Do We Still Need Pioglitazone for the Treatment of Type 2 Diabetes?

A risk-benefit critique in 2013

GUNTRAM SCHERNTHANER, MD[1]
CRAIG J. CURRIE, MD, PHD[2]
GERIT-HOLGER SCHERNTHANER, MD[3]

Type 2 diabetes mellitus (T2DM) is a serious, chronic, and progressive disease that is rapidly increasing in prevalence. The disease now affects >10% of adults in some developed countries, increasing most in Asia. People with T2DM are two to four times more likely to develop a serious cardiovascular (CV) outcome compared with those without diabetes. The majority of patients with T2DM are insulin resistant and have associated metabolic abnormalities that are themselves significant CV risk factors. It is believed that most of this increased risk is caused by lipid abnormalities, hypertension, chronic vascular inflammation, and a proatherothrombotic state. The glycemia-related contribution is evidently lower: a long-term observational study over 18 years from Finland showed that an increase of 1% in HbA_{1c} increased the risk of CV disease (CVD) mortality by 53% in type 1 diabetic patients but by only 7.5% in T2DM patients (1). Based on these observational data, it would be expected that a lowering of HbA_{1c} of 1–2% would not dramatically change the absolute risk for death in people with T2DM.

Effects of pioglitazone on CV risk factors and biomarkers

Pioglitazone is known to improve insulin sensitivity, glycemic control, dyslipidemia, hypertension, and microalbuminuria in patients with T2DM. Pioglitazone decreases fasting and postprandial plasma glucose levels by improving the sensitivity of hepatic and peripheral (muscle) tissue to insulin. A large randomized controlled trial (RCT) showed that both pioglitazone and metformin reduced HbA_{1c} by 1.5% from baseline (2). In contrast to the more commonly prescribed sulfonylureas, pioglitazone showed a significantly better durability of diabetes control in patients with T2DM (3). Similarly, pioglitazone was superior to the dipeptidyl peptidase (DPP)-4 inhibitor sitagliptin in reducing HbA_{1c} levels in drug-naïve patients (4). Pioglitazone also provides effective (lowering HbA_{1c} by 0.5–1.5%) and durable glycemic control in combination with other oral antidiabetes drugs as well in combination with insulin (5). In addition to providing sustained glycemic control in T2DM patients, pioglitazone resulted in a 70% reduction in the risk of developing T2DM in the Actos Now for the prevention of diabetes (ACT NOW) study (6).

Two large prospective studies (7,8) have each demonstrated that insulin resistance is a very strong independent predictor of CVD, myocardial infarction (MI), and stroke. Pioglitazone is the only drug available with a strong effect on insulin resistance, although metformin also has some effect in improving peripheral insulin sensitivity (9,10). In contrast to pioglitazone and metformin, treatment with either sitagliptin and exenatide once weekly had no effect on insulin resistance in the Safety and Efficacy of Exenatide Once Weekly Injection Versus Metformin, Dipeptidyl Peptidase-4 Inhibitor, or Thiazolidinedione as Monotherapy in Drug-Naive Patients With Type 2 Diabetes (DURATION 4) study (4). Although thiazolidinediones (TZDs) reduce insulin resistance and improve glycemic control, it has been hypothesized that differing CV outcomes may be due to their different effects on lipid subfractions (11,12). Pioglitazone has been shown to increase HDL cholesterol, decrease fasting triglycerides, and decrease fasting plasma free fatty acids, whereas rosiglitazone was found to improve only HDL cholesterol (11,13). In addition, total cholesterol and LDL cholesterol levels were unaffected with pioglitazone but were significantly increased with rosiglitazone (11). Head-to-head trials have confirmed these findings and demonstrated a relatively consistent and favorable impact of pioglitazone compared with rosiglitazone on serum lipids, lipoproteins, and apolipoproteins (13). In these trials, pioglitazone was associated with significant improvements in triglycerides, HDL cholesterol, non-HDL cholesterol, LDL particle size, and HDL concentration compared with rosiglitazone (13). In a report (14) from the U.S. Food and Drug Administration (FDA) analyzing the risk of CV events in 227,571 patients aged ≥65 years who were treated with TZDs, prescription of rosiglitazone compared with prescription of pioglitazone was associated with an increased risk of stroke, heart failure, and all-cause mortality and an increased risk of the composite of acute MI, stroke, heart failure, or all-cause mortality (hazard ratio [HR] 1.68 [95% CI 1.27–2.08]). In a very recent study using the U.K. The Health Improvement Network (THIN) database, rosiglitazone increased MI in a population with established ischemic CVD in contrast to pioglitazone, whereas in an unselected population both TZDs had reasonably comparable effects (15).

From the [1]Department of Medicine I, Rudolfstiftung Hospital, Vienna, Austria; the [2]Institute of Primary Care and Public Health, School of Medicine, Cardiff University, Cardiff, U.K.; and the [3]Department of Medicine II, Medical University of Vienna, Vienna, Austria.
Corresponding author: Guntram Schernthaner, guntram.schernthaner@meduniwien.ac.at.
This publication is based on the presentations from the 4th World Congress on Controversies to Consensus in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this supplement were made possible in part by unrestricted educational grants from Abbott, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Ethicon Endo-Surgery, Janssen, Medtronic, Novo Nordisk, Sanofi, and Takeda.
DOI: 10.2337/dcS13-2031

TZDs produce small but consistent reductions in both systolic and diastolic blood pressure. The effect size with pioglitazone is in the region of 3–5 mmHg after 12 months of therapy when added to either glimepiride or metformin (16). TZDs have demonstrated protective effects on a variety of atherosclerosis biomarkers and surrogate measures of CVD (17). TZDs attenuate circulating levels of proinflammatory mediators in patients with T2DM, including C-reactive protein, interleukin-6, CD40L, monocyte chemoattractant protein-1, and metalloproteinase-9 (17). These agents also increase levels of the vascular-protective adipokine adiponectin (17). The clinical significance of these findings is supported by evidence of improved endothelial function, reduced carotid intima-media thickness, and improvements in stenosis after coronary artery stent implantation in patients treated with TZDs. In addition, TZDs might also improve the circulating levels and functional activity of angiogenic endothelial progenitor cells (17), which independently predict the incidence of CV events and death.

Hypoglycemia

In contrast to treatment with insulin, sulfonylureas, or glinides, use of pioglitazone per se is not associated with an increased risk of hypoglycemia, which may be of particular relevance for the treatment of patients with CVD, who are vulnerable to increased mortality after severe hypoglycemia (18). There is epidemiological evidence suggesting that achieving low HbA_{1c} with insulin-based regimens or a sulfonylurea-metformin combination therapy increases the risk of all-cause mortality and CV events (19). Recently, a large study in U.S. veterans (20) showed that patients with hypoglycemia had significantly higher risks of CV events (HR 2.0 [95% CI 1.6–2.4]) and microvascular complications (1.76 [1.46–2.11]). Consequently, in high-risk patients, pioglitazone should be used preferentially in combination with other antidiabetes drugs not associated with increased risk for hypoglycemia, such as metformin, DPP-4 inhibitors, glucagon-like peptide-1 receptor agonists, or sodium glucose cotransporter 2 inhibitors. When combined with sulfonylureas or insulin, the increase of hypoglycemia may be explained by the combination drug and the concurrent significant lowering of glucose levels (5). The cardioprotective effects of pioglitazone are illustrated in Fig. 1.

Lessons from the PROactive study

The PROactive study was a large prospective, randomized, double-blind, secondary-prevention study that investigated the effects of pioglitazone (45 mg/day) on macrovascular outcomes in 5,238 patients with T2DM and preexisting CVD: ~50% with previous MI, 25% with previous stroke, and 25% with peripheral arterial disease (PAD). Treatment with pioglitazone or placebo was administered in addition to optimized standard care, which included glucose-lowering, antihypertensive, lipid-altering, and antithrombotic drugs. Although the primary end point—a composite of all-cause mortality, nonfatal MI, acute coronary syndrome, stroke, major leg amputation, and coronary or leg revascularization—showed only a nonsignificant 10% reduction in the pioglitazone arm, a significant reduction in a composite end point, comprising CV death plus nonfatal MI plus nonfatal stroke, was observed (HR 0.82 [95% CI 0.70–0.97]) in the 3-year follow-up period (21). Furthermore, in patients with a previous MI, pioglitazone significantly reduced the risk of subsequent MI by 28% and acute coronary syndrome by 38% (22). In patients with a previous stroke, pioglitazone decreased chances of a second stroke by 48% (23). Patients with PAD at baseline showed significantly higher rates of the primary end point, main secondary end point, all-cause mortality (all $P < 0.0001$), and stroke ($P = 0.0175$) than did those with no PAD at baseline (24). In the very-high-risk group of patients with PAD at baseline, no beneficial effect of pioglitazone was evident. Unfortunately, patients with PAD were significantly overrepresented in PROactive, which is thought to have influenced the overall outcome of the study. A meta-analysis of this study (24) revealed that the primary end point was significantly lower using pioglitazone compared with placebo when the 1,274 patients with PAD at baseline were excluded from the analysis ($P = 0.01$).

Lessons from CHICAGO and PERISCOPE

Two additional RCTs have characterized the effect of pioglitazone on the progression of atherosclerosis, with each showing favorable outcome for pioglitazone. In the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial (25) in 462 patients with T2DM, pioglitazone was observed to decrease progression of carotid intima-media thickness—an important predictor of future CV events—over an 18-month treatment period compared with glimepiride. The effect was similar across all prespecified subgroups based on age, sex, systolic blood pressure, duration of diabetes, BMI, HbA_{1c}, and statin use. In the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) study (26), coronary intravascular ultrasonography was used to assess the change in percent atheroma volume in 360 patients with T2DM and coronary artery disease treated with either

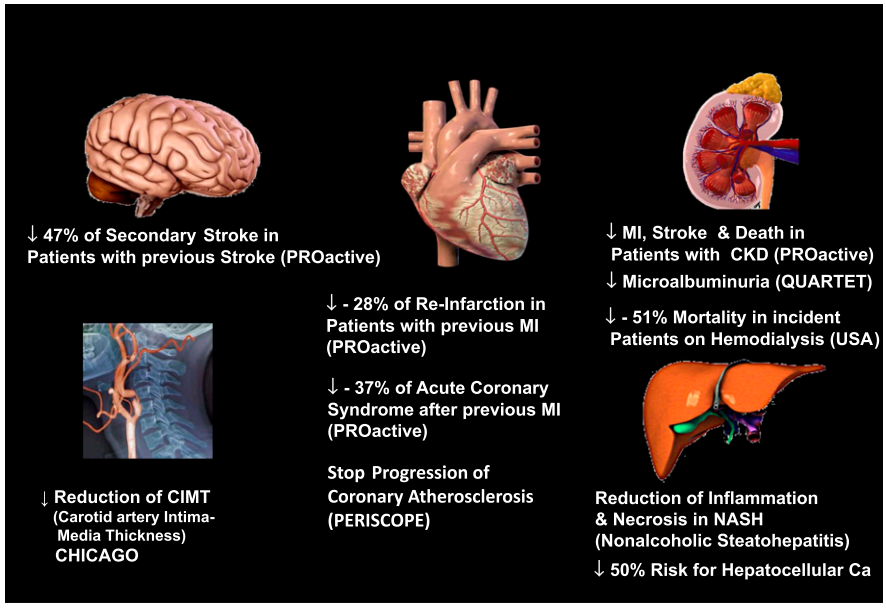

Figure 1—*Protection effects of pioglitazone relating to various organs.*

pioglitazone or glimepiride. Pioglitazone-treated patients had a significantly lower rate of progression of coronary atherosclerosis.

Effects of pioglitazone on microalbuminuria and outcome in T2DM patients with chronic kidney disease

In the QUARTET studies, a consistent lowering effect of pioglitazone on microalbuminuria (estimated as albumin-to-creatinine ratio) was evident, which was not seen with metformin or sulfonylureas (2,3). Patients with diabetes and chronic kidney disease (CKD) are at particularly high risk of CVD. In a post hoc analysis from PROactive, the effect of pioglitazone versus placebo was determined in patients with CKD, defined as an estimated glomerular filtration rate <60 ml/min/1.73 m^2 (27). CKD was present in 597 (12%) of the 5,154 patients in PROactive for whom glomerular filtration rate was available. More patients with CKD reached the primary composite end point than did patients without CKD (27.5 vs. 19.6%; $P < 0.0001$). Patients with CKD were also more likely to reach the main secondary composite end point (all-cause mortality, MI, or stroke). Patients who had CKD and were treated with pioglitazone were less likely to reach this secondary end point (HR 0.66 [95% CI 0.45–0.98]), but this association was not observed among those with better renal function.

In a retrospective analysis of 5,290 incident dialysis patients with diabetes, Brunelli et al. (28) observed a remarkable reduction (–35%) in the risk for all-cause mortality (HR 0.65 [95% CI 0.48–0.87]) in patients treated with TZDs. The risk reduction for all-cause mortality was even more pronounced (–47%) in those patients who received TZDs without insulin (0.53 [0.31–0.89]; $P < 0.02$), but the protective effect was lost in patients treated with both TZDS and insulin (0.82 [0.43–1.55]). Despite the positive findings in patients with CKD and end-stage renal disease and the fact that pioglitazone does not induce hypoglycemia, the drug should be used with caution in CKD stages 4 and 5 because of the risk of water and sodium retention and heart failure.

Decreased mortality with pioglitazone monotherapy or pioglitazone plus metformin combination therapy in observational studies

In a large retrospective cohort study using the U.K. General Practice Research Database (GPRD), Tzoulaki et al. (29) reported the risk of incident MI, congestive heart failure (CHF), and all-cause mortality in relation to oral antidiabetes drugs in 91,521 people with diabetes (mean follow-up per individual: 7.1 years). Remarkably, pioglitazone was associated with a significant 31–39% reduced risk of all-cause mortality ($P = 0.02$ to $P < 0.001$) compared with metformin, whereas first- or second-generation sulfonylureas were associated with a significant 24–61% excess risk for all-cause mortality ($P < 0.001$) compared with metformin. Again, as with any observational study, the possibility of residual confounding or confounding by indication cannot be excluded, although age, duration of diabetes at prescription, BMI, HbA_{1c}, and history of CVD were similar in patients receiving metformin or pioglitazone. Although these results should be interpreted with caution, the findings do not contradict two recent meta-analyses (30,31). In a meta-analysis of 19 RCTs with pioglitazone (30), enrolling 16,390 patients with a study–drug treatment duration ranging from 4 months to 3.5 years, death, MI, or stroke occurred in 4.4% receiving pioglitazone and in 5.7% receiving control therapy (HR 0.82 [95% CI 0.72–0.94]; $P = 0.005$). More recently, Stevens et al. (31) published a meta-analysis of 13 RCTs comparing metformin with placebo or an active comparator. The summary relative risk (RR) for all-cause mortality was 0.91 (95% CI 0.70–1.18) in trials comparing metformin with placebo/usual care and 0.97 (0.77–1.23) in trials comparing metformin with active comparators. The summary RRs were very similar across 1-year trials at 0.84 (0.52–1.38) and across trials longer than 1 year at 0.96 (0.80–1.16). From these two meta-analyses, one could conclude that, with respect to reduction of all-cause mortality, pioglitazone was at least as good as—or possibly better than—metformin.

Due to the high risk for hypoglycemia associated with insulin therapy, more patients are now receiving oral dual or oral triple combination therapy, which is in line with recent recommendations for individualized therapy by the 2012 American Diabetes Association/European Association for the Study of Diabetes statement (32). Very recently, Morgan et al. (33) analyzed the clinical outcome of 27,457 patients from the GPRD switching from metformin monotherapy to an eligible second-line therapy during the study period 2000–2010. Remarkably, metformin plus pioglitazone had significantly lower adjusted HRs for all-cause mortality (HR 0.707 [95% CI 0.515–0.970]) and the combined end point of all-cause mortality, major adverse CV events, or cancer (0.75 [0.61–0.91]) compared with a combination of metformin plus a sulfonylurea. The risks for major adverse CV events and cancer were also lower in patients treated with the combination of metformin plus a DPP-4 inhibitor but did not reach levels of significance versus metformin plus a sulfonylurea.

Safety issues with pioglitazone

The clinical use of pioglitazone is limited by the risk of adverse events, including weight gain, CHF, bone fractures, macular edema, and possibly bladder cancer. Increase in mean body weight was 3.6 kg in the PROactive study (21), but interestingly, weight gain rather than weight loss was associated with an improved survival in patients treated with pioglitazone in a post hoc analysis of the PROactive population (34). Although weight gain can be problematic in some cases, a recent large observational study (35) showed that weight gain was rarely the cause of withdrawal of pioglitazone therapy (0.9% of 12,772 patients).

Edema occurs in ~5% of patients treated with pioglitazone in monotherapy or in oral combination therapy and in ~10% of patients treated with TZDs in combination with insulin. Although edema rate may be somewhat higher in patients with contraindications for pioglitazone, a recent large observational study showed that edema was rarely the cause (0.9% of 12,772 patients) of withdrawal of pioglitazone therapy (35). In the PROactive study, 5.7 and 4.1% of pioglitazone and placebo patients, respectively, were admitted to hospital with CHF (36); however, mortality rates due to CHF were similar (0.96 vs. 0.84%; P = NS). Interestingly, fewer pioglitazone patients with serious CHF had a combined end point of death, MI, or stroke compared with placebo patients (34.9 vs. 47.2%; $P = 0.025$). The underlying mechanism of both edema and CHF exacerbation is likely to be fluid retention and plasma volume expansion (37). Mouse models show that pioglitazone activation of peroxisome proliferator–activated receptor γ receptors in the distal nephron increases sodium reabsorption through the epithelial Na^+ channel (38). In humans, pioglitazone has been

shown to decrease urine sodium excretion and also to increase plasma renin and aldosterone levels. Increased vasodilation and increased vascular permeability may also contribute to edema.

Epidemiologic and clinical trial data suggest that TZDs increase the risk of bone fractures, mainly in older women. This increased fracture risk is of a magnitude similar to that seen with several other widely used drug classes (39). The excess fractures are seen mainly in the distal upper and lower limbs (39), although some evidence suggests an increase in hip fracture risk (40). In a post hoc analysis of various adverse events in the PROactive trial (37), the rate of bone fracture was increased by 5.1% in women taking pioglitazone vs. 2.5% in women taking placebo. The excess risk of fractures for women on pioglitazone was calculated to be 0.5 fractures/100 patient-years of use. No increased fracture rate was seen in men, with fractures in 1.7% of men taking pioglitazone vs. 2.1% of men taking placebo (41). A meta-analysis (42) of 10 RCTs, involving 13,715 patients and including both rosiglitazone- and pioglitazone-treated patients, showed an overall increased risk of fracture with TZD use compared with placebo or active comparator (odds ratio [OR] 1.45 [95% CI 1.18–1.79]; $P < 0.001$). The mechanism responsible for TZD-related bone fractures remains unclear, although abnormalities in both bone formation and bone resorption have been suggested. TZDs affect the differentiation of mesenchymal stem cells, leading to increased adipogenesis at the expense of the formation of osteoblasts (43). Clinically, there are no current guidelines limiting TZD use owing to fracture risk, but it appears prudent to monitor bone density in female patients on TZD therapy and to limit TZD use in patients known to have low bone density.

A recent retrospective cohort study (44) using data from THIN showed an association between the use of TZDs and the incidence of diabetic macular edema (DME). Pioglitazone and rosiglitazone use were associated with an increased risk of DME at 1-year follow-up (HR 2.3 [95% CI 1.5–3.6]) and 10-year follow-up (2.3 [1.7–3.0]). Combination therapy with insulin plus a TZD was associated with a higher risk of DME after propensity score adjustment (3.0 [1.5–5.9]), while aspirin use (0.6 [0.4–0.9]) and ACE inhibitor use (0.4 [0.2–0.7]) were associated with a reduced risk of DME.

In a large prospective observational study conducted at Kaiser Permanente Southern California (45), pioglitazone use was associated with a modestly increased incidence of DME over 1 year (OR 1.6 [95% CI 1.4–1.8]), although there was no dose-response effect. In this analysis, insulin and meglitinide were also found to be associated with an increased risk of macular edema. The mechanism by which TZDs may contribute to DME could be fluid overload, since fluid overload for any reason can result in diffuse macular edema. Because the known association between TZDs and DME is relatively weak at this point, the most prudent course of action may be to continue routine eye exams and refer to ophthalmology if visual symptoms arise and to discontinue TZD therapy if macular edema is present.

Concern exists about an association between pioglitazone (46) and bladder cancer. In the PROactive trial (21), bladder cancer was reported in 14 case subjects treated with pioglitazone (0.5%) and 6 control subjects (0.2%). When the bladder cancers detected in the first year of study drug exposure were eliminated, only 6 versus 3 cases of bladder cancer in pioglitazone versus placebo patients were observed (P = NS). However, confirmatory studies were requested by the FDA, in particular a 10-year, prospective, observational study (47). An interim analysis has been reported in the scientific literature (47), and a further analysis is available (48) but has not been reported in a peer-reviewed format. An initial finding of increased risk of bladder cancer after 2 years' exposure with pioglitazone (HR 1.4 [1.03–2.0]; $P = 0.03$) was reported in the first article; however, there was no signal reported in the subsequent analysis either after 5 (1.17 [0.79–1.49]; P = NS) or 8 (1.07 [0.87–1.30]; P = NS) years. A retrospective study carried out by the French authorities was provided to the European Medicines Agency (EMA) in May 2011 and subsequently published (49). Based on these findings, the marketing authorization for pioglitazone was suspended in France and Germany in May 2011. In the French study (49), the reported HR was 1.22 (95% CI 1.05–1.43) when the analysis was limited to the age-group 40–79 years; however, when all patients age >40 years were included in the original analysis the HR, 1.15 (0.99–1.33), was no longer significant. In July 2011, after consideration of these data, the European Medicines Agency recommended avoiding pioglitazone in people with bladder cancer and in some further clinical situations, but pioglitazone did not receive Europe-wide suspension. This position was essentially the same as that of the FDA (50). Two further observational studies using GPRD have been published. Azoulay et al. (51) reported an increased risk of bladder cancer associated with the use of pioglitazone (HR 1.83 [95% CI 1.10–3.05]), whereas Wei et al. (52), who analyzed the risk of bladder cancer in 23,548 patients exposed to pioglitazone and in 184,166 exposed to other antidiabetes medications, could not find an increased risk for bladder cancer in patients treated with pioglitazone (1.16 [0.83–1.62]). Evidence surrounding the association between pioglitazone and bladder cancer (RR 1.22 [95% CI 1.07–1.39] and 1.17 [1.03–1.32]) in two additional meta-analyses (53,54) requires cautious interpretation because the evidence is mainly based only on retrospective observational studies. Future well-performed prospective studies are needed to clarify whether the association of pioglitazone with bladder cancer is a true one or only caused by a detection bias. After the report of the PROactive study (21), patients with vascular disease and longer diabetes duration may more often receive pioglitazone, and this fact could influence the observed modest association between pioglitazone and bladder cancer in patients with long-standing disease. In addition, since pioglitazone is used in particular in patients with albuminuria, it could be that these patients have a more careful follow-up and therefore a higher chance of diagnosis of a bladder cancer. Pioglitazone may be associated with an increased risk of bladder cancer, but the absolute risk is low and dwarfed by the risk of other serious adverse outcomes that are probably improved by pioglitazone. Our view is that physicians should remain aware of this highly specific potential hazard and include this in an overall risk-benefit–based decision about whether to prescribe this product.

General cancer outcomes

A large population study in patients with diabetes showed that the incidence of bladder cancer was four to five times lower compared with the incidences of liver, colon, and lung cancer (55). Remarkably, a recently published nationwide case-control study in >600,000 patients with T2DM (56) showed that the use of pioglitazone was associated with a significantly

decreased liver cancer incidence (OR 0.83 [95% CI 0.72–0.95]); the protective effect was stronger for higher cumulative dosage and for longer treatment duration. In addition, a decreased risk of colorectal cancer was observed in patients who had used TZDs compared with those who had never used TZDs (adjusted OR 0.86 [95% CI 0.79–0.94]), findings that are consistent with preclinical studies suggesting that peroxisome proliferator–activated receptor γ agonists have antineoplastic effects in colon cancer (57). A study in U.S. veterans showed a 33% reduction in lung cancer risk among TZD users compared with nonusers (adjusted RR 0.67 [95% CI 0.51–0.87]) (58). In accordance with this observation is a recent study from Cleveland reporting an OR of 0.47 (95% CI 0.32–0.68; $P < 0.001$) in patients for metformin or TZD use (59).

Summary

An updated algorithm for the initiation and adjustment of therapy for the management of hyperglycemia has been published as a position statement of the American Diabetes Association and European Association for the Study of Diabetes (32). According to this position statement, "pioglitazone appeared to have a modest benefit on CV events as a secondary outcome in one large trial involving patients with overt macrovascular disease." In the proposed algorithm, pioglitazone monotherapy can be considered an alternative to metformin monotherapy if metformin cannot be used (not tolerated or is contraindicated), as a combination therapy if monotherapy with metformin alone does not achieve/maintain an HbA_{1c} target, or a triple combination therapy, provided that oral agents with complementary mechanisms of action are used. Thus, pioglitazone remains an effective and useful antidiabetes drug with a unique insulin-sensitizing action. However, the clinical use of pioglitazone is currently under scrutiny because of safety issues and because of the availability of newer drugs (DPP-4 inhibitors, glucagon-like peptide-1 receptor agonists, and sodium glucose cotransporter 2 inhibitors). None of these newer drug classes target insulin resistance, however.

At the moment, the most insulin-resistant patients—identifiable by an increased waist circumference, low HDL cholesterol level, and fatty liver—may be the best candidates for treatment with pioglitazone. In addition, patients with a high risk or history of CVD are also likely to benefit from pioglitazone. It is our belief that pioglitazone represents an important therapeutic option in people with T2DM and that more commonly used regimens are both less effective and more likely to result in worse safety outcomes. So, to answer our original question: yes, we still need pioglitazone for the treatment of T2DM.

Acknowledgments—G.S. has received consulting fees or honoraria for membership in advisory boards and honoraria for speaking from Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Hoffmann-La Roche, Janssen, Sharp & Dohme GmbH, Novartis Pharma AG, Novo Nordisk A/S, Sanofi Pharma, and Takeda. C.J.C. has received research grants from various health-related organizations including Abbott, Astellas, Diabetes UK, the Engineering and Physical Sciences Research Council, the European Association for the Study of Diabetes, Ferring, GlaxoSmithKline, Lilly, the Medical Research Council, Medtronic, Merck, the National Health Service, Pfizer, Sanofi, Shire, and Wyeth and consults for Amylin, Aryx, Astellas, Boehringer Ingelheim, Bristol-Myers Squibb, Diabetes UK, Eisel, Ferring, GlaxoSmithKline, Ipsen, Lilly, Medtronic, Merck, Pfizer, Sanofi, Takeda, and Wyeth. G.-H.S. has received consulting fees or honoraria for membership in advisory boards and honoraria for speaking from AstraZeneca, Bristol-Myers Squibb, and Takeda. No other potential conflicts of interest relevant to this article were reported.

G.S. researched and edited, wrote, and reviewed the manuscript. C.J.C. and G.-H.S. reviewed, edited, and wrote the manuscript. G.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Similarity of the impact of type 1 and type 2 diabetes on cardiovascular mortality in middle-aged subjects. Diabetes Care 2008;31:714–719
2. Schernthaner G, Matthews DR, Charbonnel B, Hanefeld M, Brunetti P; Quartet [corrected] Study Group. Efficacy and safety of pioglitazone versus metformin in patients with type 2 diabetes mellitus: a double-blind, randomized trial. J Clin Endocrinol Metab 2004;89:6068–6076
3. Charbonnel B, Schernthaner G, Brunetti P, et al. Long-term efficacy and tolerability of add-on pioglitazone therapy to failing monotherapy compared with addition of gliclazide or metformin in patients with type 2 diabetes. Diabetologia 2005;48:1093–1104
4. Russell-Jones D, Cuddihy RM, Hanefeld M, et al.; DURATION-4 Study Group. Efficacy and safety of exenatide once weekly versus metformin, pioglitazone, and sitagliptin used as monotherapy in drug-naive patients with type 2 diabetes (DURATION-4): a 26-week double-blind study. Diabetes Care 2012;35:252–258
5. Derosa G. Efficacy and tolerability of pioglitazone in patients with type 2 diabetes mellitus: comparison with other oral antihyperglycaemic agents. Drugs 2010;70:1945–1961
6. DeFronzo RA, Tripathy D, Schwenke DC, et al.; ACT NOW Study. Pioglitazone for diabetes prevention in impaired glucose tolerance. N Engl J Med 2011;364:1104–1115
7. Pyörälä M, Miettinen H, Halonen P, Laakso M, Pyörälä K. Insulin resistance syndrome predicts the risk of coronary heart disease and stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. Arterioscler Thromb Vasc Biol 2000;20:538–544
8. Bonora E, Formentini G, Calcaterra F, et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. Diabetes Care 2002;25:1135–1141
9. Natali A, Ferrannini E. Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review. Diabetologia 2006;49:434–441
10. Prager R, Schernthaner G, Graf H. Effect of metformin on peripheral insulin sensitivity in non insulin dependent diabetes mellitus. Diabete Metab 1986;12:346–350
11. van Wijk JP, de Koning EJ, Martens EP, Rabelink TJ. Thiazolidinediones and blood lipids in type 2 diabetes. Arterioscler Thromb Vasc Biol 2003;23:1744–1749
12. Schernthaner G, Chilton RJ. Cardiovascular risk and thiazolidinediones—what do meta-analyses really tell us? Diabetes Obes Metab 2010;12:1023–1035
13. Deeg MA, Buse JB, Goldberg RB, et al.; GLAI Study Investigators. Pioglitazone and rosiglitazone have different effects on serum lipoprotein particle concentrations and sizes in patients with type 2 diabetes and dyslipidemia. Diabetes Care 2007;30:2458–2464
14. Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. JAMA 2010;304:411–418
15. Tannen R, Xie D, Wang X, Yu M, Weiner MG. A new "Comparative Effectiveness" assessment strategy using the THIN database: comparison of the cardiac complications of pioglitazone and rosiglitazone.

Pharmacoepidemiol Drug Saf 2013;22:86–97
16. Derosa G, Fogari E, Cicero AF, et al. Blood pressure control and inflammatory markers in type 2 diabetic patients treated with pioglitazone or rosiglitazone and metformin. Hypertens Res 2007;30:387–394
17. Schernthaner G. Pleiotropic effects of thiazolidinediones on traditional and nontraditional atherosclerotic risk factors. Int J Clin Pract 2009;63:912–929
18. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
19. Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. Lancet 2012;375:481–489
20. Zhao Y, Campbell CR, Fonseca V, Shi L. Impact of hypoglycemia associated with antihyperglycemic medications on vascular risks in veterans with type 2 diabetes. Diabetes Care 2012;35:1126–1132
21. 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 2005;366:1279–1289
22. Erdmann E, Dormandy JA, Charbonnel B, Massi-Benedetti M, Moules IK, Skene AM; PROactive Investigators. The effect of pioglitazone on recurrent myocardial infarction in 2,445 patients with type 2 diabetes and previous myocardial infarction: results from the PROactive (PROactive 05) Study. J Am Coll Cardiol 2007;49:1772–1780
23. Wilcox R, Bousser MG, Betteridge DJ, et al.; PROactive Investigators. Effects of pioglitazone in patients with type 2 diabetes with or without previous stroke: results from PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events 04). Stroke 2007;38:865–873
24. Dormandy JA, Betteridge DJ, Schernthaner G, Pirags V, Norgren L; PROactive investigators. Impact of peripheral arterial disease in patients with diabetes—results from PROactive (PROactive 11). Atherosclerosis 2009;202:272–281
25. 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 2006;296:2572–2581
26. Nissen SE, Nicholls SJ, Wolski K, et al.; PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. JAMA 2008;299:1561–1573
27. Schneider CA, Ferrannini E, DeFronzo R, Schernthaner G, Yates J, Erdmann E. Effect of pioglitazone on cardiovascular outcome in diabetes and chronic kidney disease. J Am Soc Nephrol 2008;19:182–187
28. Brunelli SM, Thadhani R, Ikizler TA, Feldman HI. Thiazolidinedione use is associated with better survival in hemodialysis patients with non-insulin dependent diabetes. Kidney Int 2009;75:961–968
29. Tzoulaki I, Molokhia M, Curcin V, et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK General Practice Research Database. BMJ 2009;339:b4731
30. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. JAMA 2007;298:1180–1188
31. Stevens RJ, Ali R, Bankhead CR, et al. Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomised clinical trials. Diabetologia 2012;55:2593–2603
32. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia 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). Diabetologia 2012;55:1577–1596
33. Morgan CL, Poole CD, Evans M, Barnett AH, Jenkins-Jones S, Currie CJ. What next after metformin? A retrospective evaluation of the outcome of second-line, glucose-lowering therapies in people with type 2 diabetes. J Clin Endocrinol Metab 2012;97:4605–4612
34. Doehner W, Erdmann E, Cairns R, et al. Inverse relation of body weight and weight change with mortality and morbidity in patients with type 2 diabetes and cardiovascular co-morbidity: an analysis of the PROactive study population. Int J Cardiol 2012;162:20–26
35. Kasliwal R, Wilton LV, Shakir SA. Monitoring the safety of pioglitazone : results of a prescription-event monitoring study of 12,772 patients in England. Drug Saf 2008;31:839–850
36. Erdmann E, Charbonnel B, Wilcox RG, et al.; PROactive investigators. Pioglitazone use and heart failure in patients with type 2 diabetes and preexisting cardiovascular disease: data from the PROactive study (PROactive 08). Diabetes Care 2007;30:2773–2778
37. Kung J, Henry RR. Thiazolidinedione safety. Expert Opin Drug Saf 2012;11:565–579
38. Guan Y, Hao C, Cha DR, et al. Thiazolidinediones expand body fluid volume through PPARgamma stimulation of ENaC-mediated renal salt absorption. Nat Med 2005;11:861–866
39. Betteridge DJ. Thiazolidinediones and fracture risk in patients with Type 2 diabetes. Diabet Med 2011;28:759–771
40. Colhoun HM, Livingstone SJ, Looker HC, et al.; Scottish Diabetes Research Network Epidemiology Group. Hospitalised hip fracture risk with rosiglitazone and pioglitazone use compared with other glucose-lowering drugs. Diabetologia 2012;55:2929–2937
41. Dormandy J, Bhattacharya M, van Troostenburg de Bruyn AR; PROactive investigators. Safety and tolerability of pioglitazone in high-risk patients with type 2 diabetes: an overview of data from PROactive. Drug Saf 2009;32:187–202
42. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. CMAJ 2009;180:32–39
43. Grey A. Skeletal consequences of thiazolidinedione therapy. Osteoporos Int 2008;19:129–137
44. Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with type 2 diabetes. Arch Intern Med 2012;172:1005–1011
45. Fong DS, Contreras R. Glitazone use associated with diabetic macular edema. Am J Ophthalmol 2009;147:583–586, e1
46. Takeda Pharmaceuticals. Highlights of prescribing information [Internet], 2011. Available from http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021073s035lbl.pdf. Accessed 29 January 2013
47. 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 2011;34:916–922
48. Pioglitazone HCl. (ACTOS). Clinical study no. 01-03-TL-OPI-524. Cohort study of pioglitazone and bladder cancer in patients with diabetes fourth interim analysis (8-year) report with data from January 1, 1997 to December 31, 2010 [article online], 2011. Available from http://www.pharmatelligence.co.uk/static/documents/01-03-tl-opi-524-8-year-interim-report.pdf. Accessed 15 March 2013
49. 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 2012;55:1953–1962
50. U.S. Food and Drug Administration. FDA Drug Safety Communication. update to ongoing safety review of Actos (pioglitazone) and increased risk of bladder cancer [article online], 2011. Available from http://www.fda.gov/drugs/drugsafety/ucm259150.htm. Accessed 29 January 2013
51. Azoulay L, Yin H, Filion KB, et al. The use of pioglitazone and the risk of bladder

cancer in people with type 2 diabetes: nested case-control study. BMJ 2012;344:e3645
52. Wei L, MacDonald TM, Mackenzie IS. Pioglitazone and bladder cancer: a propensity score matched cohort study. Br J Clin Pharmacol 2013;75:254–259
53. 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 2012;184:E675–E683
54. Zhu Z, Shen Z, Lu Y, Zhong S, Xu C. Increased risk of bladder cancer with pioglitazone therapy in patients with diabetes: a meta-analysis. Diabetes Res Clin Pract 2012;98:159–163
55. Lee MY, Lin KD, Hsiao PJ, Shin SJ. The association of diabetes mellitus with liver, colon, lung, and prostate cancer is independent of hypertension, hyperlipidemia, and gout in Taiwanese patients. Metabolism 2012;61:242–249
56. Chang CH, Lin JW, Wu LC, Lai MS, Chuang LM, Chan KA. Association of thiazolidinediones with liver cancer and colorectal cancer in type 2 diabetes mellitus. Hepatology 2012;55:1462–1472
57. Chen SW, Tsan YT, Chen JD, et al.; Health Data Analysis in Taiwan Research Group. Use of thiazolidinediones and the risk of colorectal cancer in patients with diabetes: a nationwide, population-based, case-control study. Diabetes Care 2013;36:369–375
58. Govindarajan R, Ratnasinghe L, Simmons DL, et al. Thiazolidinediones and the risk of lung, prostate, and colon cancer in patients with diabetes. J Clin Oncol 2007;25:1476–1481
59. Mazzone PJ, Rai H, Beukemann M, Xu M, Jain AK, Sasidhar M. The effect of metformin and thiazolidinedione use on lung cancer in diabetics. BMC Cancer 2012;12:410