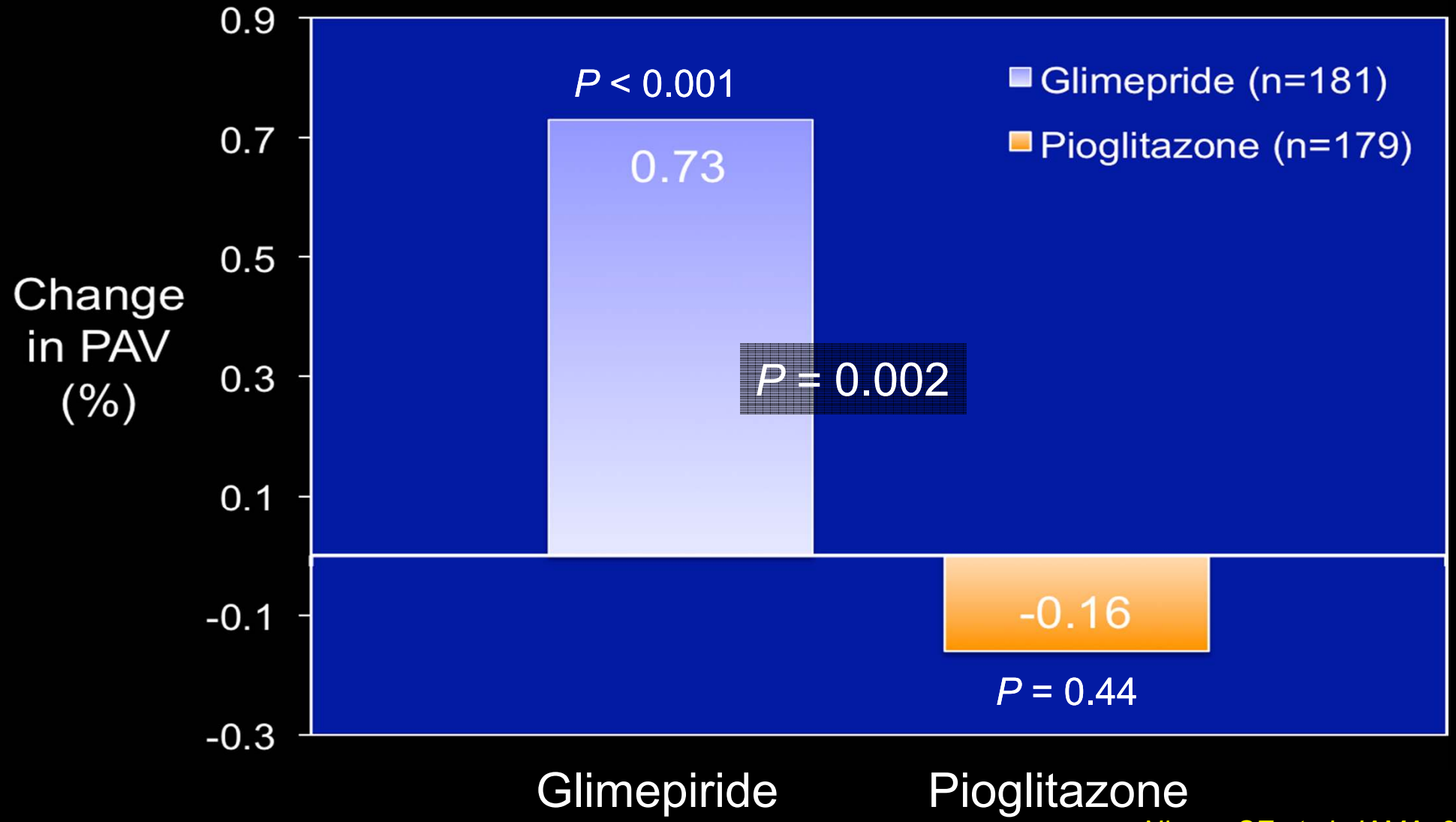
Interventions A total of 543 patients underwent coronary intravascular ultrasonography and were randomized to receive glimepiride, 1 to 4 mg, or pioglitazone, 15 to 45 mg, for 18 months with titration to maximum dosage, if tolerated. Atherosclerosis progression was measured by repeat intravascular ultrasonography examination in 360 patients at study completion.

Main Outcome Measure Change in percent atheroma volume (PAV) from baseline to study completion.

Results Least squares mean PAV increased 0.73% (95% CI, 0.33% to 1.12%) with glimepiride and decreased 0.16% (95% CI, −0.57% to 0.25%) with pioglitazone (P=.002). An

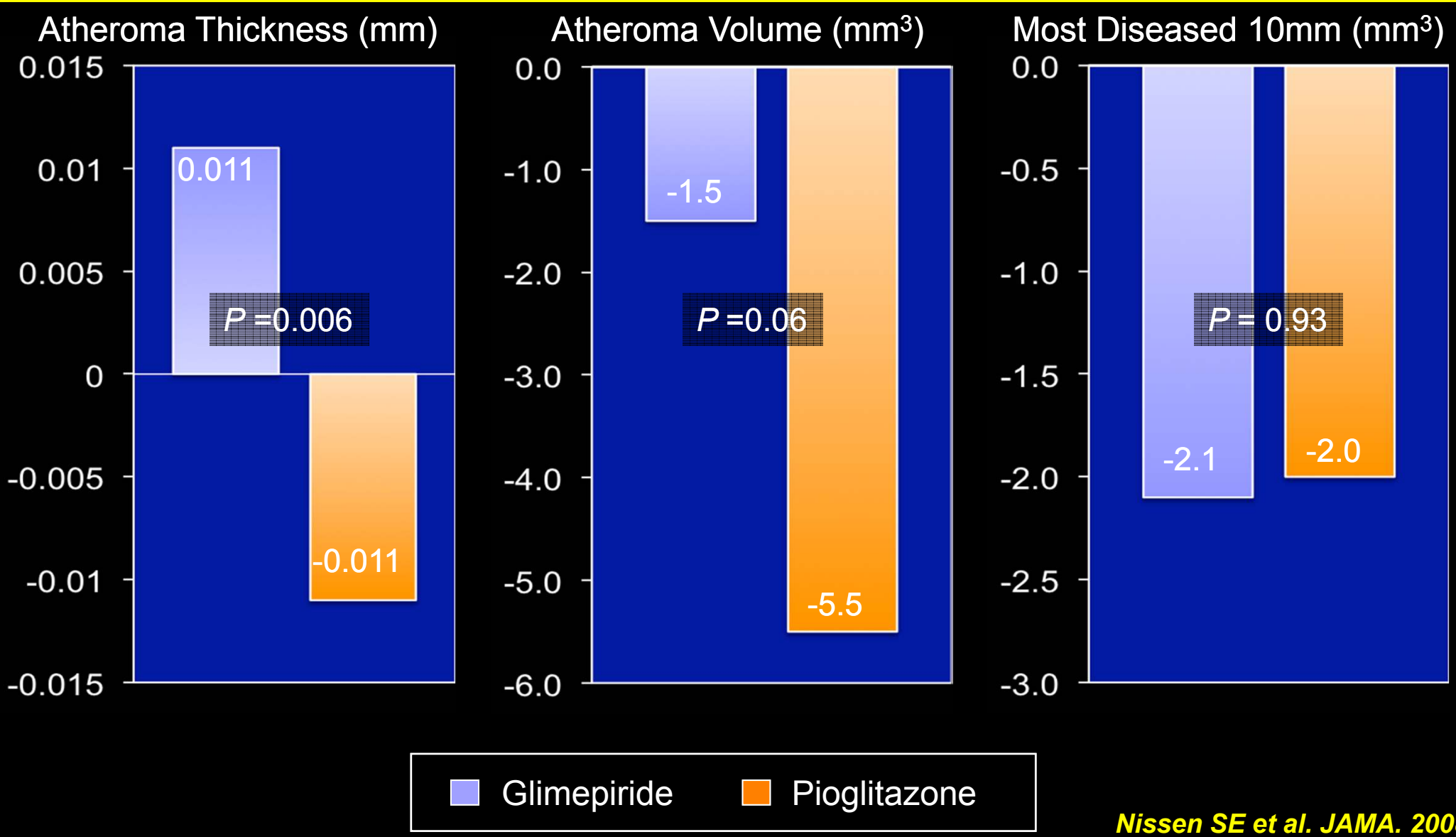
Primary Efficacy Parameter

Change in Percent Atheroma Volume (%)



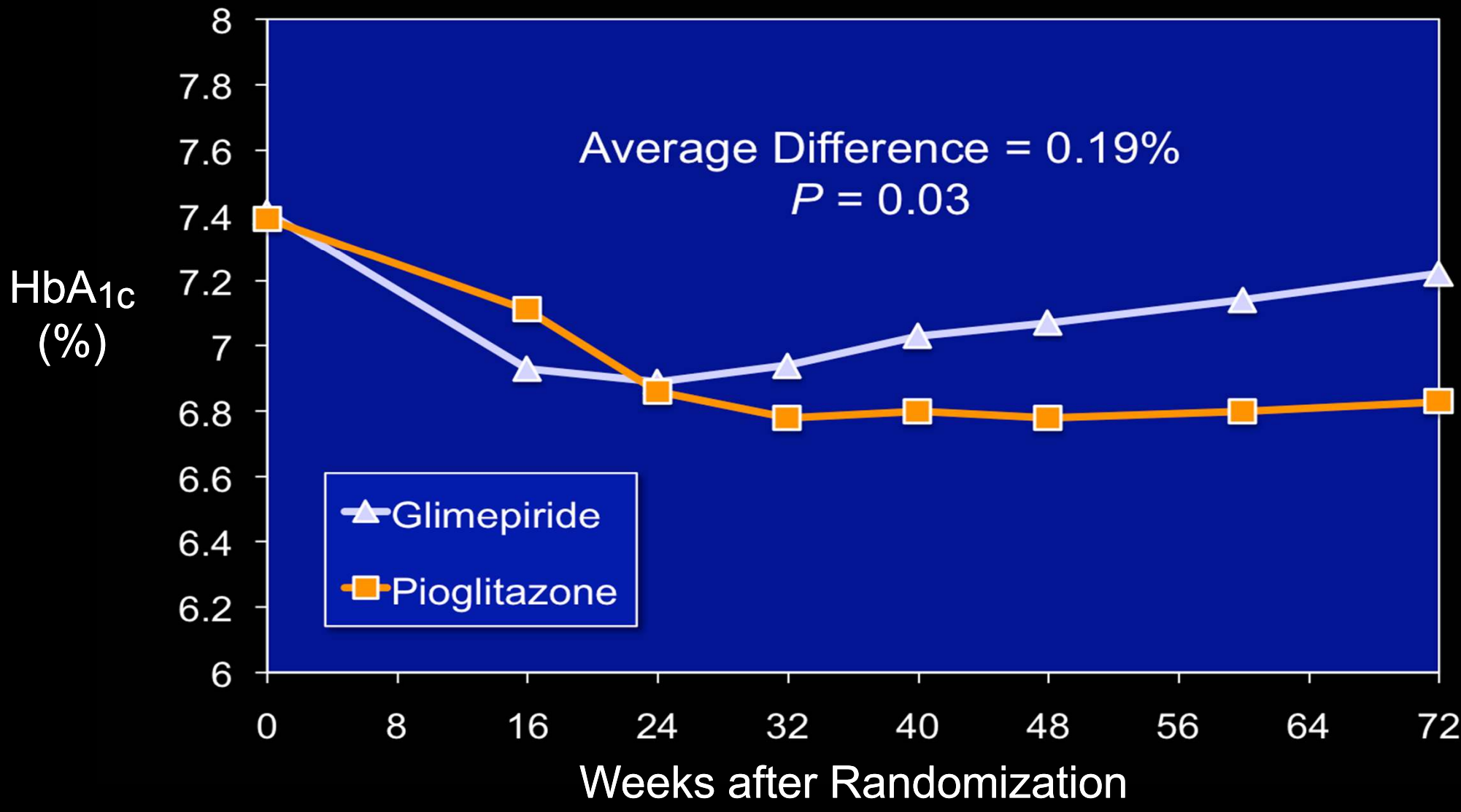
Nissen SE et al. JAMA. 2008

Intravascular Ultrasound: Secondary Endpoints



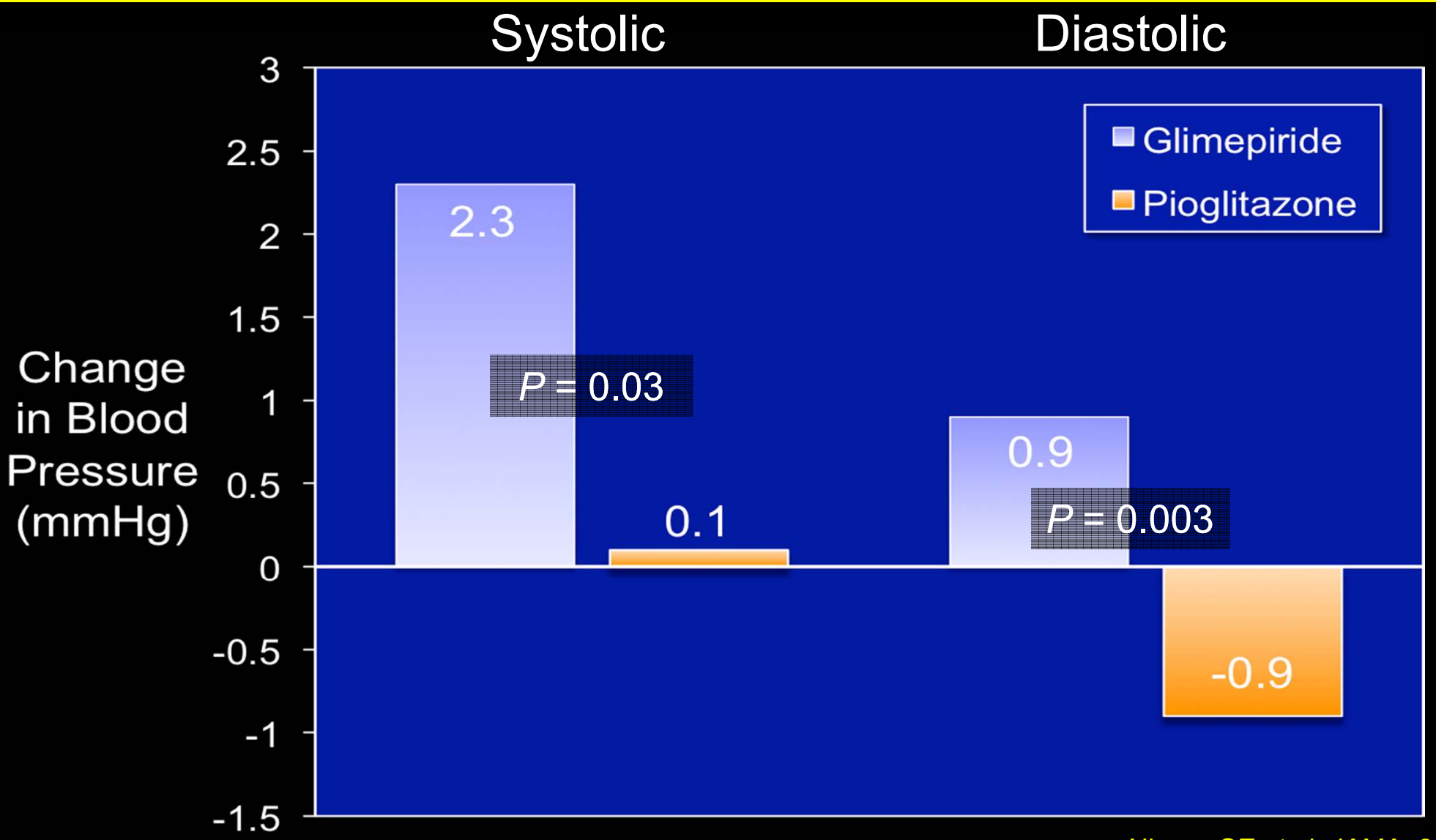
Nissen SE et al. JAMA. 2008

Glycohemoglobin Levels during the Trial



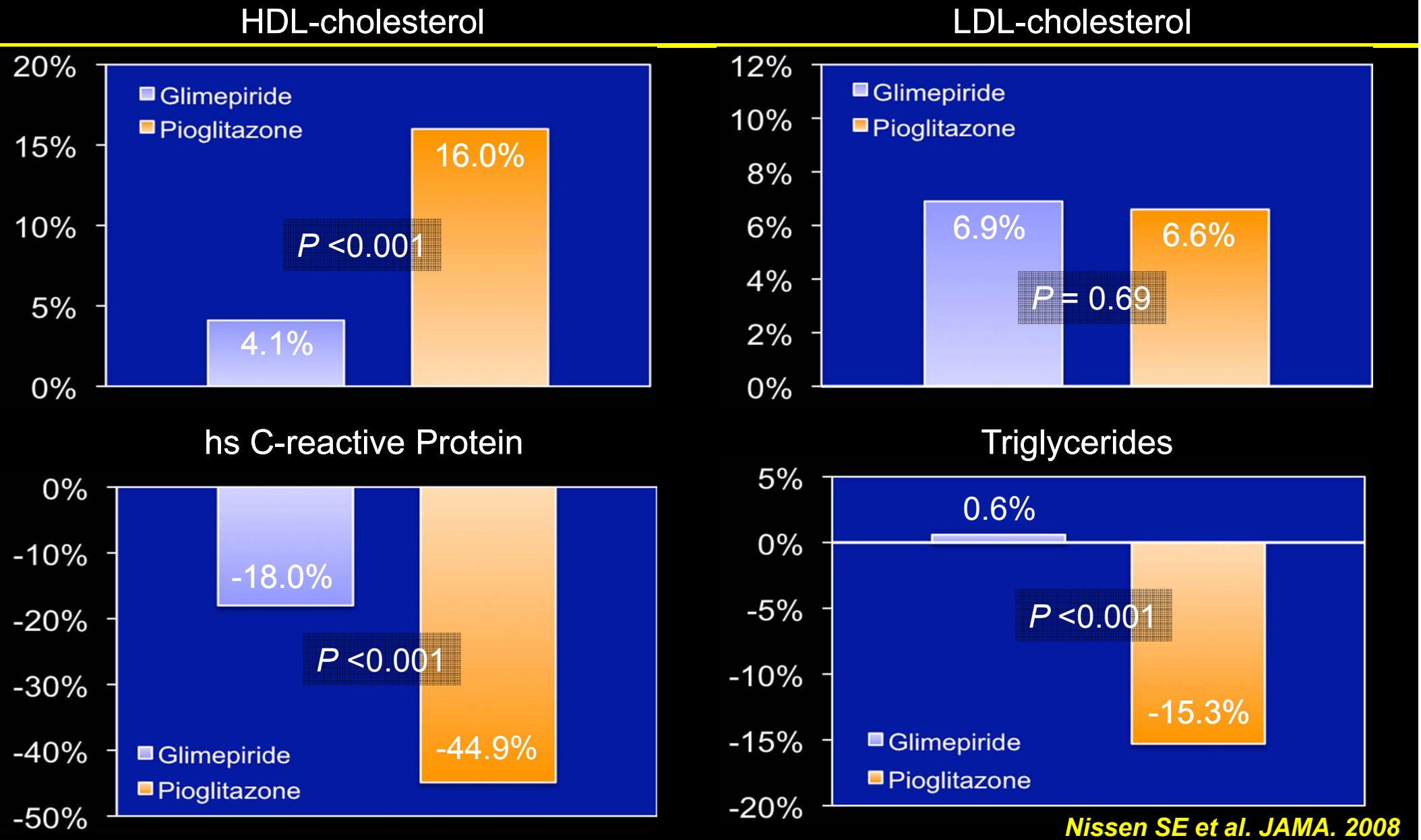
Nissen SE et al. JAMA. 2008

Mean Changes in Blood Pressure (n = 360)



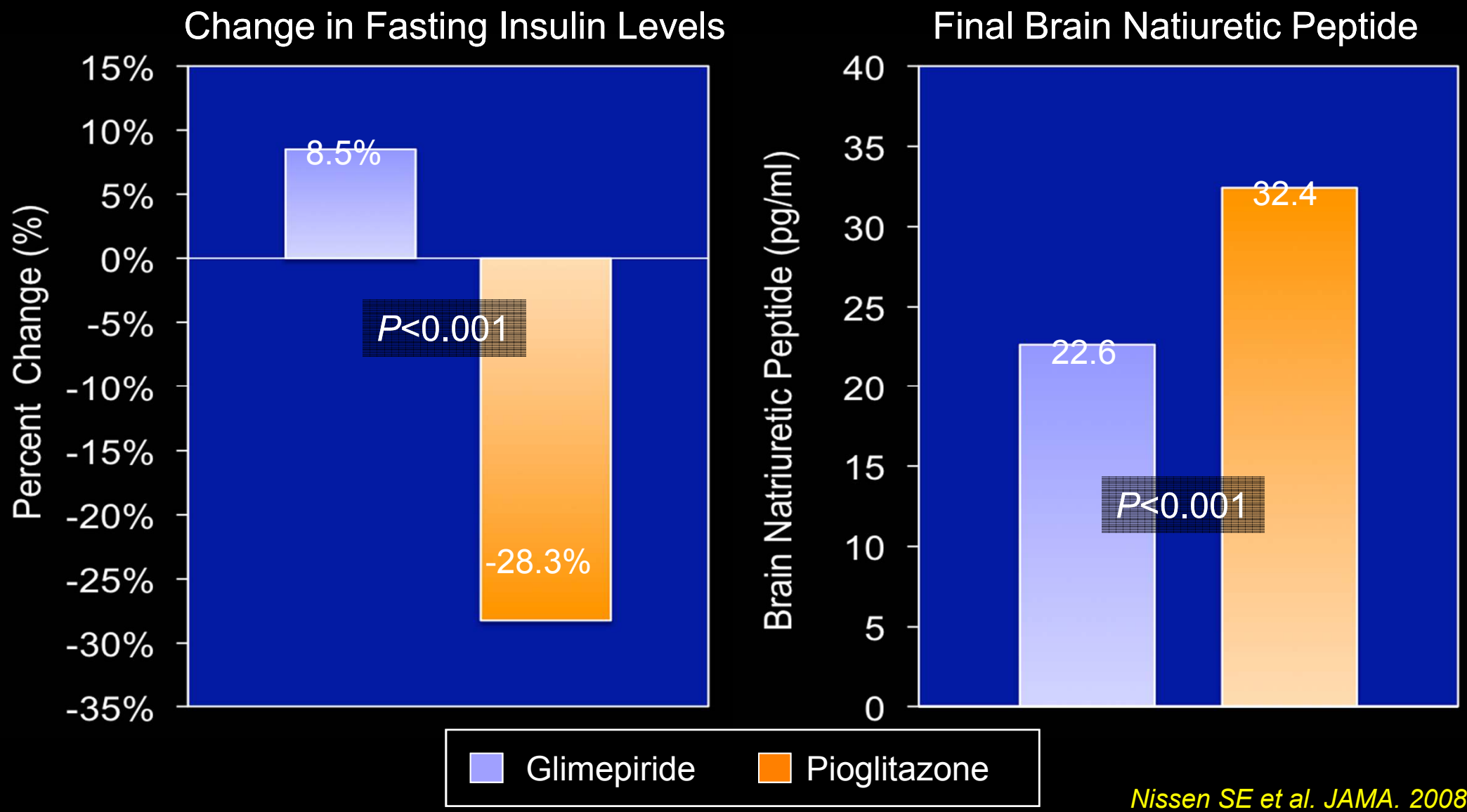
Nissen SE et al. JAMA. 2008

Percentage Changes: Biochemical Parameters



Nissen SE et al. JAMA. 2008

Other Biomarkers: Insulin Levels and BNP



Nissen SE et al. JAMA. 2008

Conclusions

- Pioglitazone, on a background of optimal medical therapy, prevented progression of coronary atherosclerosis, *P* = 0.002 compared with glimepiride.
- Compared with glimepiride, pioglitazone produced similar, although more durable, glucose-lowering.
- Pioglitazone favorably affected BP, raised HDL-C (16.0% vs. 4.1%), lowered triglycerides (-15.3% vs. +0.6%) and reduced hsCRP (-44.9% vs. -18.0%).
- Hypoglycemia and angina were more common with glimepiride treatment; edema, fractures and weight gain more frequent with pioglitazone treatment.

Nissen SE et al. JAMA. 2008

PROACTIVE

PROspective pioglitAzone Clinical Trial In macroVascular Events

Dormandy JA et al. Lancet. 2005

Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial

John A Dormandy, Bernard Charbonnel, David J A Eckland, Erland Erdmann, Massimo Massi-Benedetti, Ian K Moules, Allan M Skene, Meng H Tan, Pierre J Lefèbvre, Gordon D Murray, Eberhard Standl, Robert G Wilcox, Lars Wilhelmsen, John Betteridge, Kåre Birkeland, Alain Golay, Robert J Heine, László Korányi, Markku Laakso, Marián Mokáň, Antanas Norkus, Valdis Pirags, Toomas Podar, André Scheen, Werner Scherbaum, Guntram Schernthaner, Ole Schmitz, Jan Škrha, Ulf Smith, Jan Tatoň, on behalf of the PROactive investigators*

Summary

Background Patients with type 2 diabetes are at high risk of fatal and non-fatal myocardial infarction and stroke. There is indirect evidence that agonists of peroxisome proliferator-activated receptor γ (PPAR γ) could reduce macrovascular complications. Our aim, therefore, was to ascertain whether pioglitazone reduces macrovascular morbidity and mortality in high-risk patients with type 2 diabetes.

Methods We did a prospective, randomised controlled trial in 5238 patients with type 2 diabetes who had evidence of macrovascular disease. We recruited patients from primary-care practices and hospitals. We assigned patients to oral pioglitazone titrated from 15 mg to 45 mg (n=2605) or matching placebo (n=2633), to be taken in addition to their glucose-lowering drugs and other medications. Our primary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. Analysis was by intention to treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN NCT00174993.

Baseline characteristics

	Pioglitazone (n=2605)	Placebo (n=2633)
Patients' characteristics		
Male	1735 (67%)	1728 (66%)
White	2564 (98%)	2600 (99%)
Age (years) (mean, SD)	61·9 (7·6)	61·6 (7·8)
Time since diagnosis of diabetes (years) (median, IQR)	8 (4–13)	8 (4–14)
Body-mass index (kg/m²) (mean, SD)	30·7 (4·7)	31·0 (4·8)
Blood pressure: systolic/diastolic (mm Hg) (mean, SD)	144 (18)/83 (10)	143 (18)/83 (9)
History of hypertension	1947 (75%)	2005 (76%)
Current smoker	340 (13%)	381 (14%)
Past smoker	1199 (46%)	1159 (44%)
Microvascular disease*	1113 (43%)	1076 (41%)
Blood glucose lowering treatment		
Metformin only	253 (10%)	261 (10%)
Sulphonylureas only	508 (20%)	493 (19%)
Metformin + sulphonylureas	654 (25%)	660 (25%)
Insulin only	5 (<1%)	8 (<1%)
Insulin + metformin	456 (18%)	475 (18%)
Insulin + sulphonylureas	209 (8%)	219 (8%)
Insulin + metformin + sulphonylureas	105 (4%)	107 (4%)
Other combination	306 (12%)	305 (12%)
Diet only	109 (4%)	105 (4%)
Laboratory data		
HBA_{1c} (%) (median (IQR)	7·8 (7·0–8·9)	7·9 (7·1–8·9)
LDL cholesterol (mmol/L) (median, IQR)	2·9 (2·3–3·5)	2·9 (2·3–3·5)
HDL cholesterol (mmol/L) (median, IQR)	1·1 (0·9–1·3)	1·1 (0·9–1·3)
Triglycerides (mmol/L) (median, IQR)	1·8 (1·3–2·6)	1·8 (1·3–2·6)
Creatinine (µmol/L) (median, IQR)	79 (68–92)	79 (68–92·5)
Micral test result		
Negative	1407 (54%)	1428 (54%)
About 20 mg/L	545 (21%)	551 (21%)
About 50 mg/L	357 (14%)	377 (14%)
About 100 mg/L or more	232 (9%)	217 (8%)

Data are number (%) unless otherwise stated. *Retinopathy, nephropathy, neuropathy.

Dormandy JA et al. Lancet. 2005

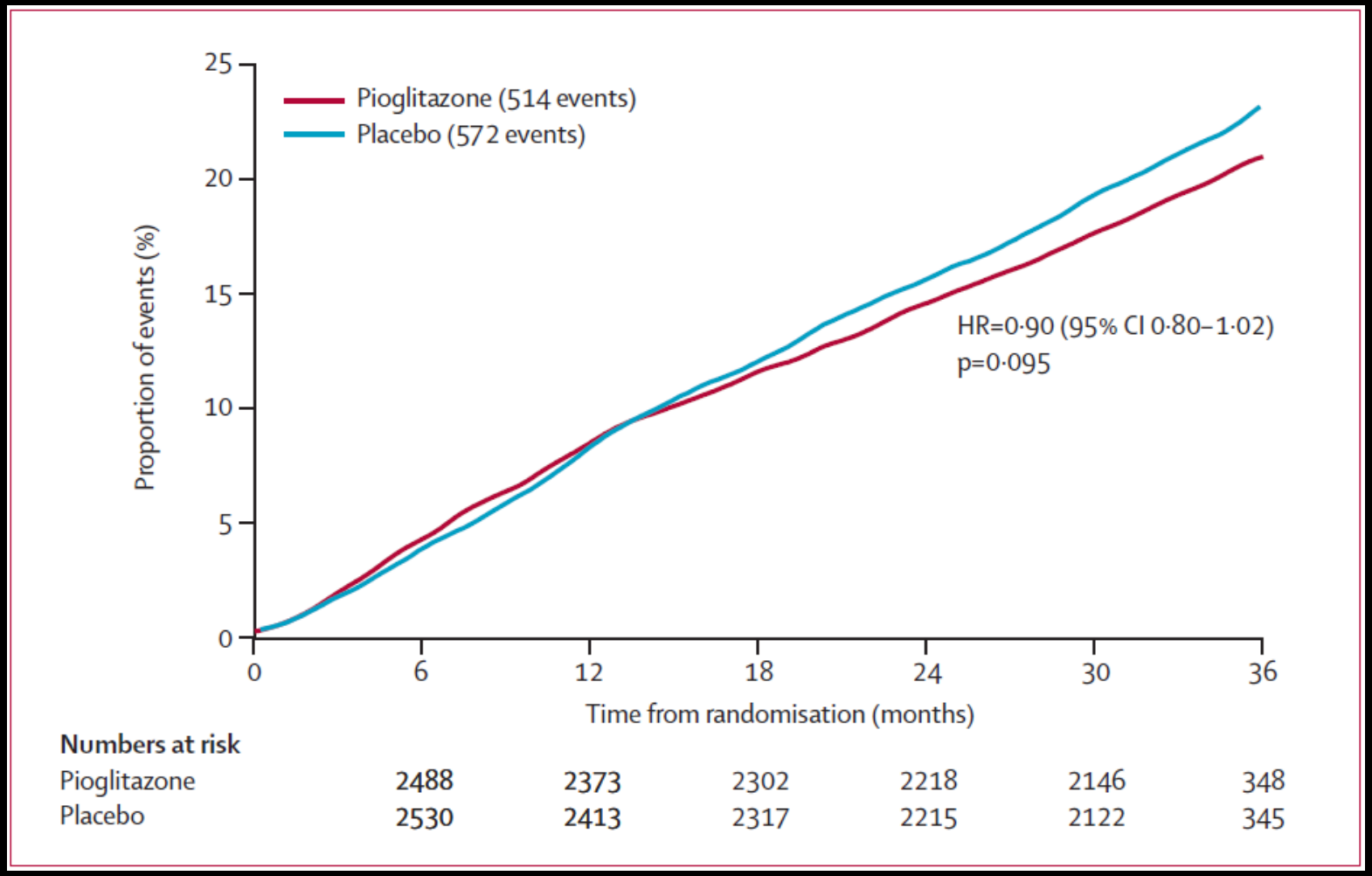
Macrovascular morbidity at study entry and associated medications

	Pioglitazone (n=2605)	Placebo (n=2633)
Entry criteria		
Previous myocardial infarction	1230 (47%)	1215 (46%)
Previous stroke	486 (19%)	498 (19%)
Previous percutaneous intervention or coronary artery bypass graft	804 (31%)	807 (31%)
Previous acute coronary syndrome	355 (14%)	360 (14%)
Objective evidence of coronary artery disease	1246 (48%)	1274 (48%)
Symptomatic peripheral arterial obstructive disease	504 (19%)	539 (20%)
Two or more macrovascular disease criteria	1223 (47%)	1278 (49%)
Baseline cardiovascular medications		
β blockers	1423 (55%)	1434 (54%)
Angiotensin-converting enzyme inhibitors	1630 (63%)	1658 (63%)
Angiotensin II antagonists	170 (7%)	184 (7%)
Calcium-channel blockers	892 (34%)	964 (37%)
Nitrates	1018 (39%)	1045 (40%)
Thiazide diuretics	401 (15%)	430 (16%)
Loop diuretics	372 (14%)	378 (14%)
Antiplatelet medications	2221 (85%)	2175 (83%)
Aspirin	1942 (75%)	1888 (72%)
Statins	1108 (43%)	1137 (43%)
Fibrates	264 (10%)	294 (11%)

Data are number (%) unless otherwise stated.

Dormandy JA et al. Lancet. 2005

Kaplan-Meier curve of time to primary endpoint



Numbers at risk

Pioglitazone	2488	2373	2302	2218	2146	348
Placebo	2530	2413	2317	2215	2122	345

Death from any cause, non-fatal myocardial infarction (including silent myocardial infarction), stroke, acute coronary syndrome, leg amputation, coronary revascularisation, or revascularisation of the leg

Dormandy JA et al. Lancet. 2005

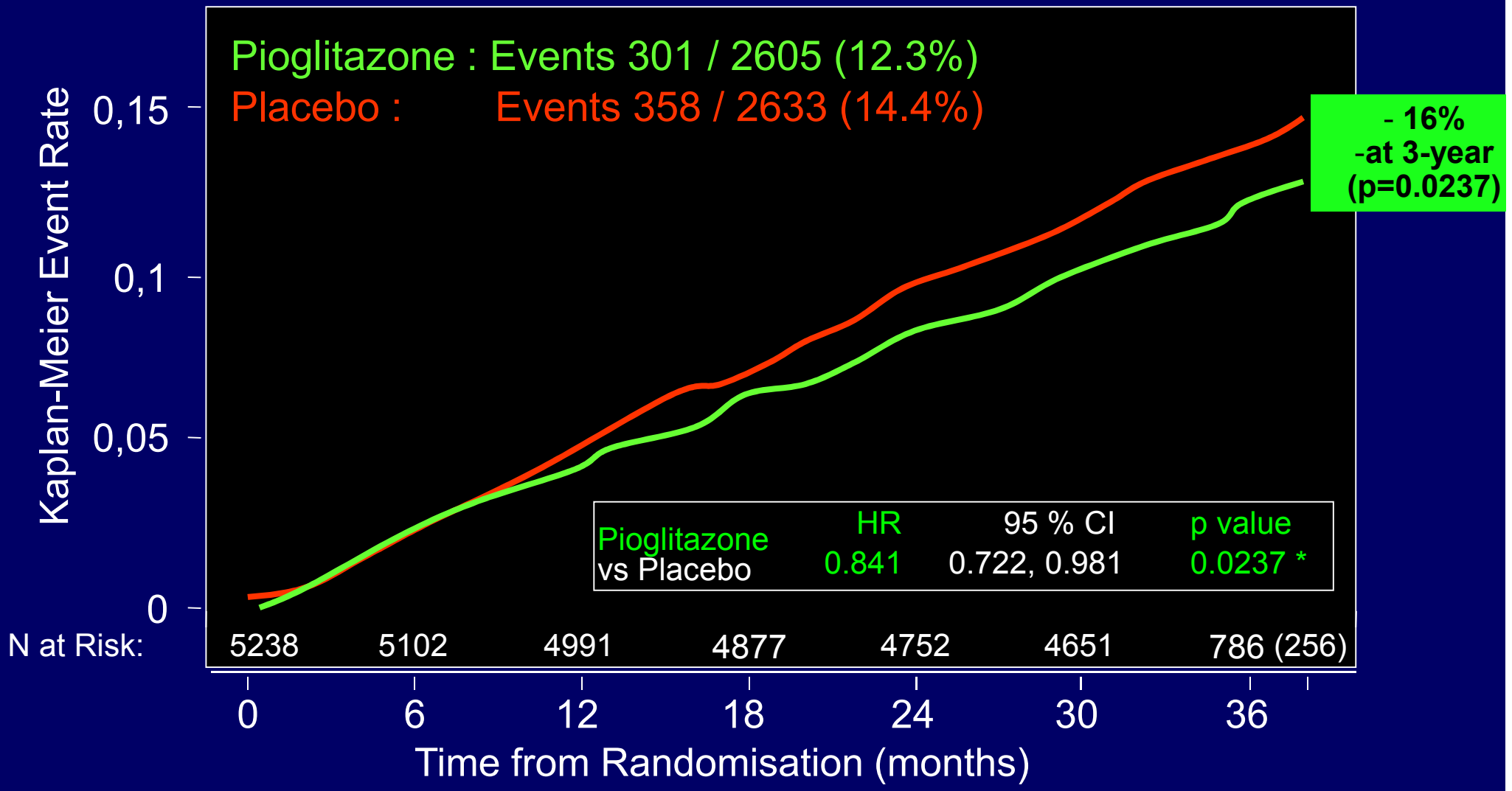
Change in laboratory data from baseline to final visit

	Pioglitazone	Placebo	p
HBA_{1c} (% absolute change)	−0·8 (−1·6 to −0·1)	−0·3 (−1·1 to 0·4)	<0·0001
Triglycerides (% change)	−11·4 (−34·4 to 18·3)	1·8 (−23·7 to 33·9)	<0·0001
LDL cholesterol (% change)	7·2 (−11·2 to 27·6)	4·9 (−13·9 to 23·8)	0·003
HDL cholesterol (% change)	19·0 (6·6 to 33·3)	10·1 (−1·7 to 21·4)	<0·0001
LDL/HDL (% change)	−9·5 (−27·3 to 10·1)	−4·2 (−21·7 to 15·8)	<0·0001
Micral test results (baseline to final visit)			
Improved (number, %)	492 of 2218 (22%)	451 of 2225 (20%)	0·286
Worsened (number, %)	555 of 2218 (25%)	563 of 2225 (25%)	

Data are median (IQR) unless otherwise stated.

Dormandy JA et al. Lancet. 2005

Significant Reduction of the combined Clinical Outcome of Death, Myocardial Infarction & Stroke



proactive-results.com

Dormandy G et al (Lancet 2005; 366: 1279-1289)

Effects of Pioglitazone in Patients With Type 2 Diabetes With or Without Previous Stroke

Results From PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04)

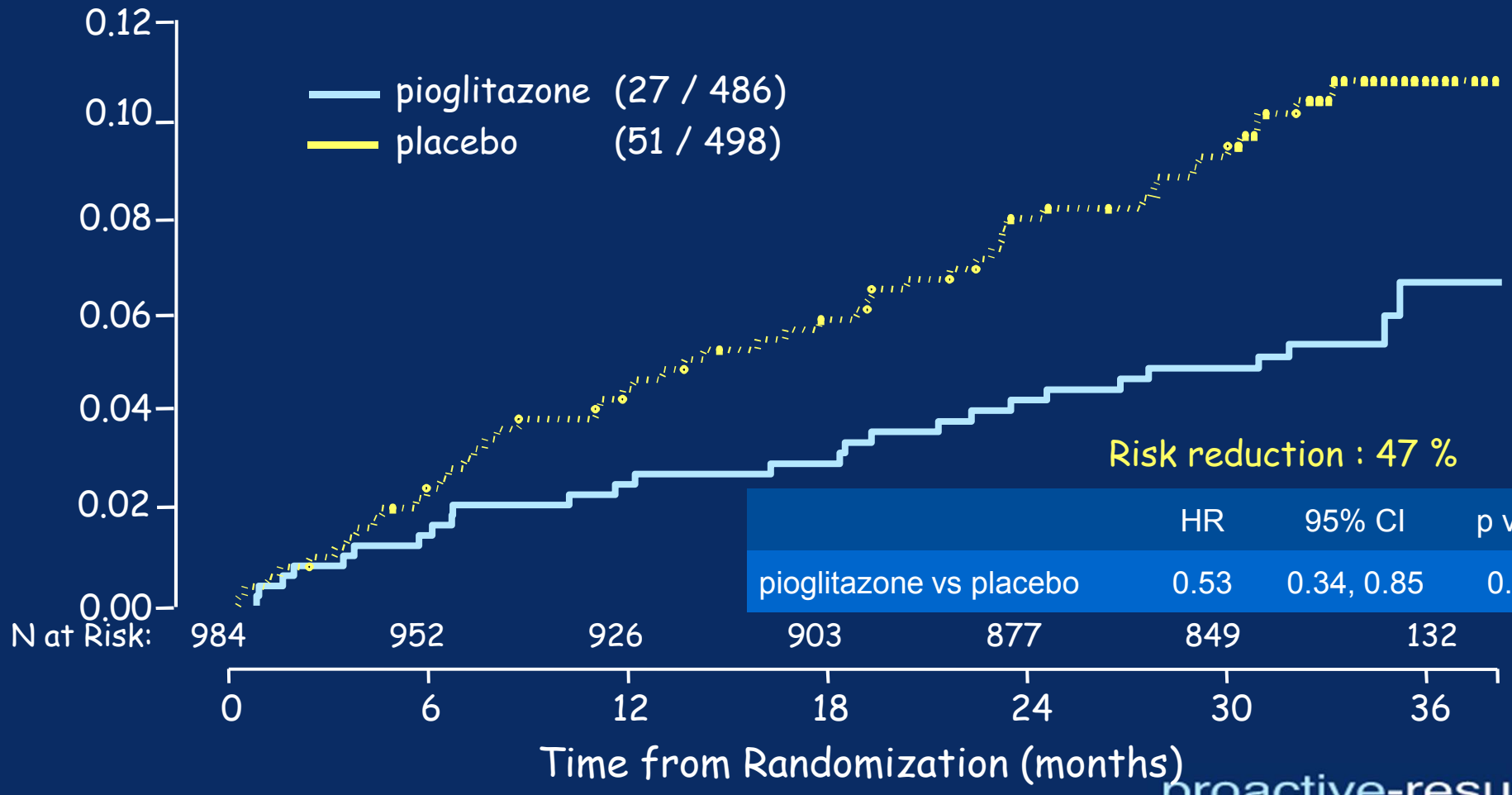
Robert Wilcox, MD; Marie-Germaine Bousser, MD; D. John Betteridge, MD; Guntram Schernthaner, MD; Valdis Pirags, MD; Stuart Kupfer, MD; John Dormandy, DSc; for the PROactive Investigators

In high-risk patients with type 2 diabetes and previous stroke, pioglitazone significantly reduced the occurrence of recurrent fatal and nonfatal stroke.

Stroke, 2007;38:865-873

Time to Fatal or Non-Fatal Stroke in Patients with Previous Stroke

Patients with previous Stroke
n=984



proactive-results.com

Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008

The European Stroke Organization (ESO) Executive Committee and the ESO Writing Committee

Peter A. Ringleb, Heidelberg, Germany; Marie-Germaine Bousser, Paris, France; Gary Ford, Newcastle, UK; Philip Bath, Nottingham, UK; Michael Brainin, Krems,

Optimal management of vascular risk factors

Recommendations

- It is recommended that blood pressure be checked regularly. Blood pressure lowering is recommended after the acute phase, including in patients with normal blood pressure **(Class I, Level A)**
- It is recommended that blood glucose should be checked regularly. It is recommended that diabetes should be managed with lifestyle modification and individualized pharmacological therapy **(Class IV, GCP)**
- In patients with type 2 diabetes who do not need insulin, treatment with pioglitazone is recommended after stroke **(Class III, Level B)**
- Statin therapy is recommended in subjects with non-cardioembolic stroke **(Class I, Level A)**
- It is recommended that cigarette smoking be discouraged **(Class III, Level C)**

eso-stroke.org

The Effect of Pioglitazone on Recurrent Myocardial Infarction in 2,445 Patients With Type 2 Diabetes and Previous Myocardial Infarction

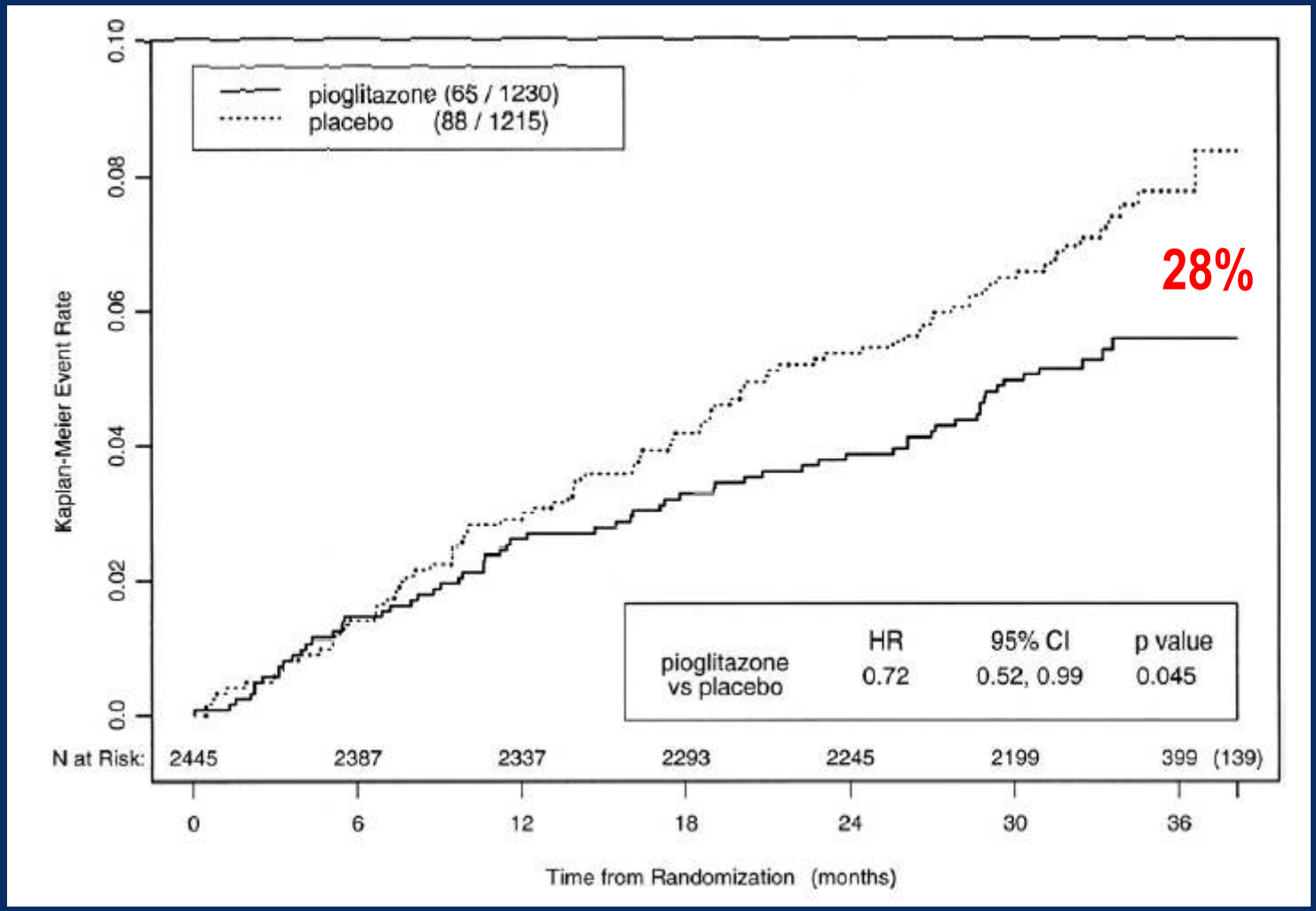
Results From the PROactive (PROactive 05) Study

Erland Erdmann, MD, FESC, FACC,* John A. Dormandy, FRCS, DSc,† Bernard Charbonnel, MD,‡ Massimo Massi-Benedetti, MD,§ Ian K. Moules, BSc (Hons),‖ Allan M. Skene, PhD,¶ on behalf of the PROactive Investigators

Journal of the American College of Cardiology Vol. 49. No. 17. 2007

In high-risk patients with type 2 diabetes and previous MI, pioglitazone significantly reduced the occurrence of recurrent fatal and nonfatal MI and ACS

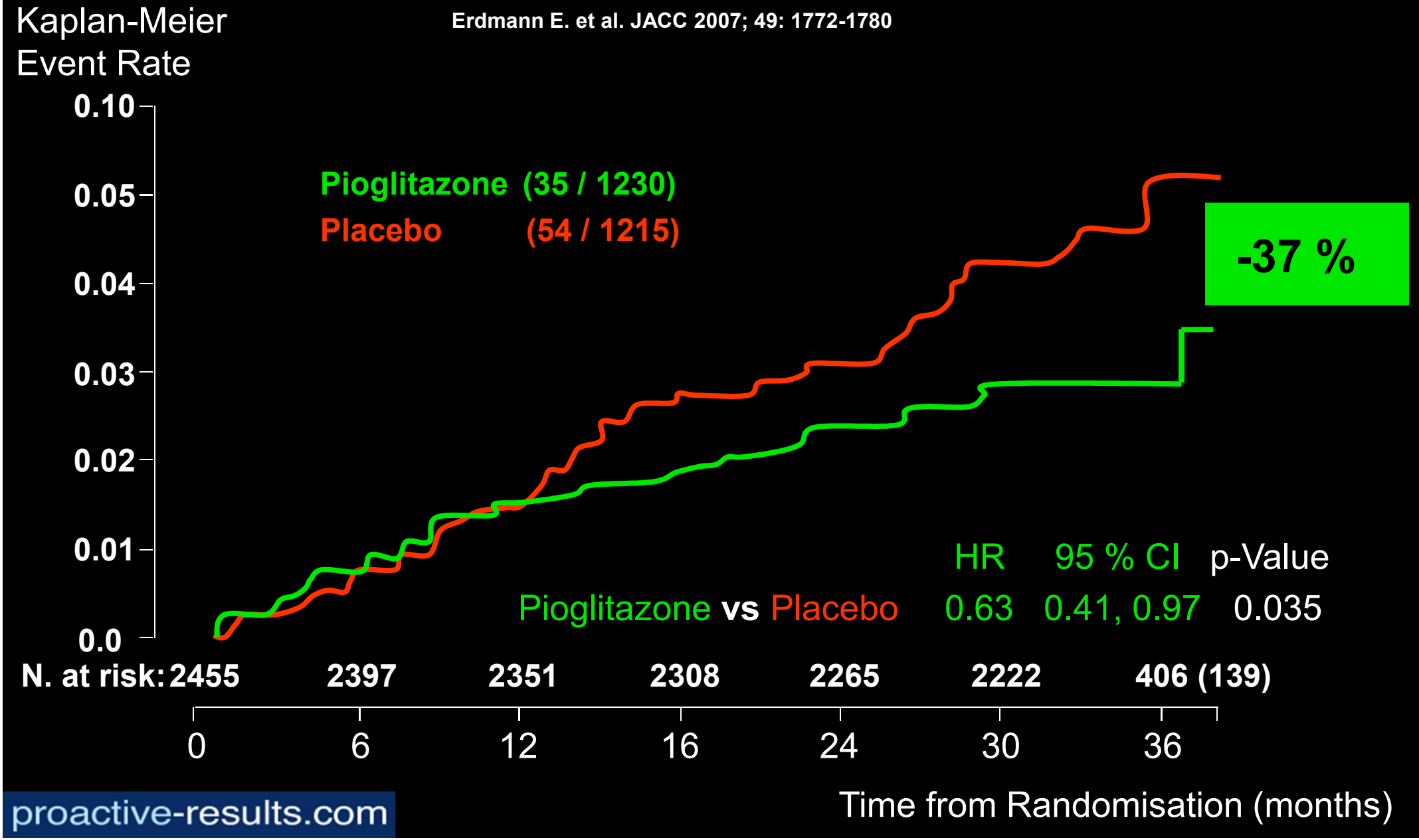
Time to Fatal/Non-fatal MI (Excluding Silent MI)



proactive-results.com

Pioglitazone's effect on Acute Coronary Syndrome in patients with previous MI

Erdmann E. et al. JACC 2007; 49: 1772-1780



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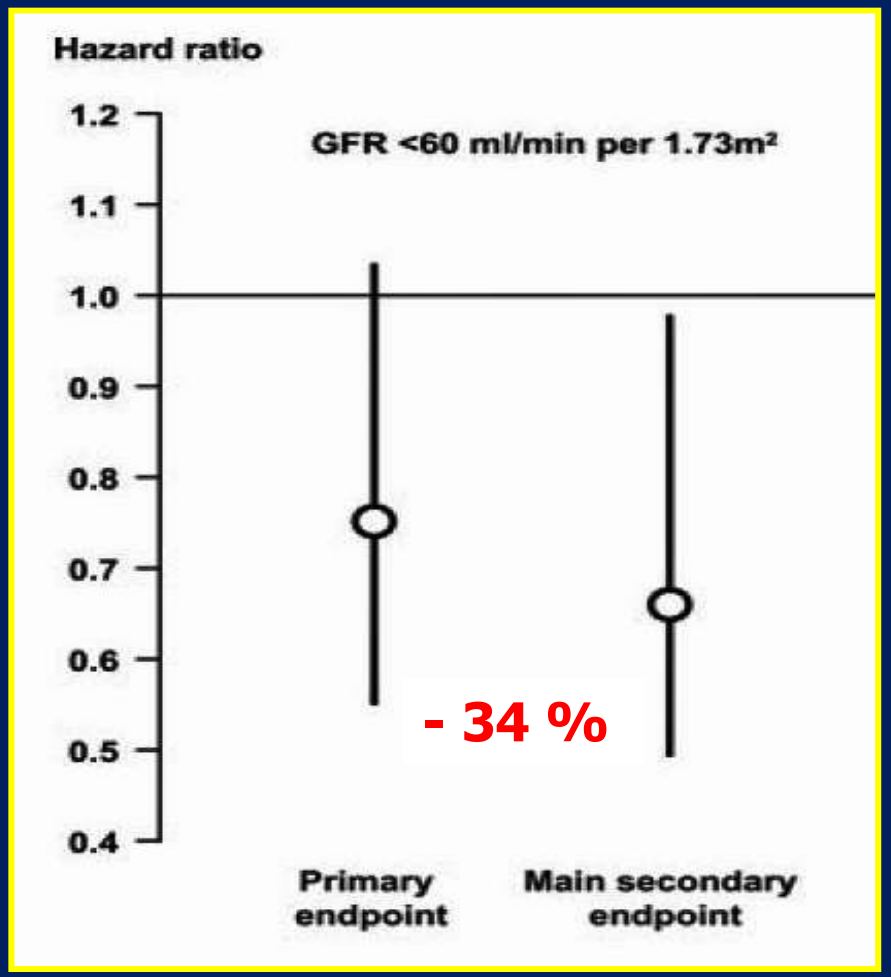
Effect of Pioglitazone on Cardiovascular Outcome in Diabetes and Chronic Kidney Disease

Christian A. Schneider, Ele Ferrannini, Ralph DeFronzo, Guntram Schernthaner, John Yates, and Erland Erdmann

Am Soc Nephrol 19: 182–187, 2008

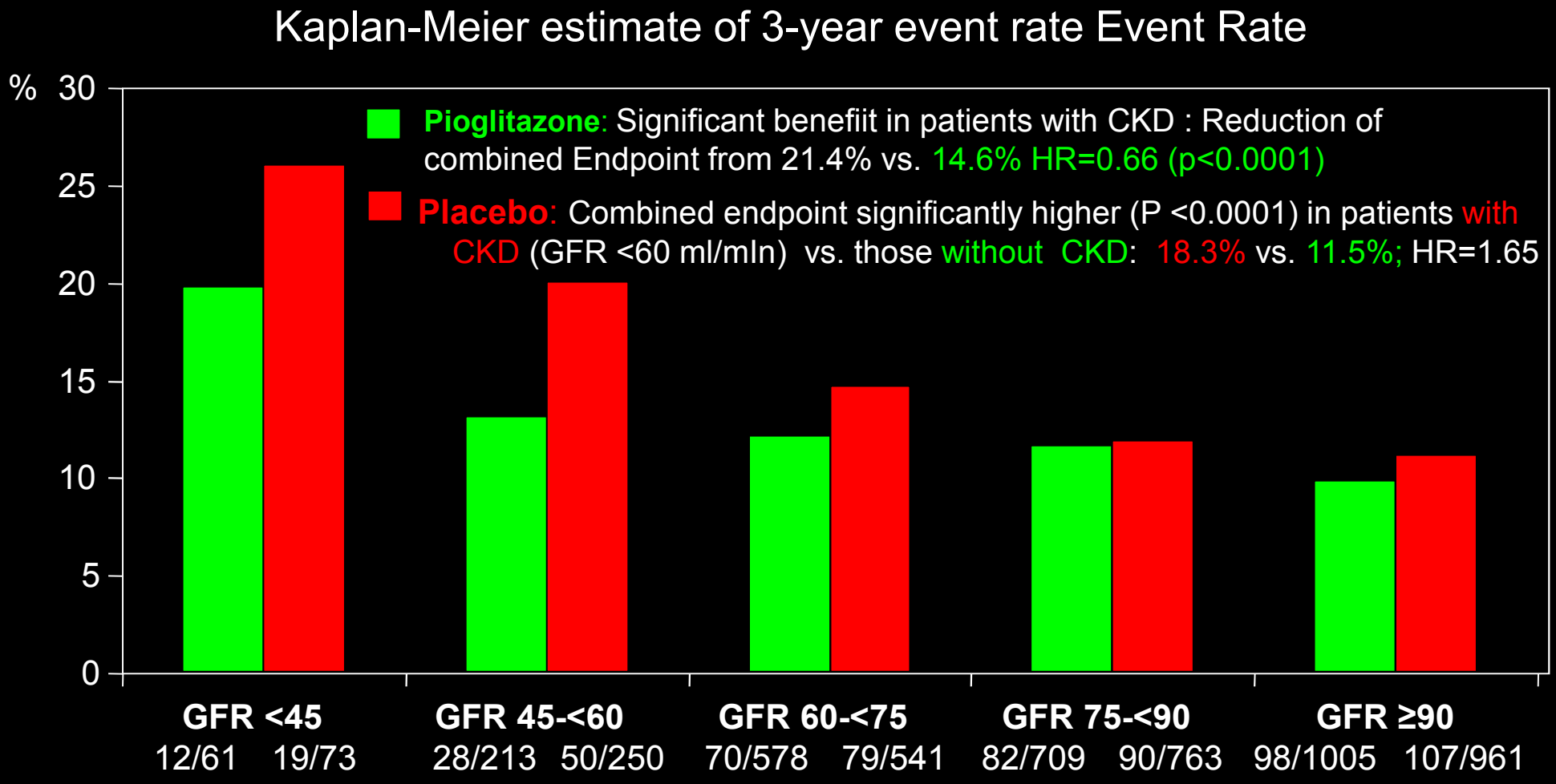


CKD patients treated with pioglitazone were less likely to reach the secondary end point (all-cause death, MI, and stroke) :

Hazard ratio 0.66
(95% confidence interval 0.45 to 0.98),

independent of the severity of renal impairment

Effect of Pioglitazone Treatment on the combined Endpoint of all-cause Mortality, Myocardial Infarction and Stroke in Patients with and without CKD (PROactive)

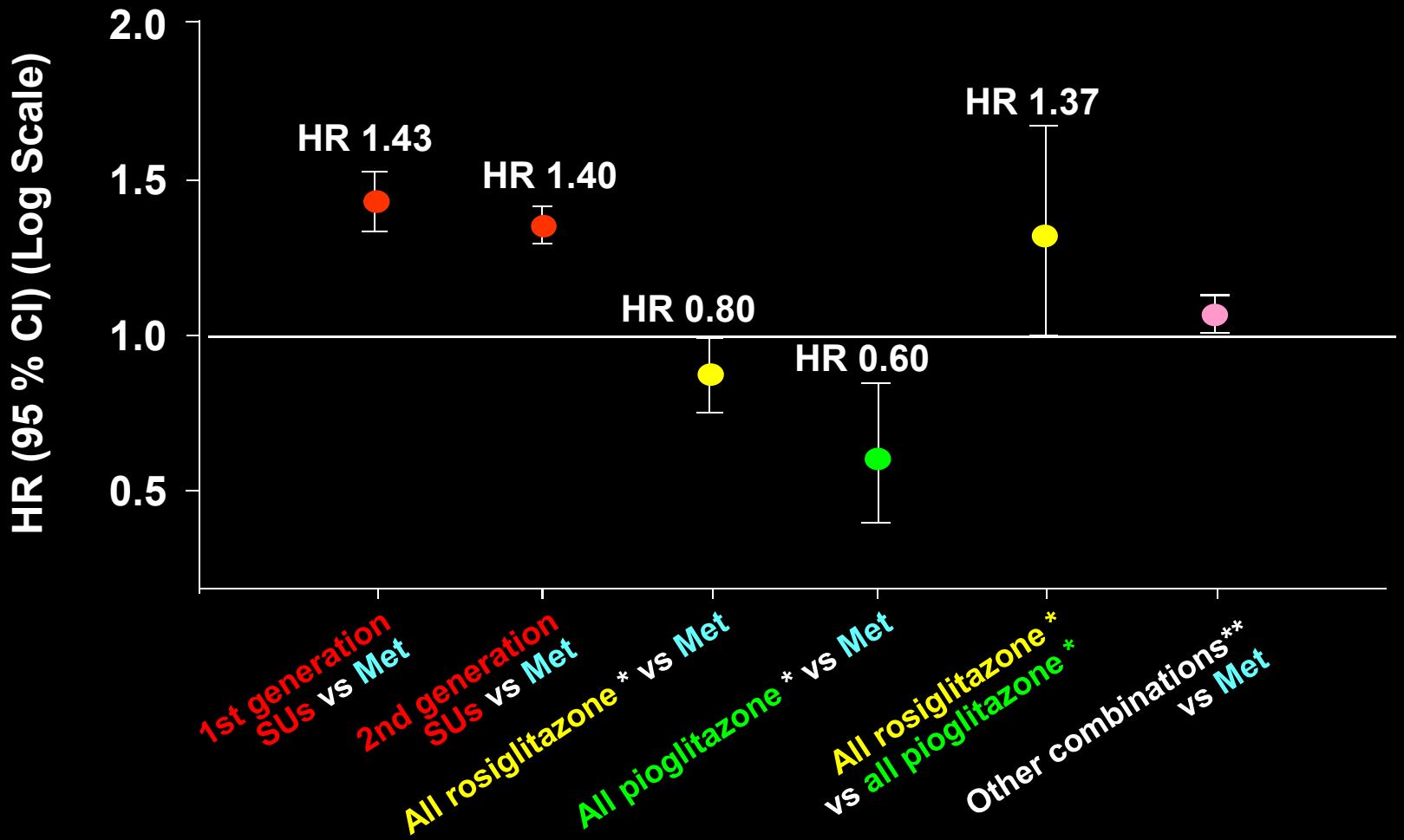


Schneider CA et al. JASN 2008; 19:182-187

Summary

Risk of All-cause Mortality for Different Comparisons of Drug Groups: Follow up of 91,521 Patients for 7.1 Years

(UK General Practice Research Database)

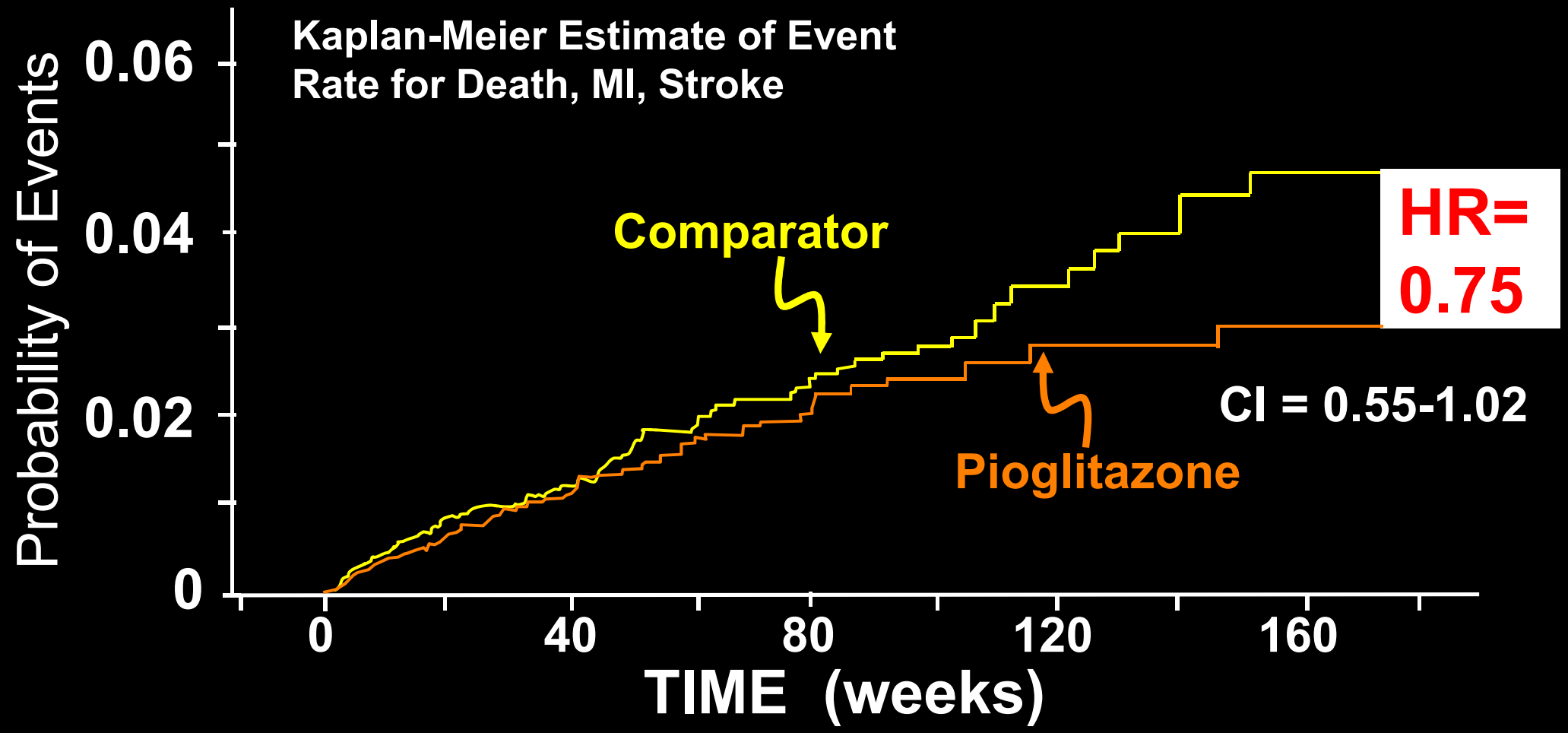


*Any therapy (monotherapy and combinations).
**Other drugs and combinations of any oral antidiabetes drugs excluding rosiglitazone and pioglitazone.

Tzoulaki I, et al. BMJ. 2009

CARDIOVASCULAR OUTCOMES FROM PIOGLITAZONE META-ANALYSIS OF CLINICAL TRIALS (excludes PROactive)

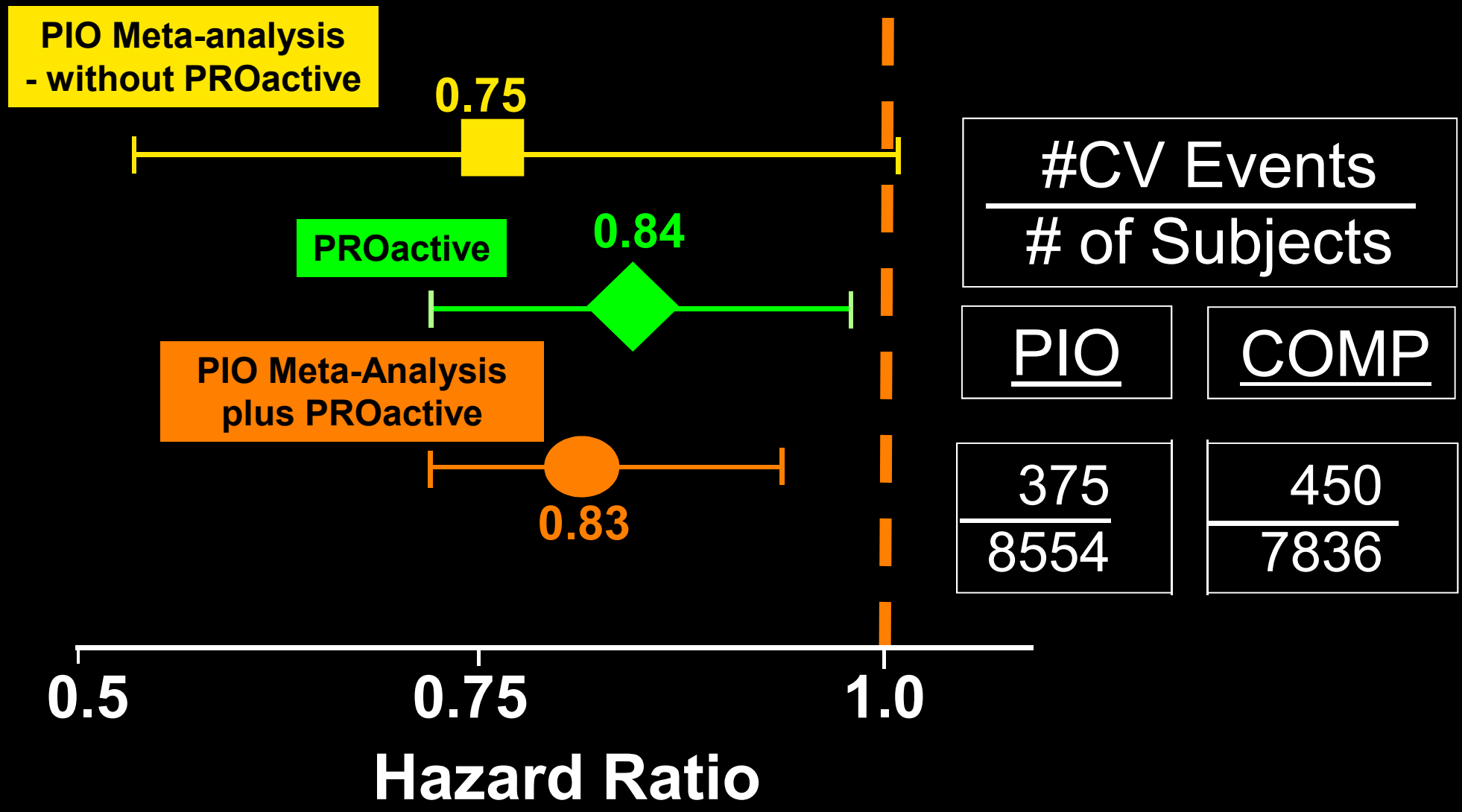
FDA and Center for Drug Evaluation & Research; July 30,2007



Comp	5203	2978	1297	488	34
Pio	5949	2859	1247	459	40

SUMMARY OF PIOGLITAZONE CLINICAL TRIALS

Center for Drug Evaluation & Research, July 30, 2007



Comparison of Recent Glycemia Trials
ACCORD, ADVANCE and VADT

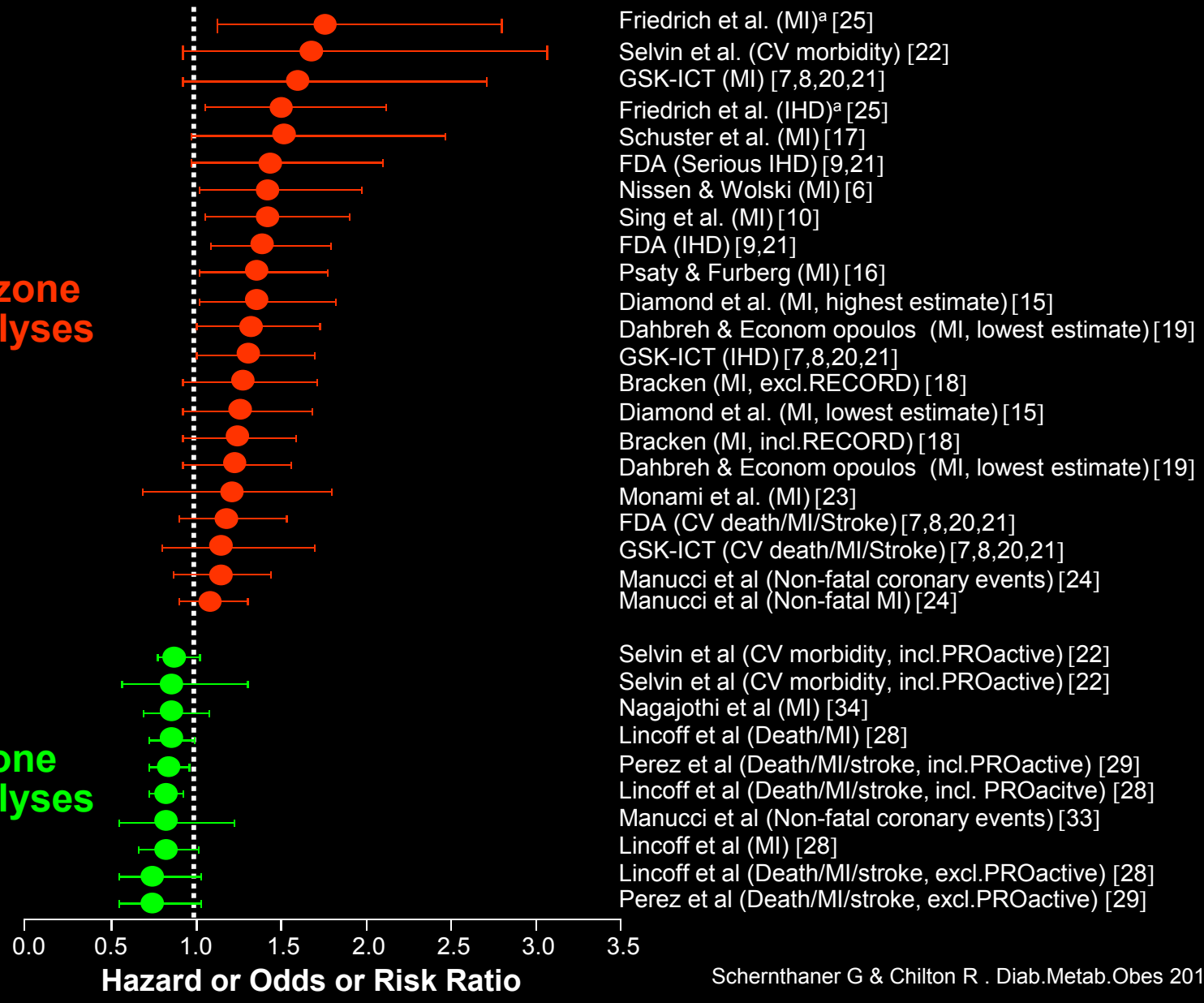
Characteristic	ACCORD	ADVANCE	VADT	PROactive
N	10,251	11,140	1,791	5,238
Mean Age	62	66	60.4	61.8
Duration of T2DM	10 yr	8 yr	11.5 yr	8 yr
History of CVD	35%	32%	40%	100%
BMI	32	28	31	31
Baseline A1C	8.3%	7.5%	9.4%	7.8%
A1C Achieved	**6.4% vs. 7.5%**	**6.5% vs. 7.3%**	**6.9% vs. 8.4%**	**7.0% vs. 7.6%**
RRR CVD Events	**0.90** (0.78 – 1.04)	**0.94** (0.84 – 1.06)	**0.88** (0.74 – 1.05)	**0.84** (0.72 – 0.98)
RRR Mortality	**1.22** (1.01 – 1.46)*	**0.93** (0.83 – 1.06)	**1.07** (0.80 – 1.42)	**0.96** (0.78 – 1.18)

ACCORD Study Group. *N Engl J Med* 2008;358:2545-59.
ADVANCE Collaborative Group. *N Engl J Med* 2008;358:2560-72.
Duckworth W *et al*. *N Engl J Med* 2009;360:129-39.
PROactive Dormandy JA, et al. *Lancet*. 2005; 366: 1279-1289

Multifactorial Effects of Pioglitazone

- Glycemic Control: in monotherapy and combination therapy reduction and maintenance of HbA1c control (for up to 3.5 years), with low risk of hypoglycaemia
- Lipid Metabolism: improved parameters of diabetic dyslipidaemia
- CV effects: completed CV outcomes trials and other studies consistently show no evidence of increased macrovascular events

Risk of MI, IHD or a composite of major Macrovascular Events from Meta-analyses of Trials with Rosiglitazone or Pioglitazone versus Comparators



Schernthaner G & Chilton R . Diab.Metab.Obes 2010; 12: 1023–1035