“Writing’s on the wall”, Sam Smith:

Diabetes medications with cardiovascular protection in the wake of EMPA-REG OUTCOME: the optimal combination may be metformin, pioglitazone and empagliflozin (and liraglutide?)

Dr Bob Ryder, City Hospital, Birmingham

ABCD Autumn meeting, Manchester

April 22, 2016

Disclusures

- None related to this presentation

Rehabilitation of pioglitazone

ROBERT EJ RYDER,[1] RALPH A DEFRONZO[2]

Background

In 2012 an editorial in the British Medical Journal stated that "it can confidently be assumed that pioglitazone increases the risk of bladder cancer".[1] Yet now, the recently announced results of a 10-year study mandated by the FDA have failed to demonstrate any association between pioglitazone and bladder cancer[2] and, because of its many beneficial effects on glucose homeostasis and potential cardiovascular protective effects, the place of pioglitazone in the treatment of diabetes warrants reconsideration.

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Abbreviations and acronyms

CHF	congestive heart failure
FDA	US Food and Drug Administration
GLP-1	glucagon like peptide
HbA_{1c}	glycated haemoglobin
MACE	major adverse cardiac events
PROactive	PROspective pioglitAzone Clinical Trial In macroVascular Events study

New perspectives

It is timely to reconsider the place of pioglitazone in our therapeutic armamentarium for diabetes. With the cloud of bladder cancer risk removed, it is our opinion that pioglitazone is being under-utilised.[7,11] It is the only diabetes agent with evidence to suggest that it reduces cardiovascular risk apart from metformin.[7,10,11,14] Indeed, there is considerable evidence for a cardioprotective effect of pioglitazone.[10] This evidence is particularly strong with regard to reducing risk in those who already have coronary artery[15] or cerebrovascular[16] disease, or those with renal impairment.[17] This is especially pertinent since type 2 diabetic patients have a 2–3 fold increase in cardiovascular events.

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http://dx.doi.org/10.15277/bjdvd.2015.021

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Pioglitazone use and risk of bladder cancer: population based cohort study

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Accepted: 29 February 2016

ABSTRACT

OBJECTIVE

To determine whether pioglitazone compared with other antidiabetic drugs is associated with an increased risk of bladder cancer in people with type 2 diabetes.

DESIGN

Population based cohort study.

SETTING

General practices contributing data to the United Kingdom Clinical Practice Research Datalink.

PARTICIPANTS

A cohort of 145 806 patients newly treated with antidiabetic drugs between 1 January 2000 and 31 July 2013, with follow-up until 31 July 2014.

MAIN OUTCOME MEASURES

The use of pioglitazone was treated as a time varying variable, with use lagged by one year for latency purposes. Cox proportional hazards models were used to estimate adjusted hazard ratios with 95% confidence intervals of incident bladder cancer associated with pioglitazone overall and by both cumulative duration of use and cumulative dose. Similar analyses were conducted for rosiglitazone, a thiazolidinedione not previously associated with an increased risk of bladder cancer.

RESULTS

The cohort generated 689 616 person years of follow-up, during which 622 patients were newly diagnosed as having bladder cancer (crude incidence 90.2 per 100 000 person years). Compared with other antidiabetic drugs, pioglitazone was associated with an increased risk of bladder cancer (121.0 *v* 88.9 per 100 000 person years; hazard ratio 1.63, 95% confidence interval 1.22 to 2.19). Conversely, rosiglitazone was not associated with an increased risk of bladder cancer (86.2 *v* 88.9 per 100 000 person years; 1.10, 0.83 to 1.47). Duration-response and dose-response relations were observed for pioglitazone but not for rosiglitazone.

CONCLUSION

The results of this large population based study indicate that pioglitazone is associated with an increased risk of bladder cancer. The absence of an association with rosiglitazone suggests that the increased risk is drug specific and not a class effect.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The association between the use of pioglitazone and bladder cancer is controversial, with studies reporting contradictory findings

Additional observational studies with longer follow-up are needed to assess whether this drug is associated with an increased risk of bladder cancer

WHAT THIS STUDY ADDS

In this large population based study, the use of pioglitazone was associated with an overall 63% increased risk of bladder cancer, with the risk increasing with increasing duration of use and dose

In contrast, the use of rosiglitazone was not associated with an increased risk, with no evidence of a duration-response or dose-response relation

These findings suggest that the association observed with pioglitazone is likely to be a drug specific and not a class effect

Introduction

Pioglitazone, an antidiabetic drug belonging to the thiazolidinedione class, has been shown to improve glycaemic levels in people with type 2 diabetes.[1] However, in 2005 the PROactive randomised controlled trial unexpectedly showed an imbalance in the number of cases of bladder cancer with pioglitazone compared with placebo.[2] In contrast, this imbalance was never observed in randomised controlled trials of rosiglitazone, the other approved drug belonging to the thiazolidinedione class.[3]

The findings of the PROactive trial were subsequently corroborated in some,[4-10] but not all, observational studies.[11-19] Indeed, in the five year interim analysis of a large observational study using the Kaiser Permanente Northern California database,[4] the use of pioglitazone for 24 months or more was associated with an increased risk of bladder cancer (hazard ratio 1.4, 95% confidence interval 1.03 to 2.0). However, in the final analysis of the Kaiser Permanente Northern California study, which used the same cohort[4] with follow-up extended to 10 years, the use of pioglitazone was no longer significantly associated with an increased risk of bladder cancer in a duration-response fashion.[20] These null findings are also consistent with those of another large multicohort study.[19] The apparent heterogeneity in this literature may be due to methodological limitations, such as the inclusion of prevalent users,[5,6,10,16,18] time lag bias,[15] immortal time bias,[20,15,18] and no consideration of disease latency.[8,10,12,17,18]

Given these discrepant findings, the methodological shortcoming of previous studies examining this association, and the apparent loss of an association in studies with longer follow-up,[20] additional studies are needed to investigate further the association between pioglitazone and bladder cancer. In a large, population based study we assessed the association between the use of pioglitazone and bladder cancer in people with type 2 diabetes.

Methods

Data source

This study was conducted using the United Kingdom Clinical Practice Research Datalink (CPRD). This

EDITORIAL

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RESEARCH

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[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, Quebec, Canada
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ABSTRACT

OBJECTIVE

To determine whether pioglitazone compared with other antidiabetic drugs is associated with an increased risk of bladder cancer in people with type 2 diabetes.

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"Writing's On The Wall"

I've been here before
But always hit the floor
I've spent a lifetime running
And I always get away
But with you I'm feeling something
That makes me want to stay

WHAT IS ALREADY KNOWN ON THIS TOPIC

The association between the use of pioglitazone and bladder cancer is controversial, with studies reporting contradictory findings

Additional observational studies with longer follow-up are needed to assess whether this drug is associated with an increased risk of bladder cancer

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Methods

Data source

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Controversies in Diabetes

Pioglitazone has a dubious bladder cancer risk but an undoubted cardiovascular benefit

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Accepted 3 November 2014

Abstract

On 8 April 2014, a US jury ordered Takeda and Eli Lilly to pay $9 bn in punitive damages after finding that they had concealed the cancer risks associated with pioglitazone. By contrast, on 28 August 2014, the long-awaited outcome of the 10-year Kaiser Permanente Northern California study was announced. That study was specifically designed to investigate whether patients exposed to pioglitazone were at an increased risk of bladder cancer and found no association; thus, at last, the controversial issue has been resolved. A review, in retrospect, of the story of the proposed link between pioglitazone and bladder cancer reveals flaws at every stage. In 2012, a *BMJ* editorial, in keeping with some other contemporary reports, stated 'it can confidently be assumed that pioglitazone increases the risk of bladder cancer'. Examination of the information which led to such a statement shows that: 1) the pre-clinical findings of bladder cancer in male rats is not indicative of human risk; 2) there is no association between bladder cancer and pioglitazone in randomized controlled trials, once cases that could not plausibly be related to treatment are removed; and 3) the observational studies that have suggested a link have over-extrapolated from the data: pioglitazone-treated patients had more risk factors for bladder cancer than those not treated with pioglitazone. Meanwhile careful study of randomized controlled trials shows evidence of cardiovascular benefit from pioglitazone in Type 2 diabetes, a condition which results, more than anything, in premature cardiovascular death and morbidity.

Diabet. Med. 32, 305–313 (2015)

Introduction

The year 2014 has seen two noteworthy events in the unfolding story of pioglitazone. On 8 April 2014, a US jury ordered the pharmaceutical companies Takeda and Eli Lilly to pay a combined $9 bn in punitive damages after finding that the companies had concealed cancer risks associated with pioglitazone. The jury also awarded compensatory damages to the plaintiff of nearly $1.5 million in the first federal lawsuit related to the drug to go to trial [1]. By contrast on 29 August 2014, the long-awaited outcome of the 10-year epidemiology study, conducted by the University of Pennsylvania and Division of Research at Kaiser Permanente Northern California (KPNC), was announced [2]. The KPNC study was undertaken at the request of the US Food and Drug Administration (FDA) as a safety study involving 193 099 patients and designed to assess whether therapy with pioglitazone increases the risk of bladder cancer [3]. The primary analysis found no association between the use of pioglitazone and the risk of bladder cancer [2]. Additionally, no association was found between the risk of bladder cancer and the duration of pioglitazone use, increased cumulative dose of pioglitazone or the time since initiating pioglitazone [2]; thus, at last, the controversial issue of whether there is a link between pioglitazone and bladder cancer has been resolved.

This is, therefore, an opportune moment to revisit the story of the proposed link between pioglitazone and bladder cancer and review, in retrospect, the flaws in the case at every stage. In the medical literature the case against pioglitazone reached its zenith when in 2012 Azoulay *et al.* [4] concluded from their observational study, published in the *BMJ*, that pioglitazone was associated with an increased risk of bladder cancer. In a *BMJ* editorial in the same issue [5], it was concluded that 'Taking into account Azoulay and colleagues' current findings and given the consistency of these results, the relative strength of the association, the dose-response effect, the known pharmacodynamic characteristics of pioglitazone, and evidence of a significant association in a meta-analysis of randomized trials it can confidently be assumed that pioglitazone increases the risk of bladder cancer. …Considering that the benefit of pioglitazone in reducing cardiovascular events is questionable, prescribers who are ultimately responsible for therapeutic choices can legitimately question

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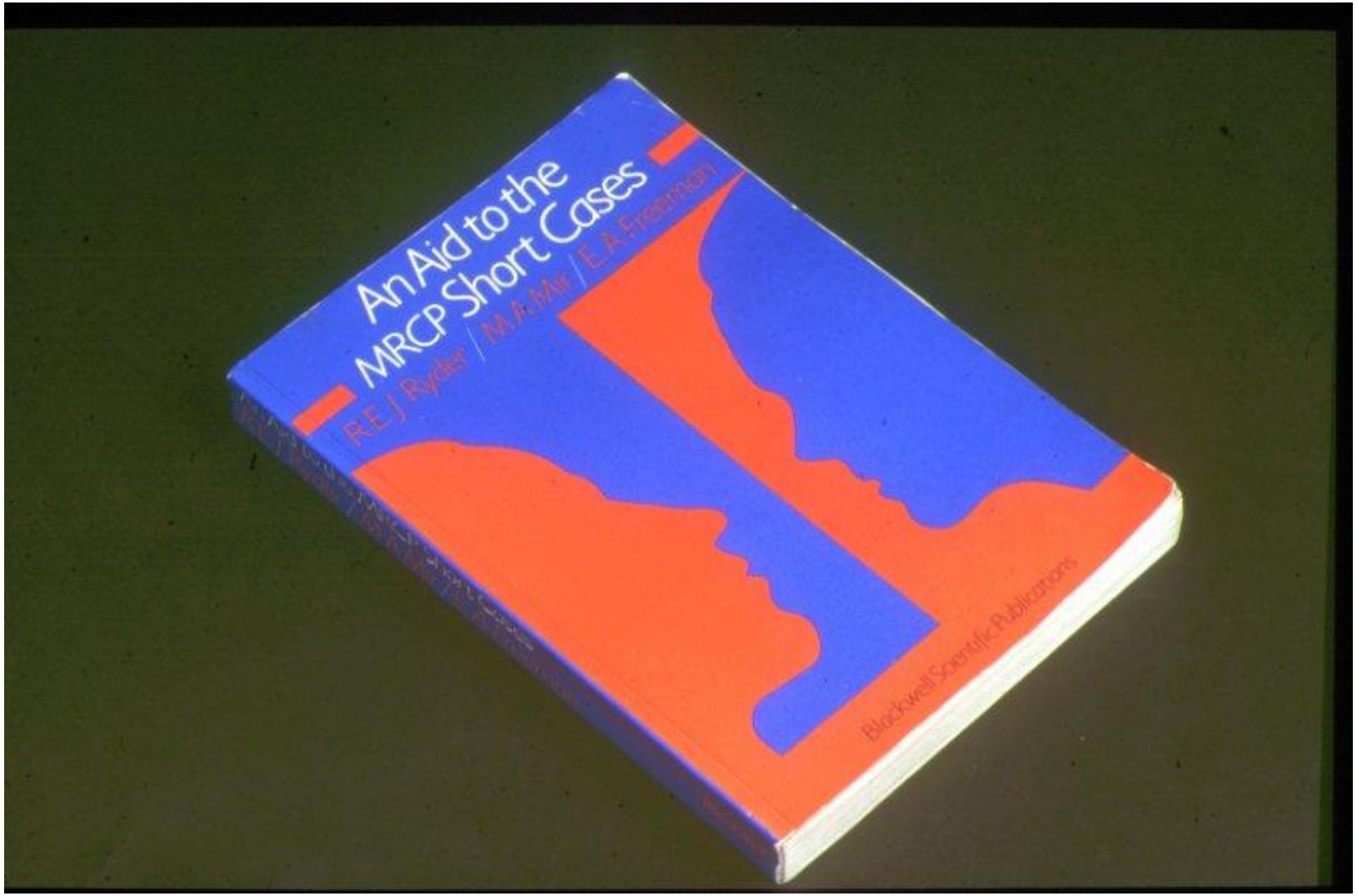
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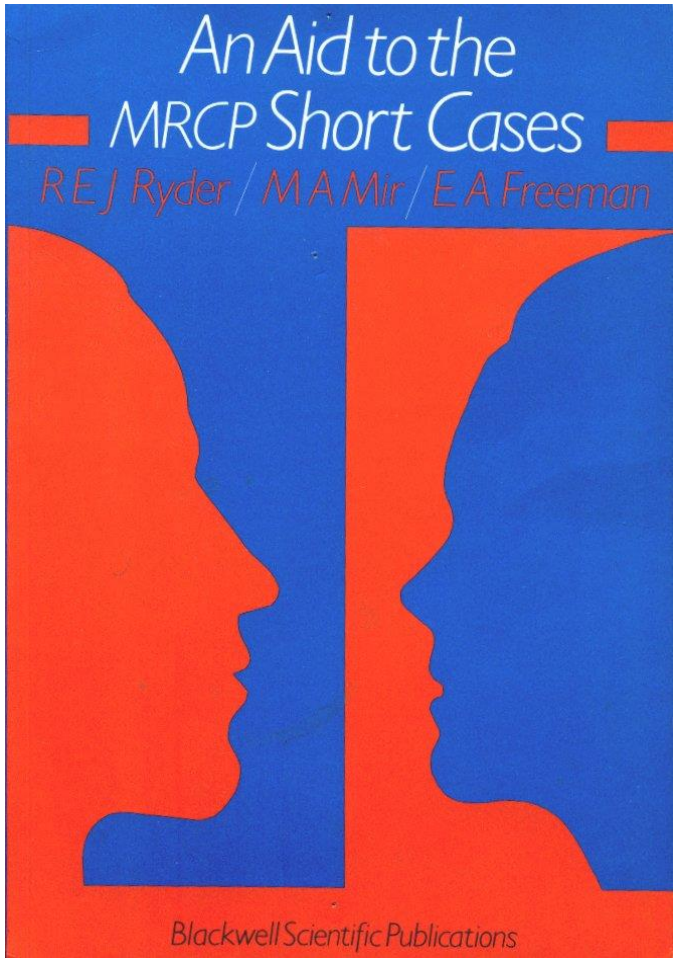
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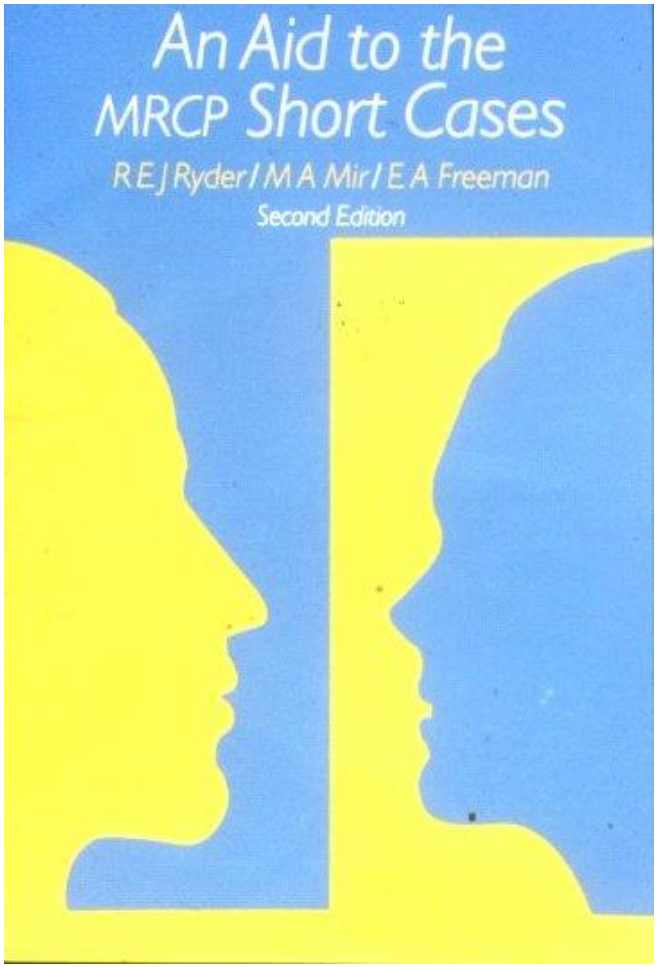
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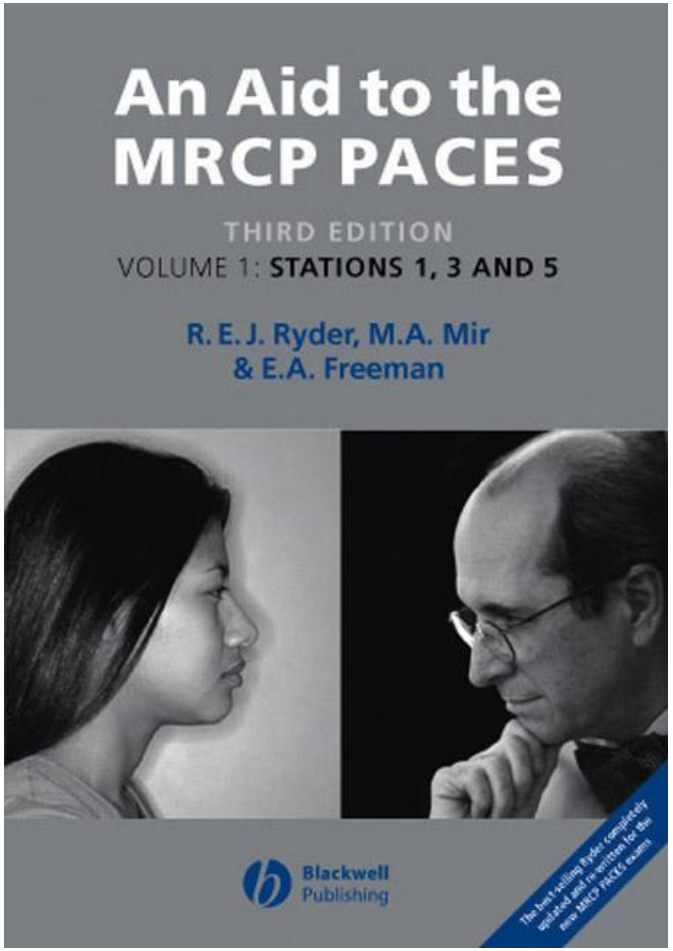
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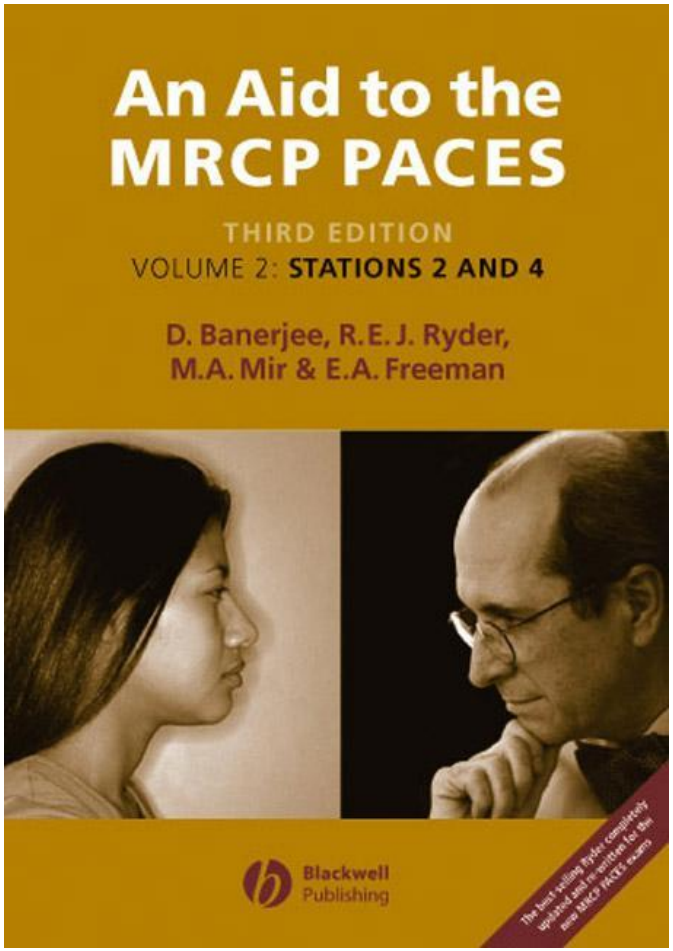
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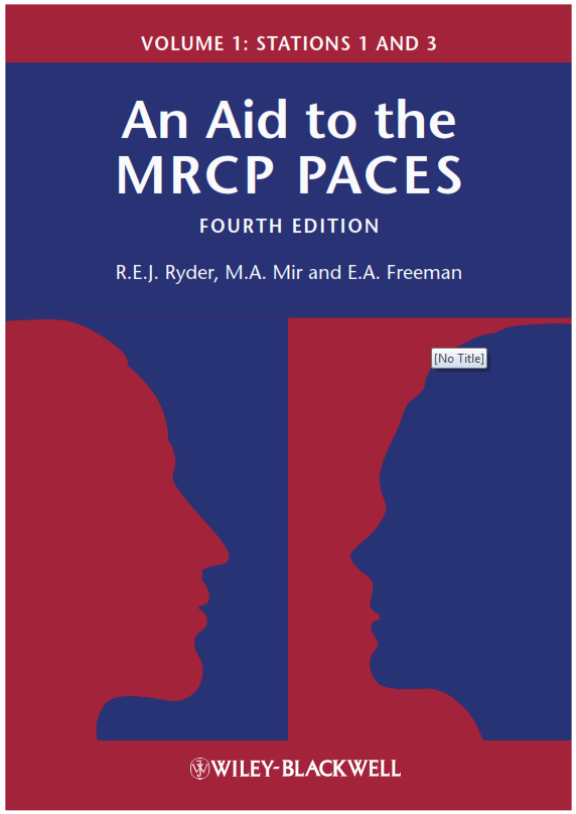
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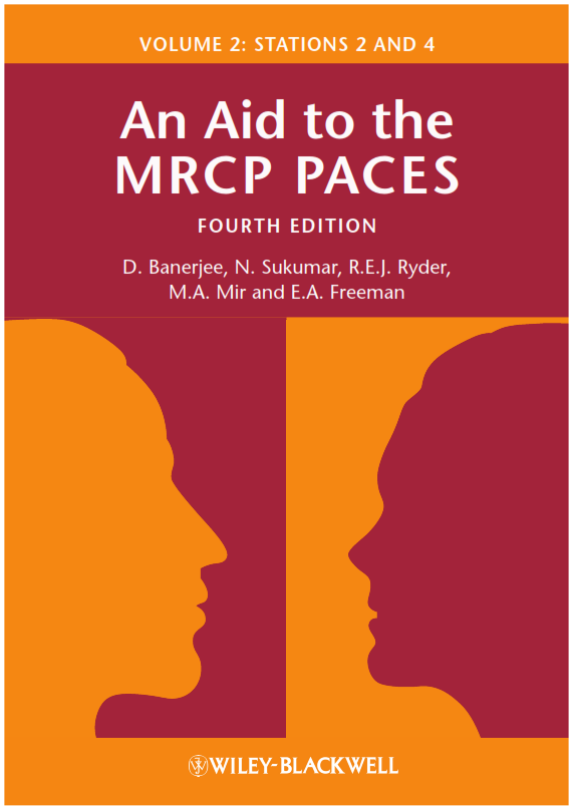
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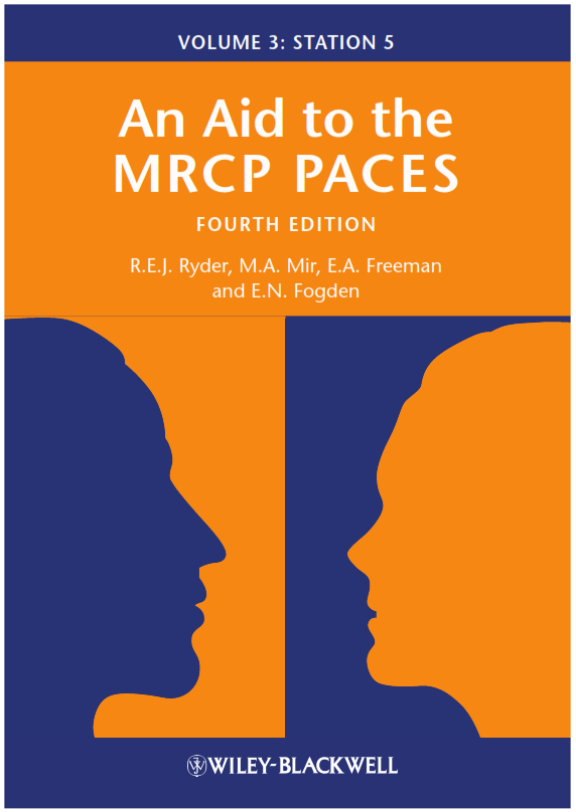
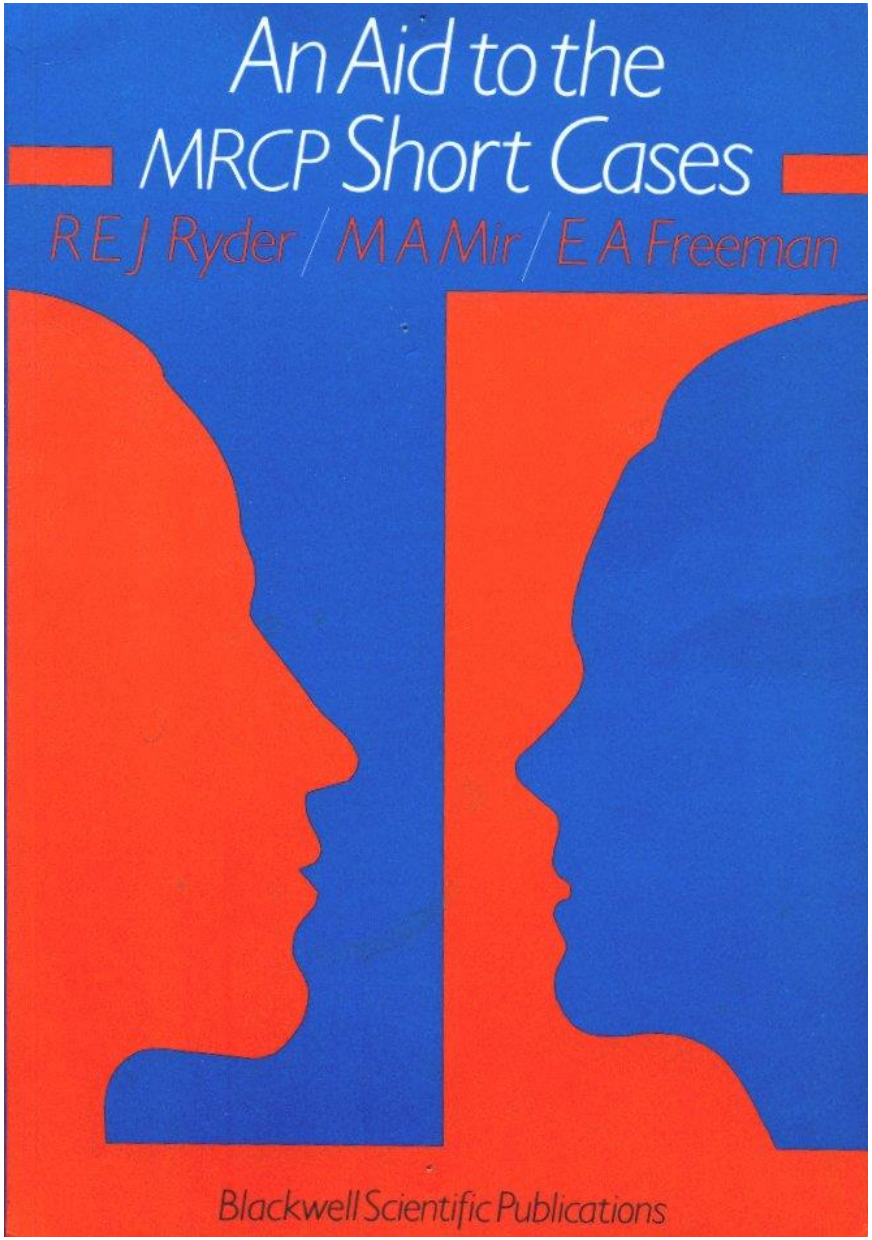

VOLUME 3: STATION 5
An Aid to the MRCP PACES
FOURTH EDITION
R.E.J. Ryder, M.A. Mir, E.A. Freeman and E.N. Fogden
WILEY-BLACKWELL

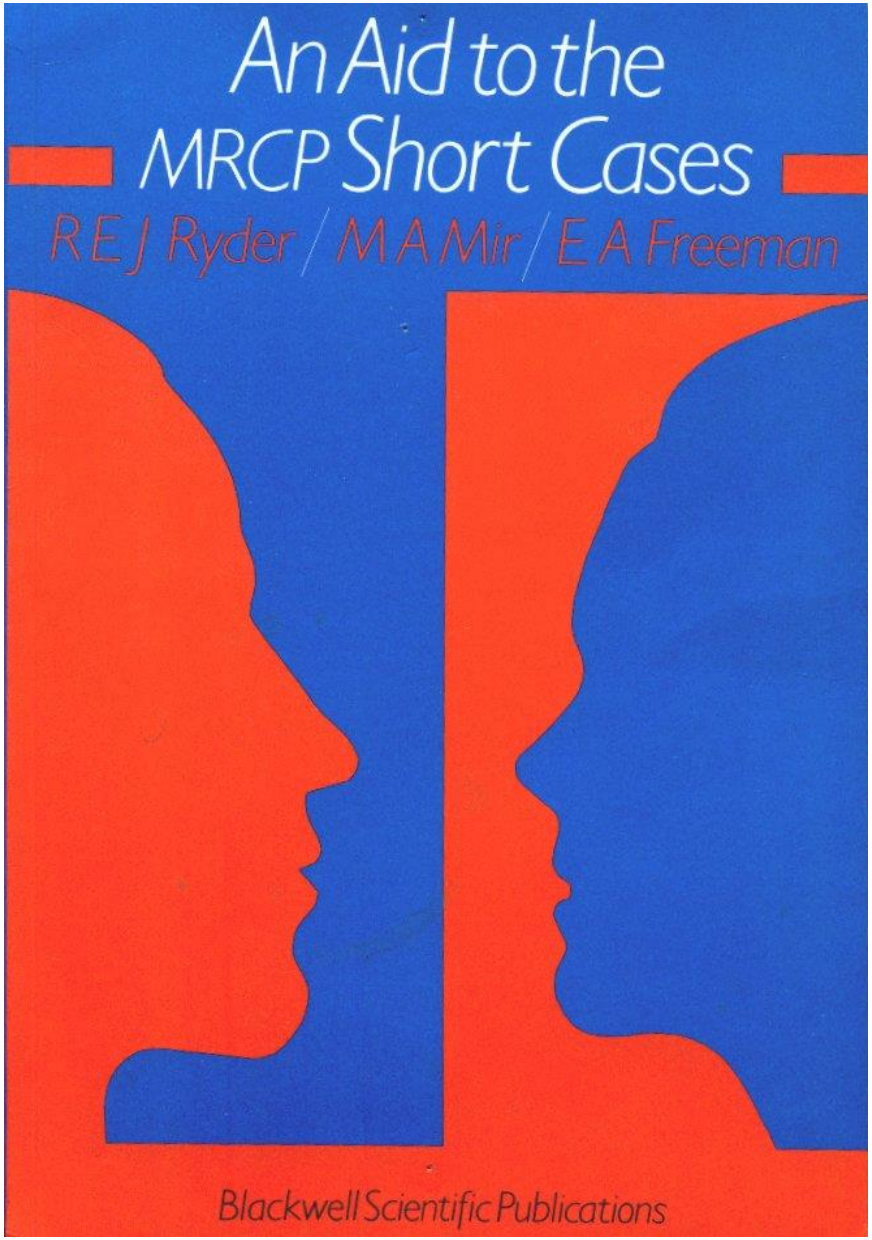
2012-2013



Section 4
Experiences, Anecdotes, Tips, Facts and Figures, Quotations

*'I know 'cos I was there'**

*MAX BOYCE



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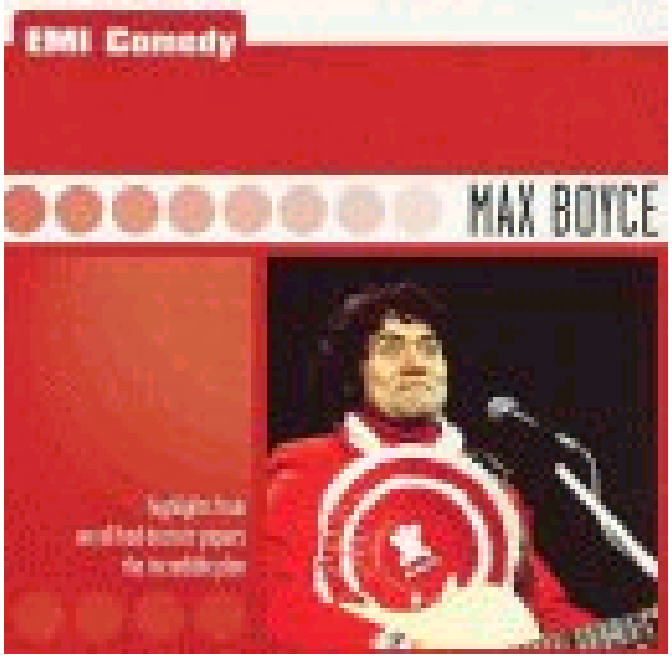

*MAX BOYCE

*"I know coz I was there!"**

- DCCT, Las Vegas, 1993
- UKPDS, Barcelona, 1998
- PROactive, Athens, 2005

*Max Boyce

I know coz I was there!

- DCCT, Las Vegas, 1993
- UKPDS, Barcelona, 1998
- PROactive, Athens, 2005
- EMPA-REG, Stockholm 2015

*Max Boyce

WHO Definition of Diabetes Mellitus

- ‘Diabetes mellitus is a state of chronic hyperglycaemia which may result from many environmental and genetic factors, often acting jointly’

WHO Expert Committee on Diabetes Mellitus 1980

WHO Definition of Diabetes Mellitus

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Re-definition of diabetes

- Diabetes is a state of premature cardiovascular death which is associated with chronic hyperglycaemia and may also be associated with blindness and renal failure

Miles Fisher Dublin 1996

Re-definition of diabetes

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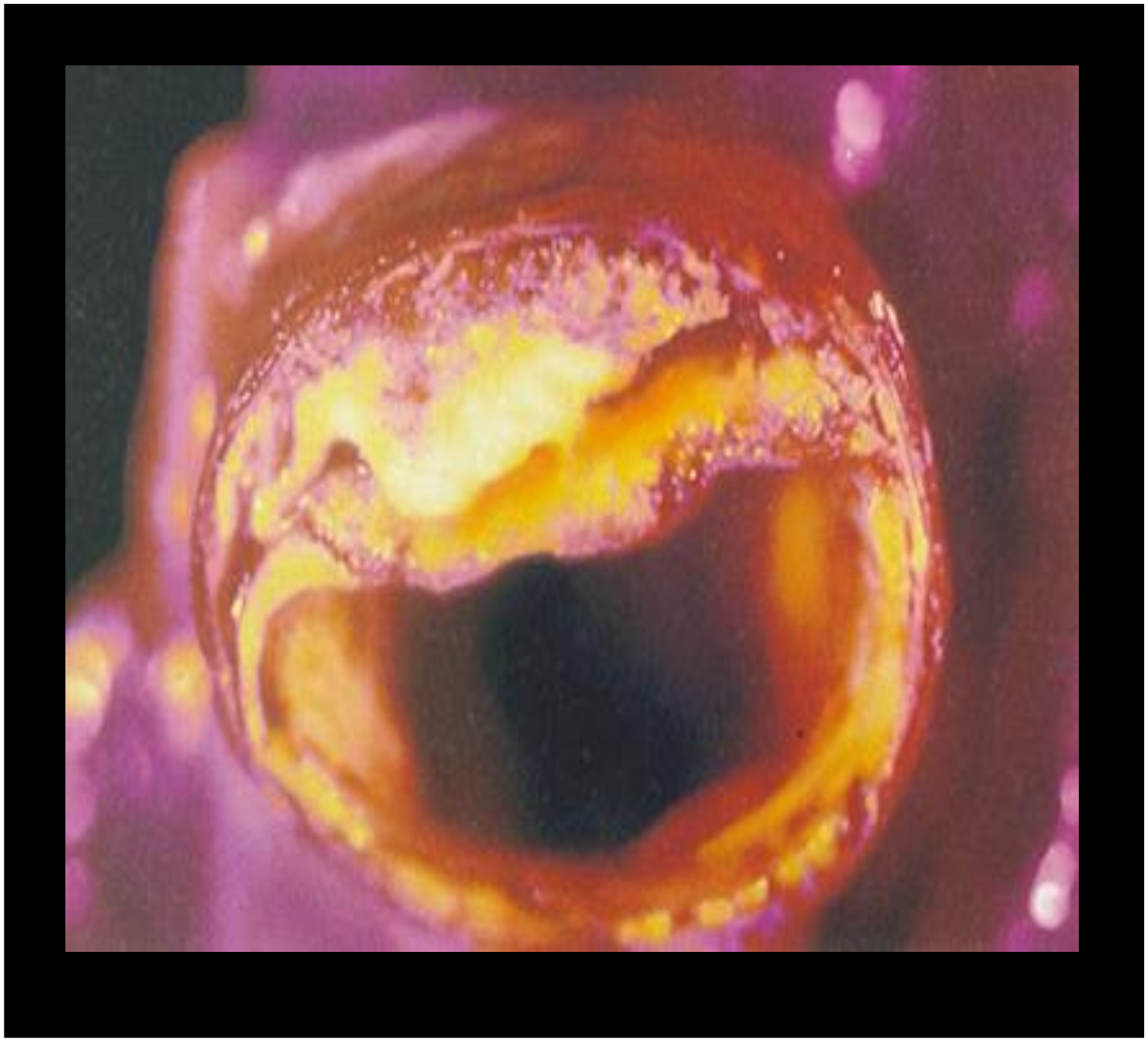
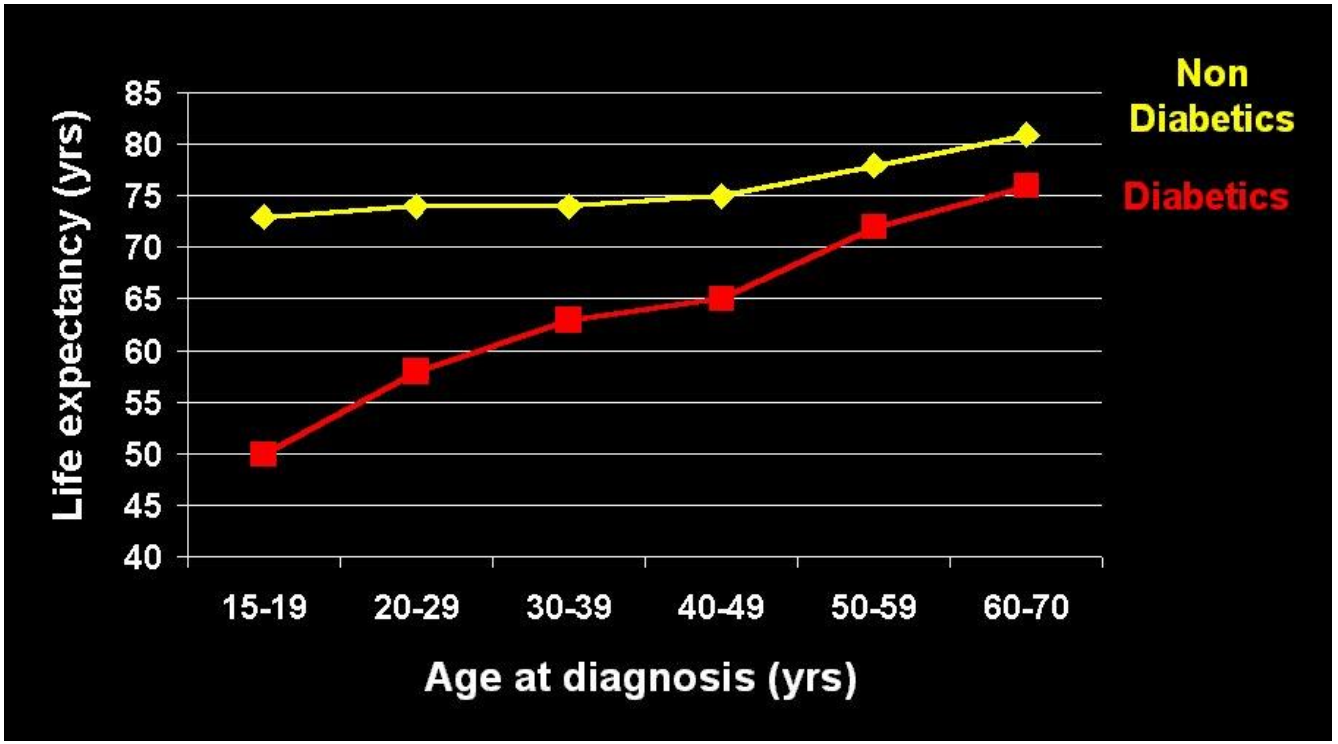
Miles Fisher Dublin 1996

Diabetes and Macrovascular Disease



Life Expectancy and Diabetes

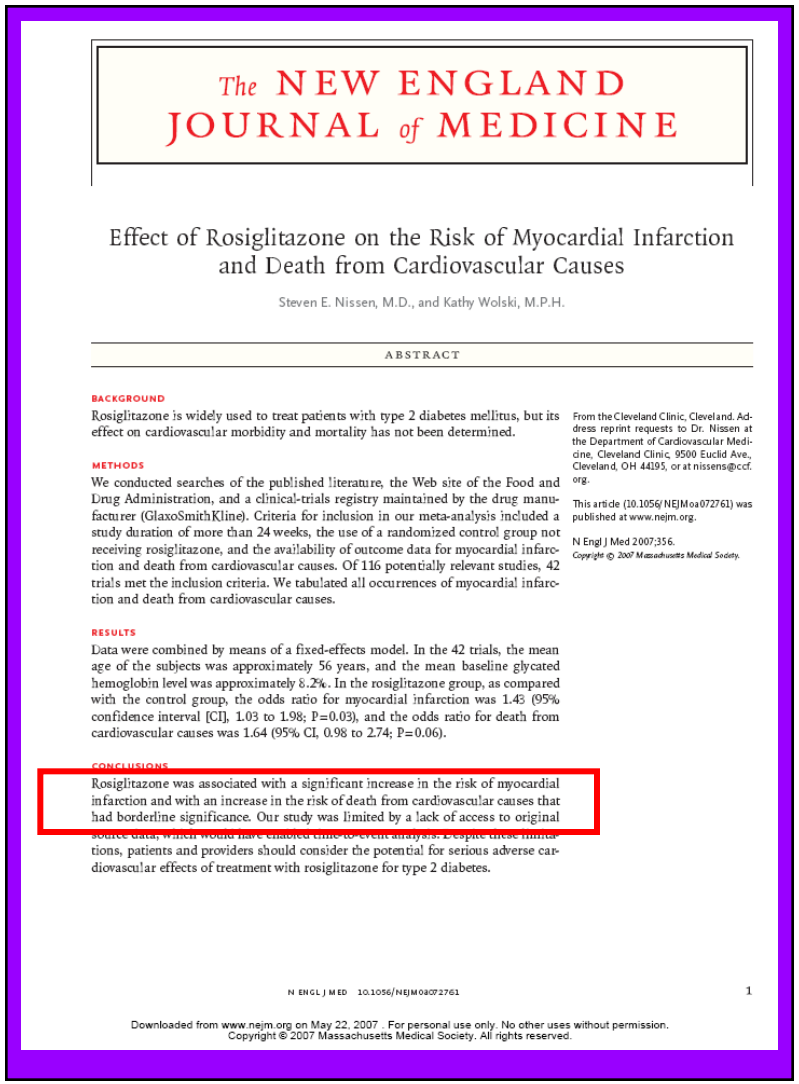


- 'Adults with diabetes have an annual mortality of about 5.4%, double the rate for non-diabetic adults. Life expectancy is decreased by 5–10 years.'

Goodkin G. Journal of Occupational Medicine 1975;17(11): 716–721.
Donnelly R, et al. British Medical Journal 2000; 320: 1062–1066.

Metanalysis

Rosiglitazone – cardiovascular harm



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.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

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).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analyses. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

This article (10.1056/NEJMoa072761) was published at www.nejm.org.

N Engl J Med 2007;356.

2007

July 2008 Advisory Committee Meeting

- Discussed pre- and post-approval cardiovascular assessment for therapies for type 2 diabetes
- Presentations by experts in endocrinology and cardiology
- Panel included endocrinologists, diabetologists, cardiologists, statisticians, drug safety experts

Transcript at www.fda.gov/ohrms/dockets/ac/cder08.html#EndocrinologicMetabolic

Diabetes Cardiovascular Guidance: Specific Recommendations

- **For new clinical studies in the planning stage:**
  - Establish an independent CV endpoints committee for prospective adjudication of all Phase 2 and 3 trials
  - Events of interest should include CV death, MI, and stroke
  - Can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints
  - Patient population should include those at higher risk for a CV event (longer duration of DM, elderly, renal impairment)
  - Studies are designed and conducted such that a MA can be performed
  - Protocol describing statistical methods for the proposed MA should be submitted

CV Outcome studies - 3 point MACE

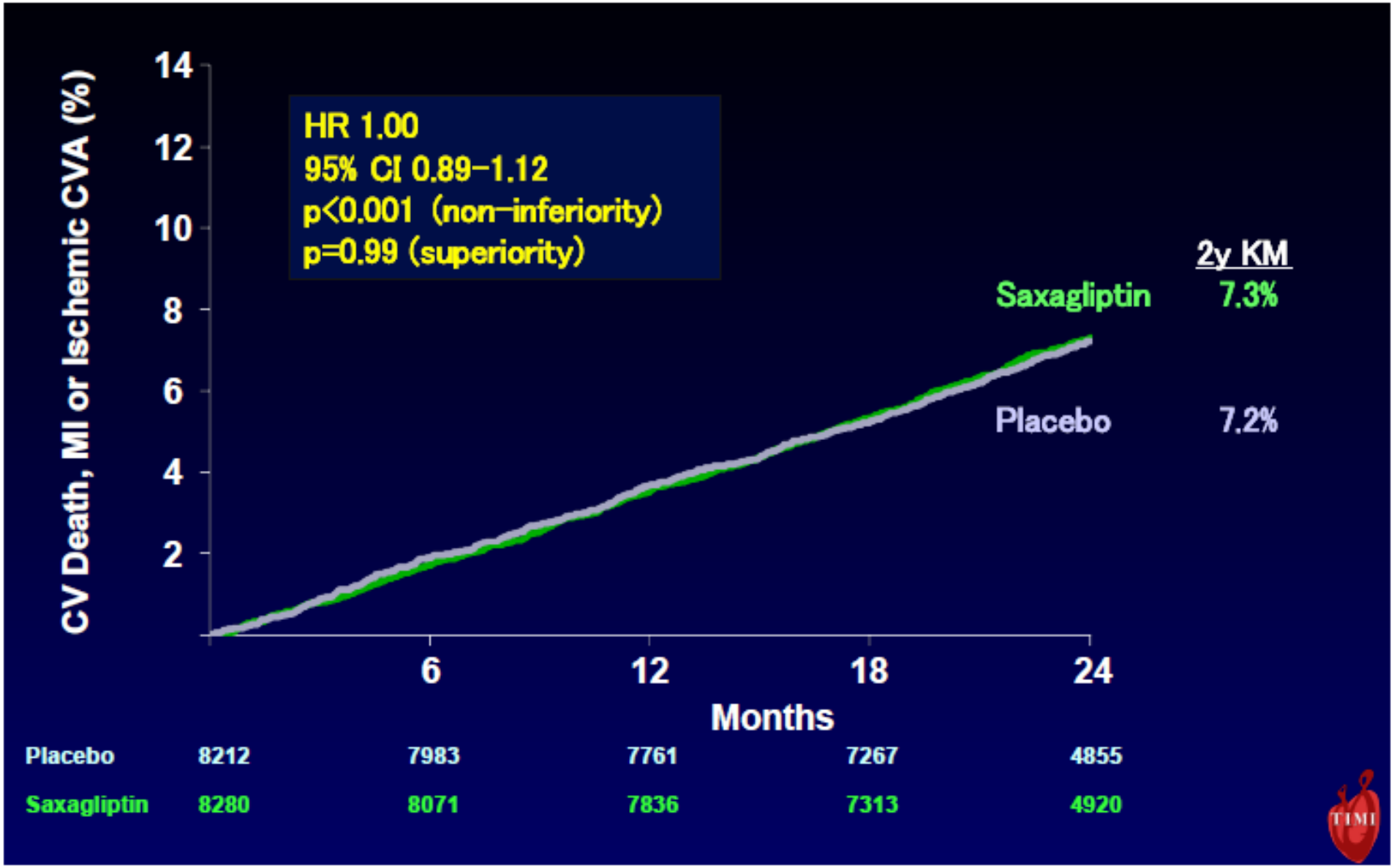
- Death
- Myocardial infarction
- Stroke

MACE = Major Adverse Cardiovascular event

Cardiovascular safety studies

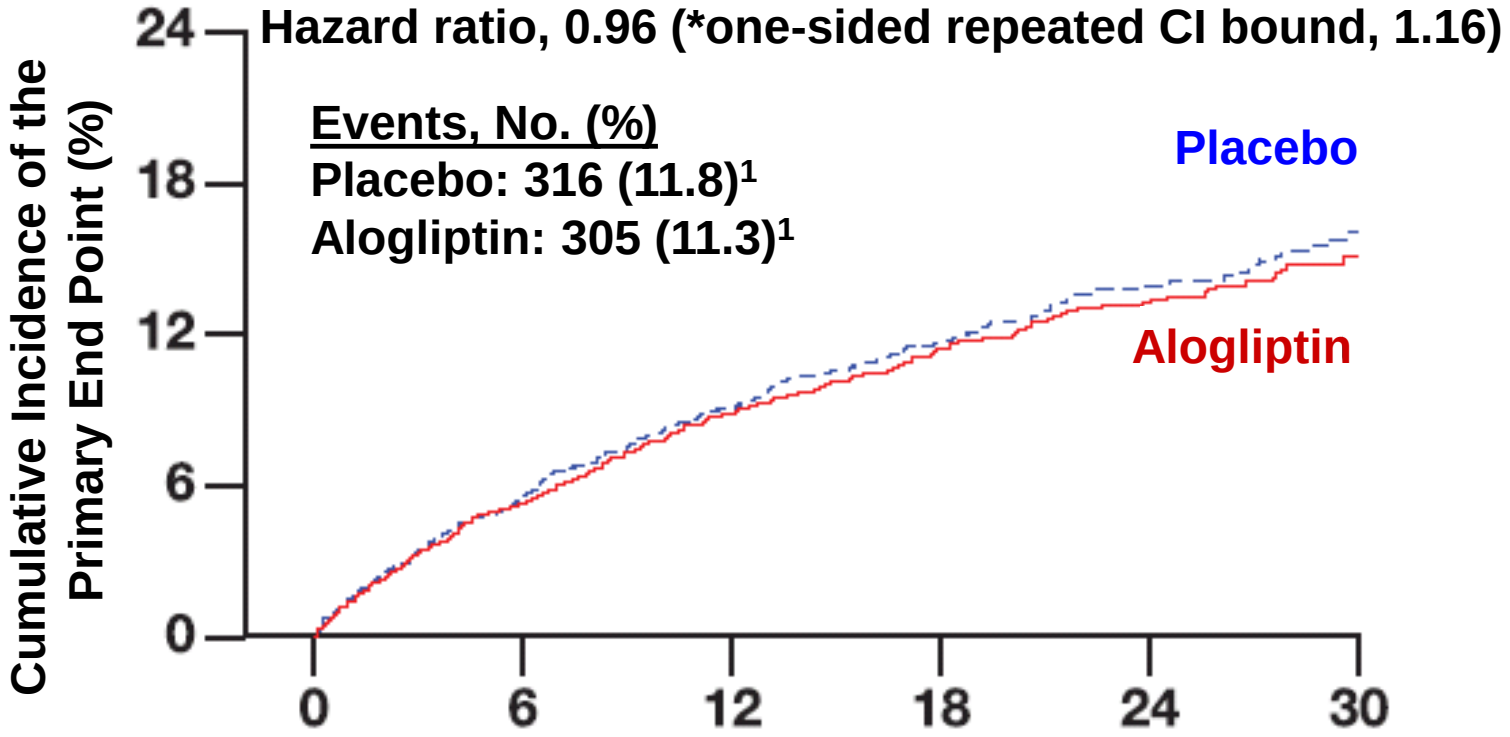
- SAVOR-TIMI 53 – EASD Vienna, 2014 (Saxagliptin)
- Examine – EASD Vienna, 2014 (Alogliptin)
- TECOS – ADA Boston, 2015 (Sitagliptin)
- Elixa – ADA Boston, 2015 (Lixisenatide)

Primary Endpoint



Scirica, B.M. et al .(2013) Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. *The New England Journal of Medicine. [online] nejm.org, available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1307684.* [Last accessed August 2015]

EXAMINE: Time to Primary End Point (CV Death, Nonfatal MI, Nonfatal Stroke)

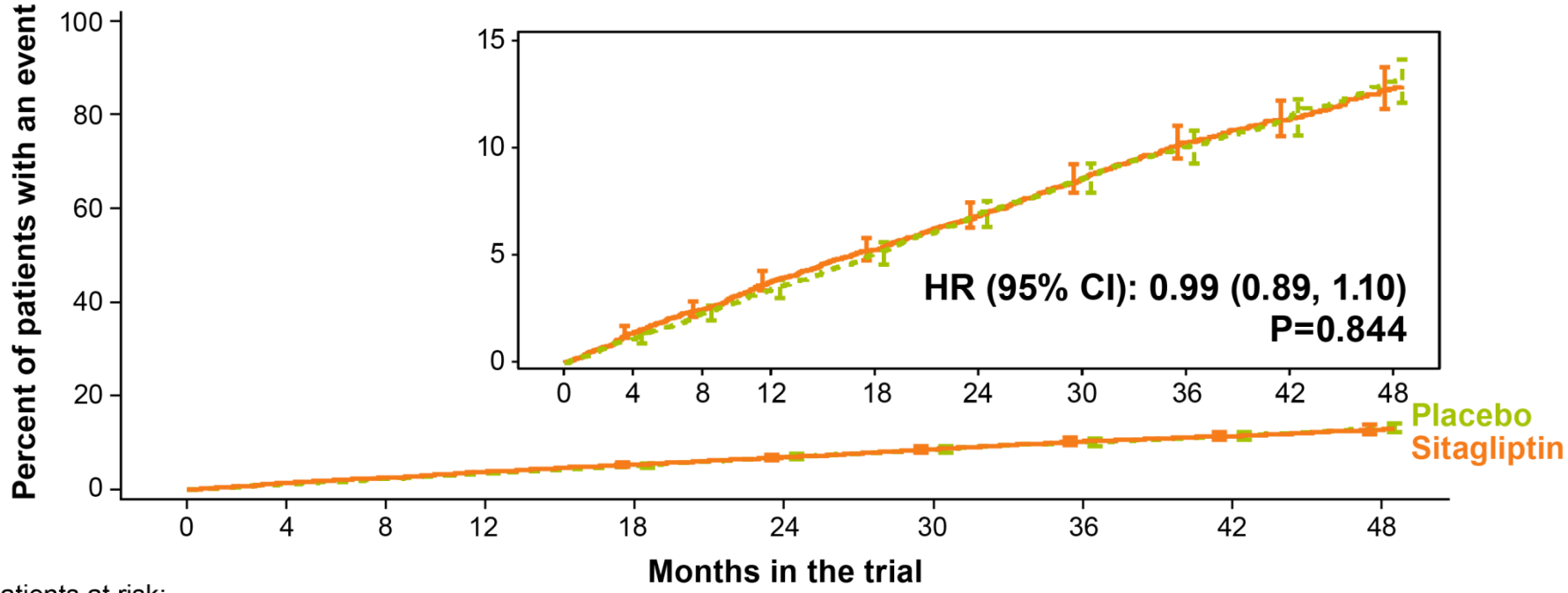


* Using alpha=0.01.

Placebo (n)[1]:	2679	2299	1891	1375	805	286
Alogliptin (n)[1]:	2701	2316	1899	1394	821	296

1. White, W.B. et al. (2013) Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes. *The New England Journal of Medicine*. [online] nejm.org, available at: http://www.nejm.org/doi/full/10.1056/NEJMoa1305889. [Last accessed August 2015]

Secondary Composite Cardiovascular Outcome*
ITT Analysis for Superiority



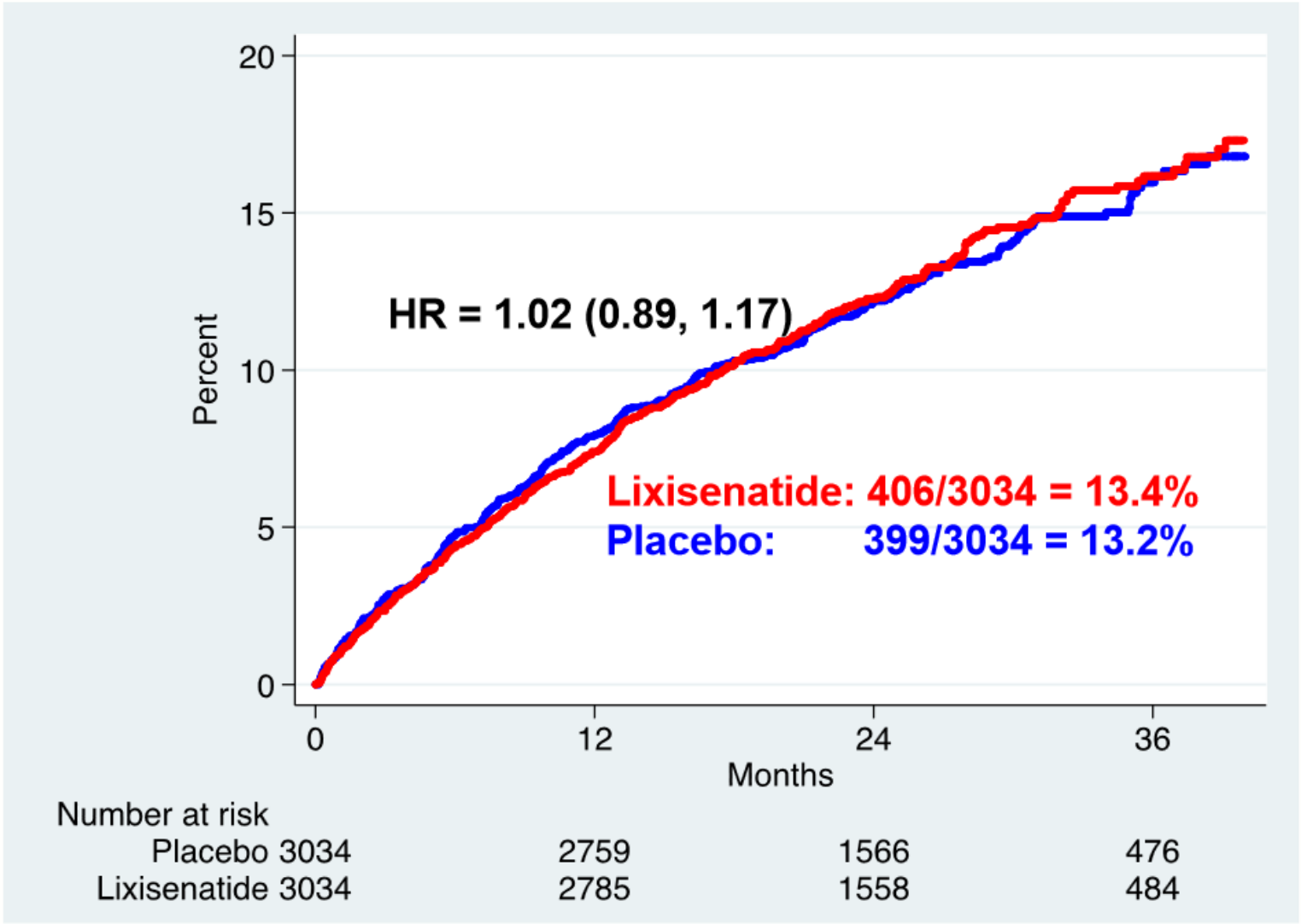
Patients at risk:										
Sitagliptin	7,332	7,145	6,969	6,817	6,638	6,457	4,584	3,396	2,097	1,270
Placebo	7,339	7,161	6,939	6,796	6,573	6,359	4,472	3,332	2,070	1,260

** CV death, nonfatal MI, nonfatal stroke*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

TECOS
TRIAL EVALUATING CARDIOVASCULAR OUTCOMES WITH SITAGLIPTIN

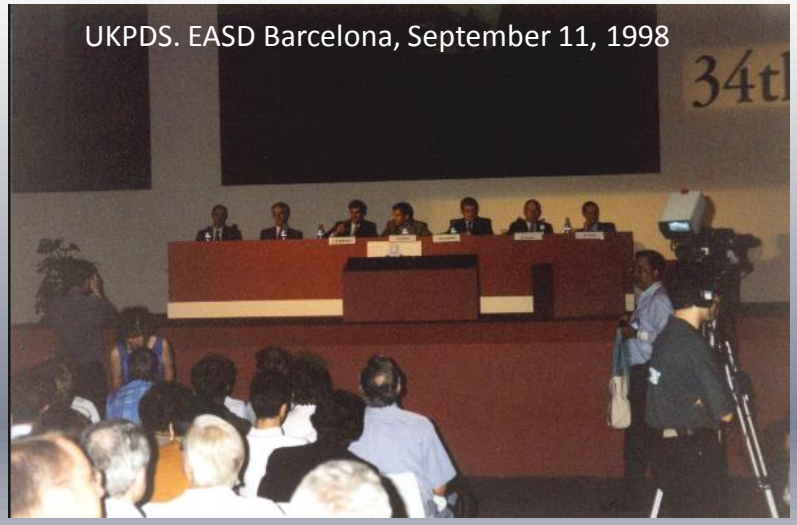
1° Outcome (CV Death, MI, Stroke or UA)



Four studies without separation of the lines

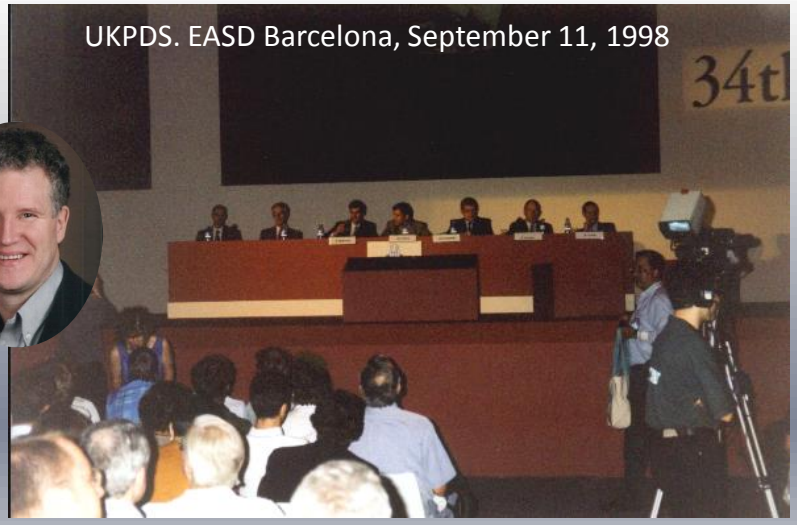
- SAVOR-TIMI 53 – EASD Vienna, 2014 (Saxagliptin)
- Examine – EASD Vienna, 2014 (Alogliptin)
- TECOS – ADA Boston, 2015 (Sitagliptin)
- Elixa – ADA Boston, 2015 (Lixisenatide)

Has there ever been separation of the lines?

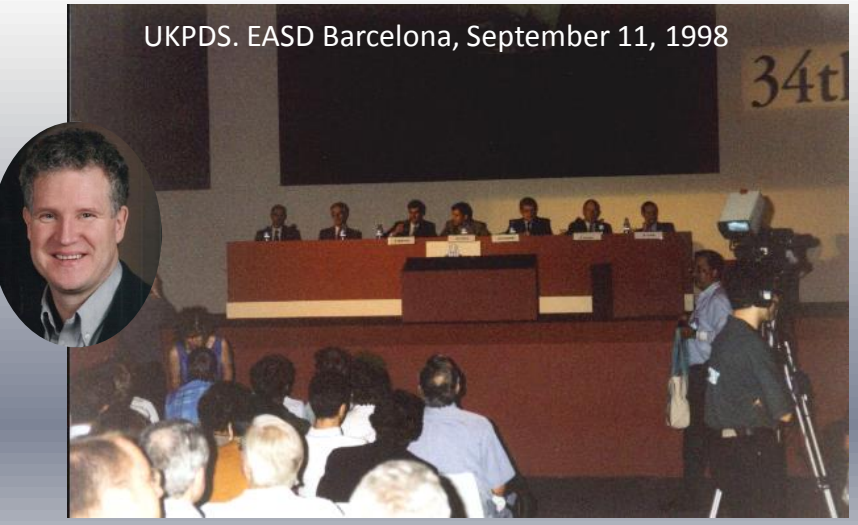

UKPDS. EASD Barcelona, September 11, 1998


PROactive. EASD Athens, September 12, 2005


EMPA-REG. EASD Stockholm, September 18, 2015



I know cos I was there!


UKPDS. EASD Barcelona, September 11, 1998

UKPDS 1998


UKPDS 1998
34t

Metformin in Overweight Patients

- compared with conventional policy

32% risk reduction in any diabetes-related endpoints	p=0.0023
42% risk reduction in diabetes-related deaths	p=0.017
36% risk reduction in all cause mortality	p=0.011
39% risk reduction in myocardial infarction	p=0.01

ukpds

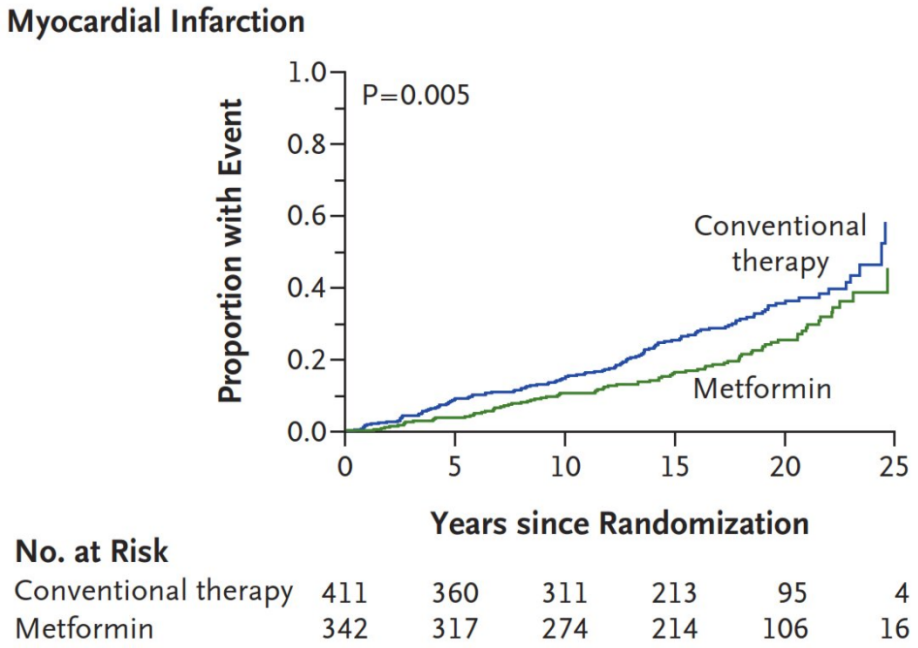


Figure 1a

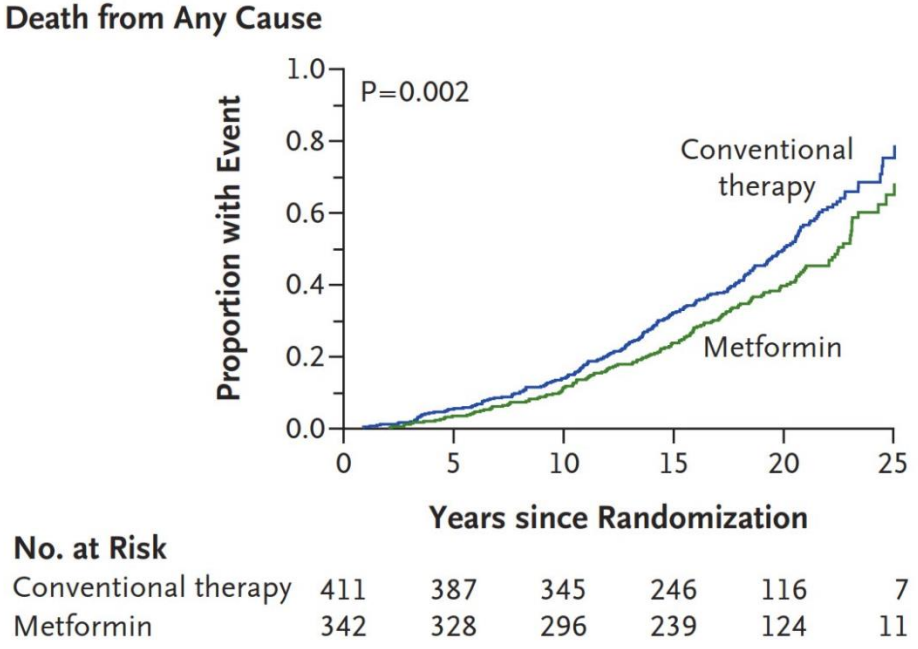
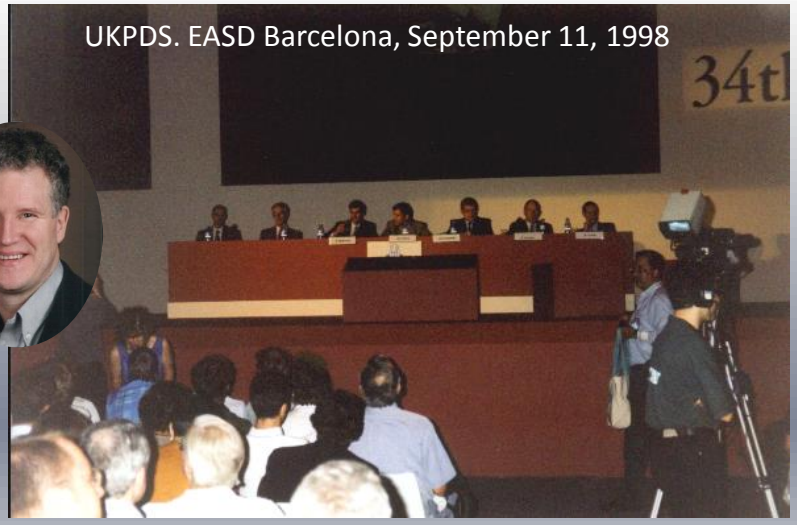


Figure 1b

The proportions of patients in the UKPDS (United Kingdom Prospective Diabetes Study) who had myocardial infarction (Figure 1a) and death from any cause (Figure 1b) for the metformin group versus the conventional therapy group. Kaplan-Meier plots cumulative incidence and log-rank P values are shown at 5-year intervals during a 25 year period from the start of the interventional trial.

Holman RR et al, N Engl J Med. 2008;359(15):1577-89



I know cos I was there!

PROactive. EASD Athens, September 12, 2005

PROactive 2005


ROactive 2005


ROactive 2005

ROactive 2005


ROactive 2005
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41st Annual Mee
of the European Ass
for the Study of D
Athens 2005


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of the Europea
for the Study
Athens

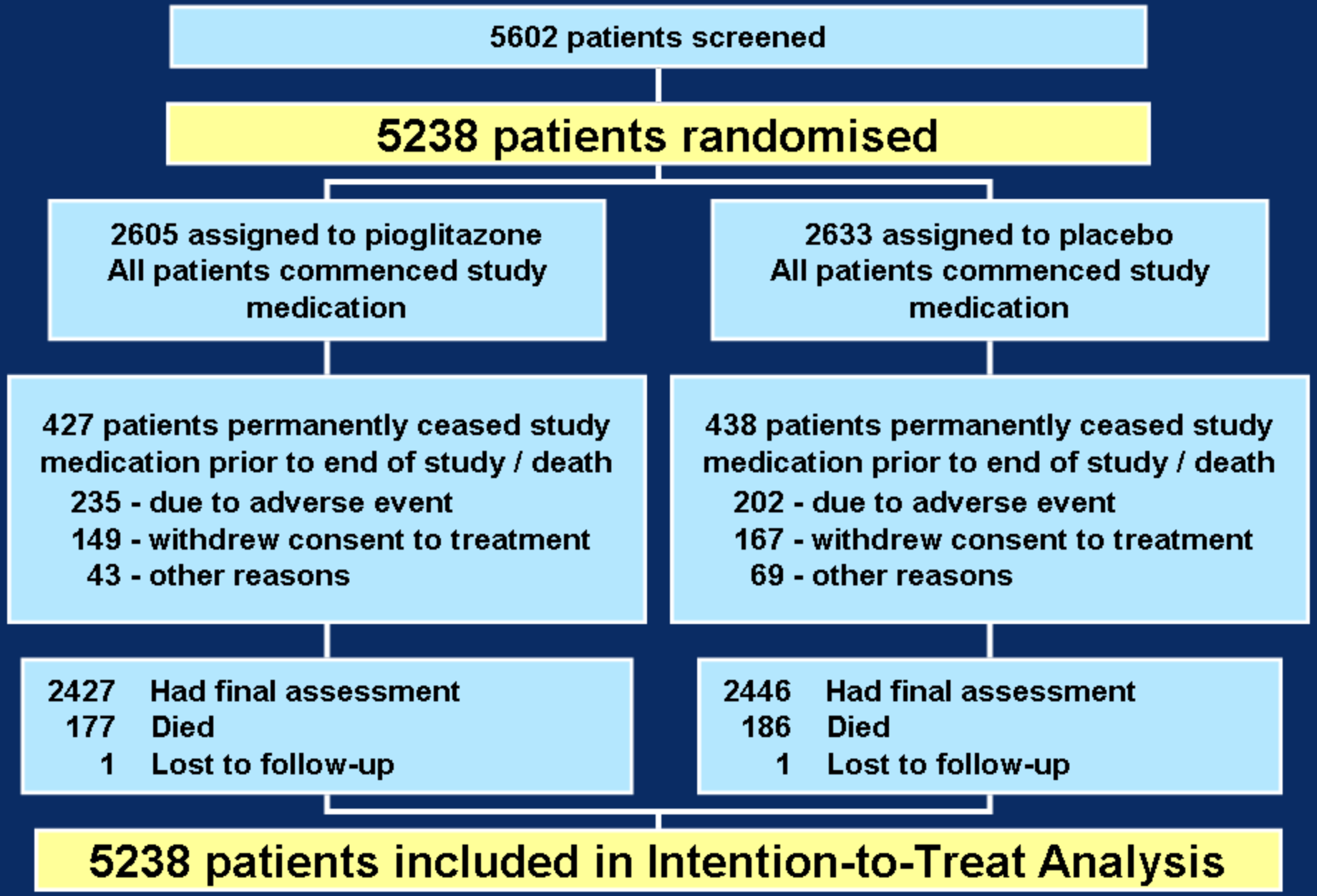
PROactive Study

PROspective PioglitAzone Clinical Trial In MacroVascular Events

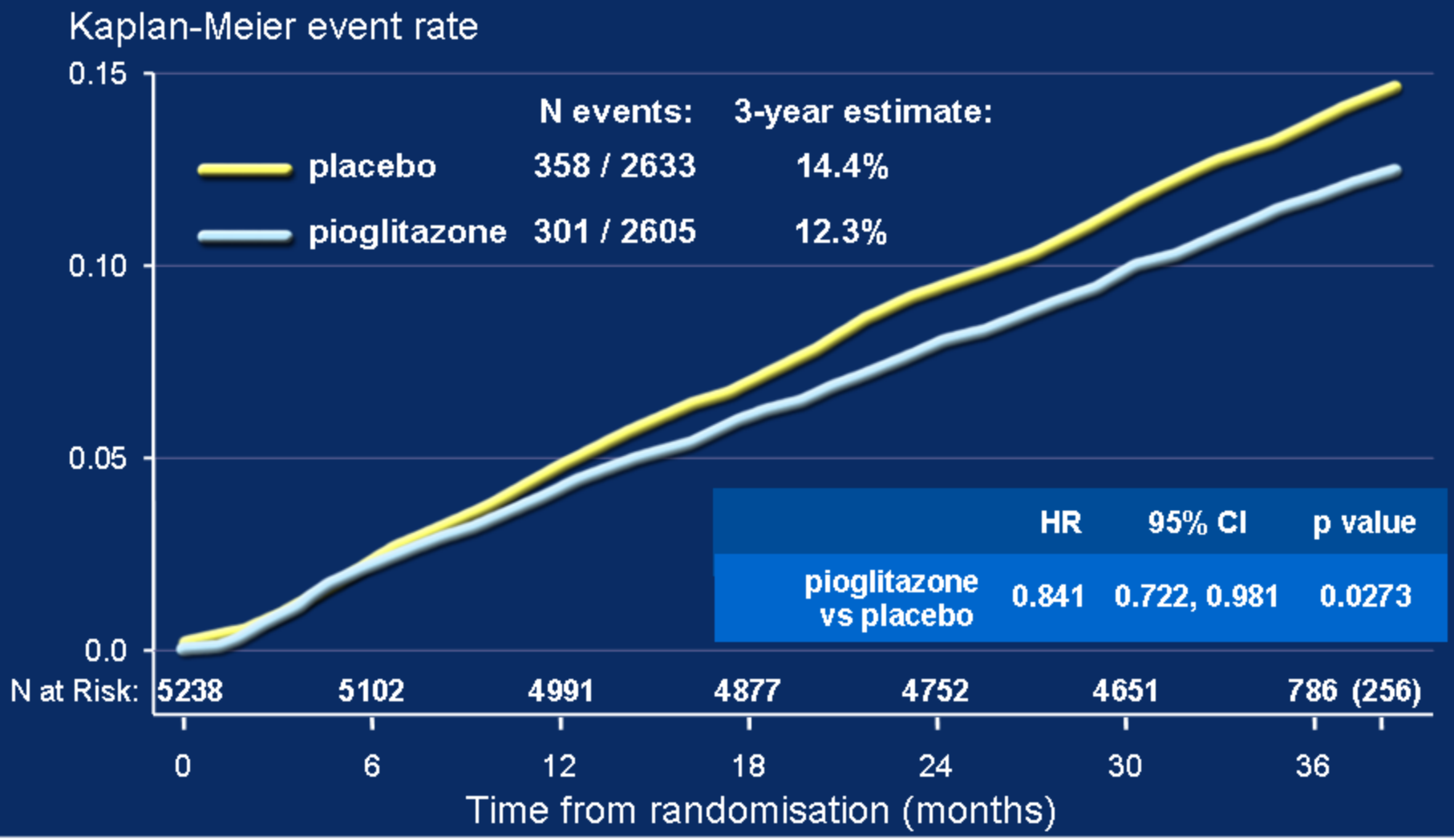
A Macrovascular Outcome Study in Type 2 Diabetic Patients Comparing Pioglitazone with Placebo in Addition to Existing Therapy

European Association for the Study of Diabetes

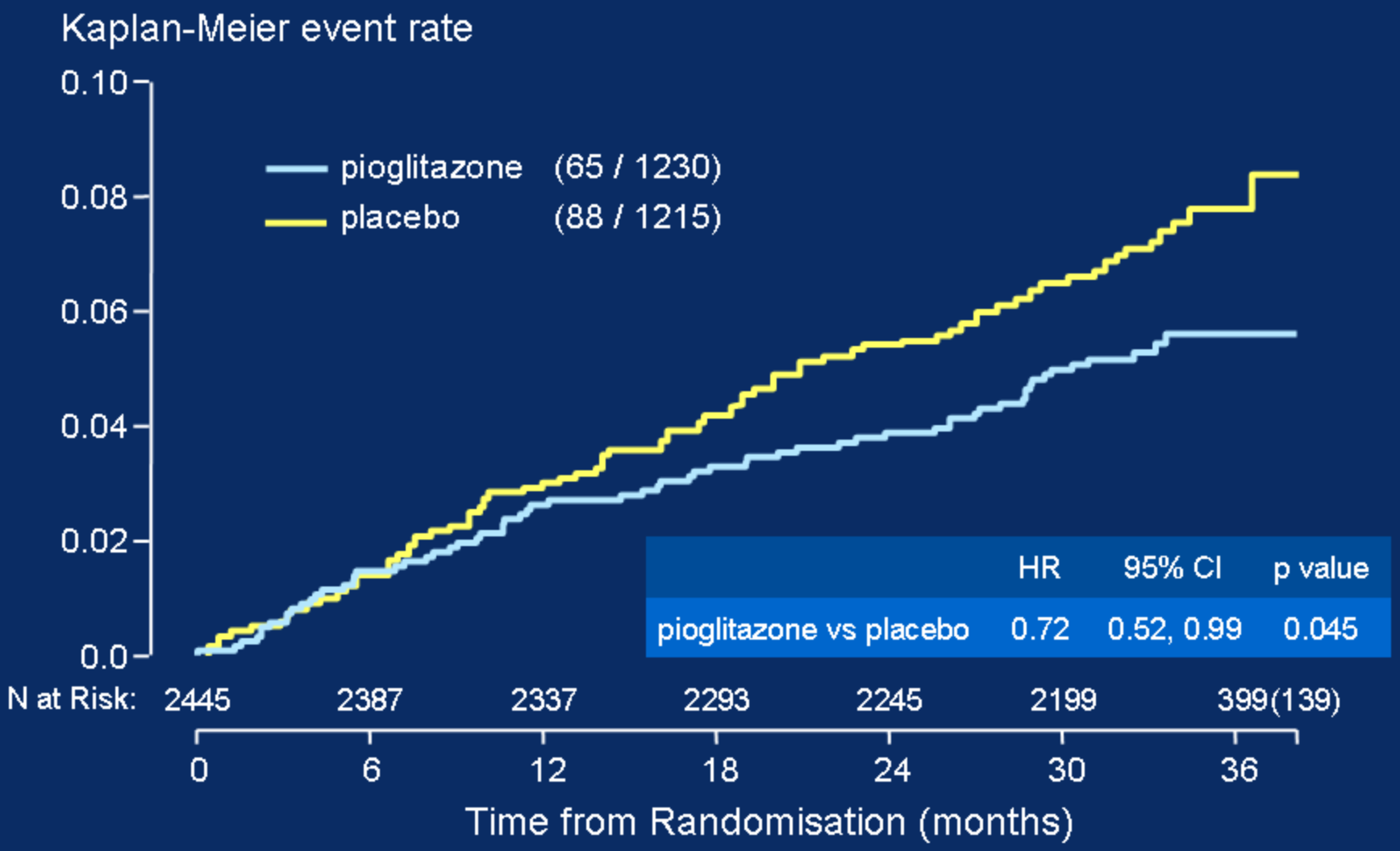
Athens 2005


5602 patients screened
5238 patients randomised
2605 assigned to pioglitazone
All patients commenced study medication
2633 assigned to placebo
All patients commenced study medication
427 patients permanently ceased study medication prior to end of study / death
235 - due to adverse event
149 - withdrew consent to treatment
43 - other reasons
438 patients permanently ceased study medication prior to end of study / death
202 - due to adverse event
167 - withdrew consent to treatment
69 - other reasons
2427 Had final assessment
177 Died
1 Lost to follow-up
2446 Had final assessment
186 Died
1 Lost to follow-up
5238 patients included in Intention-to-Treat Analysis

Time to Death, MI (Excluding Silent) or Stroke



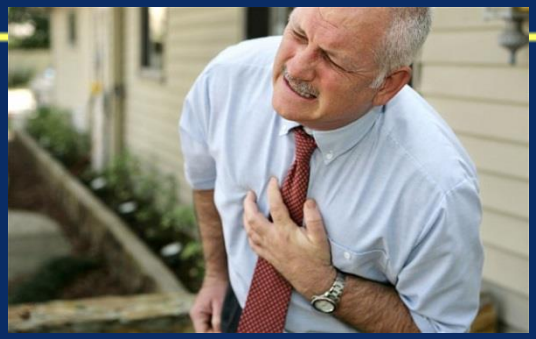
Time to Fatal/Non-fatal MI (excluding silent MI)



Erdmann E, AHA November 2005, Dallas

proactive-results.com

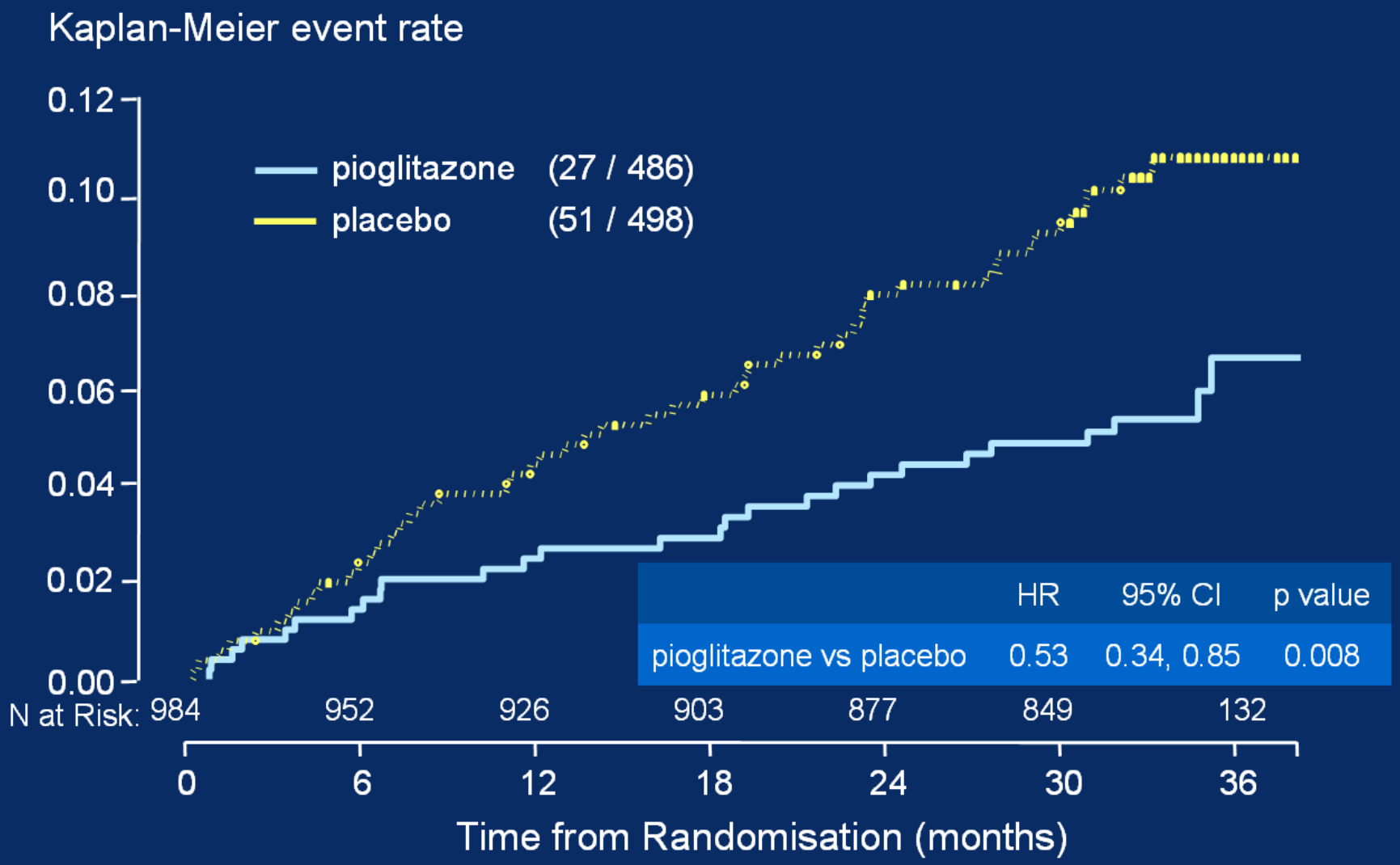
Time to Fatal/Non-fatal MI (excluding silent MI)



Erdmann E, AHA November 2005, Dallas

proactive-results.com

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



Wilcox RG et al, Stroke 2007; 38: 865-873

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

Wilcox RG et al, Stroke 2007; 38: 865-873

Effect of Pioglitazone Compared With Glimepiride on Carotid Intima-Media Thickness in Type 2 Diabetes

A Randomized Trial

Theodore Mazzone, MD
Peter M. Meyer, PhD
Steven B. Feinstein, MD
Michael H. Davidson, MD
George T. Kondos, MD
Ralph B. D'Agostino, Sr, PhD
Alfonso Perez, MD
Jean-Claude Provost, MD
Steven M. Haffner, MD

Context Carotid artery intima-media thickness (CIMT) is a marker of coronary atherosclerosis and independently predicts cardiovascular events, which are increased in type 2 diabetes mellitus (DM). While studies of relatively short duration have suggested that thiazolidinediones such as pioglitazone might reduce progression of CIMT in persons with diabetes, the results of longer studies have been less clear.

Objective To evaluate the effect of pioglitazone vs glimepiride on changes in CIMT of the common carotid artery in patients with type 2 DM.

Design, Setting, and Participants Randomized, double-blind, comparator-controlled, multicenter trial in patients with type 2 DM conducted at 28 clinical sites in the multiracial/ethnic Chicago metropolitan area between October 2003 and May 2006. The treatment period was 72 weeks (1-week follow-up). CIMT images were captured by a single ultrasonographer at 1 center and read by a single treatment-blinded reader using automated edge-detection technology. Participants were 462 adults (mean age, 60 [SD, 8.1] years; mean body mass index, 32 [SD, 5.1]) with type 2 DM (mean duration, 7.7 [SD, 7.2] years; mean glycosylated hemoglobin [HbA_{1c}] value, 7.4% [SD, 1.0%]), either newly diagnosed or currently treated with diet and exercise, sulfonylurea, metformin, insulin, or a combination thereof.

Interventions Pioglitazone hydrochloride (15-45 mg/d) or glimepiride (1-4 mg/d) as an active comparator.

Main Outcome Measure Absolute change from baseline to final visit in mean posterior-wall CIMT of the left and right common carotid arteries.

Results Mean change in CIMT was less with pioglitazone vs glimepiride at all time points (weeks 24, 48, 72). At week 72, the primary end point of progression of mean CIMT was less with pioglitazone vs glimepiride (−0.001 mm vs +0.012 mm, respectively; difference, −0.013 mm; 95% confidence interval, −0.024 to −0.002; $P=.02$). Pioglitazone also slowed progression of maximum CIMT compared with glimepiride (0.002 mm vs 0.026 mm, respectively, at 72 weeks; difference, −0.024 mm; 95% confidence interval, −0.042 to −0.006; $P=.008$). The beneficial effect of pioglitazone on mean CIMT was similar across prespecified subgroups based on age, sex, systolic blood pressure, duration of DM, body mass index, HbA_{1c} value, and statin use.

Conclusion Over an 18-month treatment period in patients with type 2 DM, pioglitazone slowed progression of CIMT compared with glimepiride.

Trial Registration clinicaltrials.gov Identifier: NCT00225264

JAMA. 2006;296:2572-2581 www.jama.com

PATIENTS WITH TYPE 2 DIABETES mellitus (DM) have a marked increase in the risk of myocardial infarction (MI), and a substantially worse prognosis after MI compared with patients without diabetes.[1-3] In recent years, it has become apparent that optimal control of blood pressure and low-density lipoprotein cholesterol (LDL-C) level can substantially reduce excess cardiovascular risk in patients with diabetes.[4-6] However, even with optimal control of these potent cardiovascular risk factors, incremental risk for cardiovascular events remains high compared with individuals without diabetes.[2,3,6] New approaches are, therefore, needed to further reduce cardiovascular risk in patients with diabetes.

Emerging evidence suggests that thiazolidinediones could be useful for reducing cardiovascular risk. In isolated vessel-wall cells, troglitazone, pioglitazone, and rosiglitazone have been shown to modulate gene expression in a manner that would be predicted to be atheroprotective in vivo.[7,8] In humans, these agents have been shown to have beneficial effects on systemic inflammatory and coagulation markers, lipoprotein profile, and endothelial cell function.[9-12] Some of these beneficial ef-

Author Affiliations are listed at the end of this article.
Corresponding Author: Theodore Mazzone, MD, University of Illinois College of Medicine, Section of Endocrinology, Diabetes and Metabolism, 1819 W Polk St, 612 CMW MC 797, Chicago, IL 60612 (tmazzone@uic.edu).

Pioglitazone slowed progression of carotid artery intima–media thickness (a marker of coronary atherosclerosis which independently predicts cardiovascular events) compared with glimepiride

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

The PERISCOPE Randomized Controlled Trial

Steven E. Nissen, MD
Stephen J. Nicholls, MBBS, PhD
Kathy Wolski, MPH
Richard Nesto, MD
Stuart Kupfer, MD
Alfonso Perez, MD
Horacio Jure, MD
Robert De Larochellière, MD
Cezar S. Staniloae, MD
Kreton Mavromatis, MD
Jacqueline Saw, MD
Bo Hu, PhD
A. Michael Lincoff, MD
E. Murat Tuzcu, MD
for the PERISCOPE Investigators

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 alternative analysis imputing values for noncompleters based on baseline characteristics showed an increase in PAV of 0.64% (95% CI, 0.23% to 1.05%) for glimepiride and a decrease of 0.06% (−0.47% to 0.35%) for pioglitazone (between-group $P=.02$). Mean (SD) baseline HbA_{1c} levels were 7.4% (1.0%) in both groups and declined during treatment an average 0.55% (95% CI, −0.68% to −0.42%) with pioglitazone and 0.36% (95% CI, −0.48% to −0.24%) with glimepiride (between-group $P=.03$). In the pioglitazone group, compared with glimepiride, high-density lipoprotein levels increased 5.7 mg/dL (95% CI, 4.4 to 7.0 mg/dL; 16.0%) vs 0.9 mg/dL (95% CI, −0.3 to 2.1 mg/dL; 4.1%), and median triglyceride levels decreased 16.3 mg/dL (95% CI, −27.7 to −11.0 mg/dL; 15.3%) vs an increase of 3.3 mg/dL (95% CI, −10.7 to 11.7 mg/dL; 0.6%) ($P<.001$ for both comparisons). Median fasting insulin levels decreased with pioglitazone and increased with glimepiride ($P<.001$). Hypoglycemia was more common in the glimepiride group and edema, fractures, and decreased hemoglobin levels occurred more frequently in the pioglitazone group.

Conclusion In patients with type 2 diabetes and coronary artery disease, treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis compared with glimepiride.

Trial Registration clinicaltrials.gov Identifier: NCT00225277

JAMA. 2008;299(13):1561-1573 www.jama.com

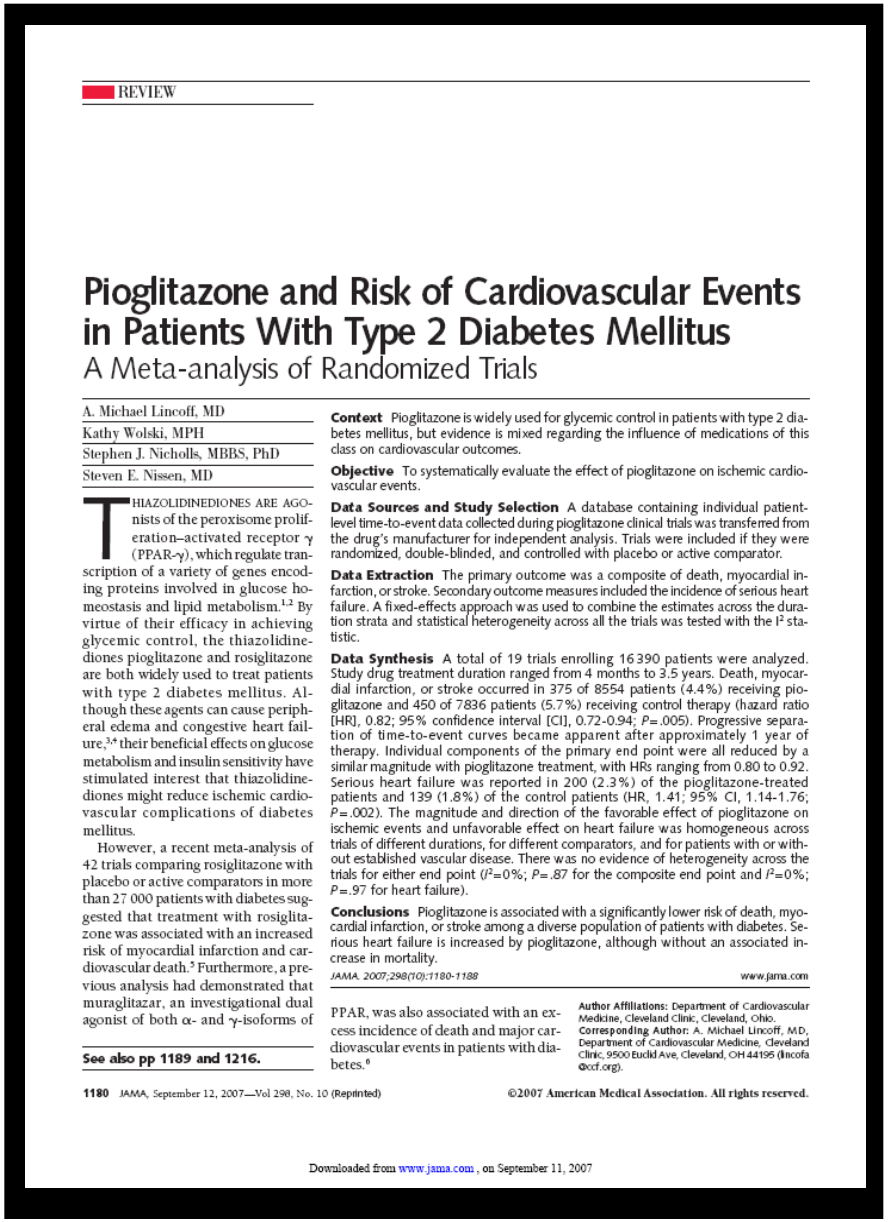
ALTHOUGH MANAGEMENT OF glucose levels represents one of the principal treatment goals of diabetes therapy, it has been difficult to demonstrate a favorable effect of improved glycemic control on the macrovascular complications of this disease.[1,2] No antidiabetic regimen has demonstrated the ability to reduce the progression of coronary atherosclerosis. Accordingly, there is little evidence to support a preference of one class of glucose-lowering medication over any other as a means to reduce atherosclerotic disease burden.[3] Sulfonylureas have been available for decades, lower blood glucose by acting as insulin secretagogues, and represent one of the most commonly-used classes of antidiabetic therapy. Thiazolidinediones (TZDs) are a relatively new class of antidiabetic agents that reduce glucose pri-

For editorial comment see p 1603.

Author Affiliations and a List of the PERISCOPE Investigators appear at the end of this article.
Corresponding Author: Steven E. Nissen, MD, Department of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195 (nissens@ccf.org).

Pioglitazone treated patients showed a significantly lower rate of progression of coronary atherosclerosis, as assessed using intravascular ultrasonography, compared to glimepiride treated patients

Metanalysis of randomized controlled trials



REVIEW

Pioglitazone and Risk of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

A Meta-analysis of Randomized Trials

A. Michael Lincoff, MD
Kathy Wolski, MPH
Stephen J. Nicholls, MBBS, PhD
Steven E. Nissen, MD

Context Pioglitazone is widely used for glycemic control in patients with type 2 diabetes mellitus, but evidence is mixed regarding the influence of medications of this class on cardiovascular outcomes.

Objective To systematically evaluate the effect of pioglitazone on ischemic cardiovascular events.

Data Sources and Study Selection A database containing individual patient-level time-to-event data collected during pioglitazone clinical trials was transferred from the drug's manufacturer for independent analysis. Trials were included if they were randomized, double-blinded, and controlled with placebo or active comparator.

Data Extraction The primary outcome was a composite of death, myocardial infarction, or stroke. Secondary outcome measures included the incidence of serious heart failure. A fixed-effects approach was used to combine the estimates across the duration strata and statistical heterogeneity across all the trials was tested with the I^2 statistic.

Data Synthesis A total of 19 trials enrolling 16 390 patients were analyzed. Study drug treatment duration ranged from 4 months to 3.5 years. Death, myocardial infarction, or stroke occurred in 375 of 8554 patients (4.4%) receiving pioglitazone and 450 of 7836 patients (5.7%) receiving control therapy (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.72-0.94; $P=.005$). Progressive separation of time-to-event curves became apparent after approximately 1 year of therapy. Individual components of the primary end point were all reduced by a similar magnitude with pioglitazone treatment, with HRs ranging from 0.80 to 0.92. Serious heart failure was reported in 200 (2.3%) of the pioglitazone-treated patients and 139 (1.8%) of the control patients (HR, 1.41; 95% CI, 1.14-1.76; $P=.002$). The magnitude and direction of the favorable effect of pioglitazone on ischemic events and unfavorable effect on heart failure was homogeneous across trials of different durations, for different comparators, and for patients with or without established vascular disease. There was no evidence of heterogeneity across the trials for either end point ($I^2=0\%$; $P=.87$ for the composite end point and $I^2=0\%$; $P=.97$ for heart failure).

Conclusions Pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. Serious heart failure is increased by pioglitazone, although without an associated increase in mortality.

JAMA. 2007;298(10):1180-1188 www.jama.com

THIAZOLIDINEDIONES ARE AGONISTS of the peroxisome proliferation–activated receptor γ (PPAR-γ), which regulate transcription of a variety of genes encoding proteins involved in glucose homeostasis and lipid metabolism.[1,2] By virtue of their efficacy in achieving glycemic control, the thiazolidinediones pioglitazone and rosiglitazone are both widely used to treat patients with type 2 diabetes mellitus. Although these agents can cause peripheral edema and congestive heart failure,[3,4] their beneficial effects on glucose metabolism and insulin sensitivity have stimulated interest that thiazolidinediones might reduce ischemic cardiovascular complications of diabetes mellitus.

However, a recent meta-analysis of 42 trials comparing rosiglitazone with placebo or active comparators in more than 27 000 patients with diabetes suggested that treatment with rosiglitazone was associated with an increased risk of myocardial infarction and cardiovascular death.[5] Furthermore, a previous analysis had demonstrated that muraglitazar, an investigational dual agonist of both α- and γ-isoforms of PPAR, was also associated with an excess incidence of death and major cardiovascular events in patients with diabetes.[6]

See also pp 1189 and 1216.

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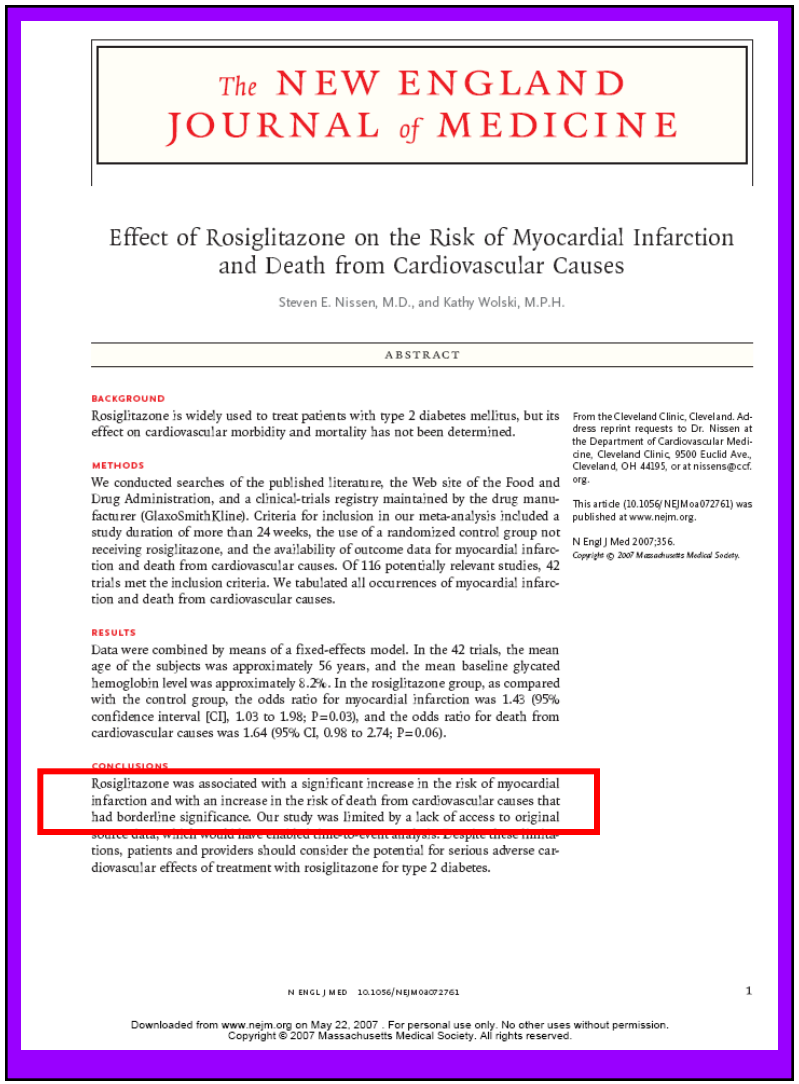
Pioglitazone receiving patients showed a significant reduction in death, myocardial infarction and stroke compared to patients receiving control therapy in meta-analysis of 19 randomised controlled trials (HR 082, CI 0•72 – 0•94, p=0•005)

Metanalysis

Rosiglitazone – cardiovascular harm



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.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

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).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analyses. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

From the Cleveland Clinic, Cleveland. Address reprint requests to Dr. Nissen at the Department of Cardiovascular Medicine, Cleveland Clinic, 9500 Euclid Ave., Cleveland, OH 44195, or at nissens@ccf.org.

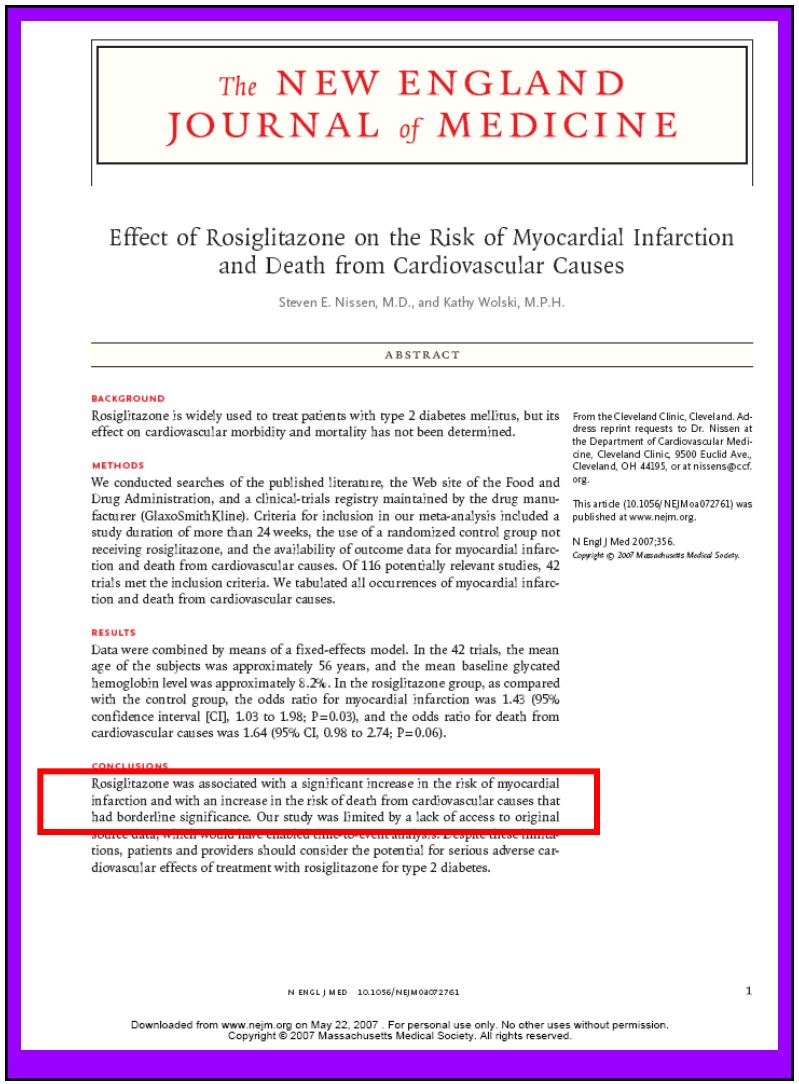
This article (10.1056/NEJMoa072761) was published at www.nejm.org.

N Engl J Med 2007;356.

2007

Metanalysis

Rosiglitazone – cardiovascular harm



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N Engl J Med 2007;356.

Pioglitazone – cardiovascular benefit

REVIEW

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The PROactive Study, 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, Aldo 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 Taton, 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.

Findings Two patients were lost to follow-up, but were included in analyses. The average time of observation was 34·5 months. 514 of 2605 patients in the pioglitazone group and 572 of 2633 patients in the placebo group had at least one event in the primary composite endpoint (HR 0·90, 95% CI 0·80–1·02, p=0·095). The main secondary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, and stroke. 301 patients in the pioglitazone group and 358 in the placebo group reached this endpoint (0·84, 0·72–0·98, p=0·027). Overall safety and tolerability was good with no change in the safety profile of pioglitazone identified. 6% (149 of 2065) and 4% (108 of 2633) of those in the pioglitazone and placebo groups, respectively, were admitted to hospital with heart failure; mortality rates from heart failure did not differ between groups.

Interpretation Pioglitazone reduces the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes who have a high risk of macrovascular events.

Lancet 2005; 366: 1279–89
See Comment page 1241

*Investigators listed at end of paper
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Introduction

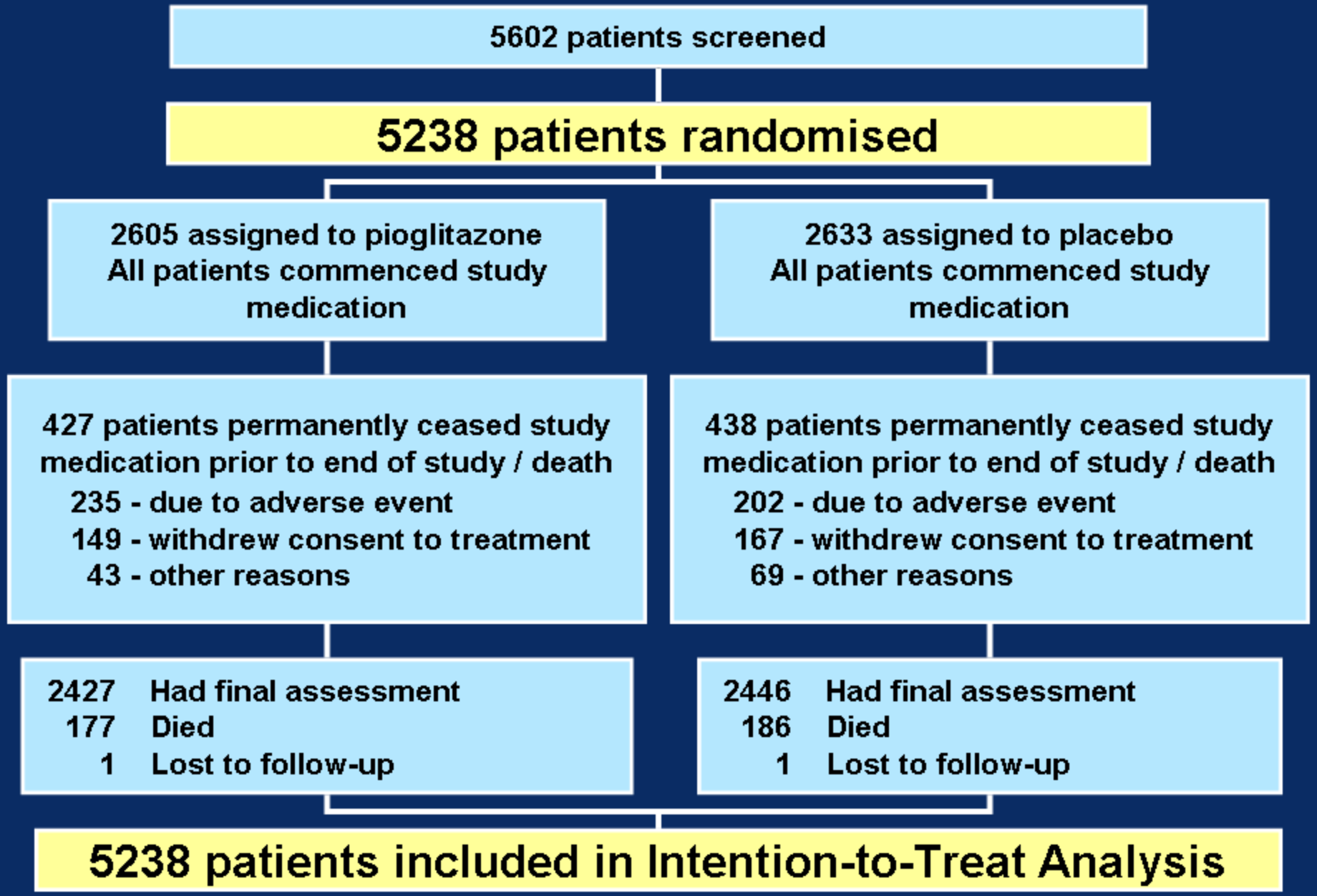
Patients with type 2 diabetes are at high risk of fatal and non-fatal macrovascular events. These events are the main reason for their decreased life expectancy, which is about 8 years shorter in a 40-year-old patient newly diagnosed with diabetes than in the general population. There is a two-fold to four-fold increased risk of a macrovascular event in patients with, compared with those without, diabetes.[1,2] Haffner and colleagues[4] noted that the risk of a cardiovascular complication in a patient with diabetes was similar to that of a patient without diabetes who had had a myocardial infarction. In the Heart Protection Study,[5] patients with diabetes and a history of cardiovascular disease at entry had almost a three-fold higher risk of a new cardiovascular event than did those without such a history.

Intensive control of glycaemia decreases microvascular complications, such as retinopathy and nephropathy, but has no great effect on macrovascular complications or all-cause mortality. However, in the UK prospective diabetes study (UKPDS),[6] findings of a retrospective analysis in a subgroup of 342 overweight patients who received metformin showed a significant decrease in cardiovascular disease and total mortality.

Pioglitazone is an agonist of peroxisome proliferator-activated receptor γ (PPAR γ) used to treat type 2 diabetes.[7] The overall pattern of changes induced by pioglitazone suggests a general improvement in various risk factors that might reduce cardiovascular morbidity and mortality. Additionally, pioglitazone reduces the levels of various inflammatory markers, such as highly sensitive C-reactive protein (hsCRP), independently of its effect on glycaemic control.[8]

The only piece of evidence at first sight not supportive of cardiovascular benefit for pioglitazone is the “primary composite endpoint” in PROactive:

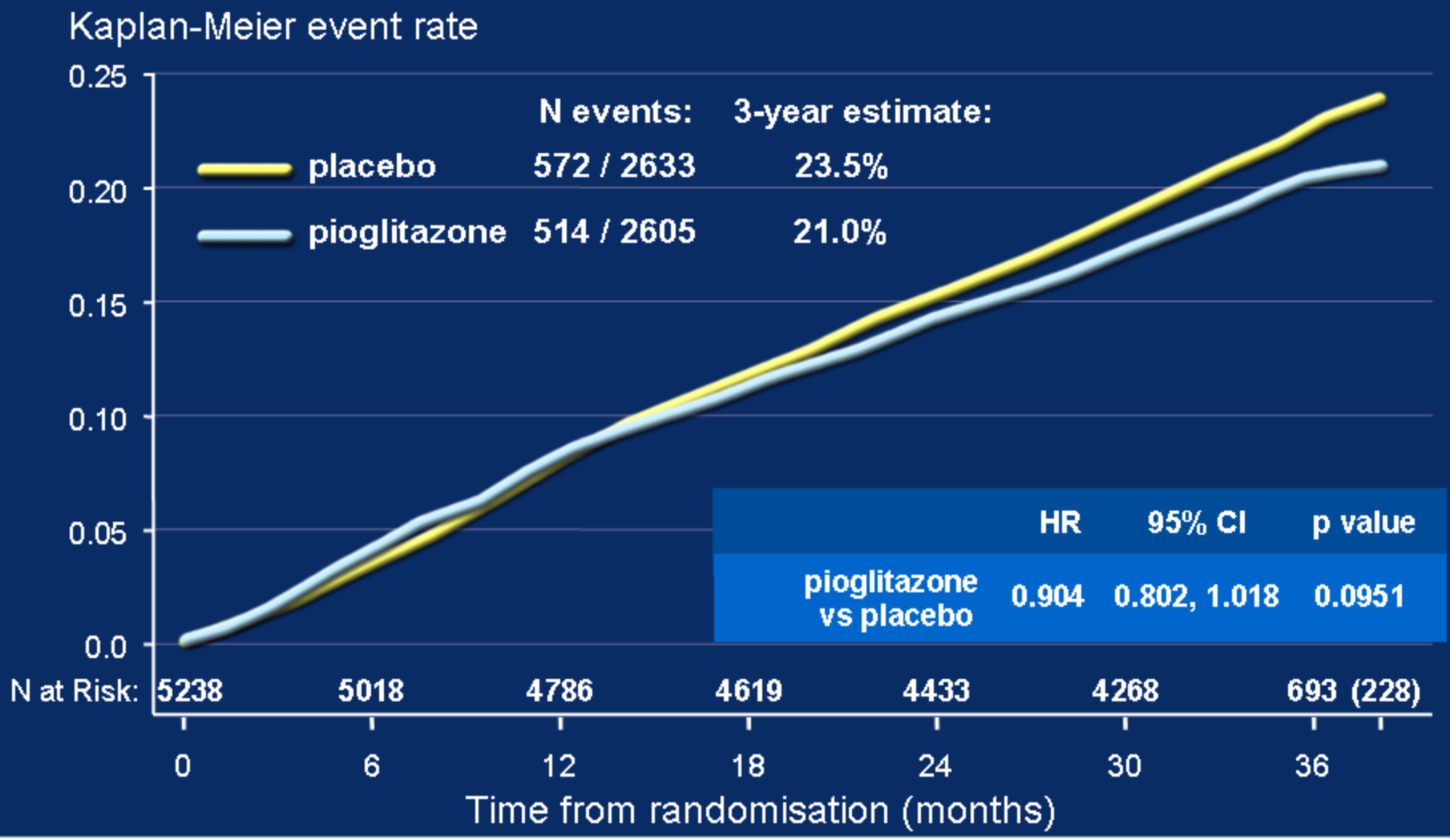
Dormandy JA et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet 2005; 366: 1279–1289.


5602 patients screened
5238 patients randomised
2605 assigned to pioglitazone
All patients commenced study medication
2633 assigned to placebo
All patients commenced study medication
427 patients permanently ceased study medication prior to end of study / death
235 - due to adverse event
149 - withdrew consent to treatment
43 - other reasons
438 patients permanently ceased study medication prior to end of study / death
202 - due to adverse event
167 - withdrew consent to treatment
69 - other reasons
2427 Had final assessment
177 Died
1 Lost to follow-up
2446 Had final assessment
186 Died
1 Lost to follow-up
5238 patients included in Intention-to-Treat Analysis

Primary Endpoint

- Time from randomisation to first occurrence of any of the events in the following composite:
  - All-cause mortality
  - Non-fatal MI (including silent MI)
  - Stroke
  - Major leg amputation (above the ankle)
  - Acute coronary syndrome (ACS)
  - Cardiac intervention including coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)
  - Leg revascularisation

Time to Primary Composite Endpoint



Numbers of First Events Contributing to the Primary Composite and Principal Secondary Endpoints

	1' Composite Endpoint		Principal 2' Endpoint	
	Piog n=2605	Pbo n=2633	Piog n=2605	Pbo n=2633
Any endpoint	**514**	**572**	**301**	**358**
Death	110	122	129	142
Non-fatal MI (excluding silent MI)	85	95	90	116
Silent MI	20	23	-	-
Stroke	76	96	82	100
Major leg amputation	9	15	-	-
Acute coronary syndrome	42	63	-	-
Coronary revascularisation	101	101	-	-
Leg revascularisation	71	57	-	-

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Chi-Sq = 7•140, p = 0 008

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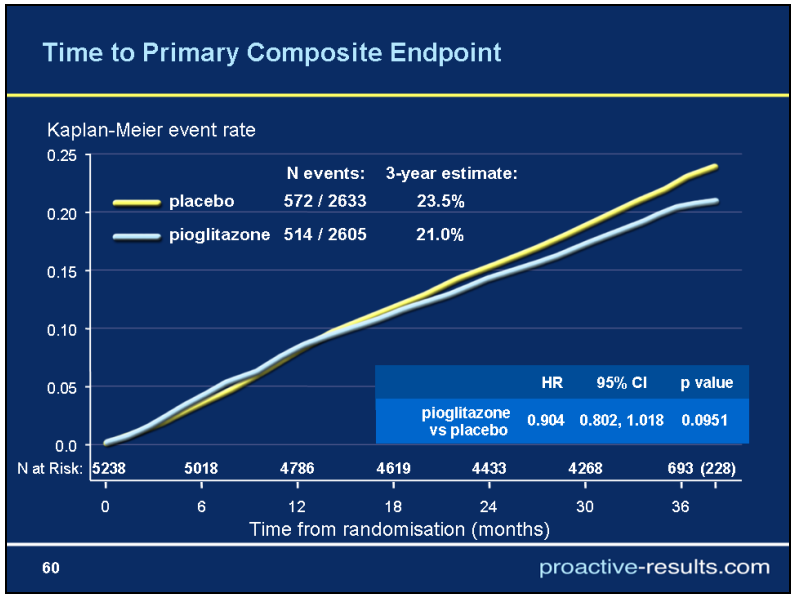
The PROactive study - is the "failure" of the primary composite endpoint real



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66 proactive-results.com

This outcome might be explained by pioglitazone preserving people from death, myocardial infarction, acute coronary syndrome, stroke and leg amputation to be available for coronary or leg revascularisation

Ryder REJ. Pioglitazone: an agent which reduces stroke, myocardial infarction and death and is also a key component of the modern paradigm for the optimum management type 2 diabetes. In press: Br J Diabetes Vasc Dis 2011; 11: Br J Diabetes Vasc Dis 2011; 11: 113-120

Effect of Pioglitazone Compared With Glimepiride on Carotid Intima-Media Thickness in Type 2 Diabetes

A Randomized Trial

Theodore Mazzone, MD
Peter M. Meyer, PhD
Steven B. Feinstein, MD
Michael H. Davidson, MD
George T. Kondos, MD
Ralph B. D'Agostino, Sr, PhD
Alfonso Perez, MD
Jean-Claude Provost, MD
Steven M. Haffner, MD

Context Carotid artery intima-media thickness (CIMT) is a marker of coronary atherosclerosis and independently predicts cardiovascular events, which are increased in type 2 diabetes mellitus (DM). While studies of relatively short duration have suggested that thiazolidinediones such as pioglitazone might reduce progression of CIMT in persons with diabetes, the results of longer studies have been less clear.

Objective To evaluate the effect of pioglitazone vs glimepiride on changes in CIMT of the common carotid artery in patients with type 2 DM.

Design, Setting, and Participants Randomized, double-blind, comparator-controlled, multicenter trial in patients with type 2 DM conducted at 28 clinical sites in the multiracial/ethnic Chicago metropolitan area between October 2003 and May 2006. The treatment period was 72 weeks (1-week follow-up). CIMT images were captured by a single ultrasonographer at 1 center and read by a single treatment-blinded reader using automated edge-detection technology. Participants were 462 adults (mean age, 60 [SD, 8.1] years; mean body mass index, 32 [SD, 5.1]) with type 2 DM (mean duration, 7.7 [SD, 7.2] years; mean glycosylated hemoglobin [HbA_{1c}] value, 7.4% [SD, 1.0%]), either newly diagnosed or currently treated with diet and exercise, sulfonylurea, metformin, insulin, or a combination thereof.

Interventions Pioglitazone hydrochloride (15-45 mg/d) or glimepiride (1-4 mg/d) as an active comparator.

Main Outcome Measure Absolute change from baseline to final visit in mean posterior-wall CIMT of the left and right common carotid arteries.

Results Mean change in CIMT was less with pioglitazone vs glimepiride at all time points (weeks 24, 48, 72). At week 72, the primary end point of progression of mean CIMT was less with pioglitazone vs glimepiride (−0.001 mm vs +0.012 mm, respectively; difference, −0.013 mm; 95% confidence interval, −0.024 to −0.002; $P=.02$). Pioglitazone also slowed progression of maximum CIMT compared with glimepiride (0.002 mm vs 0.026 mm, respectively, at 72 weeks; difference, −0.024 mm; 95% confidence interval, −0.042 to −0.006; $P=.008$). The beneficial effect of pioglitazone on mean CIMT was similar across prespecified subgroups based on age, sex, systolic blood pressure, duration of DM, body mass index, HbA_{1c} value, and statin use.

Conclusion Over an 18-month treatment period in patients with type 2 DM, pioglitazone slowed progression of CIMT compared with glimepiride.

Trial Registration clinicaltrials.gov Identifier: NCT00225264

JAMA. 2006;296:2572-2581 www.jama.com

PATIENTS WITH TYPE 2 DIABETES mellitus (DM) have a marked increase in the risk of myocardial infarction (MI), and a substantially worse prognosis after MI compared with patients without diabetes.[1-3] In recent years, it has become apparent that optimal control of blood pressure and low-density lipoprotein cholesterol (LDL-C) level can substantially reduce excess cardiovascular risk in patients with diabetes.[4-6] However, even with optimal control of these potent cardiovascular risk factors, incremental risk for cardiovascular events remains high compared with individuals without diabetes.[2,3,6] New approaches are, therefore, needed to further reduce cardiovascular risk in patients with diabetes.

Emerging evidence suggests that thiazolidinediones could be useful for reducing cardiovascular risk. In isolated vessel-wall cells, troglitazone, pioglitazone, and rosiglitazone have been shown to modulate gene expression in a manner that would be predicted to be atheroprotective in vivo.[7,8] In humans, these agents have been shown to have beneficial effects on systemic inflammatory and coagulation markers, lipoprotein profile, and endothelial cell function.[9-12] Some of these beneficial ef-

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Pioglitazone slowed progression of carotid artery intima–media thickness (a marker of coronary atherosclerosis which independently predicts cardiovascular events) compared with glimepiride

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

The PERISCOPE Randomized Controlled Trial

Steven E. Nissen, MD
Stephen J. Nicholls, MBBS, PhD
Kathy Wolski, MPH
Richard Nesto, MD
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E. Murat Tuzcu, MD
for the PERISCOPE Investigators

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 alternative analysis imputing values for noncompleters based on baseline characteristics showed an increase in PAV of 0.64% (95% CI, 0.23% to 1.05%) for glimepiride and a decrease of 0.06% (−0.47% to 0.35%) for pioglitazone (between-group $P=.02$). Mean (SD) baseline HbA_{1c} levels were 7.4% (1.0%) in both groups and declined during treatment an average 0.55% (95% CI, −0.68% to −0.42%) with pioglitazone and 0.36% (95% CI, −0.48% to −0.24%) with glimepiride (between-group $P=.03$). In the pioglitazone group, compared with glimepiride, high-density lipoprotein levels increased 5.7 mg/dL (95% CI, 4.4 to 7.0 mg/dL; 16.0%) vs 0.9 mg/dL (95% CI, −0.3 to 2.1 mg/dL; 4.1%), and median triglyceride levels decreased 16.3 mg/dL (95% CI, −27.7 to −11.0 mg/dL; 15.3%) vs an increase of 3.3 mg/dL (95% CI, −10.7 to 11.7 mg/dL; 0.6%) ($P<.001$ for both comparisons). Median fasting insulin levels decreased with pioglitazone and increased with glimepiride ($P<.001$). Hypoglycemia was more common in the glimepiride group and edema, fractures, and decreased hemoglobin levels occurred more frequently in the pioglitazone group.

Conclusion In patients with type 2 diabetes and coronary artery disease, treatment with pioglitazone resulted in a significantly lower rate of progression of coronary atherosclerosis compared with glimepiride.

Trial Registration clinicaltrials.gov Identifier: NCT00225277

JAMA. 2008;299(13):1561-1573 www.jama.com

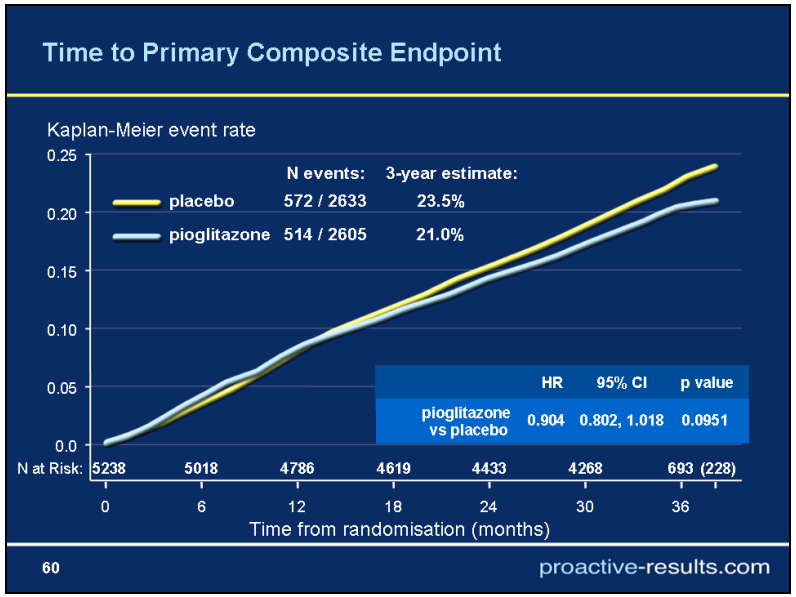
ALTHOUGH MANAGEMENT OF glucose levels represents one of the principal treatment goals of diabetes therapy, it has been difficult to demonstrate a favorable effect of improved glycemic control on the macrovascular complications of this disease.[1,2] No antidiabetic regimen has demonstrated the ability to reduce the progression of coronary atherosclerosis. Accordingly, there is little evidence to support a preference of one class of glucose-lowering medication over any other as a means to reduce atherosclerotic disease burden.[3] Sulfonylureas have been available for decades, lower blood glucose by acting as insulin secretagogues, and represent one of the most commonly-used classes of antidiabetic therapy. Thiazolidinediones (TZDs) are a relatively new class of antidiabetic agents that reduce glucose pri-

For editorial comment see p 1603.

Author Affiliations and a List of the PERISCOPE Investigators appear at the end of this article.
Corresponding Author: Steven E. Nissen, MD, Department of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195 (nissens@ccf.org).

Pioglitazone treated patients showed a significantly lower rate of progression of coronary atherosclerosis, as assessed using intravascular ultrasonography, compared to glimepiride treated patients

The PROactive study - is the "failure" of the primary composite endpoint real



Numbers of First Events Contributing to the Primary Composite and Principal Secondary Endpoints

	1' Composite Endpoint		Principal 2' Endpoint	
	Piog n=2605	Pbo n=2633	Piog n=2605	Pbo n=2633
Any endpoint	**514**	**572**	**301**	**358**
Death	110	122	129	142
Non-fatal MI (excluding silent MI)	85	95	90	116
Silent MI	20	23	-	-
Stroke	76	96	82	100
Major leg amputation	9	15	-	-
Acute coronary syndrome	42	63	-	-
Coronary revascularisation	101	101	-	-
Leg revascularisation	71	57	-	-

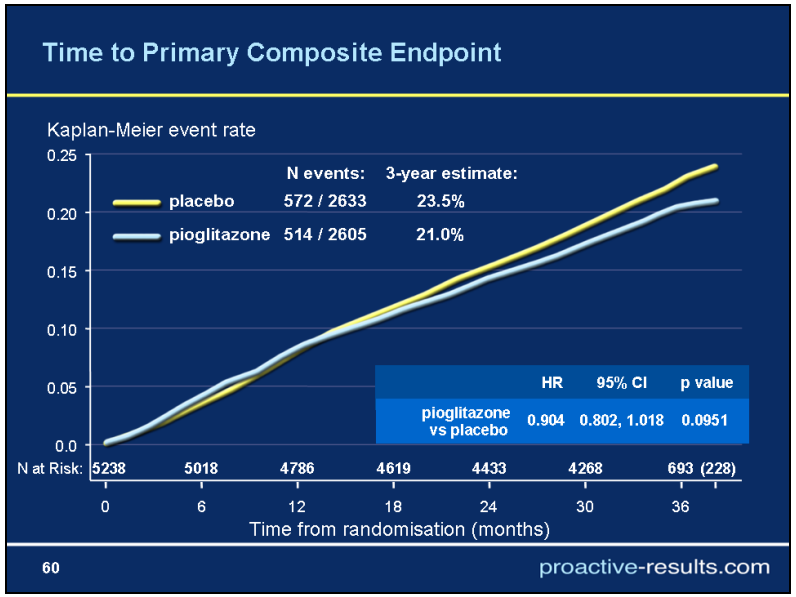
66 proactive-results.com

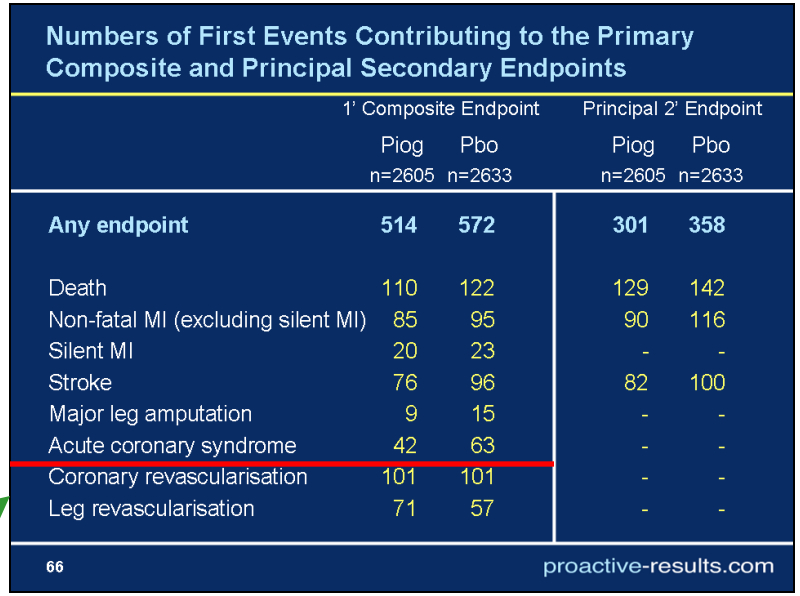
This outcome might be explained by pioglitazone preserving people from death, myocardial infarction, acute coronary syndrome stroke and leg amputation to be available for coronary or leg revascularisation

It may also be that the impact of pioglitazone on the arterial disease, makes the coronary and leg arteries more amenable to revascularisation procedures

Ryder REJ. Pioglitazone: an agent which reduces stroke, myocardial infarction and death and is also a key component of the modern paradigm for the optimum management type 2 diabetes. In press: Br J Diabetes Vasc Dis 2011; 11: Br J Diabetes Vasc Dis 2011; 11: 113-120

The PROactive study - is the "failure" of the primary composite endpoint real





This outcome might be explained by pioglitazone preserving people from death, myocardial infarction, acute coronary syndrome stroke and leg amputation to be available for coronary or leg revascularisation

It may also be that the impact of pioglitazone on the arterial disease,35,36 makes the coronary and leg arteries more amenable to revascularisation procedures

Ryder REJ. Pioglitazone: an agent which reduces stroke, myocardial infarction and death and is also a key component of the modern paradigm for the optimum management type 2 diabetes. In press: Br J Diabetes Vasc Dis 2011; 11: Br J Diabetes Vasc Dis 2011; 11: 113-120

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

W.N. Kernan, C.M. Viscoli, K.L. Furie, L.H. Young, S.E. Inzucchi, M. Gorman, P.D. Guarino, A.M. Lovejoy, P.N. Peduzzi, R. Conwit, L.M. Brass,* G.G. Schwartz, H.P. Adams, Jr., L. Berger, A. Carolei, W. Clark, B. Coull, G.A. Ford, D. Kleindorfer, J.R. O'Leary, M.W. Parsons, P. Ringleb, S. Sen, J.D. Spence, D. Tanne, D. Wang, and T.R. Winder, for the IRIS Trial Investigators†

ABSTRACT

BACKGROUND

Patients with ischemic stroke or transient ischemic attack (TIA) are at increased risk for future cardiovascular events despite current preventive therapies. The identification of insulin resistance as a risk factor for stroke and myocardial infarction raised the possibility that pioglitazone, which improves insulin sensitivity, might benefit patients with cerebrovascular disease.

METHODS

In this multicenter, double-blind trial, we randomly assigned 3876 patients who had had a recent ischemic stroke or TIA to receive either pioglitazone (target dose, 45 mg daily) or placebo. Eligible patients did not have diabetes but were found to have insulin resistance on the basis of a score of more than 3.0 on the homeostasis model assessment of insulin resistance (HOMA-IR) index. The primary outcome was fatal or nonfatal stroke or myocardial infarction.

RESULTS

By 4.8 years, a primary outcome had occurred in 175 of 1939 patients (9.0%) in the pioglitazone group and in 228 of 1937 (11.8%) in the placebo group (hazard ratio in the pioglitazone group, 0.76; 95% confidence interval [CI], 0.62 to 0.93; P=0.007). Diabetes developed in 73 patients (3.8%) and 149 patients (7.7%), respectively (hazard ratio, 0.48; 95% CI, 0.33 to 0.69; P<0.001). There was no significant between-group difference in all-cause mortality (hazard ratio, 0.93; 95% CI, 0.73 to 1.17; P=0.52). Pioglitazone was associated with a greater frequency of weight gain exceeding 4.5 kg than was placebo (52.2% vs. 33.7%, P<0.001), edema (35.6% vs. 24.9%, P<0.001), and bone fracture requiring surgery or hospitalization (5.1% vs. 3.2%, P=0.003).

CONCLUSIONS

In this trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo. Pioglitazone was also associated with a lower risk of diabetes but with higher risks of weight gain, edema, and fracture. (Funded by the National Institute of Neurological Disorders and Stroke; ClinicalTrials.gov number, NCT00091949.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Kernan at 2 Church St. S., Suite 515, New Haven, CT 06519, or at walter.kernan@yale.edu.

*Deceased.

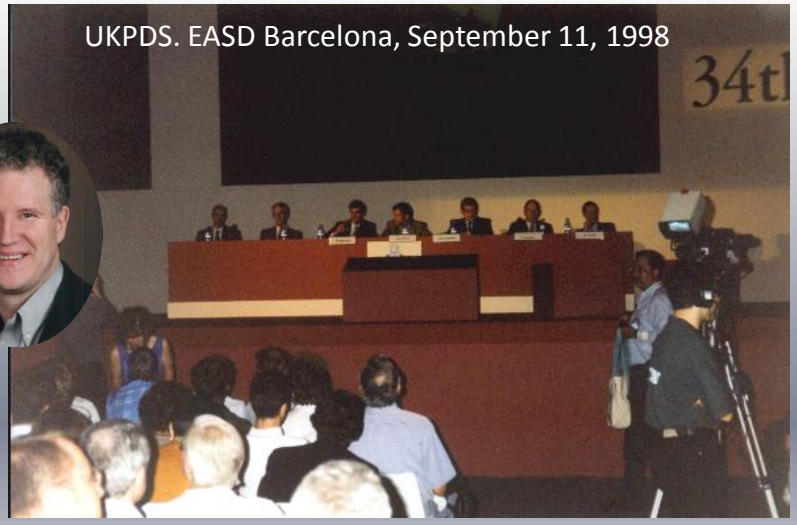
†A complete list of the Insulin Resistance Intervention after Stroke (IRIS) trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on February 17, 2016, at NEJM.org.

DOI: 10.1056/NEJMoa1508938

"In this trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was lower among patients who received pioglitazone than among those who received placebo"

Kernan WN et al. N Engl J Med 2016, published online 17 Feb



I know cos I was there!

EMPA-REG. EASD Stockholm, September 18, 2015

THE EMPA-REG OUTCOME STUDY

Key inclusion and exclusion criteria

- Key inclusion criteria
  - Adults with type 2 diabetes
  - BMI ≤45 kg/m^2
  - HbA1c 7–10%*
  - Established cardiovascular disease
    - Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease

- Key exclusion criteria
  - eGFR <30 mL/min/1.73m^2 (MDRD)

BMI, body mass index; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease
*No glucose-lowering therapy for ≥12 weeks prior to randomisation or no change in dose for ≥12 weeks prior to randomisation or, in the case of insulin, unchanged by >10% compared to the dose at randomisation

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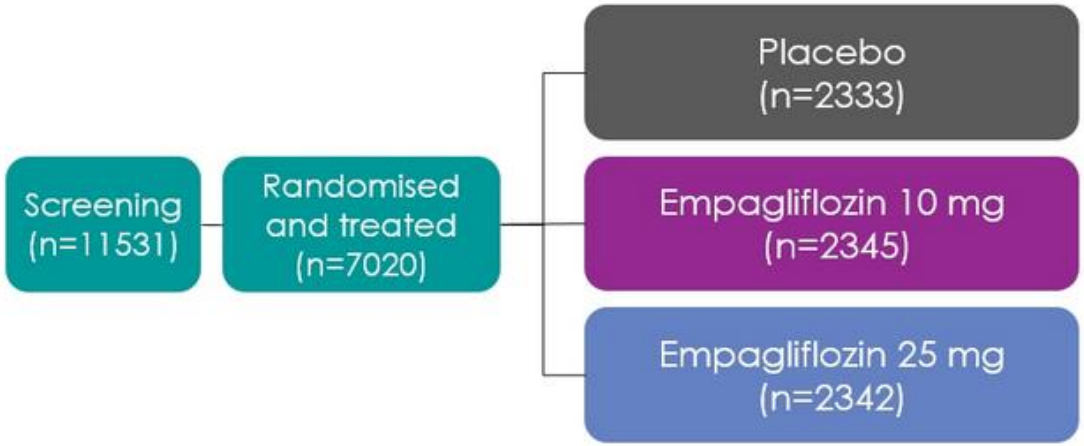
THE EMPA-REG OUTCOME STUDY

Trial design



- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

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THE EMPA-REG OUTCOME STUDY

Pre-specified primary and key secondary outcomes

- Primary outcome
  - **3-point MACE:** Time to first occurrence of CV death, non-fatal MI or non-fatal stroke
- Key secondary outcome
  - **4-point MACE:** Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalisation for unstable angina

CV, cardiovascular; MI, myocardial infarction; MACE, Major Adverse Cardiovascular Event

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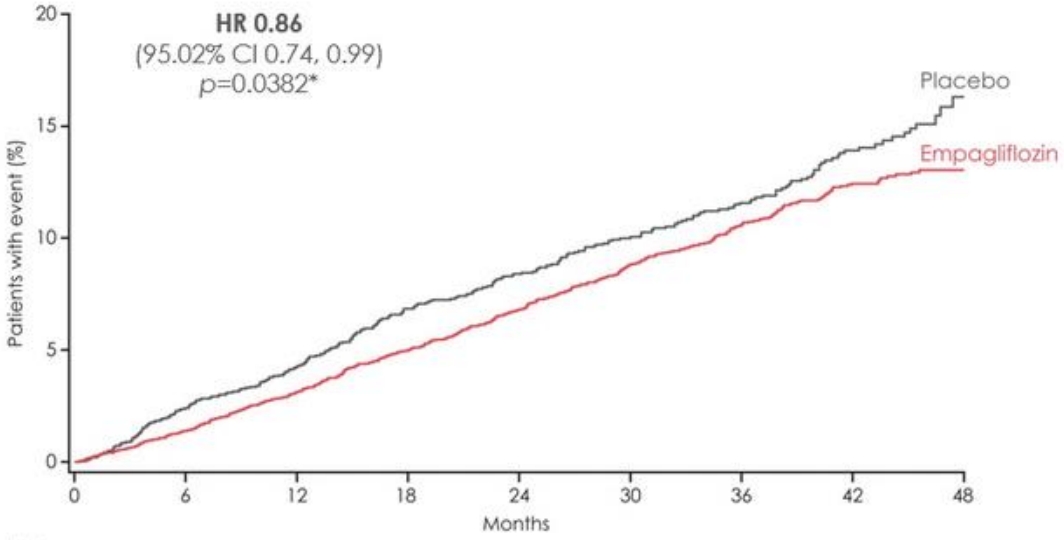
THE EMPA-REG OUTCOME STUDY

Primary outcome: 3-point MACE



No. of patients									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

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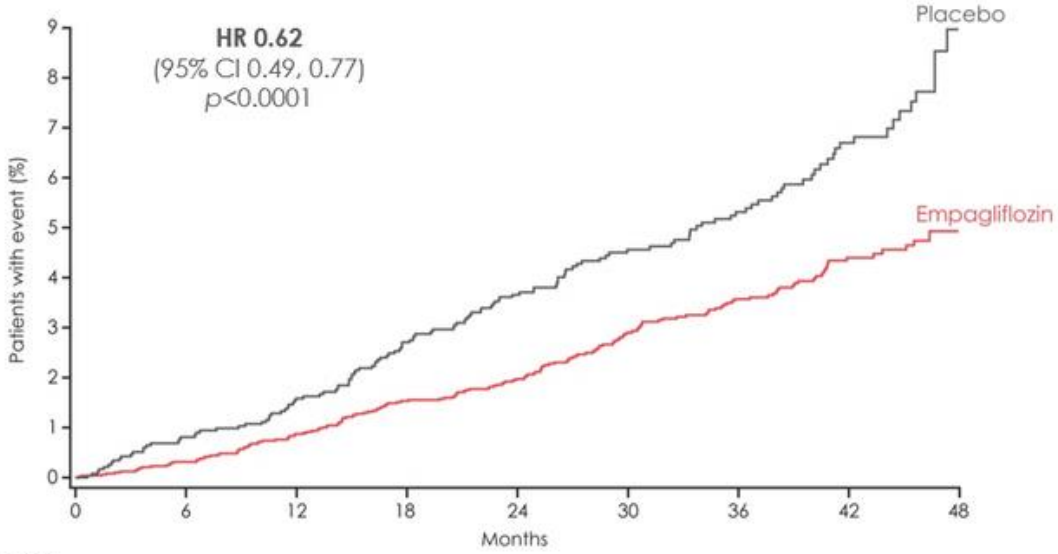
THE EMPA-REG OUTCOME STUDY

CV death



No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function. HR, hazard ratio

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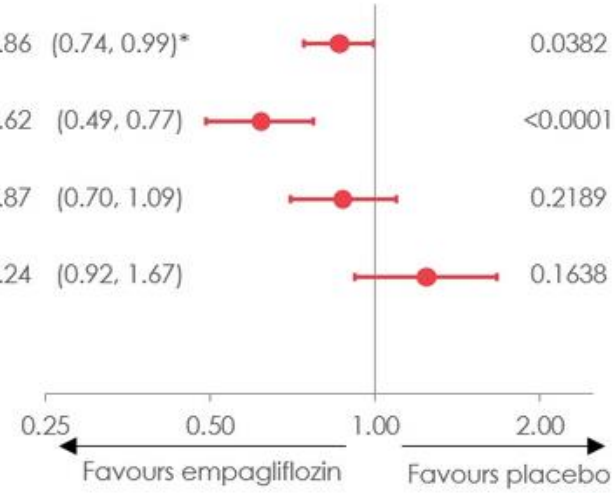
THE EMPA-REG OUTCOME STUDY

CV death, MI and stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	p-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

EMPA-REG OUTCOME®

Compare and contrast

EMPA-REG

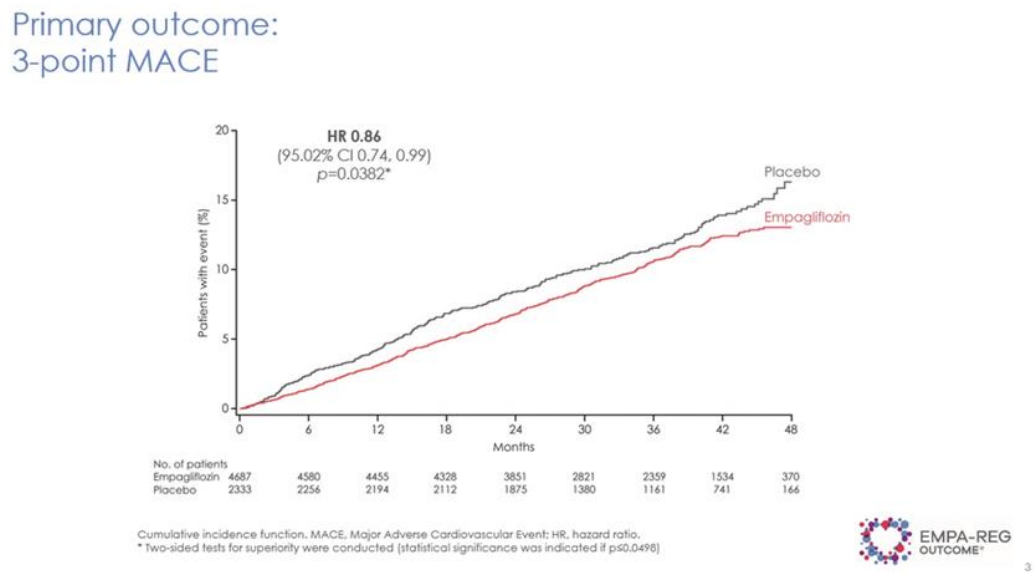
PROactive

Empagliflozin

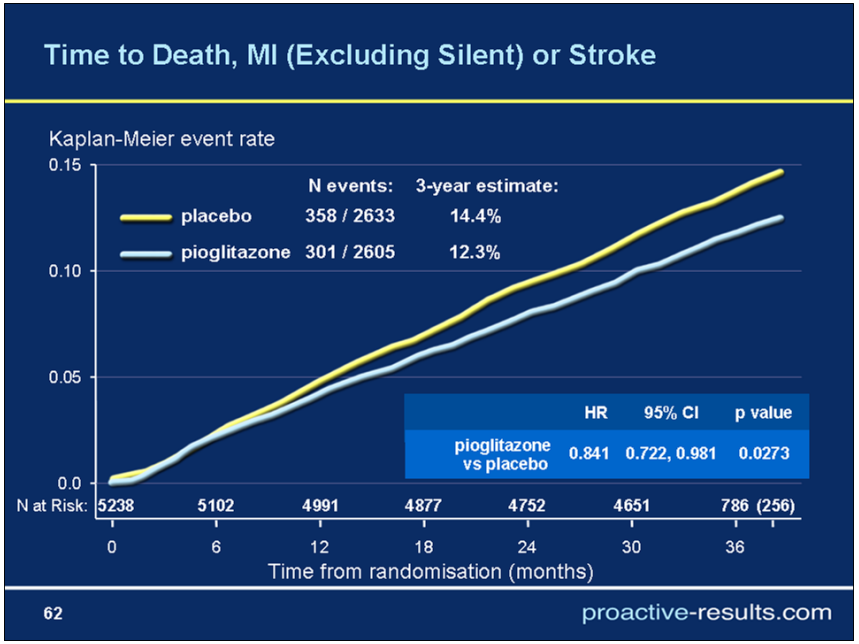
Pioglitazone

3 point MACE

EMPA-REG



PROactive

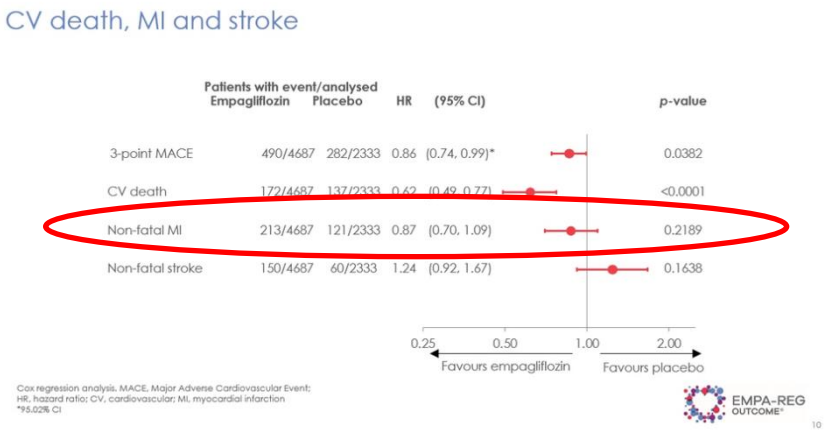


Empagliflozin

Pioglitazone

Myocardial Infarction

EMPA-REG



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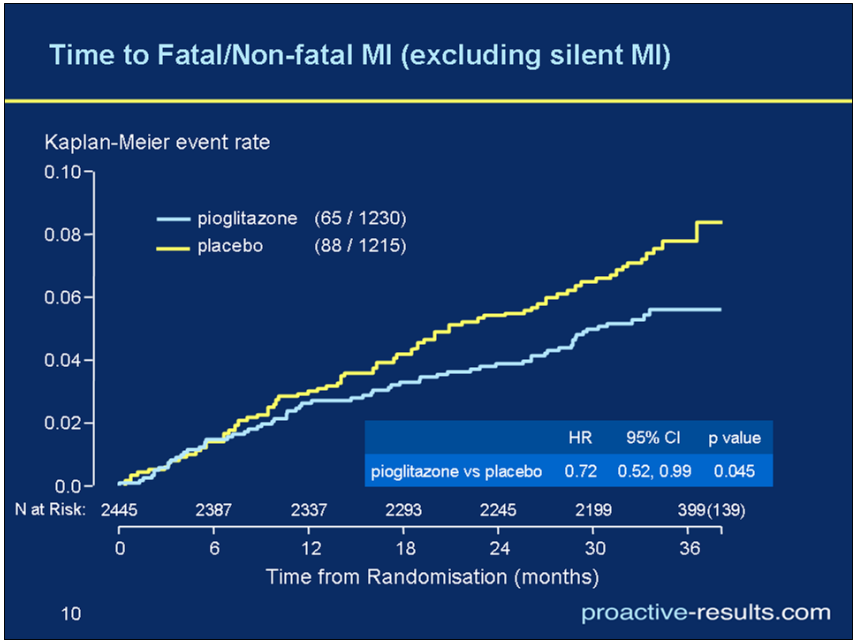
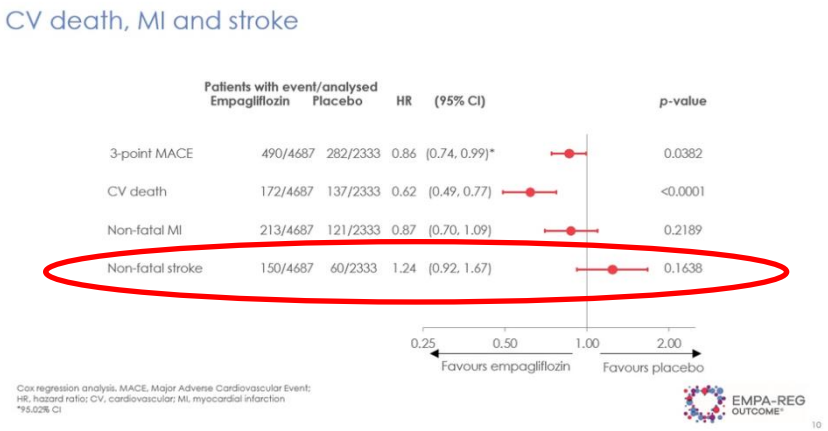


Empagliflozin - no impact

Pioglitazone - impact

Stroke

EMPA-REG



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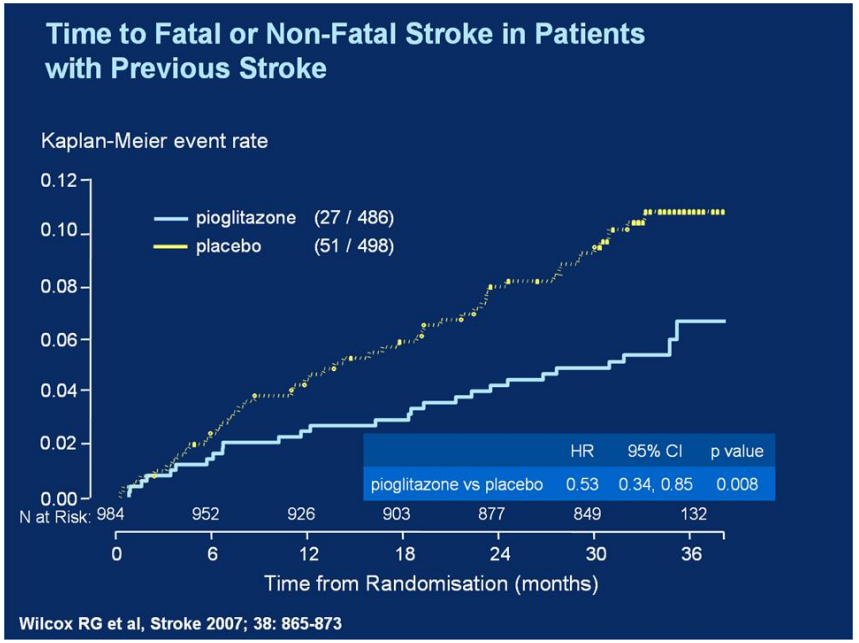
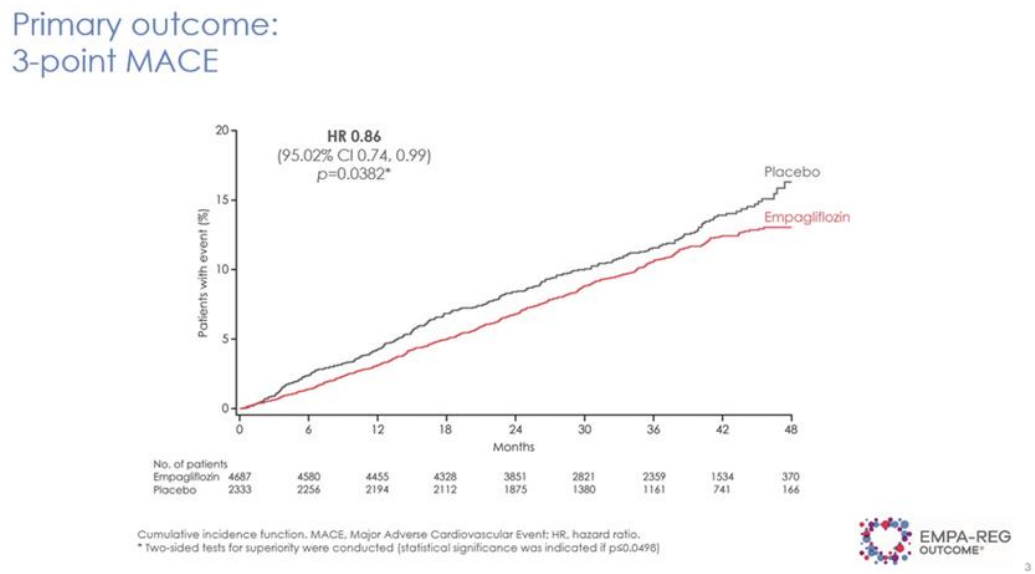


Empagliflozin - no impact

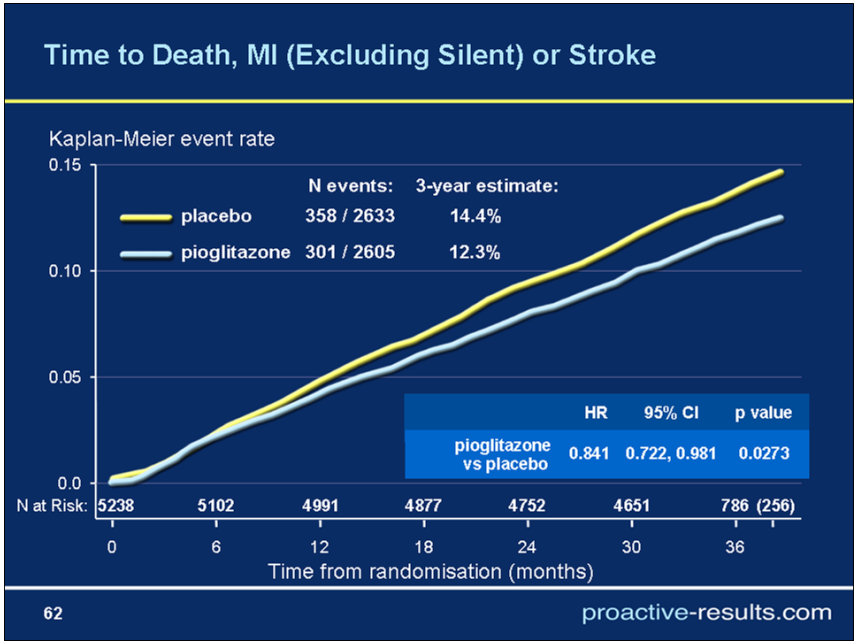
Pioglitazone - impact

Separation of the graphs

EMPA-REG



PROactive

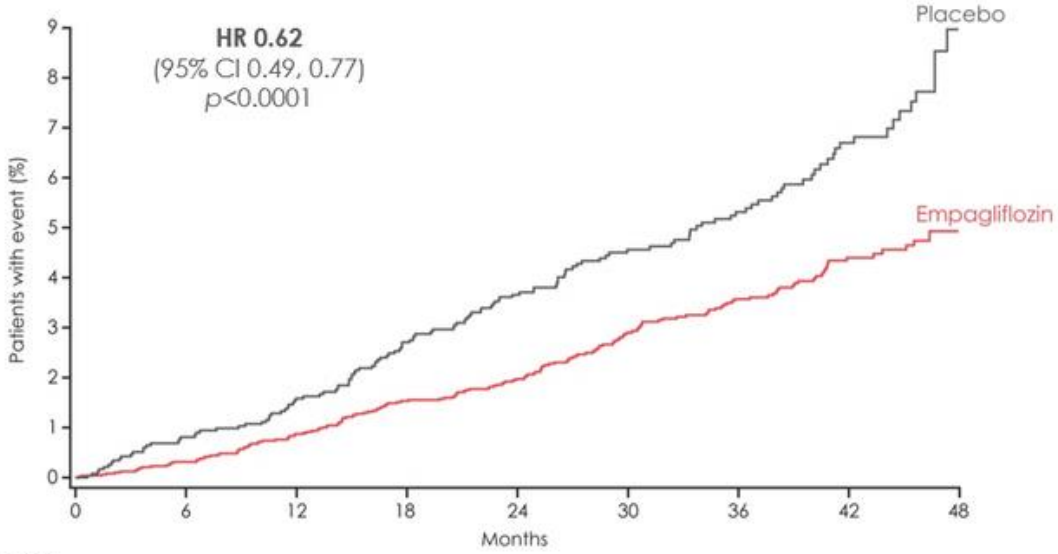


Empagliflozin

Pioglitazone

THE EMPA-REG OUTCOME STUDY

CV death



No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

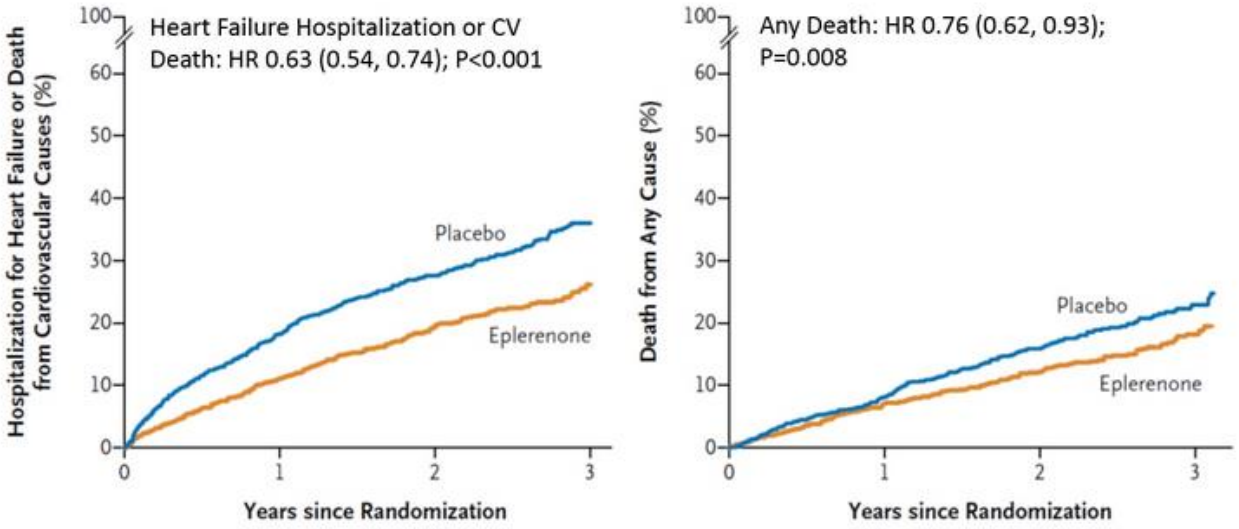
Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

NB EPHESUS heart failure trial

Time Course of Beneficial Effect
Diuretic (31% of Pts →Diabetes)

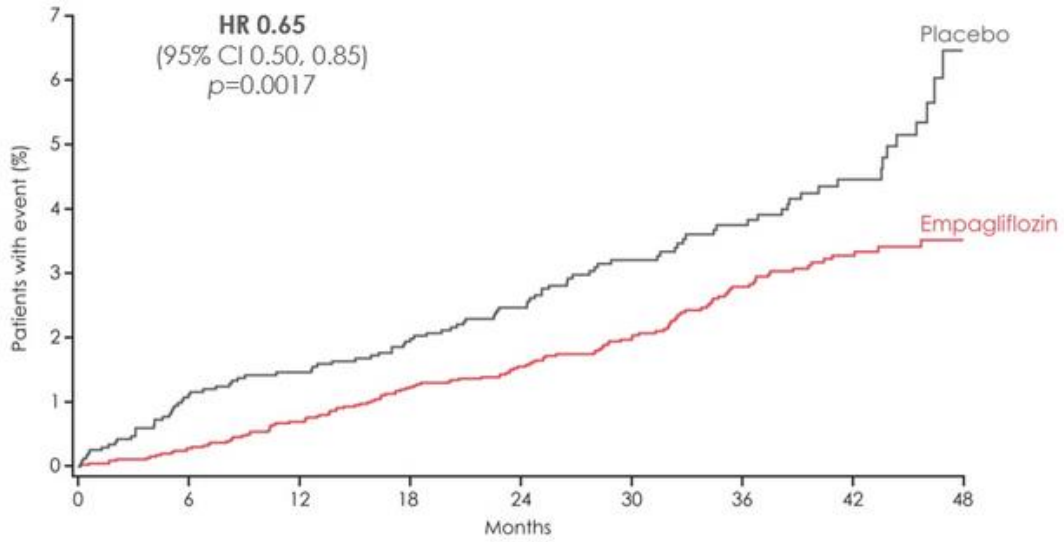
- EPHESUS HF trial: Eplerenone added to RAS drug & B-blocker in outpatients age 55+ with NYHA 2 heart failure & EF < 35%



NEJM 2011; 364:11

THE EMPA-REG OUTCOME STUDY

Hospitalisation for heart failure



No. of patients								
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

Conclusion – in the wake of EMPA-REG

- ?Optimum glycaemic treatment cocktail for cardiovascular risk:
  - Metformin
  - Pioglitazone
  - Empagliflozin

?A match made in heaven:

?The diuresing properties of empagliflozin will offset the fluid retaining properties of pioglitazone

Banting Lecture, ADA 2009

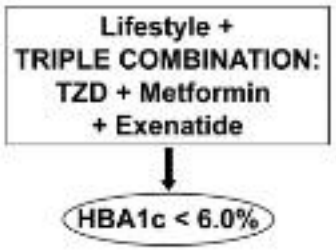


FIG. 21. Pathophysiological-based algorithm: treatment of type 2 diabetes based upon pathophysiology. See text for a detailed discussion.

DIABETES, VOL. 58, APRIL 2009

- DeFronzo: early use of a combination of metformin, pioglitazone and a GLP-1 receptor agonist as the treatment paradigm of choice for the optimum management of patients with type 2 diabetes

Banting Lecture, ADA 2009

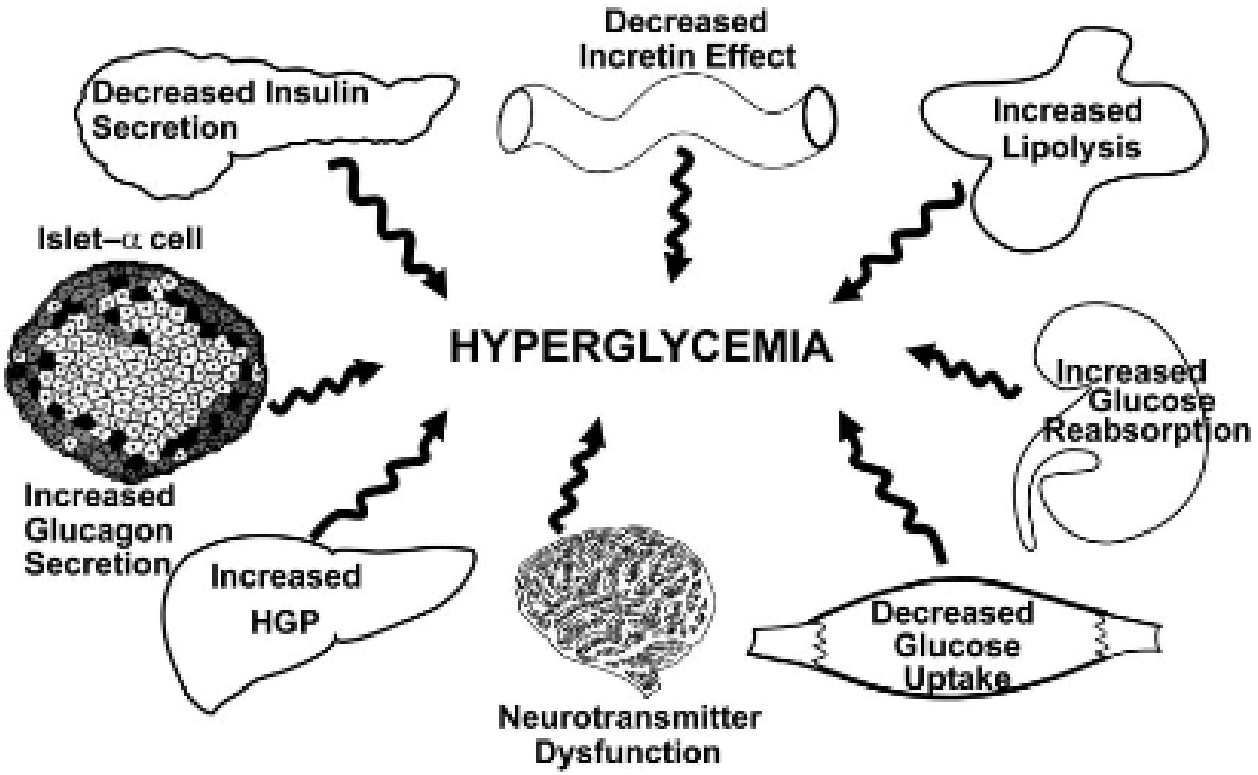


FIG. 13. The ominous octet. See text for a more detailed explanation.

BJDVD 2015

EDITORIAL

Rehabilitation of pioglitazone

ROBERT EJ RYDER,[1] RALPH A DEFRONZO[2]

Background

In 2012 an editorial in the British Medical Journal stated that "it can confidently be assumed that pioglitazone increases the risk of bladder cancer".[1] Yet now, the recently announced results of a 10-year study mandated by the FDA have failed to demonstrate any association between pioglitazone and bladder cancer[2] and, because of its many beneficial effects on glucose homeostasis and potential cardiovascular protective effects, the place of pioglitazone in the treatment of diabetes warrants reconsideration.

During pre-clinical studies, an excess of bladder cancers were found in male but not female rats treated with pioglitazone.[3] Of note, these bladder cancers could be prevented by acidification of the urine which prevents pioglitazone crystal formation.[4] As a result of the findings in rats, the FDA requested a 10-year study of pioglitazone in humans to assess safety with regard to bladder cancer.[5] The 8-year data have been published online[6] and the 10-year results recently were made public.[2] The main results of this study fail to show any association between pioglitazone and risk of bladder cancer.[7] Another large, recently reported study involving six populations, including 1.01 million diabetic individuals from six countries across the world, has come to the same conclusion.[8] Previous studies suggesting a link between pioglitazone and bladder cancer have been re-examined.[7] The link between pioglitazone and bladder cancer in many of these retrospective observational studies is likely to be explained by the fact that patients treated with pioglitazone in the various databases were different from those not treated with pioglitazone, with whom they were compared, i.e. the pioglitazone-treated patients already were at higher risk of bladder cancer from other causes.[7] Importantly, major risk factors for bladder cancer, i.e. smoking and proteinuria, were not available for most of these retrospective analyses. Initial concern about a potential link between pioglitazone and bladder cancer was derived from the PROactive study, where an apparent excess of bladder cancers was observed for pioglitazone (14) versus placebo (6, p=NS).[7,9-11] The PROactive study investigators concluded that, because most of the bladder cancers occurred during the first year following initiation

Abbreviations and acronyms

CHF	congestive heart failure
FDA	US Food and Drug Administration
GLP-1	glucagon like peptide
HbA_{1c}	glycated haemoglobin
MACE	major adverse cardiac events
PROactive	PROspective pioglitAzone Clinical Trial In macroVascular Events study

of pioglitazone therapy, the drug could not plausibly be related to the development of bladder cancer.[9] Further, the total numbers of bladder cancers (n=20) was small, making it difficult to draw any meaningful conclusion about the statistically insignificant difference between the treatment groups. It has been suggested that pioglitazone might be a tumour promoter and in this way caused the excess of bladder cancer during the first year of PROactive,[12] although there is no experimental evidence to support such an effect of pioglitazone. The actual data regarding the number of months into the trial when these bladder cancer cases were diagnosed has been published: most appeared so early into the trial (two cases were diagnosed 13 and 14 days into the trial respectively, one at one month, another at three months and a fifth at four months) that they could not possibly have been related to pioglitazone treatment.[10,11] Links between pioglitazone and bladder cancer in meta-analyses of randomised controlled trials depend entirely on inclusion of these bladder cancer cases in the first year of PROactive, which we now know could not have been related to pioglitazone.[10,11] Lastly, and most importantly, the 6-year follow up data of PROactive have been published.[13] After 6 years there were 23 cases of bladder cancer in the pioglitazone-treated group versus 22 cases in the placebo-treated group. Thus, in 2015, it is highly unlikely that there is any link between pioglitazone and bladder cancer at all in humans.[7,10,11]

New perspectives

It is timely to reconsider the place of pioglitazone in our therapeutic armamentarium for diabetes. With the cloud of bladder cancer risk removed, it is our opinion that pioglitazone is being under-utilised.[7,11] It is the only diabetes agent with evidence to suggest that it reduces cardiovascular risk apart from metformin.[7,10,11,14] Indeed, there is considerable evidence for a cardioprotective effect of pioglitazone.[10] This evidence is particularly strong with regard to reducing risk in those who already have coronary artery[15] or cerebrovascular[16] disease, or those with renal impairment.[17] This is especially pertinent since type 2 diabetic patients have a 2–3 fold increase in cardiovascular events.

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- It, therefore, can be argued that the optimum management of type 2 diabetes would involve intensive management of the earlier stages using metformin, pioglitazone and GLP-1 receptor agonists, alone or in combination, with a view to achieving a HbA 1c < 6% in order to preserve β-cell function

Conclusion – in the wake of EMPA-REG

- ?Optimum cocktail for type 2 diabetes:
  - Metformin
  - Pioglitazone
  - Empagliflozin
  - GLP1 receptor agonist

company announcement

Victoza® significantly reduces the risk of major adverse cardiovascular events in the LEADER trial

Bagsværd, Denmark, 4 March 2016 - Novo Nordisk today announced the top-line results from the LEADER trial, which investigated the cardiovascular safety of Victoza® (liraglutide) over a period of up to 5 years in more than 9,000 adults with type 2 diabetes at high risk of major adverse cardiovascular events. The trial compared the addition of either Victoza® or placebo to standard of care and met the primary endpoint of showing non-inferiority as well as demonstrating superiority, with a statistically significant reduction in cardiovascular risk. The primary endpoint of the study was defined as the composite outcome of the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The superior reduction of major adverse cardiovascular events demonstrated by Victoza® was derived from all three components of the endpoint.

The safety profile of Victoza® in LEADER was generally consistent with previous liraglutide clinical studies.

"People with type 2 diabetes generally have a higher risk of experiencing major adverse cardiovascular events. That's why we are very excited about the results from LEADER, which showed that Victoza®, in addition to helping people with type 2 diabetes control their blood sugar levels, also reduces their risk of major adverse cardiovascular events ", said Mads Krogsgaard Thomsen, executive vice president and chief science officer of Novo Nordisk. "LEADER is the largest and longest Novo Nordisk clinical trial to report to date, and we look forward to sharing the detailed results with the medical community and submitting the findings to the regulatory authorities."

The detailed results are planned to be presented at the 76th Scientific Sessions of the American Diabetes Association in June 2016.

Conference call
On 4 March 2016 at 2.00 pm CET, corresponding to 8.00 am EST, a conference call for investors will be held. Investors will be able to listen in via a link on the investor section of novonordisk.com.

Statistically significant reduction in 3 point MACE with liraglutide – full presentation of results at ADA in New Orleans in June 2016

Conclusion – in the wake of EMPA-REG

- ?Optimum cocktail for type 2 diabetes:
  - Metformin
  - Pioglitazone
  - Empagliflozin
  - ?Liraglutide

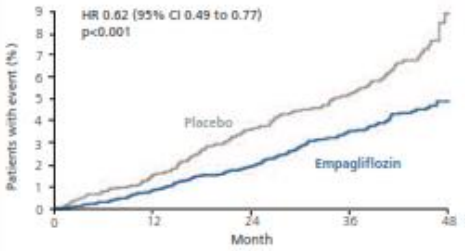
Diabetes medications with cardiovascular protection in the wake of EMPA-REG OUTCOME: the optimal combination may be metformin, pioglitazone and empagliflozin

ROBERT EJ RYDER,[1] RALPH A DEFRONZO[2]

Those of us who were in the huge, packed auditorium when the slide shown in Figure 1 went up on the screen at 17.15 on the 17th September, at the European Association for the Study of Diabetes 2015 congress in Stockholm, were aware that this was one of those landmark moments in the history of diabetes care. There was loud applause. The event was the presentation of the results of the EMPA-REG OUTCOME study, which evaluated the effect of the SGLT2 inhibitor, empagliflozin, on cardiovascular outcomes in people with type 2 diabetes at high cardiovascular risk.[1,2] As the whole story of the results unfolded, however, we realised that we were going to be left with as many questions as answers. In particular it seemed that empagliflozin reduced death from cardiac causes but did not reduce non-fatal myocardial infarction or stroke, a combination of findings which was at first sight difficult to understand. Comparing and contrasting the graphs from EMPA-REG, such as the one shown in Figure 1, with those from other studies is a quick way of getting a feel for the subject of antihyperglycaemic medications that might play a part in reducing cardiovascular risk.

Figure 2 shows the Kaplan-Meier plots for metformin in the 10-year, observational follow-up of the United Kingdom Prospective Diabetes Study (UKPDS),[3] which suggested the value of metformin as a cardioprotective agent seen in the earlier, randomised phase of the study.[4] Intensive glycaemic management with metformin, but not with a sulphonylurea or insulin, reduced cardiovascular outcomes, in comparison with the conventional (mainly diet-based) management of the time, during the original trial.[3,4] The fact that this occurred even though there was less reduction in HbA_{1c} in the metformin group (who were overweight) than the sulphonylurea-insulin group points to a special effect of metformin over and above any effect on glycaemic control.[3,4] It is noteworthy however that it took at least 3 years before the curves shown in Figure 2 for metformin really started to separate with regard to myocardial infarction or death from any cause. The patients in the UKPDS were newly diagnosed and developed their cardiovascular disease over many years. Furthermore, all of the metformin-treated subjects were overweight or obese and the number receiving this treatment (n=342) would be considered small for a cardiovascular outcomes study by today's standards.

Figure 1. The cumulative incidence of death from cardiovascular causes in the empagliflozin group versus placebo group in the EMPA-REG OUTCOME



Hazard ratios (HR) are based on Cox regression analysis. Reproduced with permission from ref 2.

The EMPA-REG OUTCOME study involved patients at high cardiovascular risk, as all had established cardiovascular disease in addition to being older (mean age 63 years at baseline), with a longer duration of diabetes (82% were diagnosed >5 years previously).[1,2] It can now be accepted by most that the status of pioglitazone as an agent of cardiovascular protection in such patients is supported by overwhelming evidence, with objections to this view no longer having credence.[5,6] Figure 3 shows side by side the effects of empagliflozin (EMPA-REG OUTCOME trial[2]) and pioglitazone (PROactive trial[7]) on 3-point major adverse cardiovascular events (MACE; death, myocardial infarction or stroke) in patient populations at high cardiovascular risk. These appear similar at first sight, but closer examination of the data reveals that empagliflozin significantly reduced cardiovascular death, but not myocardial infarction or stroke.[1,2] Also, the curves for cardiovascular death, shown in Figure 1, separate almost immediately (as do the curves in figure 3a; whereas in figure 3b there is a delay). In a meta-analysis of 19 randomised controlled trials, pioglitazone-treated patients had significantly lower rates of

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Google:
ryder empagliflozin

I know coz I was there!

- DCCT, Las Vegas, 1993
- UKPDS, Barcelona, 1998
- PROactive, Athens, 2005
- EMPA-REG, Stockholm 2015
- (LEADER, New Orleans 2016)

*Max Boyce

Post script – if time

Pioglitazone and bladder cancer

Pioglitazone use and risk of bladder cancer: population based cohort study

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ABSTRACT

OBJECTIVE
To determine whether pioglitazone compared with other antidiabetic drugs is associated with an increased risk of bladder cancer in people with type 2 diabetes.

DESIGN
Population based cohort study.

SETTING
General practices contributing data to the United Kingdom Clinical Practice Research Datalink.

PARTICIPANTS
A cohort of 145 806 patients newly treated with antidiabetic drugs between 1 January 2000 and 31 July 2013, with follow-up until 31 July 2014.

MAIN OUTCOME MEASURES
The use of pioglitazone was treated as a time varying variable, with use lagged by one year for latency purposes. Cox proportional hazards models were used to estimate adjusted hazard ratios with 95% confidence intervals of incident bladder cancer associated with pioglitazone overall and by both cumulative duration of use and cumulative dose. Similar analyses were conducted for rosiglitazone, a thiazolidinedione not previously associated with an increased risk of bladder cancer.

years; 1.10, 0.83 to 1.47). Duration-response and dose-response relations were observed for pioglitazone but not for rosiglitazone.

CONCLUSION
The results of this large population based study indicate that pioglitazone is associated with an increased risk of bladder cancer. The absence of an association with rosiglitazone suggests that the increased risk is drug specific and not a class effect.

Introduction

Pioglitazone, an antidiabetic drug belonging to the thiazolidinedione class, has been shown to improve glycaemic levels in people with type 2 diabetes.[1] However, in 2005 the PROactive randomised controlled trial unexpectedly showed an imbalance in the number of cases of bladder cancer with pioglitazone compared with placebo.[2] In contrast, this imbalance was never observed in randomised controlled trials of rosiglitazone, the other approved drug belonging to the thiazolidinedione class.[1 3]

The findings of the PROactive trial were subsequently corroborated in some,[4-10] but not all, observational studies.[11-19] Indeed, in the five year interim analysis of a large observational study using the Kaiser Permanente Northern California database,[4] the use of pioglitazone

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DIABETICMedicine

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Controversies in Diabetes

Pioglitazone has a dubious bladder cancer risk but an undoubted cardiovascular benefit

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Accepted 3 November 2014

Abstract

On 8 April 2014, a US jury ordered Takeda and Eli Lilly to pay $9 bn in punitive damages after finding that they had concealed the cancer risks associated with pioglitazone. By contrast, on 28 August 2014, the long-awaited outcome of the 10-year Kaiser Permanente Northern California study was announced. That study was specifically designed to investigate whether patients exposed to pioglitazone were at an increased risk of bladder cancer and found no association; thus, at last, the controversial issue has been resolved. A review, in retrospect, of the story of the proposed link between pioglitazone and bladder cancer reveals flaws at every stage. In 2012, a *BMJ* editorial, in keeping with some other contemporary reports, stated 'it can confidently be assumed that pioglitazone increases the risk of bladder cancer'. Examination of the information which led to such a statement shows that: 1) the pre-clinical findings of bladder cancer in male rats is not indicative of human risk; 2) there is no association between bladder cancer and pioglitazone in randomized controlled trials, once cases that could not plausibly be related to treatment are removed; and 3) the observational studies that have suggested a link have over-extrapolated from the data: pioglitazone-treated patients had more risk factors for bladder cancer than those not treated with pioglitazone. Meanwhile careful study of randomized controlled trials shows evidence of cardiovascular benefit from pioglitazone in Type 2 diabetes, a condition which results, more than anything, in premature cardiovascular death and morbidity.

Diabet. Med. 32, 305–313 (2015)

Introduction

The year 2014 has seen two noteworthy events in the unfolding story of pioglitazone. On 8 April 2014, a US jury ordered the pharmaceutical companies Takeda and Eli Lilly to pay a combined $9 bn in punitive damages after finding that the companies had concealed cancer risks associated with pioglitazone. The jury also awarded compensatory damages to the plaintiff of nearly $1.5 million in the first federal lawsuit related to the drug to go to trial [1]. By contrast on 29 August 2014, the long-awaited outcome of the 10-year epidemiology study, conducted by the University of Pennsylvania and Division of Research at Kaiser Permanente Northern California (KPNC), was announced [2]. The KPNC study was undertaken at the request of the US Food and Drug Administration (FDA) as a safety study involving 193 099 patients and designed to assess whether therapy with pioglitazone increases the risk of bladder cancer [3]. The primary analysis found no association between the use of pioglitazone and the risk of bladder cancer [2]. Additionally, no association was found between the risk of bladder cancer and the duration of pioglitazone use, increased cumulative dose of pioglitazone or the time since initiating pioglitazone [2]; thus, at last, the controversial issue of whether there is a link between pioglitazone and bladder cancer has been resolved.

This is, therefore, an opportune moment to revisit the story of the proposed link between pioglitazone and bladder cancer and review, in retrospect, the flaws in the case at every stage. In the medical literature the case against pioglitazone reached its zenith when in 2012 Azoulay *et al.* [4] concluded from their observational study, published in the *BMJ*, that pioglitazone was associated with an increased risk of bladder cancer. In a *BMJ* editorial in the same issue [5], it was concluded that 'Taking into account Azoulay and colleagues' current findings and given the consistency of these results, the relative strength of the association, the dose-response effect, the known pharmacodynamic characteristics of pioglitazone, and evidence of a significant association in a meta-analysis of randomized trials it can confidently be assumed that pioglitazone increases the risk of bladder cancer. …Considering that the benefit of pioglitazone in reducing cardiovascular events is questionable, prescribers who are ultimately responsible for therapeutic choices can legitimately question

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Explanation

- Diabetes is itself a risk factor for bladder cancer
- The longer the duration of diabetes and the poorer the control and the longer the poorer control the greater the risk

Ryder REJ. Diabet Med 2015;32:305-13

Pioglitazone use and risk of bladder cancer: population based cohort study

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Study population

Base cohort

We assembled a base cohort composed of all people newly treated for type 2 diabetes, defined as receiving a first ever prescription for a non-insulin antidiabetic drug (metformin, sulfonylureas, prandial glucose regulators, thiazolidinediones, acarbose, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide (GLP-1) agonists, sodium-glucose cotransporter-2 (SGLT2) inhibitors) between 1 January 1988 and 31 July 2013. Patients were required to be at least 40 years of age and to have at least one year of CPRD medical history before that first prescription. We excluded patients prescribed insulin any time before their first non-insulin antidiabetic prescription (as these may represent those with an

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Introduction

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Haemoglobin A1c:			
≤7.4%	27 209 (18.7)	148 (16.1)	26 793 (18.8)
>7.4%	68 309 (46.9)	537 (58.3)	66 485 (46.6)
Unknown	50 288 (34.5)	236 (25.6)	49 480 (34.7)
Mean (SD) duration of treated diabetes (years)	0.3 (1.6)	4.2 (4.6)	0.3 (1.3)

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ABSTRACT

OBJECTIVE

To determine whether pioglitazone compared with other antidiabetic drugs is associated with an increased risk of bladder cancer in people with type 2 diabetes.

DESIGN

Population based cohort study.

SETTING

General practices contributing data to the United Kingdom Clinical Practice Research Datalink.

PARTICIPANTS

A cohort of 145 806 patients newly treated with antidiabetic drugs between 1 January 2000 and 31 July 2013, with follow-up until 31 July 2014.

MAIN OUTCOME MEASURES

The use of pioglitazone was treated as a time varying variable, with use lagged by one year for latency purposes. Cox proportional hazards models were used to estimate adjusted hazard ratios with 95% confidence intervals of incident bladder cancer associated with pioglitazone overall and by both cumulative duration of use and cumulative dose. Similar analyses were conducted for rosiglitazone, a thiazolidinedione not previously associated with an increased risk of bladder cancer.

RESULTS

The cohort generated 689 616 person years of follow-up, during which 622 patients were newly diagnosed as having bladder cancer (crude incidence 90.2 per 100 000 person years). Compared with other antidiabetic drugs, pioglitazone was associated with an increased risk of bladder cancer (121.0 *v* 88.9 per 100 000 person years; hazard ratio 1.63, 95% confidence interval 1.22 to 2.19). Conversely, rosiglitazone was not associated with an increased risk of bladder cancer (86.2 *v* 88.9 per 100 000 person years; 1.10, 0.83 to 1.47). Duration-response and dose-response relations were observed for pioglitazone but not for rosiglitazone.

CONCLUSION

The results of this large population based study indicate that pioglitazone is associated with an increased risk of bladder cancer. The absence of an association with rosiglitazone suggests that the increased risk is drug specific and not a class effect.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The association between the use of pioglitazone and bladder cancer is controversial, with studies reporting contradictory findings

Additional observational studies with longer follow-up are needed to assess whether this drug is associated with an increased risk of bladder cancer

WHAT THIS STUDY ADDS

In this large population based study, the use of pioglitazone was associated with an overall 63% increased risk of bladder cancer, with the risk increasing with increasing duration of use and dose

In contrast, the use of rosiglitazone was not associated with an increased risk, with no evidence of a duration-response or dose-response relation

These findings suggest that the association observed with pioglitazone is likely to be a drug specific and not a class effect

Introduction

Pioglitazone, an antidiabetic drug belonging to the thiazolidinedione class, has been shown to improve glycaemic levels in people with type 2 diabetes.[1] However, in 2005 the PROactive randomised controlled trial unexpectedly showed an imbalance in the number of cases of bladder cancer with pioglitazone compared with placebo.[2] In contrast, this imbalance was never observed in randomised controlled trials of rosiglitazone, the other approved drug belonging to the thiazolidinedione class.[2 3]

The findings of the PROactive trial were subsequently corroborated in some,[4-10] but not all, observational studies.[11-19] Indeed, in the five year interim analysis of a large observational study using the Kaiser Permanente Northern California database,[4] the use of pioglitazone for 24 months or more was associated with an increased risk of bladder cancer (hazard ratio 1.4, 95% confidence interval 1.03 to 2.0). However, in the final analysis of the Kaiser Permanente Northern California study, which used the same cohort[4] with follow-up extended to 10 years, the use of pioglitazone was no longer significantly associated with an increased risk of bladder cancer in a duration-response fashion.[20] These null findings are also consistent with those of another large multicohort study.[19] The apparent heterogeneity in this literature may be due to methodological limitations, such as the inclusion of prevalent users,[5 6 10 16 18] time lag bias,[15] immortal time bias,[10 16 18] and no consideration of disease latency.[8 10 12 17 18]

Given these discrepant findings, the methodological shortcoming of previous studies examining this association, and the apparent loss of an association in studies with longer follow-up,[20] additional studies are needed to investigate further the association between pioglitazone and bladder cancer. In a large, population based study we assessed the association between the use of pioglitazone and bladder cancer in people with type 2 diabetes.

Methods

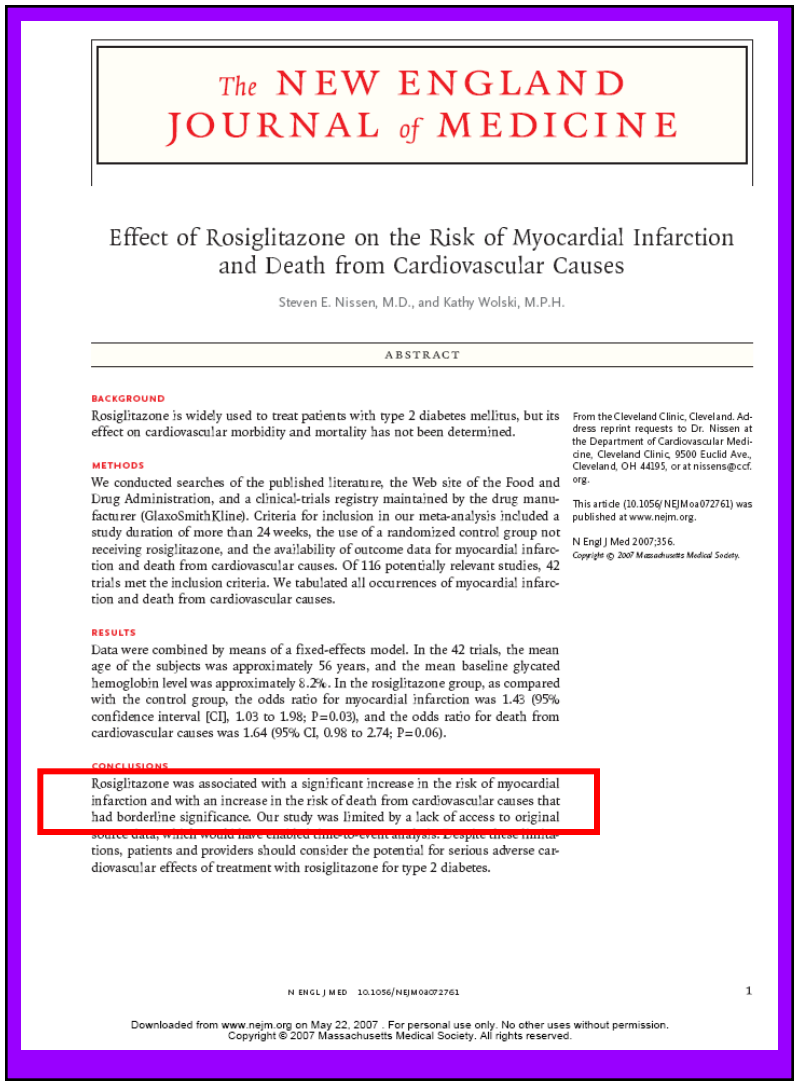
Data source

This study was conducted using the United Kingdom Clinical Practice Research Datalink (CPRD). This

Association with pioglitazone but not rosiglitazone

Metanalysis

Rosiglitazone – cardiovascular harm



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.

ABSTRACT

BACKGROUND

Rosiglitazone is widely used to treat patients with type 2 diabetes mellitus, but its effect on cardiovascular morbidity and mortality has not been determined.

METHODS

We conducted searches of the published literature, the Web site of the Food and Drug Administration, and a clinical-trials registry maintained by the drug manufacturer (GlaxoSmithKline). Criteria for inclusion in our meta-analysis included a study duration of more than 24 weeks, the use of a randomized control group not receiving rosiglitazone, and the availability of outcome data for myocardial infarction and death from cardiovascular causes. Of 116 potentially relevant studies, 42 trials met the inclusion criteria. We tabulated all occurrences of myocardial infarction and death from cardiovascular causes.

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).

CONCLUSIONS

Rosiglitazone was associated with a significant increase in the risk of myocardial infarction and with an increase in the risk of death from cardiovascular causes that had borderline significance. Our study was limited by a lack of access to original source data, which would have enabled time-to-event analyses. Despite these limitations, patients and providers should consider the potential for serious adverse cardiovascular effects of treatment with rosiglitazone for type 2 diabetes.

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This article (10.1056/NEJMoa072761) was published at www.nejm.org.

N Engl J Med 2007;356.

Pioglitazone – cardiovascular benefit

REVIEW

Pioglitazone and Risk of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

A Meta-analysis of Randomized Trials

A. Michael Lincoff, MD
Kathy Wolski, MPH
Stephen J. Nicholls, MBBS, PhD
Steven E. Nissen, MD

Context Pioglitazone is widely used for glycemic control in patients with type 2 diabetes mellitus, but evidence is mixed regarding the influence of medications of this class on cardiovascular outcomes.

Objective To systematically evaluate the effect of pioglitazone on ischemic cardiovascular events.

Data Sources and Study Selection A database containing individual patient-level time-to-event data collected during pioglitazone clinical trials was transferred from the drug's manufacturer for independent analysis. Trials were included if they were randomized, double-blinded, and controlled with placebo or active comparator.

Data Extraction The primary outcome was a composite of death, myocardial infarction, or stroke. Secondary outcome measures included the incidence of serious heart failure. A fixed-effects approach was used to combine the estimates across the duration strata and statistical heterogeneity across all the trials was tested with the I^2 statistic.

Data Synthesis A total of 19 trials enrolling 16 390 patients were analyzed. Study drug treatment duration ranged from 4 months to 3.5 years. Death, myocardial infarction, or stroke occurred in 375 of 8554 patients (4.4%) receiving pioglitazone and 450 of 7836 patients (5.7%) receiving control therapy (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.72-0.94; $P=.005$). Progressive separation of time-to-event curves became apparent after approximately 1 year of therapy. Individual components of the primary end point were all reduced by a similar magnitude with pioglitazone treatment, with HRs ranging from 0.80 to 0.92. Serious heart failure was reported in 200 (2.3%) of the pioglitazone-treated patients and 139 (1.8%) of the control patients (HR, 1.41; 95% CI, 1.14-1.76; $P=.002$). The magnitude and direction of the favorable effect of pioglitazone on ischemic events and unfavorable effect on heart failure was homogeneous across trials of different durations, for different comparators, and for patients with or without established vascular disease. There was no evidence of heterogeneity across the trials for either end point ($I^2=0\%$; $P=.87$ for the composite end point and $I^2=0\%$; $P=.57$ for heart failure).

Conclusions Pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes. Serious heart failure is increased by pioglitazone, although without an associated increase in mortality.

JAMA. 2007;298(10):1180-1188 www.jama.com

THIAZOLIDINEDIONES ARE AGONISTS of the peroxisome proliferation–activated receptor γ (PPAR-γ), which regulate transcription of a variety of genes encoding proteins involved in glucose homeostasis and lipid metabolism.[1,2] By virtue of their efficacy in achieving glycemic control, the thiazolidinediones pioglitazone and rosiglitazone are both widely used to treat patients with type 2 diabetes mellitus. Although these agents can cause peripheral edema and congestive heart failure,[3,4] their beneficial effects on glucose metabolism and insulin sensitivity have stimulated interest that thiazolidinediones might reduce ischemic cardiovascular complications of diabetes mellitus.

However, a recent meta-analysis of 42 trials comparing rosiglitazone with placebo or active comparators in more than 27 000 patients with diabetes suggested that treatment with rosiglitazone was associated with an increased risk of myocardial infarction and cardiovascular death.[5] Furthermore, a previous analysis had demonstrated that muraglitazar, an investigational dual agonist of both α- and γ-isoforms of PPAR, was also associated with an excess incidence of death and major cardiovascular events in patients with diabetes.[6]

See also pp 1189 and 1216.

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DIABETICMedicine

DOI: 10.1111/dme.12627

Controversies in Diabetes

Pioglitazone has a dubious bladder cancer risk but an undoubted cardiovascular benefit

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Accepted 5 November 2014

Abstract

On 8 April 2014, a US jury ordered Takeda and Eli Lilly to pay $9 bn in punitive damages after finding that they had concealed the cancer risks associated with pioglitazone. By contrast, on 28 August 2014, the long-awaited outcome of the 10-year Kaiser Permanente Northern California study was announced. That study was specifically designed to investigate whether patients exposed to pioglitazone were at an increased risk of bladder cancer and found no association; thus, at last, the controversial issue has been resolved. A review, in retrospect, of the story of the proposed link between pioglitazone and bladder cancer reveals flaws at every stage. In 2012, a *BMJ* editorial, in keeping with some other contemporary reports, stated 'it can confidently be assumed that pioglitazone increases the risk of bladder cancer'. Examination of the information which led to such a statement shows that: 1) the pre-clinical findings of bladder cancer in male rats is not indicative of human risk; 2) there is no association between bladder cancer and pioglitazone in randomized controlled trials, once cases that could not plausibly be related to treatment are removed; and 3) the observational studies that have suggested a link have over-extrapolated from the data: pioglitazone-treated patients had more risk factors for bladder cancer than those not treated with pioglitazone. Meanwhile careful study of randomized controlled trials shows evidence of cardiovascular benefit from pioglitazone in Type 2 diabetes, a condition which results, more than anything, in premature cardiovascular death and morbidity.

Diabet. Med. 32, 305–313 (2015)

Introduction

The year 2014 has seen two noteworthy events in the unfolding story of pioglitazone. On 8 April 2014, a US jury ordered the pharmaceutical companies Takeda and Eli Lilly to pay a combined $9 bn in punitive damages after finding that the companies had concealed cancer risks associated with pioglitazone. The jury also awarded compensatory damages to the plaintiff of nearly $1.5 million in the first federal lawsuit related to the drug to go to trial [1]. By contrast on 29 August 2014, the long-awaited outcome of the 10-year epidemiology study, conducted by the University of Pennsylvania and Division of Research at Kaiser Permanente Northern California (KPNC), was announced [2]. The KPNC study was undertaken at the request of the US Food and Drug Administration (FDA) as a safety study involving 193 099 patients and designed to assess whether therapy with pioglitazone increases the risk of bladder cancer [3]. The primary analysis found no association between the use of pioglitazone and the risk of bladder cancer [2]. Additionally, no association was found between the risk of bladder cancer and the duration of pioglitazone use, increased cumulative dose of pioglitazone or the time since initiating pioglitazone [2]; thus, at last, the controversial issue of whether there is a link between pioglitazone and bladder cancer has been resolved.

This is, therefore, an opportune moment to revisit the story of the proposed link between pioglitazone and bladder cancer and review, in retrospect, the flaws in the case at every stage. In the medical literature the case against pioglitazone reached its zenith when in 2012 Azoulay *et al.* [4] concluded from their observational study, published in the *BMJ*, that pioglitazone was associated with an increased risk of bladder cancer. In a *BMJ* editorial in the same issue [5], it was concluded that 'Taking into account Azoulay and colleagues' current findings and given the consistency of these results, the relative strength of the association, the dose-response effect, the known pharmacodynamic characteristics of pioglitazone, and evidence of a significant association in a meta-analysis of randomized trials it can confidently be assumed that pioglitazone increases the risk of bladder cancer. …Considering that the benefit of pioglitazone in reducing cardiovascular events is questionable, prescribers who are ultimately responsible for therapeutic choices can legitimately question

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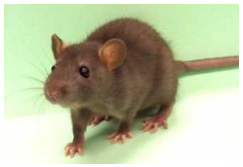
- With the publications suggesting pioglitazone causes cardiovascular benefit and those suggesting rosiglitazone causes cardiovascular harm, there was much more use of pioglitazone in the more "cardiovascular" patients with type 2 diabetes – again, those with the "more advanced form of diabetes" that would be associated with bladder cancer
- Rosiglitazone treated "cardiovascular patients" were switched to pioglitazone
- Thus, it is not surprising to find that bladder cancer is higher in pioglitazone treated patients

Ryder REJ. Diabet Med 2015;32:305-13

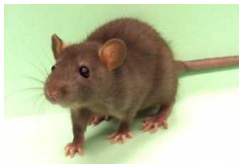
Why concern about bladder cancer in the first place?

Pre-clinical studies



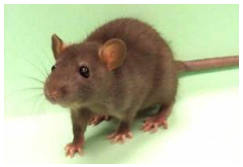
Bladder hyperplasia, metaplasia, cancer		
	Male	Female
Mouse	X	X
Rat	√	X
Dog	X	X
Monkey	X	X

Pre-clinical studies



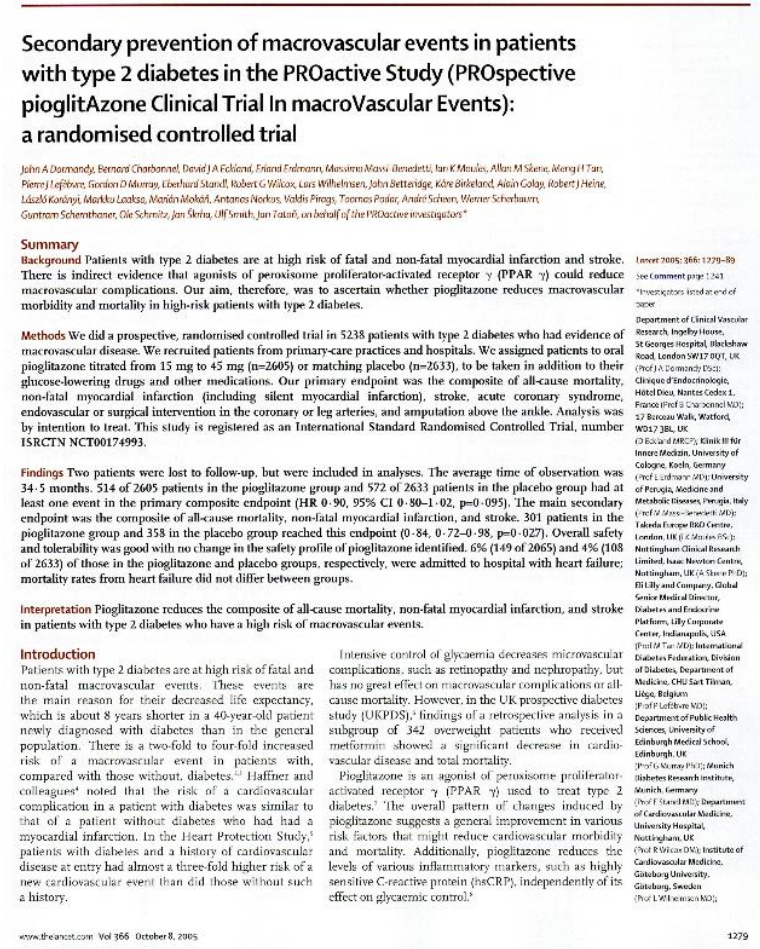
Bladder hyperplasia, metaplasia, cancer		
	Male	Female
Mouse	X	X
Rat	We now know seems to be related to high PH of male rat urine	X
Dog	X	X
Monkey	X	X

Pre-clinical studies



Bladder hyperplasia, metaplasia, cancer		
	Male	Female
Mouse	X	X
Rat	Seems to be a rat specific problem not indicative of human risk	X
Dog	X	X
Monkey	X	X

The PROactive Study, 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, Tuomas Podar, André Scheen, Werner Scherbaum, Guntram Schernthaner, Ole Schmitz, Jan Skrha, Ulf Smith, Jan Taton, 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.

Findings Two patients were lost to follow-up, but were included in analyses. The average time of observation was 34·5 months. 514 of 2605 patients in the pioglitazone group and 572 of 2633 patients in the placebo group had at least one event in the primary composite endpoint (HR 0·90, 95% CI 0·80–1·02, p=0·095). The main secondary endpoint was the composite of all-cause mortality, non-fatal myocardial infarction, and stroke. 301 patients in the pioglitazone group and 358 in the placebo group reached this endpoint (0·84, 0·72–0·98, p=0·027). Overall safety and tolerability was good with no change in the safety profile of pioglitazone identified. 6% (149 of 2065) and 4% (108 of 2633) of those in the pioglitazone and placebo groups, respectively, were admitted to hospital with heart failure; mortality rates from heart failure did not differ between groups.

Interpretation Pioglitazone reduces the composite of all-cause mortality, non-fatal myocardial infarction, and stroke in patients with type 2 diabetes who have a high risk of macrovascular events.

Lancet 2005; 366: 1279–89

See Comment page 1243

*Investigators listed at end of paper

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Introduction

Patients with type 2 diabetes are at high risk of fatal and non-fatal macrovascular events. These events are the main reason for their decreased life expectancy, which is about 8 years shorter in a 40-year-old patient newly diagnosed with diabetes than in the general population. There is a two-fold to four-fold increased risk of a macrovascular event in patients with, compared with those without, diabetes.[1,2] Haffner and colleagues[3] noted that the risk of a cardiovascular complication in a patient with diabetes was similar to that of a patient without diabetes who had had a myocardial infarction. In the Heart Protection Study,[4] patients with diabetes and a history of cardiovascular disease at entry had almost a three-fold higher risk of a new cardiovascular event than did those without such a history.

Intensive control of glycaemia decreases microvascular complications, such as retinopathy and nephropathy, but has no great effect on macrovascular complications or all-cause mortality. However, in the UK prospective diabetes study (UKPDS),[5] findings of a retrospective analysis in a subgroup of 342 overweight patients who received metformin showed a significant decrease in cardiovascular disease and total mortality.

Pioglitazone is an agonist of peroxisome proliferator-activated receptor γ (PPAR γ) used to treat type 2 diabetes.[6] The overall pattern of changes induced by pioglitazone suggests a general improvement in various risk factors that might reduce cardiovascular morbidity and mortality. Additionally, pioglitazone reduces the levels of various inflammatory markers, such as highly sensitive C-reactive protein (hsCRP), independently of its effect on glycaemic control.[6]

Dormandy JA et al. 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. Lancet 2005; 366: 1279–1289.

	Pioglitazone (n=2605)		Placebo (n=2633)		p
	Number of events	Number of patients	Number of events	Number of patients	
Any serious adverse event	2720	1204 (46%)	2978	1275 (48%)	0·110
Endpoint events*	602	389 (15%)	686	434 (16%)	0·123
Non-endpoint events	2118	1079 (41%)	2292	1150 (44%)	0·099
Most common events (excluding endpoints)†					
Angina pectoris	107	89 (3%)	145	122 (5%)	0·025
Hospital admission for diabetes control	57	55 (2%)	99	91 (3%)	0·003
Accident	53	51 (2%)	50	49 (2%)	0·798
Atrial fibrillation	47	42 (2%)	60	51 (2%)	0·374
Pneumonia	57	53 (2%)	37	35 (1%)	0·047
Transient ischaemic attack	39	34 (1%)	42	39 (2%)	0·587
Neoplasms	118	112 (4%)	117	113 (4%)	
Malignant‡	103	97 (4%)	103	99 (4%)	
Colon/rectal	..	16 (1%)	..	15 (1%)	0·834
Lung	..	15 (1%)	..	12 (1%)	0·544
Bladder	..	14 (1%)	..	6 (<1%)	0·069
Bladder (after exclusion)§	..	6 (<1%)	..	3 (<1%)	0·309
Haematological	..	6 (<1%)	..	10 (<1%)	0·327
Breast	..	3 (<1%)	..	11 (<1%)	0·034
Other	..	47 (2%)	..	46 (2%)	0·876

*Does not include silent myocardial infarctions or events resulting in death. †Events reported by more than 1% of patients, excluding heart failure (see table 9). ‡Some patients had more than one tumour type. §Cases remaining after blinded review, see main text for details.

***Table 8*: Serious adverse event summary**

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Neoplasms	118	112 (4%)	117	113 (4%)	
Malignant‡	103	97 (4%)	103	99 (4%)	
Colon/rectal	..	16 (1%)	..	15 (1%)	0·834
Lung	..	15 (1%)	..	12 (1%)	0·544
Bladder	..	14 (1%)	..	6 (<1%)	0·069
Bladder (after exclusion)§	..	6 (<1%)	..	3 (<1%)	0·309
Haematological	..	6 (<1%)	..	10 (<1%)	0·327
Breast	..	3 (<1%)	..	11 (<1%)	0·034
Other	..	47 (2%)	..	46 (2%)	0·876

*Does not include silent myocardial infarctions or events resulting in death. †Events reported by more than 1% of patients, excluding heart failure (see table 9). ‡Some patients had more than one tumour type. §Cases remaining after blinded review, see main text for details.

***Table 8*: Serious adverse event summary**

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Controversies in Diabetes

Pioglitazone: are rumours of its death exaggerated?

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In this issue of *Diabetic Medicine* Dr Bob Ryder offers a stalwart defence of pioglitazone, casts doubts on its alleged association with bladder cancer, and argues for its cardiovascular benefits. My first response is to wonder why we need to have this debate at all. Pioglitazone has been out there for 14 years, has been consumed by millions of people, has generated $16 billion in sales and yet – as Dr Ryder correctly points out – we still do not really know whether people are better off for taking it or not. This, as I shall argue, is a more fundamental cause for concern.

The story of the thiazolidinediones has not been a happy one. Troglitazone was introduced in the USA in early 1997, and was launched in Europe by Glaxo-Wellcome on 1 October 1997, only to be withdrawn 29 days later when the Board of Glaxo-Wellcome, headed by Sir Richard Sykes, reviewed the safety profile of the agent. The Board concluded that the emerging risks of troglitazone outweighed the likely benefits, and that the drug should be withdrawn from the market. This act of moral courage, amply borne out by subsequent events, has never received the recognition or credit that it deserves. Troglitazone continued to be marketed by other companies in the USA and Japan until 20 March 2000 and [according to a retrospective US Food and Drug Administration (FDA) review] was probably responsible for several thousand episodes of severe liver injury and a few hundred deaths [1]. Although this was a clear case of regulatory failure, the regulators relied on feedback from the company and advice from prominent clinicians (including representatives of the American Endocrine Society), claiming that the drug had unique benefits that justified its risks.

Rosiglitazone and pioglitazone reached the market on a wave of clinical expectation, but with little evidence to support their use [2]. Safety concerns were already present. The pivotal trials with rosiglitazone suggested cardiovascular problems, which were subsequently reported to the FDA. The FDA mandated the RECORD Trial, but did not warn clinicians of the existence of a possible signal. GSK was (coincidentally) obliged to put its data into the public domain, enabling Nissen and Wolski to publish their own analysis, which showed what the company and the regulators already knew [3]. RECORD was unblinded prematurely and the subsequent cascade of events led to a Senate Sub-Committee hearing and successive FDA consultations which damned the drug in 2011 and offered posthumous rehabilitation in 2013. The rights and wrongs of this appalling farce may never be known – or at least agreed upon – but the Senate Committee did bring one piece of evidence to light, which (if validated, and no one seems to want to) threatens the whole pharmaceutical enterprise: the suggestion of bias in the way safety data were analysed and recorded by the company [4].

Does pioglitazone confer an increased risk of bladder cancer?

Before we consider pioglitazone, some clarification is needed regarding recent litigation. A court in Louisiana awarded $1.5 million in compensatory damages to the plaintiff and a combined total of $9 billion in penal damages against the two companies involved. Punitive damages are awarded to punish wrong-doing, and this jury was incensed by evidence alleging that those concerned had consistently downplayed the potential of pioglitazone to cause bladder cancer, destroying key documents in the process [5]. Punitive damages are generally struck down on appeal, but in this instance they were reduced to around $37 million, with at least some implication of blame [6]. The company intends to appeal the verdict. The real truth, needless to say, will probably never be known.

It was known at launch that pioglitazone produced bladder cancer in rats, although the human studies available lacked power to answer this question. Five years later, Samuel Cohen reviewed evidence pointing to an excess of bladder cancer in rats treated with glitazones [peroxisome proliferator-activated receptor (PPAR)γ agonists] and glitazars (PPARα/γ agonists), and outlined the hypothesis that is linked to his name [7]. In this, he pointed out that there are two potential routes to cancer formation in the bladder: a direct route mediated by PPAR (plentifully expressed in

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Pioglitazone could be a tumour promoter to account for the increased bladder tumours during the first year of the PROactive study

Gale EAM. Diabet Med 2015; 32:431-7

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Controversies in Diabetes

Neither evidence from the PROactive study nor the KPNC supports pioglitazone as a tumour promoter

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Professor Gale [1] has challenged my proposal that the purported link between pioglitazone and bladder cancer is dubious, whereas its association with cardiovascular benefit is undoubted [2]. My full commentary on Professor Gale's case is provided as an Online Only article [3], but I present here some important points, particularly with regard to his suggestion that pioglitazone might be a tumour promoter [1].

Professor Gale proposes that pioglitazone is a tumour promoter to account for the increased tumours during the first year of PROspective pioglitAzone Clinical Trial In macroVascular Events study (PROactive) [1]. He references three systematic reviews and meta-analyses as evidence of a consistent association between pioglitazone use and bladder cancer [4–6]. However, these effectively all look at the same data and mix randomized controlled trials (RCT), observational studies, and even studies involving spontaneous reports of bladder cancer to the US Food and Drug Administration (FDA) adverse event reporting system [4–6].

I have explained at length in my paper how the data from observational studies, and studies involving spontaneous reports to adverse event reporting systems, cannot be relied upon to help [2]. With regard to RCTs in these 'meta-analyses', the positive associations depend on including cases occurring in the first year of treatment. And in fact we find, when this is done, that the dominating cases in the meta-analyses are those occurring in the PROactive study. For example, in the meta-analysis of Turner and colleagues [4], which Professor Gale cites [1], there were 16 bladder cancer cases in the pioglitazone-treated group, 14 of which were from PROactive; and 6 bladder cancer cases in the control group, 5 of which were from PROactive. Even though in the PROactive analysis external experts blind to the group in which the bladder cancer cases occurred adjudicated that 11 cases could not plausibly be related to treatment because they occurred within the first year of treatment [7], these 11 cases were included in the meta-analysis. In short, the conclusion that pioglitazone might be associated with bladder cancer from RCT evidence depends entirely on the 11 cases occurring in the first year of the PROactive study. The 11 cases, 8 in the pioglitazone arm and 3 in the placebo arm that Professor Gale suggests might be providing evidence of pioglitazone as an agent that promotes tumours [1].

Table 1 shows data that are available [8], but not previously published, regarding when during that first year of PROactive these bladder cancer cases were diagnosed. If we consider the first five cases in the table, all randomised to pioglitazone in PROactive, two cases were diagnosed 13 and 14 days into the trial respectively, one at one month, another at three months and a fifth at four months [8]. Bearing in mind that the diagnosis of bladder cancer depends upon recognition of symptoms and signs, investigations, referral for specialist assessment leading to cystoscopy and biopsy, histopathology assessment and report of the biopsy and then communication of the result to the patient, usually at

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Table 1 Bladder cancer appearing during the first year of the PROactive study [8]. The number of months into the trial when each bladder cancer was diagnosed. Cases presented in the time order that the cancer was diagnosed. Results rounded to the nearest 0.5 of a month

Case number	PROactive study group	Diagnosis of bladder cancer (months into trial)
1	Pioglitazone	0.5 (13 days)
2	Pioglitazone	0.5 (14 days)
3	Pioglitazone	1.0
4	Pioglitazone	3.0
5	Pioglitazone	4.0
6	Placebo	5.5
7	Pioglitazone	6.0
8	Placebo	7.0
9	Pioglitazone	7.5
10	Placebo	8.0
11	Pioglitazone	12.0

PROactive study = Prospective pioglitazone clinical trial in macrovascular events [7].

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"Bearing in mind that the diagnosis of bladder cancer depends upon recognition of symptoms and signs, investigations, referral for specialist assessment leading to cystoscopy and biopsy, histopathology assessment and report of the biopsy and then communication of the result to the patient, usually at specialist consultation, it is impossible that pioglitazone could have played any role in these five bladder cancer cases."

KPNC study

- Requested by the FDA and EMA
- Large 10 year prospective safety study to establish whether or not there was a link between pioglitazone and bladder cancer in humans
- Results published in 2015
- No link between pioglitazone and bladder cancer

Lewis JD, et al. JAMA 2015;314:265-77

Million patients, 6 countries study

- 1.01 million diabetic individuals
- Six countries
- Results published in 2015
- No link between pioglitazone and bladder cancer

Levin D, et al. Diabetologia 2015;58:493-504