Treatment update: thiazolidinediones in combination with metformin for the treatment of type 2 diabetes

John M Stafford[1]
Tom Elasy[2]

[1]Division of Diabetes Endocrinology and Metabolism, Vanderbilt University; [2]Vanderbilt Eskind Diabetes Clinic, Vanderbilt University Medical Center

Abstract: Type 2 diabetes mellitus (DM2) is characterized by excessive hepatic gluconeogenesis, increased insulin resistance and a progressive inability of pancreatic beta cells to produce sufficient insulin. DM2 evolves as a progression from normal glucose tolerance, to impaired glucose tolerance (IGT) to frank diabetes mellitus, reflecting the establishment of insulin resistance and beta cell dysfunction. Insulin resistance not only contributes to impaired glycemic control in DM2, but to the development of hypertension, dyslipidemia and endothelial dysfunction. Cardiovascular disease is the primary morbidity for patients with DM2. The onset of insulin resistance and cardiovascular insult likely occurs well before the onset of IGT is detected clinically. Biguanides and thiazolidinediones (TZDs) are two classes of oral agents for the management of DM2 that improve insulin resistance, and thus have potential cardiovascular benefits beyond glycemic control alone. Metformin additionally inhibits hepatic gluconeogenesis. The combined use of two of these agents targets key pathophysiologic defects in DM2. Single pill combinations of rosiglitazone/metformin and pioglitazone/metformin have recently been approved for use in the US and Europe. This article reviews the clinical data behind the use of metformin in combination with TZDs for the management of diabetes, its impact on vascular health, side effects and potential mechanisms of action for combined use.

Keywords: thiazolidinediones; metformin; Type 2 diabetes

Rationale for the combined use of thiazolidinediones and metformin from a cardiovascular perspective

Type 2 diabetes mellitus (DM2) is characterized by defects both in insulin secretion and insulin action (Ginsberg et al 1975; DeFronzo et al 1985; Lillioja et al 1988). With the use of the euglycemic insulin clamp technique, over the past two decades, it has become clear that DM2 evolves as a progression from normal glucose tolerance, to impaired glucose tolerance (IGT) to frank diabetes mellitus, reflecting the establishment of insulin resistance and beta cell dysfunction (Ginsberg et al 1975; DeFronzo et al 1985; Lillioja et al 1988; and reviewed in Granner and O'Brien (1992) and DeFronzo (2004)). This progression has been demonstrated in many populations, and is strongly correlated with the progression of obesity (Lillioja et al 1988). The progression from normal glucose homeostasis to IGT is associated with an increase in fasting plasma insulin and glucose-stimulated insulin secretion (post-prandial), and a decrease in sensitivity to insulin action (Saad et al 1988, 1989). The progression from IGT to frank DM2 is associated with an inability of the pancreatic beta cells to continue this excess secretion of insulin (Polonsky et al 1996; Roe et al 1996), however significant beta cell dysfunction may occur much earlier (DeFronzo 2004). There is only a minimal

Correspondence: John Stafford
Vanderbilt University Medical Center, 718 Preston Research Building, Nashville, TN 37232-6303, USA
Tel +1 615 936 1653
Fax +1 615 936 1667
Email john.stafford@vanderbilt.edu

additional worsening of insulin resistance at this stage of progression (DeFronzo 2004).

Cardiovascular disease is the primary morbidity for patients with DM2 (Howard et al 2002). The onset of insulin resistance itself seems to be an early event in the progression of DM2, precedes the development of overt hyperglycemia, and may contribute substantially to the development of cardiovascular disease independent of the hyperglycemia associated with DM2 (Meigs et al 2000; DeFronzo 2004). In the Framingham offspring study, elevated levels of fasting insulin were associated with impaired fibrinolysis and hypercoagulability, despite normal glucose tolerance (Meigs et al 2000). In the same study population, those with impaired fasting glucose had a 2.8 fold relative risk of cardiovascular events over a 4-year follow up period (Meigs et al 2002). Vascular dysfunction has been identified in several groups of patients with normal blood glucose levels but insulin resistance including; first degree relatives of patients with DM2 (Balletshofer et al 2000), patients with previous history of gestational diabetes (Bergholm et al 2003), patients with metabolic syndrome and patients with polycystic ovarian syndrome (reviewed in Caballero 2005). In the San Antonio heart study, impaired glucose tolerance was associated with hypertension, dyslipidemia, obesity and metabolic syndrome (Haffner et al 1990). Importantly, the risk of myocardial infarction (MI) in patients with known DM2, but without overt cardiovascular disease, is equal to patients who have had a previous MI but are free of diabetes (Haffner et al 1998). This observation has lead many to recommend the treatment of individuals with diabetes as comparable to an individual with known coronary heart disease. Still, insulin resistance itself appears to be an important risk factor for cardiovascular disease, even before the onset of hyperglycemia or DM2 (Wilson et al 2002, 2005).

Thiazolidinediones (TZDs) comprise a class of oral agents for the management of DM2 that, in addition to improvements in glycemic control, improve insulin resistance and thus have potential cardiovascular benefits beyond glycemic control alone. TZDs emerged for clinical use in the late 1990s. TZDs are ligands for the transcription factor peroxisome proliferator-activated receptor-γ (PPARγ), a member of the nuclear receptor superfamily. PPARγ is expressed predominantly in adipose tissue, but also in macrophages, beta cells of the pancreas, endothelial cells and other tissues (Kato et al 1999; Kersten et al 2000). The Olefsky group noted increased insulin sensitivity and lower blood pressure in obese patients without diabetes who were treated with troglitazone (Nolan et al 1994). There is some evidence in animal models and in human studies that TZD treatment may preserve beta cell function, one of the important changes in the progression from IGT to DM2. Ovalle and colleagues studied a small group of DM2 patients poorly controlled on metformin and sulfonylurea and added either rosiglitazone or insulin. Both groups achieved similar glycemic control, but only the rosiglitazone group had improved beta cell function as indicated by several clinical measures (Ovalle and Bell 2004).

Most additional studies have noted lower fasting and postprandial blood glucose, free fatty acids and fasting insulin levels, suggesting that TZDs improve insulin sensitivity (reviewed in Yki-Jarvinen 2004). For women with gestational diabetes, a state which reflects IGT, TZD treatment prevented the progression to DM2 (TRIPOD/PIPOD) (Xiang et al 2006). Pioglitazone has been shown to be effective in secondary prevention of macrovascular events in patients with known macrovascular disease. Over a 34 month placebo-controlled RCT, Pioglitazone reduced risk in the secondary composite endpoint of all cause mortality, non fatal MI and stroke. A1C, triglycerides, LDL were all decreased and HDL was increased significantly. There was an increase in congestive heart failure on pioglitazone (Dormandy et al 2005). A meta-analysis of 23 RCTs revealed a similar decrease in A1C (1–1.5%), but with an increase in weight (approximately 3 kg). Pioglitazone decreased TG, increased HDL and had no effect on LDL or total cholesterol. Rosiglitazone increased HDL, but was neutral on triglycerides and increased TC and LDL (Chiquette et al 2004). A similar result on lipids is reported comparing addition of pioglitazone or rosiglitazone to patients on glimeperide which found pioglitazone addition lowered TC, LDL, TG and raised HDL, where rosiglitazone addition increased TC, LDL and TG, with no change on HDL (Derosa et al 2005a). This difference may be due to activation of PPARα by pioglitazone in addition to PPARγ, by contrast to rosiglitazone which more selectively activates PPARγ (Kersten et al 2000).

In addition to insulin resistance and beta cell failure, the other principle pathophysiologic defect in DM2 is excessive hepatic gluconeogenesis (Magnusson et al 1992). Metformin is a member of the biguanide class of antidiabetic agents. Its principle clinical efficacy lies in its action to block hepatic gluconeogensis, and increase hepatic insulin sensitivity, and to a lesser extent increase insulin-mediated glucose uptake in fat and muscle tissue (Rossetti et al 1990; Perriello et al 1994; Bailey and Turner 1996; Large and Beylot 1999; Hundal et al 2000). Biguanide-containing compounds have been used since ancient times for the treatment of diabetes. Metformin

has been used clinically for over 40 years, though it has only been approved in the United States since 1995. Follow up of patients enrolled in United Kingdom prospective diabetes study (UKPDS 34) suggest that the complications of diabetes can be related to those caused by hyperglycemia and those related to insulin resistance. In this study, a subgroup of obese patients treated with metformin had significantly lower risk of any diabetes-related endpoint, all cause mortality, and stroke when compared to patients achieving similar glycemic control with a sulfonylurea or insulin therapy (UKPDS 1998).

Treatment or prevention of insulin resistance can prevent the progression from impaired glucose tolerance to overt diabetes. The diabetes prevention trial demonstrated that an intensive diet and exercise program for patients with IGT reduced the risk of progression to diabetes by 58%, and metformin treatment reduced progression to DM2 by 31% (Knowler et al 2002). Similarly, troglitazone or pioglitazone treatment of women with a history of gestational diabetes helped to prevent progression to overt DM2 and to preserve beta cell function (Xiang et al 2006). In the DREAM study, patients with impaired fasting glucose or impaired glucose tolerance, or both were randomized to receive rosiglitazone 8 mg daily or placebo and followed for three years. The composite outcome was a combination of development of diabetes or death. 26% of patients in the placebo group developed the primary outcome versus only 11% in the rosiglitazone group (Gerstein et al 2006). Since insulin resistance itself contributes to risk of cardiovascular disease, treatment of insulin resistance is a potential pathophyisiologic target for the prevention of CVD, not just diabetes. Combined use of metformin and TZDs has theoretical benefit as it targets two main pathophysiologic defects in DM2, increased gluconeogenesis and insulin resistance.

Clinical trials of combination use metformin/thiazolidinediones

Effects on glycemic control

As of May 2006, at least twelve clinical trials have been published in peer-reviewed journals designed to evaluate addition of TZD to metformin for the treatment of diabetes (Inzucchi et al 1998; Einhorn et al 2000; Fonseca et al 2000; Gomez-Perez et al 2002; Dailey et al 2004; Charbonnel et al 2005; Matthews et al 2005; Derosa et al 2005b; Weissman et al 2005; Kendall et al 2006; Rosenstock et al 2006; Umpierrez et al 2006). The initial study that demonstrated efficacy and metabolic effects of the combined use of metformin and TZDs was performed by the Shulman group at Yale (Inzucchi et al 1998). This study of 29 patients randomized to receive either metformin or troglitazone for three months, after which they were placed on both agents. Postprandial glucose was measured by mixed meal test. Insulin sensitivity was assessed with hyperinsulinemic-eugylcemic clamp at baseline, after three months of monotherapy and after three months of combination therapy. After three months of monotherapy, both metformin and troglitazone had similar decreases in fasting and postprandial plasma glucose levels. Metformin decreased endogenous glucose production, while troglitazone did not, consistent with the known effects of metformin on hepatic gluconeogeneis. Metformin had a 13% increase in insulin-mediated glucose disposal, while troglitazone had a 54% increase. Thus as single agents, metformin and troglitazone achieved similar glycemic control, metformin primarily through decreasing hepatic glucose production and troglitazone by improving insulin sensitivity. During combination therapy FPG was decreased an additional 41 mg/dl (18%), and postprandial glucose was decreased and additional 54 mg/dl (21%), both significant changes from monotherapy. Adding troglitazone to metformin did not further decrease endogenous glucose production, however significantly increased glucose disposal. The addition of metformin to the troglitazone group produced only a modest increase in glucose disposal (Inzucchi et al 1998). Thus the main efficacy of combined therapy seemed to be the effect of metformin to decrease endogenous glucose production and that of troglitazone to improve insulin sensitivity, together targeting two pathophysiologic defects in DM2.

Troglitazone was taken off the market in 1999 because of concerns for hepatic toxicity. Subsequent studies of TZDs were with either rosiglitazone or pioglitazone. The first randomized controlled trial of the combined use of metformin with TZD in a large population was with rosiglitazone, published in 2000. In this study, 348 diabetic patients were randomized to metformin plus placebo, metformin plus 4 mg/d rosiglitazone or metformin plus 8 mg/d rosiglitazone for 26 weeks. The primary endpoint was glycemic control. In this interval, addition of 4 mg rosiglitazone to metformin lowered FPG by 33 mg/dl, A1C by 0.56. The 8 mg dose of rosiglitazone, lowered FPG by 48 mg/dl and A1C by 0.78, all statistically significant changes. Treatment effects were seen by as early as 4 weeks of treatment. Insulin sensitivity was assessed by the homeostasis model of assessment (HOMA), and both groups had increased sensitivity compared to the metformin-placebo group (Fonseca et al 2000).

A RCT with pioglitazone randomized 328 patients to pioglitazone-metformin or metformin-placebo for 16 weeks and found the pioglitazone group had a significant A1c decrease of 0.83% compared to placebo-metformin. There was a significant improvement in insulin resistance by HOMA-IR (Einhorn et al 2000). When a sulfonylurea is used with metformin as a control group rather than placebo-metformin, several studies have demonstrated similar glycemic control (Charbonnel et al 2005; Matthews et al 2005; Umpierrez et al 2006). Two studies by the same group compared more long term combination use of pioglitazone added to metformin (Charbonnel et al 2005; Matthews et al 2005). One was a one year double blind study that compared metformin-pioglitazone combination with metformin-gliclazide. The authors found similar decreases in A1C and FPG with each treatment (Matthews et al 2005). The study that went for two years also found similar reductions in A1C, and slightly better FPG with metformin-pioglitazone combination compared with metformin-gliclazide (Charbonnel et al 2005). These results suggest that the glycemic effects of combination therapy with metformin-pioglitazone can be sustained for at least two years.

Of note, similar improvements in glycemic control with the combined use of metformin and thiazolidinediones were noted in Mexicans, who have a significant burden of diabetes (Gomez-Perez et al 2002). Weissman and colleagues in a multi-center double blind RCT with 766 subjects compared adding rosiglitazone to 1000 mg of metformin with dose escalation of metformin for 24 weeks. They found improvements in FPG and A1C with rosiglitazone-metformin over metformin dose escalation (Weissman et al 2005), a potential benefit for patients unable to tolerate full dose metformin. In an open labeled RCT, Dailey and colleagues added rosiglitazone vs. placebo to patients already on metformin and glyburide. They found improved A1C and FPG with the addition of rosiglitazone (Dailey et al 2004). In a randomized, open-label parallel trial either insulin glargine or rosiglitazone was added to patients with inadequate glycemic control on metformin plus sulfonylurea. These authors found similar improvements in glycemic control with both regimens (Rosenstock et al 2006).

Cardiovascular effects of combined use of metformin-TZDs

The RCT by Fonseca and colleagues with rosiglitazone described above also looked at secondary endpoints known to be important for cardiovascular health with metformin-rosiglitazone (Fonseca et al 2000). There were small but statistically significant increases in HDL cholesterol. There were no changes in triglycerides. Total cholesterol and LDL levels were statistically increased with either rosiglitazone group (LDL levels increased from 112 mg/dl to 133 mg/dl in the 8 mg/d rosiglitazone-metformin group). Free fatty acid levels, which are a potential mediator of insulin resistance, were decreased in both rosiglitazone groups. Both rosiglitazone groups had a small but significant decrease in hemoglobin levels, weight gain (Fonseca et al 2000). Several other RCTs found worsening lipid profiles with the addition of rosiglitazone to metformin (Gomez-Perez et al 2002; Weissman et al 2005; Rosenstock et al 2006). The weight gain and increase in LDL are important considerations in patients already at risk for cardiovascular disease.

Two RCTs published with pioglitazone revealed statistically significant improvements in TGs and HDL, but little change in TC or LDL (Einhorn et al 2000; Betteridge and Verges 2005), whereas two others from the same group found that at one year of combined therapy with metformin-pioglitazone, TC, HDL and TG were improved, but LDL was elevated (Matthews et al 2005), but at two years pioglitazone-metformin group had improved TG, HDL and no change in LDL (Charbonnel et al 2005). These studies are somewhat consistent with the more beneficial lipid profile of pioglitazone compared to rosiglitazone as single agents (Chiquette et al 2004). Additionally, pioglitazone influences LDL particle size with an increase in large LDL particles and a decrease in small particles, consistent with a potentially less atherogenic cholesterol profile (Perez et al 2004).

Insulin resistance is a central feature of the metabolic syndrome. An Italian study evaluated addition of glimepiride or rosiglitazone to metformin therapy for patients with poorly controlled DM2, hypertension, obesity and dyslipidemia. They found that addition of rosiglitazone to metformin brought about more rapid improvements in A1C and FPG, but glycemic control was similar at 12 months compared to addition of glimepiride to metformin. They did find modest but statistically significant improvements in systolic blood pressure and diastolic blood pressure in patients on metformin-rosiglitazone compared to the metformin-glimepiride group (Derosa et al 2005b).

Side effects and contraindications

Weight gain, edema and, depending on which TZD is selected, worsened lipid profiles are the most common side effects of adding a TZD to metformin and are similar to the side effects of the TZDs as single agents. The average weight gain on TZDs is 2.7 kg, with a range of 0.7 kg in a

Japanese study to more than 3kd in non-Japansese studies (Chiquette et al 2004). In the largest study of TZD combined with metformin, weight gain of about 2 kg occurred on the highest rosiglitazone dose with metformin (Fonseca et al 2000). Frank edema was present in about 4% of patients (GlaxoSmithKline 2007; Takeda Pharmaceuticals 2007), and body water retention is felt to contribute to about 75% of the weight gain on TZDs (Basu et al 2006). Insulin is a potent anti-natriuretic hormone (DeFronzo et al 1976), it may be that TZD treatment sensitizes to the anti-natriuretic actions of insulin, contributing to edema. Anemia was present in 4% – likely the result of hemodilution associated with fluid retention. Interestingly, a smaller part of weight gain comes from a re-distribution of fat from the visceral compartment to subcutaneous compartment (Miyazaki et al 2002). This visceral fat is classically considered more pathogenic in diabetes than subcutaneous fat, thus fat re-distribution is likely one of the major mechanisms by which TZDs mediate their beneficial effects on insulin sensitivity (Gastaldelli et al 2002). According to manufactures' prescribing information, TZD/metformin is contraindicated in patient that exhibit clinical evidence of active liver disease or increased serum transaminase levels, renal disease or renal dysfunction (eg, as suggested by serum creatinine levels $\geq$1.5 mg/dL (males), $\geq$1.4 mg/dL (females), acute or chronic metabolic acidosis. Although TZDs are contraindicated in acute liver disease, their insulin sensitizing effects may prove to be beneficial in the treatment of non-alcoholic fatty liver disease (reviewed in Caldwell et al (2006)). TZDs should be avoided in patients with CHF, severe edema or macular edema. TZDs are considered class C for pregnancy (GlaxoSmithKline 2007; Takeda Pharmaceuticals 2007). Any metformin containing drug should be stopped before radiologic procedures with iodinated IV contrast for risk of lactic acidosis. No data is available for combined use of metformin-TZD in pediatric patients.

Rosiglitazone is predominantly metabolized by CYP2C8, and to a lesser extent, CYP2C9. Gemfiborzil increases rosiglitazone levels. Rifampin reduceds rosiglitazone levels. Furosimide increases metformin levels, as does Nifedipine. Cationic drugs (eg, amiloride, digoxin, morphine, trimethoprim, and vancomycin and others) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing renal excretion (GlaxoSmithKline 2007). Pioglitazone is metabolized by CYP2C8 and to a lesser extent CYP3A4, thus drug interactions include midazolam, nifedipine ER, ketoconazole, atorvastatin (Takeda Pharmaceuticals 2007). Full details of cautions, contraindications, drug interactions and pharmacokinetics are available in the prescribing information from the manufactures (GlaxoSmithKline 2007; Takeda Pharmaceuticals 2007).

Availability

Rosiglitazone-metformin (Avandamet™) is available in the following doses of rosiglitazone/metformin, respectively; 1 mg/500 mg, 2 mg/500 mg, 4 mg/500 mg, 2 mg/1000 mg, 4 mg/1000 mg. Rosiglitazone-metformin can be titrated up to a maximal total daily dose of 8 mg/2000 mg (GlaxoSmithKline 2007). One published study of healthy volunteers received; metformin 500 mg, rosiglitazone 2 mg, or each twice daily for four days. Coadministration of rosiglitazone and metformin had no effects on steady state pharmacokinetics of either drug (Di Cicco et al 2000). Pioglitazone-metformin (Actoplus Met™) is available in doses of pioglitazone/metformin, respectively of; 15 mg/500 mg or 15 mg/850 mg with recommended maximal daily dosing of 45 mg/2550 mg (Takeda Pharmaceuticals 2007).

Mechanisms of action

The glucose lowering effects of metformin are largely attributable to an increase in glucose uptake by muscle and decrease in hepatic glucose production (Perriello et al 1994; Bailey and Turner 1996; Large and Beylot 1999; Hundal et al 2000). TZDs primarily act to improve insulin sensitivity (reviewed in Yki-Jarvinen 2004). Detailed summaries of the mechanisms of action of both metformin and TZDs have been reviewed elsewhere and are beyond the scope of this review (Bailey and Turner 1996; Kirpichnikov et al 2002; Yki-Jarvinen 2004). This section focuses on potential cellular and molecular mechanisms by which the combined use of metformin and TZD may be beneficial, and also mechanisms of possible side effects.

AMP-activated protein kinase (AMPK) is a heterotrimeric complex which responds to the energy status of the cell in that an increase in the AMP:ATP ratio causes threonine phosphorylation, and thus activation of AMPK (Hawley et al 1996). In response to AMPK activation the cell decreases ATP-consuming and increases ATP-producing pathways, thus a potential metabolic sensor for the cell (Hardie et al 1998). Both Metformin and TZDs activate AMPK through distinct pathways, thus AMPK may be a mediator of the protective effects of metformin and TZDs on insulin action (Fryer et al 2002).

The efficacy of combination of TZD and metformin may be in part due to prevention of fatty-acid induced insulin

resistance, or lipotoxicity (the concept of lipotoxicity is reviewed in Unger (2005)). Ye and colleagues demonstrated by hyperinsulinemic clamp studies in rats that both metformin and rosiglitazone improved insulin sensitivity, by improving insulin-mediated suppression of hepatic glucose output (Ye et al 2004). Rosiglitazone additionally enhanced free fatty acid (FFA) clearance, measured by 3H-R-bromopalmitate tracer technique (Ye et al 2004). Rosiglitazone increased FFA uptake by adipose and reduced uptake by the liver and muscle, as well as decreased liver long-chain CoA accumulation, a potential mediator of fatty-acid induced insulin resistance (Lee et al 1994; Ye et al 2004). Additionally this group has demonstrated that pioglitazone protects from FFA-induced insulin resistance in the liver (Ye et al 2002).

In addition to fatty acids, many inflammatory mediators, when elevated, can cause insulin resistance in animal models and may contribute to the pathogenesis of DM2. These include CRP, an important protein in leptin action (Chen et al 2006), and TNFα (reviewed in Moller 2000). In one double blind RCT of patients with metabolic syndrome, rosiglitazone 8 mg qd for 12 wks, increased adiponectin, lowered resistin, CRP and TNFα (Samaha et al 2006). Adiponectin levels are inversely correlated with cardiovascular risk, thus an increase would be predicted to benefit cardiovascular health (Pischon et al 2004). Lowering levels of resistin, CRP and TNFα should contribute to improved insulin resistance. In the study by Samaha, however, despite beneficial changes in inflammatory mediators of insulin resistance, there was very little improvement in other clinical parameters known to contribute to cardiovascular risk, with an increase in total cholesterol, and no significant changes in HDL or LDL (Samaha et al 2006).

In addition to the effects on FFA flux and glucose, TZD treatment may have beneficial effects on vascular health directly. PPAR gamma is expressed in endothelial cells, and may have important role in vascular restenosis (reviewed in (Bruemmer et al 2005). In cultured endothelial cells ligand activation of PPAR gamma has been shown to inhibit thrombin-induced endothelin-1 production (Delerive et al 1999) and plasminogen activator inhibitor type 1 expression (Kato et al 1999). In people, progression of carotid intima-media thickness, a marker of atherosclerotic disease, is improved with pioglitazone (Mazzone et al 2006). In one double blind RCT, diabetic patients were treated with metformin or rosiglitazone. In the rosiglitazone group, intra-arterial acethylcholine-mediated vasoidailation (an indicator of arterial endothelial function) was improved by 40% and correlated with a decrease in FFA and TNFα (Natali et al 2004).

In summary, the combined use of metformin and a TZD have significant improvements in glycemic control. The main efficacy of combined therapy seems to be the effect of metformin to decrease endogenous glucose production and that of TZDs to improve insulin sensitivity, together targeting two key pathophysiologic defects in DM2. Single pill combinations of both rosiglitazone-metformin (Avandamet™), and pioglitazone-metformin (Actoplus Met™) are available in Europe and the US. It is important to emphasize that potential cardiovascular benefits from the combined use of metformin and a TZD are not established in clinical trials. While there is data on the cardiovascular benefit of both drugs individually, UKPDS for metformin and PROactive for pioglitazone (UKPDS 1998; Dormandy et al 2005), little distal outcome data for the combined use of these agents in terms of morbidity or mortality is currently available. The RECORD (rosiglitazone evaluated for cardiac outcomes and regulation of glycemia in diabetes) study is underway, one arm of which will test rosiglitazone added to metformin for cardiovascular outcomes and progression of diabetes (Ovalle and Bell 2004).

Search criteria

In addition to the authors' personal knowledge of the literature in this field, databases reviewed include medline/pubmed 1966 to May Week 5 2006, *Cochrane Central Register of Controlled Trials,* Cochrane Database of Systematic Reviews, EBM Reviews-Database of Abstracts of Reviews of Effects, ACP Journal Club 1991 to May/June 2006. Search terms included Rosiglitazone/troglitazone/pioglitazone AND Metformin, thiazolidinedione, vascular, cardiovascular, endothelial, diabetes, insulin resistance.

Abbreviations

Thiazolidinedione (TZD), type two diabetes mellitus (DM2), impaired glucose tolerance (IGT), total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), high-density lipoproteins (HDL), free fatty acids (FFA), fasting plasma glucose (FPG), hemoglobin A1C (A1C), randomized control trial (RCT), Cardiovascular disease (CVD), congestive heart failure (CHF).

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