

Effects of Pioglitazone in patients with or without a history of stroke — an analysis of PROactive

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on behalf of the PROactive Executive Committee
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Background

- ▶ Type 2 diabetes is associated with an increased risk of morbidity and mortality from cerebrovascular disease *versus* the general population
- ▶ The most effective stroke prevention strategies include strict blood pressure control, anti-platelet therapy and lipid-altering therapy
- ▶ However, there are no conclusive data on the benefits of glucose-lowering therapy in patients with diabetes and stroke
- ▶ Pioglitazone, a thiazolidinedione (PPAR γ agonist), is an oral agent for type 2 diabetes that has effects over and above improvements in glucose control
- ▶ PROactive was designed to look at the impact of pioglitazone on risk for mortality and macrovascular morbidity in patients with type 2 diabetes considered to be at high risk for macrovascular events.
- ▶ This prespecified PROactive subgroup analysis evaluated the risk of stroke and other cardiovascular outcomes in patients who had entered PROactive with or without a history of stroke

PROactive Study Design

- ▶ Prospective, randomised, double-blind, placebo-controlled, study conducted in 19 European countries
- ▶ 5238 patients with type 2 diabetes and macrovascular disease were randomised to the addition of either pioglitazone (max 45mg/day) or placebo for a median of 2.85 y
- ▶ Existing therapy with diet, glucose-lowering agents, anti-hypertensives, lipid-altering agents and anti-thrombotic agents were continued
- ▶ Investigators were encouraged to treat diabetes, dyslipidaemia and hypertension according to the 1999 International Diabetes Federation (Europe) guidelines

Primary Endpoint in PROactive (Total Cohort)

- ▶ Time from randomisation to first occurrence of any of the following clinical and procedural composite events :
 - ▶ All-cause death
 - ▶ Non-fatal MI
 - ▶ Stroke
 - ▶ Acute coronary syndrome (ACS)

 - ▶ Major leg amputation (above the ankle)
 - ▶ Leg revascularisation
 - ▶ Cardiac intervention including coronary artery bypass graft or percutaneous coronary intervention

- ▶ Result - a 10% relative risk reduction ($p=0.095$) in the pioglitazone group compared with the placebo group

Main Secondary Endpoint in PROactive (Total Cohort)

- ▶ Time from randomisation to first occurrence of any of the events in the following MACE clinical composite:
 - ▶ All-cause death
 - ▶ Non-fatal MI (*excluding silent MI*)
 - ▶ Stroke
- ▶ Result – a 16% relative risk reduction ($p=0.027$) in the pioglitazone group compared with the placebo group

Subgroup Analysis of Patients with Previous Stroke

- ▶ Of the total PROactive cohort , 984 patients had a previous stroke ≥ 6 months prior to randomisation (18.8%):
 - ▶ n=486 in the pioglitazone group
 - ▶ n=498 in the placebo group
- ▶ Analyses for pioglitazone *versus* placebo in the previous and no previous stroke cohorts:
 1. Time to the primary endpoint
 2. Time to the main secondary endpoint
 3. Time to fatal or non-fatal stroke
 4. Time to cardiovascular death, non-fatal stroke, or non-fatal MI
 5. Time to all-cause mortality

Baseline Data in Patients with Previous Stroke *versus* No Previous Stroke

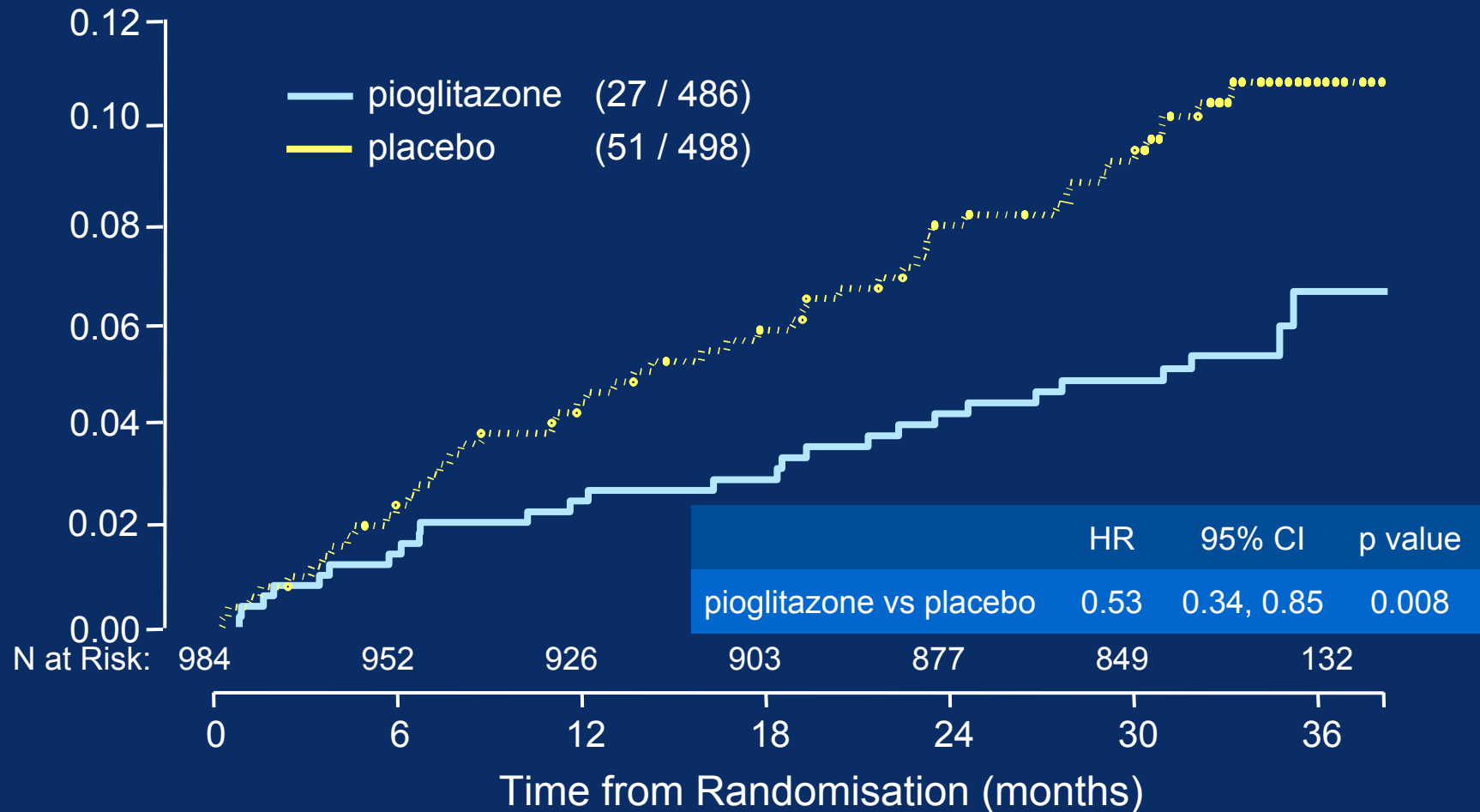
	Previous Stroke N = 984	No Previous Stroke N = 4254
Male, n (%)	596 (61)	2867 (67)
Caucasian, n (%)	973 (99)	4191 (99)
Mean age, years	62.3	61.6
Median time since diagnosis of diabetes, years	9	8
Mean BMI, kg/m ²	30.8	30.9
Mean Systolic/Diastolic BP, mmHg	145/84	143/83
History of hypertension, n (%)	819 (83)	3133 (74)
Microvascular disease, n (%)	496 (50)	1693 (40)

Entry Criteria: Evidence of Macrovascular Disease

	Previous Stroke N = 984	No Previous Stroke N = 4254
Previous MI (≥ 6 months prior), n (%)	177 (18)	2268 (53)
Previous PCI/CABG (≥ 6 months prior), n (%)	102 (10)	1509 (36)
Previous ACS (≥ 3 months prior), n (%)	50 (5)	655 (16)
Symptomatic PVD, n (%)	97 (10)	946 (22)

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

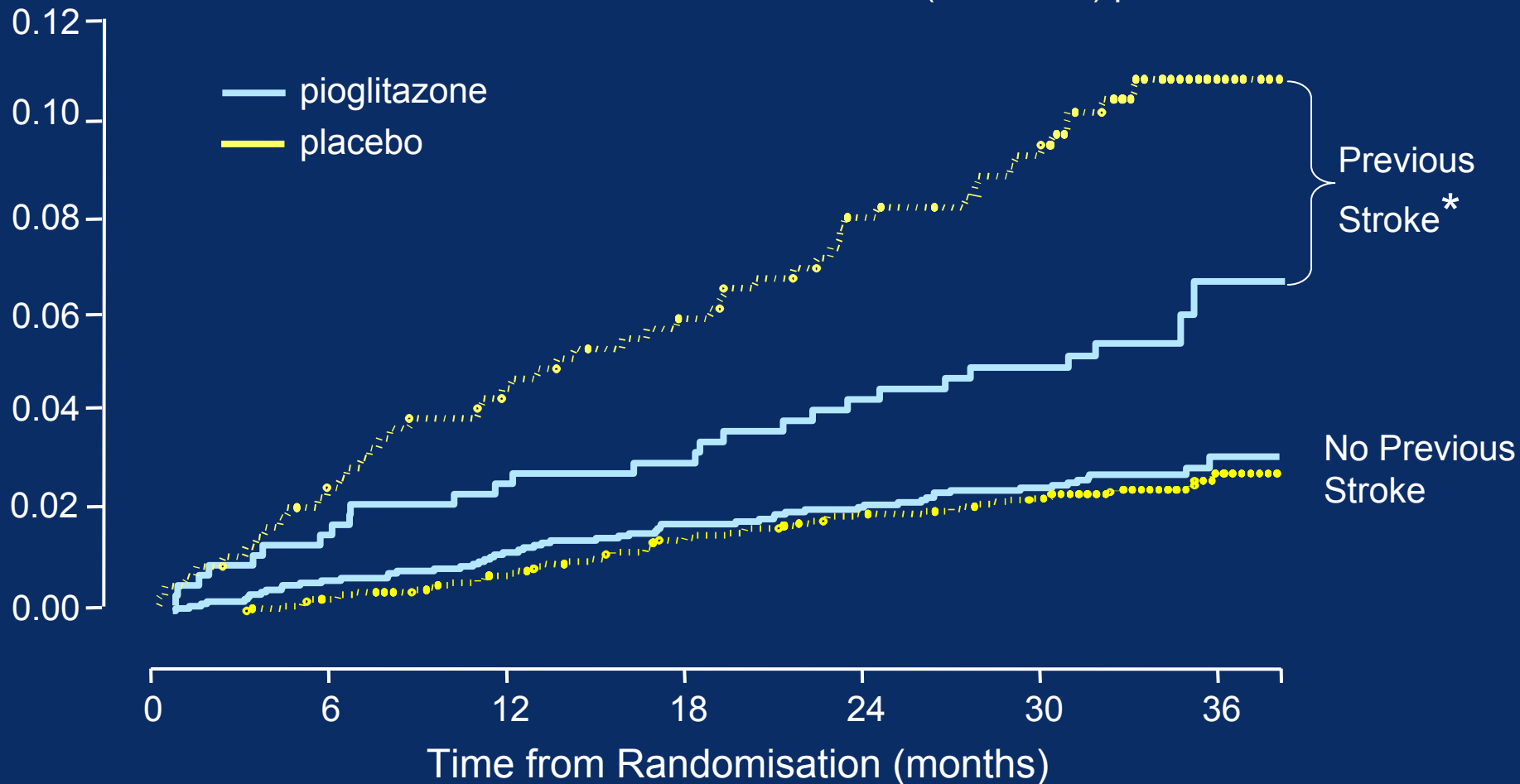
Kaplan-Meier event rate



Time to Fatal or Non-Fatal Stroke in Patients with Previous Stroke *versus* no Previous Stroke

Kaplan-Meier event rate

*HR 0.53 (0.34-0.85) p0.008



Mean Change in Laboratory Data from Baseline to Final Visit in the Previous Stroke Subgroup

	Level at baseline		Change from baseline		
	Pioglitazone	Placebo	Pioglitazone	Placebo	p
	Absolute change				
Mean HbA _{1c} , %	8.0	8.1	-0.9	-0.3	<0.0001
Mean SBP, mm Hg	145.4	144.9	-4.4	-2.7	0.2308
Mean DBP, mm Hg	84.3	83.8	-4.0	-2.6	0.0717
	% change				
Median triglycerides, mmol/L	1.8	1.8	-11.1	8.1	<0.0001
Median HDL-C, mmol/L	1.1	1.2	21.3	10.2	<0.0001
Median LDL-C, mmol/L	3.1	3.1	6.7	5.9	0.2719
Median LDL-C:HDL-C	2.6	2.6	-10.4	-4.3	0.0028

Mean Change in Laboratory Data from Baseline to Final Visit in the No Previous Stroke Subgroup

	Level at baseline		Change from baseline		
	Pioglitazone	Placebo	Pioglitazone	Placebo	p
	Absolute change				
Mean HbA _{1c} , %	8.1	8.1	-0.9	-0.4	<0.0001
Mean SBP, mm Hg	143.1	142.9	-3.9	-2.6	0.0497
Mean DBP, mm Hg	82.5	83.1	-3.2	-3.0	0.5715
	% change				
Median triglycerides, mmol/L	1.8	1.9	-12.0	0.2	<0.0001
Median HDL-C, mmol/L	1.1	1.1	18.5	10.0	<0.0001
Median LDL-C, mmol/L	2.9	2.8	7.2	4.6	0.0068
Median LDL-C:HDL-C	2.6	2.5	-9.2	-4.1	<0.0001

Multivariate Analysis

- ▶ A multivariate analysis of 25 prespecified baseline characteristics plus 12 additional factors showed that:
 - ▶ Prior stroke was itself the strongest predictor of recurrent stroke in the entire cohort of patients (HR=2.88; $p < 0.0001$)
 - ▶ Use of pioglitazone ($p=0.0076$) and statins ($p=0.0126$) were the only factors with a significant effect on the risk of recurrent stroke in patients with previous stroke
 - ▶ Age ($p=0.0002$), $\text{HbA}_{1c} \geq 7.5\%$ ($p=0.0038$), creatinine ≥ 130 $\mu\text{mol/L}$ ($p=0.0468$) and peripheral arterial disease ($p=0.0092$) were significant positive predictors of having a first stroke in patients without previous stroke

Serious Adverse Events

	Previous Stroke		No Previous Stroke	
	Pioglitazone N=486	Placebo N=498	Pioglitazone N=2119	Placebo N=2135
Any SAE	237 (49%)	256 (51%)	967 (46%)	1019 (48%)
Hospitalisation due to HF	31 (6.4%)	20 (4.0%)	118 (5.6%)	88 (4.1%)
Fatal HF	6 (1.2%)	4 (0.8%)	19 (0.9%)	18 (0.8%)

Effect of Treatment on Cardiovascular Events in the Previous Stroke Subgroup

	Pioglitazone N = 486	Placebo N = 498	HR	p
Primary endpoint	98 (20.2%)	126 (25.3%)	0.78	0.067
Main secondary endpoint	76 (15.6%)	98 (19.7%)	0.78	0.110
Fatal or non-fatal stroke	27 (5.6%)	51 (10.2%)	0.53	0.009
CV death, non-fatal stroke, or non-fatal MI	63 (13.0%)	88 (17.7%)	0.72	0.047
All-cause mortality	46 (9.5%)	49 (9.8%)	0.96	0.843

Yellow text = previous stroke group
White text = total PROactive population

Effect of Treatment on Cardiovascular Events in the No Previous Stroke Subgroup

	Pioglitazone N = 2119	Placebo N = 2135	HR	p
Primary endpoint	416 (19.6%)	446 (20.9%)	0.94	0.350
Main secondary endpoint	225 (10.6%)	260 (12.2%)	0.86	0.109
Fatal or non-fatal stroke	59 (2.8%)	56 (2.6%)	1.06	0.767
CV death, non-fatal stroke, or non-fatal MI	194 (9.2%)	225 (10.5%)	0.86	0.1289
All-cause mortality	131 (6.2%)	137 (6.4%)	0.96	0.725

Yellow text = no previous stroke group
White text = total PROactive population

Summary

- ▶ In patients with type 2 diabetes and a previous stroke:
 - ▶ The risk of recurrent fatal/non-fatal stroke was reduced by 47% in those taking Pioglitazone
 - ▶ The risk of cardiovascular death, non-fatal stroke or non-fatal MI was reduced by 28% in those taking Pioglitazone.
 - ▶ There was a trend of benefit with pioglitazone for the primary and main secondary endpoints
- ▶ Pioglitazone had no effect on reducing the risk of first strokes over this time course
- ▶ Pioglitazone significantly improved glycaemic control, HDL-C, triglycerides and LDL-C:HDL-C and gave marginally greater decreases in mean blood pressure
- ▶ There were no differences between treatment groups in the proportion of patients with SAEs
- ▶ Reports of serious heart failure were increased with pioglitazone vs placebo; however, there was no difference in the absolute number of deaths in these patients

Conclusions

- ▶ In a prespecified subgroup analysis from the PROactive trial, pioglitazone added on to other existing cardiovascular medication was associated with a reduction in the risk of recurrent stroke in high-risk patients with type 2 diabetes.
- ▶ Whether longer term therapy with pioglitazone would similarly benefit those diabetic patients without prior stroke , or indeed non-diabetic patients with prior stroke, awaits further enquiry.

Acknowledgements

Executive Committee:

J. Dormandy (Chairman), B. Charbonnel, D. Eckland,
E. Erdmann, M. Massi-Benedetti, I. Moules, A. Skene, M. Tan

Data & Safety Monitoring Committee

Endpoint Adjudication Committee

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National Principal Investigators

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Effect of Treatment on Cardiovascular Events in the Previous Stroke Subgroup and All Patients

	Pioglitazone N = 486		Placebo N = 498		HR	p
Primary endpoint	98 (20.2%)	126 (25.3%)	0.78	0.067		
	514 (21.0%)	572 (23.5%)	0.90	0.095		
Main secondary endpoint	76 (15.6%)	98 (19.7%)	0.78	0.110		
	301 (12.3%)	358 (14.4%)	0.84	0.027		
Fatal or non-fatal stroke	27 (5.6%)	51 (10.2%)	0.53	0.009		
	86 (3.3%)	107 (4.1%)	0.81	0.140		
CV death, non-fatal stroke, or non-fatal MI	63 (13.0%)	88 (17.7%)	0.72	0.047		
	250 (9.6%)	305 (11.6%)	0.82	0.020		
All-cause mortality	46 (9.5%)	49 (9.8%)	0.96	0.843		
	177 (6.8%)	186 (7.1%)	0.96	0.678		

Yellow text = previous stroke group
White text = total PROactive population

Effect of Treatment on Cardiovascular Events in the No Previous Stroke Subgroup and All Patients

	Pioglitazone		Placebo		HR	p
	N = 2119		N = 2135			
Primary endpoint	416 (19.6%)	446 (20.9%)	0.94	0.350		
	514 (21.0%)	572 (23.5%)	0.90	0.095		
Main secondary endpoint	225 (10.6%)	260 (12.2%)	0.86	0.109		
	301 (12.3%)	358 (14.4%)	0.84	0.027		
Fatal or non-fatal stroke	59 (2.8%)	56 (2.6%)	1.06	0.767		
	86 (3.3%)	107 (4.1%)	0.81	0.140		
CV death, non-fatal stroke, or non-fatal MI	194 (9.2%)	225 (10.5%)	0.86	0.1289		
	250 (9.6%)	305 (11.6%)	0.82	0.020		
All-cause mortality	131 (6.2%)	137 (6.4%)	0.96	0.725		
	177 (6.8%)	186 (7.1%)	0.96	0.678		

Yellow text = no previous stroke group

White text = total PROactive population