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Rosiglitazone and pioglitazone: A critical appraisal of the PROactive and DREAM trials

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Recently, two placebo controlled trials studying thiazolidinediones have been published. In one, the effect of pioglitazone on macrovascular events in secondary prevention patients with type 2 diabetes was evaluated (the PROactive trial)[1]. In the second, the effect of rosiglitazone on global mortality and incidence of diabetes was tested in patients with impaired fasting glucose or impaired glucose tolerance or both (the DREAM trial)[2].

In this article we evaluate the practical clinical benefits from both trials. In doing so, we describe the trials and review them with the help of a series of questions.

The PROactive Trial

Pioglitazone does not reduce macrovascular complications and increases heart failure in patients with type 2 diabetes and macrovascular disease.

Trial description[1,3]

Question

Does pioglitazone decrease all-cause mortality and macrovascular complications in patients with type 2 diabetes and macrovascular disease at baseline?

Design

Randomised, placebo-controlled, double-blind, multi-centre, parallel group trial with a mean follow up period of 34.5 months.

Setting

321 centres (including hospitals and primary care practises in 19 countries).

Patients

5,238 patients (35-75 years) were enrolled. They all had uncontrolled diabetes, glycated haemoglobin (HbA1c) $\geq$ 6.5% and one or more of the following criteria: previous myocardial infarction (MI), coronary artery bypass surgery, percutaneous coronary intervention or stroke at least 6 months before recruitment or previous acute coronary syndrome at least 3 months before recruitment, other evidence of arterial coronary disease or objective evidence for coronary artery disease in the leg, previous major amputation or intermittent claudication with an ankle or toe brachial pressure index $\leq$ 0.9). 95.9% of the patients were being treated with oral antidiabetics at the beginning of the trial.

Exclusion criteria were: patients with heart failure (NYHAC $\geq$ 2), gangrene, ulcers or rest pain in the leg, patients undergoing haemodialysis or patients with hepatic impairment (ALT $\geq$ 2.5), planned coronary or peripheral revascularization, type 1 diabetes, or who were taking only insulin. The profile of the enrolled patients is shown in Table 1.

Intervention

A total of 2,605 patients were given pioglitazone titrated from 15 mg/day to 45 mg/day while 2,633 patients were given identical placebo. Analysis was by intention to treat.

Endpoints

Primary endpoint: The primary endpoint was time from randomisation to: all-cause mortality, non-fatal myocardial infarction, acute coronary syndrome, coronary revascularization, endovascular or surgical intervention on the coronary or leg arteries, or amputation above the ankle.

Secondary endpoint initially proposed: Composite endpoint of the previous components plus cardiovascular death.

Modified secondary endpoint: All cause mortality, non-fatal myocardial infarction and stroke.

Table 1. Baseline characterictics in the PROactive trial.

PATIENTS' CHARACTERISTICS	OUTCOME
Age (mean ± SD)	61.8 ± 7.7 years
Male	66.1%
Myocardial infarction	46.7%
Revascularization	30.8%
Stroke	18.8%
Acute coronary syndrome	13.7%
Other evidence of coronary disease	48.1%
Peripheral arterial obstructive disease	19.9%
History of hypertension	75%
Systolic blood pressure (mean ± SD)	143.4 ± 17.8 mmHg
Diastolic blood pressure (mean ± SD)	83.0 ± 9.7 mmHg
Current smoker	14%
Past smoker	45%
Body-mass Index	30.9 ± 4.8 (Kg/m^2)
Time since diagnosis of diabetes (mean ± SD)	9.5 years ± 7.0
HbA1c	8.08 ± 1.41 %
BASELINE MEDICATIONS	**%PATIENTS**
Antidiabetics	95.9
Statins	40.8
Cardiovascular medication	95.0
Antiplatelet medications	83.9

Data are percentage or mean ± SD.

Outcomes

There were no statistically significant differences in the incidence of macrovascular events between the group treated with pioglitazone and the placebo, HR = 0.90 (95% CI, 0.80 - 1.02). Nor were there significant differences in any of the outcomes included in the primary composite endpoint. The only statistically significant difference found was in the modified secondary endpoint (see Table 2). 16.4% of the patients treated with pioglitazone and 16.6% of the placebo group stopped treatment before the end of the trial period.

No difference was observed in the incidence global of adverse effects. Pioglitazone caused an increase in heart failure (11% in the pioglitazone group vs 8% in the placebo group). An average increase of 3.6 kg in weight occurred in the pioglitazone group vs a reduction of 0.4 kg in the placebo group.

Authors' conclusions

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

Role of the funding source

The trial was financed by Takeda and Eli Lilly Pharmaceutical Companies. Each of the Companies had a voting member on the international steering committee and the two took part along with the other members of the executive committee in the modification of the secondary endpoint[4].

A critical appraisal of the trial

Is pioglitazone an important advancement in the available therapies to treat type 2 diabetic patients with previous cardiovascular disease?

In patients with type 2 diabetes for secondary prevention, pioglitazone has not been proven to reduce the incidence of macrovascular events

The trial results do not show that pioglitazone reduces macrovascular complications of diabetes or mortality in secondary prevention patients. Thereby, it cannot be said it has any additional value amongst this group of patients.

Internal validity

Is it well performed?

This is a randomized, double-blind trial and these two characteristics are important to ensure quality. However, there are doubts about the double-blinding of the analysis, due to the modified secondary endpoint[5]. In the initial trial protocol the composite secondary endpoint of all-cause mortality, non-fatal MI and stroke was not included. Nine days before the double-blind trial came to an end, the FDA was notified that this new endpoint would be included along with the prearranged ones. It should be kept in mind that the trial had already been going on for over three years and the final visits were completed three months before that.

Is the primary endpoint the most appropriate?

In the PROactive trial, heart failure was not included in the composite endpoint of mortality and macrovascular complications. When the inciden-

Table 2. Outcomes in the primary and secondary endpoints.

	Placebo (n= 2,633)	Pioglitazone (n= 2,605)	Hazard ratio (95%CI)
Primary endpoint	900	803	0.90 (0.80 – 1.02)
Death	186	177	0.96 (0.78 – 1.18)
Myocardial infarction	157	131	0.83 (0.65 – 1.06)
Stroke	119	92	0.81 (0.61 – 1.07)
Coronary revasculatization	240	195	0.88 (0.72 – 1.08)
Acute coronary syndrome	78	65	0.78 (0.55 – 1.11)
Major leg amputation	28	28	1.01 (0.58 – 1.73)
Leg revascularization	92	115	1.25 (0.90 – 1.73)
Modified secondary endpoint	462	400	0.84 (0.72 – 0.98)

Table 3. Outcomes in the PROactive trial.

PROactive	Placebo	Pioglitazone	NNT (95%CI)
Primary endpoint	21.7%	19.7%	50 (NNT=24 to ∞ to NNH 496)
Modified secondary endpoint	13.6%	11.6%	49 (27 - 407)
	Placebo	**Pioglitazone**	**NNH (95%CI)**
Heart failure	7.5%	10.8%	31 (21 - 59)
Oedema unrelated to heart failure	13.0%	21.6%	12 (9 - 15)

NNT= Number needed to treat
NNH= Number needed to harm

ce of heart failure is included, pioglitazone causes one incidence of heart failure for every 31 people treated. Stated another way, for each avoided case of the modified secondary endpoint, 2 cases of heart failure were caused and 4 cases of oedema unrelated to heart failure were caused[6].

Are the results presented in a simple and coherent way?

NO. Numerous graphics and data are brought together but neither the absolute risks nor the NNT are shown. Therefore in Table 3 we provide the results obtained in the two trials with the NNT (Number Needed to Treat) or the NNH (Number Needed to Harm). These concepts are now 20 years old[7] but only in the last few years have they become increasingly important as they are very useful for determining the efficiency of an intervention. NNT refers to the number of patients to be treated to avoid an outcome (eg. death, coronary event, etc.). In the case of NNH, it indicates that one adverse effect will be caused if we treat this number of patients (eg. heart failure, death, etc.).

Thus, it is necessary to treat 49 people with pioglitazone in order to avoid an event of the modified secondary endpoint but, for every 31 patients treated, a case of heart failure is caused. For every 12 patients treated a case of oedema not related to heart failure is caused by pioglitazone.

Moreover, the global incidence of macrovascular complications is not reduced[8]. This fact is highlighted in the editorial which accompanies the PROactive trial where it is affirmed that in the pioglitazone group 58 less episodes of the primary composite endpoint were observed but 221 more cases of oedema and 115 more cases of heart failure were observed (Table 3).

Pioglitazone increases the incidence of heart failure

Are the authors' conclusions consistent with the trial results?

The conclusion of the authors is that pioglitazone reduces the modified secondary endpoint. However, after critical appraisal it can be seen that the appropriate conclusion is that in type 2 diabetic patients with previous macrovascular disease, pioglitazone does not reduce macrovascular events (primary outcome) and it increases heart failure events.

This aspect has caused confusion since the secondary endpoint, which was modified shortly before closing trial, is the only outcome that is statistically significant. And this leads us to another question, **are the secondary endpoints just as valid as the primary ones?** The answer is NO. Trials are designed and carried out in order to answer one or more questions. These are formulated as hypotheses and arise from the primary endpoints. On the basis of these, the patients are selected (with criteria of inclusion and exclusion), and sample size is calculated. Information is gathered in line with the protocol, which has been previously outlined and within a specified interlude of time. In this way we can be sure that the data taken from the trial will help us to answer the question that has been formulated.

In addition to this fundamental objective, when the trial is completed, it may be possible to obtain further information about some other aspects of the trial. And this is where the secondary endpoints come into play. The information provided by these secondary endpoints is going to help us create new hypotheses and it is not to answer questions since we have seen that the design of the trial is not framed to answer questions generated by the secondary endpoints. There are numerous examples of statistically significant secondary endpoints which when later tested in a randomised controlled trial are proven not to be true[9,10].

Summary of the reassessment and role in the therapy

In the PROactive trial, pioglitazone did not show that the incidence of macrovascular events for secondary prevention in type 2 diabetic patients could be reduced, which is the primary endpoint under study. An increase in the incidence of heart

failure was shown, and consequently, the harms appear to outweigh the benefits. In a recent reassessment[11], it was concluded that this balance continues to be uncertain and that it has not been demonstrated that it improves health outcomes (a reduction in mortality and morbidity, adverse effects, improvement in the quality of life or reduction in costs).

According to the data shown in the article, the trial patients did not receive the optimal treatment for their risk factors. Thus, the control of arterial pressure was suboptimal (systolic average pressure > 140 mmHg) and only 41% were in treatment with statins. We do not know what the results of pioglitazone might have been if the use of both antihypertensive and cholesterol-lowering drugs had been optimized (they were patients in secondary prevention). It must also be taken into account that, guidelines for diabetic patients for secondary prevention with HbA1c clearly above 6.5% (mean HbA1c = 8%) recommend active treatment and not placebo.

The DREAM trial[2,12,13]

Rosiglitazone in people with a high risk of developing type 2 diabetes does not reduce total mortality, increases heart failure and reduces the incidence of diabetes.

Trial description

(N.B. This trial used a factorial design in which the efficacy of ramipril was also evaluated. Ramipril's effects are published in another journal and are not assessed in this article[13]).

Question

Does rosiglitazone prevent diabetes in patients with a high risk of developing type 2 diabetes?

Design

Randomized, double-blind trial with parallel groups, with an average duration of three years.

Setting

191 centres in 21 countries

Patients

5,269 patients over thirty years of age with impaired glucose tolerance or impaired fasting glucose, or both.

Exclusion criteria were

Patients with a history of diabetes (except gestational diabetes), cardiovascular disease (including heart failure and known low ejection fraction), or intolerance to either angiotensin-converting enzyme inhibitors or thiazolidinediones, and patients who over the 17 days previous to the randomization took less than 80% of the placebo pills. The characteristics of the patients are shown in Table 4.

Rosiglitazone reduces incident diabetes but it does not decrease the incidence of cardiovascular events

Intervention

Of the initial 24,872 pre-selected group, 5,269 were randomized. 2,635 patients received rosiglitazone titrated from 4 mg/day to 8 mg/day and 2,634 received placebo. Analysis was done by intention to treat.

Endpoints

Primary endpoint: Composite of incident diabetes or death from any cause.

Secondary endpoint: The DREAM protocol was described in detail in a previous publication[12]. A key secondary endpoint is mentioned, which consisted of a composite endpoint of cardiovascular events (MI, stroke, cardiovascular death, revascularization, heart failure, new angina or ventricular arrhythmia which required resuscitation) or renal events (progression of normoalbuminuria towards micro or macroalbuminuria, from micro to macroalbuminuria or reduction of 30% in creatinine clearance).

In the publication of the results, five secondary endpoints are mentioned: (1) return to "normal" glucaemia (2) a composite cardiovascular endpoint (which includes cardiovascular events shown in the earlier publication), (3) each one of these individual endpoints (4) renal events and a composite cardio-renal endpoint and (5) glucose concentrations.

Outcomes

A statistically significant reduction was found in the primary outcomes between the group treated with rosiglitazone and the placebo group, HR = 0.40 (95%CI, 0.35-0.46) which was due to the drop in incident diabetes, since there was no difference in the mortality rate.

There was no statistically significant differences in the cardiovascular secondary endpoint, nor in the different variables which make it up with the ex-

Table 4. Baseline clinical and biochemical characteristics of participants.

PATIENTS' CHARACTERISTICS	OUTCOME
Age*	54.7 ± 10.9
Male	41.5%
Impaired glucose tolerance (IGT)	57.5%
Impaired fasting glucose (IFG)	14%
Both IGT and IFG	28.4%
hypertension	43.5 %
Hyperlipidaemia	35.5 %
Systolic blood pressure*	136 ± 18.6 mmHg
Diastolic blood pressure*	83.4 ± 11.3 mmHg
Both current and past smokers	44.6%
Body-mass Index*	30.5 ± 5.6 Kg/m^2
Fasting glucose*	5.8 ± 0.7 mmol/mL
2-h plasma glucose concentration*	8.7 ± 1.4 mmol/mL

Data are percentage or mean ± SD.

ception of heart failure, which was increased in the group treated with rosiglitazone (see Table 5).

In the final visit 28.5% of the patients treated with rosiglitazone and 24.3% of those in the placebo group had abandoned the medication. The main reasons can be found in Table 6. A mean weight gain of 2.2 Kg was caused by rosiglitazone as compared to placebo.

Authors' conclusions

Rosiglitazone 8 mg daily for three years substantially reduces incident type 2 diabetes and increases the likelihood of regression to normoglycaemia in adults with impaired fasting glucose or impaired glucose tolerance, or both.

Role of the funding source

The trial was financed by a grant from The Canadian Institute of Health Research and the pharmaceutical companies, Sanofi-Aventis, GlaxoSmith-Kline and King Pharmaceuticals.

Critical appraisal of the trial

Is rosiglitazone a therapeutic advantage in the management of patients with a high risk of developing diabetes?

In the case of patients with a high risk of developing diabetes (DREAM trial), we need to know whether an intervention reduces cardiovascular morbidity and/or mortality. Furthermore, we would want to compare a new intervention with lifestyle interventions, which have been shown to be successful in reducing the incidence of diabetes[14,15,16]. It does not interest us to know that rosiglitazone reduces glucose figures –as we already know that– but rather to know if the benefits exceed the harms from rosiglitazone as compared to standard treatment-lifestyle changes.

Internal validity

Has the trial been properly conducted?

Yes. It is a randomized, double-blind trial and these two characteristics are important to ensure quality.

Is the primary endpoint the most appropriate?

Table 5. Outcomes in the primary and secondary endpoints in the DREAM trial.

	Placebo (n= 2,635)	Rosiglitazone (n= 2,634)	Hazard ratio (95%CI)
Primary endpoint	686	306	0.40 (0.35 – 0.46)*
Death	33	30	0.91 (0.55 – 1.49)
Incident diabetes	658	280	0.38 (0.33 – 0.44)*
Cardiovascular events composite (secondary endpoint)	55	75	1.37 (0.97 – 1.94)
Myocardial infarct	9	15	1.66 (0.73 – 3.80)
Stroke	5	7	1.39 (0.44 – 4.40)
Cardiovascular death	10	12	1.20 (0.52 – 2.77)
Confirmed heart failure	2	14	7.03 (1.60 – 30.9)*
New angina	20	24	1.20 (0.66 – 2.17)
Revascularization	27	35	1.29 (0.78 – 2.37)

(*) Statistically significant differences.

Table 6. Main causes of withdrawal in the DREAM trial.

	Placebo (n= 2,635)	Rosiglitazone (n= 2,634)
Treatment withdrawal	641 (24.3%)	752 (28.5%)
Voluntary dropouts	439 (16.7%)	503 (18.9%)
Oedema	41 (1.6%)	439 (4.8%)
Clinical decision	39 (1.5%)	50 (1.9%)
Weight increase	15 (0.6%)	50 (1.9 %)

Table 7. Outcomes in the DREAM trial.

DREAM	Placebo	Rosiglitazone	NNT (95%CI)
Primary endpoint	26.0%	11.6%	7 (7-8)
	Placebo	**Rosiglitazone**	**NNH (95%CI)**
Cardiovascular events composite (secondary endpoint)	2.1%	2.9%	132 (NNT=1,262 to ∞ to NNH 63)
Heart failure	0.1%	0.5%	220 (133 - 631)
Oedema unrelated to heart failure	1.6%	4.8%	7 (6-7)

NNT= Number needed to treat
NNH= Number needed to harm

The primary endpoint of the DREAM trial is a composite of incident diabetes or death. This is an irrational endpoint that combines events that have markedly different impact on the patient. A more appropriate combined endpoint would have been mortality and cardiovascular morbidity.

Are the results shown in a simple and coherent way?

In the DREAM trial, the NNT is 7 treated patients to avoid the diagnosis of a new case of diabetes. No reduction in the incidence of total cardiovascular events was observed. However, an increase in the incidence of heart failure was observed, 1 for every 220 patients treated and, for oedema, 1 for every 7 patients treated. A simpler way of presenting this data could have been a table like that shown in Table 7.

Are the authors' conclusions consistent with the trial results?

NO. A lack of reduction in mortality or in the incidence of cardiovascular events with an increase in the incidence of heart failure suggests that the harms exceed the benefits. The reduction in the incidence of diabetes, which is based on serum glucose, a surrogate marker, does not outweigh the harms.

A summary of the trial and its role in therapeutics

The DREAM trial studies more than 5,000 patients with a high risk of developing diabetes. No reduction was observed in mortality and there was an increase in one cardiovascular morbidity outcome, heart failure, with a NNH of 200.

This is of importance as we are dealing with primary prevention, where utmost care must be taken not to harm patients. Just recently, the FDA issued a safety alert about the increase in fractures observed in women with type 2 diabetes who received either rosiglitazone[17] or pioglitazone[18]. The improvement in glucose figures, and the consequent lower incidence of new diabetes cases, must be afforded less weight unless it is proven by following these patients long-term that rosiglitazone lowers the incidence of cardiovascular events.

Furthermore, a number of trials have been carried out which show that lifestyle interventions reduce incident diabetes similarly, in different populations and with different health systems[19,20,21]. It has been shown that the effects remained even 7 years after the intervention stopped[22] and other risk factors such as high blood pressure also were improved[23].

Just as is affirmed in the editorial which appears in the DREAM trial publication[24], changes in lifestyle should continue to be the optimal therapeutic option for the prevention of type 2 diabetes. Even if this option is more expensive to the health care system

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Changes in lifestyle, increase in physical exercise, healthy diet and a reduction in weight are best treatment options for patients with a risk of developing type 2 diabetes

Conclusions

In patients with type 2 diabetes for secondary prevention, pioglitazone has not been proven to reduce the incidence of macrovascular events as compared to placebo. Besides this, questions remain as to its safety profile.

Treatment of these patients should be centred on the control of classic risk factors (dyslipidemia, hypertension, tobacco, etc.) along with control of glucose.

In patients with high risk of developing type 2 diabetes, rosiglitazone did not reduce cardiovascular mortality and increased one cardiovascular morbidity, heart failure.

In patients who run a risk of developing diabetes, rosiglitazone should not be used.

Changes in lifestyle, increase in physical exercise, healthy diet and a reduction in weight, are best treatment options for patients with a high risk of developing type 2 diabetes.

Critical appraisal of published trials is an essential tool to determine whether the conclusions reached by the authors are validated by the trial results. The examples here demonstrate that results must not be accepted just because they are published in a prestigious journal.

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