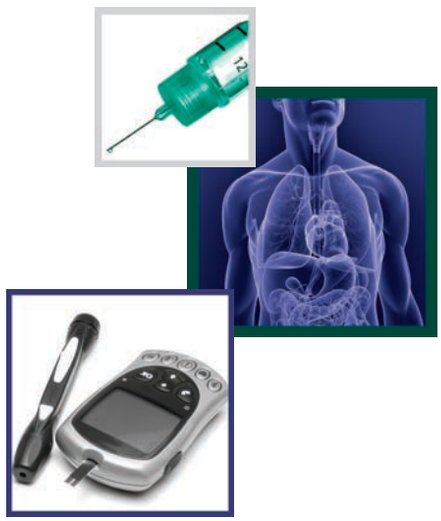

Will PPAR-γ agonist therapy still have a role in diabetes management in 2013?

George Grunberger*

Practice Points

- Thiazolidinediones, as mono- or combination therapy, improve Type 2 diabetes control (as assessed by lowering glucose and glycated hemoglobin levels) at least as well as any other oral agents available to the clinician today.
- Drugs in this class suffer from several undesirable clinical side effects such as fluid retention and a decrease in bone mass. In some patients, these can lead to peripheral edema, congestive heart failure, hemodilution, macular edema and nonosteoporotic bone fractures.
- Despite improvement in markers of cardiovascular risk as well as of carotid artery intima-media thickness, long-term cardiovascular outcomes data for thiazolidinediones (and for all other antidiabetic agents) remain uncertain.
- Due to concerns of increased adverse ischemic myocardial events caused by rosiglitazone, severe restrictions have been put on its use.
- Concern has been raised in the media over several reports of statistically significant, but probably clinically irrelevant, increases in the incidence of bladder cancers in men using large doses of pioglitazone for a long period of time.
- The current regulatory and legal environment makes it unlikely that clinicians will initiate thiazolidinediones in patients requiring intensification of their treatment.
- There is hope that a new generation of nonagonist ligands targeting PPAR-γ – which would retain the antidiabetic properties but not the undesirable effects of thiazolidinediones – will be introduced into clinical practice in the future.

SUMMARY Thiazolidinediones have been used for treatment of Type 2 diabetes since the late 1990s. They act as ligands for PPAR-γ, activating hundreds of genes in many tissues. Their actions result in favorable (insulin-sensitizing) and unfavorable (fluid retention, weight gain and decrease in bone mass) effects. This article describes the dilemma encountered by clinicians contemplating the use of these agents to improve diabetes control in the current

*Grunberger Diabetes Institute, Internal Medicine & Molecular Medicine & Genetics, Wayne State University School of Medicine, 43494 Woodward Avenue, Suite 208, Bloomfield Hills, MI 48302, USA; Tel.: +1 248 335 7740; Fax: +1 248 977 4335; grunberger@gdi-pc.com

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environment, which is currently focused on 'protecting' the patient from the putative harm ascribed to rosiglitazone (ischemic myocardial events) and pioglitazone (bladder cancer) rather than the benefits of these therapies.

With all the excitement that greeted the arrival of PPAR-γ agonists on the diabetes scene in the mid-1990s, it would have seemed inconceivable that we would even pose the question of the very survival of these drugs just 15 years later. Yet, this is where we stand today. With the demise of troglitazone, the ban and/or severe restrictions placed on rosiglitazone use, and the current legal and regulatory onslaught of potentially damaging publicity on the fate of pioglitazone, we have to ask: is there still a place for PPAR-γ agonists in the therapeutic armamentarium for patients with Type 2 diabetes?

This article is not intended to be an exhaustive review of this class of antidiabetic drugs. Thousands of manuscripts have been devoted to that subject. Rather, it will try to briefly summarize the history of the clinical use of these medications and review how we got to the current situation. It will offer a glimpse into the mind of a clinician attempting to decide whether to employ them in his/her patients in an attempt to optimize glucose management in 2013 **(Figure 1)**. Consider a case of an otherwise healthy 52-year-old man ('John') with a 2-year history of Type 2 diabetes, currently treated with metformin, 1000 mg twice daily, and latest HbA1c of 7.5%. Would one prescribe a thiazolidinedione (TZD), as would be entirely appropriate given the latest American College of Endocrinology (ACE)/American Association of Clinical Endocrinologists (AACE) or American Diabetes Association/European Association for the Study of Diabetes algorithms [1,2]?

TZDs (specifically ciglitazone) were discovered empirically as glucose-lowering compounds through the work mainly carried out by Takeda (Osaka, Japan) and Sankyo (Tokyo, Japan) [3,101–103] in the 1970s, long before the PPAR-γ hypothesis was formulated [4]. Pioglitazone was eventually selected as a therapeutic candidate in 1985; the PPAR-γ hypothesis saw the light a decade later. It was not until 1997 that the first drug in this class, troglitazone (Rezulin®, Warner–Lambert, PA, USA), was approved in the USA, in a contentious but fastest-ever approval process by the US FDA for a diabetes drug [201].

Troglitazone was touted as a revolutionary way to treat Type 2 diabetes, the first drug to attack one of the principal pathophysiological targets, insulin resistance [201]. Indeed, due to its unique mechanism, it was included in one of the arms of the NIH-funded Diabetes Prevention Program [5].

Just 2 months after its launch in the UK the manufacturer (Glaxo-Wellcome, Brentford, UK) withdrew troglitazone (Romozin®) due to the US reports of idiosyncratic hepatic reactions leading to liver failure and some deaths. "The drug's risks outweigh its benefits", stated the British Medicines Control Agency [6].

In October 1997, the FDA received 35 reports of liver failure in patients on troglitazone (Rezulin); by November the number rose to 135 patients and six deaths. When an otherwise healthy participant in the Diabetes Prevention Program on Rezulin died in May 1998 after liver failure and liver transplant, the National Institute of Diabetes and Digestive and Kidney Diseases discontinued the troglitazone arm of the study [202]. In February 1999, the number of deaths subsequent to liver failure in patients on troglitazone exceeded 100, and an additional 738 reported other serious adverse reactions. The FDA estimated that patients on troglitazone incurred a 1200-fold increased risk of hepatic failure than patients not taking it [201]. By the end of 1999, 215 deaths had been reported in association with the use of troglitazone (the FDA press office confirmed 85 cases of liver failure with 58 deaths) [201]. It was not until March 2000 that the FDA agreed to remove troglitazone from the US market, citing the availability of 'safer' alternative TZDs, rosiglitazone and pioglitazone, both marketed since 1999 (as Avandia®, GlaxoSmithKline, WV, USA and Actos®, Takeda, Japan, respectively) [203].

So, how have these two 'safer' alternative drugs fared? Both drugs were approved to improve glycemic control in patients with Type 2 diabetes who failed initial treatment with lifestyle modifications. Data gathered from large randomized, double-blind prospective Phase III trials confirmed that they were capable of lowering glucose and HbA1c levels more than placebo, and typically to the same degree as the then-marketed biguanides and sulfonylureas. Furthermore, they could be combined with either or both of those therapeutic modalities, owing to their complementary mechanism of action. Again, the goal here is not to review the data of those trials

proving the efficacy of TZDs in improving diabetes control. That issue has been settled and no one questions the ability of these drugs to lower glucose. For those readers who wish to review the results of the studies leading to regulatory approvals of Avandia and Actos, several succinct reviews have been published previously [7–9]. The issue at hand is the potential utility of these agents in our future therapeutic armamentarium, now that we have both long-term data associated with the use of rosiglitazone and pioglitazone as well as several new classes of drugs approved for patients with Type 2 diabetes.

A body of exciting evidence had accumulated for the use of both rosiglitazone for diabetes prevention and for durability of initial monotherapy [10,11], and pioglitazone for diabetes prevention and for potentially reducing the rate of cardiovascular events [12,13]. A bright future was predicted for both drugs to either prevent or delay the onset of Type 2 diabetes and possibly to ameliorate the cardiovascular risk among patients with Type 2 diabetes. The latter was an especially desired outcome given the fact that at least two thirds of these patients succumb to the consequences of cardiovascular disease [14]. The excitement was fueled by positive results of preclinical studies and by those assessing surrogate markers for cardiovascular risk (e.g., decreased inflammation, assessed by a decrease in high-sensitivity C-reactive protein, a favorable effect on NF-κB, a favorable effect on coronary and peripheral vasodilation, improved blood pressure, decreased vascular smooth muscle cell and neointimal proliferation, reduced plasma nitrotyrosine, reduced von Willebrand antigen, increased adiponectin and reduced carotid artery intima-media thickness [CIMT]) [15–18].

Investigators realized early on that, although they belong to the same therapeutic class, troglitazone, rosiglitazone and pioglitazone are not identical drugs. TZDs are all ligands for PPAR-γ, but they have varying selectivity for the receptor and in different tissues. It was revealed that there is only approximately a 25% overlap among the genes activated/inhibited by the three ligands. In a study by Sears *et al.*, 300 genes were identified to be affected by TZD, with each ligand having a unique but overlapping signature [19]. All three drugs affected only 91 genes identically. The authors noted distinct expression profiles and transcription kinetics.

PPAR agonists display distinct characteristics since, although they all contain the same

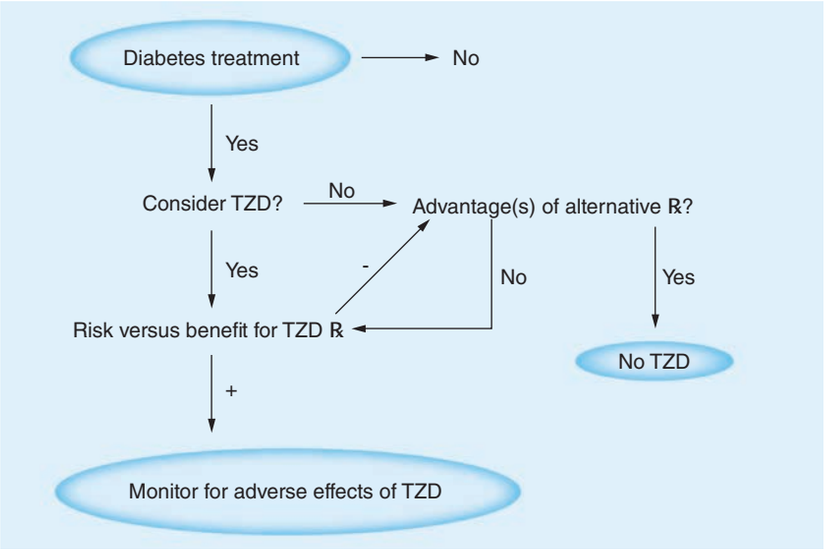

Figure 1. The clinician's thought process when considering thiazolidinediones for Type 2 diabetes.
TZD: Thiazolidinedione.

active TZD ring, they have different side chains (**Figure 2**). Thus, they differ in their pharmacological potency; the PPAR-binding affinity of rosiglitazone is 100-fold greater than that of troglitazone and over 30-times that of pioglitazone [20]. The rank order of binding affinities of the PPAR agonists (rosiglitazone > pioglitazone > troglitazone) is consistent with their dose requirements for *in vitro* stimulation of glucose transport and their antihyperglycemic activity. It was hypothesized that their effects reflect their ability to induce adipocyte differentiation, and hence to increase free fatty acid uptake in white adipose tissue. Interestingly, clinically relevant differences were clearly revealed in studies of their effects on lipid status [21].

Despite their different degrees of potency at the receptor level, all the PPAR agonists are insulin 'sensitizers' (i.e., they alleviate insulin resistance in insulin-sensitive tissues). The beneficial metabolic effects of PPAR agonist treatment of human Type 2 diabetes include lowering of glucose levels and of HbA1c, increasing insulin sensitivity and improving pancreatic islet β-cell function, increasing HDL levels and variable lowering of LDL levels, lowering of diastolic blood pressure, decreasing levels of microalbuminuria, and increasing levels of the PAI1 and tissue plasminogen activator [22].

Many of these effects are possibly interconnected. Lowering of plasma free fatty acid levels might decrease the intracellular triglyceride

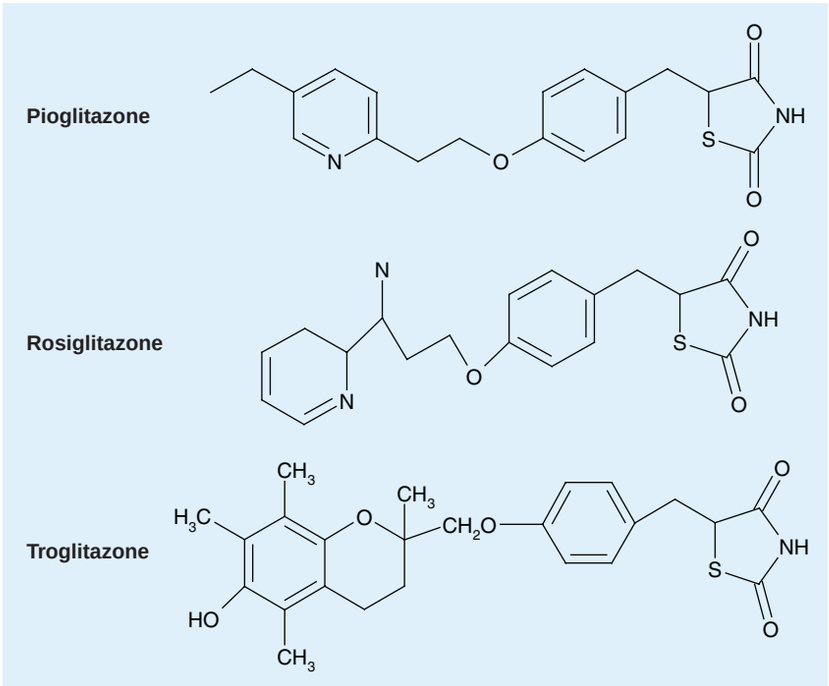

Figure 2. Structure of thiazolidinediones.

accumulation and improve 'lipotoxicity' [23] and, thus, improve the glucose metabolism in the liver, muscle and adipose tissue. This would result in improved glycemic control.

In clinical trials, all TZD agents lowered glucose levels and HbA1c to approximately the same degree, by approximately 1% [24]. Of course, as with any antidiabetic agents, a more absolute decrease in glucose levels will be noted with higher baseline HbA1c values [25]. Although there has been a dearth of head-to-head randomized control trials among antihyperglycemic drugs, most investigators believe that there is little absolute difference in the glucose-lowering abilities of major classes (e.g., metformin, sulfonylureas, TZDs and incretin analogs) [1,2,26].

The story of rosiglitazone has been a subject of many papers, TV programs, the FDA, and US Congressional hearings [204]. Briefly, the initially positive feelings about the drug (engendered by the favorable effects on cardiovascular risk factors and results of trials such as DREAM and ADOPT) were thrown into doubt by the meta-analysis of Nissen and Wolski that alleged adverse effects of rosiglitazone on cardiac event rates [27]. These allegations were supported by some [28–33,205], but not by others [34,35]. Interestingly, large-scale randomized trials did not show convincing data regarding the dangers of rosiglitazone on cardiovascular outcomes [36–39]. Regardless of actual data from randomized clinical trials, the drug was declared to be 'poison' in the court of public opinion and sentenced to a slow death, first by its being taken off the market by the EMA [206] and then severely restricted by the FDA [207].

Thus, it would be exceedingly difficult for our clinician to put John on rosiglitazone in 2013. (per Risk Evaluation and Mitigation Strategy stipulation: "Before starting a new patient on rosiglitazone, you must determine that they are unable to achieve glycemic control on other diabetes medications, and (in consultation with you), that they have decided not to take pioglitazone (Actos) for medical reasons. You must inform them of the product's risk information, including the current state of knowledge about the potential increased risk of myocardial infarction associated with the use of rosiglitazone. Also inform them that pioglitazone (Actos) has not been shown to be associated with an increased risk of myocardial infarction.")

Thus, with the rosiglitazone option all but gone, one is now left to decide whether John could be placed on pioglitazone in addition to metformin therapy in order to improve his glycemic control and hopefully prevent the dreaded long-term complications of Type 2 diabetes. There is no question that pioglitazone improves glucose control, which is the very reason for its use in someone with uncontrolled diabetes. The current question is whether that beneficial effect outweighs potential risks associated with its use. What are those adverse effects?

Aside from the potential beneficial cardiovascular effects [13], most of the effects are shared with rosiglitazone. A recent review outlined the concerns about the long-term safety of TZDs [40]. Peripheral edema, increased intravascular volume and, thus, increased weight have been noted from the earliest studies of both rosiglitazone and pioglitazone [41]. A significant increase in the rates of congestive heart failure in a certain proportion of these patients have likewise been reported early on and confirmed in later large-scale studies [13,39]. Therefore, both agents have carried a black box warning about the exacerbation of congestive heart failure from the time of their approval. Both drugs are contraindicated in patients with known class III and IV New York Heart Association congestive heart failure, and they are to be discontinued if such a complication develops. This bothersome

effect is due to PPAR-γ activation in cells of the juxtaglomerular apparatus and distal nephron, upregulating expression and translocation of the collecting duct epithelial sodium channel, leading to sodium reabsorption, increased plasma renin activity and fluid retention [41].

A significant decrease in hemoglobin, hematocrit, white blood cells and platelets has been noted with TZDs [42] and has been assumed to be due to hemodilution. However, is has been noted that total body water did not increase in the patients with decreased blood counts. It has been suggested that pioglitazone may actually suppress bone marrow, possibly by marrow fat infiltration [43].

TZDs have been shown to decrease osteoblast differentiation and increase osteoclast formation in preclinical and early clinical work [44–48]. The possible resulting bone loss was tied to PPAR-γ activation in bone marrow. The clinical impact of these findings became apparent in analysis of data from the ADOPT study (which used rosiglitazone) [11]. Women assigned to take rosiglitazone experienced approximately a doubling of nonosteoporotic fractures, mainly in the humerus, hand and foot. These results launched extensive global investigations to assess their generalizability. Reductions were indeed found in markers of bone formation and a reduction in bone mineral density along with resulting significant increases in bone fractures for both rosiglitazone and pioglitazone were found not only in women, but also in men in some analyses. Just to cite several examples, Medicare recipients on TZDs have experienced more fractures than those on metformin or sulfonylureas [49]. Women with Type 2 diabetes on TZDs in Detroit, MI, USA, had almost double the number of fractures than those treated with other agents [50], long-term exposure to TZDs was associated with more fractures and hospitalizations in women in Taiwan [51], pioglitazone was associated with an increased risk of fractures in a prospective population-based study conducted in BC, Canada [52]. It was estimated that 86 patients would have to be treated with a TZD for 3 years in order to diagnose an excess fracture [52]. A meta-analysis of ten randomized control trials and two observational studies (involving over 44,000 patients) confirmed a doubling of fractures among women taking a TZD [53]. In an analysis of the database from integrated pharmacy and medical claims involving almost 145,000 patients with Type 2 diabetes, both rosiglitazone and pioglitazone were associated with an approximately 40% increase in fractures among both women and men [54]. Finally, examination of the FDA Adverse Event Reporting System revealed higher reporting of fractures with TZD users than with other antidiabetic agents [55]. In an intriguing study attempting to elucidate mechanisms underlying the increased fracture risk, pioglitazone but not metformin use for 24 weeks increased sclerostin (a negative regulator of bone formation) and CTX in men with Type 2 diabetes [56].

The latest wrinkle introduced into the clinician and patient's consideration of using a PPAR-γ agonist was the reports of possibly increased incidence of bladder cancer among pioglitazone users. It was known since the early 1990s from preclinical work that pioglitazone increased transitional cell neoplasms in male rats [57]. Thus, after approval of Actos in 1999, the FDA mandated a 10-year observational postmarketing study to assess any possible association with bladder cancer in patients with Type 2 diabetes. It was not until 2003 that the manufacturer of pioglitazone submitted the outline of the study to the FDA. That ongoing study involves patients with Type 2 diabetes followed at Kaiser Permanente Northern California (CA, USA; cohort recruited from 1 January 1997; n = 193,009). During this follow-up period they published a planned mid-point interim analysis [58,208] that indicated that overall there was no increase of bladder cancer among the 30,173 patients who used pioglitazone. However, they found that there was increased risk (hazard ratio [HR]: 1.4; 95% CI: 1.03–2.0) for patients taking the drug for over 2 years. A higher risk was also seen with the highest cumulative dose of pioglitazone (>28,000 mg; HR: 1.5; 95% CI: 1.1–2.2). These findings were confirmed in analysis of data from the French National Health Insurance Information System [59], where they found an increased risk of bladder cancer among the 155,535 patients exposed to pioglitazone (in comparison with the remaining 1,491,060 patients who were not exposed to the drug) associated with a higher cumulative dose (HR: 1.75) and longer duration of exposure (HR: 1.36). Interestingly, in the FDA-requested 8-year interim analysis of the Kaiser Permanente data (up to 31 December 2010), the previously reported associations between the use of pioglitazone and bladder cancer have disappeared [208]. In the meantime, several other analyses

have been reported, mostly showing statistically significant increased incidence of bladder cancer associated with pioglitazone use. For example, a retrospective cohort study of general practices in the UK reported an HR of 1.83 (95% CI: 1.10–3.05) for use of pioglitazone, and the rate was increased with duration and exposure to the drug [60]. A meta-analysis involving 2,657,365 patients showed a risk ratio of 1.22 (95% CI: 1.07–1.39) for pioglitazone and no such association for rosiglitazone [61]. The FDA's Adverse Event Reporting System survey yielded an odds ratio for pioglitazone of 4.30 (95% CI: 2.82–6.52) [62]. A cohort study (n = 18,459 on a TZD) of The Health Improvement Network in the UK (from 2000 to 2010) showed that the risk of bladder cancer increased with time from the initiation of TZD, but not in those patients using a sulfonylurea [63]. For the practicing clinician, the absolute risk faced by an individual patient is more relevant; thus, in the meta-analysis [61], pioglitazone users in randomized clinical trials faced a 0.37% chance of being diagnosed with bladder cancer (i.e., 99.63% chance of not being diagnosed) as compared with a 0.24% risk in nonusers of pioglitazone. In cohort studies, the risk in pioglitazone users was 0.11% versus 0.13% in nonusers. Overall, the vast majority of newly discovered bladder cancers occur in men and in very early stages. The mechanisms underlying this observation are still being speculated, but do not appear to result from direct interaction with the receptor. The effect of pioglitazone on male rat urothelium is apparently preventable by dietary modifications, suggesting a mechanism related to altered urine milieu. It has been, for example, postulated that PPAR agonists could change the urine composition and produce toxic urinary solids that could lead to increased cell proliferation and tumor formation [64–66]. Interestingly, rosiglitazone was reported to act as a promoter of hydroxybutyl(butyl)nitrosamine-induced urinary bladder cancers in female Fischer-344 rats, suggesting another possible mechanism [67].

In any event, the regulatory agencies have amended the prescribing information for pioglitazone and declared that the agent should not be used in those with active bladder cancer and suggested that pioglitazone be used with caution in patients with a prior history of bladder cancer. Patients should be counseled to report any signs or symptoms of blood in the urine, urinary urgency, pain on urination, or back or abdominal pain [209].

The possible association of macular edema with the use of TZDs was first reported in 2006. Although the first report was from a retrospective chart review, eight out of 11 patients followed long-term had resolution of macular edema after stopping TZD [68]. In a prospective study, the overall incidence of new cases was very small (0.6%), but significantly higher (by 60%; 95% CI: 1.4–1.8) in those using pioglitazone compared with those who were not [69]. It is possible that fluid overload could be responsible for this observed association [68].

So, are there any arguments left for actually picking a TZD for our patient? It is now impossible to add rosiglitazone to his antihyperglycemic regimen in Europe and it would be exceedingly difficult to do so in the US, given the FDA-mandated restrictions on its initiation under Risk Evaluation and Mitigation Strategy. Thus, with pioglitazone as the only drug in the class still available, given the above possible adverse near- and long-term considerations, how do the pro arguments stack up in 2013? First, the drug does lower glucose and HbA1c, the *sine qua non* of antidiabetic therapy. Second, most of the widely accepted cardiovascular risk factors (lipid profile, free fatty acid levels and other indicators of insulin resistance; e.g., blood pressure and inflammation markers) lean in a favorable direction.

Third, the currently best-validated, noninvasive surrogate marker for atherosclerosis, CIMT has been affected by TZDs more positively than by other antihyperglycemic agents in most studies. CIMT is correlated with acute myocardial infarction, stroke and other indicators of cardiovascular disease, but it is not a validated risk marker (currently, only LDL-cholesterol is). For example, the CHICAGO study randomized 462 low-risk patients with Type 2 diabetes (mean duration of diabetes mellitus: 7.7 years, mean HbA1c: 7.4%, excluding those with congestive heart failure, left ventricular ejection fraction <40% and those on diuretics or angiotensin-converting enzyme inhibitors, or with significant cardiac valvular disease) [18]. The 72-week study used either pioglitazone or glimepiride. Absolute CIMT decreased slightly with pioglitazone while it increased in those treated with glimepiride ($p = 0.02$); absolute mean CIMT increased more in the glimepiride than the pioglitazone group ($p = 0.008$). The PERISCOPE trial involved patients at higher risk in a secondary prevention study, also comparing pioglitazone with

glimepiride in 547 patients [70]. Only 66% of the randomized patients actually underwent primary analysis of the data, but pioglitazone was superior to glimepiride at the primary end point (change in percent atheroma volume). The least squares mean of the percent atheroma volume increased in those on glimepiride and decreased in those on pioglitazone (p = 0.002). The APPROACH study, another intravascular ultrasound trial, randomized patients to rosiglitazone or glipizide. There was no change in primary end point (percent atheroma volume), but normalized atheroma volume was significantly reduced by the TZD (p = 0.04) [71].

Fourth, effects of TZDs on actual cardiovascular outcomes have been more difficult to come by. PROactive was the first study designed to assess the effect of an antidiabetic agent on cardiovascular outcomes [13]. In this study, randomizing 5238 high-risk patients with Type 2 diabetes, pioglitazone was compared with placebo. Ever since it was reported in 2005, spirited debate has raged about the interpretation of results of a study that failed to meet its primary (all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndrome, endovascular or surgical intervention in the coronary or leg arteries, or above-the-knee amputation; p = 0.095), but met the principal predefined secondary (all-cause mortality, myocardial infarction or stroke; p = 0.027) end point. The RECORD compared, in a randomized, open-label design, addition of rosiglitazone or placebo to metformin and sulfonylurea-failing patients with Type 2 diabetes [39]. There were no differences in the primary end point – hospitalization or death from cardiovascular causes (HR: 0.99). As in PROactive, patients in this study did have a higher incidence of congestive heart failure and fractures. As mentioned above, three large-scale cardiovascular outcomes studies in high-risk patients with Type 2 diabetes did not show any clear-cut benefit of rosiglitazone, but neither did they confirm the worries about the drug causing ischemic heart disease events [36–38]. Hopes were running high that we would finally be able to assess the cardiovascular outcomes of both TZDs in a head-to-head trial (TIDE), which was planned to be complete in 2015 [72]. One of the two points investigated was "to test the cardiovascular effects of long-term treatment with rosiglitazone or pioglitazone when used as part of standard of care compared with similar standard of care without rosiglitazone or pioglitazone in patients with Type 2 diabetes who have a history of or are at risk for cardiovascular disease." However, due to external pressures (e.g., US Senators C Grassley and M Baucus writing: "After reading these documents, we would like to know what steps the FDA has taken to protect patients in the TIDE trial, and why this trial is allowed to continue.") [210], recruitment into the study was halted and the FDA placed the trial on 'full clinical hold' in September 2010 [73]. It was considered unethical to randomize patients into the rosiglitazone arm given the cloud over the drug. Ironically, this study was designed precisely to find out whether the allegations about the causative link between rosiglitazone and ischemic myocardial events were true.

Conclusion & future perspective

One of the vexing realities in diabetes management is the imperative need to individualize or 'personalize' therapeutic choices. There is no one preferred way to treat a patient. This concept was explicitly expressed in the latest position statement of the American Diabetes Association and European Association for the Study of Diabetes, which incorporated the 'patient-centered approach' into its very title [2], and previously discussed in the AACE/ACE glycemic algorithm [1]. Many variables come to play when a clinician needs to intensify treatment choices in order to achieve optimal glucose control in a specific patient. Age, life expectancy, presence of cardiovascular disease and other diabetic complications (especially nephropathy and neuropathy), hypoglycemia unawareness, socioeconomic status, living arrangements, ability to function independently, and importantly, the patient's interest in optimizing diabetes control, serve as few of the critical considerations. When one attempts to improve diabetes control, the choice is not between another drug and placebo, but between different drugs. Most of the randomized trials referenced in the FDA-approved package inserts present data from relatively small-scale, short-term (often as brief as 12–18 weeks) Phase III studies, often with the agent in question as monotherapy or in a two-drug combination therapy tested against placebo. In the case under consideration here, our patient might be expected to live for more than 30 additional years and we simply do not have sufficient safety or outcomes data for any of the available agents (with the possible exception of insulin).

Another consideration that often gets overlooked is the patient's (and often clinician's) ability to sort out the absolute versus relative risks associated with the use of any particular agent. They are constantly assaulted with a barrage of TV or Internet advertisements for malpractice lawyer outfits emphasizing the serious risks of these drugs. For the patient trying to actually look into these claims, the package inserts or popular literature might describe 'hazard risks' or 'odds ratio', or perhaps percentage increase of a specific adverse event. What is usually not described is the absolute risk or that patient's chance of suffering from that event in absolute terms that he/she could actually understand and put into context of the risks he/she takes in the course of his/her daily life (driving a car, using power tools or taking over-the-counter preparations). For example, in the article that created the 'Avandia scare', patients on rosiglitazone had a 43% increased risk (odds ratio 1.43) of myocardial infarction and 64% increased risk of death from cardiovascular causes (odd ratio: 1.64), certainly very frightening numbers [27]. If one actually reads the manuscript, the picture is very different: the absolute rate of myocardial infarction in those taking rosiglitazone was 0.60% and those in the control group was 0.62% (i.e., higher), meaning that 99.4% of patients on rosiglitazone did not suffer myocardial infarction. For cardiovascular death, the absolute rate was 0.38% and 0.24%, respectively; meaning that 99.6% of those on rosiglitazone did not die from cardiovascular causes. One can only imagine the patient's reaction to the choice of rosiglitazone if he/she were presented with the actual and not the relative risk. In another relevant example, the 'frightening' Actos bladder cancer scare, in the initial report from the French national health insurance system the published hazard risk was 1.22, calculated from the absolute incidence rates of 49.4 and 42.8 per 100,000 person-years for pioglitazone and control groups, respectively [59]. In other words, a pioglitazone-exposed patient had an absolute risk of 0.05% (or one in 2000) per year of being diagnosed with bladder cancer or a 99.95% chance of not being diagnosed with bladder cancer. To put that into perspective, if examines the alleged benefits of taking pioglitazone in the PROactive study, for every 100 patients taking the drug, one nonfatal myocardial infarction would be prevented over 34.5 months (i.e., 1% of patients benefit); for stroke prevention, the number needed to treat was 125 [13]. Thus, although the benefit would not be overwhelming, it certainly dwarfs, in absolute terms, the putative risk of bladder cancer diagnosis. I believe that most patients would be willing to take such odds in most of their daily choices. What is usually not considered is the cost of not advancing therapy and allowing diabetes to remain uncontrolled.

To summarize, it is unlikely in the current practice environment that our clinician would choose pioglitazone as an additional agent for the regimen in our metformin-failing patient. However, it is still possible that pioglitazone might get a second chance. It recently became available as a generic drug and, thus, might soon offer a less expensive option (the US exclusivity expiration date was 17 August 2012). If the final analysis of the 10-year data on bladder cancer association turns out to be negative, that argument against its prescription might disappear. Likewise, if an analysis of long-term cardiovascular outcomes among pioglitazone users turns out to be beneficial, more clinicians might choose to prescribe it. Pioglitazone does remain an effective agent to reduce glycemia and is the only true insulin sensitizer still on the market. However, the proven increase in fracture risk might give the clinician a reason to pause, especially if faced with a young woman or someone at increased baseline risk of fractures. The potential for fluid retention and plasma volume expansion, leading in some patients to peripheral edema and even congestive heart failure, also need to be considered and discussed with the patient.

There have been some positive developments that could potentially rescue PPAR-γ-targeted therapy. It is beyond the scope of this paper to describe them. Briefly, it is clear by now that direct binding of TZDs to PPAR-γ in multiple tissues has led to the activation of many genes in multiple tissues in a nonspecific manner. This scattershot approach has given us both the desirable and undesirable clinical effects described above. The future specific approach to the PPAR-γ pathway might involve nonagonist ligands that instead block Cdk5-mediated serine 273 phosphorylation of PPAR-γ. This action results in potent antidiabetic effects without causing fluid retention or inhibition of bone formation [40,74–76]. While this approach is quite promising, it remains unavailable to our practitioner in 2013.

Financial & competing interests disclosure

Over the past 12 months, G Grunberger has received research support from GlaxoSmithKline, Eli Lilly, Amylin, Janssen and Novo Nordisk. G Grunberger has served on speakers' bureaus for Takeda, Merck, Novo Nordisk, Sanofi, Eli Lilly, Amylin and Santarus. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- of interest

1 Handelsman Y, Mechanick JI, Blonde L *et al.* American Association of Clinical Endocrinologists medical guidelines for clinical practice for developing a diabetes mellitus comprehensive care plan: executive summary. *Endocr. Pract.* 17, 288–302 (2011).

2 Inzucchi SE, Bergenstal RM, Buse JB *et al.* Management of hyperglycemia in Type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 35, 1364–1379 (2012).

3 Sohda T, Mizuno K, Imamiya E *et al.* Studies on antidiabetic agents. II. Synthesis of 5-[4-(1-methylcyclohexylmethoxy)-benzyl] thiazolidine-2,4-dione (ADD-3878) and its derivatives. *Chem. Pharm. Bull.* 30, 3580–3600 (1982).

4 Forman BM, Tontonoz P, Chen J, Brun RP, Spiegelman BM, Evans RM. 15-deoxy-Δ12, 4-prostaglandin J_2 is a ligand for the adipocyte determination factor PPAR-γ. *Cell* 83, 803–812 (1995).

5 Knowler WC, Barrett-Connor E, Fowler SE *et al.*; Diabetes Prevention Program Research Group. Reduction in the incidence of Type 2 diabetes with lifestyle intervention or metformin. *N. Engl. J. Med.* 346, 393–403 (2002).

6 *Current Problems in Pharmacovigilance (Volume 23)*. Medicines and Healthcare products Regulatory Agency, London, UK, 13–16 (1997).

7 Wagstaff AJ, Goa KL. Rosiglitazone: a review of its use in the management of Type 2 diabetes mellitus. *Drugs* 62, 1805–1837 (2002).

- **Review of pivotal rosiglitazone trials.**

8 Waugh J, Keating GM, Plosker GL, Easthope S, Robinson DM. Pioglitazone. A review of its use in Type 2 diabetes mellitus. *Drugs* 66, 85–109 (2006).

- **Review of pioglitazone characteristics and clinical trials.**

9 Norris S, Carson S, Roberts C. Comparative effectiveness of pioglitazone and rosiglitazone in Type 2 diabetes, prediabetes, and the metabolic syndrome: a meta-analysis. *Curr. Diabetes Rev.* 3, 127–140 (2007).

- **Analysis of randomized clinical trials of both rosiglitazone and pioglitazone.**

10 Gerstein HC, Yusuf S, Bosch J *et al.*; DREAM (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368, 1096–1105 (2006).

11 Kahn SE, Haffner SM, Heise MA *et al.*; For the ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N. Engl. J. Med.* 355, 2427–2443 (2006).

- **First report of an increase in bone fractures caused by a thiazolidinedione.**

12 DeFronzo RA, Tripathy D, Schwenke DC *et al.*; For the ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. *N. Engl. J. Med.* 364, 1104–1115 (2011).

13 Dormandy JA, Charbonnel B, Eckland DJ *et al.*; PROactive Investigators. Secondary prevention of macrovascular events in patients with Type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 366, 1279–1289 (2005).

14 Wannamethee SG, Shaper AG, Whincup PH, Lennon L, Sattar N. Impact of diabetes on cardiovascular disease risk and all-cause mortality in older men: influence of age at onset, diabetes duration, and established and novel risk factors. *Arch. Intern. Med.* 171, 404–410 (2011).

15 Minamikawa J, Tanaka S, Yamauchi M, Inoue D, Koshiyama H. Potent inhibitory effect of troglitazone on carotid arterial wall thickness in Type 2 diabetes. *J. Clin. Endocrinol. Metab.* 83, 1818–1820 (1998).

16 Koshiyama H, Shimono D, Kuwamura N, Minamikawa J, Nakamura Y. Inhibitory effect of pioglitazone on carotid arterial wall thickness in Type 2 diabetes. *J. Clin. Endocrinol. Metab.* 86, 3452–3456 (2001).

17 Sidhu JS, Kaposzta Z, Markus HS, Kaski JC. Effect of rosiglitazone on common carotid intima-media thickness progression in coronary artery disease patients without diabetes mellitus. *Arterioscler. Thromb. Vasc. Biol.* 24, 930–934 (2004).

18 Mazzone T, Meyer PM, Feinstein SB *et al.* Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in Type 2 diabetes: a randomized trial. *JAMA* 296, 2572–2581 (2006).

- **Potential regression of atherosclerosis by pioglitazone.**

19 Sears DD, Hsiao A, Ofrecio JM, Chapman J, He W, Olefsky JM. Selective modulation of promoter recruitment and transcriptional activity of PPAR-γ. *Biochem. Biophys. Res. Commun.* 364, 515–521 (2007).

20 Young PW, Buckle DR, Cantello BC *et al.* Identification of high-affinity binding sites for the insulin sensitizer rosiglitazone (BRL-49653) in rodent and human adipocytes using a radioiodinated ligand for peroxisomal proliferator-activated receptor-γ. *J. Pharmacol. Exp. Ther.* 284, 751–759 (1998).

21 Goldberg RB, Kendall DM, Deeg MA *et al.*; For the GLAI Study Investigators. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with Type 2 diabetes and dyslipidemia. *Diabetes Care* 28, 1547–1554 (2005).

22 Zinman B. PPAR-γ agonists in Type 2 diabetes: how far have we come in 'preventing the inevitable'? A review of the metabolic effects of rosiglitazone. *Diabetes Obes. Metab.* 3(Suppl. 1), S34–S43 (2001).

23 Unger RH, Orci L. Diseases of liporegulation: new perspective on obesity and related disorders. *FASEB J.* 15, 312–321 (2001).

24 Bennett WL, Maruthur NM, Singh S *et al.* Comparative effectiveness and safety of medications for Type 2 diabetes: an update including new drugs and 2-drug combinations. *Ann. Int. Med.* 154, 601–613 (2011).

25 Bloomgarden ZT, Dodis R, Viscoli CM, Holmboe ES, Inzucchi SE. Lower baseline glycemia reduces apparent oral agent glucose-lowering efficacy: a meta-regression analysis. *Diabetes Care* 29, 2137–2139 (2006).

26 Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P. Oral pharmacologic treatment of Type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicans. *Ann. Intern. Med.* 156, 218–231 (2012).

27 Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N. Engl. J. Med.* 356, 2457–2471 (2007).

■ **Analysis that started the 'Avandia® scare'.**

28 Psaty BM, Furberg CD. The record of rosiglitazone and the risk of myocardial infarction. *N. Engl. J. Med.* 357, 67–69 (2007).

29 Lipscombe LL, Gomes T, Levesque LE, Hux JE, Juurlink DN, Alter DA. Thiazolidinediones and cardiovascular outcomes in older patients with diabetes. *JAMA* 298, 2634–2643 (2007).

30 Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone. A meta-analysis. *JAMA* 298, 1189–1195 (2007).

31 Winkelmeyer WC, Setoguchi S, Levin R, Solomon DH. Comparison of cardiovascular outcomes in elderly patients with diabetes who initiated rosiglitazone vs pioglitazone therapy. *Arch. Intern. Med.* 168, 2368–2375 (2008).

32 Graham DJ, Oullet-Hellstrom R, MaCurdy TE *et al*. Risk of acute myocardial infarction, stroke, heart failure and death in medicare patients treated with rosglitazone or pioglitazone. *JAMA* 304, 411–418 (2010).

33 Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. *BMJ* 342, d1309 (2011).

34 Diamond GA, Bax L, Kaul S. Uncertain effects of rosiglitazone on the risk for myocardial infarction and cardiovascular death. *Ann. Intern. Med.* 147, 578–581 (2007).

35 Mannucci E, Monami M, Di Bari M *et al*. Cardiac safety profile of rosiglitazone: a comprehensive meta-analysis of randomized clinical trials. *Int. J. Cardiol.* 143, 135–140 (2010).

36 Gerstein HC, Miller ME, Byington RP *et al.* The Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in Type 2 diabetes. *N. Engl. J. Med.* 358, 2545–2559 (2008).

37 Duckworth W, Abraira C, Moritz T *et al*. Glucose control and vascular complications in veterans with Type 2 diabetes. *N. Engl. J. Med.* 360, 129–139 (2009).

38 The BARI 2D Study Group. A randomized trial of therapies for Type 2 diabetes and coronary artery disease. *N. Engl. J. Med.* 360, 2503–2515 (2009).

39 Home PD, Pocock S, Beck-Nielsen H *et al*. Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 373, 2125–2135 (2009).

40 Kung J, Henry RR. Thiazolidinedione safety. *Expert Opin. Drug Saf.* 11, 565–579 (2012).

■ **Recent review of thiazolidinedione safety and its future.**

41 Guan Y, Hao C, Cha DR *et al*. Thiazolidinediones expand body fluid volume through PPARγ stimulation of ENaC-mediated renal salt absorption. *Nat. Med.* 11, 861–866 (2005).

42 Berria R, Glass L, Mahankali A *et al*. Reduction in hematocrit and hemoglobin following pioglitazone treatment is not hemodilutional in Type II diabetes mellitus. *Clin. Pharmacol. Ther.* 82, 275–281 (2007).

43 Gimble J, Robinson C, Wu X *et al*. Peroxisome proliferator-activated receptor-γ activation by thiazolidinediones induces adipogenesis in bone marrow stromal cells. *Mol. Pharmacol.* 50, 1087–1094 (1996).

44 Grey A, Bolland M, Gamble G *et al*. The peroxisome proliferator-activated receptor-γ agonist rosiglitazone decreases bone formation and bone mineral density in healthy postmenopausal women: a randomized, controlled trial. *J. Clin. Endocrinol. Metab.* 92, 1305–1310 (2007).

45 Wei W, Wan Y. Thiazolidinediones on PPARγ: the roles in bone remodeling. *PPAR Res.* 2011, 867180 (2011).

46 Berberoglu Z, Gursoy A, Bayraktar N, Yazici AC, Bascil Tutuncu N, Guvener Demirag N. Rosiglitazone decreases serum bone-specific alkaline phosphatase activity in postmenopausal women. *J. Clin. Endocrinol. Metab.* 92, 3523–3530 2007).

47 Glintborg D, Andersen M, Hagen C, Heickendorff L, Hermann AP. Association of pioglitazone treatment with decreased bone mineral density in obese premenopausal patients with polycystic ovary syndrome: a randomized, placebo-controlled trial. *J. Clin. Endocrinol. Metab.* 93, 1696–1701 (2008).

48 Zinman B, Haffner SM, Herman WH *et al.*; For the A Diabetes Outcome Progression Trial Study Group. Effect of rosiglitazone, metformin, and glyburide on bone biomarkers in patients with Type 2 diabetes. *J. Clin. Endocrinol. Metab.* 95, 134–142 (2010).

49 Solomon DH, Cadarette SM, Choudhry NK, Canning C, Levin R, Sturmer T. A cohort study of thiazolidinediones and fractures in older adults with diabetes. *J. Clin. Endocrinol. Metab.* 94, 2792–2798 (2009).

50 Habib ZA, Havstad SL, Wells K, Divine G, Pladevall M, Williams LK. Thiazolidinedione use and the longitudinal risk of fractures in patients with Type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* 95, 592–600 (2010).

51 Hsiao FY, Mullins CD. The association between thiazolidinediones and hospitalisation for fracture in Type 2 diabetic patients: a Taiwanese population-based nested case-control study. *Diabetologia* 53, 4889–4896 (2010).

52 Dormuth CR, Carney G, Carleton B, Bassett K, Wright JM. Thiazolidinediones and fractures in men and women. *Arch. Intern. Med.* 169, 1395–1402 (2009).

53 Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in Type 2 diabetes: a meta-analysis. *CMAJ* 180, 32–39 (2009).

54 Aubert RE, Herrera V, Chen W, Haffner SM, Pendergrass M. Rosiglitazone and pioglitazone increase fracture risk in women and men with type diabetes. *Diabete Obes. Metab.* 12, 716–721 (2010).

55 Motola D, Piccinni C, Biagi C, Raschi E, Marra M, Marchesini G. Cardiovascular, ocular and bone adverse reactions associated with thiazolidinediones: a disproportionality of the US FDA adverse event reporting system database. *Drug Saf.* 35, 315–323 (2012).

56 van Lierop AH, Hamdy NA, van der Meer RW *et al*. Distinct effects of pioglitazone and metformin on circulating sclerostin and biochemical markers of bone turnover in men with Type 2 diabetes mellitus. *Eur. J. Endocrinol.* 166, 711–716 (2012).

57 Actos® (pioglitazone hydrochloride), Package Insert. Takeda Pharmaceuticals America Inc., IL, USA.

58 Lewis JD, Ferrara A, Peng T *et al*. Risk of bladder cancer among diabetic patients treated with pioglitazone. Interim report of a longitudinal cohort study. *Diabetes Care* 34, 916–922 (2011).

59 Neumann A, Weill A, Ricordeau P, Fagot JP, Alla F, Allemand H. Pioglitazone and risk of bladder cancer among diabetic patients in France: a population-based cohort study. *Diabetologia* 55, 1953–1962 (2012).

60 Azoulay L, Yin H, Filion KB *et al*. The use of pioglitazone and the risk of bladder cancer in people with type diabetes: nested case–control study. *BMJ* 344, e3645 (2012).

61 Colmers IN, Bowker SL, Majumdar SR, Johnson JA. Use of thiazolidinediones and the risk of bladder cancer among people with Type 2 diabetes: a meta-analysis. *CMAJ* 184(12), E675–E683 (2012).

62 Piccinni C, Motola D, Marchesini G, Poluzzi E. Assessing the association of pioglitazone use and bladder cancer through drug adverse event reporting. *Diabetes Care* 34, 1369–1371 (2011).

63 Mamtani R, Hayes K, Bilker WB *et al*. Long-term therapy with thiazolidinediones and the risk of bladder cancer. A cohort study. *J. Clin. Oncol.* 30(Suppl.), Abstract 1503 (2012).

64 Barbalat Y, Dombrovskiy VY, Weiss RE. Association between pioglitazone and urothelial bladder cancer. *Urology* 80, 1–4 (2012).

65 Cohen SM. Effects of PPAR-γ and combined agonists on he urinary tract of rats and other species. *Toxicol. Sci.* 87, 322–327 (2005).

66 Suzuki S, Arnold LL, Pennington KL. Effects of pioglitazone, a peroxisome proliferator-activated receptor γ agonist, on the urine and urothelium of the rat. *Toxicol. Sci.* 113, 349–357 (2010).

67 Lubet RA, Fischer SM, Steele VE, Juliana MM, Desmond R, Grubbs CHJ. Rosiglitazone, a PPAR-γ agonist: potent promoter of hydroxybutyl(butyl) nitrosamine-induced urinary bladder cancers. *Int. J. Cancer* 123, 2254–2259 (2008).

68 Ryan E, Han D, Ramsay R *et al*. Diabetic macular edema associated with glitazone use. *Retina* 25, 562–570 (2006).

69 Fong D, Contreras R. Glitazones use associated with diabetic macular edema. *Am. J. Ophthalmol.* 147, 583–586 (2009).

70 Nissen SE, Nicholls SJ, Wolski K *et al*. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with Type 2 diabetes: the PERISCOPE randomized controlled trial. 299, 1561–1573 (2008).

71 Gerstein HC, Ratner RE, Cannon CP *et al*. Effect of rosiglitazone on progression of coronary atherosclerosis in patients with Type 2 diabetes mellitus and coronary artery disease: the assessment on the prevention of progression by rosiglitazone on atherosclerosis in diabetes patients with cardiovascular history trial. *Circulation* 121, 1176–1187 (2010).

72 Punthakee Z, Bosch J, Dagenais G *et al*. Design, history and results of the Thiazolidinedione Intervention with vitamin D Evaluation (TIDE) randomised controlled trial. *Diabetologia* 55, 36–45 (2012).

73 Woodcock J, Sharfstein J, Hamburg M. Regulatory action on rosiglitazone by the U.S. Food and Drug Administration. *N. Engl. J. Med.* 363, 1489–1491 (2010).

74 Choi JH, Banks AS, Estall JL *et al*. Anti-diabetic drugs inhibit obesity-linked phosphorylation of PPARγ by Cdk5. *Nature* 466, 451–456 (2010).

75 Choi JH, Banks AS, Kamenecka TM *et al*. Antidiabetic actions of a non-agonist PPAR-γ ligand blocking Cdk5-mediated phosphorylation. *Nature* 477, 477–481 (2011).

76 Norris AW. A second chance for a PPAR-γ targeted therapy. *Circ. Res.* 110, 8–11 (2012).

- **Succinct commentary on the possible future of PPAR-γ agonists.**

■ Patents

101 Kawamatsu Y, Fujita T: US4287200 (1981).

102 Kawamatsu Y, Fujita T: JP5395673 (1978).

103 SANKYO: US4572912 (1986).

■ Websites

201 The troglitazone story. www.troglitazone-story.net/history.html

202 National Institute of Diabetes and Digestive Kidney Diseases. NIDDK discontinues troglitazone arm of "diabetes prevention program" clinical trial. www2.niddk.nih.gov/news/SearchNews/06_04_1998.htm

203 US Department of Health and Human Services. Rezulin to be withdrawn from the market. www.fda.gov/ohrms/dockets/ac/00/backgrd/3634b1a_tab6c.htm

204 Public Broadcasting Service. Timeline: the story of Avandia®. www.pbs.org/wnet/need-to-know/health/timeline-history-of-avandia/2314/#11

205 US FDA. Advisory Committee briefing document. Cardiovascular safety of rosiglitazone. www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4308b1-01-sponsor-backgrounder.pdf

206 EMA. EMA recommends suspension of Avandia®, Avandamet® and Avaglim® (2010). www.ema.europa.eu/docs/en_GB/document_library/press_release/2010/09/WC500096996.pdf

207 US FDA. FDA drug safety communication: updated Risk Evaluation and Mitigation Strategy (REMS) to restrict access to rosiglitazone-containing medicines including Avandia®, Avandamet®, and Avandaryl® (2011). www.fda.gov/Drugs/DrugSafety/ucm255005.htm

208 Cohort Study of Pioglitazone and Bladder Cancer in Patients With Type II Diabetes. http://clinicaltrials.gov/ct2/show/NCT01637935

- **First report of the possible association between long-term use of pioglitazone and bladder cancer.**

209 US FDA. US FDA drug safety communication. Update to ongoing safety review of Actos® (pioglitazone) and increased risk of bladder cancer (2011). www.fda.gov/drugs/drugsafety/ucm259150.htm

210 Baucus M, Grassley C. Letter to the honorable Margaret A Hamburg, Commissioner, US FDA (2010). www.finance.senate.gov/newsroom/chairman/release/?id=bc56b552-efc5-4706-968d-f7032d5cd2e4