Reducing cardiovascular risk in type 2 diabetes

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Consultant Diabetologist, City Hospital, Birmingham

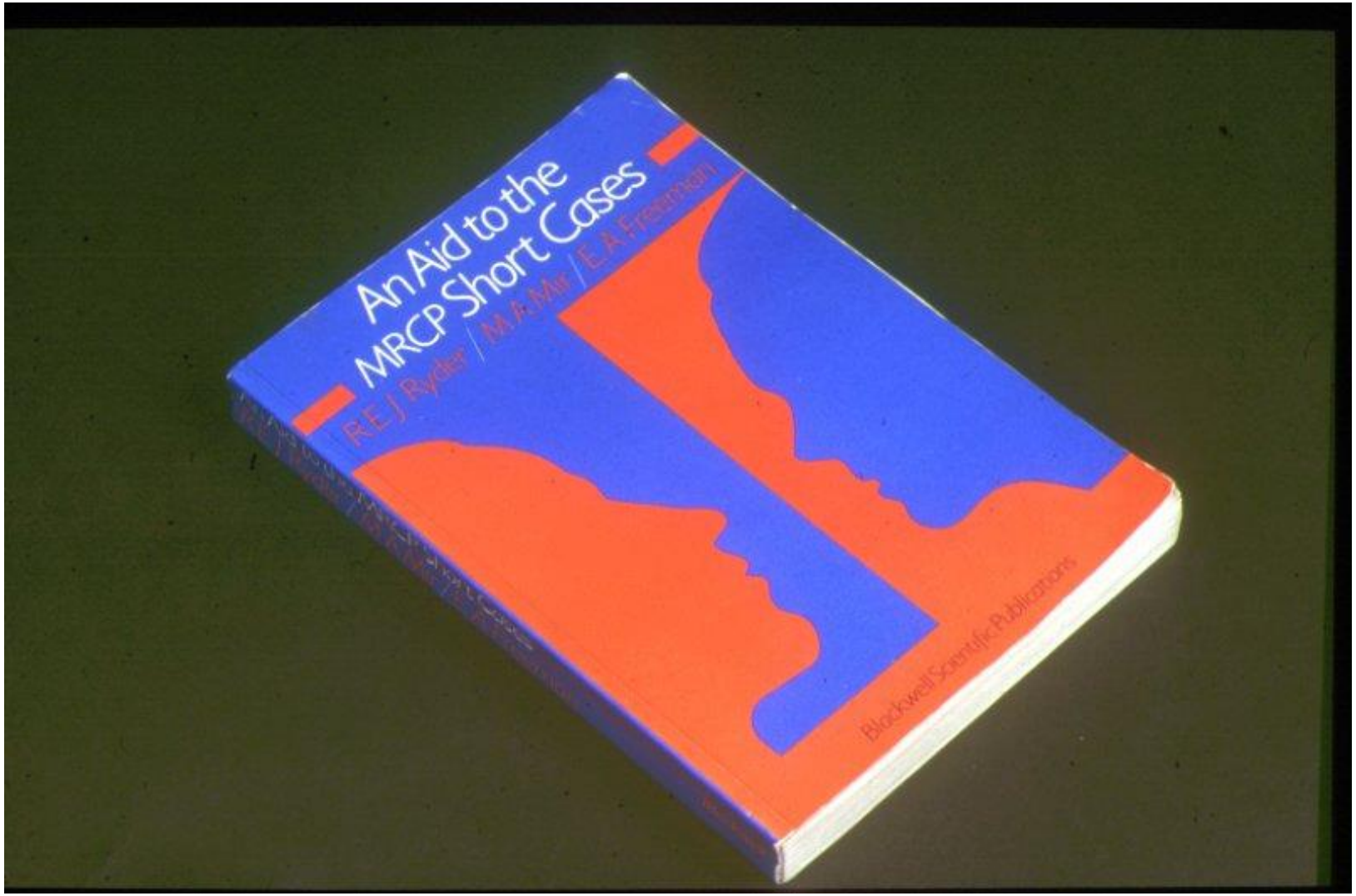
ABCD Midlands Regional Meeting 2025

1, October 2025

Disclosures

- Dr Bob Ryder has received speaker fees, and/or consultancy fees and/or educational sponsorships from Abbott, AstraZeneca, Besins, BioQuest, Morphic Medical and Novo Nordisk

Prologue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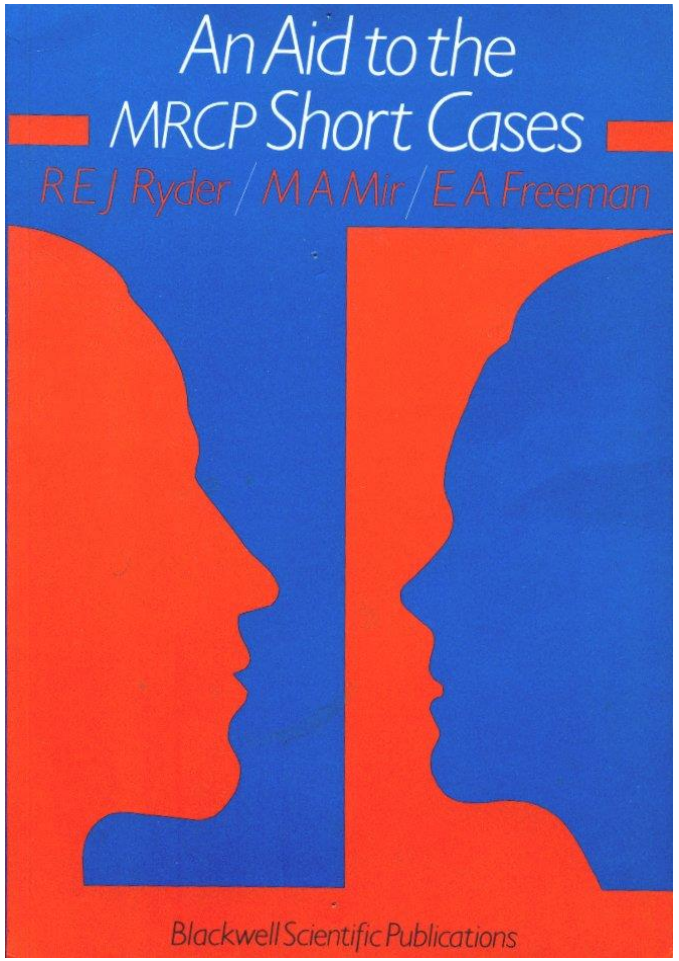
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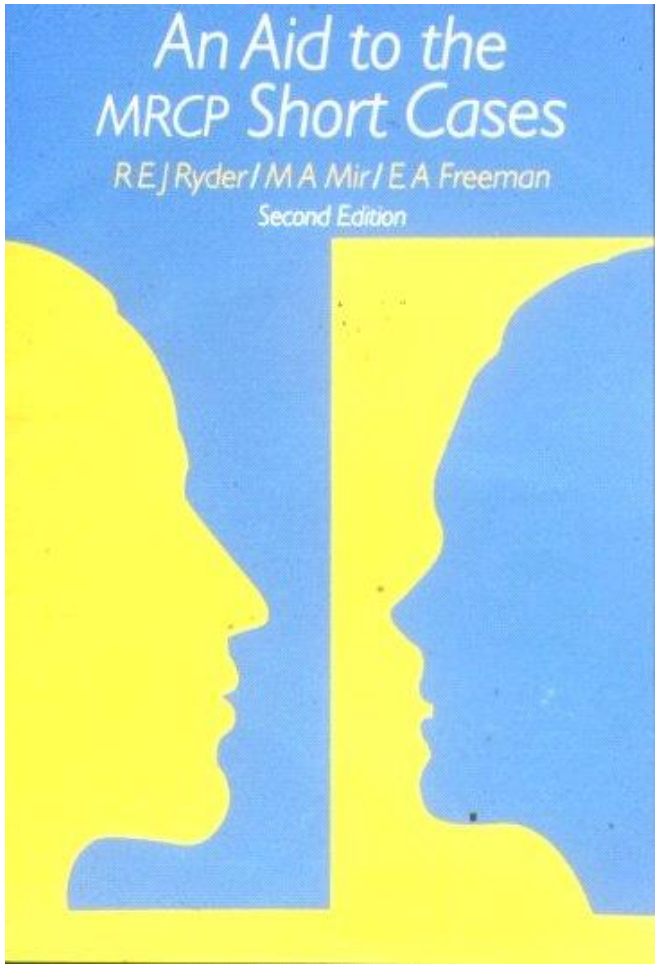
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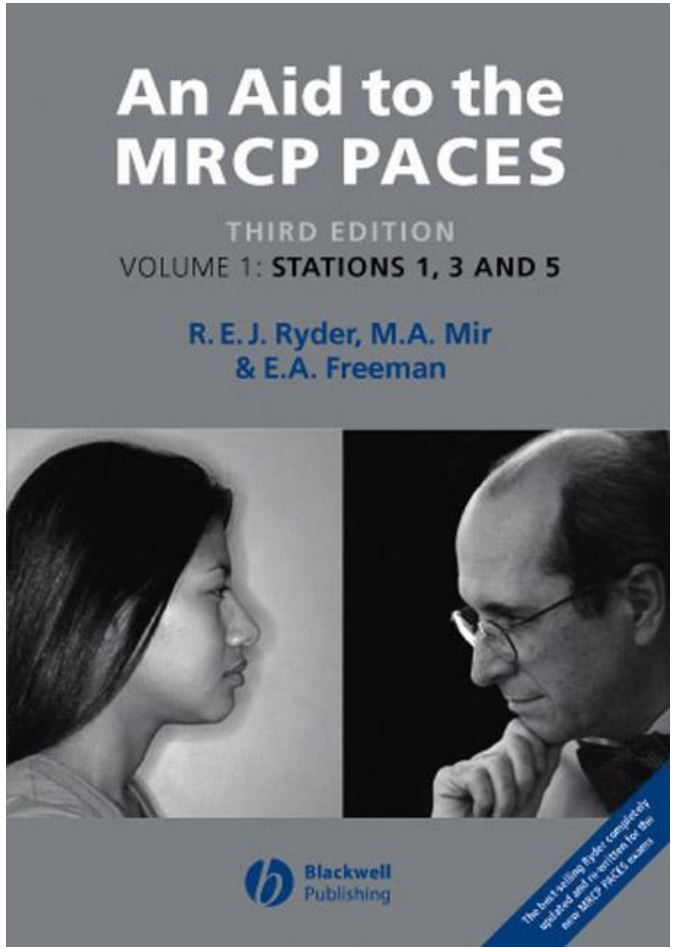
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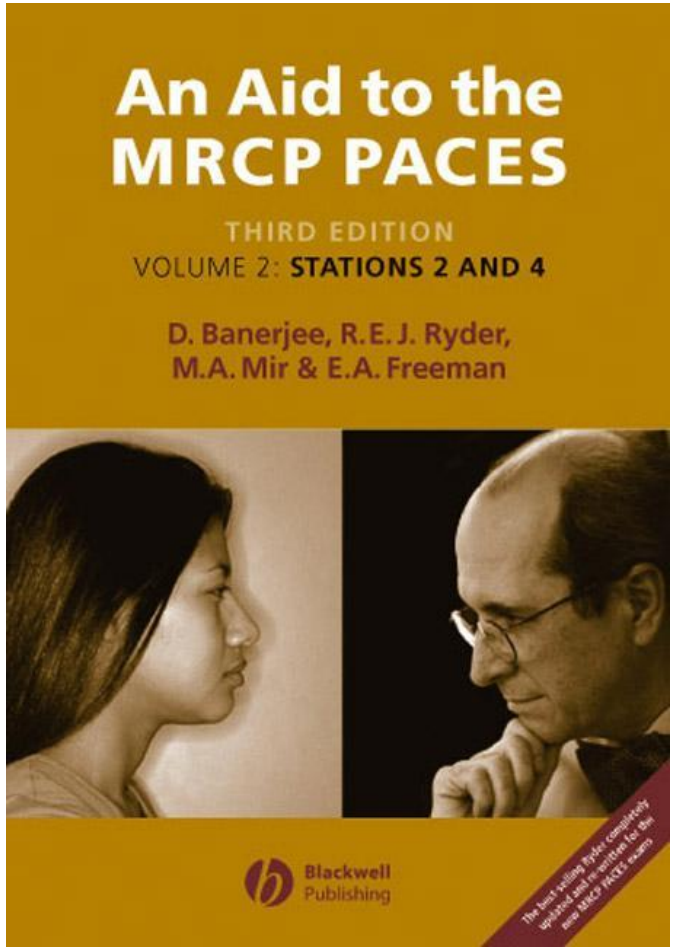
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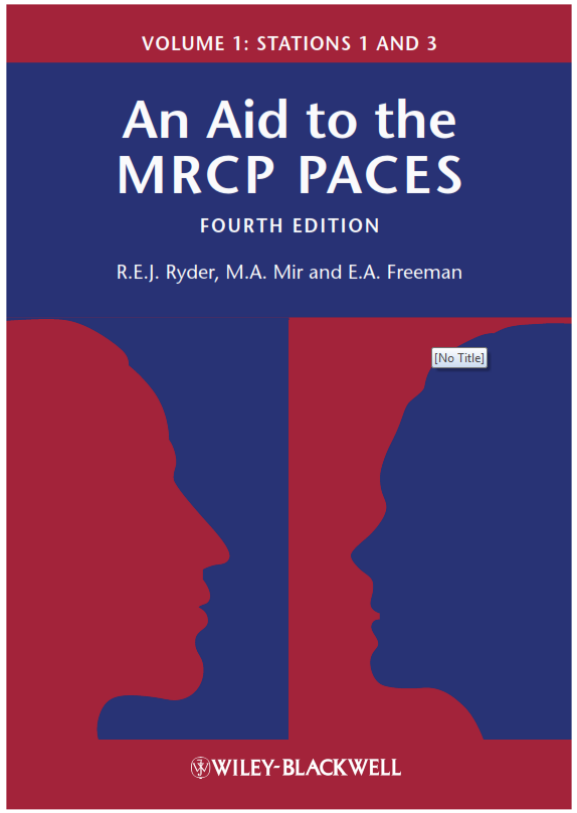
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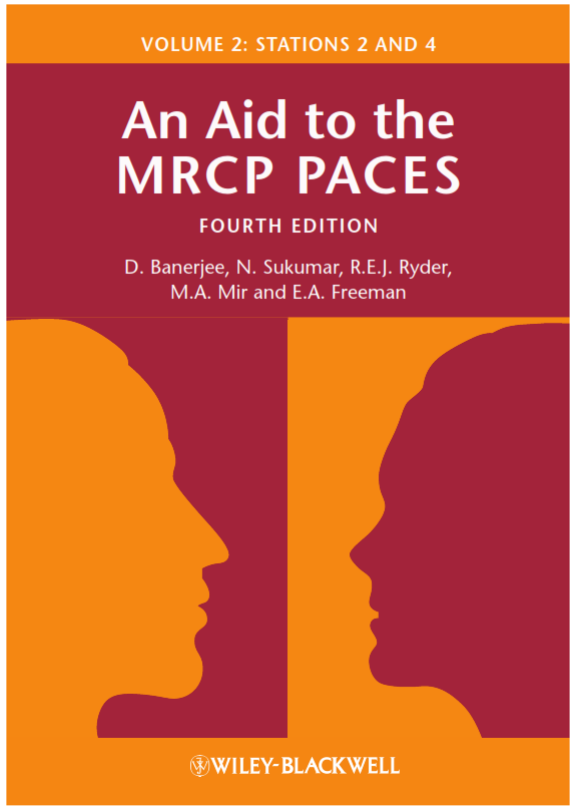
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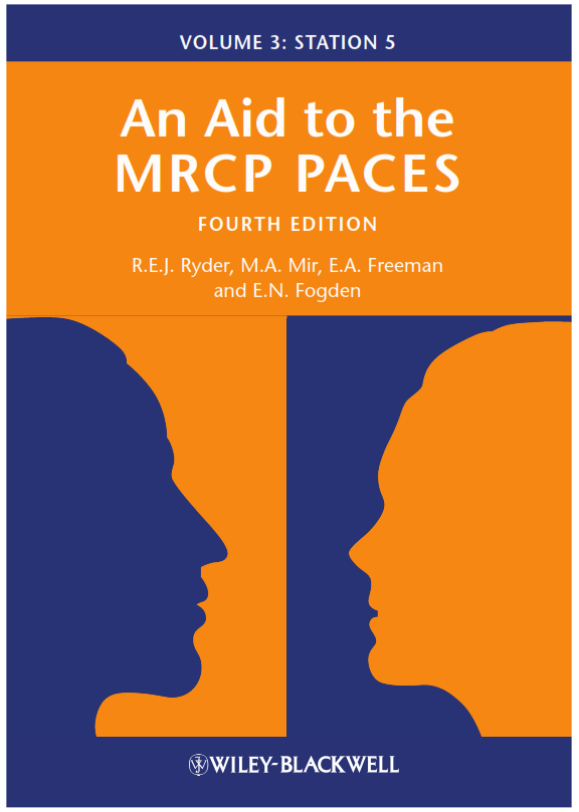
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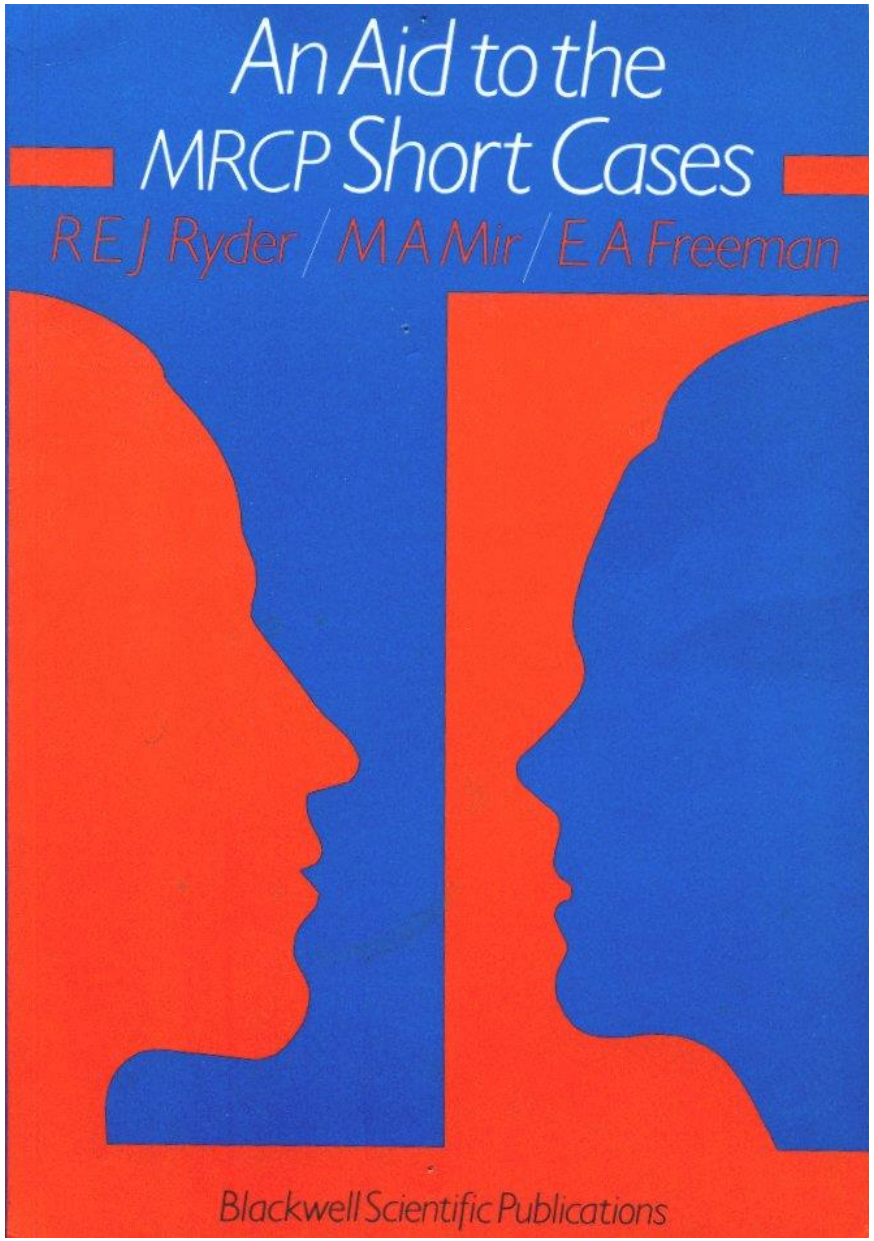

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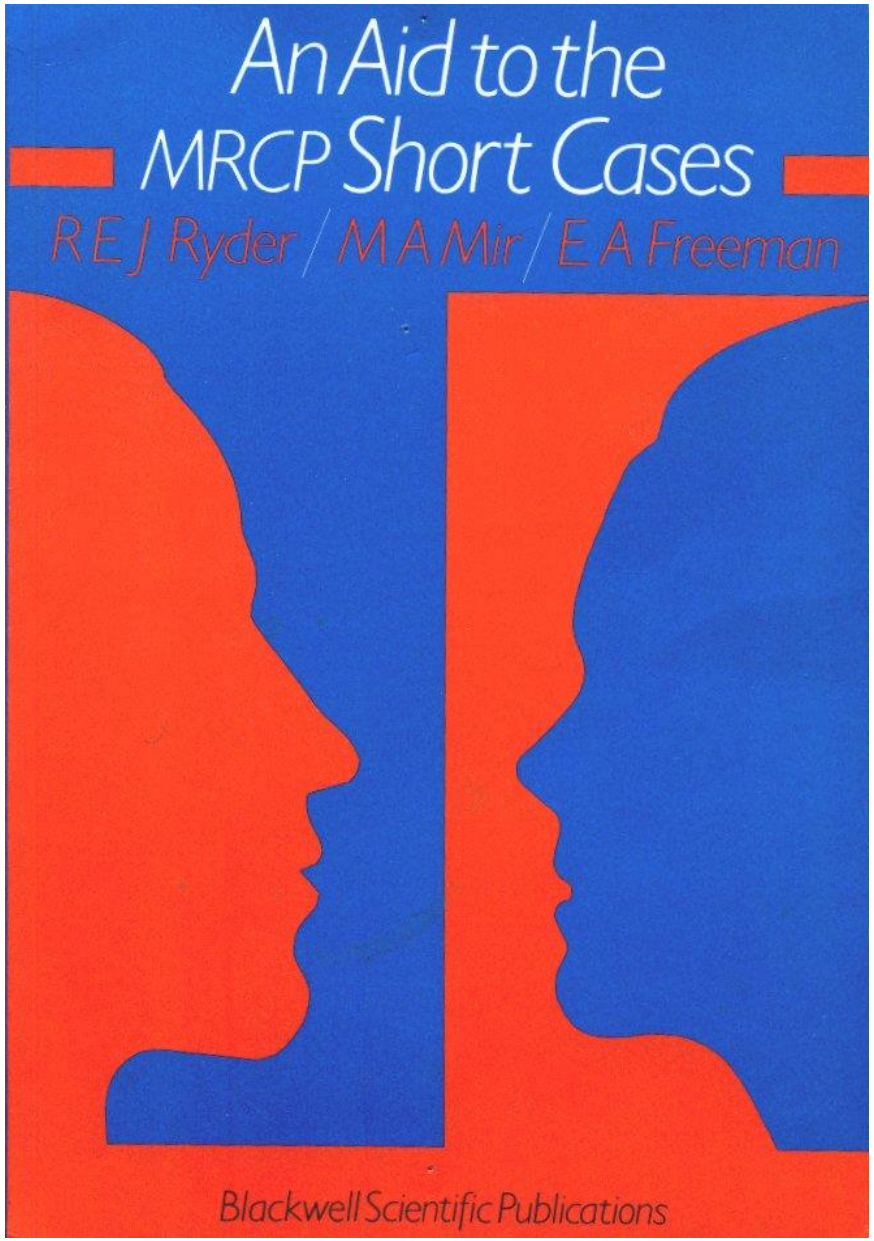
Experiences, Anecdotes, Tips, Facts and Figures, Quotations

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

*MAX BOYCE



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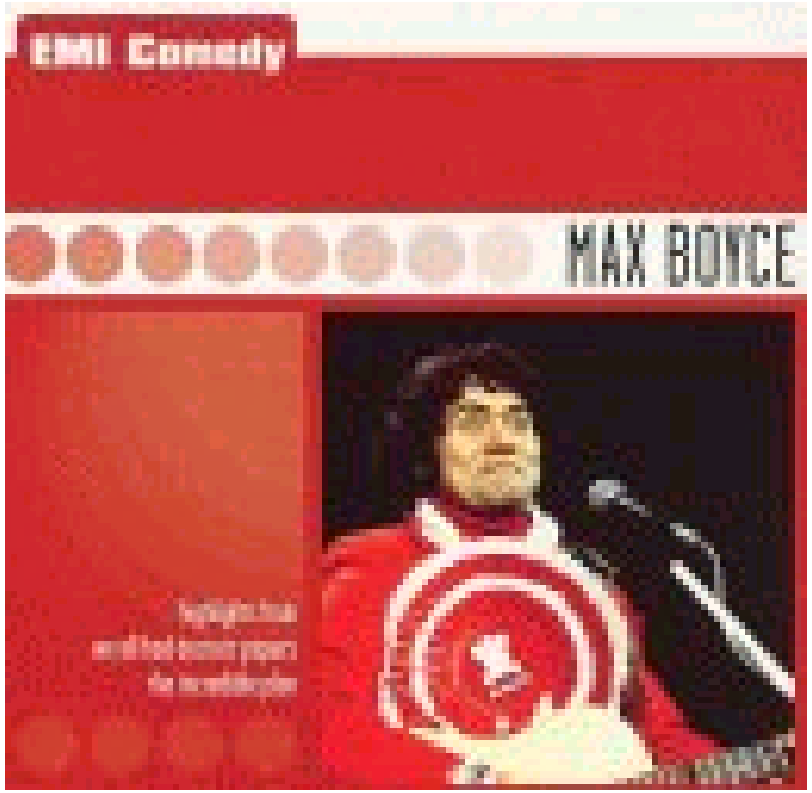
I know ’cos I was there!

Wales

New Zealand



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Questions

A SLIGHT CORRECTION!

MAX BOYCE - 'I WAS THERE'!

- STEMMED FROM LLANELLI BEATING THE 'ALL BLACKS'

IN STRADY PARK ON OCT. 31ST 1972.

FINAL SCORE - LLANELLI 9 N.Z. 3.

AND THEN THE 'PUBS RAN DRY'.

I WAS THERE AS WELL!

(SADLY, WALES HAVEN'T BEAT THE ALL BLACKS SINCE THE 1950's. HOWEVER, IN JANUARY 1973, THE BARBARIANS BEAT N.ZEALAND - WITH MANY WELSH PLAYERS IN THE SIDE!!)

Results [edit]

No.	Date	Venue	Score	Winner	Competition
1	16 December 1905	Cardiff Arms Park, Cardiff	3–0	Wales	The Original All Blacks tour
2	29 November 1924	St Helen's, Swansea	0–19	New Zealand	1924–25 New Zealand tour of France, Great Britain and Ireland
3	21 December 1935	National Stadium, Cardiff	13–12	Wales	1935–36 New Zealand tour of Canada, Great Britain and Ireland
4	19 December 1953	National Stadium, Cardiff	13–8	Wales	1953–54 New Zealand tour of Europe and North America
5	21 December 1963	National Stadium, Cardiff	0–6	New Zealand	1963–64 New Zealand tour of Europe and North America
6	11 November 1967	National Stadium, Cardiff	6–13	New Zealand	1967 New Zealand tour of Great Britain, France and Canada
7	31 May 1969	Lancaster Park, Christchurch	19–0	New Zealand	1969 Wales tour of New Zealand, Australia and Fiji
8	14 June 1969	Eden Park, Auckland	33–12	New Zealand	
9	2 December 1972	National Stadium, Cardiff	16–19	New Zealand	1972–73 New Zealand tour of Europe and North America
10	11 November 1978	National Stadium, Cardiff	12–13	New Zealand	1978 New Zealand tour of Great Britain and Ireland
11	1 November 1980	National Stadium, Cardiff	3–23	New Zealand	1980 New Zealand tour of North America and Wales
12	14 June 1987	Ballymore Stadium, Brisbane (Australia)	49–6	New Zealand	1987 Rugby World Cup Semi-finals
13	28 May 1988	Lancaster Park, Christchurch	52–3	New Zealand	1988 Wales tour of New Zealand
14	11 June 1988	Eden Park, Auckland	54–9	New Zealand	
15	4 November 1989	National Stadium, Cardiff	9–34	New Zealand	1989 New Zealand tour of Great Britain, Ireland and North America
16	31 May 1995	Ellis Park, Johannesburg (South Africa)	34–9	New Zealand	1995 Rugby World Cup Pool match
17	29 November 1997	Wembley Stadium, London (England)	7–42	New Zealand	1997 New Zealand tour of Great Britain and Ireland
18	23 November 2002	Millennium Stadium, Cardiff	17–43	New Zealand	2002 Autumn International
19	21 June 2003	Waikato Stadium, Hamilton	55–3	New Zealand	2003 Wales tour of Australia and New Zealand
20	2 November 2003	Stadium Australia, Sydney (Australia)	53–37	New Zealand	2003 Rugby World Cup Pool match
21	20 November 2004	Millennium Stadium, Cardiff	25–26	New Zealand	2004 Autumn International
22	5 November 2005	Millennium Stadium, Cardiff	3–41	New Zealand	2005 Autumn International
23	25 November 2006	Millennium Stadium, Cardiff	10–45	New Zealand	2006 Autumn International
24	22 November 2008	Millennium Stadium, Cardiff	9–29	New Zealand	2008 Autumn International
25	7 November 2009	Millennium Stadium, Cardiff	12–19	New Zealand	2009 Autumn International
26	19 June 2010	Carisbrook, Dunedin	42–9	New Zealand	2010 Wales tour of New Zealand
27	26 June 2010	Waikato Stadium, Hamilton	29–10	New Zealand	
28	27 November 2010	Millennium Stadium, Cardiff	25–37	New Zealand	2010 Autumn International
29	24 November 2012	Millennium Stadium, Cardiff	10–33	New Zealand	2012 Autumn International
30	22 November 2014	Millennium Stadium, Cardiff	16–34	New Zealand	2014 Autumn International
31	11 June 2016	Eden Park, Auckland	39–21	New Zealand	2016 Wales tour of New Zealand
32	18 June 2016	Wellington Regional Stadium, Wellington	36–22	New Zealand	
33	25 June 2016	Forsyth Barr Stadium, Dunedin	46–6	New Zealand	
34	25 November 2017	Millennium Stadium, Cardiff	18–33	New Zealand	2017 Autumn International
35	1 November 2019	Tokyo Stadium, Chōfu (Japan)	40–17	New Zealand	2019 Rugby World Cup Bronze Final
36	30 October 2021	Millennium Stadium, Cardiff	16–54	New Zealand	2021 Autumn International
37	5 November 2022	Millennium Stadium, Cardiff	23–55	New Zealand	2022 Autumn International

Results:
Wales vs All Blacks

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Results:
Wales vs All Blacks

BBC NEWS

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The day the Scarlets made history

The 1972 side which beat the All Blacks is still revered

Around Llanelli, people will still remind you of the day the Scarlets beat the mighty All Blacks.

Rugby was already the conversation topic of choice in the town where "scarlet fever" was a common condition. But the 9-3 victory for the club against one of the best nations in the world still remains a source of pride.

October 31, 1972, had been a miserable day around Stradey Park, but the pubs ran dry at night, as Carwyn James - just returned from coaching a successful British Lions trip to New Zealand - led his club to victory.

Stradey Park is the home of West Wales rugby

Captain Delme Thomas had given individual team talks to each player, bringing tears to the eyes of Phil Bennett. The squad was given a police escort to the ground, where a crowd of 20,000 awaited, packed into their Stradey fortress.

It could barely have

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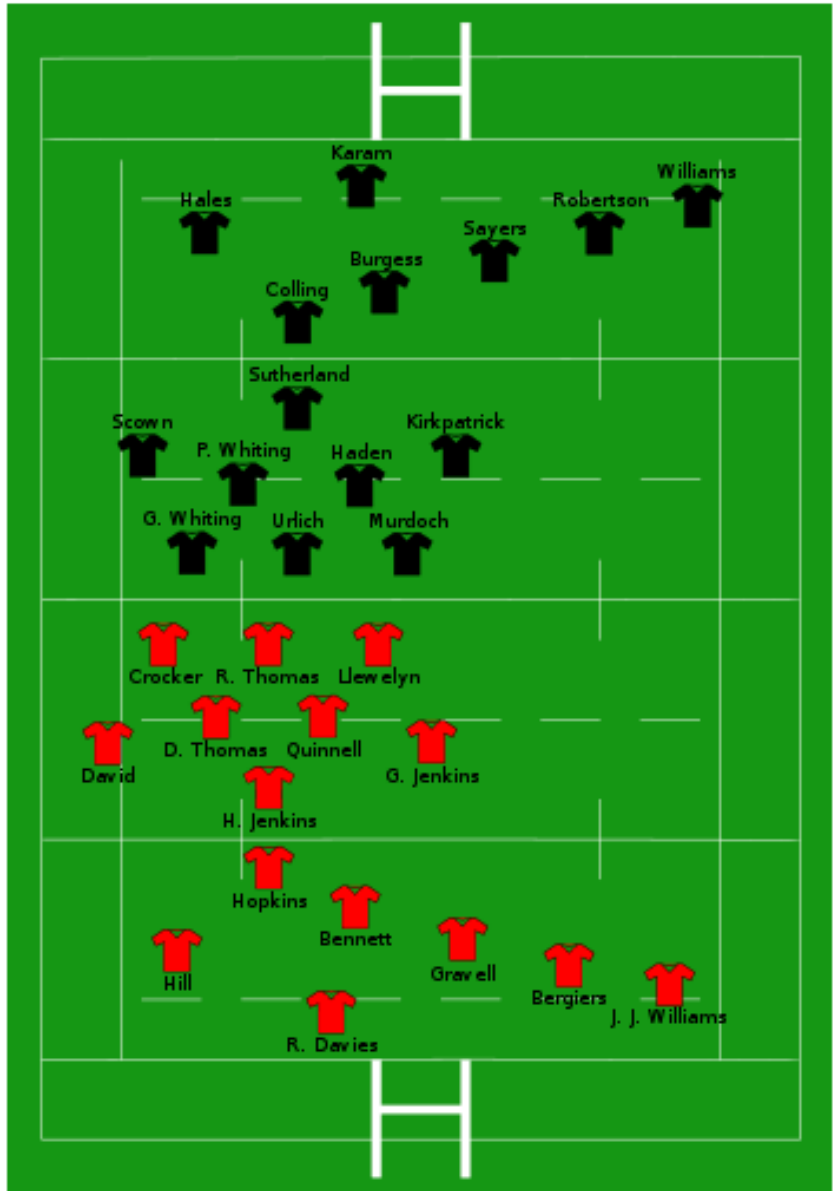

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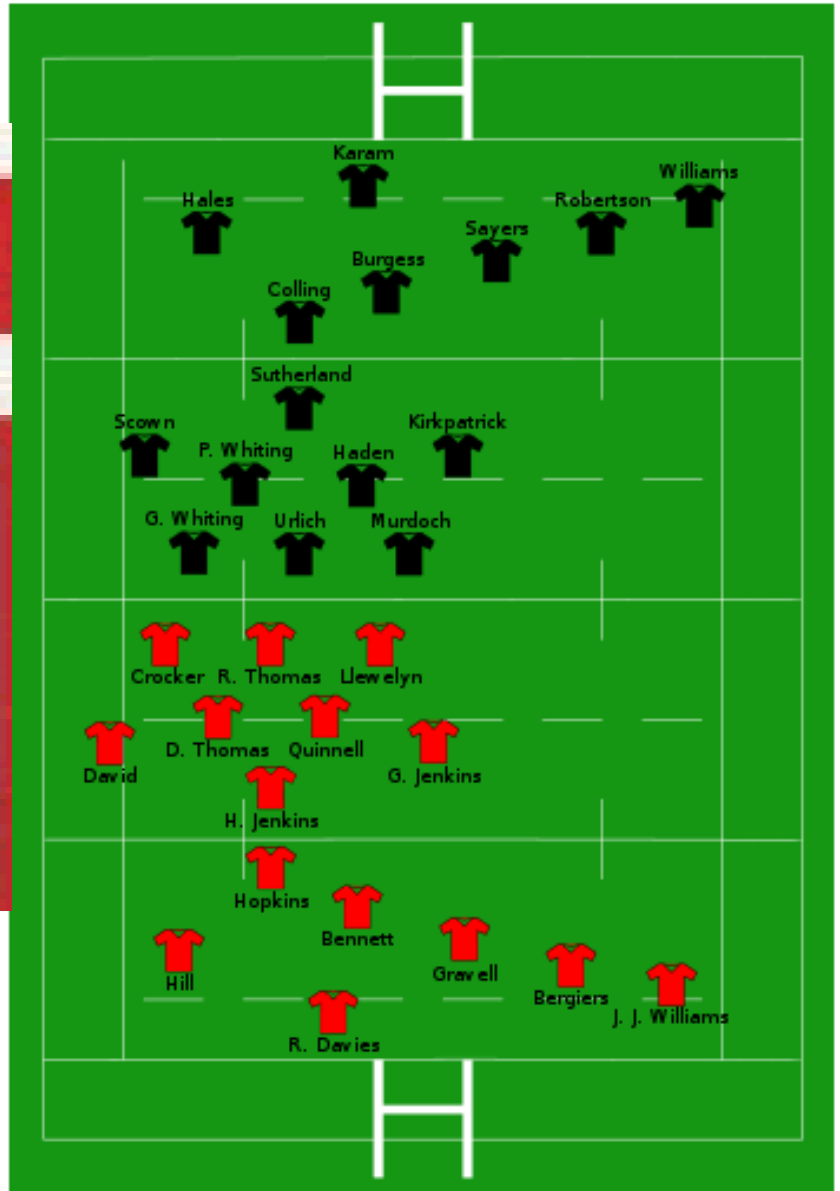


Preface

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’

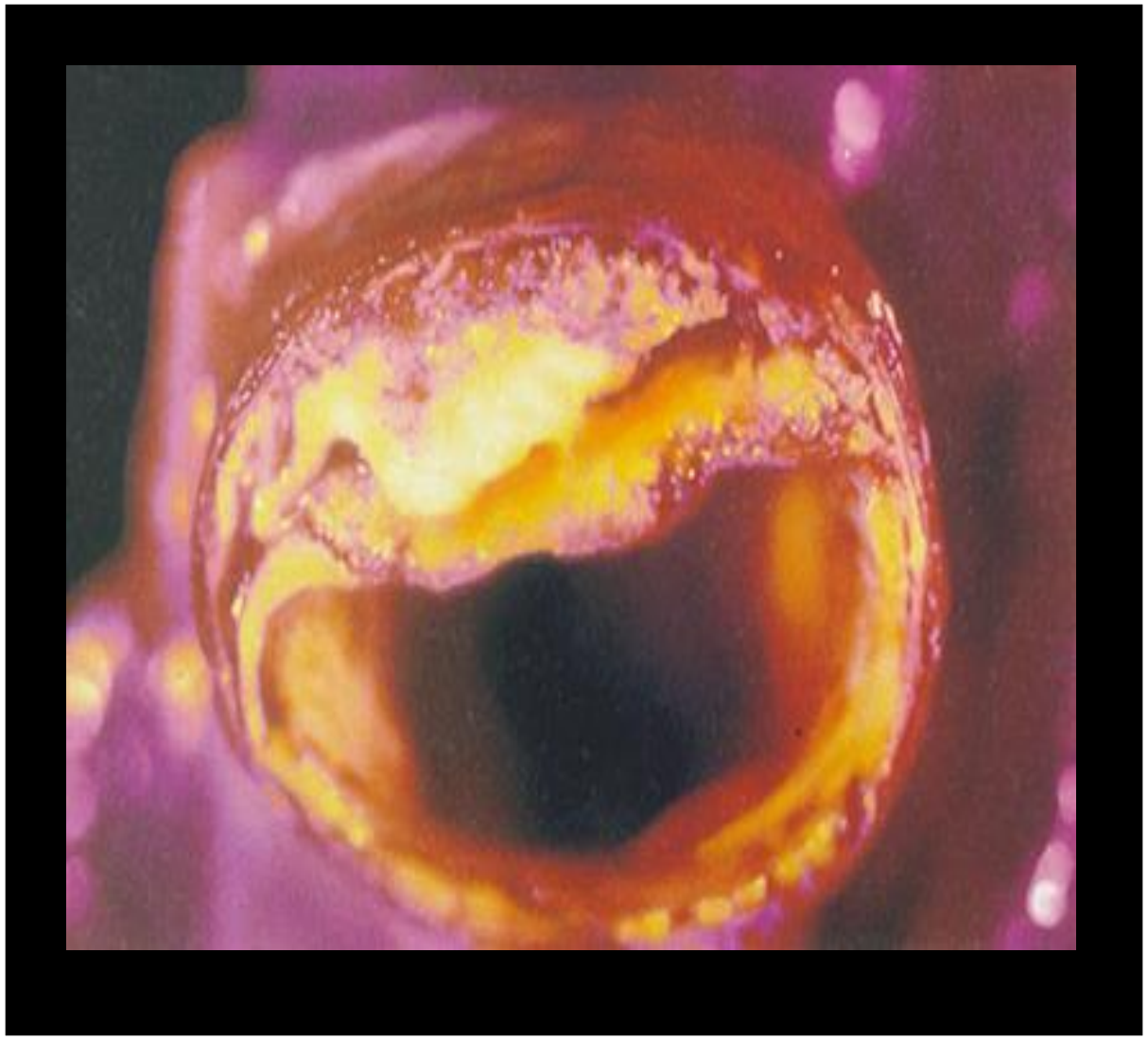
WHO Expert Committee on Diabetes Mellitus 1980

Re-definition of diabetes

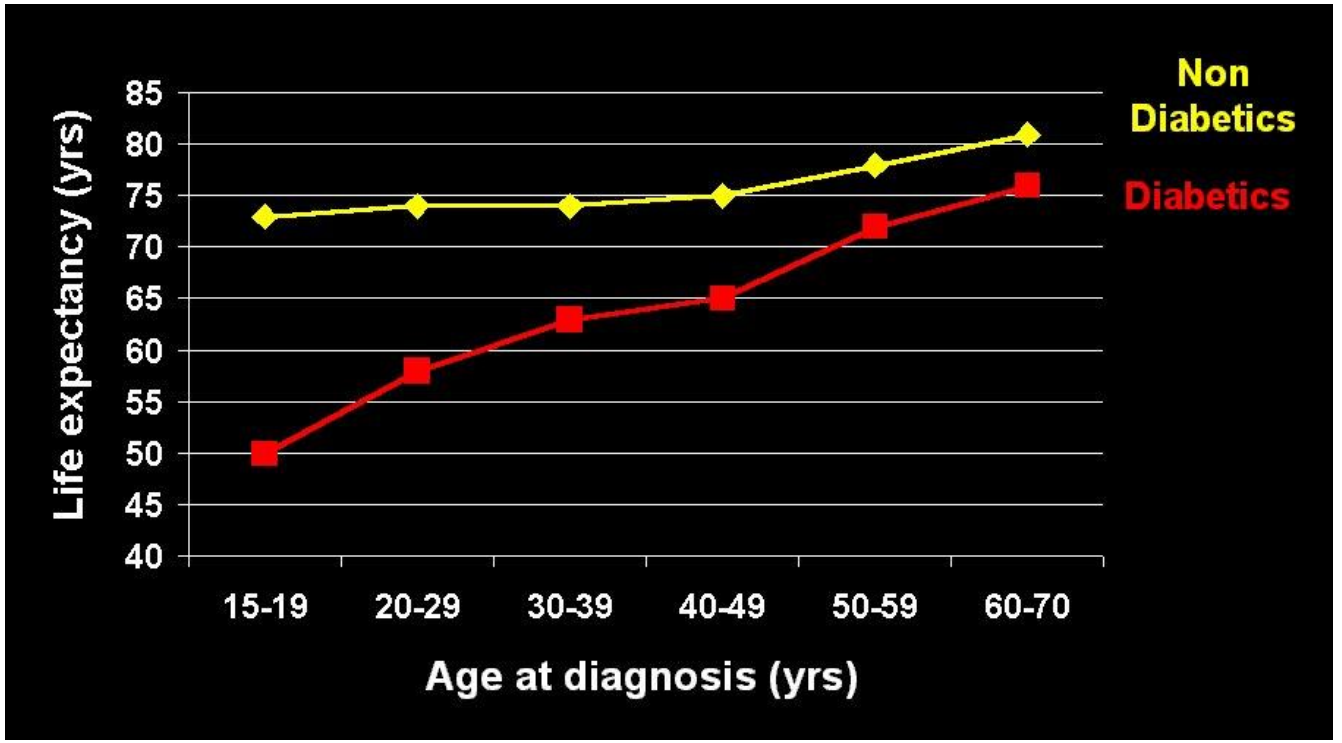
- ‘Diabetes is a state of **premature cardiovascular death** which is associated with **chronic hyperglycaemia** and may also be associated with **blindness** and **renal failure**’

Miles Fisher, British Diabetes Association , Dublin, 1996

Diabetes and Macrovascular Disease



Life Expectancy and Diabetes

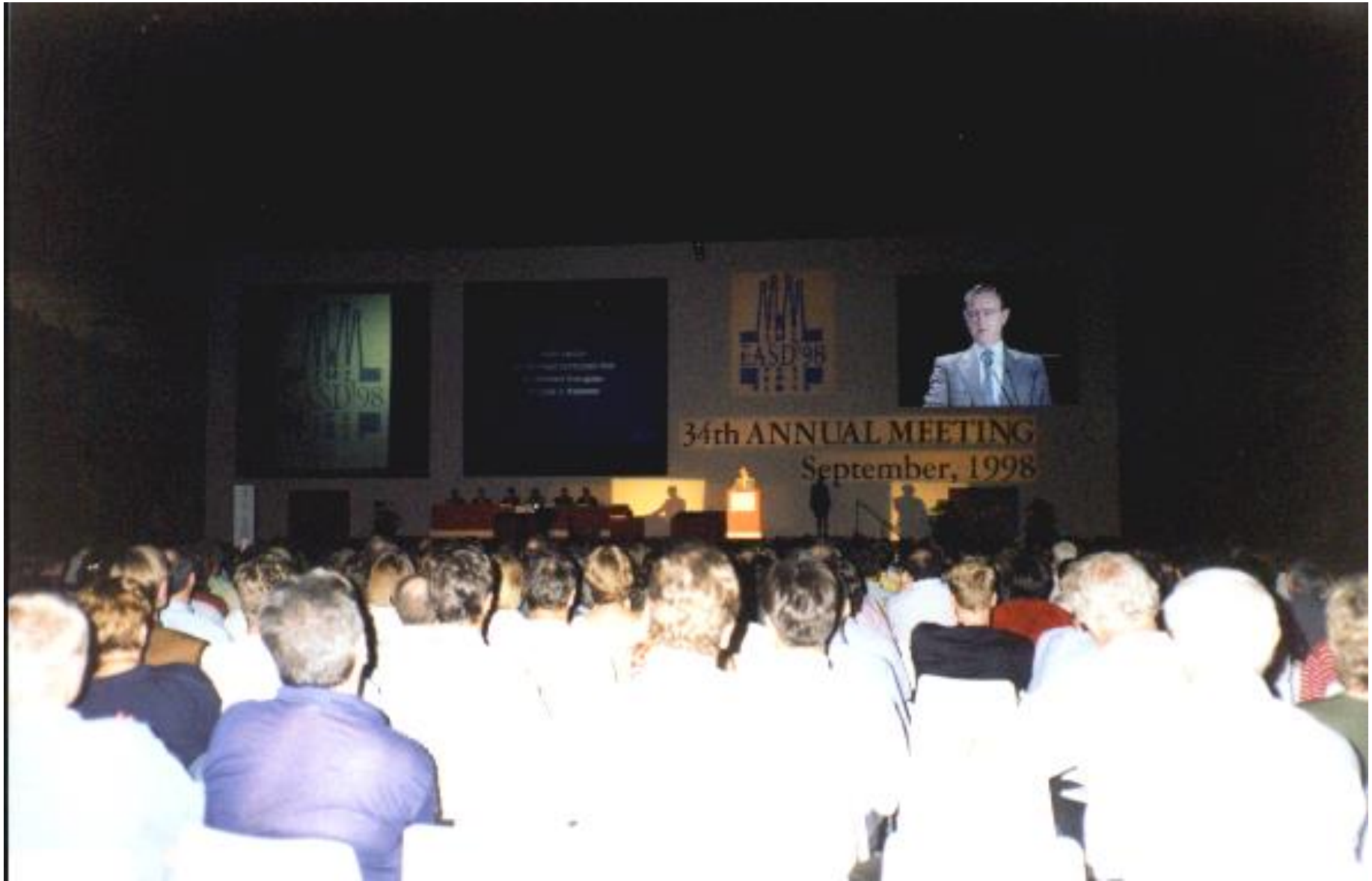


- 'Adults with diabetes have an annual mortality of about 5.4%, double the rate for non-diabetic adults. Life expectancy is decreased by 5–10 years.'

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

How can we reduce this risk

UKPDS EASD Barcelona 1998 – I was there!



UKPDS EASD Barcelona 1998 – I was there!

Blood Pressure Control Study

In 1148 Type 2 diabetic patients a tight blood pressure control policy which achieved blood pressure of 144 / 82 mmHg gave reduced risk of:

- 24 % for any diabetes-related endpoint p=0.0046
- 32% for diabetes-related deaths p=0.019
- 44% for stroke p=0.013
- 37% for microvascular disease p=0.0092
- 56% for heart failure p=0.0043
- 34% for retinopathy progression p=0.0038
- 47% for deterioration of vision p=0.0036

effect across these subgroups.

What did this study do?

This study included 123 large-scale randomised controlled trials with over 600,000 participants published between 1966 and 2015. All studies were required to have a minimum of 1000 patient-years of follow up in each group. Standard systematic review and meta-analysis methods were used. One medical database was searched and the reference lists of eligible studies were also hand searched to identify further relevant studies. The quality of the included studies was assessed: the majority of the studies (113) were judged to be of low risk of bias.

What did it find?

- Every 10 mm Hg systolic blood pressure reduction reduced the risk of major cardiovascular events by 20% (relative risk [RR] 0.80, 95% confidence interval [CI] 0.77 to 0.83), coronary heart disease by 17% (RR 0.83, 95% CI 0.78 to 0.88), stroke by 27% (RR 0.73, 95% CI 0.68 to 0.77), heart failure by 28% (RR 0.72, 95% CI 0.67 to 0.78), and death from all causes by 13% (RR 0.87, 95% CI 0.84 to 0.91).
- The size of these proportional reductions was broadly consistent across several major high-risk groups of patients (slightly less, but still significant, in diabetes and kidney disease), suggesting that blood pressure lowering provides broadly generalisable benefits.
- In stratified analyses, the proportional effects were similar in trials that included people with lower baseline systolic blood pressure (<130 mm Hg), and major cardiovascular events were clearly reduced in high-risk patients with various baseline comorbidities. Five different types of blood pressure lowering drugs were

effect across these subgroups.

What did this study do?

This study included 1[illegible]

[illegible] bias.

Every 10 mm Hg systolic blood pressure reduction reduced the risk of major cardiovascular events by 20%

[illegible]od pressure reduction reduced the risk of major cardiovascular events by 20% [illegible]isk [RR] 0.80, 95% confidence interval [CI] 0.77 to 0.83), coronary heart disease by 17% (RR 0.83, 95% CI 0.78 to 0.88), stroke by 27% (RR 0.73, 95% CI 0.68 to 0.77), heart failure by 28% (RR 0.72, 95% CI 0.67 to 0.78), and death from all causes by 13% (RR 0.87, 95% CI 0.84 to 0.91).

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How can we reduce this risk

- Control Blood Pressure

THE LANCET

ARTICLES · Volume 344, Issue 8934, P1383-1389, November 19, 1994 Download Full Issue

Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S)

Scandinavian Simvastatin Survival Study Group [1,2]

Affiliations & Notes Article Info

1994 – the 4S study

Show Outline

Abstract

Summary

Drug therapy for hypercholesterolaemia has remained controversial mainly because of insufficient clinical trial evidence for improved survival. The present trial was designed to evaluate the effect of cholesterol lowering with simvastatin on mortality and morbidity in patients with coronary heart disease (CHD). 4444 patients with angina pectoris or previous myocardial infarction and serum cholesterol 5·5-8·0 mmol/L on a lipid-lowering diet were randomised to double-blind treatment with simvastatin or placebo.

Over the 5·4 years median follow-up period, simvastatin produced mean changes in total cholesterol, low-density-lipoprotein cholesterol, and high-density-lipoprotein cholesterol of -25%, -35%, and +8%, respectively, with few adverse effects. 256 patients (12%) in the placebo group died, compared with 182 (8%) in the simvastatin group. The relative risk of death in the simvastatin group was 0·70 (95% CI 0·58-0·85, p=0·0003). The 6-year· probabilities of survival in the placebo and simvastatin groups were 87·6% and 91·3%, respectively. There were 189 coronary deaths in the placebo group and 111 in the simvastatin group (relative risk 0·58, 95% CI 0·46-0·73), while noncardiovascular causes accounted for 49 and 46 deaths, respectively. 622 patients (28%) in the placebo group and 431 (19%) in the simvastatin group had one or more major coronary events. The relative risk was 0·66 (95% CI 0·59-0·75, p<0·00001), and the respective probabilities of escaping such events were 70·5% and 79·6%. This risk was also significantly reduced in subgroups consisting of women and patients of both sexes aged 60 or more. Other benefits of treatment included a 37% reduction (p<0·00001) in the risk of undergoing myocardial revascularisation procedures.

2002 – the Heart Protection Study

THE LANCET

FAST TRACK — ARTICLES · Volume 360, Issue 9326, P7-22, July 06, 2002 Download Full Issue

MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebocontrolled trial

Heart Protection Study Collaborative Group

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Show Outline

Summary

Background

Throughout the usual LDL cholesterol range in Western populations, lower blood concentrations are associated with lower cardiovascular disease risk. In such populations, therefore, reducing LDL cholesterol may reduce the development of vascular disease, largely irrespective of initial cholesterol concentrations.

Methods

20 536 UK adults (aged 40–80 years) with coronary disease, other occlusive arterial disease, or diabetes were randomly allocated to receive 40 mg simvastatin daily (average compliance: 85%) or matching placebo (average non-study statin use: 17%). Analyses are of the first occurrence of particular events, and compare all simvastatin-allocated versus all placebo-allocated participants. These “intention-to-treat” comparisons assess the effects of about two-thirds (85% minus 17%) taking a statin during the scheduled 5-year treatment period, which yielded an average difference in LDL cholesterol of 1·0 mmol/L (about two-thirds of the effect of actual use of 40 mg simvastatin daily). Primary outcomes were mortality (for overall analyses) and fatal or non-fatal vascular events (for subcategory analyses), with subsidiary assessments of cancer and of other major morbidity.

- The Heart Protection Study (HPS) demonstrated that statin therapy with simvastatin significantly reduces the risk of major vascular events (heart attacks, strokes, and revascularization procedures) and all-cause mortality in high-risk individuals, including those with existing coronary heart disease, diabetes, and stroke patients

An official Publication of the Indian Pharmacological Society
Indian Journal of Pharmacology

Indian J Pharmacol. 2012 Mar-Apr;44(2):261–263. doi: 10.4103/0253-7613.93864

A comparative effect of atorvastatin with other statins in patients of hyperlipidemia

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Abstract

Objective:

The objective of the study was to evaluate the safety and efficacy of atorvastatin compared with simvastatin and pravastatin in patients of hyperlipidemia.

Materials and Methods:

This was a randomized, parallel group, open-label study conducted at KG hospital, Coimbatore, Tamilnadu, India. Twenty hyperlipidemia patients each taking atorvastatin 20 mg, pravastatin 20 mg and simvastatin 20 mg tablets were selected for the study after

statin therapy for lipid profile. The liver enzyme levels (SGOT, SGPT, ALP), albumin, bilirubin, protein and biochemical infraction parameters (Creatine Kinase, Creatine Kinase - Myocardial Band) after 5th month of treatment with statins were also reviewed.

Results:

The results showed that atorvastatin significantly reduced the lipid levels (LDL-C, TC, TG, VLDL) when compared to simvastatin and pravastatin after 3rd and 5th month of treatment. Atorvastatin increased the HDL-C levels significantly when compared to simvastatin and pravastatin after 5 months of treatment. Atorvastatin also significantly reduced the CK levels when compared to pravastatin but no increase in liver enzyme levels was observed.

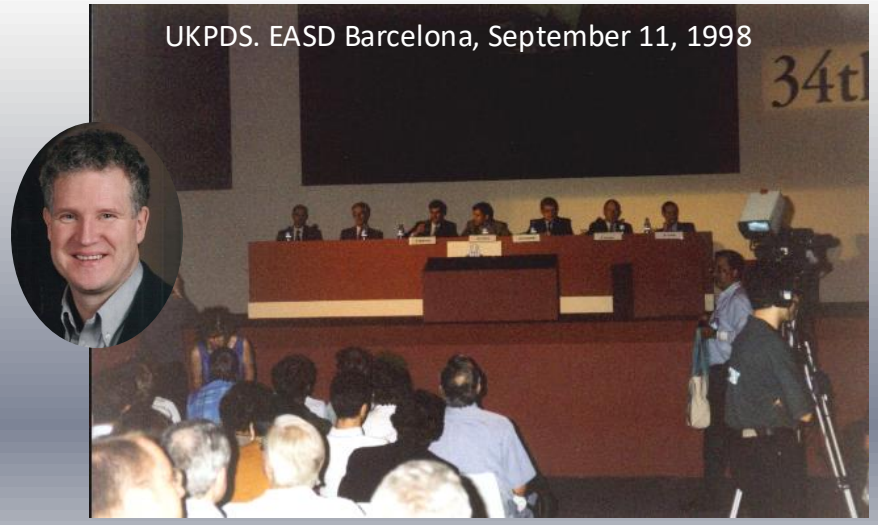
Conclusion:

The study showed that atorvastatin is more effective when compared to simvastatin and pravastatin in patients with hyperlipidemia.

KEY WORDS: Creatine kinase, creatine kinase - myocardial band, pravastatin, simvastatin

How can we reduce this risk

- Control Blood Pressure
- Use a statin in highest tolerated dose



I know cos I was there!

UKPDS. EASD Barcelona, September 11, 1998

PROactive. EASD Athens, September 12, 2005

UKPDS 1998


UKPDS 1998
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Spice Girls
Same stage
Barcelona
1998

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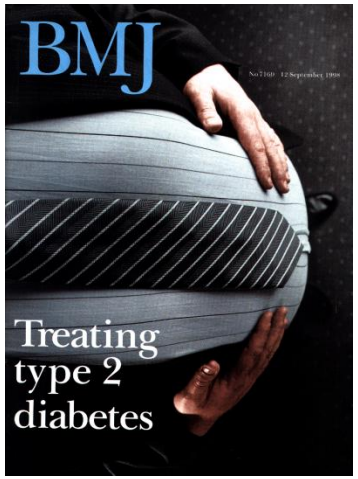
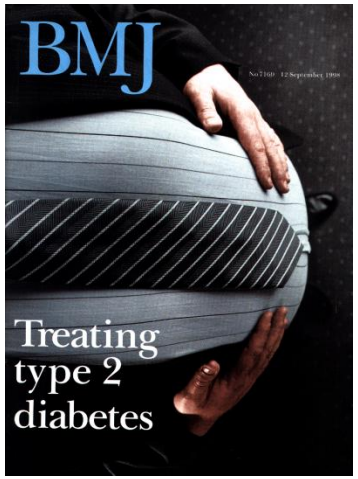
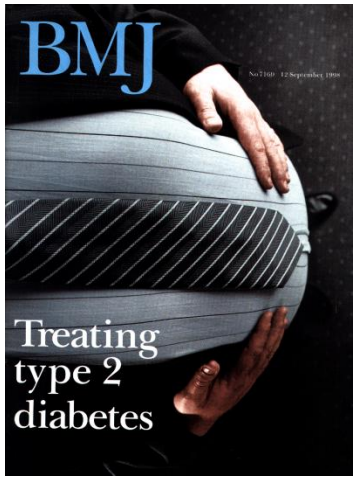
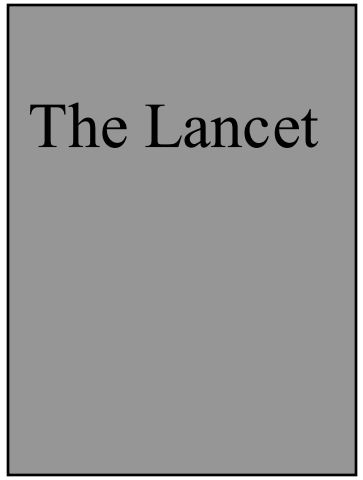
I know ’cos I was there!

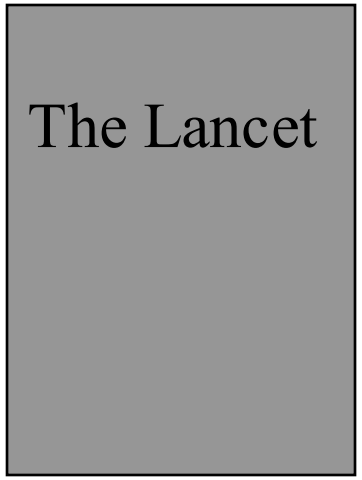
- UKPDS, Barcelona, 1998











Glucose Control Study Summary

The intensive glucose control policy maintained a lower HbA_{1c} by mean 0.9 % over a median follow up of 10 years from diagnosis of type 2 diabetes with reduction in risk of:

12%	for any diabetes related endpoint	p=0.029
25%	for microvascular endpoints	p=0.0099
16%	for myocardial infarction	p=0.052
24%	for cataract extraction	p=0.046
21%	for retinopathy at twelve years	p=0.015
33%	for albuminuria at twelve years	p=0.000054

ukpds

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ukpds

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

Metformin - UKPDS

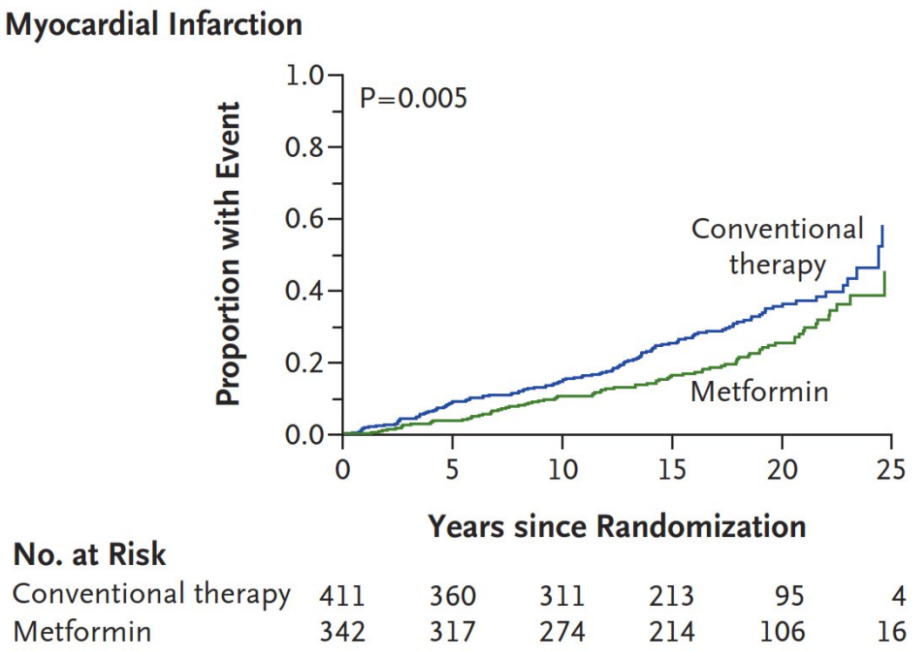


Figure 1a

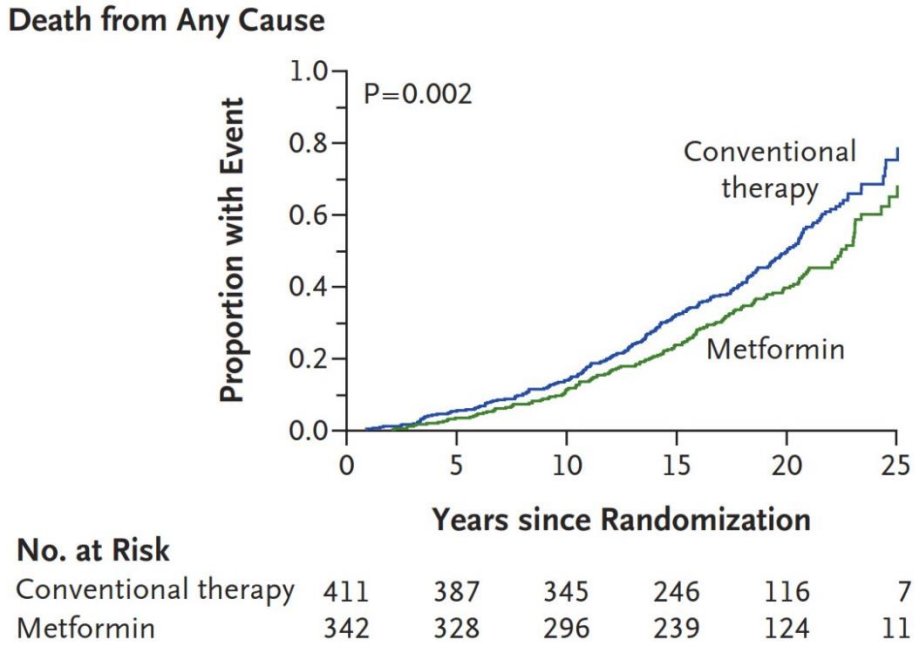
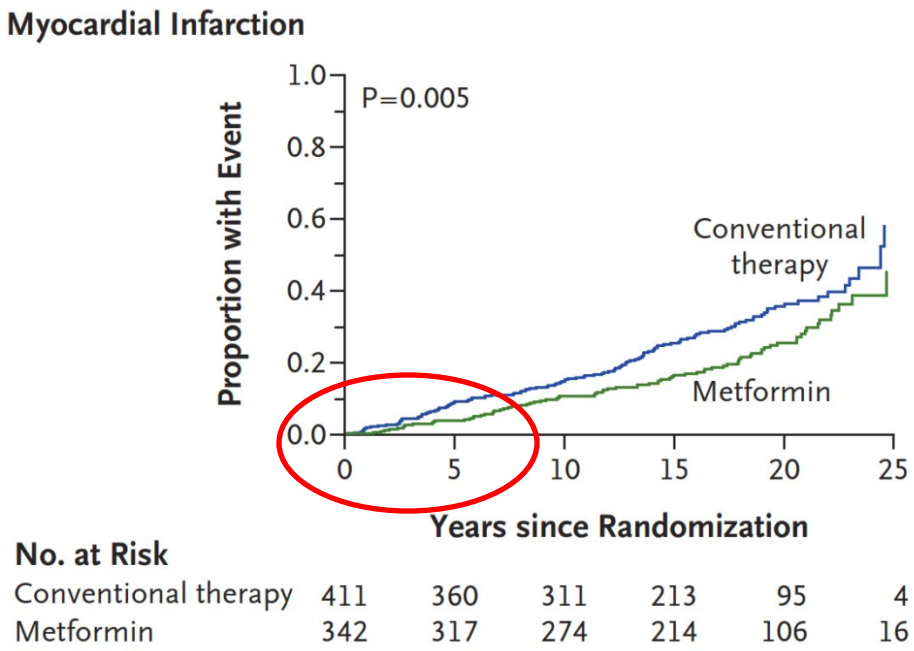


Figure 1b

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

Metformin - UKPDS



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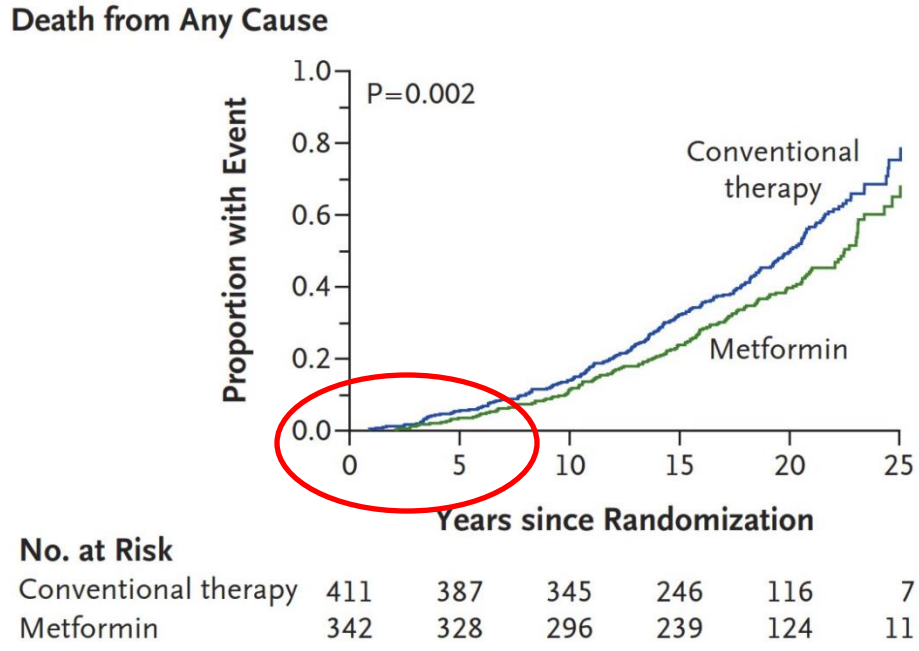

Figure 1b

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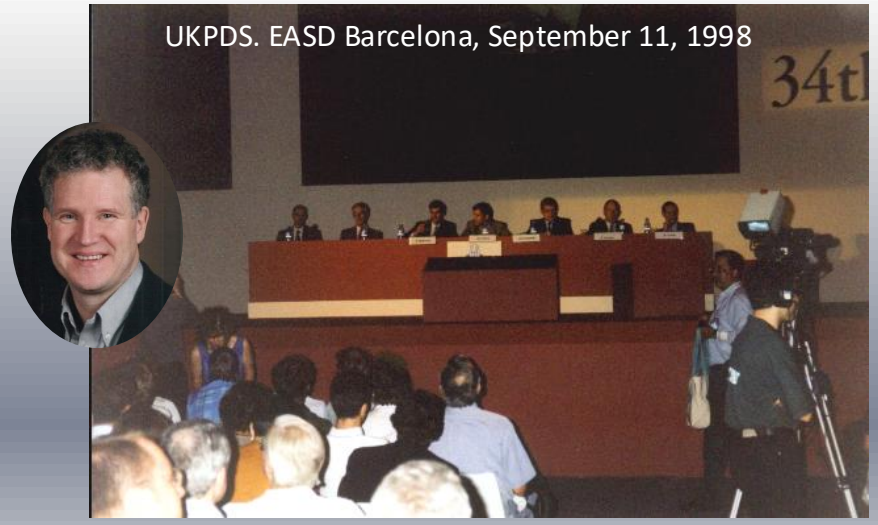
Holman RR et al, N Engl J Med. 2008;359(15):1577-89

How can we reduce this risk

- Control Blood Pressure
- Use a statin in highest tolerated dose
- Use metformin in all patients if tolerated



I know cos I was there!

PROactive. EASD Athens, September 12, 2005


PROactive 2005

PROactive 2005

PROactive 2005

PROactive 2005

PROactive 2005

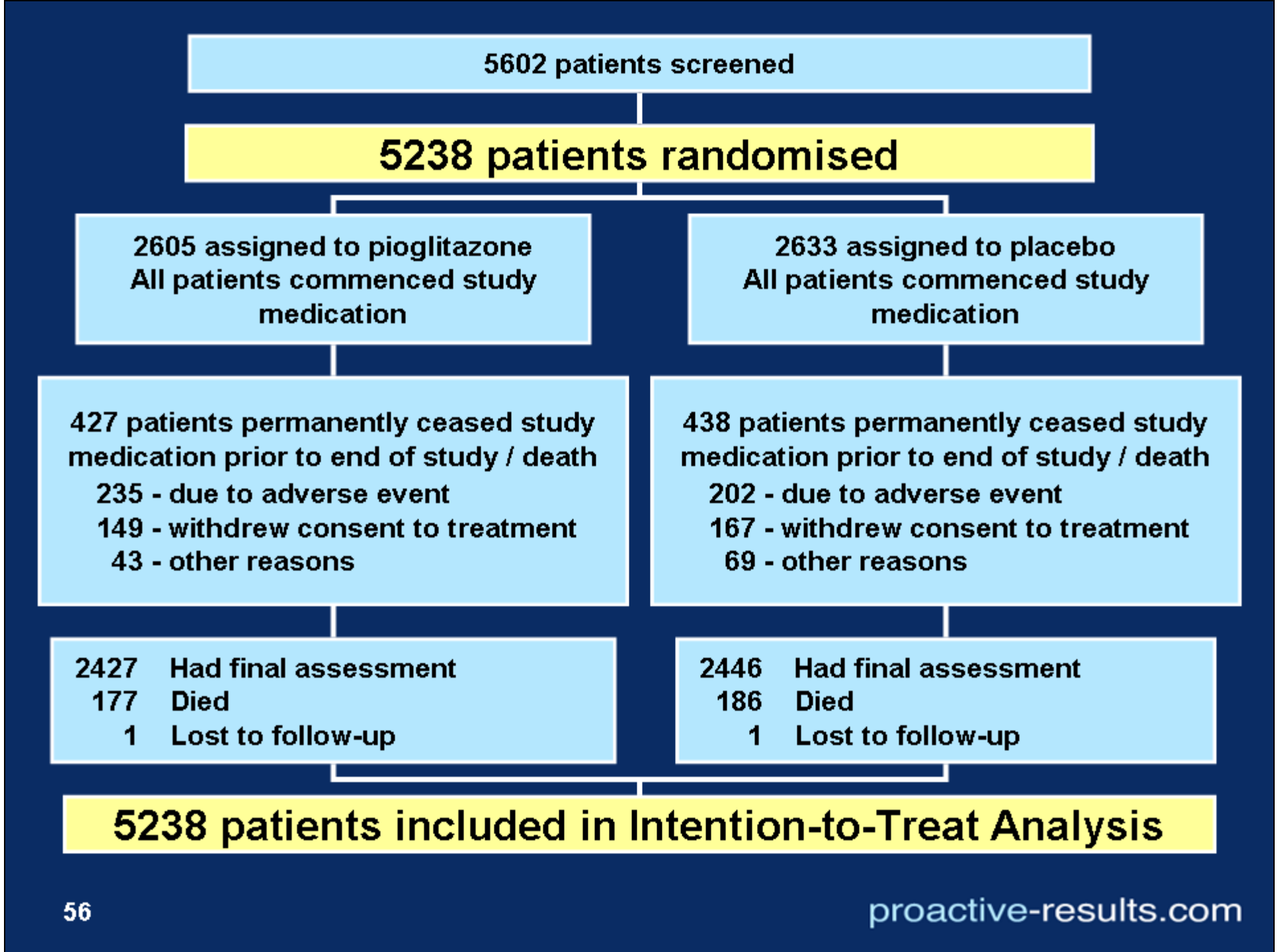
PROactive Study

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

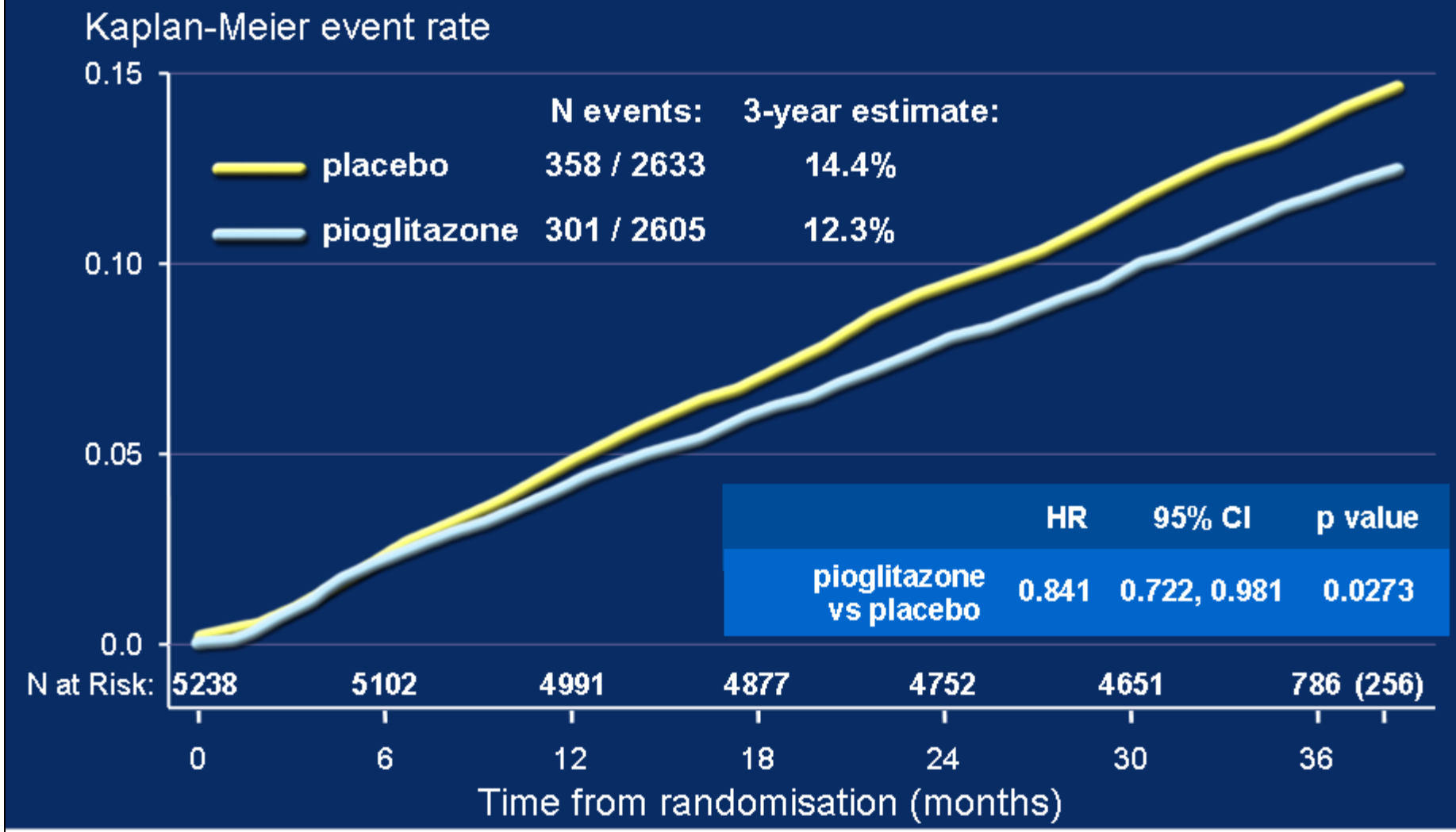

5602 patients screened
5238 patients randomised
2605 assigned to pioglitazone
All patients commenced study medication
2633 assigned to placebo
All patients commenced study medication
427 patients permanently ceased study medication prior to end of study / death
235 - due to adverse event
149 - withdrew 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

CV Outcome Studies - 3 point MACE

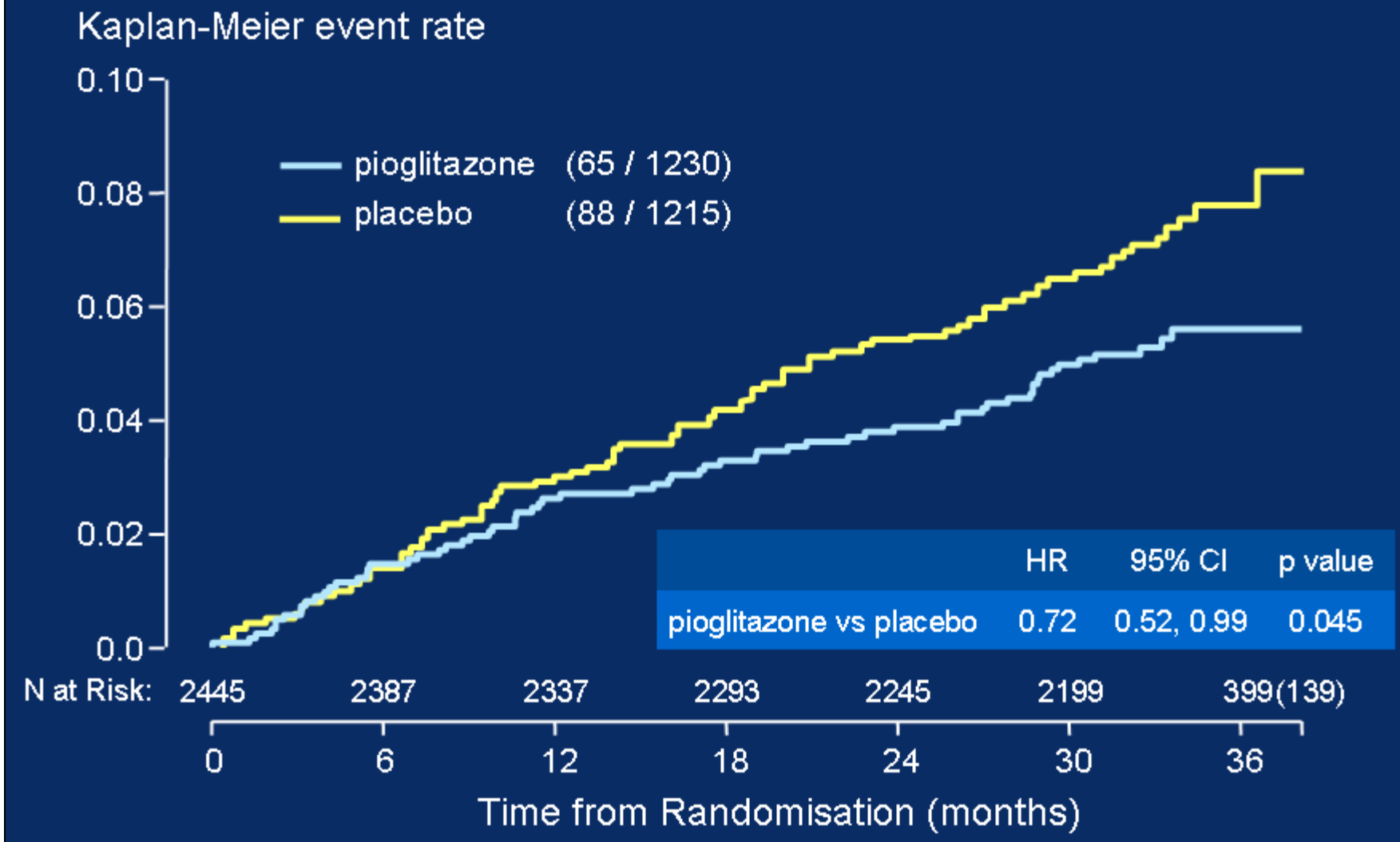
- Death
- Myocardial infarction
- Stroke

MACE = Major Adverse Cardiovascular event

Time to Death, MI (Excluding Silent) or Stroke



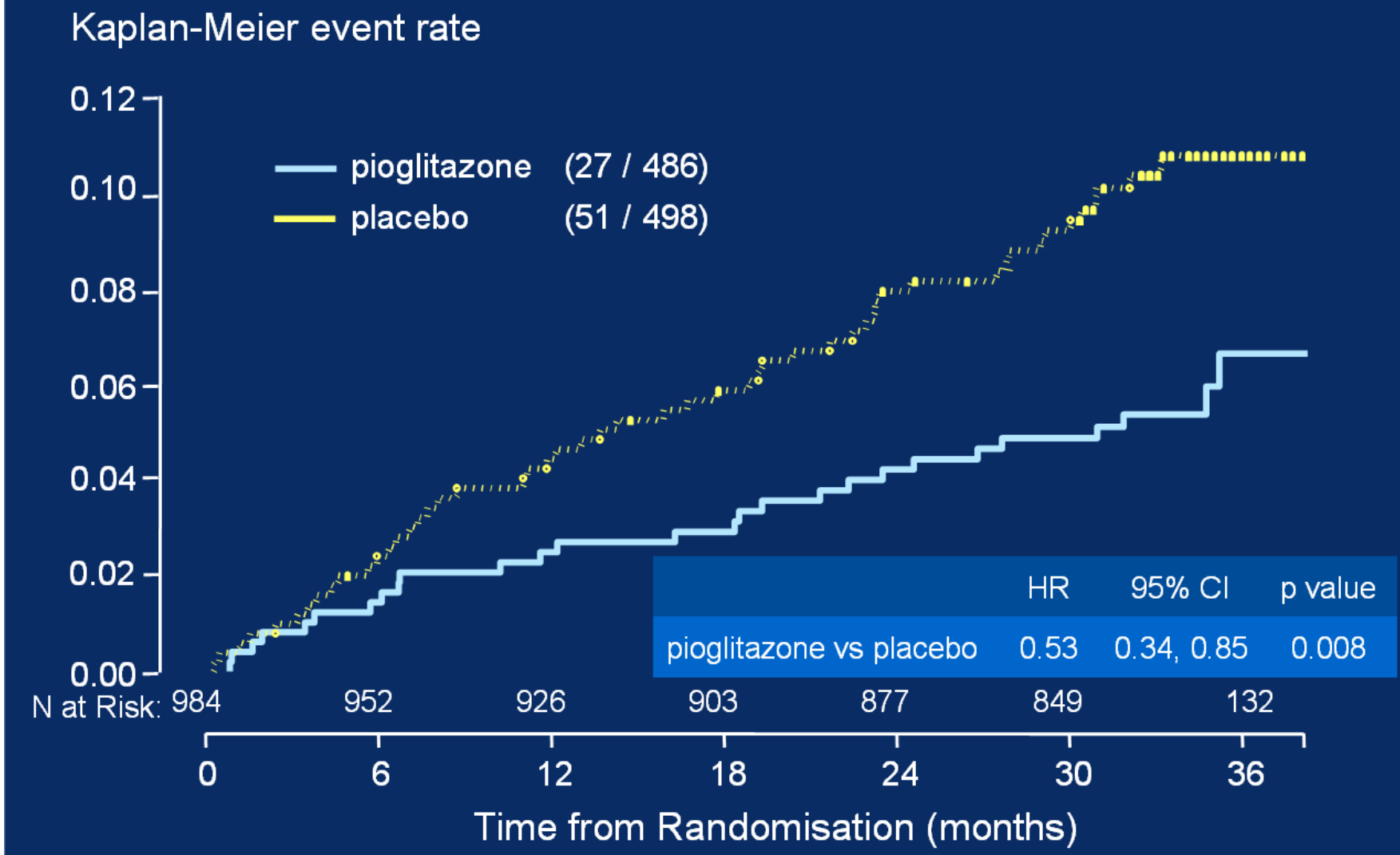
Time to Fatal/Non-fatal MI (excluding silent MI)



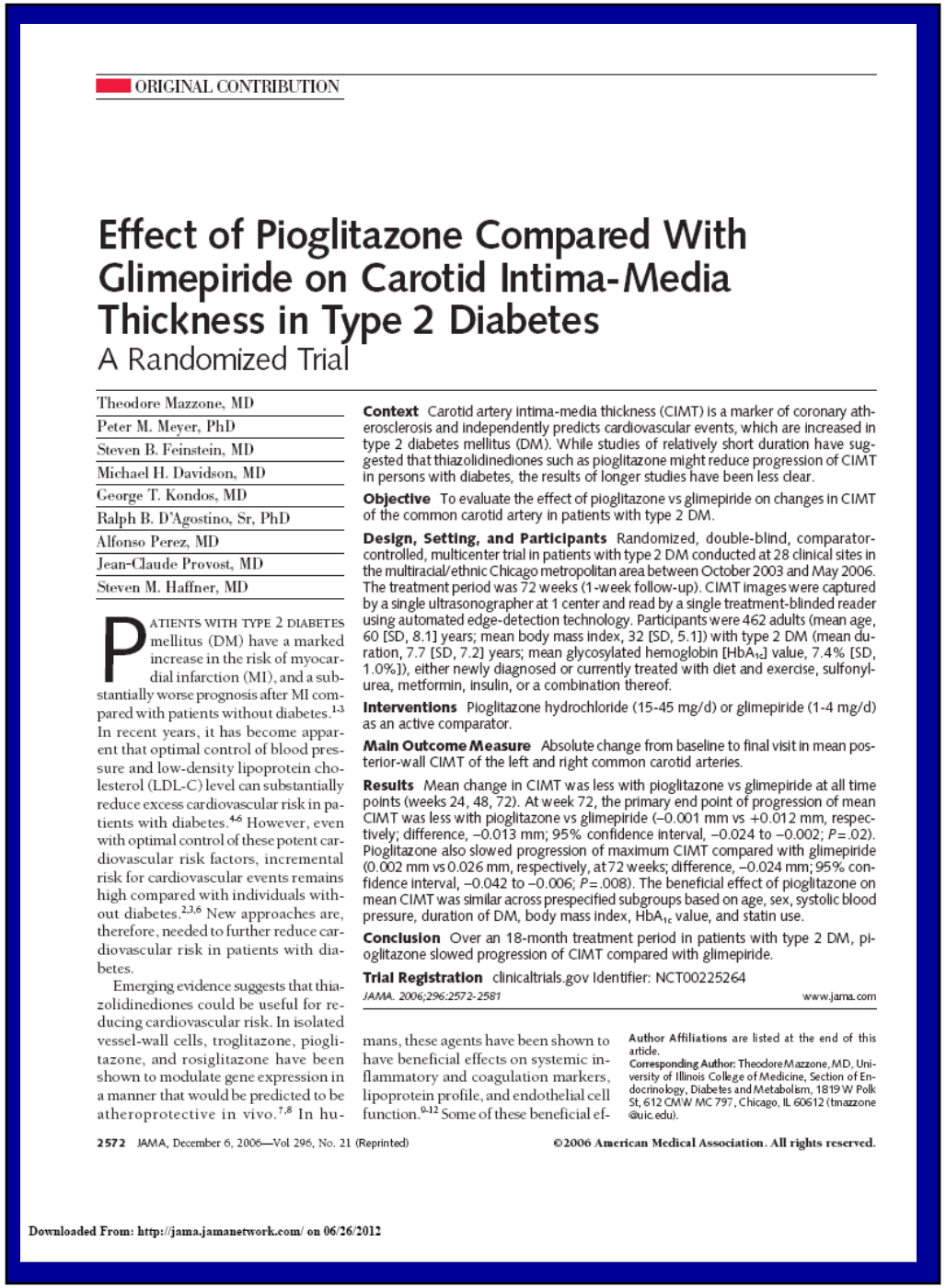
Erdmann E, AHA November 2005, Dallas

proactive-results.com

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



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



ORIGINAL CONTRIBUTION

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
Stuart Kupfer, MD
Alfonso Perez, MD
Horacio Jure, MD
Robert De Larochellière, MD
Cezar S. Staniloae, MD
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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.
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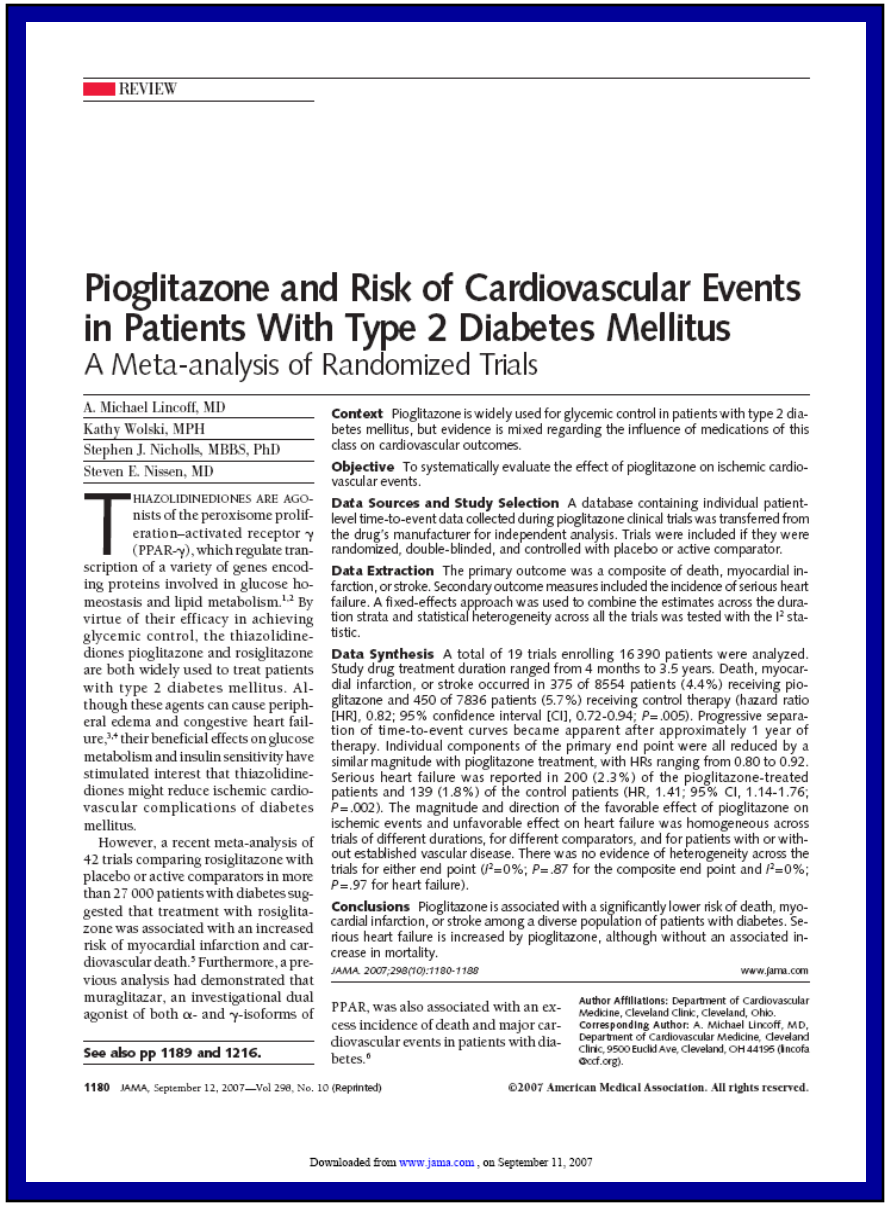
Pioglitazone treated patients showed a significantly lower rate of progression of coronary atherosclerosis, as assessed using intravascular ultrasonography, compared to glimepiride treated patients

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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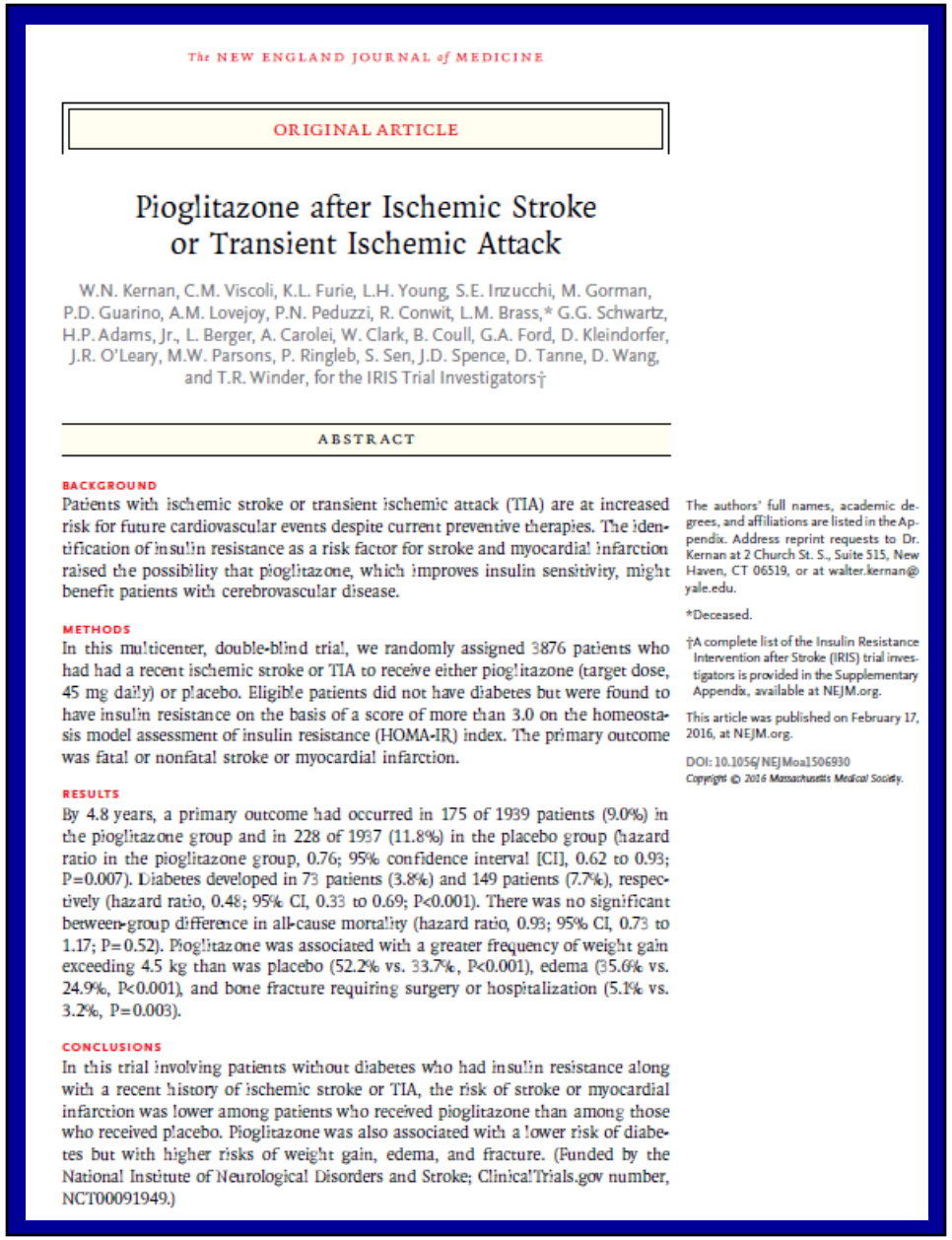
Pioglitazone receiving patients showed a significant reduction in death, myocardial infarction and stroke compared to patients receiving control therapy in meta-analysis of 19 randomised controlled trials
(HR 0.82, CI 0.72 – 0.94, p=0.005)

2016 – The IRIS Trial

Pioglitazone in insulin resistant patients without diabetes



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/NEJMoa1506930

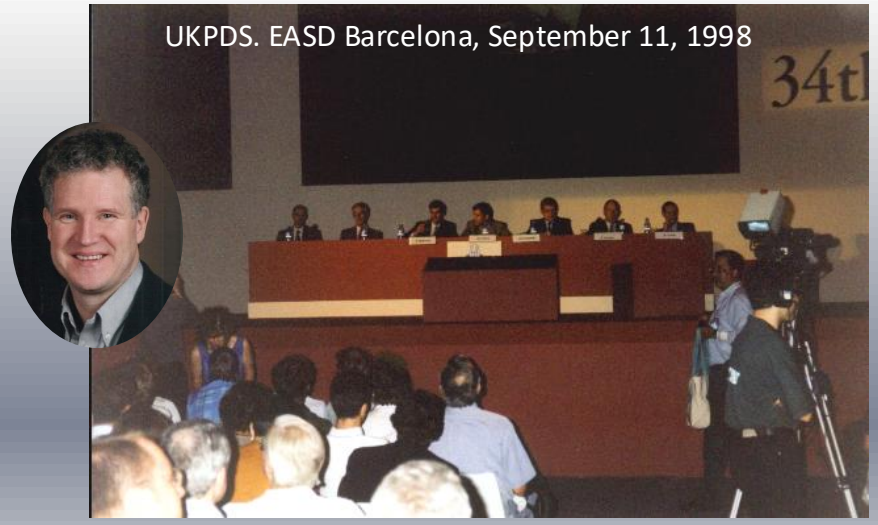
In this trial involving patients without diabetes who had insulin resistance along with a recent history of ischemic stroke or TIA, the risk of stroke or myocardial infarction was reduced by 24% in patients who received pioglitazone versus those who received placebo

Summary

- The accumulated evidence suggests that pioglitazone reduces cardiovascular death, myocardial infarction and stroke by slowing down, or even reversing, the atherosclerotic process

How can we reduce this risk

- Control Blood Pressure
- Use a statin in highest tolerated dose
- Use metformin in all patients if tolerated
- Use pioglitazone to slow or reverse the atherosclerosis



I know cos I was there!

EMPA-REG. EASD Stockholm, September 18, 2015


IMG_1059

THE EMPA-REG OUTCOME STUDY

Key inclusion and exclusion criteria

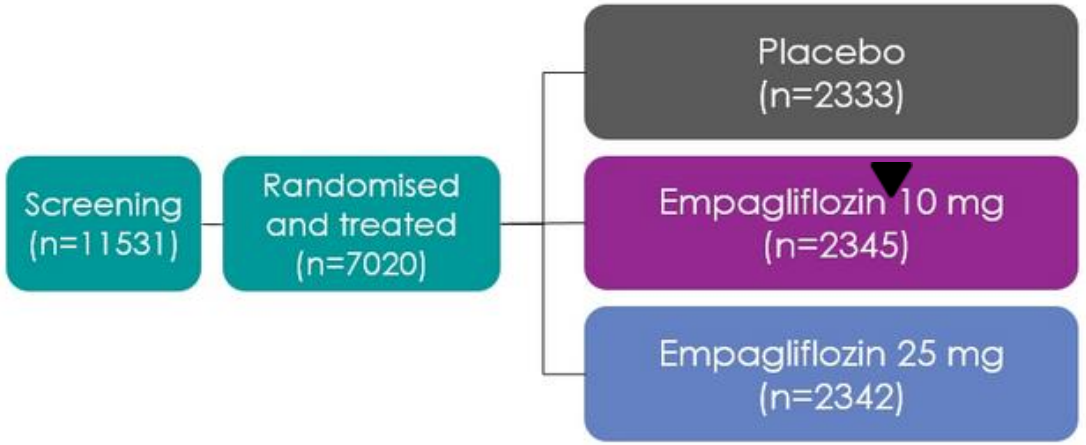
- Key inclusion criteria
  - Adults with type 2 diabetes
  - BMI ≤45 kg/m^2
  - HbA1c 7–10%*
  - Established cardiovascular disease
    - Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease
- Key exclusion criteria
  - eGFR <30 mL/min/1.73m^2 (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

EMPA-REG OUTCOME®

THE EMPA-REG OUTCOME STUDY

Trial design

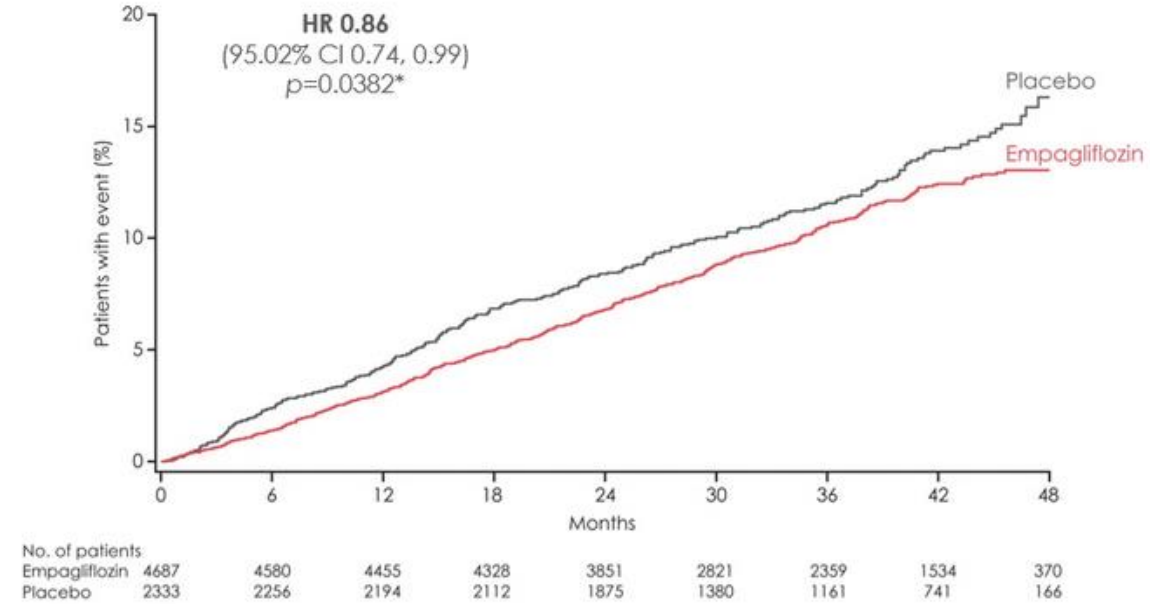


- Study medication was given in addition to standard of care
  - Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

EMPA-REG OUTCOME®

THE EMPA-REG OUTCOME STUDY

Primary outcome: 3-point MACE

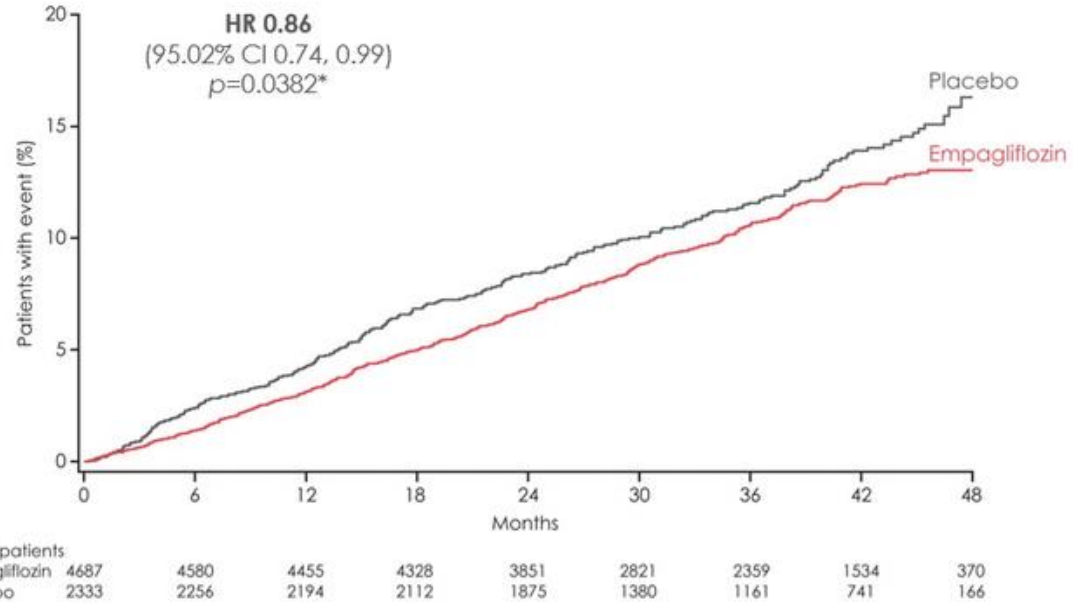


Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

EMPA-REG OUTCOME®

THE EMPA-REG OUTCOME STUDY

Primary outcome:
3-point MACE

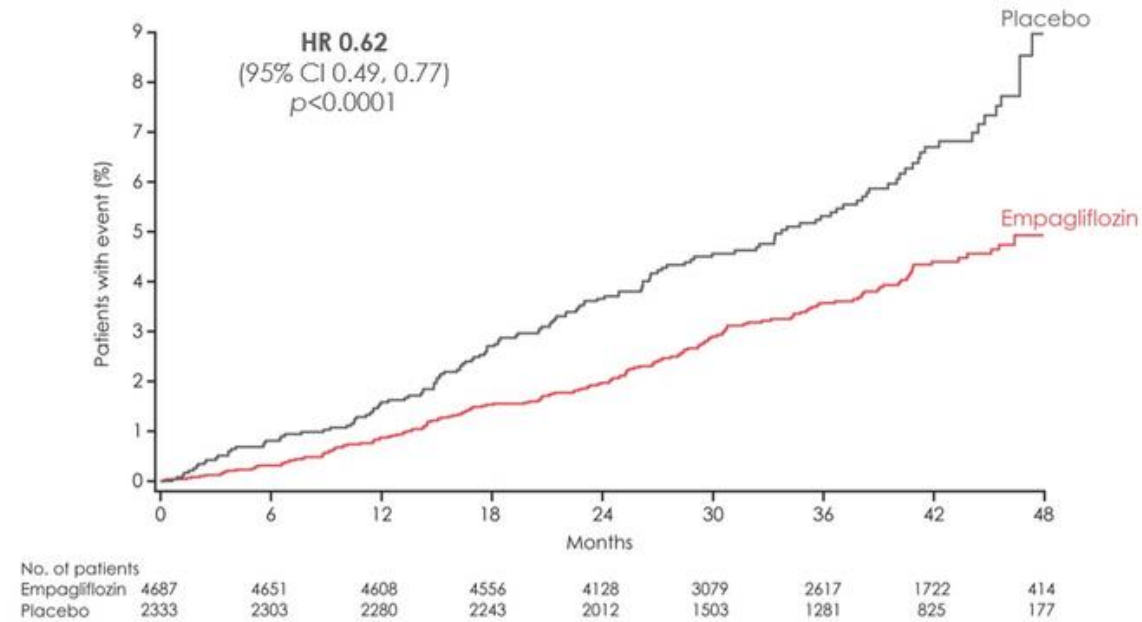


Cumulative incidence function. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio.
* Two-sided tests for superiority were conducted (statistical significance was indicated if p≤0.0498)

EMPA-REG OUTCOME®

THE EMPA-REG OUTCOME STUDY

CV death



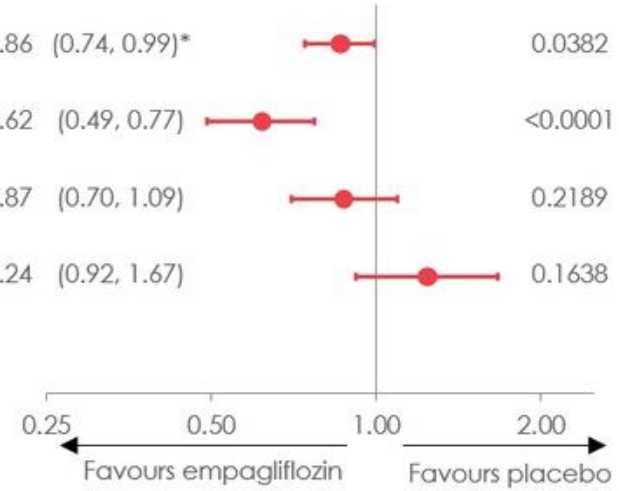
Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

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

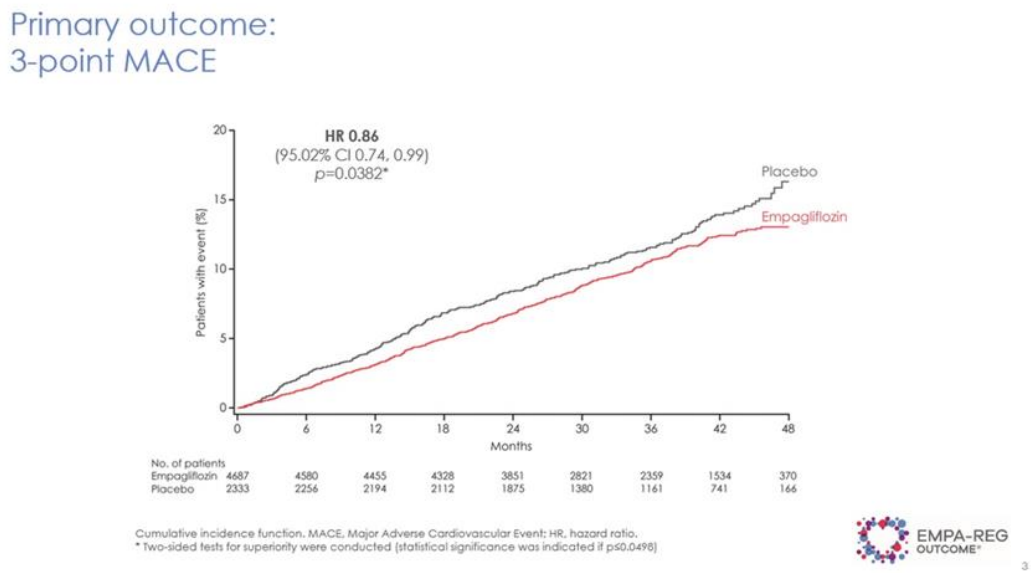
PROactive

Empagliflozin

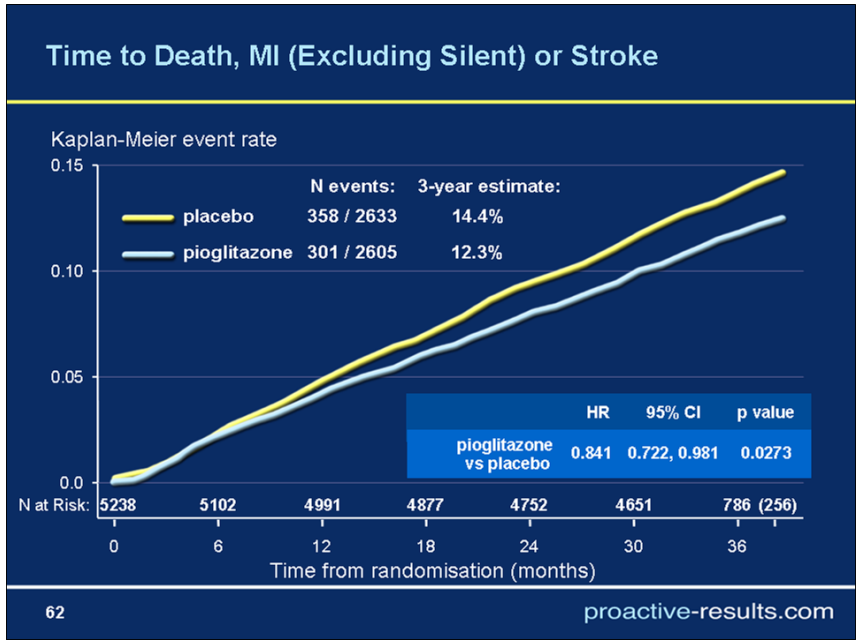
Pioglitazone

3 point MACE

EMPA-REG



PROactive

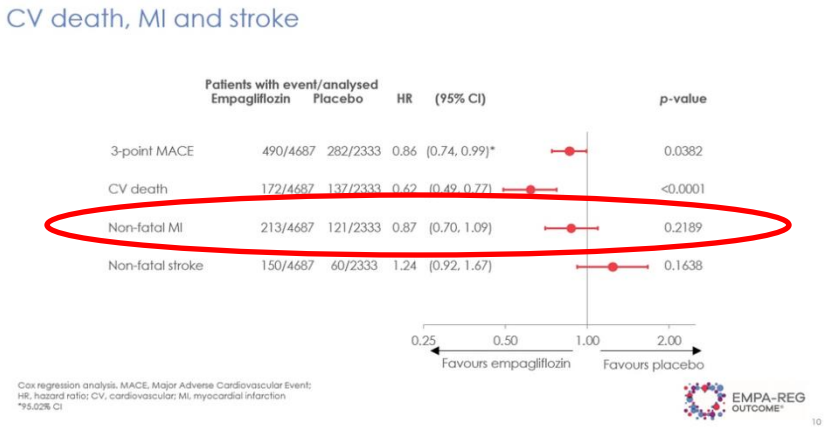


Empagliflozin

Pioglitazone

Myocardial Infarction

EMPA-REG



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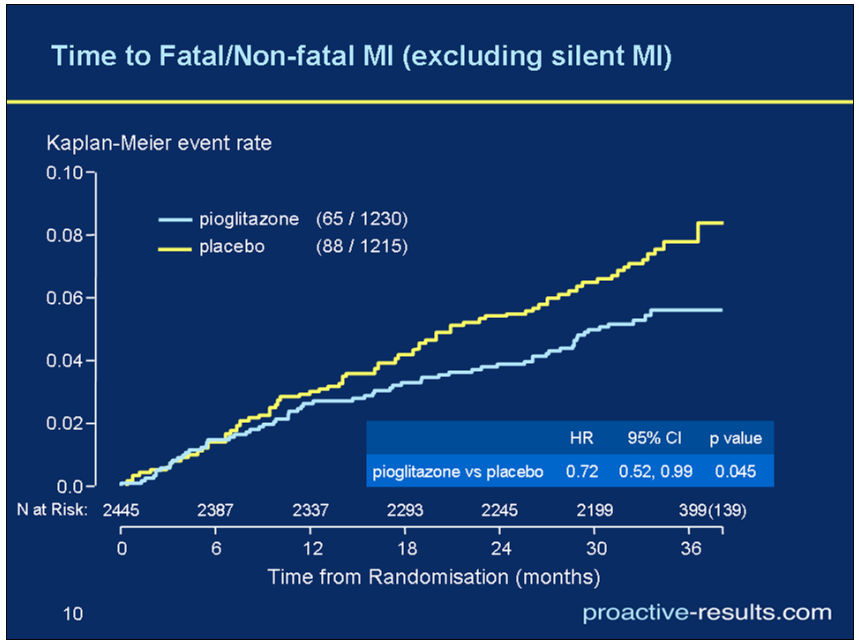
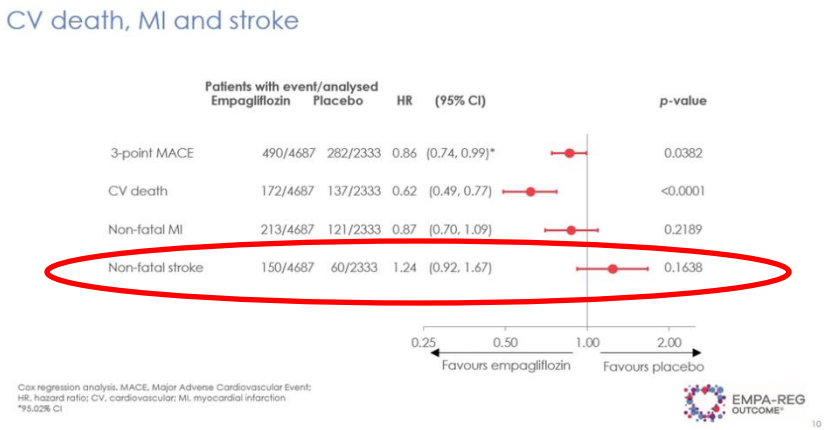


Empagliflozin - no impact

Pioglitazone - impact

Stroke

EMPA-REG



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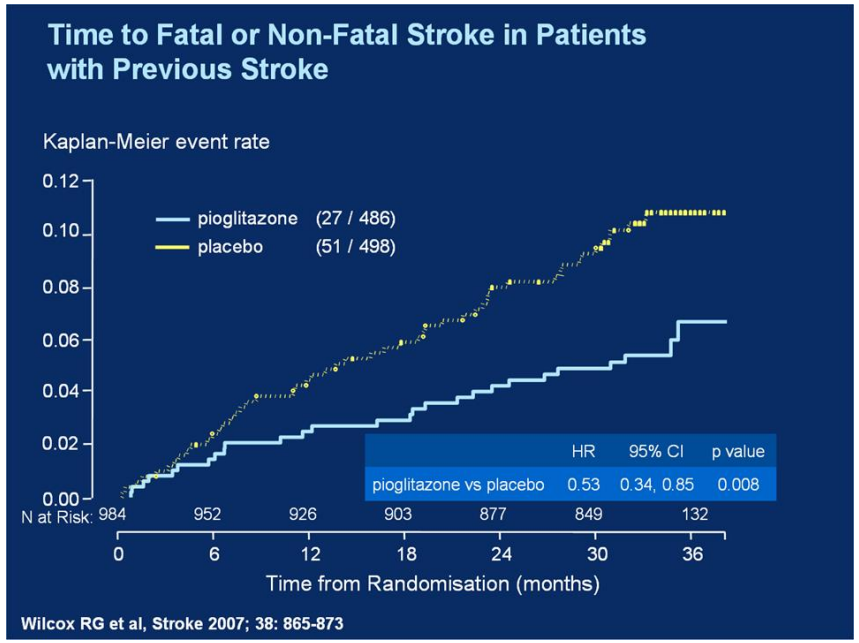
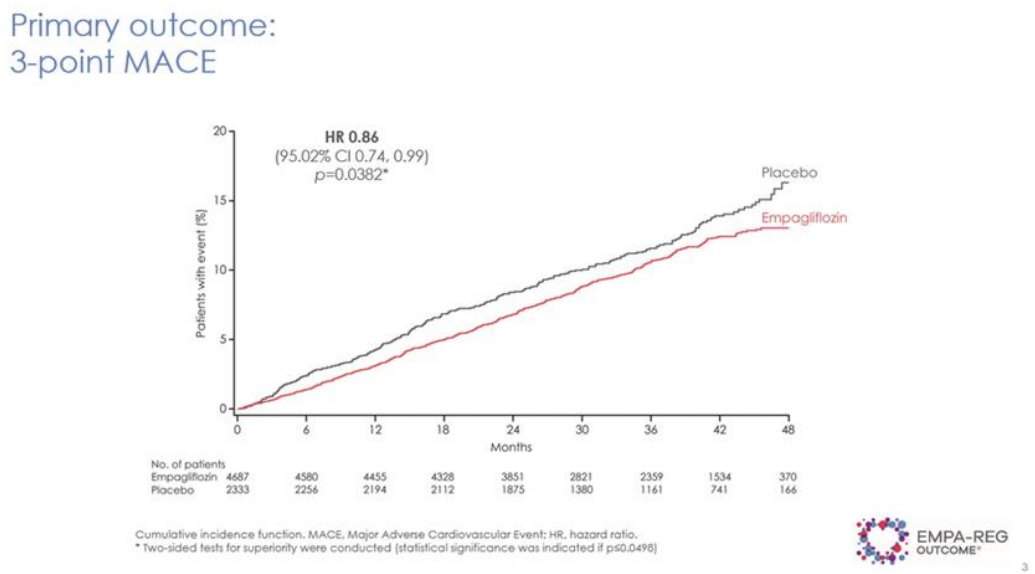


Empagliflozin - no impact

Pioglitazone - impact

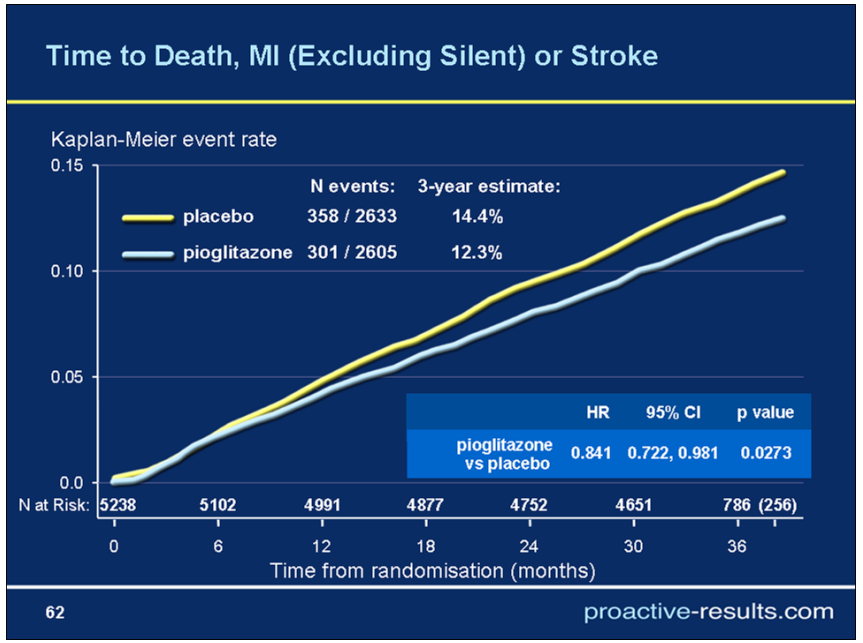
Separation of the graphs

EMPA-REG



Empagliflozin

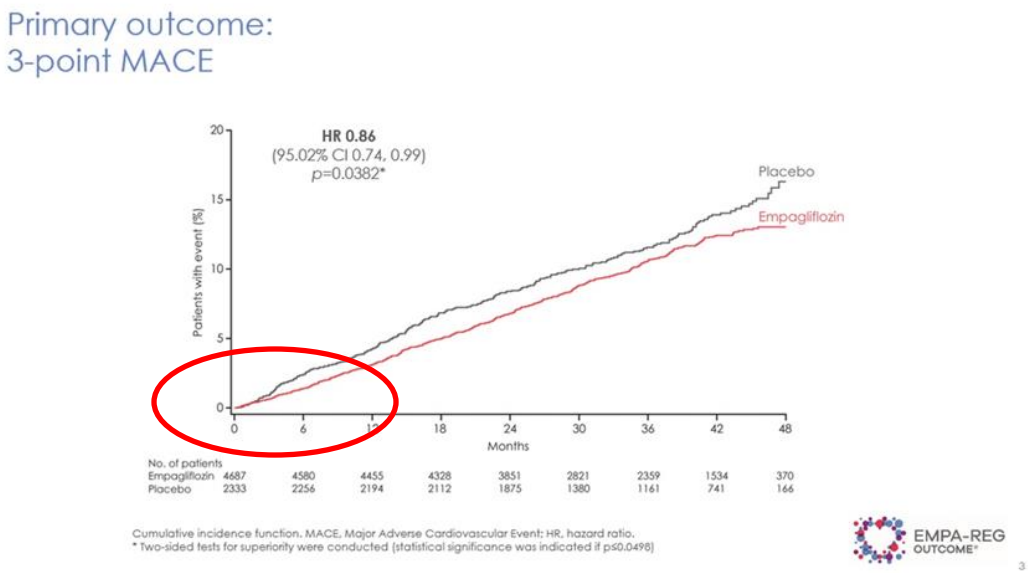
PROactive



Pioglitazone

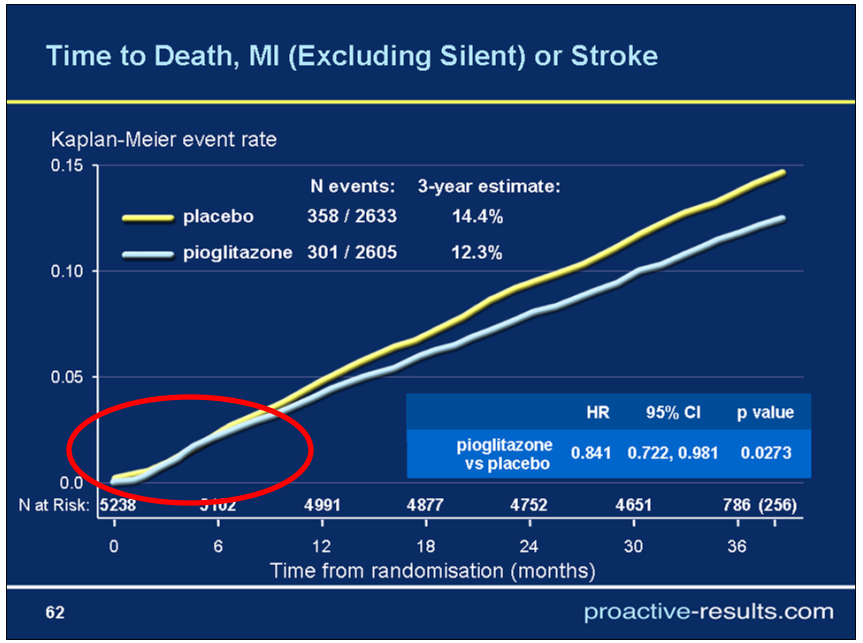
Separation of the graphs

EMPA-REG



Empagliflozin

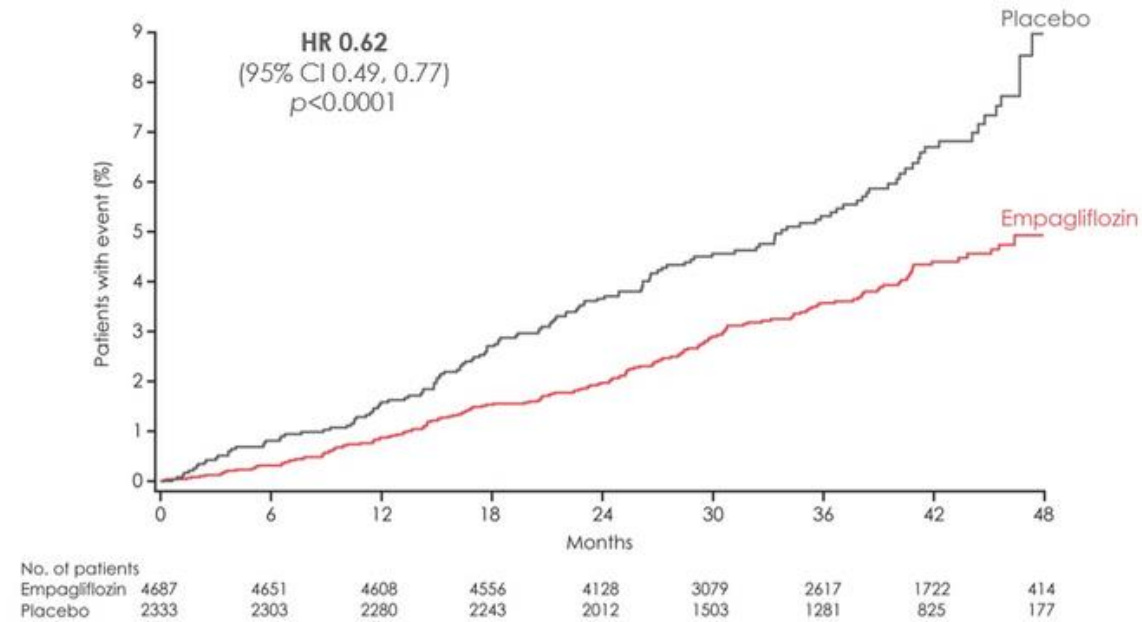
PROactive



Pioglitazone

THE EMPA-REG OUTCOME STUDY

CV death

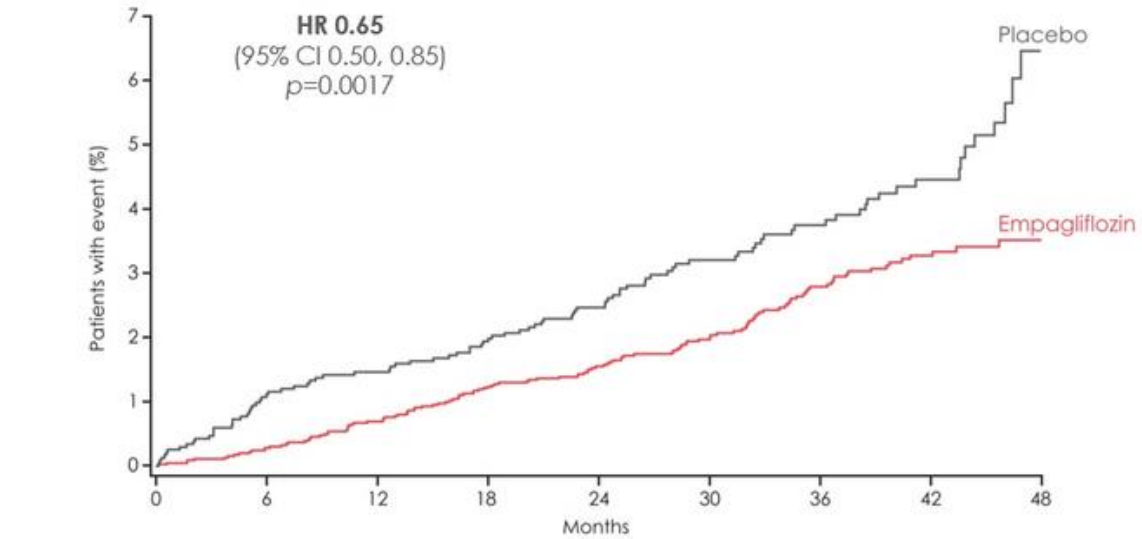


Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

THE EMPA-REG OUTCOME STUDY

Hospitalisation for heart failure



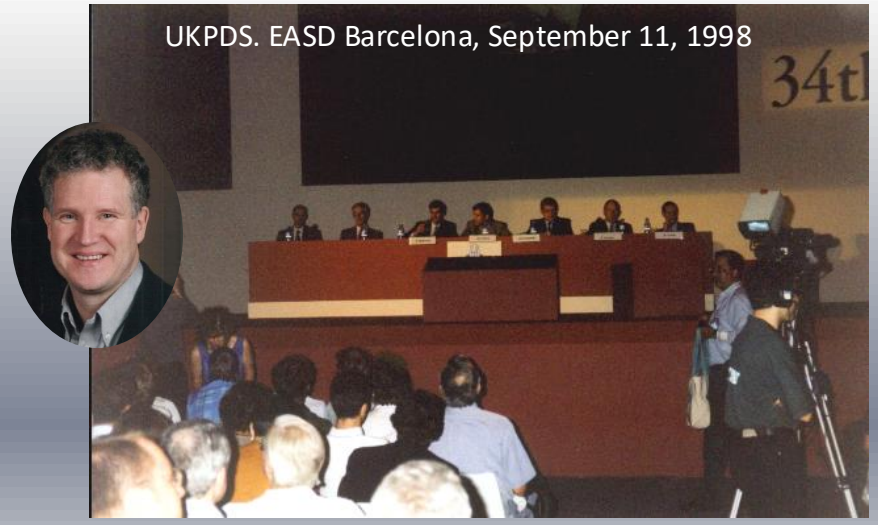
No. of patients									
Empagliflozin	4687	4614	4523	4427	3988	2950	2487	1634	395
Placebo	2333	2271	2226	2173	1932	1424	1202	775	168

Cumulative incidence function. HR, hazard ratio

EMPA-REG OUTCOME®

Summary

- The accumulated evidence suggests that pioglitazone reduces cardiovascular death, myocardial infarction and stroke by slowing down, or even reversing, the atherosclerotic process
- The EMPA-REG OUTCOME™ trial suggests that empagliflozin reduces cardiovascular death but does not reduce either stroke or myocardial infarction, signifying a different mechanism to that of pioglitazone, more hemodynamic in nature

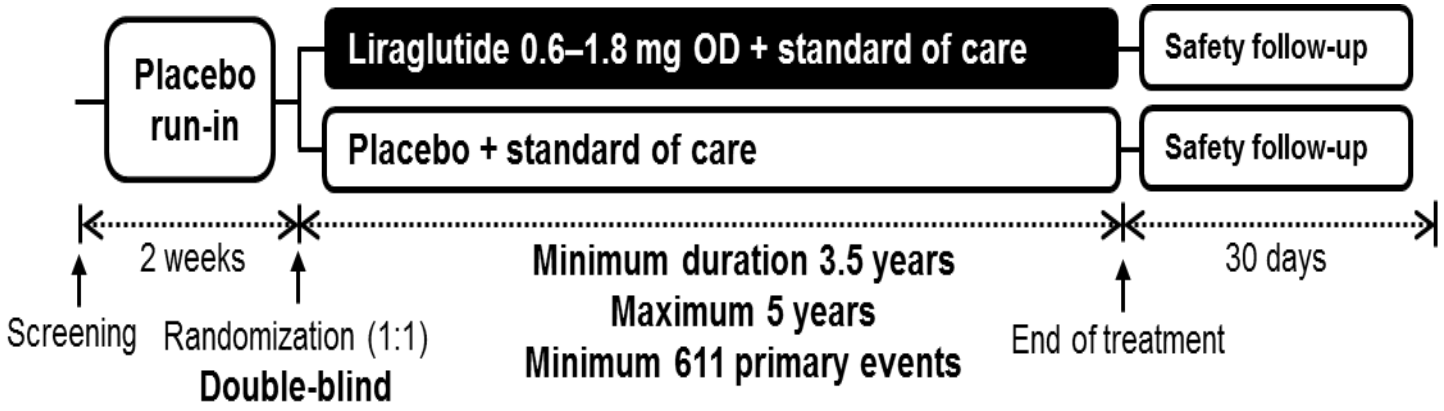


I know cos I was there!

LEADER. ADA New Orleans, June 13, 2016


Hall F
Hall F

LEADER: Study design



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure

  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

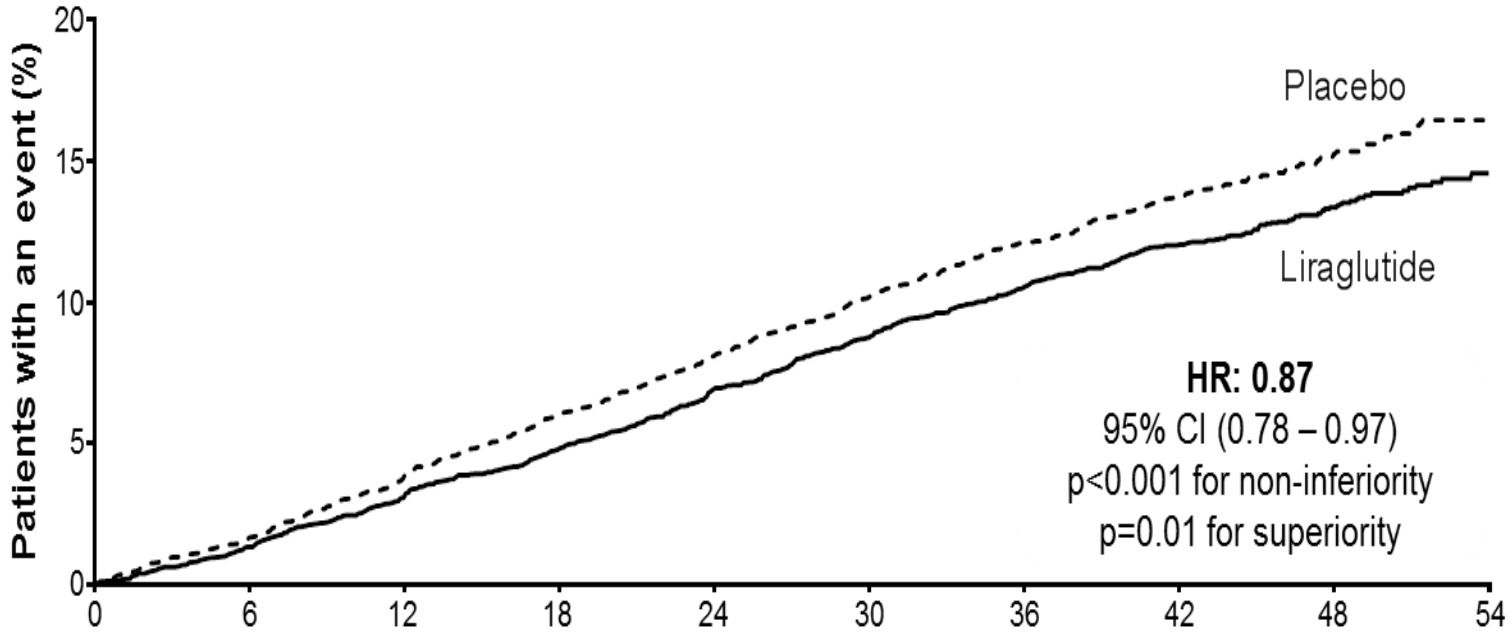
LEADER®
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

CV: cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; HbA_{1c}: glycated hemoglobin; MEN-2: multiple endocrine neoplasia type 2; MTC: medullary thyroid cancer; OAD: oral antidiabetic drug; OD: once daily; T2DM: type 2 diabetes mellitus.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Primary outcome

CV death, non-fatal myocardial infarction, or non-fatal stroke



Patients at risk										
Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

LEADER®
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

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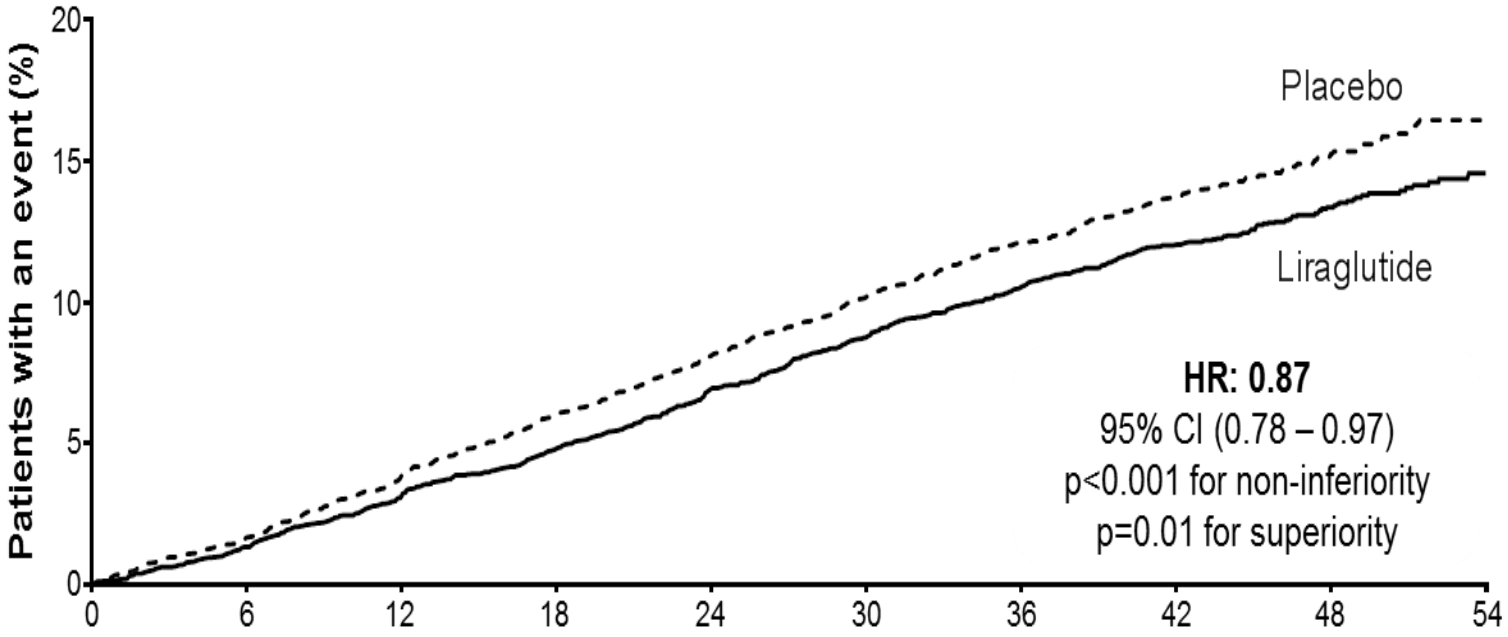

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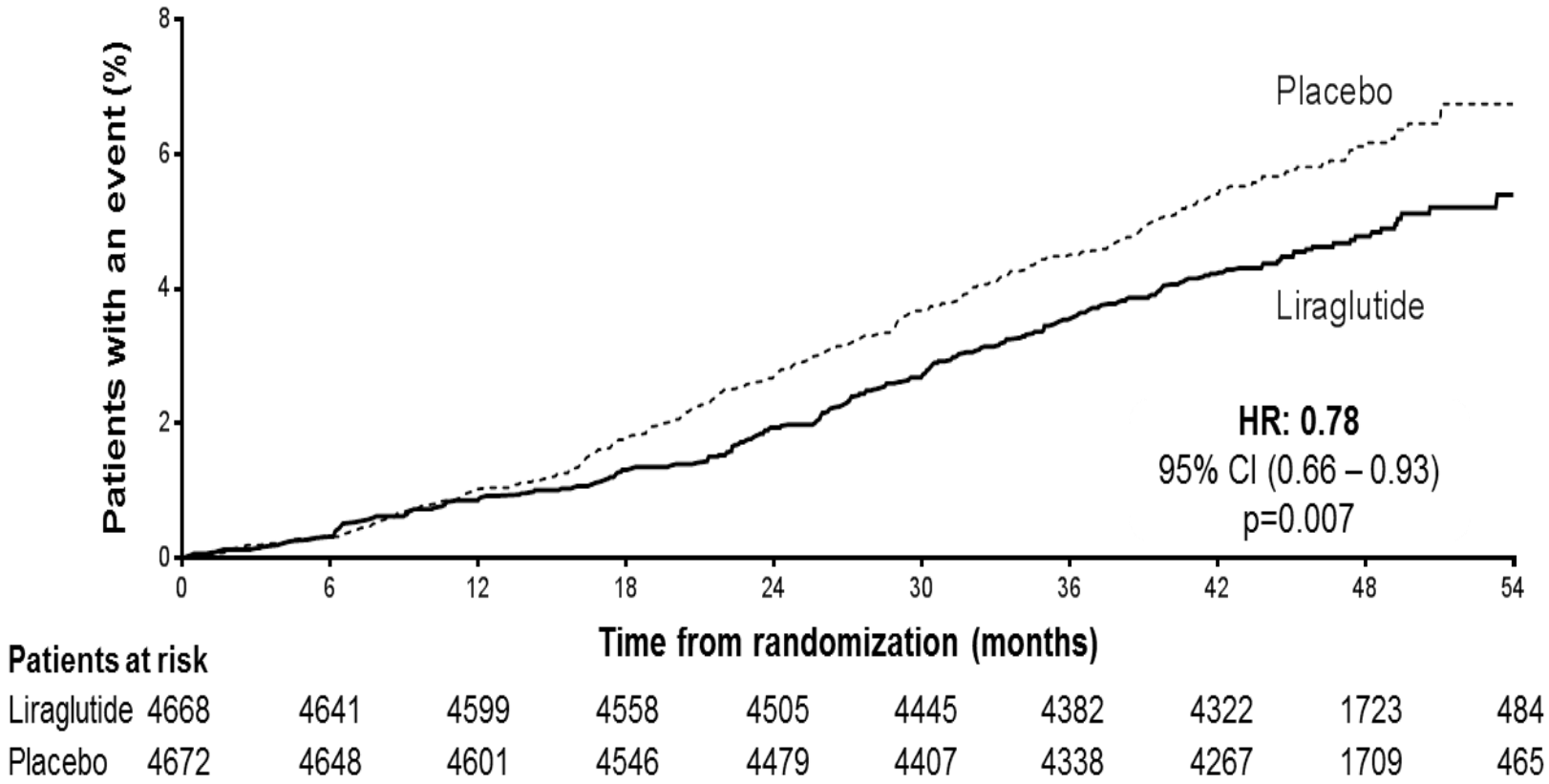
CV death



Patients at risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

LEADER®
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.
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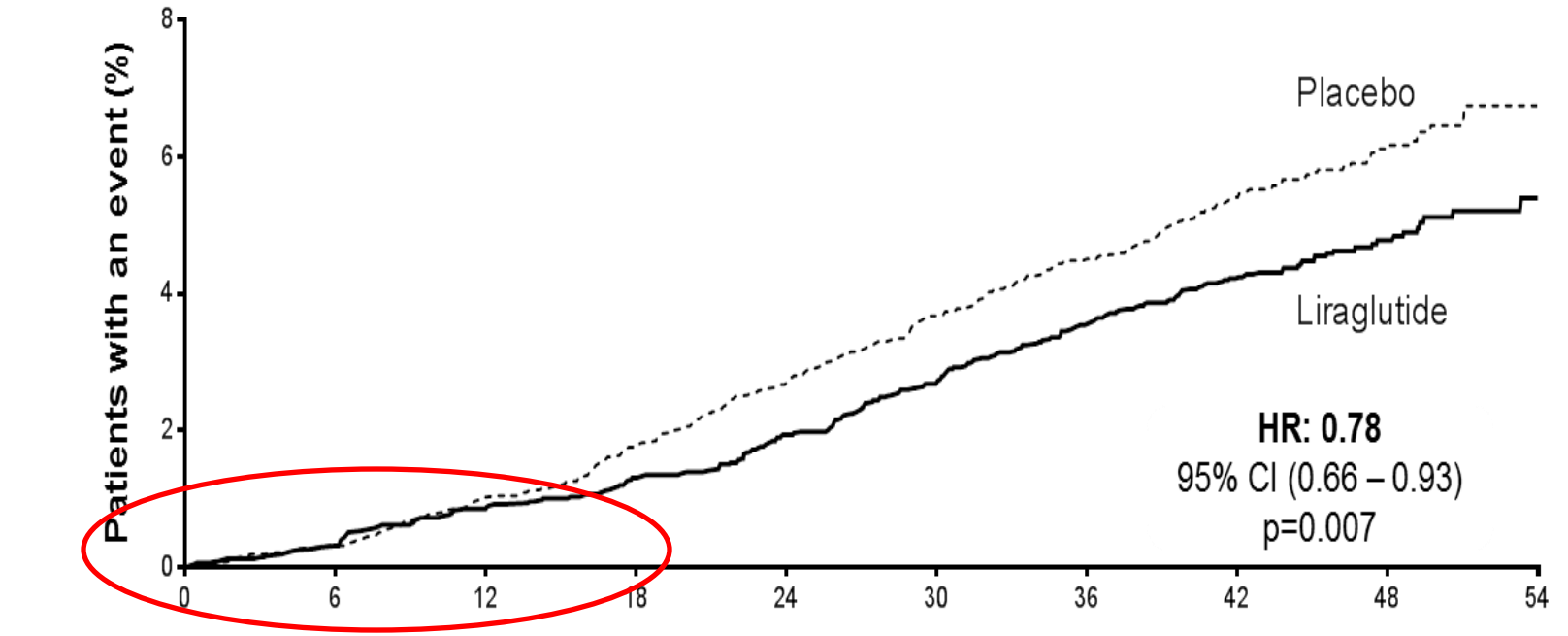

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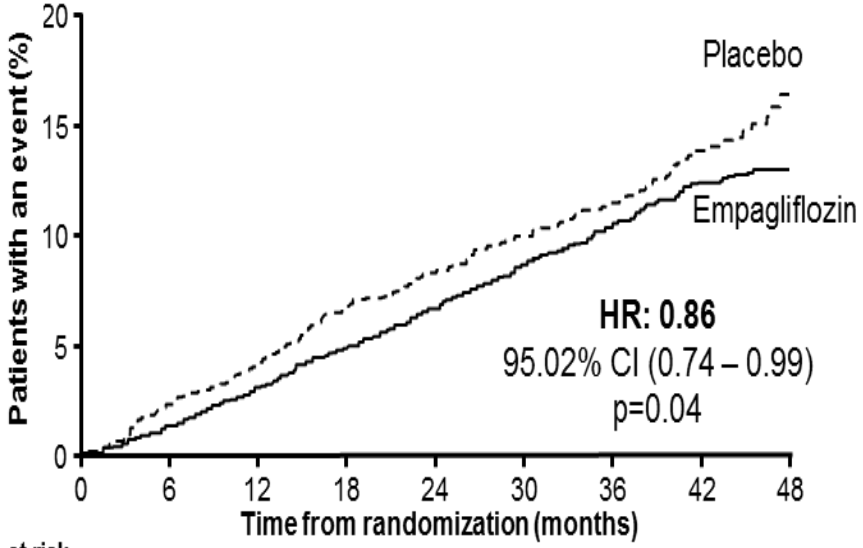
Empagliflozin and Liraglutide

EMPA-REG OUTCOME

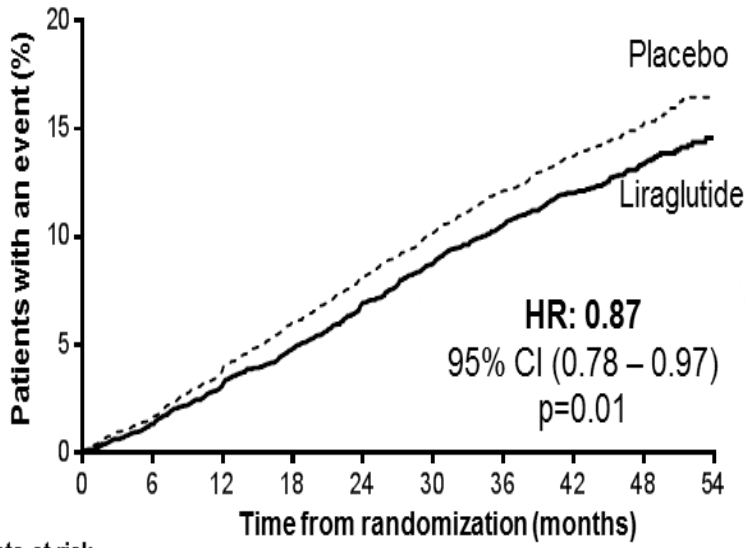
CV death, non-fatal MI, or non-fatal stroke



Patients at risk									
Empagliflozin	4687	4580	4455	4328	3851	2821	2359	1534	370
Placebo	2333	2256	2194	2112	1875	1380	1161	741	166

LEADER

CV death, non-fatal MI, or non-fatal stroke



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LEADER®
Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction.
Zinman B et al. *N Engl J Med* 2015;373:2117-2128.

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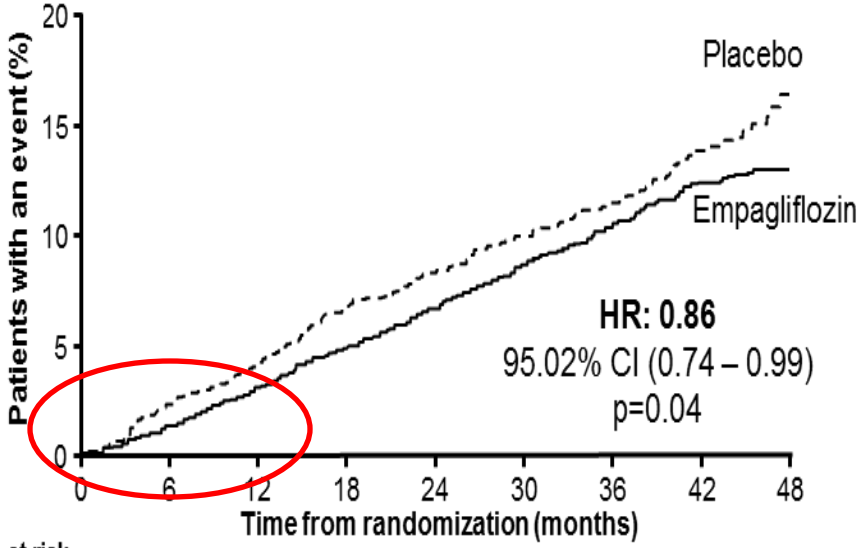
Empagliflozin and Liraglutide

EMPA-REG OUTCOME

CV death, non-fatal MI, or non-fatal stroke



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LEADER

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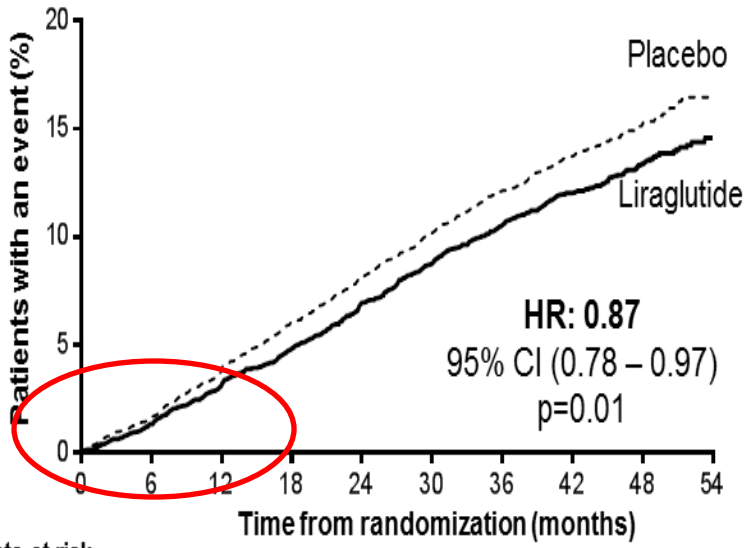

Patients at risk

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LEADER®
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

CI: confidence interval; CV: cardiovascular; HR: hazard ratio; MI: myocardial infarction.
Zinman B et al. *N Engl J Med* 2015;373:2117-2128.

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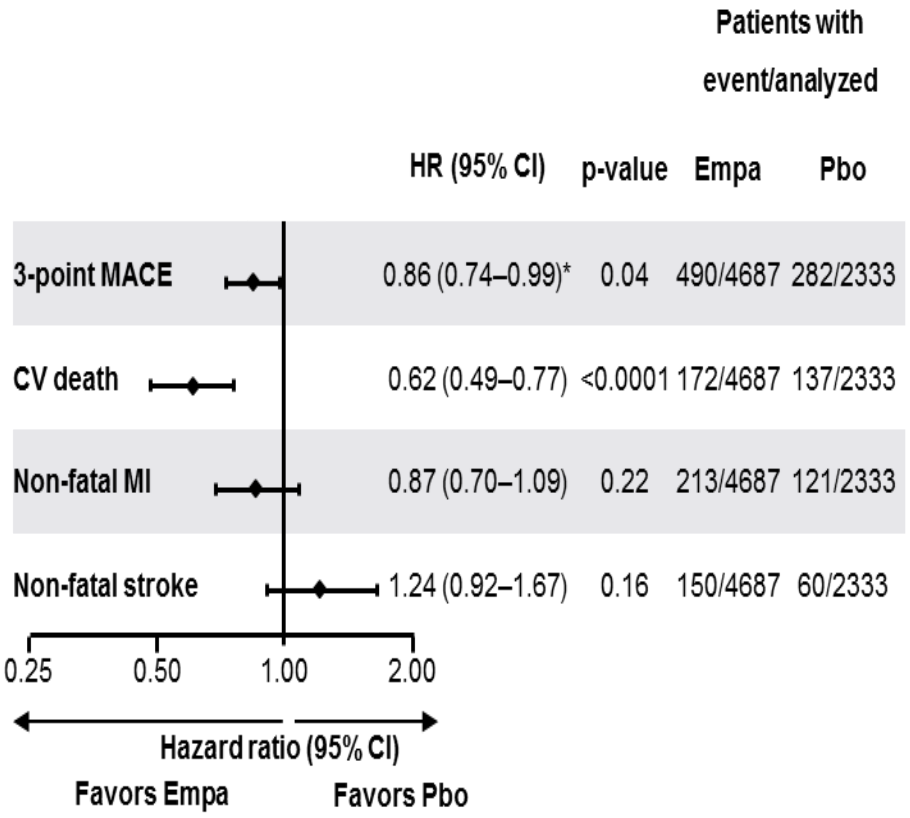
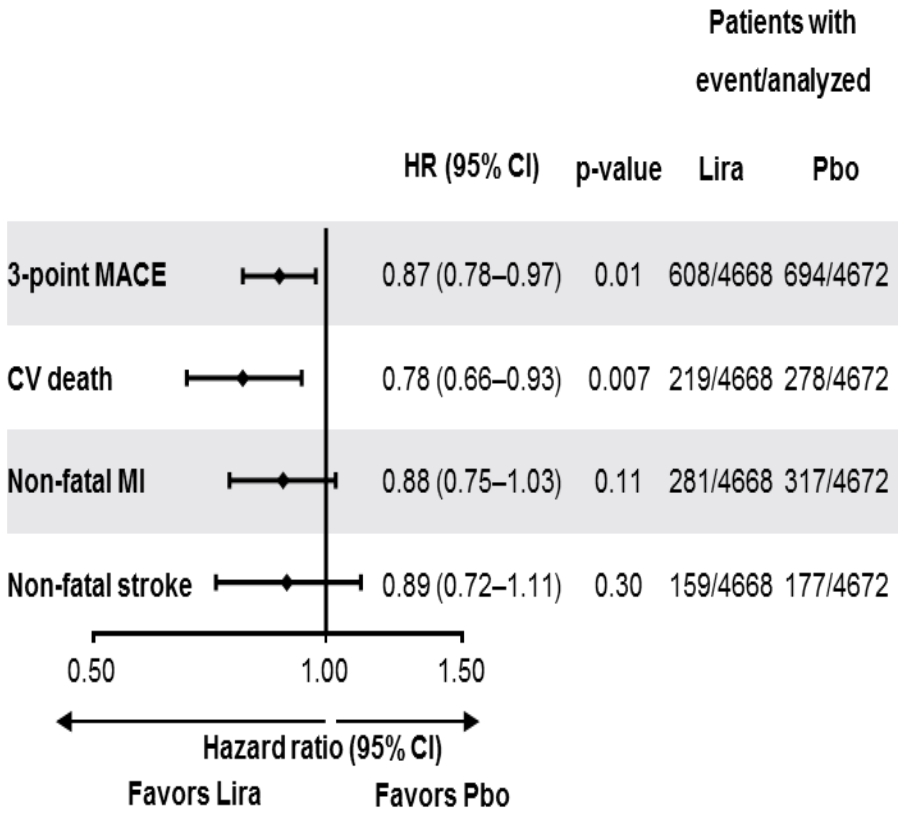
Individual components of the primary endpoint

EMPA-REG OUTCOME



LEADER



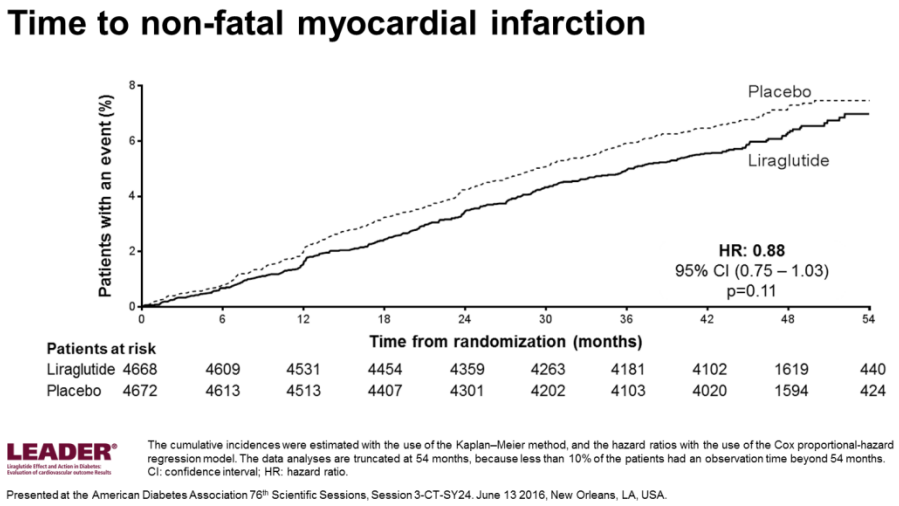
LEADER®
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

*95.02% CI.
CV: cardiovascular; Empa: empaglifloin; Lira: liraglutide; MACE: major adverse cardiovascular event; MI: myocardial infarction; Pbo: placebo.
Zinman B et al. Presented at European Association for the Study of Diabetes 2015, Stockholm, Sweden.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

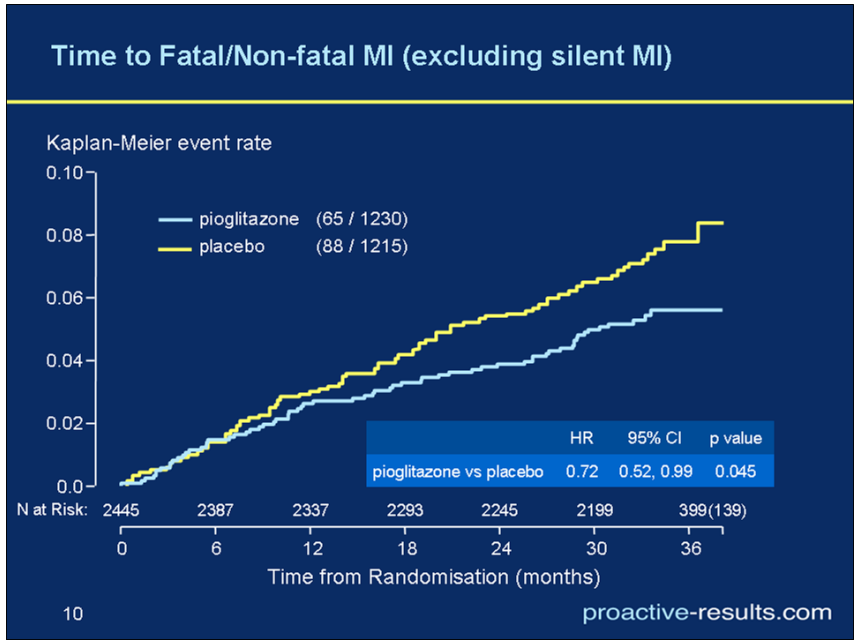
Myocardial Infarction

LEADER



Liraglutide - ?less impact

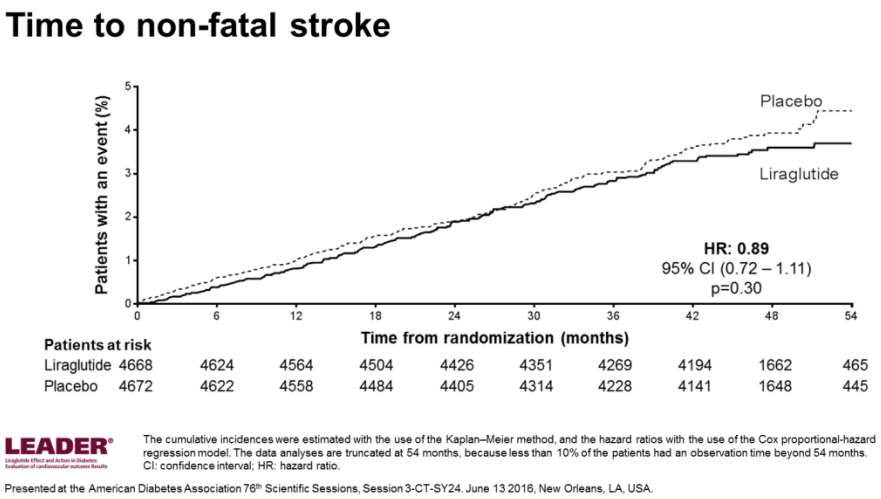
PROactive



Pioglitazone - ?more impact

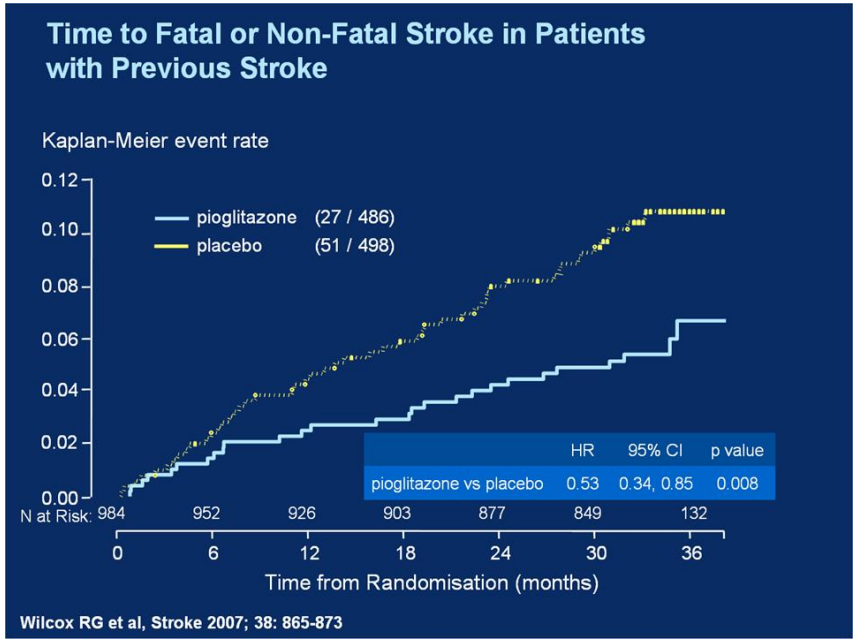
Stroke

LEADER



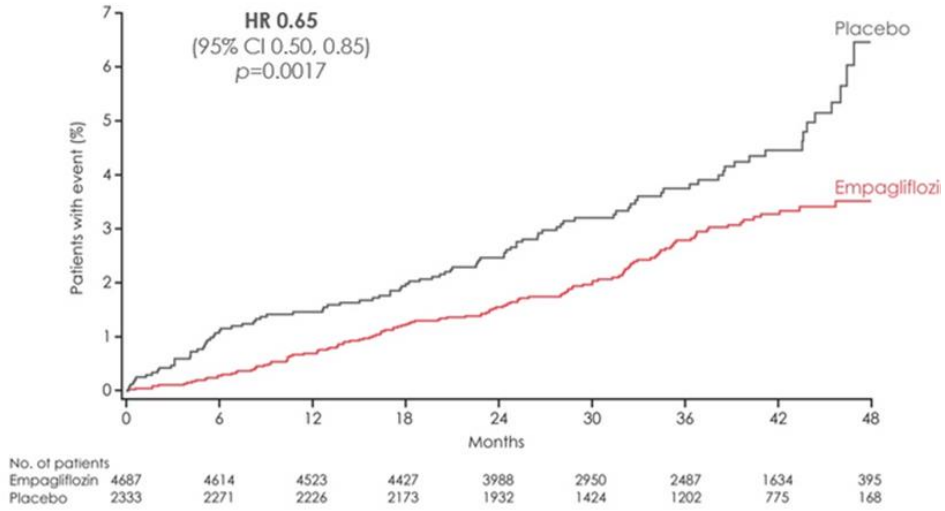
Liraglutide - ?less impact

PROactive

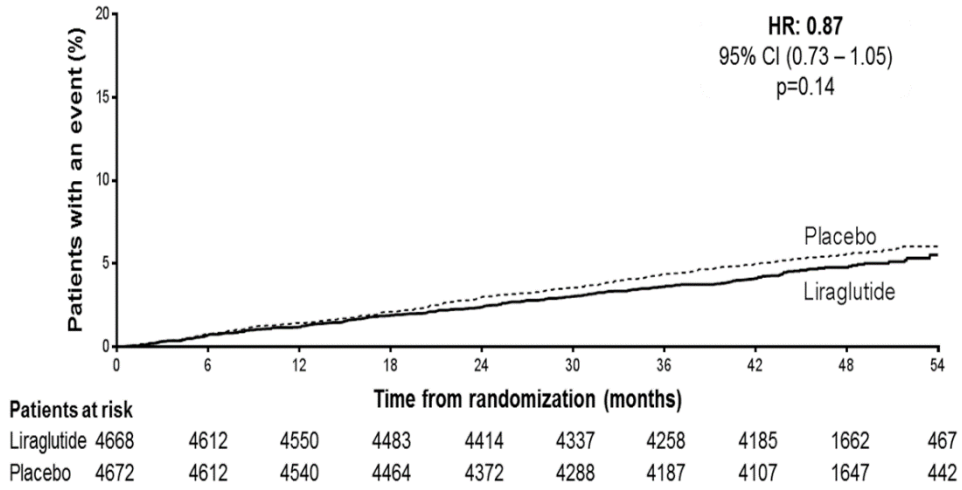


Pioglitazone – more impact

Hospitalisation for heart failure

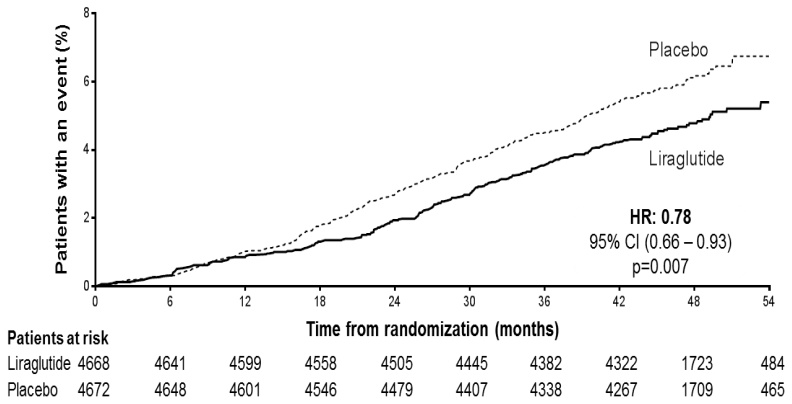


Empagliflozin



Liraglutide

Liraglutide – how does it cause cardiovascular benefit?



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Cell Metabolism

Perspective

The Cardiovascular Biology of Glucagon-like Peptide-1

Daniel J. Drucker[1,*]

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*Correspondence: drucker@lunenfeld.ca

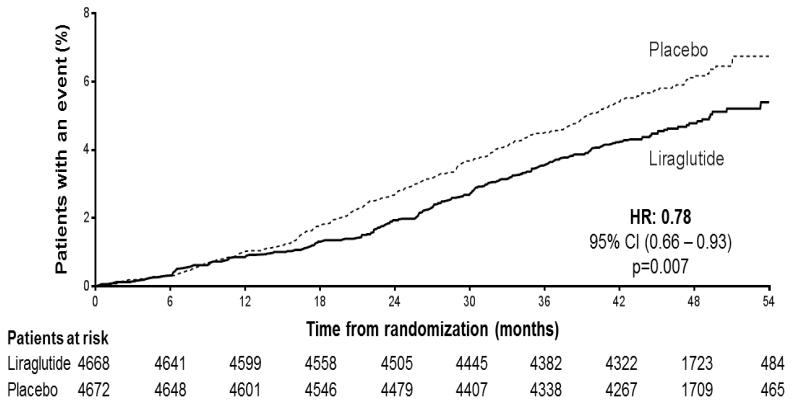
http://dx.doi.org/10.1016/j.cmet.2016.06.009

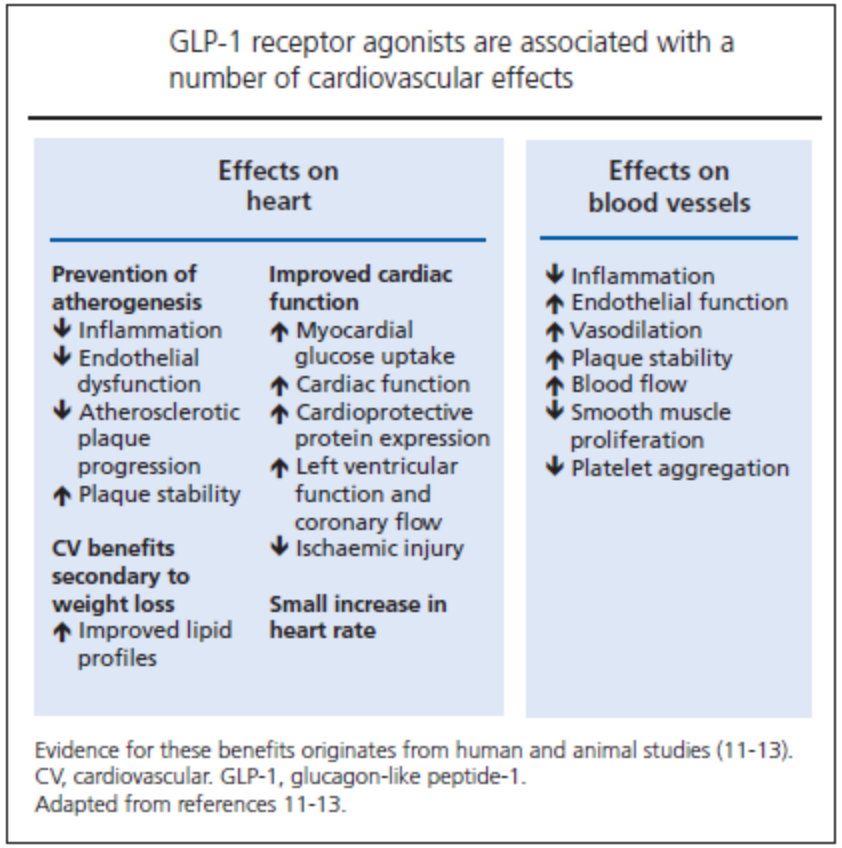
Glucagon-like peptide-1, produced predominantly in enteroendocrine cells, controls glucose metabolism and energy homeostasis through regulation of islet hormone secretion, gastrointestinal motility, and food intake, enabling development of GLP-1 receptor (GLP-1R) agonists for the treatment of diabetes and obesity. GLP-1 also acts on the immune system to suppress inflammation, and GLP-1R signaling in multiple tissues impacts cardiovascular function in health and disease. Here we review how GLP-1 and clinically approved GLP-1R agonists engage mechanisms that influence the risk of developing cardiovascular disease. We discuss how GLP-1R agonists modify inflammation, cardiovascular physiology, and pathophysiology in normal and diabetic animals through direct and indirect mechanisms and review human studies illustrating mechanisms linking GLP-1R signaling to modification of the cardiovascular complications of diabetes. The risks and benefits of GLP-1R agonists are updated in light of recent data suggesting that GLP-1R agonists favorably modify outcomes in diabetic subjects at high risk for cardiovascular events.

Among several dozen peptides secreted from enteroendocrine cells (EECs), glucagon-like peptide-1 (GLP-1(7-36)amide and GLP-1(7-37), collectively referred to as GLP-1) has become the most extensively studied gut hormone with the greatest translational relevance. Initial studies of GLP-1 focused on its role as the treatment of obesity (Drucker, 2015; Meier, 2012; Ussher and Drucker, 2014). Collectively, the interest in these new agents has fostered considerable research activity, and new information on mechanisms of action and clinical data on long-term safety continue to accumulate (Campbell and Drucker, 2013; Drucker,

Drucker DJ. Cell Metab. 2016 Jun 22. pii: S1550-4131(16)30295-9.

Liraglutide – how does it cause cardiovascular benefit?





Drucker DJ. Cell Metab. 2016 Jun 22. pii: S1550-4131(16)30295-9.

Summary

- The accumulated evidence suggests that pioglitazone reduces cardiovascular death, myocardial infarction and stroke by slowing down, or even reversing, the atherosclerotic process
- The EMPA-REG OUTCOME™ trial suggests that empagliflozin reduces cardiovascular death but does not reduce either stroke or myocardial infarction, signifying a different mechanism to that of pioglitazone, more hemodynamic in nature
- The LEADER® trial again shows a bigger impact of liraglutide on cardiovascular death than on stroke and myocardial infarction but, in contrast to empagliflozin, no impact on heart failure. This suggests different mechanisms for liraglutide to those of both pioglitazone and empagliflozin

Potential for agents to complement each other

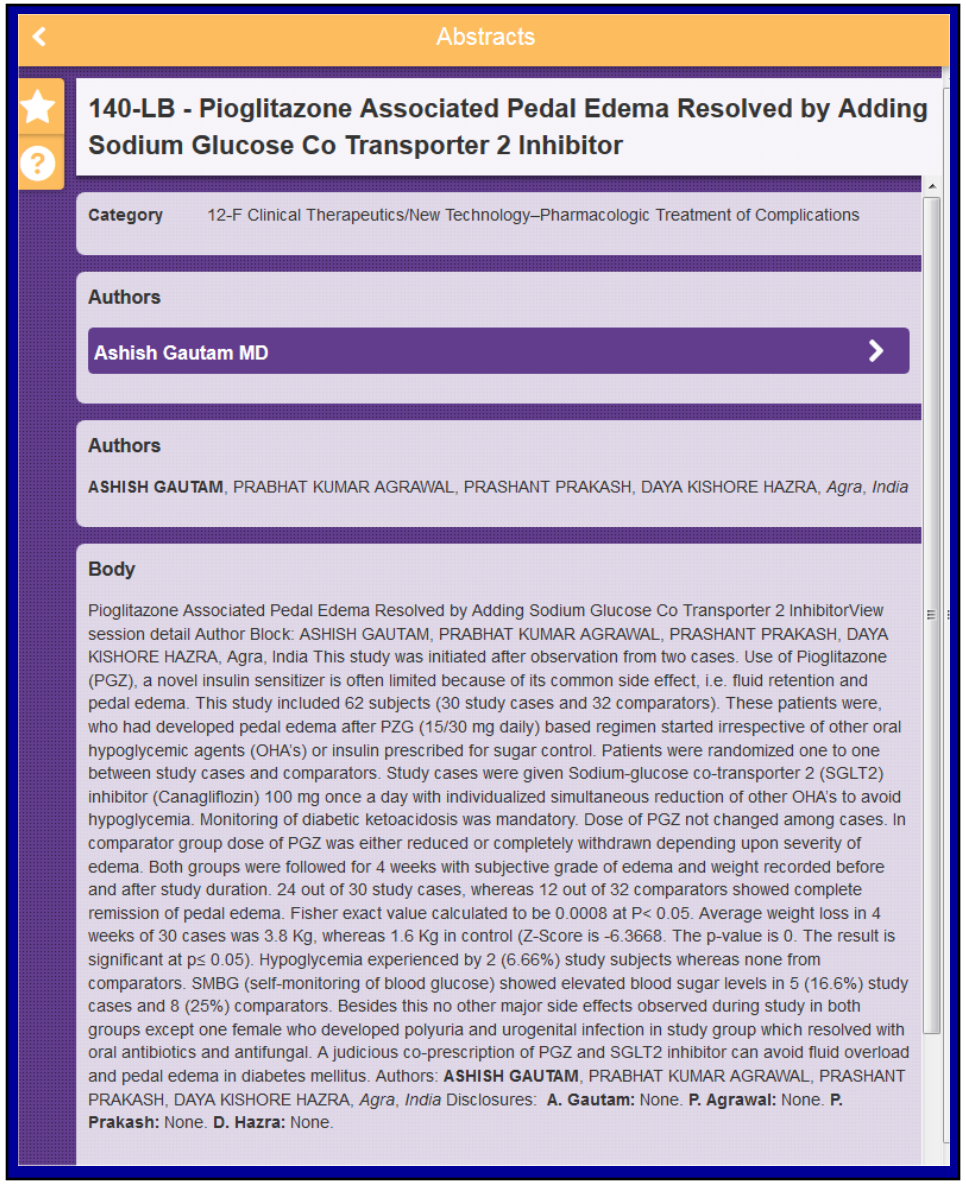
Benefit

- Pioglitazone:
  - reduction of cardiovascular death, myocardial infarction and stroke by reduction of atherosclerotic process
- Empagliflozin:
  - reduction of heart failure
  - reduction of cardiovascular death
  - NB weight loss
- Liraglutide:
  - reduction of cardiovascular death but not heart failure
  - NB weight loss

Side effect

- Fluid retention, weight gain
- Genital infection
- GI side effects

Pioglitazone and SGLT2 inhibitor



Abstracts

140-LB - Pioglitazone Associated Pedal Edema Resolved by Adding Sodium Glucose Co Transporter 2 Inhibitor

Category 12-F Clinical Therapeutics/New Technology–Pharmacologic Treatment of Complications

Authors

Ashish Gautam MD

Authors

ASHISH GAUTAM, PRABHAT KUMAR AGRAWAL, PRASHANT PRAKASH, DAYA KISHORE HAZRA, *Agra*, *India*

Body

Pioglitazone Associated Pedal Edema Resolved by Adding Sodium Glucose Co Transporter 2 InhibitorView session detail Author Block: ASHISH GAUTAM, PRABHAT KUMAR AGRAWAL, PRASHANT PRAKASH, DAYA KISHORE HAZRA, Agra, India This study was initiated after observation from two cases. Use of Pioglitazone (PGZ), a novel insulin sensitizer is often limited because of its common side effect, i.e. fluid retention and pedal edema. This study included 62 subjects (30 study cases and 32 comparators). These patients were, who had developed pedal edema after PZG (15/30 mg daily) based regimen started irrespective of other oral hypoglycemic agents (OHA's) or insulin prescribed for sugar control. Patients were randomized one to one between study cases and comparators. Study cases were given Sodium-glucose co-transporter 2 (SGLT2) inhibitor (Canagliflozin) 100 mg once a day with individualized simultaneous reduction of other OHA's to avoid hypoglycemia. Monitoring of diabetic ketoacidosis was mandatory. Dose of PGZ not changed among cases. In comparator group dose of PGZ was either reduced or completely withdrawn depending upon severity of edema. Both groups were followed for 4 weeks with subjective grade of edema and weight recorded before and after study duration. 24 out of 30 study cases, whereas 12 out of 32 comparators showed complete remission of pedal edema. Fisher exact value calculated to be 0.0008 at P< 0.05. Average weight loss in 4 weeks of 30 cases was 3.8 Kg, whereas 1.6 Kg in control (Z-Score is -6.3668. The p-value is 0. The result is significant at p≤ 0.05). Hypoglycemia experienced by 2 (6.66%) study subjects whereas none from comparators. SMBG (self-monitoring of blood glucose) showed elevated blood sugar levels in 5 (16.6%) study cases and 8 (25%) comparators. Besides this no other major side effects observed during study in both groups except one female who developed polyuria and urogenital infection in study group which resolved with oral antibiotics and antifungal. A judicious co-prescription of PGZ and SGLT2 inhibitor can avoid fluid overload and pedal edema in diabetes mellitus. Authors: **ASHISH GAUTAM**, PRABHAT KUMAR AGRAWAL, PRASHANT PRAKASH, DAYA KISHORE HAZRA, *Agra*, *India* Disclosures: **A. Gautam:** None. **P. Agrawal:** None. **P. Prakash:** None. **D. Hazra:** None.

Fluid retention and weight gain associated with pioglitazone mitigated by SGLT2 inhibitor

Potential for agents to complement each other

Benefit

- Pioglitazone:
  - reduction of cardiovascular death, myocardial infarction and stroke by reduction of atherosclerotic process
- Empagliflozin:
  - reduction of heart failure
  - reduction of cardiovascular death
  - NB weight loss
- Liraglutide:
  - reduction of cardiovascular death but not heart failure
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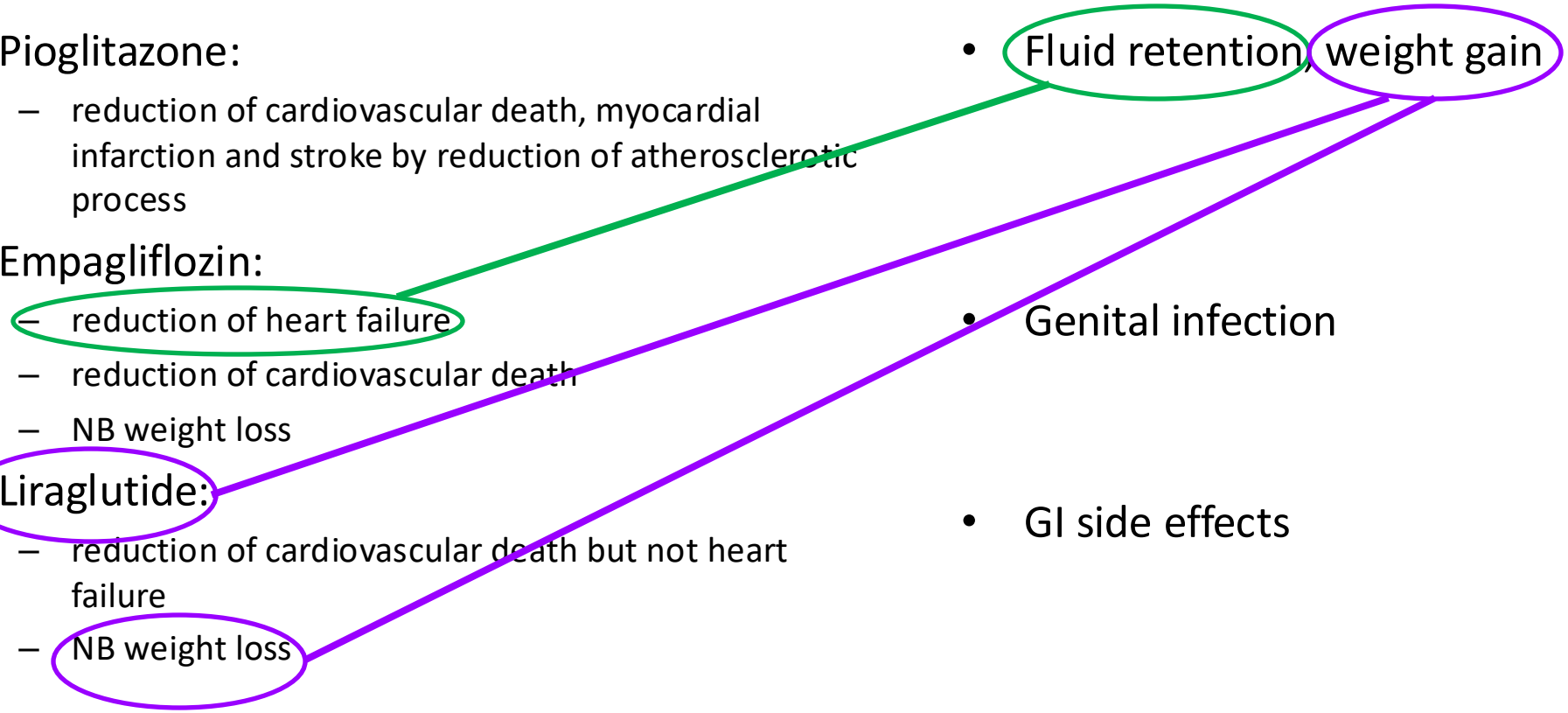
Side effect

- Fluid retention, weight gain
- Genital infection
- GI side effects



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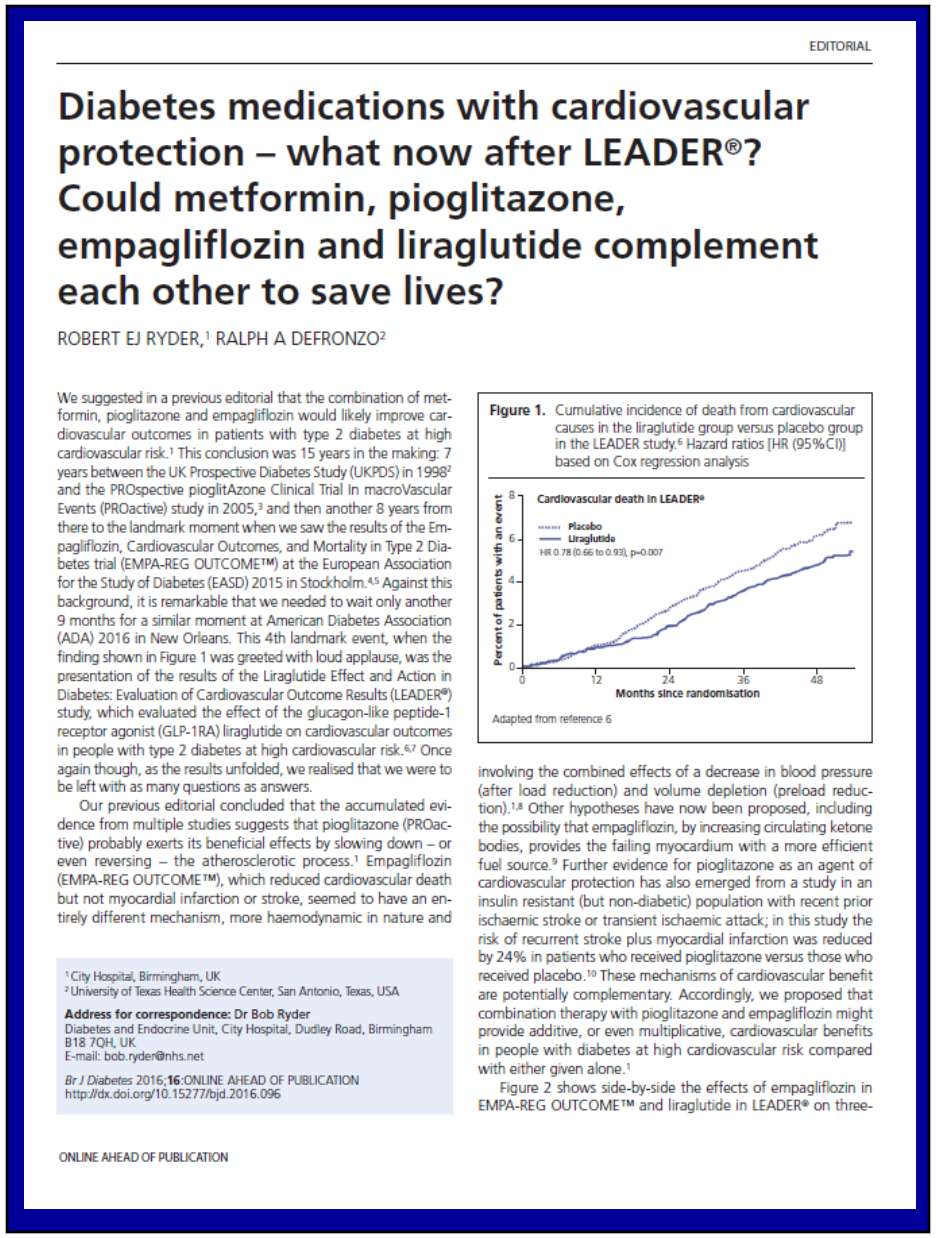
Conclusion



EDITORIAL

Diabetes medications with cardiovascular protection – what now after LEADER®? Could metformin, pioglitazone, empagliflozin and liraglutide complement each other to save lives?

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

We suggested in a previous editorial that the combination of metformin, pioglitazone and empagliflozin would likely improve cardiovascular outcomes in patients with type 2 diabetes at high cardiovascular risk.[1] This conclusion was 15 years in the making: 7 years between the UK Prospective Diabetes Study (UKPDS) in 1998[2] and the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study in 2005,[3] and then another 8 years from there to the landmark moment when we saw the results of the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes trial (EMPA-REG OUTCOME™) at the European Association for the Study of Diabetes (EASD) 2015 in Stockholm.[4,5] Against this background, it is remarkable that we needed to wait only another 9 months for a similar moment at American Diabetes Association (ADA) 2016 in New Orleans. This 4th landmark event, when the finding shown in Figure 1 was greeted with loud applause, was the presentation of the results of the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER®) study, which evaluated the effect of the glucagon-like peptide-1 receptor agonist (GLP-1RA) liraglutide on cardiovascular outcomes in people with type 2 diabetes at high cardiovascular risk.[6,7] Once again though, as the results unfolded, we realised that we were to be left with as many questions as answers.

Our previous editorial concluded that the accumulated evidence from multiple studies suggests that pioglitazone (PROactive) probably exerts its beneficial effects by slowing down – or even reversing – the atherosclerotic process.[1] Empagliflozin (EMPA-REG OUTCOME™), which reduced cardiovascular death but not myocardial infarction or stroke, seemed to have an entirely different mechanism, more haemodynamic in nature and involving the combined effects of a decrease in blood pressure (after load reduction) and volume depletion (preload reduction).[1,8] Other hypotheses have now been proposed, including the possibility that empagliflozin, by increasing circulating ketone bodies, provides the failing myocardium with a more efficient fuel source.[9] Further evidence for pioglitazone as an agent of cardiovascular protection has also emerged from a study in an insulin resistant (but non-diabetic) population with recent prior ischaemic stroke or transient ischaemic attack; in this study the risk of recurrent stroke plus myocardial infarction was reduced by 24% in patients who received pioglitazone versus those who received placebo.[10] These mechanisms of cardiovascular benefit are potentially complementary. Accordingly, we proposed that combination therapy with pioglitazone and empagliflozin might provide additive, or even multiplicative, cardiovascular benefits in people with diabetes at high cardiovascular risk compared with either given alone.[1]

Figure 2 shows side-by-side the effects of empagliflozin in EMPA-REG OUTCOME™ and liraglutide in LEADER® on three-

Figure 1. Cumulative incidence of death from cardiovascular causes in the liraglutide group versus placebo group in the LEADER study.[6] Hazard ratios [HR (95%CI)] based on Cox regression analysis

Adapted from reference 6

[1] City Hospital, Birmingham, UK
[2] University of Texas Health Science Center, San Antonio, Texas, USA

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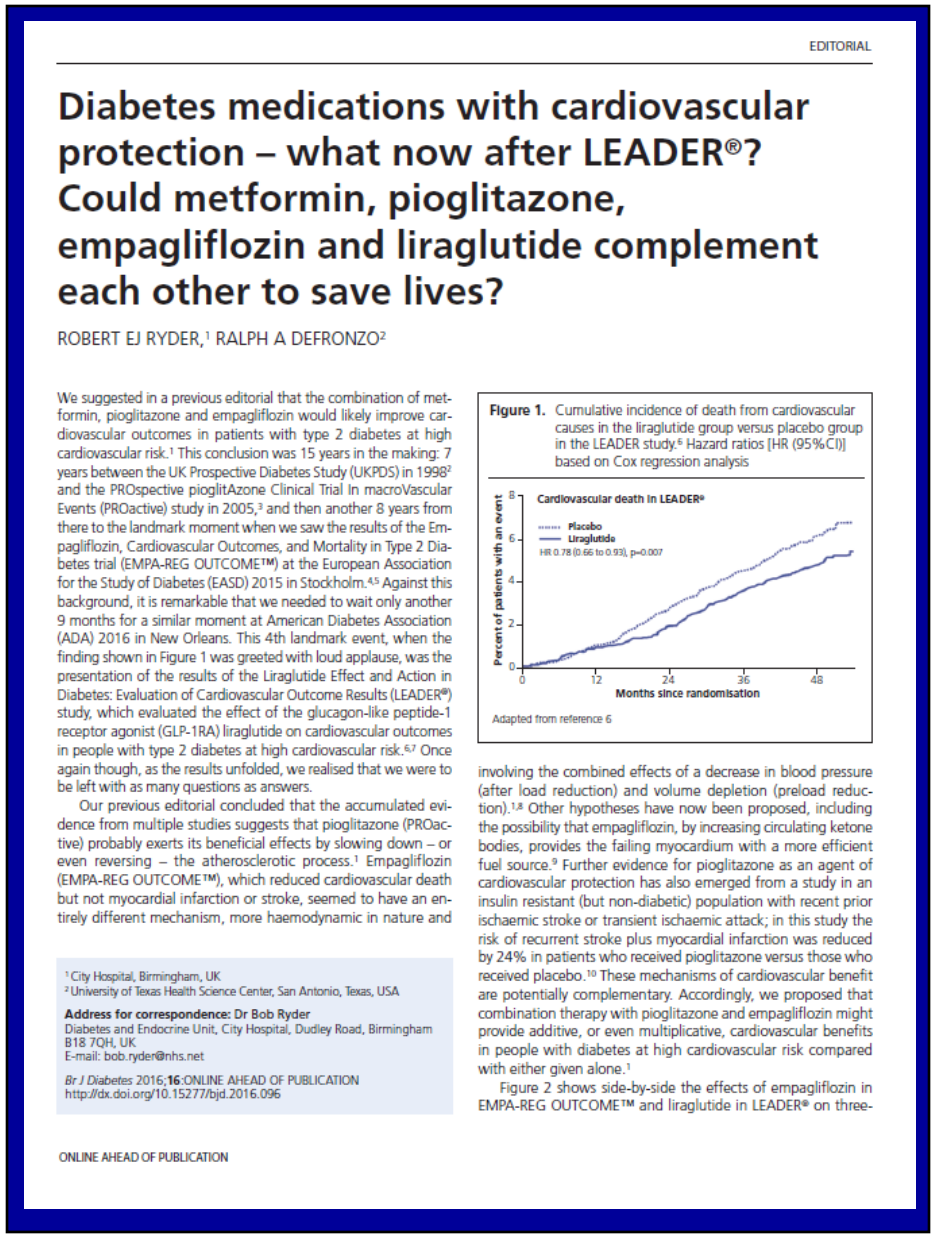
Br J Diabetes 2016;**16**:ONLINE AHEAD OF PUBLICATION
http://dx.doi.org/10.15277/bjd.2016.096

ONLINE AHEAD OF PUBLICATION

The combination of metformin, pioglitazone, empagliflozin and liraglutide now appears to be the optimum cocktail of medications for improving both glycaemic control and cardiovascular outcomes for people with type 2 diabetes at high cardiovascular risk. The evidence we have today suggests that these agents in combination could complement each other to prevent cardiovascular events and save lives

Br J Diabetes 2016;**16**:103-106

Conclusion



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What about since 2016?

What about since 2016?

- My name is Dr Bob Ryder and I am a “being at the cardiovascular outcome trial presentation-oholic”

Has there ever been separation of the lines?

Metformin	UKPDS	EASD	September	1998	Barcelona
Pioglitazone	PROactive	EASD	September	2005	Athens
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Exenatide QW	EXCEL	EASD	September	2017	Lisbon
Albiglutide	HARMONY Outcomes	EASD	September	2018	Berlin
Dapagliflozin	DECLARE-TIMI 58	AHA	November	2018	Chicago
Dulaglutide	Rewind	ADA	June	2019	San Francisco
Oral semaglutide	Pioneer 6	ADA	July	2019	San Francisco
Dapagliflozin	DAPA-HF	EASD	September	2019	Barcelona
Ertugliflozin	VERTIS-CV	ADA	June	2020	Virtual
Empagliflozin	EMPEROR-reduced	EASD	September	2020	Virtual
Sotagliflozin	SCORED and SOLOIST	AHA	November	2020	Virtual
Efpeglenatide	Amplitude-O	ADA	June	2021	Virtual
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Dapagliflozin	DELIVER	EASD	September	2022	Stockholm

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I know cos I was there!

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SGLTi

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GLP1-RA

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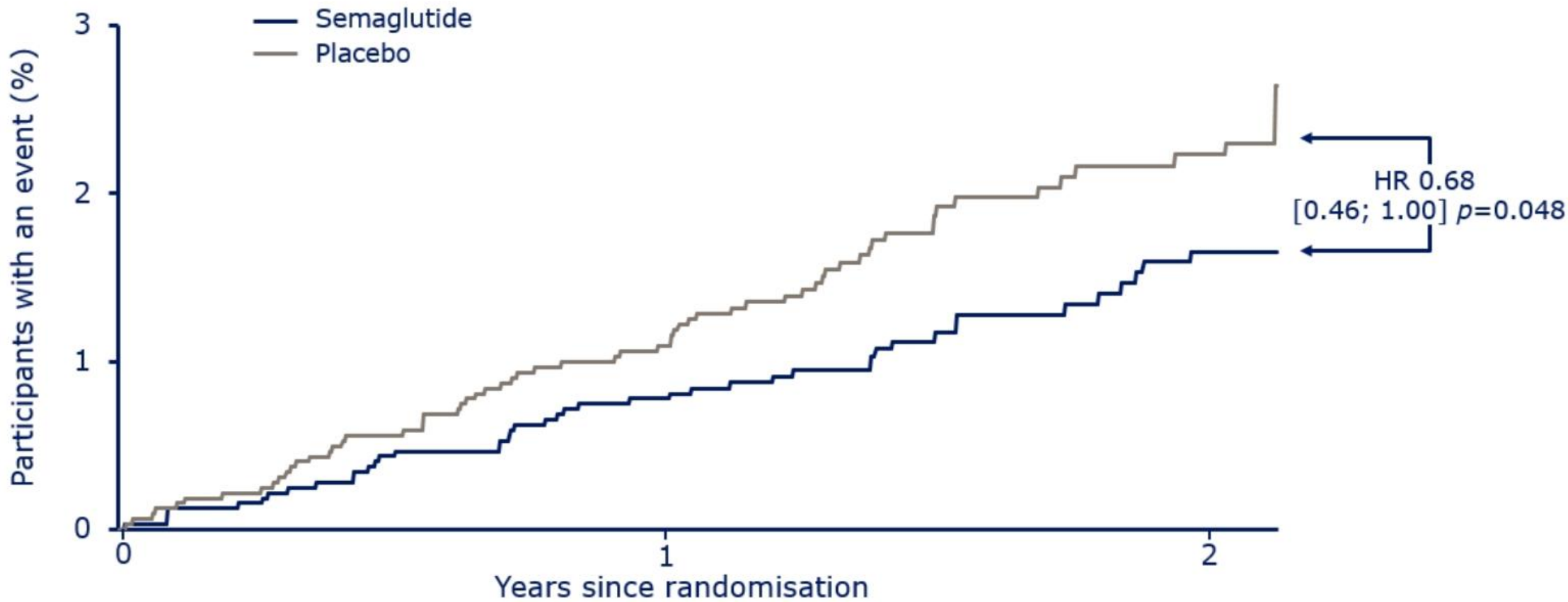
I know cos I was there!

Semaglutide reduces incidence of stroke

Cumulative incidence of stroke over time



GLP-1, glucagon-like peptide 1; HR, hazard ratio

Presented at the 56th Annual Meeting of the European Association for the Study of Diabetes (EASD), 21–25 September 2020

Effects of liraglutide and semaglutide on stroke subtypes in patients with type 2 diabetes: a *post hoc* analysis of the LEADER, SUSTAIN 6 and PIONEER 6 trials

UNIVERSITY OF EXETER | MEDICAL SCHOOL

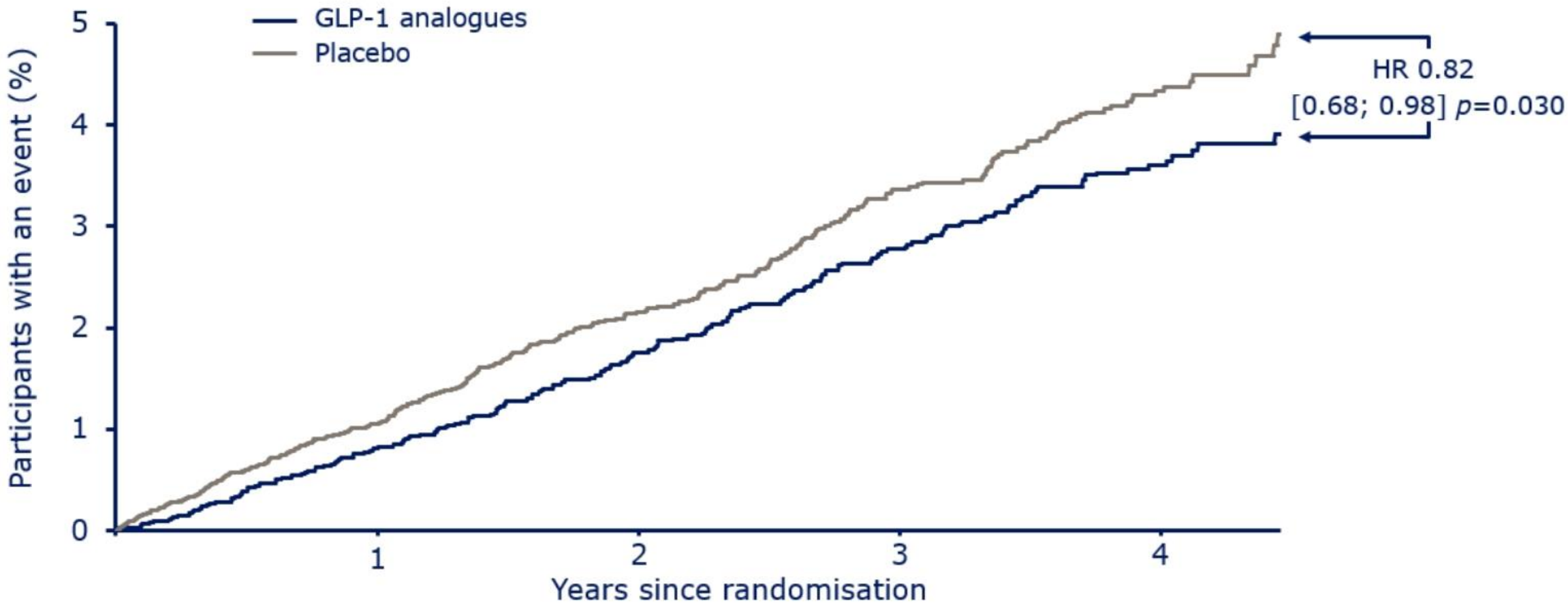
W. David Strain, Søren Rasmussen, Hans A. Saevereid, Martin A. James

NCT01179048; NCT01720446; NCT02692716

Presented at the 56th Annual Meeting of the European Association for the Study of Diabetes (EASD), 21–25 September 2020

GLP-1 analogues reduce incidence of stroke

Cumulative incidence of stroke over time



GLP-1, glucagon-like peptide 1; HR, hazard ratio

Presented at the 56th Annual Meeting of the European Association for the Study of Diabetes (EASD), 21–25 September 2020

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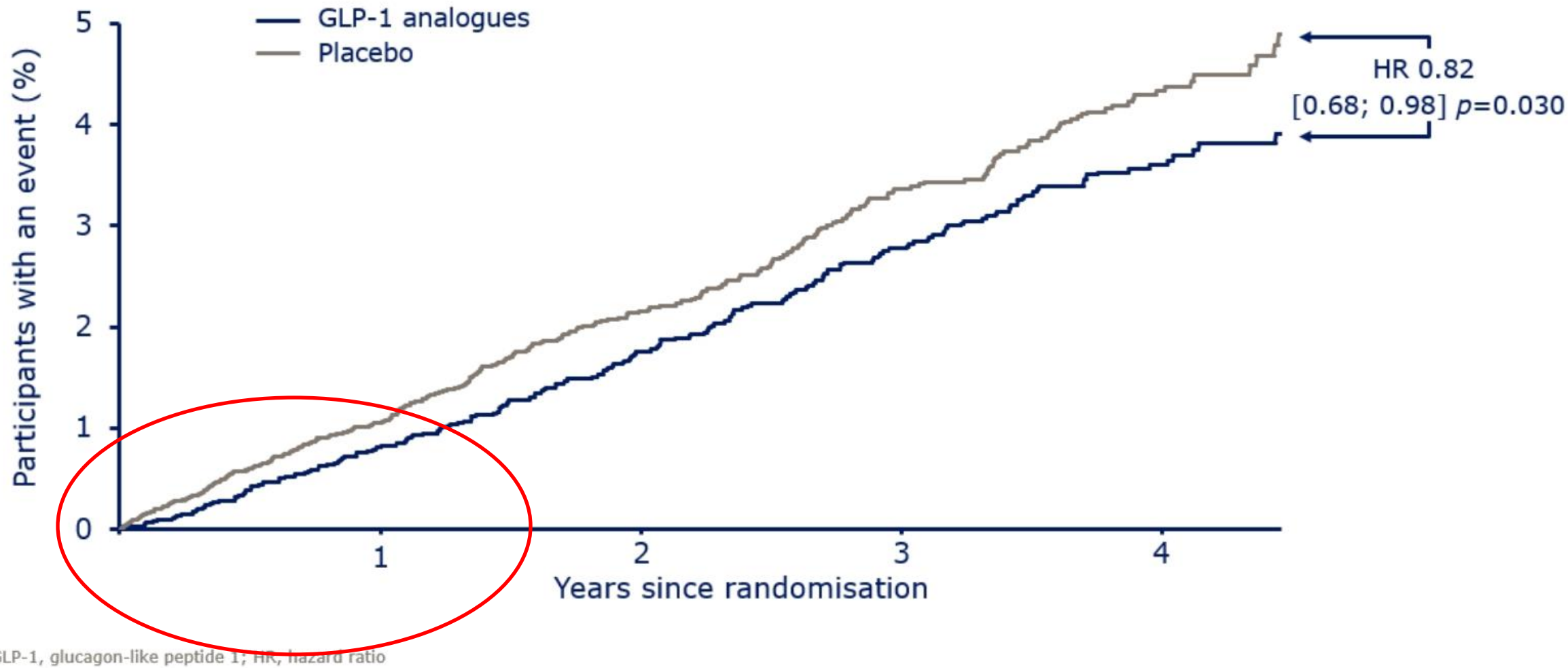

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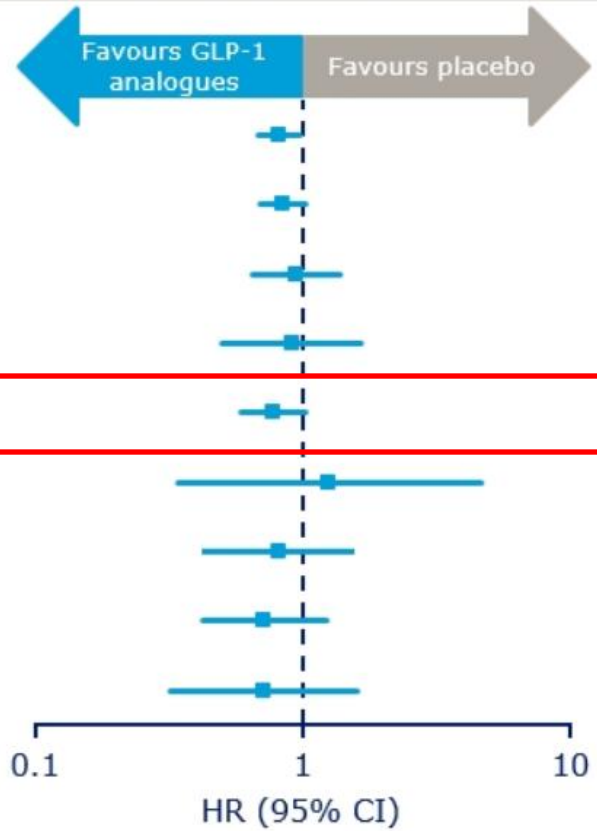
Effect of GLP-1 analogues on stroke and stroke subtypes

Time-to-first event analysis

	n (%)		HR (95% CI)	*p*-value
	GLP-1 analogues‡ (N=7,907)	Placebo (N=7,913)		
All strokes	216 (2.7)	262 (3.3)	0.82 (0.68–0.98)	0.030
Ischaemic stroke*	186 (2.4)	220 (2.8)	0.84 (0.69–1.02)	0.08
Large artery atherosclerosis	53 (0.7)	56 (0.7)	0.94 (0.65–1.37)	0.75
Cardioembolism	21 (0.3)	23 (0.3)	0.91 (0.50–1.64)	0.75
Small vessel occlusion	93 (1.2)	119 (1.5)	0.78 (0.59–1.02)	0.07
Other determined cause	5 (0.1)	4 (0.1)	1.25 (0.34–4.65)	0.74
Undetermined cause†	17 (0.2)	21 (0.3)	0.81 (0.43–1.53)	0.51
Haemorrhagic stroke	23 (0.3)	32 (0.4)	0.72 (0.42–1.22)	0.22
Undetermined stroke	10 (0.1)	14 (0.2)	0.71 (0.32–1.60)	0.41



*Ischaemic strokes were subcategorised according to TOAST criteria by an external, blinded reviewer. †Included patients with ≥2 causes of stroke, undetermined cause despite extensive evaluation and cause of stroke not known due to incomplete evaluation. ‡Included liraglutide, and OW s.c. and daily oral semaglutide. CI, confidence interval; GLP-1, glucagon-like peptide-1; HR, hazard ratio; OW, once weekly; s.c., subcutaneous; TOAST, Trial of Org10172 in Acute Stroke Treatment

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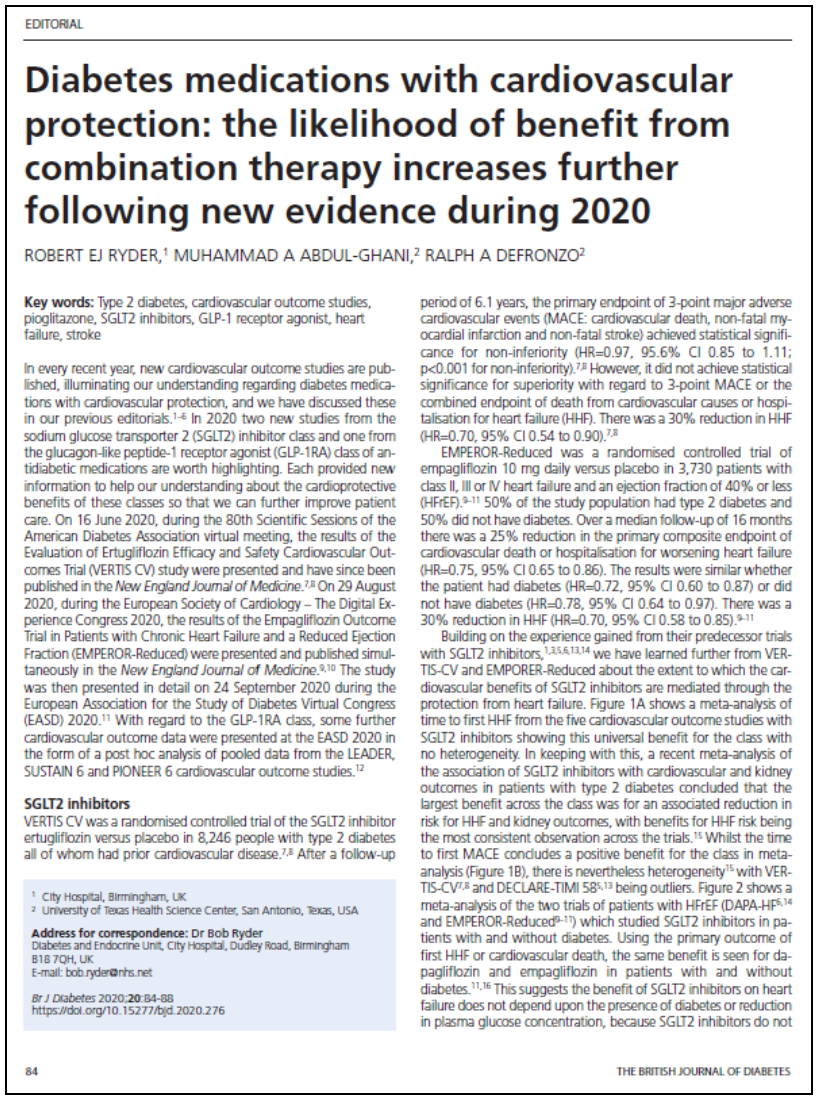
Conclusion



EDITORIAL

Diabetes medications with cardiovascular protection: the likelihood of benefit from combination therapy increases further following new evidence during 2020

ROBERT EJ RYDER,[1] MUHAMMAD A ABDUL-GHANI,[2] RALPH A DEFRONZO[2]

Key words: Type 2 diabetes, cardiovascular outcome studies, pioglitazone, SGLT2 inhibitors, GLP-1 receptor agonist, heart failure, stroke

In every recent year, new cardiovascular outcome studies are published, illuminating our understanding regarding diabetes medications with cardiovascular protection, and we have discussed these in our previous editorials.[1–6] In 2020 two new studies from the sodium glucose transporter 2 (SGLT2) inhibitor class and one from the glucagon-like peptide-1 receptor agonist (GLP-1RA) class of antidiabetic medications are worth highlighting. Each provided new information to help our understanding about the cardioprotective benefits of these classes so that we can further improve patient care. On 16 June 2020, during the 80th Scientific Sessions of the American Diabetes Association virtual meeting, the results of the Evaluation of Ertugliflozin Efficacy and Safety Cardiovascular Outcomes Trial (VERTIS CV) study were presented and have since been published in the *New England Journal of Medicine*.[7,8] On 29 August 2020, during the European Society of Cardiology – The Digital Experience Congress 2020, the results of the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPEROR-Reduced) were presented and published simultaneously in the *New England Journal of Medicine*.[9,10] The study was then presented in detail on 24 September 2020 during the European Association for the Study of Diabetes Virtual Congress (EASD) 2020.[11] With regard to the GLP-1RA class, some further cardiovascular outcome data were presented at the EASD 2020 in the form of a post hoc analysis of pooled data from the LEADER, SUSTAIN 6 and PIONEER 6 cardiovascular outcome studies.[12]

SGLT2 inhibitors

VERTIS CV was a randomised controlled trial of the SGLT2 inhibitor ertugliflozin versus placebo in 8,246 people with type 2 diabetes all of whom had prior cardiovascular disease.[7,8] After a follow-up period of 6.1 years, the primary endpoint of 3-point major adverse cardiovascular events (MACE: cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) achieved statistical significance for non-inferiority (HR=0.97, 95.6% CI 0.85 to 1.11; p<0.001 for non-inferiority).[7,8] However, it did not achieve statistical significance for superiority with regard to 3-point MACE or the combined endpoint of death from cardiovascular causes or hospitalisation for heart failure (HHF). There was a 30% reduction in HHF (HR=0.70, 95% CI 0.54 to 0.90).[7,8]

EMPEROR-Reduced was a randomised controlled trial of empagliflozin 10 mg daily versus placebo in 3,730 patients with class II, III or IV heart failure and an ejection fraction of 40% or less (HFrEF).[9–11] 50% of the study population had type 2 diabetes and 50% did not have diabetes. Over a median follow-up of 16 months there was a 25% reduction in the primary composite endpoint of cardiovascular death or hospitalisation for worsening heart failure (HR=0.75, 95% CI 0.65 to 0.86). The results were similar whether the patient had diabetes (HR=0.72, 95% CI 0.60 to 0.87) or did not have diabetes (HR=0.78, 95% CI 0.64 to 0.97). There was a 30% reduction in HHF (HR=0.70, 95% CI 0.58 to 0.85).[9–11]

Building on the experience gained from their predecessor trials with SGLT2 inhibitors,[1,3,5,6,13,14] we have learned further from VERTIS-CV and EMPORER-Reduced about the extent to which the cardiovascular benefits of SGLT2 inhibitors are mediated through the protection from heart failure. Figure 1A shows a meta-analysis of time to first HHF from the five cardiovascular outcome studies with SGLT2 inhibitors showing this universal benefit for the class with no heterogeneity. In keeping with this, a recent meta-analysis of the association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes concluded that the largest benefit across the class was for an associated reduction in risk for HHF and kidney outcomes, with benefits for HHF risk being the most consistent observation across the trials.[15] Whilst the time to first MACE concludes a positive benefit for the class in meta-analysis (Figure 1B), there is nevertheless heterogeneity[15] with VERTIS-CV[7,8] and DECLARE-TIMI 58[5,13] being outliers. Figure 2 shows a meta-analysis of the two trials of patients with HFrEF (DAPA-HF[5,14] and EMPEROR-Reduced[9–11]) which studied SGLT2 inhibitors in patients with and without diabetes. Using the primary outcome of first HHF or cardiovascular death, the same benefit is seen for dapagliflozin and empagliflozin in patients with and without diabetes.[11,16] This suggests the benefit of SGLT2 inhibitors on heart failure does not depend upon the presence of diabetes or reduction in plasma glucose concentration, because SGLT2 inhibitors do not

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The combination of metformin, pioglitazone, an SGLT2 inhibitor and a long acting GLP-1 receptor agonist now appears to be the optimum cocktail of medications for improving both glycaemic control and cardiovascular outcomes for people with type 2 diabetes at high cardiovascular risk. The evidence we have today suggests that these agents in combination could complement each other to prevent cardiovascular events and save lives

Ryder, Abdul-Ghani, DeFronzo. *Br J Diabetes* 2020;**20**:84-88

In conclusion 1

- Pioglitazone improves cardiovascular outcomes by slowing down or even reversing the atherosclerotic process
- SGLT2 inhibitors as a class exert cardiovascular benefit by improving heart failure in people with and without diabetes
- Pioglitazone and SGLT2 inhibitors may compliment each other to improve cardiovascular outcomes by different means and reduce side effects

In conclusion 2

- There also seems to be a class effect for long-acting GLP-1RAs with regard to improving cardiovascular outcomes, and it seems likely that this class of agents confers benefits by mechanisms that are different from both pioglitazone and SGLT2 inhibitors
- Pioglitazone, SGLT2 inhibitors and GLP1-receptor agonists may compliment each other to improve cardiovascular outcomes by different means and reduce side effects

In conclusion 3

- Pioglitazone and some GLP-1 receptor agonists reduce stroke by different means –
  - GLP-1 receptor agonists through a rapid effect that may be mediated by an effect of small vessel occlusion
  - Pioglitazone by a slower effect mediated by reduction in atherosclerosis
- Randomised controlled trials should be undertaken comparing GLP-1 receptor agonists (eg semaglutide) and pioglitazone on their own and in combination to reduce stroke risk as they may compliment each other

How can we reduce this risk

- Control Blood Pressure
- Use a statin in highest tolerated dose
- Use metformin in all patients if tolerated
- Use pioglitazone to slow or reverse the atherosclerosis
- Use an SGLT2i to reduce cardiovascular death and HHF

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- Use metformin in all patients if tolerated
- Use pioglitazone to slow or reverse the atherosclerosis
- Use an SGLT2i to reduce cardiovascular death and HHF
- Use a GLP1-RA to reduce cardiovascular death and stroke