CME CREDIT

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Do thiazolidinediones cause heart failure? A critical review

ABSTRACT

Concern has been raised about whether the fluid retention caused by thiazolidinediones (TZDs, ie, rosiglitazone and pioglitazone) can cause or exacerbate congestive heart failure. Although fluid retention is a worrisome side effect of TZDs, current evidence does not link fluid retention caused by TZDs with worsening heart function. TZDs have many benefits for patients with diabetes and can even be used cautiously in patients with mild heart failure, with careful monitoring of volume status.

KEY POINTS

In randomized trials, the incidence of fluid retention and peripheral edema ranged from about 5% when current TZDs were used as monotherapy to about 15% when they were added to insulin therapy.

The incidence of congestive heart failure reported in clinical trials is less than 1% and appears to be related to underlying dysfunction, with decompensation caused by sodium retention and fluid accumulation rather than a direct cardiac suppressive effect.

Fluid retention can often be reversed by stopping the TZD. Other strategies have been tried, including lowering its dose or adding a loop or thiazide diuretic, spironolactone, or angiotensin-converting enzyme inhibitor.

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive; Lancet 2005; 366:1279–1289) found that the use of a TZD was associated with a 16% reduction in the combined end point of heart attack, stroke, and death, despite increased rates of edema and hospitalization for heart failure.

THE POSSIBILITY that the glucose-lowering thiazolidinedione drugs (TZDs, also called "glitazones") may cause or exacerbate congestive heart failure has led some physicians to avoid using these drugs. Although many patients do retain fluid while taking TZDs, the mechanism does not seem to be cardiogenic, the pattern is mostly that of slowly developing peripheral edema rather than "flash" pulmonary edema, and the fluid retention often resolves if the drug is stopped. Furthermore, TZDs may provide benefits beyond glycemic control, including reducing the rate of heart attack, stroke, and death.

This article reviews the evidence on TZDs with regard to their association with fluid retention and heart failure, their possible benefits in patients with heart failure, and how to monitor for their side effects and manage them.

DIABETES AND HEART FAILURE ARE RELATED

Diabetes mellitus and heart failure are increasing in prevalence, and many patients have both. More than 40% of patients hospitalized for decompensated heart failure have a known history of diabetes mellitus, and many more have unrecognized abnormal glucose metabolism.

The two conditions are likely linked. Diabetes can lead to heart failure either by promoting atherosclerosis and coronary artery disease with resulting ischemic heart failure,

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or via direct effects on the cardiac muscles (so-called diabetic cardiomyopathy). Bell[1] described heart failure as "the frequent, forgotten, and often fatal complication of diabetes," and called for its early detection and timely treatment in patients with diabetes.

Heart failure may be more likely to develop in diabetic patients with poor glycemic control.[2] The United Kingdom Prospective Diabetes Study,[3] involving more than 3,600 patients with diabetes, found that the incidence of heart failure declined by 16% for each 1% reduction in hemoglobin A_{1c}.

Many patients with diabetes and heart failure need to take multiple drugs for each condition, and the possible side effects and interactions can be challenging to manage. Compounding the problem, care is compartmentalized: cardiologists deal with the heart failure, endocrinologists deal with the diabetes, and one specialist may be unaware of the impact—good or bad—of the treatment prescribed by the other specialist.

Moreover, little attention has been paid to the side effects of antidiabetes drugs in patients with chronic heart failure. Insulin has long been associated with sympathetic overactivation and sodium retention. Some sulfonylurea drugs are thought to abolish ischemic preconditioning, leaving the myocardium more susceptible to injury. Metformin is contraindicated in patients with heart failure because it is thought to cause lactic acidosis if the patient has renal dysfunction, which is common in patients with heart failure.

TABLE 1

Risks and benefits of thiazolidinediones in patients with heart disease

Benefits

Increased:
- Coronary vasodilation
- Glucose uptake

Decreased:
- Angiotensin II levels
- Blood pressure
- Endothelin-1 levels
- Ischemic-reperfusion injury
- Left ventricular end-diastolic pressure
- Left ventricular hypertrophy
- Myocardial infarct size
- Peripheral vascular resistance
- Tumor necrosis factor alpha levels

Improved:
- Endothelial function
- Lipid profile

Risks

Increased:
- Adiposity and weight
- Atrial natriuretic peptide and B-type natriuretic peptide levels
- Circulating plasma volume, total body water
- Fluid retention, peripheral edema
- Left ventricular end-diastolic volume

Decreased:
- Hematocrit (transiently)

BENEFITS OF TZDs

The two TZDs available in the United States—rosiglitazone (Avandia) and pioglitazone (Actos)—are increasingly used as first-line and second-line agents for treating type 2 diabetes mellitus, making up a substantial proportion of the oral antidiabetic drug market share.

TZDs directly improve insulin sensitivity, pancreatic beta-cell function, and endothelial function. They work in the cell nuclei by binding and activating peroxisome proliferator-activated receptor gamma (PPAR gamma), which presumably regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization.[4]

In placebo-controlled trials, TZDs in maximal doses reduced hemoglobin A_{1c} levels as effectively as sulfonylureas and metformin.

Furthermore, TZDs may provide clinical benefits beyond glycemic control (TABLE 1): they modestly reduce blood pressure, and pioglitazone improves the overall lipid profile, possibly reducing the risk of atherosclerosis.

In patients with heart failure, other theoretical advantages of TZDs are that they reduce afterload, improve neurohormonal function (reducing levels of angiotensin II and endothelin), and reduce levels of tumor necrosis factor alpha.[5] They may improve myocardial insulin resistance by raising myocardial glucose uptake and reducing reliance on fatty acid oxidation in the failing heart. In animal models, TZDs promote regression of left ven-

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TABLE 2

Frequency of edema and congestive heart failure in double-blind studies in patients with diabetes

TREATMENT	N	EDEMA (%)	WITHDRAWAL DUE TO EDEMA (NO.)	HEART FAILURE (%)
Rosiglitazone				
Alone	2,526	4.8	1	0.2
+ metformin	338	4.4	1	0.3
+ sulfonylurea	405	4.0	0	0.5
+ insulin	408	14.7	1	2.5
Placebo	601	1.3	1	0.2
Metformin alone	225	2.2	0	0
Sulfonylurea alone	626	1.0	0	0.5
Insulin alone	203	5.4	0	1.0
Pioglitazone				
Alone	606	4.8	0	0
+ metformin	168	6.0	0	0.6
+ sulfonylurea	373	7.2	1	0
+ insulin	379	15.3	1	1.1
Placebo	259	1.2	0	0
Metformin alone	160	2.5	0	0
Sulfonylurea alone	187	2.1	0	1.1
Insulin alone	187	7.0	0	0

DATA FROM AVANDIA [PACKAGE INSERT]. RESEARCH TRIANGLE PARK, NC: GLAXOSMITHKLINE; 2000, AND ACTOS [PACKAGE INSERT]. LINCOLNSHIRE, IL: TAKEDA PHARMACEUTICAL AMERICA, INC.; 2002.

tricular hypertrophy and reduce left ventricular remodeling following acute myocardial infarction.

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive)[6] included more than 5,000 patients with type 2 diabetes and evidence of macrovascular disease (meaning they were at high risk of cardiovascular events). They were randomized to receive either oral pioglitazone (titrated from 15 to 45 mg) or placebo. Patients in both groups continued to take their regular glucose-lowering drugs and other medications. At nearly 3 years, patients taking pioglitazone had a 16% lower combined risk of heart attack, stroke, and premature death ($P = .027$) compared with patients taking placebo.

TZDs CAUSE FLUID RETENTION

On the negative side, TZDs tend to cause fluid retention, which has led to concern that they may induce or worsen heart failure. Case reports of marked edema and pulmonary edema began to appear as TZDs gained wider use. (Troglitazone, the first TZD to become available, was withdrawn because of cases of hepatic dysfunction, another issue entirely.)

In the clinical trials that led to the approval of rosiglitazone and pioglitazone,[7,8] the incidence of fluid retention was about 5% when these drugs were used as monotherapy, 4% to 7% when they were used in combination with metformin or a sulfonylurea, and 15% when used in combination with insulin (**TABLE 2**).

However, Niemeyer and Janney[9] studied 166 patients started on TZDs at a Veterans Administration medical center and found that 30 (18.1%) developed fluid retention, of whom 16 had to discontinue TZD therapy.

The two available TZDs seem to be approximately equal in causing fluid retention. Goldberg et al[10] compared rosiglitazone and pioglitazone as monotherapy in a study of 802 patients with type 2 diabetes without heart failure. At the end of 6 months, both groups had gained weight (2.7 kg ± 0.2 with rosiglitazone and 3.0 kg ± 0.2 with pioglitazone) and had increased categorical edema (0.29 ± .03 with rosiglitazone and 0.34 ± .04 with pioglitazone). Overall, 13% of patients reported worsening edema. The differences in weight gain and edema were not significant between the two groups. One episode of congestive heart failure was reported.

Fluid retention also occurred in phase II clinical trials of the two dual PPAR-alpha/gamma agonists, muraglitazar (9.2% vs 7.2% with pioglitazone[11]) and tesaglitazar (4.2%–6.8% vs 4.2% with pioglitazone[12]).

RISK OF HEART FAILURE IS LESS CLEAR

The risk of developing congestive heart failure is less clear, but in randomized clinical studies with adjudicated end points it was rare, occurring in about 0.5% to 1% of patients taking TZDs.[7,8]

Reports of pulmonary edema and weight gain associated with troglitazone first appeared in 1999,[13,14] followed by several reports about pioglitazone and rosiglitazone.

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From 1999 to 2004, 14 case reports involving 41 patients described significant fluid retention, heart failure, or both when TZDs were started.[13–26] All but four patients had no preexisting diagnosis of heart failure; 11 patients were taking insulin. The signs and symptoms appeared within weeks to months after starting a TZD; presentations tended to be of volume overload that had slowly accumulated in the weeks after starting drug therapy rather than of acute hemodynamic compromise.

Retrospective cohort studies

Marceille et al[27] studied 139 Veterans Administration patients with type 2 diabetes who were taking insulin and started rosiglitazone therapy. More patients needed a medical intervention (such as a diuretic or other heart failure drug) for heart failure symptoms during the 6 months after starting rosiglitazone than during the 6 months before (36% vs 14%, respectively, $P < .0001$), despite significantly fewer physician visits in the period after starting treatment (42 in the 6 months before starting treatment vs 30 in the 6 months after, $P = .002$). Seven patients were newly diagnosed with heart failure after starting rosiglitazone. The most common symptom was peripheral edema, the only symptom that occurred significantly more often during therapy than before therapy (36% vs 18% respectively, $P < .0001$).

Delea et al[28] used an insurance database to identify 5,441 patients with new prescriptions for a TZD. At 36 months, their adjusted risk of developing heart failure was 12.4%, compared with 8.4% in a control group. Heart failure was defined as a hospitalization or outpatient visit with a diagnosis of heart failure.

Karter et al[29] studied 23,440 patients in the Kaiser Permanente Northern California Diabetes Registry who started diabetes drugs between 1999 and 2001. Patients who started pioglitazone did not subsequently have a significantly higher adjusted rate of hospitalizations for heart failure than those starting a sulfonylurea drug (hazard ratio [HR] 1.28; 95% confidence interval [CI] 0.85–1.92). Starting insulin was associated with a higher risk, and starting metformin with a lower risk.

Masoudi et al[30] used Medicare registries to identify 16,417 patients with diabetes who were discharged after being hospitalized with a principal diagnosis of heart failure. Based on multivariate analysis, patients taking a TZD had a slightly higher rate of subsequent heart failure hospitalizations (HR 1.06, 95% CI 1.00–1.09) but a significantly lower mortality rate at 1 year (HR 0.87, 95% CI 0.80–0.94).

The same investigators did a similar study in 24,953 patients discharged after being hospitalized for myocardial infarction and found similar trends: the hazard ratio with TZD use was 1.06 for heart failure hospitalizations and 0.92 for 1-year mortality.[31]

Comment. Although the strengths of such studies are their large sample sizes, a weakness is that congestive heart failure is a subjective diagnosis that cannot be confirmed by objective variables and can be erroneously diagnosed in patients presenting with only fluid retention. Recent reviews of postmarketing reports found that most cases of edema and weight gain with rosiglitazone and pioglitazone were not associated with the development of congestive heart failure. The use of administrative data (eg, the International Classification of Diseases, Ninth Revision diagnosis of "congestive heart failure") as end points in these studies may drastically limit their findings. That being said, fluid retention can be evident in some patients who are more vulnerable, and should be carefully monitored after starting TZDs.

The prospective PROactive study[6] has further provided insight into the issue of fluid retention with TZD use. After about 3 years of follow-up, nonadjudicated heart failure events had occurred in 10.8% of patients in the pioglitazone group vs 7.5% in the placebo group (***P* < .0001**).* Patients taking pioglitazone had a 5.7% rate of hospitalization for heart failure vs 4.1% in the placebo group (***P* = .007**).* Edema without heart failure occurred in 21.6% of patients in the pioglitazone group vs 13% in the placebo group (***P* not reported**).*

The two available TZDs seem to be equal in causing fluid retention

EXPERIENCE IN PATIENTS WITH HEART FAILURE

Few studies have investigated the safety and efficacy of TZDs in patients with preexisting chronic heart failure, despite widespread

*Corrected June 2006. The version published in April 2006 incorrectly stated these differences were not statistically significant.

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TABLE 3

Patterns of fluid retention in patients taking or not taking thiazolidinediones

	TAKING A TZD (N = 19)	NOT TAKING A TZD (N = 80)
Pulmonary edema	11%	80%
Jugular venous distention	32%	73%
Ascites	0%	18%
Peripheral edema	95%	63%

DATA FROM TANG WH, FRANCIS GS, HOOGWERF BJ, YOUNG JB. FLUID RETENTION AFTER INITIATION OF THIAZOLIDINEDIONE THERAPY IN DIABETIC PATIENTS WITH ESTABLISHED CHRONIC HEART FAILURE. J AM COLL CARDIOL 2003; 41:1394–1398.

recognition of the metabolic syndrome and the potential benefits of TZDs. In fact, rosiglitazone and pioglitazone are officially contraindicated in patients with New York Heart Association (NYHA) class III or IV heart failure because these patients were excluded from the clinical trials that led to approval of these drugs. Most of the data come from sporadic case reports.

Not all weight gain with TZDs is due to fluid retention

In a retrospective study at The Cleveland Clinic,[32] we identified 111 patients with diabetes and pre-existing heart failure (NYHA class I–III) who had been treated with TZDs and 814 similar patients who did not receive TZDs. In the TZD group, 19 patients (17.1%) developed significant fluid retention, as did 9.8% of the no-TZD group. (Fluid retention was arbitrarily defined by objective evidence of weight gain plus subjective assessment of signs of fluid retention such as jugular venous distention, peripheral edema, ascites, or hepatomegaly.)

The pattern of fluid retention was different in the two groups, being mainly peripheral in the TZD group and central in the no-TZD group (TABLE 3). The severity of heart failure (assessed by chart and echocardiographic review) was similar between the two groups at baseline.

Further studies are needed to determine if TZDs can help patients with stable chronic heart failure. In view of the significant benefits of TZDs, meticulous and objective assessment of their safety is warranted, particularly for patients with heart failure.

IS FLUID RETENTION CAUSED BY THE DRUG OR BY DISEASE?

We suspect that although some patients develop TZD-related edema leading to decompensation, many cases of TZD-related "heart failure" are actually peripheral edema that is unrelated to impaired myocardial performance.

How TZDs cause fluid retention is not well understood. As with some other drugs that cause fluid retention (eg, dihydropyridine calcium channel blockers, minoxidil, estrogen, and fludrocortisone), a myriad of underlying mechanisms independent of direct cardiotoxic effects may come into play.

TZDs increase intravascular volume by up to 7%, which can be enough to dilute the blood cells and transiently lower the hematocrit. TZDs may also increase the amount of fluid that leaks out of blood vessels into susceptible tissues, such as the lungs, kidneys, and lower extremities. Another possible mechanism is that patients who develop fluid retention have increased levels of vascular endothelial growth factor; its actions on endothelial cells in the periphery may lead to peripheral edema or other mechanisms of increased vascular permeability.[33] Various mechanisms of neurohormonal activation can also cause fluid retention.

TZDs probably do not harm the heart itself; if TZDs have an effect on cardiac contractility, it is a positive effect.

St. John Sutton et al[34] randomly assigned 203 patients without evidence of heart failure to take either rosiglitazone (4 mg twice a day) or glyburide (titrated to achieve glycemic control) for 1 year and found no significant worsening of left ventricular contractility (assessed by ejection fraction) in either group.

Preliminary studies have found that in patients with mild heart failure (NYHA class I or II), neither rosiglitazone nor pioglitazone has any long-term detrimental effects on left ventricular mass or systolic function.[35,36]

New studies indicate that TZD-induced fluid retention is less likely to be due to a cardiac cause and more likely to be from a drug interaction with genetically determined receptors on sodium channels.

Hansen et al,[37] in a preliminary study in

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Denmark, performed genotyping in 345 patients receiving a TZD. They estimated that the most important risk factor for edema was a variant gene for PPAR gamma-2 (Pro12Ala), and that withholding TZDs from people with this variant gene would eliminate 57% of cases of TZD-associated edema. Baseline body mass index, ethnicity, or dose did not contribute significantly to the risk.

Zhang et al[38] found that knockout mice lacking a collecting-duct-specific PPAR-gamma gene in the kidney did not gain weight or retain fluid after being fed rosiglitazone. In addition, in vitro experiments showed that rosiglitazone activates sodium transport in the collecting duct cells expressing the PPAR-gamma gene. This may explain findings from clinical experience that treating TZD-induced fluid retention with loop diuretics is less effective than using aldosterone receptor antagonists or withdrawing TZDs.

New selective PPAR gamma modulators now in preclinical development appear to activate a subset of genes that control glucose levels without causing fluid retention.[39] A preliminary study of metaglidasen, a new insulin sensitizer currently in early clinical development, showed it to lower blood glucose and lipid levels powerfully without significant side effects of weight gain and edema.[40]

IDENTIFYING RISK OF EDEMA AND HEART FAILURE WITH TZD USE

Although fluid retention seems to be unpredictable in most cases, it is more likely to occur in patients using insulin, in patients with underlying cardiac dysfunction (eg, diastolic dysfunction or a history of congestive heart failure), or in patients with conditions such as chronic renal insufficiency that tend to cause fluid retention.

When a patient with diabetes develops fluid retention, underlying cardiac causes (eg, ischemia, heart failure) should be ruled out, and fluctuations in glycemic control leading to signs and symptoms mimicking heart failure should be considered. Patients with both diabetes and renal disease are at increased risk of edema regardless of TZD use.

Distinguishing between weight gain from increased fat, progressive heart failure decompensation, and fluid retention can be challenging. Both rosiglitazone and pioglitazone commonly cause weight gain, possibly due to increased calorie retention and fluid retention. Combining either drug with a sulfonylurea tends to cause a gain of 1.8 to 2.9 kg, which may plateau in time. Combining a TZD with insulin tends to cause even more weight gain (2–5 kg) independent of fluid retention.

Monitoring heart failure with BNP

B-type natriuretic peptide (BNP) is one of a family of naturally occurring hormones that are synthesized in the cardiac ventricles.

Extensive clinical data show that sequential plasma BNP measurements accurately track the degree of cardiac dysfunction; elevated levels are associated with higher intracardiac filling pressures in patients with left ventricular dysfunction and can provide reliable diagnostic and prognostic information.

Measuring BNP sequentially is a novel strategy to monitor the response to therapy and the development of fluid retention in patients starting TZDs. Dargie et al[41] found that higher baseline plasma BNP levels are associated with a greater risk of developing fluid retention in patients started on rosiglitazone. Ogawa et al[42] monitored the change in plasma BNP levels after 4 weeks of treatment with pioglitazone in 30 patients with diabetes and no sign of heart failure and found that BNP levels were a good marker of underlying left ventricular dysfunction. However, results must be interpreted in their clinical context, as plasma BNP levels can vary widely, and renal disease can confound measurements. Hence, further studies are needed before we can reliably use natriuretic peptide testing to detect those at risk of developing fluid retention. At present, there is not enough evidence to support the routine use of BNP testing for screening purposes in otherwise asymptomatic patients.

Before starting a TZD, assess for heart failure

MANAGING FLUID RETENTION

Fluid retention can occur even at the lowest doses of a TZD. However, for most patients the edema is mild. Partial or complete resolution has occurred in the majority of cases, and few serious adverse effects have been reported, particularly when TZDs are stopped.

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Diuretics and ACE inhibitors have a variable effect on edema caused by TZDs. Loop diuretics help to some degree, but in many cases where profound fluid retention occurs, withdrawal of TZDs may be the only option. Other strategies include adding spironolactone or reducing the TZD dosage. It is also important to make sure that fluid retention is not due to hyperglycemia, since effects of glucose-lowering can be delayed, particularly in the setting where TZDs are needed to replace other diabetic drugs.

GUIDELINES FOR TZD USE IN PATIENTS WITH HEART FAILURE

In a consensus statement, the American Heart Association and American Diabetes Association caution about the use of TZDs in patients with known or suspected heart failure.[43] Some have even suggested that TZDs may unmask previously asymptomatic cardiac insufficiency by increasing plasma volume. Building on the same principles for prescribing heart failure drugs, the recommendations, in short, are as follows:

- Before prescribing a TZD, perform a thorough history and physical examination for risk factors, such as a previous myocardial infarction or significant valvular disease, that could predispose a patient to congestive heart failure. Record any baseline dyspnea or edema.
- Consider other medications, such as vasodilators, that may contribute to fluid retention. Agents such as nonsteroidal anti-inflammatory drugs should be discontinued if possible.
- Peripheral edema is not a contraindication for TZD use, but it should be monitored during TZD therapy.

Warn those starting a TZD to watch for fluid retention, or other signs of congestive heart failure

- After starting a TZD, patients should be instructed to report a weight gain of more than 3 kg, new pedal edema, dyspnea, or fatigue. Patients should be warned that these side effects may occur around 4 to 8 weeks after starting the drug.
- In patients without known heart disease but with one or more cardiac risk factors, start the TZD at a low dose and increase it cautiously, with special attention to fluid overload.
- TZDs may be used with close supervision in patients with mild to moderate congestive heart failure (NYHA class I or II). However, one should start with a very low dose, and increase it slowly and cautiously, watching for significant weight gain (> 6 pounds or 3 kg within a few weeks), pedal edema, or acute onset of shortness of breath.
- TZDs should be avoided in patients with moderate to severe heart failure (NYHA class III or IV).
- If fluid retention develops during TZD therapy, especially in the first few months of treatment, thoroughly investigate for congestive heart failure with an electrocardiogram or echocardiogram, and, if needed, confirm with a serum BNP measurement.
- If a patient treated with a TZD has evidence of fluid retention, the TZD dosage may be lowered or discontinued. Adding an angiotensin-converting enzyme inhibitor with or without a thiazide diuretic may reduce edema.
- Consider discontinuing TZD treatment for any patient who develops congestive heart failure. After it is discontinued, symptoms of volume overload usually resolve quickly with short-term diuretic therapy. ■

REFERENCES

1. **Bell DS.** Heart failure: the frequent, forgotten, and often fatal complication of diabetes. Diabetes Care 2003; 26:2433–2441.
2. **Iribarren C, Karter AJ, Go AS, et al.** Glycemic control and heart failure among adult patients with diabetes. Circulation 2001; 103:2668–2673.
3. **Stratton IM, Adler AI, Neil HA, et al.** Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000; 321:405–412.
4. **Yki-Jarvinen H.** Thiazolidinediones. N Engl J Med 2004; 351:1106–1118.
5. **Wang CH, Weisel RD, Liu PP, Fedak PW, Verma S.** Glitazones and heart failure: critical appraisal for the clinician. Circulation 2003; 107:1350–1354.
6. **Dormandy JA, Charbonnel B, Eckland DJ, et al.** 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.
7. Avandia [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2000.
8. Actos [package insert]. Lincolnshire, IL: Takeda Pharmaceutical America, Inc.; 2002.
9. **Niemeyer NV, Janney LM.** Thiazolidinedione-induced edema. Pharmacotherapy 2002; 22:924–929.
10. **Goldberg RB, Kendall DM, Deeg MA, et al.** A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care 2005; 28:1547–1554.
11. **Rubin CJ, Viraswami-Appanna K, Fiedorek FT.** Glycemic efficacy and

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safety of muraglitazar, a novel dual peroxisome proliferator-activated receptor-alpha/gamma agonist, in patients with type 2 diabetes: results of a double-blind, randomized, parallel group, dose-comparison study [abstract 860]. Endocr Pract 2005; 2005:24.
12. **Goldstein BJ, Rosenstock J, Anzalone D, Tou C, Ohman P.** Tesaglitazar improves glucose and lipid abnormalities in patients with type 2 diabetes [abstract 83-OR]. Diabetes 2005; 54:A21.
13. **Gorson DM.** Significant weight gain with rezulin therapy [letter]. Arch Intern Med 1999; 159:99.
14. **Hirsch IB, Kelly J, Cooper S.** Pulmonary edema associated with troglitazone therapy. Arch Intern Med 1999; 159:1811.
15. **Thomas ML, Lloyd SJ.** Pulmonary edema associated with rosiglitazone and troglitazone. Ann Pharmacother 2001; 35:123–124.
16. **McMorran M, Vu D.** Rosiglitazone (Avandia): hepatic, cardiac and hematological reactions. CMAJ 2001; 165:82–87.
17. **Wang F, Aleksunes LM, Reagan LA, Vergara CM.** Management of rosiglitazone-induced edema: two case reports and a review of the literature. Diabetes Technol Ther 2002; 4:505–514.
18. **Page RL 2nd, Gozansky WS, Ruscin JM.** Possible heart failure exacerbation associated with rosiglitazone: case report and literature review. Pharmacotherapy 2003; 23:945–954.
19. **Kermani A, Garg A.** Thiazolidinedione-associated congestive heart failure and pulmonary edema. Mayo Clin Proc 2003; 78:1088–1091.
20. **Bell DS.** Unilateral edema due to a thiazolidinedione. Diabetes Care 2003; 26:2700.
21. **Jamieson A, Abousleiman Y.** Thiazolidinedione-associated congestive heart failure and pulmonary edema. Mayo Clin Proc 2004; 79:571.
22. **Srivastava PM, Calafiore P, MacIsaac RJ, Hare DL, Jerums G, Burrell LM.** Thiazolidinediones and congestive heart failure—exacerbation or new onset of left ventricular dysfunction? Diabet Med 2004; 21:945–950.
23. **Singh N.** Rosiglitazone and heart failure: long-term vigilance. J Cardiovasc Pharmacol Ther 2004; 9:21–25.
24. **Shah M, Kolandaivelu A, Fearon WF.** Pioglitazone-induced heart failure despite normal left ventricular function. Am J Med 2004; 117:973–974.
25. **Cheng AY, Fantus IG.** Thiazolidinedione-induced congestive heart failure. Ann Pharmacother 2004; 38:817–820. Epub 2004 Mar 23.
26. **Wang F, Vergara C, Carabino J, Desilets A, Vasquez R.** Continuation of thiazolidinedione therapy in patients without left ventricular dysfunction who developed edema and congestive-heart-failure symptoms. Am J Health Syst Pharm 2004; 61:1604–1608.
27. **Marceille JR, Goins JA, Soni R, Biery JC, Lee TA.** Chronic heart failure-related interventions after starting rosiglitazone in patients receiving insulin. Pharmacotherapy 2004; 24:1317–1322.
28. **Delea TE, Edelsberg JS, Hagiwara M, Oster G, Phillips LS.** Use of thiazolidinediones and risk of heart failure in people with type 2 diabetes: a retrospective cohort study. Diabetes Care 2003; 26:2983–2989.
29. **Karter AJ, Ahmed AT, Liu J, Moffet HH, Parker MM.** Pioglitazone initiation and subsequent hospitalization for congestive heart failure. Diabet Med 2005; 22:986–993.
30. **Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM.** Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. Circulation 2005; 111:583–590.
31. **Inzucchi SE, Masoudi FA, Wang Y, et al.** Insulin sensitizers following acute myocardial infarction: effects on mortality and readmission [abstract 256-OR]. Diabetes 2005; 54:A63.
32. **Tang WH, Francis GS, Hoogwerf BJ, Young JB.** Fluid retention after initiation of thiazolidinedione therapy in diabetic patients with established chronic heart failure. J Am Coll Cardiol 2003; 41:1394–1398.
33. **Emoto M, Anno T, Sato Y, et al.** Troglitazone treatment decreases plasma vascular endothelial growth factor in diabetic patients and its mRNA in 3T3-L1 adipocytes. Diabetes 2001; 50:1166–1170.
34. **St. John Sutton M, Rendell M, Dandona P, et al.** A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. Diabetes Care 2002; 25:2058–2064.
35. **Perez A, Khan M, Gallagher P, Chen Y.** Evaluation of echocardiographic parameters in patients with mild heart failure receiving pioglitazone or glyburide [abstract 53]. Endocr Pract. 2004; 10:19.
36. **Dargie H, Hildebrandt PR, Riegger G, et al.** Rosiglitazone does not adversely affect cardiac structure and function as determined by echocardiography in patients with type 2 diabetes and class I/II heart failure [abstract 874-3]. J Am Coll Cardiol 2005; 45:186A.
37. **Hansen L, Ekstrom CT, Palacios RTY, Wassermann I, Reinhardt R.** The Pro12Ala variant of PPARg-2 gene is a pharmacogenetic risk factor for PPARg agonist induced edema in type 2 diabetic patients [abstract 1194-P]. Diabetes 2005; 54:A291.
38. **Zhang H, Zhang A, Kohan DE, Nelson RD, Gonzalez FJ, Yang T.** Collecting duct-specific deletion of peroxisome proliferator-activated receptor gamma blocks thiazolidinedione-induced fluid retention. Proc Natl Acad Sci U S A 2005; 102:9406–9411.
39. **Berger JP, Petro AE, Macnaul KL, et al.** Distinct properties and advantages of a novel peroxisome proliferator-activated protein γ selective modulator. Mol Endocrinol 2003; 17:662–676.
40. **Rosenstock J, Flores-Losano F, Schwartz S, Gonzalez-Galvez G, Karpf DB.** MBX-102: A novel non-TZD insulin sensitizer that improves glycemic control without causing edema or weight gain in patients with type 2 diabetes mellitus (T2DM) on concomitant insulin therapy [abstract 44-OR]. Diabetes 2005; 54:A11.
41. **Dargie H, Hildebrandt PR, Riegger G, et al.** Baseline B-type natriuretic peptide identifies patients with type 2 diabetes and class I/II heart failure at risk of fluid retention when treated with rosiglitazone [abstract 1048-173]. J Am Coll Cardiol 2005; 45:139A.
42. **Ogawa S, Takeuchi K, Ito S.** Plasma BNP levels in the treatment of type 2 diabetes with pioglitazone. J Clin Endocrinol Metab 2003; 88:3993–3996.
43. **Nesto RW, Bell D, Bonow RO, et al.** Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. Circulation 2003; 108:2941–2948.

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