Weighing up the cardiovascular benefits of thiazolidinedione therapy: the impact of increased risk of heart failure

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Type 2 diabetes and heart failure commonly occur together and this combination is associated with poor outcomes. The relationship is likely to be multifactorial and also may involve a specific, though ill-defined, diabetic cardiomyopathy. Glucose-lowering therapies may also be associated with an increased risk of heart failure. Data from recent large-scale clinical trials have drawn particular attention to the thiazolidinediones that appear to increase the risk of heart failure in patients with type 2 diabetes. Although pioglitazone therapy has been shown to decrease the risk of macrovascular events, the overall cardiovascular benefit needs to be addressed together with the apparent increase in heart failure risk. In this review, we provide appropriate context for assessing this balance from several perspectives. First, we consider the high underlying risk of heart failure already present in type 2 diabetes. Secondly, we highlight a potential distinction between genuine heart failure due to cardiac dysfunction and thiazolidinedione-associated oedema that may simply unmask previously undiagnosed cardiac dysfunction without itself having any direct impact on heart muscle. Most importantly, we emphasize the apparent lack of any long-term mortality consequences and a relative improvement in outcomes associated with thiazolidinedione-induced ‘heart failure’ and discuss the potential mechanisms underlying this apparent paradox. Finally, we review the current guidelines for thiazolidinedione use and heart failure and suggest potential future strategies for avoiding and/or minimizing this association.

Keywords
Heart failure • Oedema • Pioglitazone • Rosiglitazone • Thiazolidinediones • Type 2 diabetes

Introduction: type 2 diabetes and heart failure—a common partnership

Epidemiological studies reveal that approximately 10% of patients with type 2 diabetes have heart failure—2–4 times the rate in people without diabetes.1–3 Furthermore, approximately 25% of patients in heart failure trials and observational studies have diabetes,2 and approximately 0.5% of the general population have both heart failure and type 2 diabetes.4 Accordingly, the American Heart Association (AHA) classifies all patients with diabetes as being at high risk of developing heart failure.4 Interestingly, the presence of heart failure also appears to be an independent risk factor for developing diabetes.5 Heart failure patients with diabetes also have poorer outcomes compared to those without diabetes.6,7 Approximately one-quarter to one-third of patients hospitalized for heart failure die within 1 year6,7 and median survival in those with diabetes is only 3.6 years compared with 5.4 years for those without diabetes.6 Even when accounting for traditional risk factors, diabetes is associated with a 40–50% increase in the risk of mortality after hospitalization.6,7 The reasons underlying the increased risk of heart failure and poorer outcomes are likely to be complex and multifactorial.
First, type 2 diabetes is commonly associated with many comorbid conditions that are also risk factors for heart failure, including coronary artery disease, hypertension, renal dysfunction, and obesity. Furthermore, several of the metabolic and functional disturbances associated with diabetes, such as hyperglycaemia, increased free fatty acids (FFAs) and insulin resistance may contribute to heart failure risk.

Whatever the contributing factors, the concept of ‘diabetic cardiomyopathy’ has been proposed as a distinct disease process leading to myocardial dysfunction and the development of heart failure in patients with diabetes, independently of atherosclerotic disease and hypertension. Diabetic cardiomyopathy is characterized by functional deficits that are evident among patients without overt cardiac disease, and significant subclinical left ventricular (LV) dysfunction is evident in approximately one-third of patients with diabetes. This is often evident as diastolic dysfunction, but may also be mixed diastolic and systolic dysfunction, or more rarely, isolated systolic dysfunction.

Various plausible mechanisms have been proposed to explain the association between diabetes and cardiomyopathy. It is worth noting that there is a strong association between any form of glucose-metabolic perturbation (not just full-blown diabetes) and heart failure. In fact, poor glycaemic control is associated with increased risk of heart failure and hospitalization and/or death due to heart failure. In the UKPDS, there was a 16% increase in heart failure risk for each 1% increase in HbA1c. Poor glycaemic control may also be associated more specifically with systolic dysfunction. Hyperglycaemia-induced myocardial fibrosis and formation of advanced glycation endproducts (AGEs) may also be associated with diastolic dysfunction. Other potential contributors to diabetic cardiomyopathy include myocardial insulin resistance, abnormal calcium handling, altered myocardial autonomic function, altered vasoconstrictor and vasodilator responses [altered nitric oxide (NO) regulation] and altered myocardial energy metabolism (related to FFA-induced lipotoxicity). The relative contributions of these different factors to the clinically very relevant syndrome of heart failure remain to be determined.

Thiazolidinediones are PPARγ agonists that target insulin resistance directly. They are effective glucose-lowering agents that have many potential cardiovascular benefits. The recent PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) showed that the thiazolidinedione, pioglitazone, reduced the risk of the primary endpoint (a composite of disease- and procedure-related endpoints) by a non-significant 10%; hazard ratio (HR) = 0.90; 95% confidence interval (CI) = 0.80, 1.02; P = 0.095) and the risk of secondary ‘hard’ (disease-related) macrovascular events by a significant 16% relative to placebo (HR = 0.84; 95%CI = 0.72, 0.98; P = 0.27) in a high-risk patient population with type 2 diabetes and established macrovascular disease. There is currently no clear evidence for any macrovascular benefit of the other frequently used thiazolidinedione, rosiglitazone. On the contrary, a recent meta-analysis of clinical trials has suggested an increased risk of myocardial infarction with rosiglitazone. Furthermore, an interim analysis from the ongoing Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) study shows slightly more events of hospitalization or death from cardiovascular causes (the primary endpoint) with rosiglitazone when added to a sulfonylurea or metformin compared with a metformin/sulfonylurea combination (HR = 1.08; 95%CI = 0.89, 1.31; P = 0.43), as well as slightly higher incidence of myocardial infarction (HR = 1.16; 95%CI = 0.75, 1.81; P = 0.50). At best, this suggests a lack of cardiovascular benefit with rosiglitazone, and at worst, a possible adverse impact on cardiovascular outcomes. Thus, only for pioglitazone is there evidence of efficacy in reducing the risk of macrovascular events, especially recurrent myocardial infarction and recurrent stroke (from the pre-specified subgroup analyses of PROactive data).

Both pioglitazone and rosiglitazone appear to be associated with an increase in non-fatal heart failure. In this article, we review the latest literature assessing the relationship between thiazolidinedione therapy, heart failure, and mortality in type 2 diabetes. The aim is to provide a useful context in which to judge the relative macrovascular benefits of these widely used agents.

### Do thiazolidinediones cause heart failure?

In clinical efficacy/safety trials, pioglitazone and rosiglitazone in monotherapy do not appear to impart an increase in the incidence of heart failure compared with metformin or sulfonylureas, although the risk may be increased when used in combination with insulin. In these studies (which excluded patients with NYHA class III/IV heart failure), adjudicated heart failure was a rare event, occurring in <1% of patients receiving pioglitazone or rosiglitazone as either monotherapy or in combination with metformin or sulfonylureas. However, four recent large-scale outcomes studies show an increased risk of non-fatal heart failure vs. comparator drugs or placebo in four very different patient populations—high-risk patients with type 2 diabetes and established cardiovascular disease (PROactive), low-risk people with pre-diabetes, and no evidence of pre-existing cardiovascular disease (DREAM), pharmacotherapy-naive patients with type 2 diabetes (ADOPT), and patients with type 2 diabetes (some with previous cardiovascular disease) who were inadequately controlled on a sulfonylurea or metformin (RECORD).

In PROactive, which was a cardiovascular disease secondary prevention trial (that excluded patients with NYHA class ≥II heart failure), an event of heart failure (defined as evidence of ventricular dysfunction, e.g. ECG, echo or auscultation, accompanied by signs or symptoms of heart failure) was reported in 10.8% of patients receiving pioglitazone compared with 7.5% of patients receiving placebo over an average of nearly 3 years (P < 0.0001). Serious heart failure (leading to hospitalization, among other criteria) was reported in 5.7 and 4.1% of patients, respectively (HR = 1.41; 95%CI = 1.10, 1.80; P = 0.007). Although these were not adjudicated events, a subsequent independent review of the data confirmed these investigator-reported diagnoses. Of the 149 pioglitazone-treated patients who had an event of serious heart failure, 57 (38.3%) were also receiving insulin prior to the event compared with 58/108 (53.7%) on placebo. The improved prognosis of diabetic patients after ACE inhibitor and β-blocker treatment is well known. Most of the patients in PROactive were treated with both drugs according to the guidelines. In the

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Thiazolidinediones and heart failure—exacerbation due to oedema or altered cardiac function?

Despite the reports of increased risk of heart failure, there is no evidence available in the literature to suggest that thiazolidinediones have any direct effect on cardiac function. On the contrary, data from several sources indicate that thiazolidinediones are, at the very least, benign in this respect and may even be beneficial. In an open-label study in patients with type 2 diabetes, 1 year of rosiglitazone therapy did not have any significant effect on cardiac structure or function.43 Although both rosiglitazone and the comparator glyburide produced clinically insignificant increases in LV end-diastolic volume, neither drug produced an increase in LV mass index that exceeded one standard deviation and, more importantly, ejection fraction did not change. Other studies have shown improvements in function. For example, pioglitazone has been shown to improve LV diastolic function without LV mass regression in hypertensive patients and troglitazone has been shown to increase cardiac output and stroke volume without affecting LV mass in patients with type 2 diabetes.44,45 Recent studies in patients with pre-existing heart failure also show similar neutral or beneficial changes in cardiac function (see below). Animal data further support these observations. For instance, pioglitazone has been shown to improve LV remodelling and function in mice with post-MI heart failure (a chronic heart failure model).46

Nevertheless, the association of thiazolidinedione use with peripheral oedema (especially in combination with insulin) is well established, raising the possibility that these agents, by their well known effects on salt and water retention, might simply reveal an undiagnosed pre-existing cardiac dysfunction.42,47 In other words, heart failure that develops due to thiazolidinedione therapy could represent a reversible condition that should not be associated with any adverse outcome.
Several mechanisms provide possible explanations for the propensity of thiazolidinediones to cause fluid retention. First, thiazolidinediones may increase vascular permeability. In hypertensive and insulin resistant fructose-fed rats, there is a marked reduction in capillary permeability in skeletal muscle that is associated with a down-regulation of NO synthase. Rosiglitazone increases permeability and NO synthase activity in this model. Vascular endothelial growth factor (VEGF) stimulates increased vascular permeability and it has been suggested that thiazolidinedione-induced oedema may be related to the ability of these agents to increase production of VEGF by vascular smooth muscle cells. Pioglitazone has been shown to increase plasma VEGF levels in people with type 2 diabetes.

Increased extracellular fluid volume with thiazolidinediones may also be a consequence of decreased urinary sodium excretion via several mechanisms—for example, via an indirect effect resulting from arterial vasodilation causing a compensatory response on proximal retention or a direct effect on distal nephron sodium retention. Treatment with pioglitazone decreases vascular resistance in the absence of a compensatory increase in cardiac output or plasma catecholamine concentrations in people with type 2 diabetes. It has been suggested that the resultant decrease in renal perfusion pressure might enhance sodium and fluid retention. A placebo-controlled study in healthy subjects also shows a pioglitazone-induced increase in plasma renin activity on both high- and low-salt diets, as well as a fall in proximal tubular sodium excretion during pioglitazone treatment on a low-salt diet. More recently, animal knockout models have highlighted the distal nephron as a potential key site of thiazolidinedione effects on sodium retention. Collecting duct-specific deletion of PPARγ blocks thiazolidinedione-induced fluid retention and weight gain. Furthermore, thiazolidinedione-induced weight gain is also blocked by the collecting duct-specific diuretic amiloride. A recent study in patients with type 2 diabetes also suggests that diuretics acting primarily (spironolactone) or at least partly (hydrochlorothiazide) on the collecting duct can significantly reduce rosiglitazone-induced fluid retention, whereas the loop diuretic furosemide is relatively ineffective. Thus, there appears to be a primary role for sodium and water retention via the collecting duct of the kidney in the weight gain elicited by thiazolidinediones in mice. A recent clinical study also suggests that the majority of the weight gain seen with pioglitazone is related to increases in total body water. It is also possible that other mechanisms could play a role in thiazolidinedione-induced oedema, such as increased sympathetic tone, and altered interstitial ion transport.

### Thiazolidinedione use in patients with type 2 diabetes and pre-existing heart failure

The use of thiazolidinediones in patients with diabetes and heart failure has been increasing, despite recommendations against their prescription in such patients. Among over 25,000 (n = 12,505 in 1998–1999 and 13,158 in 2000–2001) Medicare patients hospitalized for heart failure, 7.2% were discharged with a prescription for a thiazolidinedione (troglitazone) in 1998–1999 and this increased to 16.1% (pioglitazone or rosiglitazone) in 2000–2001. Furthermore, more than 80% of patients discharged with a thiazolidinedione prescription were receiving a drug of that class on admission.

Retrospective observational data suggest that fluid retention due to thiazolidinedione therapy (troglitazone, pioglitazone, or rosiglitazone) in 111 patients with pre-existing chronic heart failure (NYHA class I–III) is primarily peripheral in nature and reversible upon treatment discontinuation and does not correlate with underlying heart failure severity. Thus, thiazolidinedione-induced oedema should not necessarily be equated with worsening heart failure in these patients.

Clinical trial data on thiazolidinedione use specifically in patients with type 2 diabetes and pre-existing heart failure have been lacking, but are now beginning to emerge. A recent study of 224 patients managed with rosiglitazone suggests that, while thiazolidinediones worsen oedema compared with placebo in patients with pre-existing mild-to-moderate stable heart failure (NYHA class II) they do not appear to have any adverse impact on echocardiographic function parameters (including the primary endpoint of LVEF) over 1 year.

### Thiazolidinediones and outcomes after heart failure

Despite the apparent increased incidence of heart failure with thiazolidinediones, evidence from several sources suggests that there may in fact be a relative improvement in outcomes following an event of heart failure. A retrospective cohort study of over 16,000 Medicare beneficiaries with diabetes who were discharged after hospitalization for heart failure showed a significant 13% reduction in mortality over 1 year for those prescribed a troglitazone, pioglitazone, or rosiglitazone compared with those not prescribed insulin sensitizers. A similar reduction in mortality over 1 year with metformin was seen in this study, and also in another analysis from a separate health database. Re-admissions for heart failure were not increased with metformin (decrease of 8%), but were increased by 6% with thiazolidinediones. Interestingly, the combination of a thiazolidinedione and metformin appeared to be even more effective, with a 24% reduction in mortality. Preliminary data from the ambulatory cohort of over 7000 patients with diabetes and heart failure reported by Aguilar et al. suggest no difference in 2-year mortality between thiazolidinedione users and those not using an insulin sensitizer (HR = 0.98).

These observations are supported by the results of PROactive (n = 2605 patients in the pioglitazone group and 2633 in the placebo group). Despite an increased rate of diagnosed heart failure and serious heart failure (defined as heart failure that required hospitalization or prolonged a hospitalization stay, was fatal or life threatening, or resulted in persistent significant disability or incapacity) with pioglitazone, absolute rates of mortality due to heart failure were similar to placebo. Subsequent all-cause mortality in patients with serious heart failure occurred in 40 out of 149 patients with serious heart failure in the pioglitazone group (26.8%) compared with 37 out of 108 (34.3%) in the
placebo group (HR = 0.71; 95% CI = 0.454, 1.111; \( P = 0.1338 \); Figure 1A). In addition, 52/149 (34.9%) in the pioglitazone group experienced a main secondary composite endpoint of all-cause mortality, non-fatal MI, and stroke compared with 51/108 (47.2%) in the placebo group (HR = 0.64; 95% CI = 0.436, 0.946; \( P = 0.025 \); Figure 1B).

What mechanisms might underlie the potential thiazolidinedione benefits in patients with heart failure?

Thiazolidinediones have multiple potentially beneficial cardiovascular effects, including improved glycemic control, improved endothelial function, lipid effects, increased cardiac insulin sensitivity, reduced lipotoxicity (reduced FFAs), reduced ventricular modelling post-myocardial infarction, anti-inflammatory effects, and reduced restenosis, among others.\(^{18,19}\) In terms of improving outcomes associated with heart failure, several mechanisms may be relevant. Certainly, thiazolidinediones appear to improve cardiac function (see above)—pioglitazone improves LV diastolic function without LV mass regression in hypertensive patients in proportion to the improvements in whole-body insulin sensitivity and studies in rodents show that rosiglitazone can specifically improve cardiac insulin sensitivity.\(^{44}\) Rosiglitazone also improves myocardial glucose uptake in patients with type 2 diabetes.\(^{64}\)

Improvements in cardiac energy metabolism may represent one mechanism that could be particularly relevant to reduced mortality. Myocardial phosphocreatine-to-ATP ratio (PCr/ATP) provides a measure of cardiac high-energy phosphate metabolism, which is known to be reduced in type 2 diabetes and is associated with LV diastolic dysfunction in these patients.\(^{65}\) Of particular note, the PCr/ATP ratio is a strong predictor of both total and cardiovascular mortality in patients with dilated cardiomyopathy.\(^{66}\) The PCr/ATP ratio correlates with FFA levels and it has been proposed that inappropriate use of elevated FFAs as a metabolic substrate may lead to energy depletion in the failing human myocardium and contribute to diabetic cardiomyopathy.\(^{65}\) Rosiglitazone significantly improves the PCr/ATP ratio in patients with type 2 diabetes, indicating an improvement in cardiac energy metabolism.\(^{67}\) However, it remains unclear whether the beneficial impact of thiazolidinediones on heart failure outcomes is associated with reduced FFA levels.

Numerous other factors may also be involved in improved cardiac function with thiazolidinediones, including reduced oxidative stress, decreased collagen accumulation/fibrosis, and reductions in inflammatory cytokines.\(^{44,46,68}\) For instance, improved LV remodelling and function with pioglitazone in an experimental animal model of chronic heart failure were associated with a decrease in interstitial fibrosis and reduced LV expression of TNFa, transforming growth factor \(\alpha\) and monocyte chemoattractant protein-1.\(^{46}\) Like metformin, thiazolidinediones increase intracellular levels of 5' AMP-activated protein kinase (AMPK), which decreases the breakdown of ATP and can ultimately cause hypertrophy of cardiac muscle. At the whole body level, this effect is probably mediated through a thiazolidinedione-induced increase in the adipokine, adiponectin in ventricular cardiomyocytes.\(^{69}\)

Conclusions—potential consequences for clinical practice

When considering the risk of heart failure in patients with type 2 diabetes treated with thiazolidinediones, three fundamental concepts stand out. First, one needs to appreciate the high underlying risk associated with the multiple risk factors already present in this patient group. Secondly, a distinction between genuine heart failure and thiazolidinedione-associated oedema should be appreciated; and thirdly, one should be aware of the apparent lack of any long-term mortality consequences.

It is worth noting that, in clinical studies, the occurrence of oedema with thiazolidinediones has not been associated with an
increase in heart failure events. Nevertheless, there may be clear-cut cases of thiazolidinedione-associated heart failure and it is worth considering potential strategies for minimizing the risk of oedema and/or heart failure. Prior to commencing thiazolidinedione therapy, current recommendations advocate careful assessment of underlying risk factors, ongoing drug treatments, and any evidence of pre-existing oedema or heart failure (for a summary of recommendations see Figure 2). Importantly, oedema from causes not related to heart failure should not preclude thiazolidinedione use. It is also important that patients on thiazolidinediones receive adequate follow up for signs of oedema or heart failure and doses should be adjusted slowly to achieve target HbA1c. Those who develop oedema while on thiazolidinediones should also be screened for other possible causes, including nephrotic syndrome and venous insufficiency and other drugs, such as non-steroidal anti-inflammatory agents and calcium channel blockers. In patients without apparent heart failure, thiazolidinediones should be prescribed according to the current guidelines, which do not preclude their use even in patients with existing NYHA class I/II heart failure, but rather advocate a sensible cautious approach with close control of fluid retention. The available evidence suggests that rosiglitazone and pioglitazone do not differ in their propensity to cause oedema. However, although data from PROactive suggest that macrovascular outcomes are improved with pioglitazone, there is no clinical outcomes evidence available to support a similar benefit with rosiglitazone—in fact, current evidence suggests that the impact of rosiglitazone on macrovascular events is neutral at best.

The effectiveness of diuretics to treat oedema in these patients may be variable, although some evidence suggests that collecting duct-specific drugs may be more effective. In particular, spironolactone has the benefit of improving LV volume and function. Other approaches, such as low-salt diets may also be appropriate, but remain untested at present. Some diagnostic techniques, such as brain natriuretic peptide measurement, may have a role in improving the management of heart failure. In the context of thiazolidinedione therapy, this may help to identify those patients most likely to develop heart failure during therapy as well as

![Figure 2 Recommendations regarding thiazolidinedione use and heart failure from the American Heart Association and American Diabetes Association. Reprinted with permission (copyright © 2007 American Diabetes Association). BNP, brain natriuretic peptide; CCB, calcium channel blocker; CHF, congestive heart failure; CXR, chest X-ray; ECG, electrocardiogram; ECHO, echocardiogram; EF, ejection fraction; LV, left ventricular; NSAID, non-steroidal anti-inflammatory drug; TZD, thiazolidinedione](http://eurheartj.oxfordjournals.org/Downloaded)
establishing whether the symptoms do indeed reflect genuine heart failure. 75

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