Thiazolidinedione Use, Fluid Retention, and Congestive Heart Failure

A consensus statement from the American Heart Association and American Diabetes Association

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Diabetes is a chronic, progressively worsening disease associated with a variety of microvascular and macrovascular complications. Cardiovascular disease (CVD) is the main cause of death in these patients (1,2). During the past decade, numerous drugs have been introduced for the treatment of type 2 diabetes that, used in monotherapy or in combination therapy, are effective in lowering blood glucose to achieve glycemic goals and in reducing diabetes-related end-organ disease.

Two such drugs, rosiglitazone and pioglitazone, belong to the class called thiazolidinediones (TZDs) (3). Troglitazone, the first agent of this class to be approved, was effective in controlling glycemia but was removed from the market because of serious liver toxicity. Both rosiglitazone and pioglitazone are indicated either as monotherapy or in combination with a sulfonylurea, metformin, or insulin when diet, exercise, and a single agent do not result in adequate glycemic control (4) (package insert Avandia [rosiglitazone maleate; GlaxoSmithKline] and Actos (5) [pioglitazone hydrochloride; Takeda Pharmaceuticals]). In addition to lowering blood glucose, both drugs may benefit cardiovascular parameters, such as lipids, blood pressure, inflammatory biomarkers, endothelial function, and fibrinolytic status (6,7).

These beneficial effects of TZDs on glycemia and cardiovascular risk factors have made them attractive agents in patients with type 2 diabetes who are at high risk for CVD. There is a growing recognition, however, that edema can occur in patients treated with either drug. Because people with diabetes are at increased risk for CVD and many have preexisting heart disease, the edema that sometimes accompanies the use of a TZD can be cause for concern, as it may be a harbinger or sign of congestive heart failure (CHF). An analysis of Medicare beneficiaries hospitalized with the diagnosis of diabetes and CHF indicated that the number of these patients discharged on TZDs had increased from 7.2% to 16.2% over a 3-year period (8). As the number of patients taking these drugs to control glycemia increases, practitioners should be aware of the safety profile of TZDs in patients with and without underlying heart disease.

The clinical trials evaluating the safety and efficacy of both TZD drugs excluded subjects in New York Heart Association (NYHA) class III or IV cardiac functional status. In other words, patients with moderate to severe limitation of physical activity due to symptoms of angina or CHF during daily activities or at rest were not enrolled. In addition, although these trials did include patients with class I or II NYHA cardiac status, it is not clear exactly what percentage of the total patients studied fell into these latter two categories. Also, clinicians or investigators may have knowingly excluded patients with significant underlying heart disease. Regardless, there were very few serious cardiac events in the short-term clinical trial data submitted with the new drug applications for either TZD.

Risk factors for CHF, such as coronary artery disease and hypertension, frequently occur in patients with diabetes (1,9). These risk factors act synergistically in diabetes to increase the risk for CHF. Diabetes also may affect cardiac structure and systolic or diastolic function, independent of other established risk factors for CHF, as a result of diabetic cardiomyopathy (10–12). Therefore, diabetes is a strong and independent risk factor for CHF. For example, an analysis of a large number (n = 9,591) of registrants with type 2 diabetes in the Kaiser Permanente Northwest Division demonstrated that CHF was present in 11.8% of diabetic subjects at baseline, and an additional 7.7% developed CHF over a 30-month follow-up period (13). Clinicians should be cognizant that CHF or left ventricular dysfunction (systolic or diastolic) may be present at the time TZDs are first prescribed or may occur over time during TZD treatment. Patients with type 2 diabetes who have significant underlying asymptomatic heart disease may also be prescribed these drugs, even though their safety in such patients has not been fully established.

The package inserts for both rosiglitazone and pioglitazone indicate that patients with more advanced heart disease (class III or IV) were excluded in premarketing clinical trials, and hence, these drugs are not recommended in such patients. At present, there are no guidelines on the use of TZDs in patients with diabetes who have any degree of heart disease or for those already on a TZD who develop CHF. Because edema is a more frequent side effect of TZD therapy and by itself is often a perplexing clinical dilemma with multiple causes (14), clini-

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cians may need guidance when edema (or unexpected weight gain) is encountered in a patient on a TZD. For these reasons, the American Diabetes Association and the American Heart Association assembled a workgroup to evaluate the use of TZDs in patients with preexisting heart disease and in those who develop edema or unexpected weight gain during the course of TZD therapy. This statement is a summary of the workgroup's findings and recommendations.

DEVELOPMENT OF WEIGHT GAIN AND TZDS — In a 52-week study comparing rosiglitazone to a sulfonylurea (glyburide, median dose 7.5 mg/day), a mean weight gain of 1.9 kg was observed in both the sulfonylurea group and the rosiglitazone group at the 4-mg daily dose, and a 2.9-kg weight gain was observed at the rosiglitazone 8-mg daily dose (4). When coadministered with a sulfonylurea in a 26-week study, rosiglitazone at 4 mg/day was associated with a 1.8-kg weight gain compared with sulfonylurea alone. Similar weight gain has been observed when rosiglitazone is added to metformin. When added to insulin therapy, however, weight gain may be more dramatic. After 6 months of treatment, weight gains of 4.1 kg and 5.4 kg were encountered when rosiglitazone, at the 4-mg and 8-mg daily doses, respectively, was added to insulin (mean dose 70 units/day), compared with a weight gain of ~1 kg in patients treated with insulin alone (4). Similar increases have been observed with pioglitazone, either as monotherapy or in combination with other hypoglycemic therapies, although the duration of treatment was not identical (15). Compared with placebo, pioglitazone monotherapy caused median weight gains of 0.9, 1.0, and 2.6 kg at the 15-, 30-, and 45-mg daily doses, respectively (5). Median weight gains of 2.3 and 3.6 kg occurred when pioglitazone at 15 and 30 mg daily was added to insulin. In contrast to trials with rosiglitazone, which included changes in weight gain at rosiglitazone's highest recommended daily dose (8 mg), the clinical trial data submitted to the U.S. Food and Drug Administration in support of pioglitazone did not include data on weight gain at its highest recommended daily dose of 45 mg when coadministered with sulfonylurea, metformin, or insulin, although these data have recently been cited. Thus, the weight gain associated with TZD use seems to be dose dependent, although in one 4-month randomized open-label trial, similar increases in body weight (~2 kg) were seen across the entire dose ranges of rosiglitazone (2 to 8 mg/day) and pioglitazone (15 to 45 mg/day) (16).

The weight gain associated with the use of TZDs is probably due to several interacting factors. In general, improvement in glycemic control with decreased glycosuria and caloric retention may result in increased weight. Several studies have shown that the weight gain with TZDs may be associated with an increase in subcutaneous adipose tissue and a concomitant decrease in visceral fat; although subcutaneous fat area increases, visceral fat area and the ratio of visceral to subcutaneous fat decrease (17,18). This change in fat distribution may explain in part the improvement in glycemic control despite an overall increase in body weight (19). A decrease in leptin levels and an increase in appetite have been seen with troglitazone treatment (20); however, it is not clear if weight gain associated with rosiglitazone or pioglitazone can be attributed to this effect. Fluid retention, of course, is another potential cause of increased body weight. TZDs, whether administered alone or in combination with metformin, sulfonylurea, or insulin, are often accompanied by an increase in plasma volume. In healthy volunteers who received rosiglitazone (8 mg once daily) for 8 weeks, there was a small but statistically significant increase in mean plasma volume of ~1.8 ml/kg compared with placebo (4). For rosiglitazone, the fall in hemoglobin ranged from 0.8 to 1.1 g/dl (with a similar fall in hematocrit ranging from 2.3% to 3.6%) relative to whether the drug was used as monotherapy or combination with other oral agents or insulin (4). Similar decreases in hemoglobin have been observed with pioglitazone (5). These changes in weight gain and blood profile are usually observed during the first weeks of therapy and plateau thereafter. No clinically significant changes in other cellular components of blood have been seen, nor has an increase in red blood cell turnover been demonstrated, which suggests that TZDs have no effect on erythropoiesis (21,22). Thus, the changes in hemoglobin and hematocrit may reflect, in part, hemodilution resulting from increased plasma volume. With an increase in plasma volume, mild to moderate edema and CHF might be anticipated side effects of treatment with these drugs, dependent to some degree on whether TZDs are used in conjunction with insulin (see below) and on the presence and degree of concomitant heart disease.

DEVELOPMENT OF EDEMA AND TZDS — When used as monotherapy, the incidence of pedal edema ranges from 3% to 5% for each of the TZDs. The incidence is greater when the drugs are used in combination with other glucose-lowering agents. In the U.S. placebo-controlled trials, edema occurred in 4.8% of subjects on pioglitazone monotherapy, versus 1.2% on placebo (23). When pioglitazone was combined with sulfonylureas, edema was noted in 7.5% of patients compared with 2.1% on sulfonylureas alone. Edema was seen in 6.0% of patients on a pioglitazone/metformin combination versus 2.5% on metformin alone (24,25). In double-blind trials with rosiglitazone, the incidence of edema was 4.8% in the rosiglitazone group compared with 1.3% on placebo. When combined with metformin or sulfonylurea, edema was observed in 3% to 4% of patients compared with 1.1% to 2.2% on either comparator drug alone (4). These data suggest that edema is a side effect of each of the TZD drugs to a similar degree, either when used as monotherapy or when combined with other oral diabetes agents. Edema is more common when the TZD is used in combination therapy.

Practitioners are most likely to see edema as a consequence of TZD therapy when either of the TZDs is used in combination with insulin. For example, rosiglitazone 4 or 8 mg per day in combination with insulin was associated with a 13.1% and 16.2% incidence of edema, respectively, compared with 4.7% in those taking insulin alone (26). Pioglitazone at 15 mg or 30 mg daily in combination with insulin resulted in a combined 15.3% incidence of edema, compared with 7.0% for insulin alone (27). Therefore, the incidence of edema is higher when either of the TZDs is combined with insulin, compared with when TZDs are used in combination therapy with additional oral hypoglycemic agents. It should be noted, however, that edema occurs more often in patients treated with insulin than in patients on other oral hypoglycemic drugs. Type 2 diabetes patients on insulin usually have had

diabetes for many years and thus are likely to be older and have a greater prevalence of hypertension, left ventricular hypertrophy, and a history of coronary artery disease—all conditions more likely to be associated with edema. Indeed, among 166 diabetic patients treated with TZD who had numerous comorbid conditions and were monitored at a Veterans Affairs Clinic over 14 months, edema developed in 18.1%. Baseline azotemia, prior CHF, and coronary artery disease were common in this group (28). The prevalence of background CHF in patients treated with insulin alone may also be higher than in patients not receiving insulin (2.5% in some rosiglitazone trials) (28,29). thereby contributing to a higher incidence of edema when a TZD is added to insulin compared with other glucose-lowering agents. Although the TZDs have not been compared with each other at equipotent dosages, the incidence of edema was similar when either drug was combined with other hypoglycemic drugs in a short-term, nonrandomized clinical study (16).

PATHOGENESIS OF EDEMA WITH TZD USE — The reasons for fluid retention and peripheral edema with TZD use are not fully understood and are likely to be multifactorial. The increase in plasma volume related to TZDs has already been cited and may result from a reduction in renal excretion of sodium and an increase in sodium and free water retention (30). TZDs may interact synergistically with insulin to cause arterial vasodilatation, leading to sodium reabsorption with a subsequent increase in extracellular volume, and thereby resulting in pedal edema. Increased sympathetic nervous system activity (31), altered interstitial ion transport (32), alterations in endothelial permeability (33), and peroxisome proliferator–activated receptor-γ–mediated expression of vascular permeability growth factor (34) represent other possible mechanisms for edema with these agents.

TZDS AND CHF — In clinical trials using TZDs, CHF was not frequently encountered. The incidence of CHF was <1% for rosiglitazone monotherapy or when rosiglitazone was added to sulfonylurea or metformin, and was similar to that observed during treatment with a placebo (4). When rosiglitazone at either 4 or 8 mg/day was added to insulin therapy, however, CHF increased to 2% and 3% of the study population, respectively, compared with 1% in the group treated with insulin alone (4). It is important to note that preexisting microvascular and cardiovascular comorbidity was more prevalent in those clinical trials in which rosiglitazone was added to insulin therapy than in those trials in which rosiglitazone was either used alone and compared with placebo or combined with metformin or sulfonylureas. The patients who developed CHF on rosiglitazone plus insulin were also older and had diabetes of longer duration.

The data on pioglitazone are somewhat similar. In a placebo-controlled trial (5), 2 of 191 patients (1.1%) receiving 15 mg pioglitazone plus insulin and 2 of 188 (1.1%) patients receiving pioglitazone (30 mg) plus insulin developed CHF, compared with none of the 187 patients receiving insulin alone. All four of these patients had underlying coronary artery disease.

The rosiglitazone and pioglitazone trials are not entirely comparable, as the rosiglitazone maximum recommended daily dose (8 mg/day) was evaluated in the rosiglitazone trials, whereas pioglitazone was not evaluated at its highest dose of 45 mg/day when combined with other hypoglycemic agents. Also, here too, the duration of treatment differed appreciatively—26 weeks with rosiglitazone and 16 weeks with pioglitazone. It is unlikely, however, that the drugs differ with regard to the risk of CHF, as they incur similar degrees of volume expansion. In summary, the incidence of CHF in TZD-treated patients is very low but is definitely higher in patients already treated with insulin who receive higher doses of the TZD and who have other risk factors for CHF.

PATHOGENESIS OF CHF WITH TZD USE — The peripheral edema or CHF associated with the use of the drugs would suggest that an increase in plasma volume is the main culprit, either alone or superimposed on preexisting heart disease. The effect of TZDs on cardiac structure and function has been reported in a few studies. An increase in left ventricular mass as an adaptation to volume expansion has been noted in animals given long-term troglitazone administration at doses exceeding those used in the clinical setting (35). In clinical trials, however, treatment with troglitazone did not result in any significant change in left ventricular mass after 48 weeks of observation (36). In a recent study (37), 203 patients were randomly assigned to either rosiglitazone (4 mg b.i.d.) or glyburide (mean dose 10.5 mg q.d. and titrated to ≤20 mg/day). An echocardiogram was performed on 118 of these patients before and 52 weeks after treatment to assess left ventricular mass index, ejection fraction, and end-diastolic volume. Neither drug produced an increase in left ventricular mass index that exceeded one standard deviation or a decrease in left ventricular ejection fraction in either group, and both drugs were associated with clinically insignificant increases in left ventricular end-diastolic volume. Fluid retention resulting in increased plasma volume was thought to explain the small but insignificant increase in left ventricular end-diastolic volume seen with rosiglitazone in this study. Similarly, a preliminary report (38) using pioglitazone evaluated cardiac mass and function in patients with type 2 diabetes in a long-term, open-label study. Pioglitazone to a maximum dose of 60 mg q.d. for up to 48 weeks had no adverse effect on cardiac structure and function as evaluated by echocardiography. Unfortunately, there are no published data on cardiac structure and function in patients on long-term TZD therapy who have preexisting left ventricular dysfunction or who develop an acute coronary event while receiving TZD therapy. There are, however, animal studies suggesting that TZDs may have a beneficial effect on left ventricular remodeling and function after ischemic injury (39,40).

The effect of rosiglitazone on the left ventricular response to ischemia has been assessed in an ischemia-reperfusion model in experimental animals. When rosiglitazone was administered immediately before an episode of ischemia, the full recovery of left ventricular function after reperfusion was more rapid compared with control animals (39). A recent study has also demonstrated that pioglitazone improved left ventricular remodeling and partially normalized systolic function in mice after extensive anterior myocardial function (40). These cardioprotective effects of TZDs are independent of glucose lowering and may be due to antioxidant, anti-inflammatory, or calcium channel–blocking properties of the

drugs. Hence, it is possible that TZDs may have direct effects on cardiac muscle that prevent heart failure in the setting of acute ischemia.

CLINICAL PRACTICE EXPERIENCE WITH TZDS — Epidemiological studies have also examined the relationship between TZDs and the risk of CHF. Delea and coworkers (41), in a retrospective, observational study of health insurance claims, determined the risk of heart failure among diabetic patients prescribed TZDs over a 5-year period (1996–2001), with a mean follow-up period of 8.5 months. The risk of heart failure was 4.5% in the groups exposed to TZDs and 2.6% in those not exposed to a TZD. The increased risk (hazard ratio of 1.6, $P < 0.001$) persisted after adjustment for potential confounders, including age, history of complications of diabetes, risk factors for CHF, and use of various medications for diabetes or CHF. Increased risk was also associated with advanced age, history of coronary artery disease, diabetes-related end-organ disease, and the use of angiotensin-converting enzyme inhibitors, β-blockers, or insulin.

In another preliminary report by Karter and coworkers (42), using the Kaiser Permanente Northern California Registry, the incidence of CHF was evaluated in ~27,000 patients with diabetes not previously treated with oral hypoglycemic drugs who were prescribed pioglitazone or other glucose-lowering drugs in a nonrandomized manner and monitored for 1.5 years in a prospective, observational cohort study. Overall, 74 (0.2%) of the 24,973 subjects without prior history of CHF experienced a first episode of CHF, and 69 (3.5%) of the 1,964 patients with a history of CHF experienced a subsequent bout. Compared with patients given a sulfonylurea, the hazard ratio for CHF in patients receiving pioglitazone was 1.8. Patients in this study treated with pioglitazones or insulin, either alone or in combination, had a higher risk profile for CHF before initiation of glucose-lowering therapy. Such patients also were more likely to have diabetes of longer duration, a history of hypertension, or microalbuminuria or to be treated for hyperlipidemia. When adjusted for risk factors associated with heart failure as well as determinants of diabetes severity and socioeconomic status, the TZD hazard ratio decreased to 1.2 and was similar to that of insulin combined with other oral hypoglycemic agents. The risk for recurrent heart failure in those subjects in whom a diagnosis of CHF had been made in the 5 years before implementation of glucose-lowering therapy was not significantly elevated in the pioglitazone group or in the group treated with insulin in combination with either metformin or sulfonylurea, compared with those given a sulfonylurea. These authors concluded that the risk profiles of patients initiated on pioglitazone therapy (or on insulin) identified them as being at increased risk for CHF before TZD treatment was begun and that there appeared to be no significant increase in CHF with pioglitazone treatment after adjusting for preexisting disease severity.

This Karter study suggests that despite the common occurrence of edema with TZDs, the excess risk of CHF attributable to the TZD itself in relative terms is very small. A report from the Cleveland Clinic (43) evaluated the occurrence and characteristics of fluid retention in an observational analysis of patients with type 2 diabetes, class I to III CHF, and a documented ejection fraction of ≤45% who were treated with troglitazone, rosiglitazone, or pioglitazone over a 2-year period. Of the 111 subjects, 19 (17.1%) developed fluid retention, defined as a weight gain of ≥10 lb associated with peripheral edema. Of these 19, 6 (5.4%) manifested worsening jugular venous distension, and 2 experienced pulmonary edema. Fluid retention was related to female gender and concomitant insulin use but not related to degree of underlying CHF severity. Although not a prospective study, this study suggested that despite posing a "significant" risk for edema, TZDs could be used in diabetic patients with "stable" CHF as long as they are closely monitored for signs of fluid overload. Several clinical trials are underway that will help define the level of risk for CHF in TZD-treated patients. Many of these prospective controlled studies have predetermined cardiovascular end points and are being carried out in subjects with impaired glucose tolerance or type 2 diabetes with and without underlying heart disease.

Despite the low incidence of CHF in clinical trials and cohort studies, there have been a small number of case reports that have described CHF in these patients treated with TZDs (28,44–48). These reports are noteworthy inasmuch as TZDs were used in patients with diabetes and a wide spectrum of background cardiovascular conditions, and this experience could illustrate what may be encountered in clinical practice. In these reports, CHF occurred in patients with either depressed or normal systolic function and was usually encountered when the TZD was used in combination with insulin. In most cases, the onset of CHF was preceded by the appearance of edema after initiation of TZD treatment. CHF in the setting of normal systolic function may be particularly common in the setting of diabetes, as diabetes may decrease left ventricular compliance even in the absence of hypertension and ischemic heart disease. Considering the volume sensitivity of such patients, a new diagnosis of CHF in a patient recently begun on TZDs could be attributable to the increase in plasma volume unmasking previously asymptomatic and unrecognized diastolic dysfunction. These case reports indicate that significant CHF can occur and may be directly attributable to TZD therapy. Although warnings exist on the use of TZDs in patients with significant heart disease, clinicians should be aware that CHF can sometimes occur in the patient with diabetes who otherwise appears to be at low risk for such adverse events. Despite these reports and the possibility of underreporting of drug-related adverse events or side effects, the risk of CHF seems to be very low, given the number of patients treated with TZDs.

RECOMMENDATIONS — On consideration of the above information, the workgroup recommends the following (see Fig. 1):

Before TZD treatment, the physician should:

A. Ascertain whether the patient has underlying cardiac disease—i.e., previous myocardial infarction or other evidence of coronary artery disease, prior episodes of CHF, or significant aortic or mitral valve disease.
B. Note whether the patient is taking any drugs associated with fluid retention (e.g., vasodilators, nonsteroidal anti-inflammatory drugs) or pedal edema (e.g., calcium channel–blocking drugs).
C. Evaluate the pathogenesis of edema

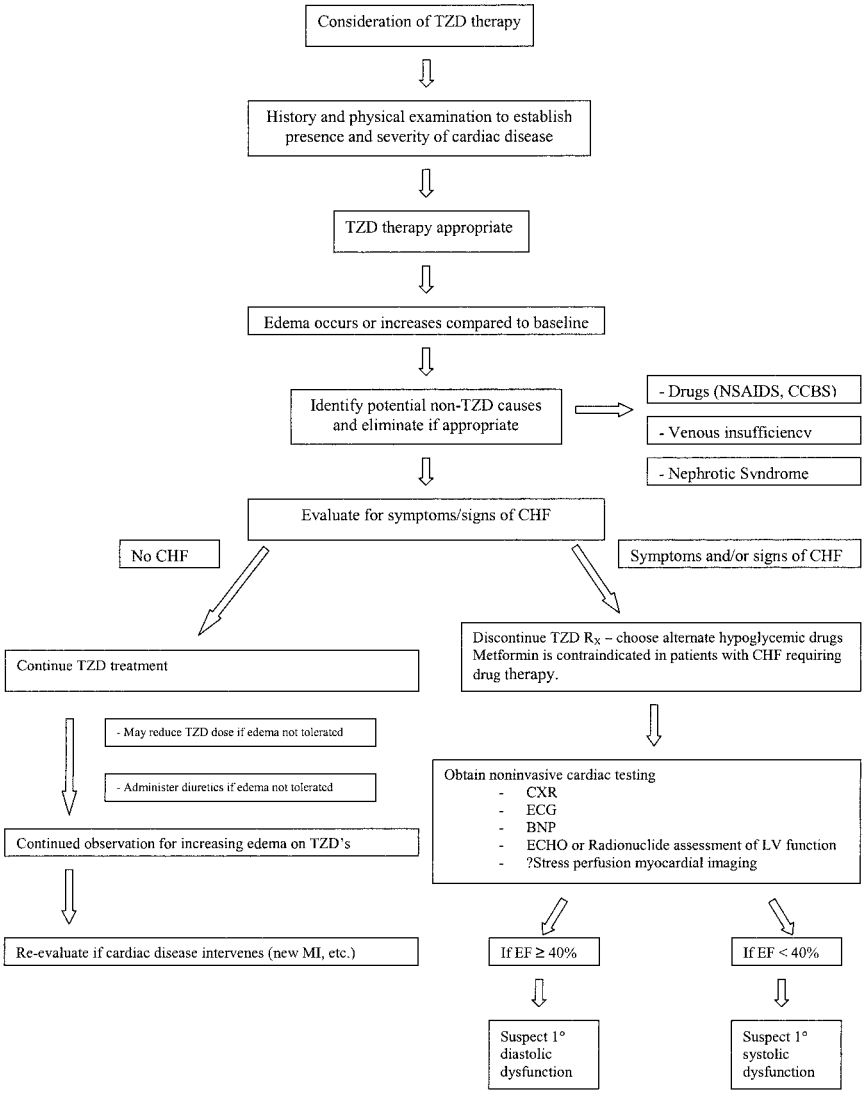

Figure 1

that may be already present to be sure that CHF is not present at the time the TZD is prescribed. The presence of edema, when not caused by CHF, is not a contraindication for TZD use. However, if present, the degree of edema should be monitored carefully during TZD administration.

D. Determine whether the patient has any shortness of breath, particularly with exertion, that might be due to cardiac or other causes (e.g., asthma, chronic obstructive pulmonary disease, obesity) so that an adequate assessment of baseline symptoms is established. Patients with these symptoms should be monitored carefully, particularly in the first 3 months of TZD treatment.

E. Review most recent ECG, if indicated. The ECG may show a clinically silent myocardial infarction or left ventricular hypertrophy—two conditions that are risk factors for CHF.

F. Instruct the patient before initiation of TZD to report any new sign or symptom during the course of treatment, such as weight gain >3 kg, pedal edema (particularly if the onset is acute and the amount progresses rapidly), shortness of breath, or fatigue without other apparent cause.

Use of TZDs in Patients With Diabetes and Without Symptomatic Heart Disease

- In patients without established heart disease, both pioglitazone and rosiglitazone should be prescribed according to the package insert guidelines for each drug. It should be recognized that weight gain and/or edema will be encountered more often in patients on concomitant insulin treatment.
- When a TZD is prescribed to patients who do not have established heart disease but have one or more risk factors for CHF (see Table 1), one should consider starting with low doses (e.g., rosiglitazone 4 mg q.d. or pioglitazone 15 mg q.d.) and increase the dosage gradually as required to optimize glycemic control, while observing for any signs of excessive weight gain, peripheral edema, or CHF.
- In patients who do not have symptoms or signs of CHF but are known to have

Table 1—*Risk factors for heart failure in patients treated with TZDs*

1.	History of heart failure (either systolic or diastolic)
2.	History of prior myocardial infarction or symptomatic coronary artery disease
3.	Hypertension
4.	Left ventricular hypertrophy
5.	Significant aortic or mitral valve heart disease
6.	Advanced age (>70 years)
7.	Long-standing diabetes (>10 years)
8.	Preexisting edema or current treatment with loop diuretics
9.	Development of edema or weight gain on TZD therapy
10.	Insulin coadministration
11.	Chronic renal failure (creatinine >2.0 mg/dl)

a depressed ejection fraction (e.g., <40%), TZDs may be used at the lower dosage range of each drug. Dosages can be adjusted gradually after several months of treatment to optimize glycemic control with careful observation for edema and symptoms and signs of CHF. It is not uncommon for patients with diabetes without symptomatic heart disease to have had determinations of left ventricular function with noninvasive cardiac testing in the course of screening for coronary artery disease or as part of a preoperative evaluation for surgical procedures. This recommendation is presented because patients with depressed cardiac function are at higher risk for CHF due to fluid retention from any cause, despite the absence of cardiac symptoms. The results of ongoing clinical trials will help to determine the safety of TZD use in these patients.

Use of TZDs in Patients With Diabetes and Symptomatic Heart Disease

- In patients with class I or II NYHA CHF categories, TZDs may be used cautiously, with initiation of treatment at the lower dosage of each drug (e.g., rosiglitazone 2 mg q.d. or pioglitazone 15 mg q.d.). Observation with gradual dose escalation is warranted to identify weight gain, edema, or an exacerbation of CHF. One should allow more time than usual to achieve a target HbA_{1c} in these patients. Ongoing clinical trials will help to establish the safety of TZD use in these patients.
- In patients with symptoms and signs of NYHA class III or IV CHF, TZDs should not be used at this time.

Monitoring Patients on TZD Therapy

- Once on TZDs, patients should be instructed to monitor for weight gain or the presence of pedal edema. If edema develops, particularly within the first few months of TZD therapy, the physician should determine whether CHF is present. Symptoms suggestive of CHF may include orthopnea, paroxysmal nocturnal dyspnea, unexplained cough or fatigue, or pedal edema. A physical examination should be performed to determine if there are signs of CHF (e.g., jugular venous distention, an S_3 gallop, pulmonary rales). Pedal edema in conjunction with any of these symptoms or signs may indicate that the edema is a manifestation of CHF even in the absence of a prior history of heart disease. A noninvasive cardiac evaluation including an ECG and echocardiogram should also be performed, and brain natriuretic peptide measurement may also be helpful. Even in the absence of prior cardiac disease, such an evaluation may reveal changes in cardiac function that have occurred during the course of TZD treatment. An exercise tolerance test or stress imaging (echo or perfusion) study may also be indicated if any of the symptoms are thought to be ischemic in origin.
- If edema occurs and CHF is not present during TZD therapy, other causes of the edema should be investigated before attributing it to the TZD. For example, other drugs associated with pedal edema or venous insufficiency may be responsible. The presence of edema with prior proteinuria may indicate nephrotic syndrome. Diuretics may be prescribed or the dose of diuretic increased (when prescribed as an antihypertensive agent) for those patients who do not tolerate pedal edema, although the effectiveness of diuretics in TZD-related edema may be variable. Several studies have suggested that the addition of an angiotensin-converting enzyme inhibitor with or without a thiazide diuretic may reduce the edema associated with dihydropyridine calcium channel blockers. To the extent that "vasodilatory" edema also occurs with TZDs, this strategy may be helpful (49,50). In this situation also, the dose of TZD might be lowered or alternative drugs to control glycemia instituted.
- If a new diagnosis of CHF is made or considered likely, even in the absence of prior left ventricular dysfunction, the use of the TZD should be reconsidered. Dosage change and temporary or permanent discontinuance are the obvious options, but no one of these is preferred for all patients. Treatment directed to CHF should be initiated according to current guidelines (51). In the absence of systolic dysfunction, only diuretics such as furosemide may be necessary. The duration of diuretic therapy can be quite variable, as the need for diuresis may be temporary if the patient improves and fluid retention disappears with the discontinuation of the TZD.
- For patients with known left ventricular dysfunction who develop CHF while on a TZD, the drug should be discontinued, and therapy with diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and digoxin should be considered and titrated according to the severity of the patient's condition and current treatment guidelines for CHF.

CONCLUSIONS

The primary treatment goal in type 2 diabetes is restoration and maintenance of normoglycemia and the prevention of CVD. The range of therapeutic options has been extended with the introduction of TZDs used as monotherapy or in combination with oral hypoglycemic drugs or insulin. There is substantial interest in whether these agents may reduce or modify risk of CVD through a wide range of peroxisome proliferator–activated receptor-γ–mediated effects on the cardiovascular system, in addition to their recognized efficacy as glucose-lowering drugs to treat type 2 diabetes (6,7).

Edema is a recognized side effect of these drugs, particularly when combined

with insulin. Both patients and health care providers should be cognizant of the risk of CHF when TZDs are used in patients with type 2 diabetes. Prospective clinical trials are currently underway to ascertain the cardiovascular safety of TZDs in patients with diabetes and underlying heart disease.

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