REVIEW

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The Cardiovascular Effects of Peroxisome Proliferator-activated Receptor Agonists

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ABSTRACT

Although peroxisome proliferator-activated receptor agonists are prescribed to improve cardiovascular risk factors, their cardiovascular safety is controversial. We therefore reviewed the literature to identify landmark randomized controlled trials evaluating the effect of peroxisome proliferator-activated receptor gamma agonists (pioglitazone and rosiglitazone), alpha agonists (fenofibrate and gemfibrozil), and pan agonists (bezafibrate, muraglitazar, ragaglitazar, tesaglitazar, and aleglitazar) on cardiovascular outcomes. Pioglitazone may modestly reduce cardiovascular events but also may increase the risk of bladder cancer. Rosiglitazone increases the risk of myocardial infarction and has been withdrawn in European and restricted in the United States. Fibrates improve cardiovascular outcomes only in select subgroups: fenofibrate in diabetic patients with metabolic syndrome, gemfibrozil in patients with dyslipidemia, and bezafibrate in patients with diabetes or metabolic syndrome. The cardiovascular safety of the new pan agonist aleglitazar, currently in phase II trials, remains to be determined. The heterogenous effects of peroxisome proliferator-activated receptor agonists to date highlight the importance of postmarketing surveillance. The critical question of why peroxisome proliferator-activated receptor agonists seem to improve cardiovascular risk factors without significantly improving cardiovascular outcomes requires further investigation.

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Peroxisome proliferator-activated receptors are ligand-activated transcription factors that regulate energy homeostasis.[1] The 3 peroxisome proliferator-activated receptor isoforms (gamma, alpha, and delta) have distinct functions and ligand affinities, and synthetic agonists targeting the same isoform can have variable effects.[1,2] Although peroxisome proliferator-activated receptor delta agonists are not currently in clinical use,[3] other agonists are commonly prescribed. Peroxisome proliferator-activated receptor gamma agonists, also known as thiazolidinediones, are used to treat type 2 diabetes mellitus by improving insulin sensitivity.[1] Peroxisome proliferator-activated receptor alpha agonists (fibrates) are used to treat dyslipidemia by decreasing triglyceride levels and increasing high-density

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lipoprotein (HDL) levels.[4] Peroxisome proliferator-activated receptor alpha/gamma (pan) agonists are used to treat both conditions simultaneously. Peroxisome proliferator-activated receptor activation also may have positive vascular effects and reduce atherosclerosis.[1] Thus, peroxisome proliferator-activated receptor agonists have the potential to improve several cardiovascular risk factors.[5]

At the same time, the cardiovascular safety of peroxisome proliferator-activated receptor agonists remains controversial. After years of clinical use, rosiglitazone was withdrawn in Europe and restricted in the United States after governmental safety reviews identified an increased risk of myocardial ischemia.[6,7] A recent phase II clinical trial (NCT00461058) investigating the new pan agonist aleglitazar was terminated early because of safety concerns. We previously reviewed peroxisome proliferator-activated receptor alpha agonists' effect on lipid profiles and cardiovascular outcomes by reviewing randomized controlled trials published up to June 2007.[8] The current article reviews the literature to June 2011 to identify landmark randomized controlled trials evaluating the effects of peroxisome proliferator-activated receptor gamma, alpha, and pan agonists on cardiovascular outcomes, updating and expanding on our previous work. Table 1 summarizes the peroxisome proliferator-activated receptor agonists' standard dosages, side effects, and impact on lipid profiles and glycemia. Table 2 summarizes the trials included in this review and their cardiovascular outcomes.

CLINICAL SIGNIFICANCE

- Peroxisome proliferator-activated receptor agonists have heterogeneous cardiovascular effects.
- Rosiglitazone increases the risk of myocardial infarction and has been restricted; pioglitazone may modestly improve cardiovascular outcomes but may have noncardiovascular safety issues.
- Fibrates improve cardiovascular outcomes in select patients: fenofibrate in diabetic patients with metabolic syndrome, gemfibrozil in patients with dyslipidemia, and bezafibrate in patients with diabetes or metabolic syndrome.
- The safety of new peroxisome proliferator-activated receptor agonists such as aleglitazar should be thoroughly reviewed before widespread clinical use.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR GAMMA AGONISTS

Peroxisome proliferator-activated receptor gamma regulates adipogenesis, lipid metabolism, glucose control, and inflammation/vascular pathways.[1] Peroxisome proliferator-activated receptor gamma agonists are used to treat type 2 diabetes mellitus. They improve insulin sensitivity by upregulating adipogenesis, decreasing free fatty acid levels, and reversing insulin resistance due to lipotoxicity.[2] However, peroxisome proliferator-activated receptor gamma agonists also cause water retention, which can lead to weight gain, peripheral edema, and congestive heart failure.[9] Peroxisome proliferator-activated receptor gamma agonists also decrease hemoglobin levels, which can increase physiologic stress.[10] Such effects may contribute to adverse cardiovascular outcomes despite apparent improvements in other risk factors. Troglitazone was withdrawn worldwide in 2000 because of rare but severe hepatotoxicity. Pioglitazone and rosiglitazone were recently restricted in some countries as well.

PIOGLITAZONE

Typically, pioglitazone (Actos, Takeda Pharmaceuticals America, Deerfield, Ill) is administered to diabetic patients with other glucose-lowering therapies such as metformin.[11] The 2005 PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) trial randomized 5238 diabetic patients with macrovascular cardiovascular disease to pioglitazone or placebo.[12] The composite primary end point was all-cause mortality, nonfatal myocardial infarction, stroke, acute coronary syndromes, endovascular or surgical intervention in the coronary or leg arteries, and amputation above the ankle. After a mean follow-up of 5 years, there was no reduction in primary end point with pioglitazone (hazard ratio [HR] 0.90; 95% confidence interval [CI], 0.80-1.02). However, pioglitazone reduced a composite secondary end point of all-cause mortality, non-

Table 1 Peroxisome Proliferator-Activated Receptor Agonists Used to Treat Cardiovascular Risk Factors: Impact on Triglycerides, High-Density Lipoprotein, Low-Density Lipoprotein, Glycemia, and Side Effects

PPAR Class	Drug	Standard Dosage (mg/d)	TG	HDL	LDL	Glycemia	Side Effects
Gamma	Pioglitazone	15-45	↓	↑	↓	↓	Peripheral edema/CHF/bladder cancer
	Rosiglitazone	4-8	↓	↑	↓	↓	Peripheral edema/CHF
Alpha	Fenofibrate	48-400	↓	↑	NS	NR	Rhabdomyolysis
	Gemfibrozil	1200	↓	↑	NS	NR	Rhabdomyolysis
Pan	Bezafibrate	400-600	↓	↑	NS	NS	Rhabdomyolysis

↑ = increase; ↓ = decrease; CHF = congestive heart failure; NR = not reported; NS = not significant; PPAR = peroxisome proliferator-activated receptor activator; TG = triglycerides.

Table 2 Summary of Trials Examining the Cardiovascular Effects of Peroxisome Proliferator-Activated Receptor Agonists

PPAR Class	Drug/Trial*	Dosage (mg/d)	N	Patient Characteristics	CVD Death	Nonfatal MI
Gamma	Pioglitazone					
	PROactive[12]	15-40	5238	CVD, DM2	HR 0.96; CI, 0.78-1.18	HR 0.83; CI, 0.65-1.06
	PERISCOPE[17]¶	15-45 vs glimepiride 1-4	543	CAD, DM2	1.1% vs 0.36%, $P = .37$	0.7% vs 1.5%, $P = .69$
	Rosiglitazone					
	DREAM[24]‖	8 vs ramipril 15	5269	IGT or IFG	HR 1.20; CI, 0.52-2.77	HR 1.66; CI, 0.73-3.8
	ADOPT[25] ¶	4 vs metformin 200 or glyburide 2.5	4360	DM2	NR	1.7% vs 1.4% vs 1.0%, P = NR
	PPAR[31]	8	200	MetS, PCI	1.2% vs 2.3%, $P = .57$§	5.2% vs 8.4%, $P = .36$
	RECORD[28]¶	4-8 vs metformin + sulfonylurea	4447	DM2	HR 0.84; CI, 0.59-1.18	HR 1.14; CI, 0.80-1.63†
	STARR[32]‖	8 vs ramipril 15	1425	IFG or IGT	0.28% vs 0.14%, P = NR	0.14% vs 0.14%, P = NR
	APPROACH[33]¶	4 vs glipizide 5	672	DM2, atherosclerosis	1.2% vs 0.9%, $P = .50$	2.1% vs 1.8%, $P = .71$
Alpha	Fenofibrate					
	FIELD[42]	1200	9795	DM2, dyslipidemia	HR 1.11; CI, 0.87-1.41	HR 0.76; CI, 0.62-0.94
	ACCORD[45]	160 vs simvastatin 20-40	5518	DM2, high CV risk	HR 0.86; CI, 0.66-1.12	HR 0.91; CI, 0.74-1.12
	Gemfibrozil					
	HHS[47]	1200	4081	Dyslipidemia	2.19% vs 2.07%, $P > .05$§	2.19% vs 3.50%, $P < .02$
	VA-HIT[48]	1200	2531	CAD, dyslipidemia	RRR = 22%; CI, −2 to 41	RRR = 23%; CI, 4-38
Pan	Bezafibrate					
	SENDCAP[51]	400	164	DM2	NR	NR
	BIP[52,53]‡	400	1470	CAD, MetS	HR 0.74; CI, 0.54-1.03§	HR 0.67; CI, 0.49-0.91
	Aleglitazar					
	SYNCHRONY[57]	50-600 μg vs pioglitazone 45	332	DM2	NR	NR

ACCORD = Action to Control Cardiovascular Risk in Diabetes; APPROACH = Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetic Patients with Cardiovascular History; BIP = Bezafibrate Infarction Prevention; CAD = coronary artery disease; CI = confidence interval; CV = cardiovascular; CVD = cardiovascular disease; DM2 = diabetes mellitus type 2; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; HHS = Helsinki Heart Study; HR = hazard ratio; IFG = impaired fasting glucose; IGT = impaired glucose tolerance; N = sample size; NR = not reported; MetS = metabolic syndrome; MI = myocardial infarction; PCI = percutaneous coronary intervention; PERISCOPE = Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation; PPAR = peroxisome proliferator-activated receptor activator; PROactive = PROspective pioglitAzone Clinical Trial In macroVascular Events; SENDCAP = St Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention; STARR = STudy of Atherosclerosis with Ramipril and Rosiglitazone; SYNCHRONY = Effect of the Dual Peroxisome Proliferator-activated Receptor-α/γ Agonist Aleglitazar on Risk of Cardiovascular Disease in Patients with Type 2 Diabetes; VA-HIT = Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial.

*Trials were placebo-controlled unless otherwise indicated.

†Fatal and nonfatal myocardial infarction and cardiac death.

‡Data from post hoc analysis on patients with metabolic syndrome.

§All-cause mortality.

‖2×2 factorial design with placebo.

¶Not placebo controlled.

fatal myocardial infarction, and stroke (HR 0.84; 95% CI, 0.72-0.98). The number needed to treat to prevent 1 event was 48. The pioglitazone group had a higher incidence of nonfatal congestive heart failure (11% vs 8%; $P < .0001$), but there was no difference in fatal congestive heart failure. Subgroup analyses showed that pioglitazone significantly reduced stroke in high-risk patients with diabetes mellitus[13] and fatal and nonfatal reinfarction in patients with previous myocardial infarction.[14] However, the null effect in the primary analysis means PROactive's secondary outcomes should be considered hypothesis-generating; pioglitazone's cardiovascular effects remain controversial.[15,16]

The later Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial[17] compared pioglitazone and glimepiride in 543 patients with diabetes mellitus and coronary disease. The primary outcome was change in percent atheroma volume from baseline. At 18-month follow-up, pioglitazone effectively reduced progression of coronary atherosclerosis compared with glimepiride (−0.16% vs +0.73%, $P = .002$). The pioglitazone and glimepiride groups had a similar incidence of cardiovascular death and nonfatal myocardial infarction (1.1% vs 0.36%, $P = .37$ and 0.7% vs 1.5%, $P = .69$, respectively). There was no difference in the incidence of other cardiovascular outcomes, such as coronary revascularization and hospitalization for congestive heart failure.

In September 2010, the United States Food and Drug Administration (FDA) began a safety review of pioglitazone because of evidence that it may increase the risk of bladder cancer.[18] The European Medicines Agency also began a review in March 2011.[19] In June 2011, after reviewing a 5-year interim analysis of an ongoing epidemiologic study, the FDA announced that medication labels would be revised to indicate that pioglitazone use of more than 1 year may increase risk of bladder cancer.[18] The FDA also recommended that pioglitazone be used cautiously in patients with past bladder cancer and not used in patients with active bladder cancer.[18] In the same month, a French retrospective cohort study suggested that pioglitazone increased risk in bladder cancer;[18,20] in response, France suspended pioglitazone use and Germany recommended that no new patients begin taking pioglitazone.[21,22] Thus, although pioglitazone may modestly improve cardiovascular outcomes, it cannot

be recommended until its impact on bladder cancer is clarified.

ROSIGLITAZONE

The cardiovascular safety profile of rosiglitazone (Avandia, GlaxoSmithKline, Philadelphia, Penn) has been controversial for several years.[10] In 2006, the DREAM trial investigated rosiglitazone in patients with impaired glucose tolerance.[23,24] By using a 2×2 factorial design, 5269 patients were randomized to ramipril, rosiglitazone, ramipril and rosiglitazone, or placebo. The composite primary end point, incidence of diabetes mellitus or death, was significantly lower with rosiglitazone after 3 years (11.6% vs 26.0%; HR 0.40; 95% CI, 0.35-0.46). This was driven by reduction in diabetes; death was not significantly reduced (HR 0.91; 95% CI, 0.55-1.49). Furthermore, the rosiglitazone group had a nonsignificant increase in cardiovascular events (HR 1.37; 95% CI, 0.97-1.94) and a significant increase in congestive heart failure (0.5% vs 0.1%, HR 7.03; 95% CI, 1.60-30.9).

A Diabetes Outcome Progression Trial (ADOPT)[25] randomized 4360 patients with diabetes mellitus to rosiglitazone, metformin, or glyburide monotherapy. The primary outcome was time to monotherapy failure (plasma glucose levels > 10.0 mmol/L after an overnight fast). At 5 years, the cumulative incidence of the primary outcome was 15% with rosiglitazone, 21% with metformin, and 34% with glyburide. Rosiglitazone reduced the relative risk by 32% compared with metformin ($P < .001$) and 63% compared with glyburide ($P < .001$). The cumulative incidence of myocardial infarction was 1.8% with rosiglitazone, 1.5% with metformin, and 1.2% with glyburide.

DREAM and ADOPT were among the trials included in a 2007 meta-analysis examining the cardiovascular impact of rosiglitazone.[10] Nissen and Wolski[10] found that rosiglitazone increased the risk of myocardial infarction (odds ratio [OR] 1.43; 95% CI, 1.03-1.98) and may increase the risk of cardiovascular death (OR 1.64; 95% CI, 0.98-2.74). However, the use of a fixed-effect model and lack of source data limited this study. When these data were reanalyzed by Diamond et al,[26] using a random-effects model and incorporating zero-event trials, the results were similar but no longer significant.

After the meta-analysis by Nissen and Wolski,[10] the then-ongoing rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD) trial conducted an unplanned interim analysis.[27] RECORD was an open-label noninferiority trial comparing rosiglitazone with metformin/sulfonylurea combination therapy in 4447 patients with diabetes mellitus.[28] The primary end point was cardiovascular hospitalization or mortality. At a mean follow-up time of 3.75 years, interim data showed no difference between the groups in risk of myocardial infarction or cardiovascular death. However, the rosiglitazone group had a higher rate of congestive heart failure (HR 2.15; 95% CI, 1.30-3.57). The investigators concluded that the interim data were not sufficient to determine whether rosiglitazone increased the risk of myocardial infarction.

Despite this controversy, an FDA Advisory Committee voted in July 2007 to keep rosiglitazone on the market.[29] However, the FDA also issued a "black box" warning to alert physicians and patients of the potential cardiovascular risk. The American Diabetes Association and the European Association for the Study of Diabetes also explicitly recommended pioglitazone over rosiglitazone.[30]

In the same month, the peroxisome proliferator-activated receptor study was published.[31] This study randomized 200 patients with metabolic syndrome undergoing percutaneous coronary intervention to rosiglitazone or placebo. The primary outcome was change in carotid intima-media thickness, a surrogate for cardiovascular risk, at 12 months. Rosiglitazone was not found to have a significant effect on this outcome. The rosiglitazone group also had a nonsignificant reduction in the composite end point of death, myocardial infarction, or stroke (11.9% vs 6.4%, $P = .19$).

The 2009 STudy of Atherosclerosis with Ramipril and Rosiglitazone trial enrolled 1425 patients with impaired glucose tolerance or impaired fasting glucose, but without cardiovascular disease.[32] Patients were randomized to ramipril, rosiglitazone, ramipril/rosiglitazone combination therapy, or placebo in a 2×2 factorial design. The primary outcome was change in aggregate maximum carotid intima-media thickness. After a median follow-up of 3 years, the rosiglitazone group had a nonsignificant improvement in carotid intima-media thickness (-2.7 ± 1.7 μm, $P = .08$). After a minimum clinical follow-up of 6 months, the 4 treatment groups were not found to have any significant differences in major cardiovascular event rates (composite or individual).

The later Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetic Patients with Cardiovascular History (APPROACH) trial[33] randomized 672 patients with diabetes mellitus and ≥ 1 atherosclerotic plaque to rosiglitazone or glipizide. The primary end point was progression of coronary atherosclerosis, as measured by change in percent atheroma volume in the longest, least-angulated, native epicardial coronary artery. Rosiglitazone was not found to reduce the primary outcome compared with glipizide (-0.64%, $P = .12$). The rosiglitazone group had nonsignificant increases in incidence of cardiovascular disease death (1.2% vs 0.9%, $P = .50$) and nonfatal myocardial infarction (2.1% vs 1.8%, $P = .71$).

When RECORD was completed in 2009,[28] with a mean follow-up of 5.5 years, rosiglitazone was shown to increase the risk of hospitalization or death due to congestive heart failure compared with metformin/sulfonylurea (HR 2.10; 95% CI, 1.35-3.27). However, there was no difference in the rate of cardiovascular death (HR 0.84; 95% CI, 0.59-1.18), myocardial infarction (HR 1.14; 95% CI, 0.80-1.63), or stroke (HR 0.72; 95% CI, 0.49-1.06). RECORD was criticized for its short time period, lack of cardiac end points, open-label design, and inadequate statistical power.[34]

A subsequent FDA advisory meeting concluded that rosiglitazone carried considerable risk, and many members voted to withdraw the drug.[35] Ultimately, the FDA kept rosiglitazone on the market but greatly restricted its availability. In September 2010, the European Medicines Agency concluded that rosiglitazone's risks outweighed its benefits and recommended market withdrawal.[36] Eight months later, the FDA announced further restrictions, removing rosiglitazone from retail pharmacies as of November 2011 and requiring physicians and patients using rosiglitazone to enroll in the Avandia-Rosiglitazone Medicines Access Program.[37] Rosiglitazone seems to pose a major cardiovascular risk and cannot be recommended. It remains unclear why rosiglitazone has cardiovascular risks not observed with pioglitazone. The low-density lipoprotein (LDL) elevation caused by rosiglitazone may be a contributing factor but does not entirely explain the apparent hazard.[10]

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR ALPHA AGONISTS

Peroxisome proliferator-activated receptor alpha regulates fatty acid oxidation, lipid metabolism, and inflammation/vascular pathways.[1] The peroxisome proliferator-activated receptor alpha agonists fenofibrate and gemfibrozil are used to treat dyslipidemia.[38] They increase HDL levels by increasing transcription of major HDL apolipoproteins.[1,39] They also decrease triglyceride levels by both increasing transcription of lipoprotein lipase, which hydrolyzes triglyceride-rich lipoproteins, and reducing its inhibition.[1,40] Fibrates are associated with an increased incidence of rhabdomyolysis (up to 0.12%).[41]

FENOFIBRATE

The Fenofibrate Intervention and Event Lowering in Diabetes Study randomized 9795 patients with diabetes mellitus and dyslipidemia to fenofibrate (Tricor, Lipidil Micro, Lipidil Supra, Abbott Laboratories, Abbott Park, Ill) or placebo.[42,43] Compared with placebo, fenofibrate did not reduce the composite primary end point of nonfatal myocardial infarction and coronary heart disease mortality (HR 0.89; 95% CI, 0.75-1.05). Fenofibrate significantly reduced nonfatal myocardial infarction (HR 0.79; 95% CI, 0.62-0.94) and nonsignificantly increased coronary heart disease mortality (HR 1.19, 95% CI, 0.90-1.57). Fenofibrate also significantly reduced the composite end point of cardiovascular disease mortality, myocardial infarction, stroke, and coronary or carotid revascularization (HR 0.89; 95% CI, 0.80-0.99). A post hoc analysis found that fenofibrate similarly reduced 5-year composite risk of myocardial infarction, stroke, and death in subjects with metabolic syndrome in addition to diabetes mellitus (adjusted HR 0.89; 95% CI, 0.79-1.00) and without (adjusted HR 0.88; 95% CI, 0.65-1.19). However, because of their higher baseline risk, participants with metabolic syndrome experienced greater absolute benefits.[44]

The Action to Control Cardiovascular Risk in Diabetes lipid trial[45,46] randomized 5518 patients with diabetes mellitus, glycosylated hemoglobin concentration levels greater than 7.5%, and elevated cardiovascular disease risk factors to masked fenofibrate or placebo, each on a background of open-label simvastatin. The primary outcome was the first occurrence of a major cardiovascular event (including nonfatal myocardial infarction, stroke, or cardiovascular death). After a mean follow-up time of 4.7 years, annual primary outcome rates were 2.2% with fenofibrate and 2.4% with placebo (HR 0.92, 95% CI, 0.79-1.08).[45] The fenofibrate group had a nonsignificant reduction in nonfatal myocardial infarction and death from cardiovascular causes. The investigators concluded this combination therapy did not improve cardiovascular outcomes.

GEMFIBROZIL

Two large randomized controlled trials have examined the effect of gemfibrozil (Lopid, Pfizer, New York, NY) on cardiovascular events. The Helsinki Heart Study[47] randomized 4180 men to gemfibrozil or placebo. Study participants were aged 40 to 55 years with primary dyslipidemia (defined as non-HDL cholesterol level $>$ 5.2 mmol/L). Within 1 year, gemfibrozil caused a 10% improvement in each of HDL and LDL, whereas changes with placebo were minimal. Compared with placebo, gemfibrozil had a relative risk reduction (RRR) of 34% (95% CI, 8.2-52.6) for myocardial infarction (fatal or nonfatal) at 5-year follow-up. Similar results were found in the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial, which randomized 2531 men with cardiovascular disease, HDL $<$ 1.0 mmol/dL, and LDL $<$ 3.6 mmol/dL to gemfibrozil or placebo.[48] After 5 years, gemfibrozil caused 22% RRR (95% CI, 7-35) in the primary composite end point of combined incidence of nonfatal myocardial infarction or cardiac death. The RRR was 23% (95% CI, 4-38) in nonfatal myocardial infarction and 22% (95% CI, -2 to 41) in cardiac death. Thus, these trials indicate that gemfibrozil may reduce the incidence of myocardial infarction and cardiac death in high-risk patients.

PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR PAN AGONISTS

Peroxisome proliferator-activated receptor pan agonists, by combining the effects of alpha and gamma agonists, have the potential to treat diabetes and dyslipidemia in a single drug.[49] Development of peroxisome proliferator-activated receptor pan agonists has become an area of increasing interest.[50] It remains unclear whether pan agonists will be able to overcome the limitations of alpha and gamma agonists to date.

BEZAFIBRATE

Bezafibrate (Bezalip, Hoffmann-La Roche Ltd., Mississauga, ON, Canada) is the first and most studied peroxisome proliferator-activated receptor pan agonist. In 1998, the St Mary's, Ealing, Northwick Park Diabetes Cardiovascular Disease Prevention (SENDCAP) Study reported on the cardiovascular impact of bezafibrate.[51] The SENDCAP Study randomized 164 patients with diabetes mellitus to bezafibrate or placebo. The primary end point was change in carotid and femoral maximal intimal medial thickness; neither parameter varied between treatment groups ($P = .5$ and $P = .8$, respectively). However, compared with placebo, bezafibrate significantly decreased the incidence of definite coronary heart disease events over 3 years (7.4% vs 22.6%, $P = .01$).

The later Bezafibrate Infarction Prevention study randomized 3090 patients with a previous myocardial infarction or stable angina, total cholesterol of 180 to 250 mg/dL, HDL-cholesterol $\leq$ 45 mg/dL, triglyceride $\leq$ 300 mg/dL, and LDL cholesterol $\leq$ 180 mg/dL to 400 mg/day of bezafibrate or placebo.[52] The composite primary end point was fatal or nonfatal myocardial infarction or death. After a mean follow-up of 6.2 years, bezafibrate did not significantly decrease crude rates of the primary end point (13.6% vs 15.0%, $P = .26$), fatal myocardial infarction (1.2% vs 1.1%, $P = .18$), or nonfatal myocardial infarction (9.7% vs 11.2%, $P = .87$) compared with placebo. The reduction in cumulative incidence of the primary end point was 7.3% ($P = .24$) in the overall cohort and 39.5% ($P = .02$) in a post hoc analysis of the high baseline triglyceride (>200 mg/dL) subgroup. Another post hoc analysis of patients with $\geq$ 3 metabolic syndrome components showed that bezafibrate decreased rates of any myocardial infarction (HR 0.71; 95% CI, 0.54-0.95) and nonfatal myocardial infarction (HR 0.67; 95% CI, 0.49-0.91) compared with placebo.[53] In patients with $\geq$ 4 metabolic syndrome components, bezafibrate caused a 56% RRR in cardiovascular mortality (HR 0.44; 95% CI, 0.25-0.80). Together, SENDCAP and Bezafibrate Infarction Prevention suggest that bezafibrate reduces the incidence of cardiovascular events in patients with diabetes mellitus or metabolic syndrome.

MURAGLITAZAR, RAGAGLITAZAR, AND TESAGLITAZAR

Experimental pan agonists muraglitazar, ragaglitazar, and tesaglitazar were initially promising, but alarming side effects were observed during development. A meta-analysis of phase II and III clinical trials found that muraglitazar increased the composite risk of nonfatal myocardial infarction, nonfatal stroke, or all-cause mortality in diabetic patients compared with placebo or pioglitazone (N = 3725; relative risk = 2.23; 95% CI, 1.07-4.66).[54] Ragaglitazar had significant carcinogenic effects in rodent bladders and is no longer being developed for human use.[55] Tesaglitazar's development was discontinued because it severely increased serum creatinine in diabetic patients.[56]

ALEGLITAZAR

Aleglitazar is a new pan agonist currently under investigation in phase II clinical trials, including one (NCT01042769) of patients who recently had acute coronary syndromes. Another trial (NCT00461058) investigating aleglitazar in patients with diabetes and class I heart failure was terminated early because of concerns of the safety of thiazolidinediones in patients with symptomatic heart failure. The completed Effect of the Dual Peroxisome Proliferator-activated Receptor-α/γ Agonist Aleglitazar on Risk of Cardiovascular Disease in Patients with Type 2 Diabetes (SYNCHRONY) trial found favorable safety and efficacy,[57] but the limited sample size and follow-up preclude conclusions about aleglitazar's cardiovascular safety.[58]

CONCLUSIONS

Pioglitazone may modestly improve cardiovascular outcomes but also may increase the risk of bladder cancer. Rosiglitazone increases the risk of myocardial infarction and has been withdrawn in Europe and greatly restricted in the United States. Fibrates improve cardiovascular outcomes only in specific high-risk populations: fenofibrate in diabetic patients with metabolic syndrome, gemfibrozil in patients with dyslipidemia, and bezafibrate in patients with diabetes or metabolic syndrome. Muraglitazar, ragaglitazar, and tesaglitazar caused serious adverse effects, and their development was suspended before widespread use. Aleglitazar's cardiovascular effects require further investigation. The diversity of these cardiovascular effects, as well as other side effects, underlines the importance of thoroughly evaluating new peroxisome proliferator-activated receptor agonists before and after widespread clinical use. Further research is required to understand why peroxisome proliferator-activated receptor agonists seem to improve cardiovascular risk factors while having only modest, or even negative, effects on cardiovascular outcomes.

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