Thiazolidinediones and Cardiovascular Disease: Balancing Benefit and Harm

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Cardiovascular disease is the leading cause of mortality among older adults with type II diabetes. The thiazolidinediones (rosiglitazone and pioglitazone) lower blood sugar levels among individuals with type II diabetes. The thiazolidinediones have favourable effects on surrogate markers of cardiovascular disease such as microalbuminuria, carotid intimal thickness, and blood pressure. Emerging evidence from recent randomized clinical trials has confirmed both that thiazolidinediones increase the risk of heart failure, and that rosiglitazone increases the risk of myocardial infarction among those with type II diabetes. Clinicians should avoid thiazolidinediones for older individuals with type II diabetes who are at risk for cardiovascular events as the negative cardiovascular effects of the thiazolidinediones outweigh any potential benefits on surrogate markers.

Key words: *thiazolidinediones, pioglitazone, rosiglitazone, heart failure, myocardial infarctions*

Introduction

Cardiovascular disease is the leading cause of mortality and morbidity among persons with type II diabetes. The prevalence of coronary artery disease among individuals with type II diabetes is approximately 22%.[1] A recent prospective longitudinal prevalence study showed that the prevalence of heart failure among older adults with newly diagnosed type II diabetes over a period of 10 years of follow-up was 57.6%.[2]

The currently available thiazolidinediones are rosiglitazone and pioglitazone. These drugs lower blood sugar levels among individuals with type II diabetes. They have been shown to favourably affect surrogate markers of cardiovascular disease such as carotid intimal thickness,[3] serum C-reactive protein levels,[4] blood pressure levels,[5] and microalbuminuria.[6] However, recent systematic reviews have alerted us to the emerging cardiovascular risks of the thiazolidinediones in randomized clinical trials.[7–11]

Thiazolidinediones and Heart Failure

The risk of heart failure appears to be a class effect of the thiazolidinediones. Our systematic review of three randomized controlled trials (RCTs) involving 10,731 patients showed that the thiazolidinediones doubled the risk of heart failure (odds ratio [OR] 2.1, 95% CI 1.08–4.08; p = .03) compared with controls (Table 1).[8] The median duration for the onset of heart failure with the thiazolidinediones was approximately 24 weeks.[8] We estimate the number needed to harm (NNH) for hospitalization for heart failure with the thiazolidinediones to be 110 per year.[8] The NNH for rosiglitazone among older adults with diabetes (age 63 years without a history of heart failure) is even more unfavourable at 30 per year.[9] Another systematic review of seven RCTs found a similar increase in the risk of heart failure with the thiazolidinediones (nearly 72%), without any deleterious effect on cardiovascular mortality.[11]

Regulatory agencies have provided information about the risk of heart failure with the thiazolidinediones but have given differing recommendations on the severity of heart failure required to restrict the use of these agents. In Europe, these agents have been contraindicated for patients with heart failure and any history of heart failure since approval.[12] Health Canada have also recently updated their recommendation to warn against use in patients with any degree of heart failure.[13] In the U.S., thiazolidinediones have been contraindicated only for persons with NYHA class III and IV heart failure, recently highlighted by a prominent black box warning (added to the labeling of drugs by the Food and Drug Administration [FDA] when serious adverse reactions or special problems occur, particularly those that may lead to death or serious injury).[14] The impact of these restrictions on physician prescribing practices is uncertain as these agents continue to be prescribed for patients with heart failure.

We determined that the thiazolidinediones could cause heart failure even among prediabetic individuals without a history of heart failure, among individuals not assigned to insulin, and among a younger population.[8] Three of the rosiglitazone trials applied stringent criteria to exclude participants with heart failure; despite this careful patient selection process, the meta-analysis still showed a significant increase in the number of patients with heart failure due to rosiglitazone use. There are similar excess rates of heart failure for pioglitazone in the

large PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study, (RR 1.43, 95% CI 1.20–1.70; p<0.001) even though persons with NYHA class III or IV heart failure were excluded from the study. Careful screening (based on history and clinical examination) by physicians will not be sufficient to prevent new heart failure cases arising as a result of thiazolidinedione therapy. Regulatory authorities also recommend close monitoring of cardiac signs and symptoms, which may be likely to pose a considerable additional burden to physicians and patients.

The mechanism of heart failure due to the thiazolidinediones is via fluid retention (Figure 1). Both these agents act on renal peroxisome proliferator–activated receptor gamma (PPAR gamma) and lead to increased sodium retention, fluid retention, and consequent heart failure among persons with diabetes.[15] Thiazolidinedione-induced heart failure requires immediate discontinuation of the drug and may not respond to loop diuretics such as furosemide. Clinicians should consider the use of potassium-sparing agents such as spironolactone or amiloride.[16]

Thiazolidinediones and Myocardial Infarction

The currently available thiazolidinediones differ in their ischemic risk profile. In a meta-analysis of 42 short- and long-term trials in patients with heterogeneous conditions (diabetes and Alzheimer's disease, as well as psoriasis), Nissen and Wolski showed that rosiglitazone increased the risk of myocardial infarction (MI) (OR 1.43, 95% CI 1.03–1.98; p = .03) and nonsignificantly increased the risk of cardiovascular death (OR 1.64, 95% CI 0.98–2.64; p = .06).[7] In contrast, our meta-analysis of four long-term trials with rosiglitazone among individuals with diabetes in which the cardiovascular events were monitored showed that rosiglitazone increased the risk of MI by 42% (relative risk [RR] 1.42, 95% CI 1.06–1.91) compared with other oral hypoglycemic agents without an increase in the risk of cardiovascular death (RR 0.90, 95% CI 0.63–1.26; p = .53) (Table 2).[9] The improved glucose control seen with rosiglitazone does not appear to confer cardiovascular benefits. Persons taking rosiglitazone in ADOPT (A Diabetes Outcome Progression Trial) had a mean glycosylated hemoglobin (HbA1C) after 4 years that was 0.42% lower than those in the glyburide arm, but the rate of MIs was higher in the rosiglitazone arm—1.8% as opposed to 1.2% with glyburide.[17] The RCTs were inadequately powered to detect mortality outcomes; hence, this increased risk of MI with rosiglitazone is not reflected in an increase in cardiovascular mortality. An internal review by the U.S. FDA using patient-level data confirmed this increased ischemic risk with rosiglitazone.[18] The combination of rosiglitazone and insulin accentuates this ischemic risk even further. The FDA panel voted overwhelmingly that rosiglitazone increased the ischemic risk but allowed it to remain on the market.

Table 1: Thiazoldinediones and the Risk of Heart Failure: A Teleo-analysis

Studies (n)	Intervention	Baseline Event Rate	Number Needed to Harm per Year with Thiazolidinediones
3 RCTs involving 10,371 patients	Thiazolidinedione vs. placebo	7.3% vs. 3.9%	110 per year

On the other hand, pioglitazone does not increase the risk of MI. The claim of any cardiovascular benefit of pioglitazone in the systematic review by Lincoff *et al.*[10] on an artificial composite of MI, stroke, and death will require corroboration from adequately powered long-term trials as pioglitazone failed to meet its primary end point in the only large clinical trial measuring cardiovascular outcomes—PROactive (Hazard Ratio 0.90, 95% CI 0.80–1.02; p=.100).[19] The differences in ischemic risk may be explained by the thiazolidinediones' varying effects on lipid levels—pioglitazone lowers low-density lipoprotein cholesterol while rosiglitazone raises it.[20]

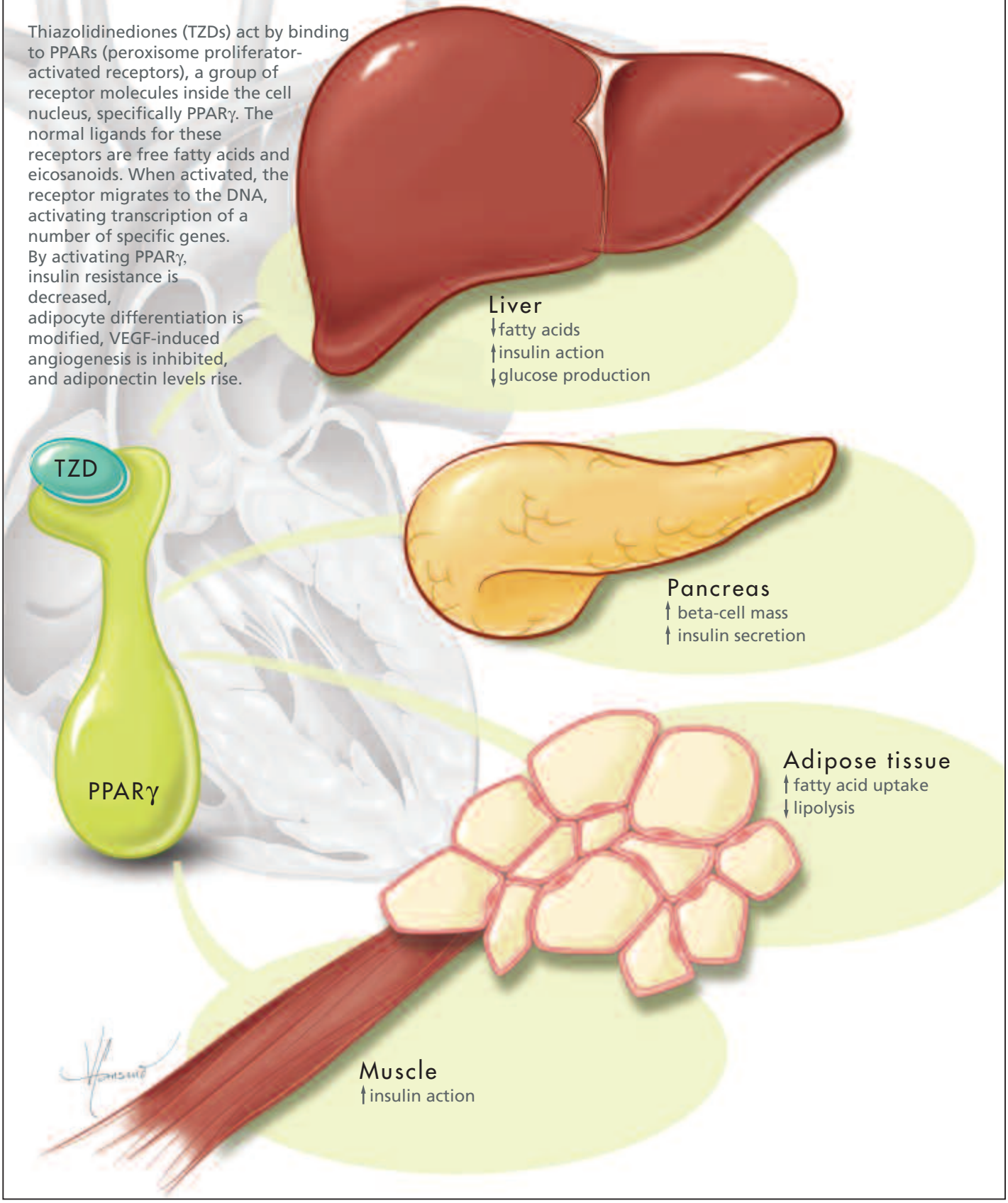
Accumulating evidence from long-term trials has demonstrated the negative effects of the thiazolidinediones on cardiovascular disease among individuals with type II diabetes. The risk of heart failure is a class effect of the thiazolidinediones, whereas the ischemic cardiovascular risk is confined to rosiglitazone. The public health impact of the use of the thiazolidinediones among older adults with type II diabetes is substantial. According to an FDA review, more than 205,000 cardiovascular ischemic events may have occurred among rosiglitazone users from its approval in 1999 until 2006.[18] Their benefit on a surrogate measure such as HbA1C should be balanced against their complex actions elsewhere in the body,

Table 2: Long-term Rosiglitazone Use- and the Risk of Cardiovascular Events (Myocardial Infarction and Heart Failure)

	Studies	Intervention	Baseline Event Rate	Number Needed to Harm Per Year with Rosiglitazone
Myocardial Infarction	4 RCTs involving 14,291 patients	Rosiglitazone vs. controls	1.46% vs 1.05%	822[379–5748]
Heart Failure	4 RCTs involving 14,291 patients	Rosiglitazone vs. controls	1.59% vs 0.78%	383[22–802]

Figure 1:

Thiazolidinedione Use, Fluid Retention, and Congestive Heart Failure



Key Points

Cardiovascular disease is the leading cause of morbidity and mortality among older adults with type II diabetes.

Rosiglitazone increases the risk of myocardial infarction by nearly 40% and doubles the risk of heart failure, without an increase in cardiovascular mortality.

Pioglitazone increases the risk of heart failure without an increase in the risk of ischemic events, possibly explained by differences in lipid effects.

Suggestions for Thiazolidinedione Use in Older Diabetic Adults:

Newly diagnosed older diabetic patients should not be started on a thiazolidinedione.

Both the thiazolidinediones should be avoided for older adults with type II diabetes who have heart failure or are at risk for heart failure.

Rosiglitazone should be avoided in older type II diabetic patients at risk for cardiovascular disease.

Older type II diabetic patients with poor glycemic control should be switched from a thiazolidinedione to a nonthiazolidinedione regimen.

Strong consideration should be given to switching older adults with type II diabetes well controlled on a thiazolidinedione to a nonthiazolidinedione regimen.

In a case where a clinician has exhausted all other therapeutic options, pioglitazone may be the preferred thiazolidinedione.

including a doubling of the risk of bone fractures among women, which may negate any potential gain.

A recent systematic review highlighted that older agents (metformin and sulfonylureas) are less expensive and more effective for the treatment of type II diabetes and do not carry the negative cardiovascular risks of the thiazolidinediones.[21] In another recent systematic review, metformin was the only antidiabetic agent not associated with harm among individuals with heart failure and diabetes.[22]

Health Canada issued a safety update in November 2007 based on a review of these studies.[13] According to the update, rosiglitazone is not approved for use alone, or with a sulfonylurea drug, except when metformin is contraindicated. Rosiglitazone is also not indicated in combination with Insulin or as triple therapy for patients with type II diabetes mellitus. Rosiglitazone is not indicated for patients with heart failure or a history of heart failure.

A recent American Diabetes Association/European Association for the Study of Diabetes update considers that thiazolidinediones should still be a possible second step option in the algorithm for management of patients with type II diabetes who are not well controlled on diet/lifestyle/metformin, as an alternative to insulin (most effective) and sulfonylureas (cheapest).[23] However, "the weight of the new information should prompt clinicians to consider more carefully whether to use this class of drugs." They also urge "greater caution in using thiazolidinediones in people with or at risk for congestive heart failure."[23]

A recent case-control study highlights the specific dangers of thiazolidinedione use in older people (age above 66 years) with diabetes.[24] This health care database study from Ontario, Canada found that that current thiazolidinedione therapy was associated with a significantly increased risk of heart failure (RR, 1.60, 95% CI, 1.21–2.10; p<0.001), acute myocardial infarction (RR 1.40, 95% CI 1.05–1.86;p=0.02) and death (RR 1.29, 95% CI, 1.02–1.62; p=0.03) compared with oral hypoglycemic agents. The increased risk with thiazolidinedione use seemed to be mainly with rosiglitazone.

Recommendations

Based on the available evidence, we recommend that newly diagnosed patients with type II diabetes not be assigned a thiazolidinedione. Individuals with type II diabetes who have heart failure or a history of heart failure should not be prescribed thiazolidinediones and should be switched to alternative regimens. Rosiglitazone should be avoided in persons with cardiovascular disease (angina, MI), and these patients should be switched to alternative regimens. Current patients with poor glycemic control taking the thiazolidinediones should be switched immediately to alternative agents such as metformin and insulin. Even for those who are well controlled on the thiazolidinediones, strong consideration should be given to alternative regimens that do not include a thiazolidinedione. In the case where a clinician has exhausted other therapeutic options, pioglitazone may be the preferred thiazolidinedione.

Conclusions

The thiazolidinediones carry significant cardiovascular risks (heart failure, MI) and are associated with negative effects elsewhere in the body (bone fractures). In the absence of any meaningful benefits to patients, thiazolidinediones should be avoided for older adults with diabetes who are at risk of cardiovascular events (heart failure, heart attack). Ongoing and future trials in diabetes should measure patient-oriented outcomes rather than surrogates.

No competing financial interests declared.

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