10-Year Observational Follow-Up of PROactive: a randomized cardiovascular outcomes trial evaluating pioglitazone in type 2 diabetes

Erland Erdmann[1], Sarah Harding[2], Hung Lam[3], Alfonso Perez[3]

[1]Medical Clinic III, University of Cologne, Germany

[2]Takeda Development Centre, Europe, London, UK

[3]Takeda Development Center Americas, Inc., Deerfield, Illinois, USA

Corresponding author:

Prof. Dr. med. Erland Erdmann, FESC, FACC, FAHA

em. Direktor der Klinik III für Innere Medizin

Herzzentrum der Universität zu Köln

Franz-Seiwert-Str. 8

D-50933 Köln

Germany

e-mail: erland.erdmann@uni-koeln.de

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/dom.12608

Abstract

Aims: PROactive evaluated pioglitazone for secondary prevention of macrovascular events in patients with type 2 diabetes and pre-existing macrovascular disease. A 10-year, observational follow-up of patients completing PROactive investigated whether trends of cardiovascular benefit with pioglitazone and imbalances in specific malignancies persisted over time.

Methods: Macrovascular endpoints and malignancies were compared based on original randomization to pioglitazone or placebo and "Any" *versus* "No pioglitazone use" for bladder and prostate cancer.

Results: Of 4873 patients completing PROactive, 74% entered the follow-up. During follow-up (mean 7.8 years), there were no statistically significant differences in the primary (all-cause mortality, myocardial infarction [MI], cardiac intervention, stroke, major leg amputation, leg revascularization) or main secondary (death, MI, stroke) endpoints for subjects originally randomized to pioglitazone and placebo, except for leg amputations during follow-up (4.1% pioglitazone, 5.6% placebo; HR=0.74 [95%CI0.55–0.99]; p=0.046). During follow-up, the incidence of total malignancies was similar between groups; bladder cancer was reported in 0.8% of patients (n=14) in the pioglitazone *versus* 1.2% (n=21) in the placebo group (RR=0.65 [95%CI0.33–1.28]), and prostate cancer was reported in 44 (3.7%) men in the pioglitazone *versus* 29(2.5%) men in the placebo group (RR=1.47 [95%CI0.93–2.34]).

Conclusions: The trends of macrovascular benefits of pioglitazone compared with placebo during PROactive did not persist in the absence of continued pioglitazone during this 10-year follow-up. Trends of decreased bladder cancer and increased prostate cancer were observed in the pioglitazone group during follow-up; however, these imbalances should be interpreted with caution due to limitations of the observational study design.

Introduction

The PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) was a prospective, event-driven, multicenter, randomized, double-blind, placebo-controlled study to evaluate the effects of pioglitazone on cardiovascular disease outcomes in high-risk patients with pre-existing macrovascular disease and type 2 diabetes mellitus (T2DM) over a mean 3-year period (pioglitazone=2605, placebo=2633).[1,2] Pioglitazone resulted in a non-significant 10% relative risk reduction in the primary composite endpoint (all-cause mortality, myocardial infarction [MI], acute coronary syndrome [ACS], cardiac intervention, stroke, major leg amputation, and leg revascularization (hazard ratio [HR]=0.90 [95% confidence intervals (CI) 0.80–1.02]; p=0.095).[2] There was a statistically significant reduction with pioglitazone relative to placebo in the main secondary endpoint of all-cause mortality, MI, and stroke (HR=0.84 [95%CI 0.72–0.98]; p=0.027)[2] as well as several planned and ***post-hoc*** analyses (e.g., recurrent MI (HR=0.72 [95%CI 0.52–0.99]; p=0.045) and recurrent stroke (HR=0.53 [95%CI 0.34–0.85]; p=0.009).[3,4]

During PROactive, pioglitazone was not associated with an increased overall incidence of cancer ***versus*** placebo (3.7% ***vs*** 3.8%). There were 14 cases of

bladder cancer in the pioglitazone group and five in the placebo group.[2,5,6] However, the majority of cases were reported in the first year, suggesting biological implausibility for pioglitazone given the prolonged latency period generally associated with bladder cancer.[5,6]

This 10-year observational follow-up investigated whether prior long-term treatment with pioglitazone had an effect on the composite outcome of all-cause mortality and macrovascular events and compared the incidence of newly diagnosed malignancies according to originally assigned pioglitazone or placebo in PROactive.

Materials and methods

Detailed methodology, study design, and statistical analyses of PROactive are given in previous publications.[1,2]

Patients

Patients who had previously completed the final visit of PROactive were eligible for enrolment into this 10-year European, multicenter, observational study. Written consent was obtained. There were no exclusion criteria and patients were free to discontinue their participation in the study at any time.

Management Strategy

During this follow-up, patients received medical care according to their physician's discretion, with no specified drug allocation.

Assessments

The follow-up was designed to assess total mortality, macrovascular morbidity, and malignancies.

Patients were assessed (vital status, events, malignancies, and current medications) at nominal visits every 6 months as previously reported.[7] Detailed information on daily dose and duration of use was captured at each visit for thiazolidinediones (TZDs; either pioglitazone or rosiglitazone) only. The same macrovascular endpoints evaluated in PROactive were evaluated in the follow-up, with the exception of ACS, which was omitted due to the absence of an endpoint adjudication committee. All macrovascular events and new malignancies were analyzed every 2 years[7] Additional information was collected on bladder cancer cases, including history of chronic bladder irritation, schistosomiasis (bilharziasis), or hematuria, family history of bladder cancer, and histological type of bladder cancer.

Fatal events were classified as cardiovascular unless there was a clear non-cardiovascular cause (e.g. trauma). Cardiovascular deaths were classified as MI, other cardiac, cerebrovascular, or other.

No clinical laboratory tests were carried out as part of the follow-up protocol.

Endpoints

The primary endpoint for the 10-year follow-up was a composite of all-cause mortality, non-fatal MI (including silent MI), stroke, endovascular, or surgical intervention in the coronary or leg arteries, and amputation above the ankle. The main secondary composite endpoint comprised non-adjudicated all-cause mortality, non-fatal MI, and non-fatal stroke.

The incidence of malignancies was reported.

No other safety data or adverse events were recorded.

Statistical Analyses

The study population comprised patients *who* completed the final visit of PROactive and subsequently enrolled in the observational follow-up. The first analysis compared treatment groups (according to original randomization) only during this observational follow-up, i.e. from date of entry to end of follow-up. The second analysis compared treatment groups during the PROactive and observational follow-up periods combined, i.e. from date of randomization into PROactive to end of follow-up. Kaplan-Meier survival curves were generated for each treatment group and HR estimates calculated using Cox regression methods. There were no adjustments for multiplicity.

No formal statistical analysis was planned for malignancies; however, relative risks and corresponding 95%CI were calculated if there was a sufficient frequency of a malignancy.

Results

Study Disposition

Of the 4873 patients completing PROactive, 73.9% (3599) enrolled in the follow-up (n=1820 previously randomized to pioglitazone; n=1779 previously randomized to placebo). As expected, the percentage of patients who continued to return for the scheduled 6-month visits declined substantially over the 10 years of follow-up (**Supplementary Figure 1**). A similar percentage of patients on pioglitazone or placebo groups withdrew consent to follow-up (<1%), were confirmed lost to follow-up (approximately 9%), and had an unconfirmed status (i.e. last contact ≥ 9 years [<5%]).

Approximately 18.5% of patients used TZDs during the follow-up (20.8% in the pioglitazone group and 16.1% in the placebo group).

Mean duration of follow-up was approximately 7.8 years in both groups (based on the date of last contact, including death). Total mean duration of follow-up for PROactive plus the observational follow-up was approximately 10.7 years in both groups.

The mean daily dose in the 468 patients exposed to pioglitazone during the follow-up was 30.8±10.3 mg/day compared with a mean daily dose of 45.5±29.6 mg/day at the time of entry into the follow-up period. The mean daily dose of rosiglitazone in the 270 patients receiving it during the follow-up was 5.0±2.0 mg/day.

Macrovascular outcomes

Primary composite endpoint

The proportion of patients who experienced a primary endpoint event during the follow-up period alone and during the combined PROactive and follow-up periods was comparable between the pioglitazone and placebo groups (**Table 1**).

During the follow-up, the incidence of primary endpoint events was nominally lower in TZD users at any time than in non-TZD users, although the sample size was small (**Supplementary Table 1**).

A forest plot shows the primary composite endpoint during the 10-year follow-up and the PROactive plus follow-up periods combined (**Figure 1**); no differences in the primary endpoint were observed between the pioglitazone and placebo groups for any of the follow-up periods.

Main secondary composite endpoint

There were no statistically significant differences for pioglitazone v*ersus* placebo in patients experiencing an event from the main secondary endpoint during the follow-up and during the combined PROactive and follow-up periods (**Table 1; Supplementary Figure 2**). As with the primary endpoint, the percentage of patients who had an event from the main secondary endpoint at any time during the follow-up was nominally lower in TZD users than in non-TZD users (**Supplementary Table 1**). The incidence of main secondary endpoint events was similar in the PROactive pioglitazone/"No TZD use" and PROactive placebo/"No TZD use" groups (and nominally higher compared with the four groups with any TZD use (pioglitazone/pioglitazone, pioglitazone/rosiglitazone, placebo/pioglitazone, placebo/rosiglitazone) (**Supplementary Table 1**).

Individual components of the primary endpoint

The incidences of individual components within the primary endpoint were also similar and non-statistically significant for pioglitazone v*ersus* placebo, with the exception of major leg amputation, which was significantly lower in the pioglitazone group for the follow-up period (**Table 1**).

There was no statistically significant difference between the two groups in time to cardiovascular death (**Table 1**).

Results were generally similar for those patients in the follow-up population who did not receive pioglitazone during the follow-up (**Supplementary Table 1**). The incidence of stroke was nominally higher in the "No TZD use" groups compared with the four groups with any TZD use (**Supplementary Table 1)**.

The forest plot shows the individual components of the primary composite endpoint during the 10-year follow-up and the PROactive plus follow-up periods combined (**Figure 1**).

Mortality

Cause of death during PROactive was assigned by an adjudication committee; however, cause of death during the follow-up was assigned by the investigators. The percentage of patients who died for any reason during the follow-up was 34.0% (n=618) in the pioglitazone group and 36.4% (n=648) in the placebo group (**Figure 2**). The most frequently reported causes of death were "other cardiac", "other", and "MI".

In the follow-up population, the percentage of patients who died in the "No TZD use" groups (37–39%) was nominally higher than that in the "TZD use" groups (16%–28%) (**Supplementary Table 1**). Mortality results were similar when combining data from PROactive and observational follow-up periods (30.5% [n=795] with pioglitazone and 31.7% [n=834] with placebo).

Malignancies

The number of patients reporting at least one malignancy and individual malignancies during the study are given in **Table 2**. There was no difference in the incidence of total malignancies between pioglitazone and placebo groups during the 10-year follow-up or combined PROactive plus follow-up periods. For individual malignancies, a nominally significant increase in prostate cancer and decrease in brain cancer were observed for pioglitazone compared with placebo in the PROactive plus follow-up period. Non-significant imbalances were observed during the follow-up period for some more commonly reported

individual cancers, including bladder, haematological, and lung. Findings for prostate and bladder cancer are described in more detail below.

Bladder Cancer

Bladder cancer was reported in more pioglitazone (n=14; 0.5%) than placebo patients (n=5; 0.2%) in PROactive.[5] The imbalance in bladder cancer during PROactive was reversed during the 10-year follow-up. Bladder cancer was reported in 14 patients in the pioglitazone group (0.8%) *versus* 21 in the placebo group (1.2%; RR=0.65; 95%CI [0.33–1.28]) (**Table 2**). During both study periods combined, bladder cancer was reported in 27 patients in the pioglitazone group (1.0%) and 26 patients in the placebo group (1.0%; RR=1.05 [95%CI 0.61–1.79]) (**Table 2**).

Prostate Cancer

During PROactive, the incidence of prostate cancer was low in both groups (n=14 [0.8%] men in the pioglitazone group and 7 [0.4%] men in the placebo group); however, during the follow-up, prostate cancer was reported in 44 (3.7%) men in the pioglitazone group *versus* 29 (2.5%) men in the placebo group (RR=1.47 [95%CI 0.93–2.34]) (**Table 2**). During both study periods combined, prostate cancer was reported in 58 patients in the pioglitazone group (3.3%) and 35 patients in the placebo group (2.0%; RR=1.59 [95%CI 1.04–2.41]) (**Table 2**). Approximately 84% of patients who reported prostate cancer during the follow-up, including patients randomized to pioglitazone during PROactive, had no pioglitazone use in the follow-up. The median age of men when randomized into PROactive was 62.0 years in both groups, whereas the median age at onset of

diagnosis of prostate cancer was higher in the pioglitazone (72.0 years) than the placebo group (69.0 years).

Glycemic control

Although samples for analysis of HbA_{1c} were not routinely collected, the results were collected for analysis over the course of the observational study period when performed as part of the subject's routine care. At observational study entry (last HbA_{1c} value assessed during PROactive), mean HbA_{1c} values were significantly lower ($p<0.0001$) in the pioglitazone group (7.10%) compared with the placebo group (7.65%; 1567). Six months after the end of PROactive, the treatment difference in mean HbA_{1c} was no longer statistically significant: the mean HbA_{1c} value in the pioglitazone group (n=823) had increased to 7.65% compared with 7.72% in the placebo group (n=803). Throughout the observational study period, mean HbA_{1c} values remained similar between groups. At Month 120, the mean HbA_{1c} value was 7.59% in the pioglitazone group (n=466) and 7.51% in the placebo (n=431) group.

Discussion

Our analysis of 10-year observational follow-up data based on the original randomization treatment from PROactive found no statistically significant differences between pioglitazone and placebo in the incidence of the primary composite or main secondary endpoint after the 13-year combined period. These results are not unexpected given that patients were not assigned any specific treatment during the 10-year follow-up and confirm previous interim analyses; however, the findings do not suggest an overall legacy effect.[7] There were also no statistically significant differences in individual components of the

primary endpoint, with the exception of major leg amputations, which were significantly lower in the pioglitazone group during the follow-up. When considering TZD use during the follow-up, the incidences of the primary and main secondary composite endpoints were nominally higher in those who did not use a TZD (irrespective if originally randomized to pioglitazone or placebo) than in those who used TZDs during the follow-up (**Supplementary Table 1**).

Importantly, the incidence of cardiovascular mortality and all-cause mortality at the end of follow-up were also comparable between those originally randomized to pioglitazone *versus* placebo. In fact, the incidence of deaths was nominally lower in those who continued on pioglitazone (20.3%) or switched to rosiglitazone (28.3%) compared with the group that did not receive TZDs during the follow-up (36.5%). This high mortality rate is not unexpected, given that the patient population was elderly and at high risk for a serious event, such as MI. There is a paucity of long-term cardiovascular safety data in people with diabetes. The UK Prospective Diabetes Study (UKPDS) is the only other cardiovascular study of glucose-lowering agents with a ≥10-year post-trial follow-up, although it should be noted that the UKPDS evaluated lower-risk patients with newly diagnosed T2DM and different treatment strategies in the context of minimal contemporary cardiovascular risk factor management. The initial randomized part of the UKPDS suggested potential cardiovascular risk reduction with more intensive glucose lowering. The 10-year follow-up of 3277 patients from the UKPDS revealed modest reductions in the risk of MI and all-cause mortality in patients who received more intensive therapy in the original randomized part of the study, a so-called "legacy effect".[8] Similarly, the significant reduction in

major leg amputation reported here may reflect a long-term legacy effect with pioglitazone treatment in PROactive.[2] This observation contrasts with the increased incidence in leg revascularization events in the first year of pioglitazone treatment in PROactive.[2,9] Six-year follow-up data are available for the more recent Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) factorial trial. No differences between the intensive glucose control and the standard glucose control groups were observed during follow-up in the risk of all-cause mortality (HR=1.00) or major macrovascular events (HR=1.00).[10]

As in PROactive,[5] the incidence of total malignancies reported during the follow-up and both study periods combined was similar and non-statistically significant between the treatment groups (all 12–13%). Thus, the overall risk of cancer was not increased in pioglitazone-treated patients. This finding is consistent with epidemiologic data, which suggest that there is no risk signal for overall malignancy among TZD users.[11,12] Although one study did find an association between a diagnosis of any cancer and TZD use, this was attributed to rosiglitazone rather than pioglitazone.[11]

Epidemiologic studies to date suggest that there is no significant association between pioglitazone use (or TZD use in general) and risk for a number of individual cancer types, including breast, lung/bronchus, liver, endometrial, colon, non-Hodgkin lymphoma, kidney/renal pelvis, rectal, and melanoma.[12–16] During PROactive, bladder cancer was diagnosed more frequently in the pioglitazone group than in the placebo group (n=14 *vs* 6, [1 case of bladder cancer in the placebo group was later recategorized as benign]).[5] However, as

there is a prolonged latency period for bladder cancer (typically in the duration of 20 years, and never before 1 year),[17] independent blinded review of the 20 PROactive bladder neoplasms concluded that the 11 cases reported within the first year of exposure could not be caused by short-term exposure (8 in the pioglitazone group and 3 in the placebo group). Details of when the bladder cancer was diagnosed in these 11 patients have been published (diagnosis was within the first 2 weeks for two patients).[18] During the 10-year follow-up, bladder cancer was reported in fewer patients in the pioglitazone group (n=14 [0.8%]) than in the placebo group (n=21 [1.2%]), resulting in a total of 27 patients in the pioglitazone group (1.0%) and 26 patients in the placebo group (1.0%) during both periods combined (p=NS). These reassuring data confirm the previous suggestion that the early bladder malignancy signal can be accounted for by random variability and that there is no residual risk of developing bladder cancer after stopping treatment with pioglitazone.[5,7]

The PROactive long-term, combined results for bladder cancer are consistent with three recently published studies with long follow-ups, robust methodology, and relatively large sample sizes of people with type 2 diabetes. A 10-year epidemiologic study of 193 099 people conducted by the University of Pennsylvania utilizing the Kaiser Permanente Northern California (KPNC) database found no association of pioglitazone "ever use" with bladder cancer risk, nor any association between the risk of bladder cancer and the duration of use, cumulative dose, or time since initiating pioglitazone.[19,20] Furthermore, a large, independent multi-population analysis (using a time-dependent approach to minimize bias) of pooled data from six databases (1.01 million persons for over

5.9 million person-years of follow-up) from European countries and Canada,[21] and a propensity score-matched (1:1) cohort study of 112,674 people from six databases across four European countries observed no increased risk of bladder cancer associated with pioglitazone use[22]. In addition, some short-term, population-based cohorts in the USA,[15] India,[23] Japan,[24] Korea,[25] Taiwan,[26,27] and the UK[28] also reported no association between pioglitazone and bladder cancer. In contrast, other short-term, observational database studies have suggested an association between exposure to pioglitazone and incidence of bladder cancer, including a retrospective cohort study using French National Health Insurance Plan data,[29] and nested case-control studies in Taiwan,[30] the UK,[31] and Korea.[32]

During both PROactive study periods combined, prostate cancer was reported in more men in the pioglitazone group (n=58) than in the placebo group (n=33). Although the study by Lewis et al.[20] found a slight increased risk of prostate cancer with pioglitazone use, the majority of studies assessing the risk of a number of cancer types have found no association between TZD use and the incidence of prostate cancer.[13,14] In the KPNC study, ever use of pioglitazone was associated with a small increase in the risk of prostate cancer [HR=1.13; 95%CI [1.02–1.26]); however, no clear pattern was observed with increasing time since initiation, duration, or dose of pioglitazone. Furthermore, there was no longer a statistically significantly association of pioglitazone use and risk of prostate cancer with additional adjustment for prostate-specific antigen screening, BPH treatment, and proteinuria testing.[21]

Methodological limitations may have contributed to the prostate cancer imbalance in the PROactive follow-up. Firstly, the observational follow-up period was not blinded, potentially resulting in detection bias due to increased screening of pioglitazone-treated patients by an urologist because of the publicity regarding bladder cancer. Secondly, age is a risk factor for prostate cancer and may have impacted the results as the mean and median age at onset of prostate cancer were higher in the pioglitazone group compared with those in the placebo group. Thirdly, imbalances between PROactive treatment groups reported during the follow-up could be due to the small sample size observed. Finally, it is worth noting that a recent review of data from human trials suggests that TZDs are effective as chemotherapy in prostate cancer.[33]

Limitations of the study design

There are a number of limitations, in particular, the open-label, observational nature of the 10-year follow-up, leading to potential detection bias. Furthermore, only a small percentage of patients randomized to pioglitazone in PROactive also took pioglitazone during the 10-year follow-up. Thus, pioglitazone exposure in patients in the pioglitazone group during the observational study period was low, and consequently there are no statistics for this group. Baseline patient characteristics were not re-collected at the start of the follow-up; therefore, potentially relevant interval medical history may have been omitted from endpoint assessments. Likewise, laboratory data and safety narratives were not collected systematically during follow-up, making it difficult to conduct a more detailed analysis comparing cases within the PROactive population. Event collection methods were not as comprehensive as in PROactive. For example,

endpoint events were not adjudicated, which may have led to inconsistent reporting. On the other hand, more specific information was collected for cases of bladder cancer, although detailed information for other malignancies was not captured. Although use of TZDs was collected during the follow-up, use of TZDs and other glucose-lowering therapies were not controlled or specified during the observational follow-up, potentially confounding any effects related to original treatment assignment. Analyses from the combined PROactive and follow-up periods should be interpreted with caution due to differences in methodology and populations (e.g. omission of ACS during the follow-up period; approximately 25% of patients who completed PROactive did not enter the follow-up).

Conclusions

The results of this long-term observational study suggest that the trends of macrovascular benefits observed with pioglitazone during PROactive did not persist in the absence of continued pioglitazone treatment during the 10-year follow-up. However, there was no rebound effect following discontinuation of pioglitazone, nor were there any long-term cardiovascular safety issues in this high-risk, type 2 diabetes patient population. Furthermore, the incidence of deaths was nominally lower in those who received a TZD during the follow-up. There was no overall increase in malignancies, and the imbalance in bladder cancer cases observed during the double-blind period of PROactive did not persist. An imbalance in prostate cancer was observed; however, this result could be due to limitations of the study and requires further investigation. Taken together, these findings support a positive benefit:risk profile of pioglitazone.

Acknowledgments

The observational follow-up study described in this article was supported by Takeda Pharmaceutical Company, Ltd.

Medical writing support was provided by Susan Crawford of Absolute Healthcare Communications, Ltd.

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Figure legends

Figure 1. Forest plot of the primary composite endpoint, main secondary composite endpoint, and individual components of the primary composite endpoint

Figure 2. Kaplan-Meier curve of time to all-cause mortality.

A) 10-year observational period only. B) Combined PROactive double-blind and 10-year observational period

Table 1. Number (%) of patients with mortality or macrovascular morbidity events during PROactive observational follow-up according to original double-blind therapy and regardless of subsequent treatment.

	Original treatment during double-blind period		**Hazard ratio [95% CI]**
	Pioglitazone	**Placebo**	**(pioglitazone *versus* placebo)**
10-year observational follow-up only (mean 7.8 years)	**(n=1820)**	**(n=1779)**	
Primary endpoint	1056 (58.0%)	1072 (60.3%)	0.96 [0.88–1.04], p=0.3444
Main secondary endpoint	847 (46.5%)	854 (48.0%)	0.98 [0.89–1.07], p= 0.6211
All-cause mortality	618 (34.0%)	648 (36.4%)	0.93 [0.84–1.04], p=0.2311
Non-fatal MI	220 (12.1%)	201 (11.3%)	1.07 [0.88–1.30], p=0.4827
Stroke	239 (13.1%)	217 (12.2%)	1.09 [0.90–1.31], p=0.3749
Cardiac intervention	376 (20.7%)	386 (21.7%)	0.95 [0.82–1.09], p=0.4655
Major leg amputation	75 (4.1%)	99 (5.6%)	0.74 [0.55–0.99], p=0.0460
Leg revascularization	114 (6.3%)	133 (7.5%)	0.84 [0.65–1.08], p=0.1635
CV mortality	420 (23.1%)	450 (25.3%)	0.91 [0.80–1.05], p=0.1899

Double-blind period + 10-year observational follow-up (mean 10.7 years)	**(n=2605)**	**(n=2633)**	
Primary endpoint	1373 (52.7%)	1416 (53.8%)	0.94 [0.87–1.01], p=0.1001
Main secondary endpoint	1092 (41.9%)	1132 (43.0%)	0.94 [0.87–1.03], p=0.1699
All-cause mortality	795 (30.5%)	834 (31.7%)	0.94 [0.85–1.04], p=0.2143
Non-fatal MI	306 (11.7%)	310 (11.8%)	0.97 [0.83–1.14], p=0.7078
Stroke	317 (12.2%)	312 (11.8%)	1.00 [0.86–1.17], p=0.9727
Cardiac intervention	515 (19.8%)	545 (20.7%)	0.92 [0.82–1.04], p=0.1981
Major leg amputation	98 (3.8%)	121 (4.6%)	0.79 [0.61–1.04], p=0.0890
Leg revascularization	175 (6.7%)	184 (7.0%)	0.94 [0.76–1.16], p=0.5577
CV mortality	547 (21.0%)	586 (22.3%)	0.92 [0.82–1.04], p=0.1674

Table 2. Number (%) of patients with malignancies during PROactive observational follow-up according to original double-blind therapy and regardless of subsequent treatment

	Observational follow-up only (mean 7.8 years)			**Double-blind period + 10-year observational follow-up (mean 10.7 years)**		
	Pioglitazone (n=1820)	**Placebo (n=1779)**	**Relative risk [95%CI] (pioglitazone *versus* placebo)**	**Pioglitazone (N=2605)**	**Placebo (N=2633)**	**Relative risk [95%CI] (pioglitazone *versus* placebo)**
Any malignancy	235 (12.9%)	234 (13.2%)	0.98 (0.83–1.16)	326 (12.5%)	322 (12.2%)	1.02 (0.89–1.18)
Adrenal	2 (0.1%)	0	N/A	3 (0.1%)	0	N/A
Biliary	4 (0.2%)	1 (0.1%)	3.91 (0.44–34.95)	5 (0.2%)	3 (0.1%)	1.68 (0.40–7.04)
Brain	2 (0.1%)	8 (0.4%)	0.24 (0.05–1.15)	3	14	0.28 (0.08–0.99)
Bladder	14 (0.8%)	21 (1.2%)	0.65 (0.33–1.28)	27 (1.0%)	26 (1.0%)	1.05 (0.61–1.79)
Breast	13 (2.1%)	11 (1.8%)	1.17 (0.53–2.59)*†	16 (0.6%)	23 (0.9%)	0.70 (0.37–1.33)*†
Cervix	1 (0.2%)	2 (0.3%)	0.50 (0.05–5.45)*	1 (0.1%)	2 (0.2%)	0.52 (0.05–5.73)*

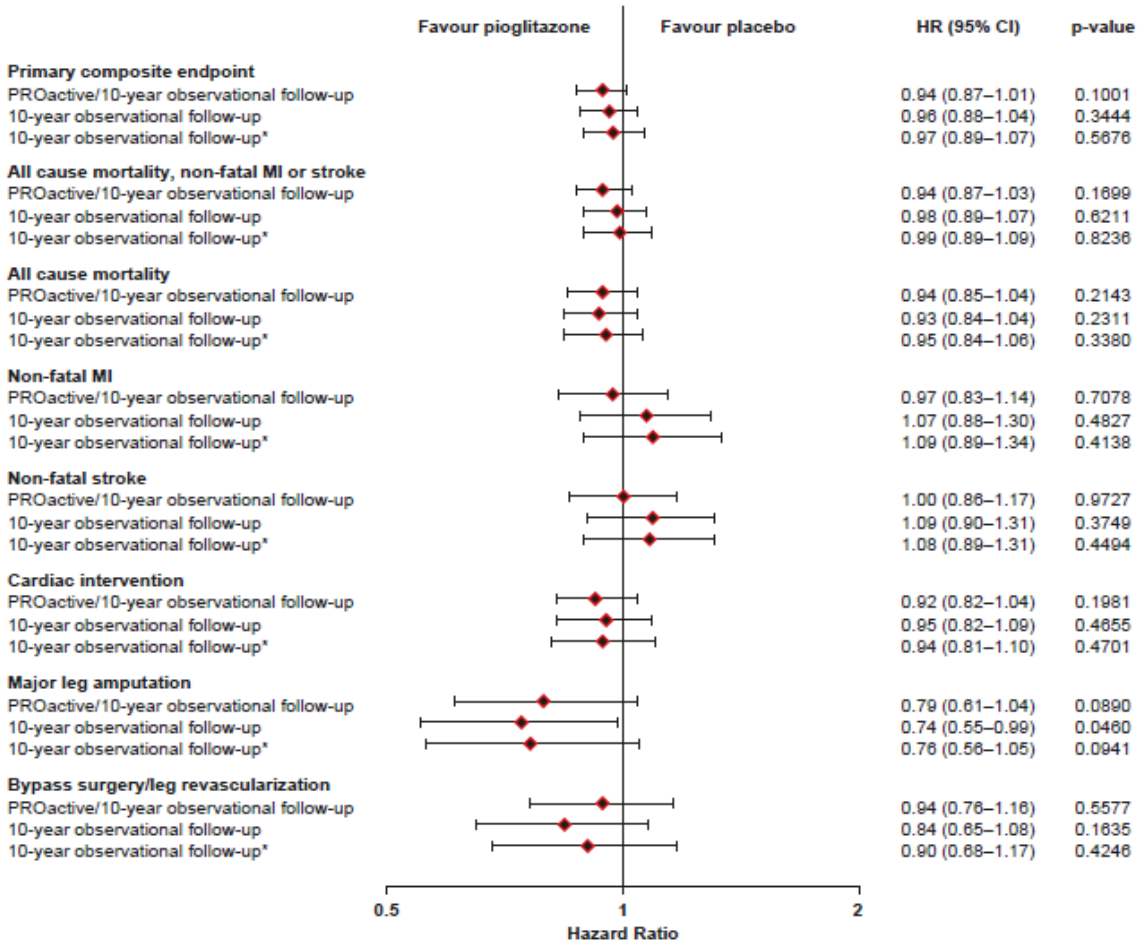
Colon/rectal	34 (1.9%)	30 (1.7%)	1.11 (0.68–1.80)	49 (1.9%)	45 (1.7%)	1.10 (0.74–1.64)
Gastric	12 (0.7%)	13 (0.7%)	0.90 (0.41–1.97)	17 (0.7%)	19 (0.7%)	0.90 (0.47–1.74)
Haematological	18 (1.0%)	12 (0.7%)	1.47 (0.71–3.03)	24 (0.9%)	22 (0.8%)	1.10 (0.62–1.96)
Hepatic	6 (0.3%)	5 (0.3%)	1.17 (0.36–3.84)	6 (0.2%)	5 (0.2%)	1.21 (0.37–3.97)
Lung	33 (1.8%)	43 (2.4%)	0.75 (0.48–1.18)	48 (1.8%)	55 (2.1%)	0.88 (0.60–1.29)
Mesotheliomia	0	0	N/A	2 (1.0%)	1 (<0.1%)	2.02 (0.18–22.28)
Metastases	7 (0.4%)	6 (0.3%)	1.14 (0.38–3.39)	12 (0.5%)	11 (0.4%)	1.10 (0.49–2.49)
Oesophageal	2 (0.1%)	2 (0.1%)	0.98 (0.14–6.93)	2 (0.1%)	2 (0.1%)	1.01 (0.14–7.17)
Oropharyngeal	4 (0.2%)	6 (0.3%)	0.65 (0.18–2.31)	5 (0.2%)	8 (0.3%)	0.63 (0.21–1.93)
Ovarian/uterine	6 (0.9%)	5 (0.8%)	1.19 (0.36–3.87)*	10 (1.1%)	10 (1.1%)	1.04 (0.44–2.49)*
Pancreas	7 (0.4%)	11 (0.6%)	0.62 (0.24–1.60)	15 (0.6%)	17 (0.6%)	0.89 (0.45–1.78)
Prostate	44 (3.7%)	29 (2.5%)	1.47 (0.93–2.34)**	58 (3.3%)	35 (2.0%)	1.59 (1.04–2.41)**
Renal	10 (0.5%)	10 (0.6%)	0.98 (0.41–2.34)	13 (0.5%)	17 (0.6%)	0.77 (0.38–1.59)
Skin	29 (1.6%)	33 (1.9%)	0.86 (0.52–1.41)	35 (1.3%)	36 (1.4%)	0.98 (0.62–1.50)
Other	5 (0.3%)	8 (0.4%)	0.61 (0.20–1.86)	6 (0.2%)	10 (0.4%)	0.61 (0.22–1.67)

*Calculated using only female patients

**Calculated using only male patients

†Excludes two cases of breast cancer in male patients in the pioglitazone group. When both male and female patients were included in the analysis, the relative risk was 1.14 [0.53–2.46] for the 10-year observational period and 0.70 [0.37–1.33] for the combined period.CI=confidence interval; N/A=not available.

Figure 1



Primary composite endpoint consists of all-cause mortality, non-fatal MI, cardiac intervention, stroke, major leg amputation, bypass surgery or revascularization of the leg.

*Excluding patients that took pioglitazone during observational study period (pioglitazone=270, placebo=196).

Figure 2