Thiazolidinediones and Risk of Repeat Target Vessel Revascularization Following Percutaneous Coronary Intervention

A meta-analysis

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OBJECTIVE — Thiazolidinediones (TZDs) (rosiglitazone and pioglitazone) are a class of antidiabetes agents that have a high affinity for peroxisome proliferator–activated receptor-γ. TZDs initiate a multitude of physiologic processes that may elicit benefits as systemic agents for the prevention of restenosis requiring revascularization following percutaneous coronary intervention (PCI). Numerous trials have evaluated the impact of TZDs on repeat target vessel revascularization (TVR) in patients following PCI; however, several limitations (small sample size, inconclusive results, and risk factor stratification) complicate definitive conclusions. A meta-analysis was performed to evaluate the impact of TZDs on repeat TVR following PCI.

RESEARCH DESIGN AND METHODS — Included trials met the following criteria: *1*) prospective, randomized controlled trials evaluating available TZDs versus standards of care; *2*) well-described protocol; *3*) minimum of 6 months of follow-up; and *4*) data provided on repeat TVR. Data are presented as relative risks (RRs) with 95% CIs.

RESULTS — Seven clinical trials ($n = 608$) met the inclusion criteria. Upon meta-analysis, the risk of repeat TVR was significantly reduced in patients who received TZD therapy compared with standards of care (RR 0.35 [95% CI 0.22–0.57]). In studies using rosiglitazone (0.45 [0.25–0.83]) and pioglitazone (0.24 [0.11–0.51]), risk of repeat TVR was significantly reduced. Risk of repeat TVR was also significantly reduced among patients with (0.34 [0.19–0.63]) and without (0.37 [0.18–0.77]) diabetes.

CONCLUSIONS — Results from this meta-analysis suggest that TZDs effectively reduce the risk of repeat TVR following PCI.

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Restenosis requiring revascularization is a significant limitation of percutaneous coronary intervention (PCI). Despite the advent of improved mechanics and drug-eluting stents, the cumulative restenosis rate remains 20–30% in the general PCI population and approaches 40% among patients with diabetes (1–5). It is possible that an inhibitory effect on restenosis may result from a synergistic combination of local and systemic strategies aiming at different mechanisms for reducing pathological neointimal formation (6). Several attempts have been made to reduce in-stent restenosis rates via systemic pharmacological agents, but, to date, these results have been disappointing (7,8).

Peroxisome proliferator–activated receptors (PPARs) are nuclear receptor isoforms (including PPAR-α, PPAR-γ, and PPAR-δ) that play a critical role in many physiologic processes (9). Endogenous ligands are hypothesized to affect lipid regulation and metabolism, whereas more potent synthetic PPAR ligands, such as the fibrates and thiazolidinediones (TZDs), are effective in the treatment of dyslipidemia and diabetes (10).

TZDs, commonly referred to as glitazones, are a class of antidiabetes agents that represent the first synthetic compounds identified as high-affinity selective PPAR-γ agonists. Two glitazones, rosiglitazone (Avandia; GlaxoSmithKline) and pioglitazone (Actos; Takeda/Lilly), are commercially available for the treatment of type 2 diabetes. The first approved TZD, troglitazone (Rezulin; Warner-Lambert), was withdrawn from the market in 2000 due to idiosyncratic hepatitis.

TZDs activate PPAR-γ receptors providing improved insulin sensitivity and glucose control. TZDs also demonstrate favorable effects in artherogenic dyslipidemia without dramatic changes in LDL concentrations (11). In addition to the benefit on glycemia and lipids, TZDs inhibit inflammatory cell responses, as well as inhibit proliferation of vascular smooth muscle cells (VSMCs), development of artherosclerotic lesions, and neointimal formation, possibly independent of PPAR activity (9,12–14). Proliferation of VSMCs is a crucial physiological response to arterial injury, ultimately contributing to the endothelialization of atherosclerotic lesions and coronary heart disease (15). Endothelial dysfunction is markedly accelerated in patients with diabetes and is hypothesized to be associated with insulin resistance (13,16). Inhibition of VSMCs and concomitant reduction in neointimal tissue proliferation after PCI may contribute to TZD's preventative mechanism against restenosis (7,17–19). The efficacy of TZDs in preventing restenosis requiring target vessel revascularization (TVR) remains inconclusive (7,20–22,24). It has been suggested that

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Abbreviations: PCI, percutaneous coronary intervention; PPAR, peroxisome proliferator–activated receptor; TVR, target vessel revascularization; TZD, thiazolidinedione; VSMC, vascular smooth muscle cell.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Summary of included trials*

Study	TZD; dose (mg/day)	TVR rate (%)*	Restenosis rate (%)*	Mean age (years)	Initiation of therapy	Study population and standard pharmacologic therapy
Marx et al. (24) $n = 42$*	PIO; 30	PIO: 12.9; SOC: 29*	PIO: 9.7; SOC: 32.3*	62.1	1st dose pre-PCI	No diabetes; standard CAD medications: β-blocker, ACE inhibitor, statin
Takagi et al. (17) $n = 44$	PIO; 30	PIO: 12; SOC: 38	PIO: 19; SOC: 46	64.5	2 weeks post-PCI	Type 2 diabetes (non–insulin or insulin dependent); conventional diabetes therapy titrated to A1C goal of <6.5%; most common agents: sulfonylurea, acarbose, insulin
Nishio et al. (13) $n = 54$	PIO; 30	PIO: 7.7; SOC: 57.1	PIO: 7.7; SOC: 57.1	66.9	8 ± 2 days post-PCI	Type 2 non–insulin-dependent diabetes; α-glucosidase inhibitor, statin, and sulfonylurea used in ~50% of patients
Cao et al. (23) $n = 297$	ROSI; 4	ROSI: 4.6; SOC: 11.7	NR	60.1	1 day pre-PCI	Metabolic syndrome (IDF definition) without diabetes; standard medications used but not reported
Wang et al. (21) $n = 70$	ROSI; 4	ROSI: 0; SOC: 5.7	NR	61.1	NR	Type 2 non–insulin-dependent diabetes; most received β-blocker, ACE inhibitor, and antihyperlipidemic drug(s); ~40% of patients took unknown oral antidiabetes agents
Choi et al. (7) $n = 83$	ROSI; 8 × 1 dose, then 4	ROSI: 10.5; SOC: 20	ROSI: 17.6*; SOC: 38.2*	60.4	1 day pre-PCI	Type 2 diabetes (non-insulin or insulin dependent); conventional therapy with sulfonylurea, metformin, and/or α-glucosidase inhibitor or insulin titrated to A1C goal of <7%; antihyperlipidemic drug(s) not adjusted; BP therapy adjusted for goal <130/85 mmHg
Osman et al. (22) $n = 16$	ROSI; 4 × 1 month, then 8	ROSI: 25; SOC: 37.5	NR	55.4	Within 6 h of PCI	Type 2 diabetes; metformin therapy allowed, no other details on diabetes medications provided; study stopped early due to slow enrollment

*Results reported as percent of lesions or percent of stents (not percent of patients). BP, blood pressure; CAD, coronary artery disease; IDF, International Diabetes Federation; NR, not reported; PIO, pioglitazone; ROSI, rosiglitazone; SOC, standard of care.

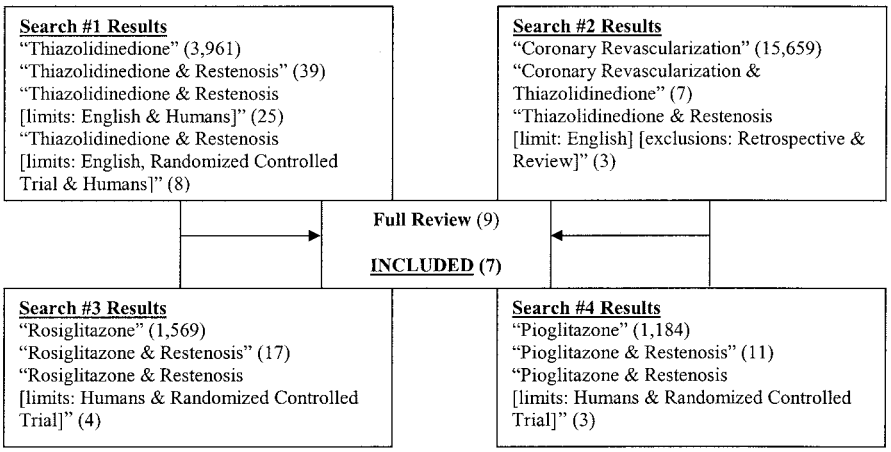

Figure 1— *Search strategy diagram.*

clinical trials powered to assess restenosis are needed before TZDs can be recommended as routine oral antidiabetes drug therapy following PCI (25). To evaluate the effect of TZDs on reducing the risk of repeat TVR following revascularization in a larger patient population, we conducted a meta-analysis of randomized controlled trials published through August 2006.

RESEARCH DESIGN AND METHODS

— We searched Medline, EMBASE, Cinahl, and the Cochrane Database from earliest available date through August 2006. A search strategy using the MeSH and text keywords "thiazolidinedione," "rosiglitazone," "pioglitazone," "restenosis," "coronary," and "revascularization" was utilized (Fig. 1). All searches were limited to clinical trials of human subjects published in English. References from these trials were scrutinized to reveal additional citations. Abstracts from the American Heart Association, the American College of Cardiology, and the American Diabetes Association meetings from 2001 to 2006 were also searched. To be included in this meta-analysis, studies had to be prospective, randomized, controlled trials comparing currently available TZD therapy to standards of care in patients receiving PCI with a minimum 6-month follow-up. Data had to be provided for the number of patients receiving repeat TVR (rather than number of lesions revascularized) in each study group.

The following methodological features most relevant to the control of bias were assessed: randomization, random allocation concealment, masking of treatment allocation, blinding, and withdrawals. All studies were evaluated by three independent reviewers (D.M.R., R.V., and N.N.H.), with disagreement resolved by consensus.

The following information was sought from each article: author identification, year of publication, type of study design, study population, study protocol, medications utilized, and incidence of repeat TVR in standard-of-care and treatment groups. A successful attempt was made to contact corresponding authors for numerical values not provided in the text.

This meta-analysis was completed through the use of StatsDirect statistical software version 2.4.5 (available at http://www.statsdirect.com). Summary statistics were combined, and weighted averages were calculated using a random effects (DerSimonian and Laird methodology) model. Statistical heterogeneity was evaluated via the Q statistic ($P < 0.1$ was considered representative of significant statistical heterogeneity). Publication bias was assessed through visual inspection of funnel plots, and the Egger weighted regression method with $P < 0.05$ was considered representative of significant statistical publication bias. Data are presented as relative risks (RRs) with 95% CIs.

RESULTS

— Search strategy is described in Fig. 1. Nine studies (7,13,17, 20–24,26) received full publication review with seven trials ($n = 608$) providing data adequate for meta-analysis (Table 1) (7,13,17,21–24). All included studies were placebo controlled and compared TZD therapy with standard pharmacological therapy (Table 1) in TZD-naïve patients with ($n = 5$ studies) or without ($n = 2$ studies) diabetes. All studies reported incidence of repeat TVR at 6 months. The majority of studies were conducted in an Asian patient population (Chinese, Japanese, or Korean). The mean age of study participants did not vary largely between the individual studies (Table 1). There were approximately twice as many men than women in each group evaluated. All patients received aspirin in combination with clopidogrel, ticlopidine, or cilostazol. Average baseline A1C in patients with diabetes was 7.97% in TZD groups and

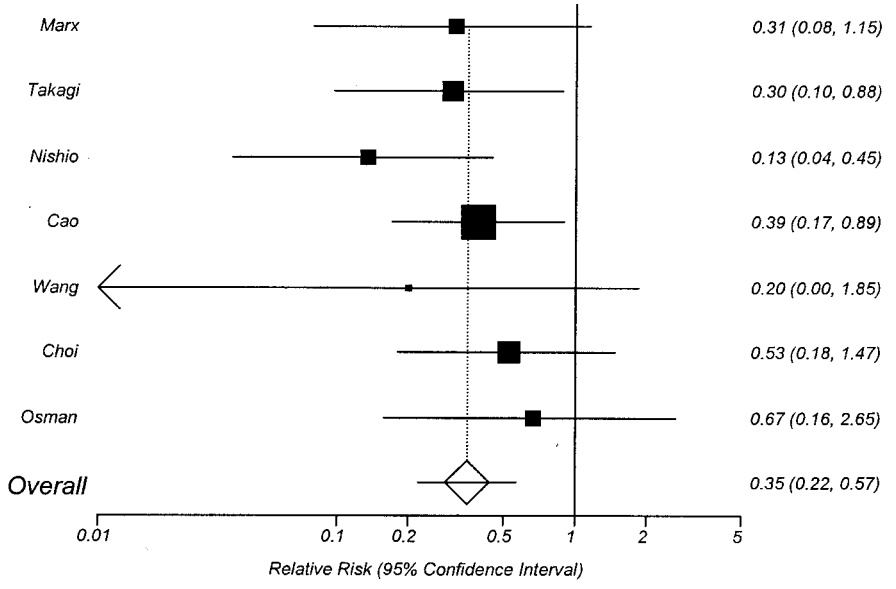

Figure 2— *Repeat TVR. The size of the data markers represents the relative weight of the trial according to size and occurrence of the outcome being measured.*

Table 2—*Subgroup analyses*

Outcome measure	No. of studies	Treatment group (events/participants)	Standard-of-care group (events/participants)	RR (95% CI)	Q statistic (*P* value)
Pioglitazone (refs. 13,17,24) TVR	3	7/69	32/71	0.24 (0.11–0.51)	0.6038
Rosiglitazone (refs. 7,21–23) TVR	4	13/233	31/233	0.45 (0.25–0.83)	0.865
Diabetes (refs. 7,13,17,21,22) TVR	5	11/130	39/137	0.34 (0.19–0.63)	0.4863
No diabetes (refs. 23,24) TVR	2	9/172	24/167	0.37 (0.18–0.77)	0.7949

7.47% in standard-of-care groups, with all but one study reporting an average A1C <8%.

Upon meta-analysis, the risk of repeat TVR was significantly reduced in patients who received TZD therapy compared with standard of care (RR 0.35 [95% CI 0.22–0.57]) (Fig. 2). Statistical heterogeneity was not significant ($P = 0.75$). In studies using rosiglitazone ($n = 4$ studies, 466 patients), the risk of repeat TVR was significantly reduced (0.45 [0.25–0.83]) (Table 2). In studies using pioglitazone ($n = 3$ studies, 140 patients), the risk of repeat TVR was significantly reduced (0.24 [0.11–0.51]) (Table 2). The risk of repeat TVR was also significantly reduced among patients with and without diabetes (Table 2). The potential for publication bias was low based on the symmetrical appearance of the funnel plots (data not shown) and Egger weighted regression *P* values ($P = 0.533$ for total)

CONCLUSIONS — This meta-analysis illustrates that TZDs significantly reduce the risk of repeat TVR following PCI. Despite >50% of the studies (four of seven) in this meta-analysis reporting nonsignificant reductions in the rate of repeat TVR, the totality of evidence demonstrated a significant benefit of TZDs. To the best of our knowledge, this is the first meta-analysis to evaluate this end point in this patient population. Reduced repeat TVR rates is a critical finding for patients with insulin resistance with or without diabetes, especially considering their risk of complications is significantly higher than insulin-sensitive populations (27). Reducing the risk of developing complications by improved insulin sensitivity is beneficial for both the patient and the health care system (27,28). Repeat TVR risk reduction appears to be consistent regardless of TZD evaluated.

A large retrospective analysis by Cho et al. (20) did not demonstrate a benefit among 325 patients with diabetes (25% of patients received a TZD) and found a lower rate of repeat TVR in patients who did not receive a TZD. One complicating factor in this analysis is that patients were taking a TZD for an unknown duration before PCI. In fact, all diet-controlled patients were excluded since there was no consideration to initiate a TZD after intervention. Also, the retrospective design of this analysis limits its findings for multiple reasons (i.e., unknown compliance rates with TZDs or other medications). In addition, this study duration was 1 year, while all but one of the prospective analyses continued for only 6 months. Repeat TVR rates after 6 months may substantially differ, though the majority of restenosis typically occurs early after stent placement (29,30).

The mechanism behind the benefit of TZD therapy on atherosclerotic plaques remains unclear and should be further investigated. Though insulin sensitization may play a significant role, TZD's benefit in reducing repeat TVR is likely related to improved endothelial function, decreased inflammation, and reduced proliferation of VSMCs, independent of PPAR-γ activity (9,12–14). Although other insulin sensitizers (i.e., metformin) could also impact the rate of restenosis, the mechanism of TZD's benefit is multifaceted and substantially different from simple sensitization (31). In accordance with this hypothesis, only three studies in our analysis included patients on other insulin sensitizers (7,21,22). None of these studies demonstrated significant reductions in repeat TVR. Though TZDs were well tolerated throughout, studies did report mild increases in incidence of weight gain, edema, and heart failure (17,21,23).

Several limitations to this meta-analysis should be noted. Although the results of one rosiglitazone study seemed to drive the overall effect in the rosiglitazone subgroup, the existence of a power-related phenomenon is more likely than a drug failure or study design–related issue.

Recently, restenosis rates have been directly correlated to the type of stent used in PCI (32). Specifically, the use of drug-eluting stents can provide additional benefit at the local site of action (8). The type of stent used was neither well documented nor uniform across all studies. In fact, some studies enrolled patients receiving up to four different brands of stents without mention of drug-eluting agent. The combination of TZDs with newer drug-eluting stents may more dramatically reduce the risk of restenosis requiring revascularization; however, it should be evaluated further.

Other pharmacologic prophylaxis (including anticoagulation and antiplatelet therapy) was not consistent among studies. Cilostazol, an agent with less-convincing evidence for use following PCI, was used in a group of patients in one study (33), rather than a thienopyridine (i.e., clopidgrel or ticlopidine). In this study, more patients received cilostazol in the pioglitazone group than in the standard-of-care group, and the rate of TVR in the pioglitazone group remained significantly less (17).

The trials evaluated in our meta-analysis predominately enrolled Asian male subjects. As such, the application of these results to the more diverse patient population with diabetes and insulin resistance would not be appropriate. The potential benefit of TZD prophylaxis in other ethnic patient populations should be evaluated. Also, all doses evaluated in the constituent trials were moderate (4 mg rosiglitazone and 30 mg pioglitazone). Speculation on the effect of higher or lower doses is difficult. Based on baseline A1C values, these patients would not be considered poorly controlled. The magnitude of TZD effect on TVR may be different in patients with well-controlled versus uncontrolled diabetes.

Results from this meta-analysis suggest that TZDs are an effective strategy to reduce repeat TVR following percutaneous coronary intervention, especially in TZD-naïve patients with some degree of insulin resistance.

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