Pioglitazone in the management of Type 2 diabetes and beyond

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The prevalence of Type 2 diabetes mellitus is increasing rapidly and this disease has become an alarming healthcare problem in recent years. Both insulin resistance and β-cell dysfunction play important roles in the pathophysiology of Type 2 diabetes mellitus. Pioglitazone, a thiazolidinedione, has been demonstrated to improve both impairments and is currently used as monotherapy or in combination with insulin, sulfonylureas or metformin for the treatment of Type 2 diabetes mellitus. Clinical studies have confirmed the efficacy, safety and tolerability profile of pioglitazone and, furthermore, a large outcomes trial has recently demonstrated positive cardiovascular effects. Ongoing studies have shown that pioglitazone has possible applications beyond the treatment of diabetes in conditions such as nonalcoholic steatohepatitis or polycystic ovarian syndrome. This review provides an overview of the pharmacology, clinical efficacy and safety of pioglitazone, focusing primarily on the most recent data.

The number of patients with Type 2 diabetes has increased considerably in recent years with a worldwide prevalence of approximately 150 million at present, which is projected to increase to approximately 225 million by the end of the decade and to as many as 300 million by 2025 [1]. Even more dramatic is the fact that these numbers represent only diagnosed diabetes; however, in general populations up to 10% of people suffer from unknown Type 2 diabetes mellitus and up to 20% from impaired glucose tolerance [2]. In high-risk populations, the proportion of unknown disturbances in glucose metabolism is considerably higher [3,4]. Patients with diabetes face a two- to five-times higher cardiovascular mortality and morbidity than nondiabetics [5], and diabetes care already takes 2–7% of the total national healthcare budgets of Western European countries [1]. Landmark clinical intervention trials, such as the UK Prospective Diabetes Study (UKPDS) [6] in Type 2 diabetics or the Diabetes Control and Complication Trial (DCCT) [7] in Type 1 diabetics have shown that improved glycemic control reduces macrovascular and microvascular morbidity and mortality. In addition, the UKPDS also highlighted the progressive nature of Type 2 diabetes as glycemic control deteriorated despite treatment with oral antidiabetic agents or insulin over time [8]. Furthermore, the Finnish Diabetes Prevention Study [9], the Diabetes Prevention Program (DPP) [10] and, more recently, the Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication (DREAM) trial [11], showed a progression rate from impaired glucose tolerance to overt Type 2 diabetes of approximately 10% per year without intervention as further proof of the ongoing deterioration in glucose metabolism disturbances.

Today, it is well established that the development of Type 2 diabetes mellitus results from an interaction of the subjects genetic makeup and environmental influences, and that increasing age and obesity in Western populations produces a Type 2 diabetes epidemic. Pathophysiologically, insulin resistance as well as β-cell dysfunction play the main roles in the development of Type 2 diabetes. Today, it is established that both abnormalities are present very early in the development of the disease [12]. Insulin resistance or sensitivity are determined by a number of factors, including genetics [13], aging [14], exercise [15] and, of course, obesity [16]. For the latter factor, fat distribution is a very important point, since intra-abdominal fat accumulation is known to play a pivotal role in insulin resistance [17]. β-cell function in turn, seems to be impaired early in Type 2 diabetes development, and as β-cell function progressively declines, glucose metabolism deteriorates from normal to impaired glucose tolerance and finally diabetes [12].

Pioglitazone (Actos®), a member of the peroxisome proliferator-activated receptor (PPAR)-γ agonists family, has been demonstrated to improve insulin sensitivity [18,19] and β-cell function [18]. Therefore, there has been increasing interest in pioglitazone for the management of Type 2 diabetic patients in recent years.

Keywords: cardiovascular disease, insulin resistance, nonalcoholic steatohepatitis, pioglitazone, PPAR-γ, thiazolidinediones, Type 2 diabetes mellitus

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Overview of the market

Several antidiabetic agents are available on the expanding worldwide market, which are discussed below.

Metformin is an antidiabetic drug that acts by increasing tissue sensitivity to insulin, principally in the liver and the muscle. The molecular mechanisms of metformin action have still not been definitively determined. It increases insulin receptor tyrosine kinase activity and increases glucose transporter-4 translocation and activity in the muscle. Phosphorylation of key enzymes in the gluconeogenetic pathway, and therefore inhibition of gluconeogenesis may explain hepatic effects of metformin.

Thiazolidinediones (TZDs), such as pioglitazone and rosiglitazone, are 'insulin-sensitizing drugs' that both act via activation of the PPAR-γ. In this way, these drugs effect expression of genes involved in various processes, among them genes coding for proteins involved in metabolic pathways. Even if rosiglitazone and pioglitazone belong to the same family of antidiabetic drugs, they actually show different patterns in gene-expression regulation, since, for example, only pioglitazone shows beneficial effects on dyslipidemia.

Sulfonylureas, such as glimepiride or gliclazide, stimulate insulin secretion through the activation of the sulfonylurea receptor (SUR). SUR activation leads to a closure of the ATP-regulated potassium channels in the β-cell of the pancreas. This step initiates depolarization of the cell with concomitant increased exocytosis of insulin. Insulin secretagogues with the same mechanism of action but with considerably shorter half-lives have been developed (repaglinide and nateglinide). They have to be administered with every meal but reduce the risk of hypoglycemia in comparison with sulfonylureas owing to their short duration of action.

α-glucosidase inhibitors, such as acarbose or miglitol, act in the gut by slowing down carbohydrate splitting and lead to a decreased postprandial plasma glucose peak. Intake of these drugs is often associated with meteorism and diarrhea.

Exenatide is a glucagon-like peptide (GLP)-1 mimetic agent that augments glucose-stimulated insulin secretion, inhibits glucagon secretion, delays gastric emptying and increases β-cell mass. Long-term data are not available, but it seems to be a promising antidiabetic agent for the future.

Inhibitors of the enzyme dipeptidylpeptidase (DPP) IV are another strategy in diabetes treatment. DPP IV inactivates GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Inhibitiors of DPP IV (gliptins) prolong and enhance the activity of endogenous GLP-1 and GIP that act as stimulators of insulin secretion and regulators of blood glucose control.

Introduction to pioglitazone

Pioglitazone belongs to the family of TZDs that act as agonists of the PPARγ. PPARγ is a member of the nuclear hormone receptor superfamily and can be found in adipose tissue, liver, skeletal muscle, vascular smooth muscle cells, endothelial cells and monocytes, macrophages [20,21]. Activation of PPAR by 15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) or the synthetic TZDs leads to the formation of heterodimers with retinoid-X receptors (RXRs). These dimers bind to specific DNA-binding sites called peroxisome proliferators-response elements and regulate transcription of target genes. In general, PPARγ regulates genes involved in the glucose homeostatis, fatty acid uptake and storage, and in processes of inflammation.

Pioglitazone was approved in the USA on July 15th 1999, and in the EU on October 13th, 2000.

Chemistry

Pioglitazone hydrochloride, 5-2,4-thiazolidinedione hydrochloride salt (previously U-72107A, AD-4844) was developed by Takeda Chemical Industries (Osaka, Japan) with a molecular weight of 392,91 Da. Pioglitazone is an enantiomeric drug, which is administered as a racemate. The chiral conversion of pioglitazone in humans is 1:1 [22] No difference in pharmacological activity was found between the two enantiomers [23].

Pharmakokinetics, pharmacodynamics & metabolism

Pioglitazone is well absorbed after oral administration and has an oral bioavailability of approximately 83% with peak concentrations after approximately 1.5 h after administration (for summary see **Table 1**). Food intake does not alter the absorption of pioglitazone [22]. It is highly bound to plasma proteins (>97%) with a low volume of distribution. Pioglitazone is metabolized in the liver via cytochrome P (CYP) 450 isoenzymes, mainly CYP2C8, CYP2C9 and CYP3A4. Pioglitazone undergoes hepatic metabolism by hydroxylation of methylene groups (M-I, M-II and M-IV), by the oxidation of the methyl group (M-V) and by oxidation of M-IV to M-III and M-V to M-VI [22]. There are three active metabolites: M-III

Table 1. Summary of pharmacokinetic parameters after oral pioglitazone administration.

t_{max}	1.5–2.5 h
Bioavailability	83%
Plasma protein binding	>97%
Clearance	2.4 l/h
Serum half-life	Approximately 5–9 h (pioglitazone), 26–30h (M-III, M-IV)
Elimination	Mostly feces, 15–30% urine

Data from [22,23].

(ketoderivate of pioglitazone), M-IV (hydroxyderivate of pioglitazone) and to a lesser extent M-II (hydroxyderivate of pioglitazone). In animal models, these three metabolites showed a hypoglycemic potency of 40–60% of the parent compound. The triglyceride-lowering potency of M-II is nearly twice that of pioglitazone. M-III and M-IV have considerably longer half-lives (~26–28 h) than the parent compound (5–9 h). The metabolites are mainly excreted in bile and eliminated in the feces. Approximately 15–30% of the metabolites can be recovered in the urine. Budde *et al.* investigated the pharmacokinetics in patients with impaired renal function and found that neither pioglitazone, nor the metabolites M-III and M-IV, accumulated in patients with renal impairment [24].

Insulin sensitivity, β-cell function & glucose levels

Pioglitazone consistently reduces fasting and postprandial hyperglycemia in patients with Type 2 diabetes [18,25,26]. Peripheral insulin sensitivity is improved [19,27] and peripheral glucose uptake as well as splanchnic glucose uptake are enhanced by pioglitazone therapy [28,29]. Furthermore, pioglitazone was shown to reduce hepatic insulin resistance in terms of the ability of insulin to suppress endogenous glucose production [19,30]. In addition, improvement of β-cell function was suggested by Miyazaki *et al.* who reported a significant increase of the insulinogenic index (Δ area under the curve [AUC] insulin/ΔAUC glucose during an oral glucose tolerance test) after 26 weeks of treatment with pioglitazone 30 or 45 mg (0.13 ± 0.03 to 0.27 ± 0.05; $p < 0.05$) [18]. Two recent clamp studies support the suggestion of improvement of β-cell function by pioglitazone treatment [31,32]. Improvements of β-cell function could be directly mediated by activation of PPARγ, which can be found in pancreatic β-cells, or indirectly by lowering lipotoxicity or reductions in β-cell stress associated with reduced insulin resistance [33].

Lipid metabolism

Dyslipidemia with elevated triglycerides (TGs), low high-density lipoportein (HDL) cholesterol and small-dense low-density lipoprotein (LDL) cholesterol is commonly observed in diabetic patients [34]. Pioglitazone has consistently been demonstrated to reduce TG levels by 12–30% [26,35,36] and elevate HDL-cholesterol by 15–20% [26,35]. Data on mechanisms underlying the effects of pioglitazone on lipids are rare. Nagashima *et al.* demonstrated an increased efficiency of TG clearance from plasma, almost certainly mediated by increased lipoproteinlipase-associated lipolysis by 12 weeks pioglitazone treatment [36]. No influence of the TZD on the production rates of very low-density lipoproteins could be observed. Another study investigating the effect of pioglitazone on fasting and postprandial lipid metabolism [25], showed an almost restoring effect on postprandial lipemia to normal as well as reduced fasting TGs. Reduced hepatic lipoproteinlipase activity could be observed, whereas lipoproteinlipase activity was unaffected by pioglitazone in this study.

Adipose tissue

Paradoxically, metabolic parameters improve while patients gain weight and increase subcutaneous adipose-tissue mass. Animal [37], as well as human [19], studies have shown that TZDs cause a shift of fat distribution from visceral to subcutaneous adipose depots. *In vitro* pioglitazone, along with other TZDs, was shown to enhance adipocyte differentiation [38] and brought the cell to a state active for storage (for a review see [39]).

Pioglitazone regulates the expression of more than 100 target genes in the adipocyte, among them genes of various adipokines, such as adiponectin, tumor necrosis factor α or resistin [40]. Adiponectin is produced in adipose tissue only and has inter alia insulin sensitizing properties [41]. *In vivo* treatment in humans with pioglitazone increases circulating concentrations of adiponectin [42–44].

Clinical efficacy

Glucose metabolism

Monotherapy versus placebo

Several studies focused on glycemic control of pioglitazone as monotherapy in double-blind, placebo-controlled, multicenter trials with a duration of 12–26 weeks [45–48]. HbA1c reduction was between -0.8 and -1.05% (**Table 2**), depending on baseline HbA1c and pioglitazone dose. Pioglitazone 15, 30 and 45 mg reduced

Table 2. Glycemic efficacy in placebo-controlled monotherapy trials.

Study	Dose of Pioglitazone (mg)	Patients (n)	Duration (weeks)	Baseline HbA1c (mean, %)	HbA1c change (mean, %)	FPG change (mean, mmol/l)	Ref.
Aronoff *et al*.	Placebo	79	26	10.4	0.7*	0.5	[45]
	7.5	80		10.0	0.2	-1.0*§	
	15	79		10.2	-0.3*§	-1.6*§	
	30	85		10.2	-0.3*§	-1.8*§	
	45	76		10.3	-0.9*§	-3.1*§	
Rosenblatt *et al*.	Placebo	96	23	10.4	0.76*	0.4	[47]
	30	101		10.7	-0.60*§	-2.8*§	
Scherbaum *et al*.	Placebo	84	26	8.75	-0.34	-0.1	[46]
	15	89		9.14	-0.9	-1.9¶	
	30	78		9.06	-1.05¶	-2.0#	
Herz *et al*.	Placebo	99	16	7.5	-0.2*	-0.1	[48]
	30	99		7.5	-0.8‡	-1.4‡	
	45	99		7.6	-0.9‡	-1.6‡	

**$p \leq 0.05$ versus baseline; ‡$p < 0.001$ versus baseline and placebo; §$p \leq 0.05$ versus placebo; ¶$p < 0.01$ versus placebo; #$p < 0.001$ versus placebo.*
FPG: Fasting plasma glucose.

HbA1c levels significantly in comparison with placebo, with the exception of the 15 mg group of the Scherbaum *et al*. study [46]. Likewise significant were the reductions of fasting plasma glucose (FPG) in all dosages of pioglitazone in comparison with placebo.

Monotherapy versus other antidiabetic drugs

Pioglitazone has been compared in monotherapy against all commonly used oral antidiabetic drugs (**Table 3**). It showed HbA1c-lowering effects comparable to that of metformin [49,50] in a range of -1.3 to -1.6%, as well as comparable effects to that of sulfonylureas (glibenclamide, gliclazide and glimepiride) [51–54]. Goldberg *et al*. compared pioglitazone with rosiglitazone in a 24-week trial and, with regards to glycemic control, both were comparable (HbA1c change from baseline -0.7% for pioglitazone vs -0.6% for rosiglitazone; p = not significant) [26]. Another trial compared both glitazones head-to-head but all patients were previously treated with troglitazone [55]. After a washout period of only 2 weeks, study medication, pioglitazone 45 mg or rosiglitazone 8 mg, was started. Therefore, the additional glucose-lowering effect of both comparators seen in this study is very small (approximately -0.3%, estimated from a graph). Nevertheless, this study confirmed that the two TZDs available lower blood glucose to the same extent when they are used in the maximum dose.

One group investigated the efficacy of pioglitazone in comparison to acarbose and found the glitazone to be superior to the α-disaccharidase-inhibitor (HbA1c: -1.1 vs -0.5%; $p < 0.001$) [56].

Combination therapy

Pioglitazone has been investigated in combination with all commonly used oral antidiabetic drugs (**Table 4**). Pioglitazone in combination with metformin was significantly more effective in blood glucose lowering than metformin plus placebo [57]. In a 2-year long-term study, patients inadequately controlled with doses of metformin up to 2550 mg were randomized to either pioglitazone (15–45 mg) or gliclazide (80–320 mg) [58]. Both combinations could lower HbA1c by approximately 0.8%, and 30.6% of patients in the pioglitazone group versus 25.2% (p = 0.128) in the gliclazide group achieved a target HbA1c level of less than 7%. The fasting insulin decreased in the pioglitazone group from baseline to week 104 by 18.1%, whereas the addition of gliclazide to metformin increased fasting insulin by 13.2% ($p < 0.001$) throughout the study.

Recently, Derosa and colleagues investigated the efficacy of pioglitazone (15 mg) and rosiglitazone (4 mg) when added to metformin in a 52-week trial [59]. With regards to glycemic control, both TZDs demonstrated comparable effects (HbA1c: -1.3 to -1.4%).

Table 3. Glycemic efficacy of pioglitazone monotherapy in comparison with other oral antidiabetic drugs.

Study	Drug and daily dosage	Patients (n)	Duration (weeks)	Baseline HbA1c (mean, %)	HbA1c change (mean, %)	FPG change (mean, mmol/l)	Ref.
Pio vs metformin							
Pavo *et al*.	Pio 30–45 mg	105	32	8.6	-1.3	-3.0	[49]
	Metformin 850–2550 mg	100		8.6	-1.5	-2.8	
Schernthaner *et al*.	Pio 30–45 mg	597		8.7	-1.4	-2.5*	[50]
	Metformin 850–2550 mg	597	52	8.7	-1.5	-2.3	
Pio vs SU							
Tan *et al*.	Pio 30–45 mg	91	52	8.5	-1.2‡	-0.7‡	[51]
	Glibenclamide 1.75–10.5 mg	109		8.4	-0.6	+0.2	
Periello *et al*.	Pio 30–45 mg	146	52	8.8	-0.8	-1.0	[53]
	Gliclazide 80–320 mg	137		8.7	-0.8	-0.7	
Charbonell *et al*.	Pio 30–45 mg	1270	52	8.7	-1.4	-2.4§	[35]
	Gliclazide 80–320 mg	1270		8.7	-1.4	-2.0§	
Tan *et al*.	Pio 15–45 mg	121	52	8.2	-0,8	-0.6¶	[52]
	Glimepiride 2–8 mg	123		8.5	-0,7	+0.6¶	
Pio vs Rosi							
Goldberg *et al*.	Pio 30–45 mg	363	24	7.6	-0.7	-1.8	[26]
	Rosi 4–8 mg	356		7.5	-0.6	-2.0	
Khan *et al*.	Pio 45 mg	67	16	7.9	-0.3#	Not reported	[55]
	Rosi 8 mg	60		8.0	-0.4#	Not reported	
Pio vs acarbose							
Goke *et al*.	Pio 45 mg	129	26	8.9	-1.1**	-3.1**	[56]
	Acarbose 50–300 mg	136		9.0	-0.5**	-1.3**	

**p = 0.016 for pioglitazone versus metformin; ‡p < 0.005 for pioglitazone versus glibenclamide; §p = 0.002 for pioglitazone versus gliclazide; ¶p = 0.01 for pioglitazone versus glimepiride; #Estimated from a graph. Patients who were previously treated with troglitazone and pioglitazone or rosiglitazone were started after a 2-week washout period; **p < 0.001 for pioglitazone versus acarbose.*
Pio: Pioglitazone; Rosi: Rosiglitazone; SU: Sulfonylurea.

Kipnes *et al*. performed a study where placebo or pioglitazone (15 or 30 mg) was added to a sulfonylurea therapy [60]. Both dosages of pioglitazone improved HbA1c, as well as improving fasting plasma glucose significantly in comparison with placebo ($p \leq 0.05$).

In a 52-week trial, either pioglitazone (15–45 mg) or metformin (850–2550 mg) were added to sulfonylurea therapy in inadequately controlled patients with Type 2 diabetes [61]. Equivalent improvements in glycemic control were obsereved for both combinations. Fasting insulin decreased by 10% in the sulfonylurea plus pioglitazone group and by 6% in the sulfonylurea plus metformin group ($p = 0.199$). Furthermore, the investigators report a significant reduction of the urinary albumin:creatinine ratio from baseline to week 52 in the sulfonylurea plus pioglitazone group (-15%) in comparison to the sulfonylurea plus metformin group (+2%; $p = 0.017$).

One 24-week trial in 246 patients investigated the combination therapy of repaglinide (0.5–4.0 mg) and pioglitazone (30 mg) [62]. The combination was significantly more effective in lowering HbA1c or fasting plasma glucose values than both components alone.

Dorkhan *et al*. investigated the effects of pioglitazone in triple oral therapy with metformin and insulin secretagogues [63]. Unfortunately it was not a placebo-controlled trial, but the addition of pioglitazone reduced HbA1c by 1.5 % (baseline 7.8%; $p < 0.001$).

A 42-week triple-therapy study was reported by Charpentier *et al*., where pioglitazone or placebo was added to therapy in patients inadequately controlled by metformin and sulfonylurea [64]. Change in HbA1c from baseline was -0.90% in the pioglitazone group and +0.28% in the placebo group ($p < 0.001$). In total, 65% in the

Table 4. Glycemic efficacy of pioglitazone in combination with other oral antidiabetic drugs.

Study	Therapies and daily dosage	Patients (n)	Duration (weeks)	Baseline HbA1c (mean, %)	HbA1c change (mean, %)	FPG change (mean, mmol/l)	Ref.
Pio plus MF							
Charbonnel *et al.*	MF + pio 15–45 mg	317	104	8.7	-0.89	-1.8*	[58]
	MF + gliclazide 80–320 mg	313		8.5	-0.77	-1.1*	
Einhorn *et al.*	MF + pio 30 mg	168	16	9.9	-0.83‡	-2.1‡	[57]
	MF + Pl	160		9.8	+0.2‡#	-0.3‡#	
Derosa *et al.*	MF + pio 15 mg	48	52	8.2	-1.4	-1.2	[59]
	MF + rosi 4 mg	48		8.1	-1.3	-1.0	
Pio plus SU							
Hanefeld *et al.*	SU + pio 15–45 mg	319	52	8.8	-1.21	-2.2	[61]
	SU + 850–2550 mg MF	320		8.8	-1.35	-2.3	
Charbonnel *et al.*	SU + pio 15–45 mg	319	104	8.8	-1.16	-1.9	[58]
	SU + MF 850–2550 mg	320		8.8	-1.03	-2.0	
Kipnes *et al.*	SU + 15 mg pio	184	16	10.0	-0.8	-1.9	[60]
	SU + pio 30 mg	189		9.9	-1.2§	-2.9§	
	SU + Pl	187		9.9	+0.1	+0.3	
Ceriello *et al.*	SU + pio 15–45 mg	105	52	8.7	-1.25	-2.2	[72]
	SU + MF ≤2550 mg	95		8.7	-1.46	-2.2	
Pio plus Rep							
Jovanovic *et al.*	Pio 30 mg	62	24	9.1	+0.3	-1.0	[62]
	Rep 0.5–4.0 mg	61		9.0	-0.2	-1.9	
	Pio 30 mg + rep 0.5–4.0 mg	123		9.3	-1.76¶	-4.6¶	

**p < 0.001 for pioglitazone versus gliclazide; ‡p ≤ 0.05 for pioglitazone versus placebo; §p ≤ 0.05 versus other groups; ¶p < 0.001 versus other groups; #Estimated from a graph.*
FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; MF: Metformin; Pio: Pioglitazone; Pl: Placebo; Rep: Repaglinide; Rosi: Rosiglitazone; SU: Sulfonylurea.

pioglitazone group in comparison with 10% on placebo reached an HbA1c target less than 7% ($p < 0.001$).

Combination therapy with insulin

Since insulin monotherapy is not always adequate to control glucose metabolism in patients with Type 2 diabetes, pioglitazone was added to insulin therapy in poorly controlled patients. In a placebo-controlled, double-blinded trial, pioglitazone 15 and 30 mg or placebo were randomized for 16 weeks to patients on stable insulin regimens for ≥30 days [65]. HbA1c decreased by 1.0% in the pioglitazone 15 mg group and 1.26% in the pioglitazone 30 mg group, respectively ($p = 0.01$ for comparison with baseline and placebo). The proportion of patients who had greater than 25% reduction in their insulin dose was 2.1% among placebo, 3.7% among pioglitazone 15 mg and 16.0% among pioglitazone 30 mg treated patients.

Mattoo and coworkers investigated the effect of the addition of pioglitazone 30 mg to insulin therapy in a placebo-controlled 6-month trial (n = 289) [66]. First, insulin therapy was intensified for 3 months and afterwards patients were randomized. The mean decrease in HbA1c was 0.69% in the pioglitazone group ($p < 0.002$ for comparison with baseline and placebo). In contrast to the aforementioned study [65], mean baseline Hba1c was lower in this investigation (8.85 vs 9.80%).

Another study compared the effects of added pioglitazone 30 or 45 mg in patients (n = 690) with Type 2 diabetes, poorly controlled with insulin therapy [67]. The duration of the trial was 24 weeks, it was not placebo controlled and the mean baseline HbA1c was 9.78%. The mean decrease in HbA1c was 1.17% for pioglitazone 30 mg and 1.46% for the 45 mg group ($p \leq 0.05$ for comparison of both dosages versus baseline and for comparison between groups). Furthermore, insulin dosages

decreased significantly from baseline in both groups (-6.5% and -10.5%, respectively; $p \leq 0.05$ vs baseline).

The most commonly reported side effects in the pioglitazone groups were hypoglycemia (up to 63% of patients), whereas severe hypoglycemia was very rare (<1.0%). Peripheral edemas were reported in up to 15% of patients and mean bodyweight gain was up to 4 kg.

Postprandial hyperglycemia

In current practice, HbA1c and fasting blood glucose are primarily determined when assessing glycemic control. However, recently, postprandial (hyper)glycemia is becoming more important, since we are in a postprandial or postabsorptive state for the majority of the time and postprandial hyperglycemia contributes to HbA1c [68,69]. In addition, postprandial hyperglycemia is a better predictor for cardiovascular mortality than fasting plasma glucose [70]. Pioglitazone was shown to reduce postprandial hyperglycemia, measured by the AUC of plasma glucose during an oral glucose tolerance test [35,50,71,72]. The reduction in mean incremental $AUC_{0–3h}$ of plasma glucose was significantly greater in patients treated with pioglitazone (-5.0 mmol/l*h) than in those treated with gliclazide (-0.4 mmol/l*h; $p < 0.001$) [35]. Likewise, the reduction in mean incremental $AUC_{0–3h}$ of plasma glucose in the pioglitazone group (-5.0 mmol/l*h) was significant in comparison with the metformin group (-2.3 mmol/l*h; $p < 0.001$).

Gastaldelli and colleagues investigated the effect of pioglitazone on postprandial glucose in a mixed meal [30]. Mean plasma glucose during the mixed meal (360 min) decreased significantly in the pioglitazone group in comparison with placebo ($p = 0.02$).

Lipid metabolism

In placebo-controlled monotherapy trials, pioglitazone lowered triglyceride levels by approximately 16% [45,47,48] in the 45 mg dosage and elevated HDL-cholesterol by 15.8–20% (**Table 5**) [45,47,48]. Total cholesterol (TC) and LDL-cholesterol levels slightly increased in the pioglitazone groups but were not significantly different from those in the placebo groups.

Goldberg and colleagues compared pioglitazone and rosiglitazone head-to-head regarding the lipid effects [26]. Both TZDs increased TC as well as LDL cholesterol, but mean changes from baseline to end (28 weeks) were significantly less with pioglitazone (TC +5.7 vs +15.9% with rosiglitazone; $p < 0.001$, LDL-cholesterol +15.7 vs +23.3%; $p = 0.002$). Furthermore, HDL-cholesterol increased more (+14.9 vs +7.8%; $p < 0.001$) with pioglitazone, TGs decreased with pioglitazone (-12.0%) while increased with rosiglitazone (+14.9%; $p < 0.001$). Mean LDL particle size was increased with both agents, but the effect observed with pioglitazone was significantly greater ($p = 0.005$ between treatments).

Derosa and colleagues compared pioglitazone and rosiglitazone in combination with metformin treatment for the duration of 1 year. The results were analogous to those reported above, but combination therapy (pioglitazone + metformin) also lowered TC as well as LDL-cholesterol (TC -9.8%; LDL-cholesterol -6.9%; $p < 0.05$ vs baseline and rosiglitazone-treated group) [59].

Table 5. Lipids in placebo-controlled, monotherapy trials.

Study	Dose (mg)	Patients (n)	Duration (weeks)	ΔTotal-C (%)	ΔLDL (%)	ΔHDL (%)	ΔTriglycerides (%)	Ref.
Aronoff *et al.*	7.5	79	26	+0.8	+3.5	+7.1*	-17.2	[45]
	15	80		+2.8	+4.7	+12.3*	-20.3	
	30	79		+2.2	+2.8	+10.3*	-13.7	
	45	85		+5.8	+6.8	+16.9*	-16.1	
	Pl	76		+3.0	+2.2	+6.2*	-3.8	
Rosenblatt *et al.*	30	101	23	+3.0¶	+4.8¶	+15.8‡	-16.6§	[47]
	Pl	96		0.0¶	+5.0¶	+3¶	+1.8	
Herz *et al.*	30	99	16	+4	+7	+16§	-5	[48]
	45	99		+1¶	+2¶	+20‡	-16‡	
	Pl	99		+2¶	+3¶	+9	+1¶	

**p ≤ 0.05 for study-end vs baseline; ‡p < 0.01 for pioglitazone vs placebo; §p < 0.05 for pioglitazone vs placebo; ¶Estimated from a graph.*
HDL: High-density lipoprotein; LDL: Low-density lipoprotein; Pl: Placebo; Total-C: Total cholesterol.

Cardiovascular effects

Since PPARγ are expressed in all cell types involved in vascular injury, it seems unsurprising that agonists of these receptors might have an impact on atherogenesis and, therefore, cardiovascular complications.

Experimental data

In an animal model of chronic heart failure, pioglitazone was examined in comparison with placebo [73]. In mice with extensive anterior myocardial infarction, pioglitazone treatment attenuated the expression of proinflammatory cytokines such as TNF-α or transforming growth factor-β1. Furthermore, left ventricular cavity dilation and dysfunction were significantly reduced by pioglitazone.

Another study investigated the effect of pioglitazone on thrombotic response after a photochemical injury of the carotid artery in insulin resistant, obesity-prone mice in comparison with glipizide or placebo [74]. Pioglitazone treatment significantly ($p < 0.05$) prolonged time to thrombotic occlusion in comparison with glipizide and placebo treatment. Platelet activation was found to be an important factor, since pioglitazone significantly decreased platelet p-selectin expression.

Clinical-experimental data

In humans, TZDs were demonstrated to suppress the expression of adhesion molecules [75], and reduce proinflammatory cytokines as soluble CD40 ligands [76], as well as inflammatory markers such as C-reactive protein [77].

Recently, endothelial progenitor cells, which seem to play a critical role in maintaining endothelial function because they are involved in processes of vascular repair and vasculogenesis, were shown to be increased by pioglitazone treatment [78].

Endothelial dysfunction, an important early step in atherogenesis [79], was shown to be improved by pioglitazone therapy [80,81]. In patients with proven coronary artery disease and newly diagnosed diabetes mellitus Type 2, pioglitazone (30 mg) significantly improved endothelial function measured by pulse wave analysis independently of glycemia [80].

First, in a Japanese study [82] and followed by a German study [83], pioglitazone was found to significantly decrease carotid intima-media thickness (CIMT) (-0.054 to -0.084 mm in 24 weeks), which has been indicated as a surrogate parameter for future cardiovascular events [84]. Mazzone and colleagues investigated the effect of pioglitazone on CIMT in a long-term randomized trial (72 weeks, 462 patients with Type 2 diabetes) in comparison with glimepiride [85]. Pioglitazone slowed progression of CIMT (-0.001 mm) in comparison with glimepiride (+0.012 mm; $p = 0.02$).

Marx *et al.* investigated the effect of pioglitazone in neointima volume in 50 nondiabetic patients after coronary artery stent implantation [86]. In this placebo-controlled, double-blind study, pioglitazone reduced neointima volume within the stented segment compared with placebo after 6 months (2.3 ± 1.1 mm³/mm in the pioglitazone group vs 3.1 ± 1.6 mm³/mm in the placebo group; $p = 0.04$). The degree of stenosis 6 months after stenting was $22.1 \pm 12.7\%$ of the luminal diameter in the pioglitazone group and $37.3 \pm 24.2\%$ in the placebo group ($p = 0.01$).

Clinical data

The full clinical implications of the above data were seen in the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) trial, a prospective, randomized, placebo-controlled trial in 5238 patients with Type 2 diabetes over a period of 34.5 months (**Box 1**) [87]. All patients had to have Type 2 diabetes and evidence of extensive macrovascular disease for inclusion in the study. Pioglitazone treatment was associated with a 10% reduction in the Kaplan–Meier estimates for primary composite end point (death from any cause, nonfatal myocardial infarction – including silent myocardial infarction, stroke, acute coronary syndrome, leg amputation, coronary revascularisation or revascularisation of the leg) that was not significant, possibly due to inclusion of revasculizing procedures in the primary end point. The 16% reduction in the secondary end point (death from any cause, nonfatal myocardial infarction – excluding silent myocardial infarction and stroke) by pioglitazone in comparison with placebo was significant ($p = 0.027$).

In a prespecified subgroup analysis in 2445 patients with myocardial infarction 6 months or earlier previous to randomization, pioglitazone significantly reduced 28% ($p = 0.045$) hazard ratio for fatal or nonfatal myocardial infarction [88]. Likewise, in patients with previous stroke ($n = 984$), pioglitazone reduced fatal or nonfatal stroke by 47% ($p = 0.0085$) [89]. As a consequence of such substudies, it can be stated that in patients without previous atherothrombotic event, which were of substantially

Box 1. PROactive study overview.

Aim:

- Can pioglitazone reduce macrovascular morbidity and mortality in high-risk patients with Type 2 diabetes?

Methods:

- 5238 patients (66% male) with Type 2 diabetes

Inclusion:

- Age 35–75 years
- HbA1c >6.5%
- Evidence of extensive macrovascular disease before recruitment (myocardial infarction or stroke ≥6 months before entry, percutaneous coronary intervention or coronary artery bypass surgery ≥6 months before entry, acute coronary syndrome ≥3 months before recruitment, objective evidence of coronary artery disease, obstructive arterial disease in the leg)
- Prospective, double-blinded, randomized, placebo-controlled trial with pioglitazone, titrated from 15–45 mg

Results:

- Average time of observation: 34.5 months

Primary end point:

- Composite of all-cause mortality, non-fatal myocardial infarction – including silent myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical interventions in the coronary or leg arteries and amputations above the ankle
- HR 0.90 (95% CI: 0.80–1.02; p = 0.095)

Secondary end point:

- Composite of all-cause mortality, nonfatal myocardial infarction and stroke): HR 0.84 (95% CI: 0.72–0.98; p = 0.027)

CI: Confidence interval; HR: Hazard ratio.

lower risk, pioglitazone did not prevent vascular disease in the PROactive trial. This seems of importance since it challenges the concept of risk factor treatment and suggests that TZDs do not reduce vascular events in populations at lower risk, despite equal metabolic effects. Statins, by contrast, were shown to reduce cardiovascular risk independently of the initial LDL cholesterol in a linear pattern in primary as well as secondary prevention [90].

A late-breaking meta-analysis of randomized trials with piogliazone evaluated the effect of pioglitazone on ischemic cardiovascular events [91]. A total of 19 trials (including the PROactive trial) with 16,390 patients and a duration of between 4 months and 3.5 years were analyzed. The occurrence of the composite endpoint of death, myocardial infarction and stroke was reduced by 18% (hazard ratio [HR] 0.82, [0.72–0.94], p = 0.005) in the patient group receiving pioglitazone.

Other effects

Nonalcoholic steatohepatitis

Nonalcoholic steatohepatitis (NASH) is a chronic liver condition that may progress in up to 20% of patients to liver cirrhosis. Insulin resistance and obesity represent the most important risk factors for the development of nonalcoholic fatty liver disease or, furthermore, NASH.

A pilot study was conducted with pioglitazone (30 mg) in 18 patients with biopsy-proven NASH [92]. After 48 weeks, serum alanine aminotransferase values fell to normal in 72% of patients and histological features of steatosis significantly improved from baseline ($p < 0.05$).

The results of the pilot study were confirmed in a placebo-controlled, randomized trial in 55 patients with impaired glucose tolerance or diabetes mellitus Type 2 and biopsy-proven NASH [93]. Standard therapy in both groups was hypocaloric diet. Liver fat content decreased by 54% from baseline to 6 month in the pioglitazone group ($p < 0.001$), whereas it was unchanged in the placebo group. Alanine aminotransferase levels were reduced by 58% in patients obtaining pioglitazone as compared with 34% ($p < 0.001$) in patients obtaining placebo. The combined necroinflammation score improved in 85% of patients in the pioglitazone group as compared with 38% ($p < 0.001$) in the placebo group. Furthermore, pioglitazone improved significantly hepatic insulin sensitivity (48 vs 14%; p = 0.008).

Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is an endocrine disorder with a frequency of 5–8% among reproductive-aged women. It is characterized by long-standing oligo- or amenorrhea, hirsutism and/or hyperandrogenism and other endocrine disorders. Although the exact pathomechanisms have not yet been elucidated, hyperinsulinism is observed in the majority of affected patients [94].

A randomized, placebo-controlled study in 40 premenopausal women with PCOS was conducted, where pioglitazone (30 mg) was administered for 3 months [95]. Fasting serum insulin levels declined by 22% in the pioglitazone group ($p < 0.02$ vs placebo), as did the AUC of insulin after a glucose load ($p < 0.02$ vs placebo). A total of 41.2% of the patients treated with pioglitazone had laboratory and clinical signs of normal cycles, in comparison with 5.6% in the placebo group ($p < 0.02$).

Ortega-Gonzàlez and colleagues compared pioglitazone with metformin, the most widely used drug to treat women with insulin resistance

and PCOS [96]. Both drugs lowered fasting serum insulin as well as the area under the curve for insulin after an oral glucose load in a comparable manner. Furthermore, hirsutism and serum concentrations of free testosterone declined to a similar extent in both treatment groups. In this small study pioglitazone was shown to be as effective as metformin in the treatment of insulin resistance in women with PCOS.

However, further studies have to be performed to confirm the beneficial effects of piogitazone on metabolic parameters, ovulatory performance and also to demonstrate improvement of fertility.

Safety & tolerability

In general, pioglitazone was well tolerated in monotherapy and in combination with sulfonylureas, metformin, repaglinide and insulin. At least one adverse event during treatment with pioglitazone 45 mg was reported in approximately 14–76% in contrast to 7–85% of patients receiving placebo.

The most frequent adverse event reported was hypoglycemia (more than 5% of patients), which occurred only in combination with sulfonylurea, repaglinide or insulin. In placebo-controlled monotherapy trials, the most commonly reported adverse events were upper respiratory tract infections (15.2% in pioglitazone recipients), headache (12.5%), influenza-like symptoms (9%), edema (3–4%) and urinary tract infections (2.5%) [45]. There were no significant differences in the frequency of these adverse events between the pioglitazone and placebo group except edema (see below).

Liver toxicity

Since the withdrawal of troglitazone from the market owing to drug-related liver toxicity, TZDs have been closely monitored regarding liver parameters. In the PROactive study, the alanine transferase (ALT) levels in pioglitazone-treated patients were slightly reduced (-5%) in contrast to a small rise in the placebo group (+8%). Increases in the ALT levels above three-times the upper limit of normal occurred in 20 pioglitazone recipients and 33 patients with placebo, respectively. No cases of acute liver toxicity were found in this study.

Kawamori and colleagues designed an observational study to confirm the hepatic safety in Type 2 diabetic patients [97]. In 28,008 patient-years, no cases of hepatic failure were reported and neither temporal nor dose relations were found between pioglitazone and ALT abnormalities.

Weight gain

In placebo-controlled monotherapy trials (6 months), pioglitazone 30 mg daily was associated with weight gain of 0.8–1.3 kg in contrast to a slight weight reduction in the placebo group (-1.1 to -1.3 kg) [35,45,46]. In combination with other oral antidiabetic agents (metformin and sulfonylurea) weight gain was between 2.5–3.7 kg [58,60,61].

Mean increase in bodyweight in the PROactive trial was 3.6 kg in comparison with a decrease of 0.4 kg in the placebo group ($p < 0.0001$) after almost 3 years [87].

Edema & congestive heart failure

TZDs have been found to induce fluid retention, which can lead to peripheral edema. The mechanisms of glitazone-induced edema are not yet fully elucidated. Guan and colleges demonstrated that PPARγ is most abundant in the collecting duct of the nephrone and, by activation with glitazones, renal salt absorption is enhanced [98].

In clinical trials edema was reported in 3–8.7% of subjects in monotherapy trials [35,45,46] and in 7.0–10.7% of patients in combination with metformin or sulfonylurea [58,60,61], is in contrast to 0–4% of patients on placebo or other hypoglycemic agents. The most important data regarding heart failure as a result of fluid retention derive from the PROactive trial, since the average time of observation was 34.5 months [87]. The heart failure rate was increased by pioglitazone (11%) in comparison with placebo (8%); however, mortality due to heart failure did not differ between the two groups (1% in both groups).

Therefore, in the USA, pioglitazone is not recommended in patients with congestive heart failure New York Heart Association Functional Classification (NYHA) III and IV, and patients should be observed for signs of heart failure. In the EU pioglitazone is contraindicated in congestive heart failure NYHA I-IV.

A very recent publication from the PROactive trial analyzed this topic extensively [99]. Among patients who developed severe heart failure during the study period, pioglitazone treatment neither increased the risk for death primarily caused by heart failure, nor was it associated with increased subsequent all-cause mortality (26.8% in the pioglitazone group vs 34.3% in the placebo group; HR: 0.71; 95% confidence interval [CI]: 0.454–1.111; $p = 0.1338$).

Furthermore, patients who developed severe heart failure had fewer subsequent events of the primary composite end point (see PROactive

study overview) when they were randomized to the pioglitazone group (71 of 149 patients [47.7%], 62 of 108 patients [57.4%] in the placebo group, HR: 0.72; 95% CI: 0.512–1.013; p = 0.059). Likewise, fewer patients in the pioglitazone group had events of the secondary composite end point (see PROactive study overview) (52 of 149 [34.9%]) than in the placebo-treated group (51 of 108, [47.2%]; HR: 0.64; 95% CI: 0.436–0.946; p = 0.025) after onset of severe heart failure.

Hematocrit

A small decrease in hematocrit and hemoglobin can be observed in patients treated with pioglitazone. The decline in clinical studies was between 2 and 4% [23]. The changes occur in the first 3 months of therapy and remain stable thereafter [23]. The reasons, therefore, are not clearly established. The decrease in hematocrit may be related to hemodilution [100,101]. However, elevation in total body water was not confirmed by all studies [102]. Berria *et al.* suggested a possible suppressive effect on bone marrow as cause for the decrease in hematocrit [102].

Bone mass & fractures

After the A Diabetes Outcomes Progression (ADOPT) trial, where rosiglitazone treatment was accompanied by an increased number of peripheral fractures in women, pioglitazone also came under suspicion for causing bone loss in diabetic patients [103]. The literature on *in vitro* as well as *in vivo* data regarding the effects of TZDs and in particular pioglitazone is rare and inconclusive. Gimble and colleagues reported an induction of adipogenesis in bone marrow stromal cells *in vitro*, suggesting adipocyte differentiation of this precursor [104]. Okazaki and coworkers confirmed this in part, but could also demonstrate an inhibition of the osteoclast-like cell formation suggesting a suppression of bone resorption in diabetic patients by TZDs [105].

However, TZDs (mainly rosiglitazone) were reported to cause bone loss in rodent models [106,107].

An observational study comparing 69 Type 2 diabetic patients using TZDs (troglitazone, pioglitazone and rosiglitazone) with 597 patients on other antidiabetic medication, revealed a significantly greater bone mineral density loss in TZD-treated female patients [108]. In men no difference was observed. Recently, Takeda released data from 8100 patients treated with pioglitazone in comparison with more than 7400 patients treated with a comparator, regarding frequency of bone fractures [109]. The fracture incidence was 1.9 per 100 patient-years in the pioglitazone group, and 1.1 in the comparator group. These results, of course, have to be proven in randomized, controlled trials. The PROactive trial, however, provides no further information to clarify this question [87].

Carcinogenesis

Carcinogenicity studies with high doses (approximately 14-times recommended human oral dose) in rodents demonstrate increased incidence of urinary bladder tumors [23]. In the PROactive trial, no difference in tumor incidence could be observed between the two treatment groups [87]. However, there was an imbalance in some subtypes of cancer: breast cancer was diagnosed in three and 11 patients (p = 0.034) in the pioglitazone and placebo group, respectively. Regarding urinary bladder tumors, 14 cases in the pioglitazone versus six cases in the placebo group (p = 0.069) were registered. Data were intensively analyzed by an extern committee. A total of 11 cases (eight from the pioglitazone group, three on placebo) that occurred during 1 year after randomization were considered to be not plausibly related to therapy. Some of the other cases had known risk factors and the committee concluded that the imbalance is improbably related to pioglitazone treatment.

The impact of TZDs on tumorgenesis or growth has to be further elucidated because some data indicate potential direct inhibitory effects on various carcinoma cell types. In addition, insulin resistance and hyperinsulinemia increase the risk for carcinoma [110] and a reduction in these risk factors might have an impact on carcinoma incidence.

Pharmacoeconomic studies

There are some studies in various countries evaluating the cost–effectiveness of pioglitazone treatment. Neeser and colleagues investigated the cost–effectiveness of pioglitazone combination therapy in Type 2 diabetic patients [111]. They used the Markov model that was adapted for Type 2 diabetic patient management. Results were reported as incremental costs per life-year gained (LYG), and costs of diabetes medications as well as treatment costs of diabetes complications were included in the lifetime treatment costs. After discounting costs and life expectancy at 5% per year, the incremental cost–effectiveness ratio was €47,636 per LYG for pioglitazone in

Executive summary

- Type 2 diabetes mellitus is a major health burden with rapidly growing prevalence.
- Insulin resistance and β-cell dysfunction play an important role in the pathogenesis of Type 2 diabetes.

Mechanisms of action

- Pioglitazone is an activator of peroxisome proliferator-activated receptor (PPAR)–γ.
- PPARγ regulates genes involved in glucose homeostasis, fatty acid uptake and storage and the processes of inflammation.
- Pioglitazone improves both pathogenetic pathways of Type 2 diabetes mellitus: insulin resistance and β-cell dysfunction.

Pharmakokinetics, pharmacodynamics & metabolism

- The bioavailability of pioglitazone after oral administration is approximately 83% with a peak concentration after approximately 1.5 h.
- Pioglitazone is highly bound to plasma proteins (>97%) and metabolized in the liver via cytochrome P450 (CYP), mainly CYP2C8, CYP2C9 and CYP3A4.
- The metabolites are mainly excreted in bile and eliminated in feces; up to 30% of metabolites can be found in the urine.
- Pioglitazone improves peripheral and hepatic insulin sensitivity and pancreatic β-cell function.
- Dyslipidemia in diabetic patients improves in terms of triglyceride-lowering and HDL-raising by pioglitazone treatment.
- Adipocyte differentiation and bringing the cell at a state active for storage is favored by pioglitazone. A shift of fat distribution from visceral to subcutaneous adipose depots can be found.

Clinical efficacy

- Clinical efficacy regarding blood glucose regulation was demonstrated in several trials and more than 1000 patients were included in placebo-controlled montherapy trials.
- HbA1c was lowered by 0.3–1.05% depending on the dose of pioglitazone in placebo-controlled monotherapy trials.
- Several trials proved efficacy of pioglitazone in combination with metformin, sulfonylurea, repaglinide, acarbose or insulin.
- The PROactive trial demonstrated a significant 16% risk reduction in the composite of all-cause mortality, nonfatal myocardial infarction and stroke by pioglitazone therapy.

Safety & tolerability

- The most important adverse event of pioglitazone is edema, which has been reported in up to 11% of patients treated.
- In the PROactive trial heart failure rate was increased in the pioglitazone group, while mortality due to heart failure was not.
- Weight gain of approximately 0.8 kg per year of treatment is evident.
- Recently, an increase in the incidence of peripheral fractures in women by thiazolidinediones has been reported.

combination with metformin versus sulfonylurea/metformin, and €19,745 per LYG for pioglitazone/sulfonylurea versus metformin/sulfonylurea. The question of what is an acceptable cost–effectiveness ratio is not easy to answer; however, a value of US$60 000 was used previously [112] as a cut-off for 'good value for money'.

In a Canadian study, pioglitazone as first-line treatment was evaluated compared with glibenclamide, metformin and diet and exercise [113]. Six complications of Type 2 diabetes mellitus were incorporated: hypoglycemia, acute myocardial infarction, stroke, lower extremity amputation, nephropathy and retinopathy. The discounted incremental cost per LYG was CAN$54,000 compared with metformin, CAN$42,000 compared with glibenclamide and CAN$27,000 compared with diet and exercise. A Swedish study showed incremental cost per LYG (discounted at 3%) of pioglitazone combination therapy compared with other combination therapies between 42,401 and 146,196 Swedish crowns [114]. In a recent study, Tilden and colleagues compared the costs and benefits of pioglitazone versus rosiglitazone in combination with metformin [115]. The model was calculated based on a comparison trial of rosiglitazone versus pioglitazone [26]. The lifetime healthcare costs per patients were estimated to be GB£10,299 for rosiglitazone and GB£9585 for pioglitazone.

Expert commentary & future perspective

Given the growing prevalence of Type 2 diabetes mellitus, the market for pioglitazone will rise strongly in coming years. Pioglitazone is currently approved in the USA as an adjunct to diet and exercise for use as monotherapy as well as in combination with sulfonylureas, metformin or insulin. In Europe, pioglitazone is available as monotherapy in patients with contraindication or known hypersensitivity to metformin. Pioglitazone can also be administered in combination with insulin or sulfonylureas in patients for whom metformin is inappropriate owing to contraindications or intolerance. Several diabetes

associations currently adapt their guidelines and clearly recommend TZDs as second-line drug therapy after metformin or first-line therapy in patients with metformin incompatibility, whereas sulfonylureas in the same time are placed in a later position. There is much evidence for the efficacy and safety of pioglitazone that justifies this re-evaluation. Furthermore, it has to be kept in mind that pioglitazone is the only TZD that was shown in a prospective, randomized, placebo-controlled trial (the PROactive study) to have beneficial cardiovascular effects. This fact becomes even more important in light of the recent debate, whether rosiglitazone is possibly accompanied by increased cardiovascular mortality [116].

Besides the well-known effects, TZDs exhibit further effects that have to be elucidated. Further investigations in different areas showed that pioglitazone or related compounds may have many more indications in the future. Since the anti-inflammatory effects are well established, pulmonary indications such as chronic obstructive pulmonary disease or asthma bronchiale, or gastrointestinal indications such as chronic inflammatory bowel disease, were discussed as possible domains for TZD treatments in the future.

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