

Thiazolidinediones and Heart Failure: A Teleo-Analysis

Received for publication 23 January 2007 and accepted in revised form 18 May 2007.

Running Title: *Thiazolidinediones and heart failure*

Sonal Singh MD<sup>1\*</sup>  
Yoon K Loke MBBS MD<sup>2\*</sup>  
Curt D Furberg MD PhD<sup>3</sup>

1 Internal Medicine, Wake Forest University School of Medicine, NC  
2 School of Medicine, Health Policy and Practice, University of East Anglia, UK  
3. Division of Public Health Sciences, Wake Forest University School of Medicine, NC

\* Equal co-authors

Corresponding author  
Sonal Singh  
Section on General Internal Medicine  
Wake Forest University School of Medicine  
One Medical Center Blvd  
Winston-Salem, NC 27157  
Email: [sosingh@wfubmc.edu](mailto:sosingh@wfubmc.edu)

**OBJECTIVE-**Thiazolidinediones are known to increase the risk of heart failure in patients with type 2 diabetes. We aimed to evaluate the magnitude of the risk of heart failure with thiazolidinediones and classify this adverse effect under the novel Dose-Time-Susceptibility system.

**RESEARCH DESIGN AND METHODS** - Evidence from randomized trials, controlled observational studies, anecdotal case reports, case-series and spontaneous reports in the Canadian Adverse Events Database (CADRMP) were analyzed in a teleo-analysis.

**RESULTS-**Random effects meta-analysis of 3 randomized controlled trials showed an odds ratio of 2.1 (95% CI: 1.08 – 4.08;  $p = 0.03$ ) for the risk of heart failure in patients randomized to thiazolidinediones compared to placebo. 4 observational studies, revealed an odds ratio of 1.55 (95% CI: 1.33 – 1.80;  $p < 0.00001$ ) for heart failure with thiazolidinediones. A Dose-Time-Susceptibility analysis of 28 published reports, and 214 spontaneous reports from the CADRMP database showed that heart failure was more likely to occur after several months, with median treatment duration of 24 weeks after initiation of therapy. Heart failure occurred equally at high and low doses. The adverse reaction was not limited to the elderly, with 42/ 162 (26%) of the reported cases occurring in patients below the age of 60 years.

**CONCLUSIONS-** Our teleo-analysis confirms the increased magnitude of the risk of heart failure with thiazolidinediones. We estimate the Number-Needed-to-Harm with thiazolidinediones to be around 50 over 2.2 years. Existing guidelines and package inserts may have to be revised to incorporate these risk-characteristics of thiazolidinediones.

## INTRODUCTION

Thiazolidinediones have an important role in the management of type 2 diabetes. Clinicians have been urged to exercise caution and several published case reports and guidelines have raised concerns that these drugs may increase the risk of heart failure. (1-9) However, there is uncertainty surrounding the exact magnitude of the risk of heart failure and the susceptibility factors that may potentiate this risk. It would also help if we could define specific characteristics of the adverse reaction such as dose responsiveness and the duration of onset to heart failure.

Information on this topic has expanded with the publication of new studies with thiazolidinediones. (10) We aimed to a) estimate the magnitude of the risk of heart failure with thiazolidinediones using data from controlled observational studies and randomized controlled trials. b) Classify this adverse effect under the novel Dose-Time-Susceptibility system, using data from published case reports and spontaneous reports to the Canadian Adverse Events Database (CADRMP) database. (11)

## RESEARCH, DESIGN AND METHODS

Data from randomized controlled trials (RCTs), observational studies and anecdotal case reports were analyzed in a *teleo-analysis*. A teleo-analysis attempts to determine the adverse effect of a drug by complementing information from different study designs across all grades of evidence.(12) Controlled data from randomized trials and observational studies are used to evaluate the statistical association between a drug and its adverse effect, and estimate the frequency of the adverse event. This is complemented by data from individual case reports, which allows us to evaluate specific characteristics of the adverse effect such as dose, time and susceptibility factors. We searched without

language restrictions, and contacted authors when specific aspects of the data required clarification.

**Randomized Controlled Trials:** We retrieved potentially relevant citations by looking at trials identified in existing published meta-analysis. (13,14). PubMed was searched from 2003 – to September 2006 for more recent trials, by applying the ‘Randomized Controlled Trial’ search filter to the [MeSH] terms [pioglitazone OR rosiglitazone] – this yielded 221 citations. We retrieved unpublished RCTs for rosiglitazone from the manufacturer’s website (15). No unpublished RCTs were available for pioglitazone. Included RCTs were a) at least 6 months duration of thiazolidinedione for treating, or preventing type 2 diabetes, b) Direct head-to-head between a thiazolidinedione alone (rosiglitazone or pioglitazone) versus placebo alone and c) provided numerical data on patients experiencing heart failure.

**Observational Studies:** PubMed was searched using the [MeSH] terms:” Thiazolidinediones” AND “Case-Control Studies” OR “Cohort Studies” in September 2006. We used the bibliographies of relevant studies, the Web of Knowledge Cited References list, and the ‘Related Articles’ link in PubMed to identify additional studies. Included articles were controlled observational studies containing data which enabled us to calculate the odds ratio of new onset of heart failure developing in patients receiving thiazolidinediones, compared to patients receiving other oral anti-diabetic medications with or without insulin.

**Case reports:** Pubmed, Embase and Google scholar were searched using the terms “Thiazolidinediones:” and “heart failure” to identify case reports and case-series in

September 2006. We used the bibliographies of relevant studies, the Web of Knowledge Cited References list, and the 'Related Articles' link in PubMed to identify additional articles. We identified 28 published reports. All Adverse Drug Reactions (ADRs) reported with pioglitazone (n= 195) or rosiglitazone (n=830) to Health Canada's Spontaneous Adverse event reporting system (CADRMP) - the only English language regulatory authority database that allows easy, unrestricted web access, were reviewed in September 2006 to identify reports of heart failure or pulmonary edema. (16) Reports describing only edema were excluded. 51 reports of heart failure with pioglitazone and 163 reports of heart failure with rosiglitazone were identified. Information on age, sex, duration, dose of thiazolidinedione, outcome of reaction and concomitant medications was abstracted from both the published case reports and the spontaneous reports.

**Data synthesis:** We used RevMan 4.28 to calculate summary odds ratios (random effects model) and heterogeneity.

## RESULTS

**Randomized Controlled Trials:** We identified 3 trials of 10,731 patients that provided numerical information on heart failure events. (10, 17, 18) (Table 1) The pooled odds ratio for heart failure was 2.1 (95% CI: 1.08 – 4.08; p = 0.03). (Figure 1) There is moderate heterogeneity around this estimate ( $I^2 = 59\%$ ) – attributable to the different populations, and varying criteria for ascertaining heart failure events.

**Observational Studies** 4 observational studies of 67,382 patients were included. (19)(20)(21)(22) (Table 2a). The pooled odds ratio for heart failure with thiazolidinediones was 1.55 (95% CI: 1.33 – 1.80; p <0.00001). (Figure 1) Moderate heterogeneity was found ( $I^2 = 47\%$ ), due to the differences in

population and co-existing morbidity. Sensitivity analysis shows the heterogeneity to have an  $I^2$  of 0% if we excluded Inzucchi's study (which focused on diabetic patients after myocardial infarction, rather than diabetic patients in general). (21)

**Excluded observational studies** Two observational studies were excluded as they did not fulfill the selection criteria (Table 2 (b)) (23, 24) Masoudi looked at readmission rates for patients on thiazolidinediones who already had a recent admission for heart failure (23). Rajagopalan's study compared the rates of heart failure solely between patients on pioglitazone and insulin (24). Our selection criteria were based on patients potentially being able to receive other oral hypoglycemic agents, with or without insulin. The use of a control group comprising patients on insulin is particularly prone to confounding, as patients with the most severe type 2 diabetes are the ones likely to receive insulin.

**Case Reports: Age:** A DoTs analysis of 162 analyzable cases showed that the age ranged from 31 – 88 years with the median age at 67 years. The adverse effect was not limited to the elderly as 42/ 162 cases (26%) were below the age of 60 years.

**Dose and Duration:** Among 99 analyzable cases, the median duration for the onset of heart failure was 24 weeks (range 1 - 260 weeks), suggesting that the reaction is a delayed or late-onset in nature (Figure 2). Patients on low doses were also at risk of developing heart failure soon after starting treatment. One patient on pioglitazone and 9 patients on rosiglitazone developed heart failure in the first four weeks of low-dose therapy defined as pioglitazone 15 mg or below or rosiglitazone 4mg or below. Heart failure did not develop much earlier in those receiving thiazolidinediones in the high dose

range (Figure 3). Heart failure due to thiazolidinediones use also did not occur as a function of the cumulative ingested dose.

Heart failure can occur even at doses below those used for therapeutic benefit, and the relatively low daily doses of pioglitazone 15-mg or rosiglitazone 2 mg are already at the top end of the dose-effect curve for triggering off episodes of heart failure.

*Susceptibility:* We were unable to identify any particular susceptibility factors. Heart failure occurred equally among 110 males and 88 females. Death occurred in 9 patients.

### **Discussion**

Our teleo-analysis provides useful clinical information on the increased risk of heart failure with thiazolidinediones. This evidence on the increased risk of heart failure should be judged in the context of a recent systematic review of pioglitazone which found little evidence for beneficial effects on hard clinical endpoints. (25)

Diabetes and the use of any therapy for the treatment of diabetes is associated with an increased risk of heart failure. (26) The background incidence of heart failure in patients with diabetes is approximately 1.9% over 2.2 years (27). The estimated number-needed-to-harm (NNH) with thiazolidinediones, based on an odds ratio of 2.10, would be 50 over a 2.2 year follow-up period.

**Biological basis of the reaction:** The development of heart failure is a class effect of the thiazolidinediones, mediated through increased plasma volume, rather than through a direct effect on the myocardium. (9, 17, 28) A recent meta-analysis of RCTs found the odds ratio for edema with thiazolidinediones to be 2.26 [95% CI 2.02-2.53], (14) similar to our estimates of heart failure. Fluid retention

due to thiazolidinediones may trigger (clinically apparent) episodes of heart failure in susceptible individuals, or may unveil the disease in those with latent heart failure (no previous cardiac history). This theory is supported by echocardiographic evaluation of heart failure patients where no deterioration in left ventricular function was found with thiazolidinedione therapy. (5) (17). Similarly, a 52-week study of rosiglitazone did not show any decline in the left ventricular ejection fraction. (29). Fluid retention appears to be mediated through increased sodium reabsorption by the renal PPAR gamma dependent pathway in the collecting tubules, suggesting a possible therapeutic role for amiloride, rather than loop diuretics for which resistance has been reported (30).

The rosiglitazone package insert warns against the use of rosiglitazone in NYHA Stage III and IV heart failure patients and cautions about the increased risk of heart failure in combination with insulin. (31) Similarly, the package insert of pioglitazone cautions against this increased risk of heart failure. (32) However, this increased risk is not confined to patients on insulin. None of the patients were on Insulin in the DREAM trial (10), only one-third of patients required Insulin in PROActive. (18) We were unable to obtain information on concomitant medications in GSK-211 (17) (Table 1)

A consensus review in 2003 by the American Heart Association and the American Diabetic Association rightly recommend that thiazolidinediones be avoided in patients with New York Heart Association (NYHA) Stage III and IV heart failure (as RCTs of thiazolidinediones excluded these patients). (9) However, they also recommend that thiazolidinedione therapy be initiated at low dose, and slowly increased and closely monitored in diabetic patients with Stage NYHA I and II heart failure, those with

depressed ejection fractions (<40%), and 1 or more cardiac risk factors without heart disease. (9) Recommendations for their use even at low-doses in NYHA Stage 1 and II heart failure patients, and in those with risk factors for heart failure may need to be carefully reevaluated as heart failure occurred even among patients with no history of heart failure in the DREAM trial and observational studies. Heart failure also occurred at the lowest dose range for thiazolidinediones in spontaneous reports and at both the low (4 mg) and high (8 mg) doses of rosiglitazone used in clinical trials. The occurrence of heart failure several months after initiation of thiazolidinediones suggests a long-term effect of the drug, which may not be avoided by slow dose titration, and mandates the need for long-term vigilance.

Further research studies should evaluate intraclass differences in the risk of heart failure between the thiazolidinediones, and optimal management strategies in patients experiencing heart failure on thiazolidinediones, including immediate withdrawal and the role of diuretics such as amiloride or spironolactone. (33) Studies need to distinguish between the heart failure requiring hospitalization versus that which can be managed as an outpatient (the severity of heart failure) are also needed.

*Limitations:* There are a number of limitations to our study. The diagnosis of heart failure is challenging and may require subjective clinical interpretation of symptoms, signs and additional investigations (such as chest radiographs, or echocardiography). Inconsistent diagnostic criteria across studies may have led to some heterogeneity. Patients with progressive pedal edema from fluid retention could potentially have been erroneously classified as heart failure cases. This seems unlikely here though, as all 3 included RCTs were designed from the start

to actively seek out cases of heart failure, and heart failure information in two of the large published studies was subjected to independent masked adjudication based on prespecified criteria (Table 1). Moreover, three of the four observational studies used fairly stringent criteria in that the patients required hospital admission due to heart failure.

Anecdotal case reports may not be entirely representative of the population, were often incomplete, and were not necessarily causal as they cannot rule out the role of concomitant medicines (metformin, insulin) in exacerbating heart failure. Case reports are subject to publication bias, which was minimized by the use of spontaneous reports from the CADRMP database. Spontaneous reports and case reports represent the observation of the individual health professionals and layperson and should not be used for numerically estimating the risk of ADR as the denominator is unknown. We used data from RCTs and observational studies to statistically determine the association between thiazolidinediones and heart failure. Observational studies are susceptible to confounding. We corroborated observational data with results from RCTs, and the risk of heart failure was consistent in magnitude and direction.

*Conclusions:* Our teleo-analysis confirms the increased magnitude of the risk of heart failure with thiazolidinediones. The Number-Needed-to-Harm with thiazolidinediones was estimated to be around 50 over 2.2 years. Heart failure can occur at both high and low doses, usually weeks to months after initiation of thiazolidinediones. It can occur in the absence of insulin, even in patients without a history of heart failure. Existing guidelines and package inserts may have to be revised to incorporate these risk-characteristics of thiazolidinediones.

## References

1. Thomas M, Lloyd S: Pulmonary edema associated with rosiglitazone and troglitazone. *Ann Pharmacother* 35:23-124, 2001
2. Woollorton E: Rosiglitazone (Avandia) and pioglitazone (Actos) and heart failure. *CMAJ* 166:219, 2002
3. Page RL, 2nd, Gozansky WS, Ruscin JM: Possible heart failure exacerbation associated with rosiglitazone: Case report and literature review. *Pharmacotherapy* 23:945-954, 2003
4. Tang WHW, 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* 41:1394-1398, 2003
5. Shah M, Kolandaivelu A, Fearon WF: Pioglitazone-induced heart failure despite normal left ventricular function. *Am J Med* 117:973-974, 2004
6. Kermani A, Garg A: Thiazolidinedione-associated congestive heart failure and pulmonary edema. *Mayo Clin Proc* 78:1088-1091, 2003
7. Jamieson A, Abousleiman Y: Thiazolidinedione-associated congestive heart failure and pulmonary edema. *Mayo Clin Proc* 79:575-577, 2004
8. Cheng AY, Fantus IG: Thiazolidinedione-induced congestive heart failure. *Ann Pharmacother* 38:817-20, 2004
9. Nesto RW, Bell D, Bonow RO, Fonseca V, Grundy SM, Horton ES, Le Winter M, Porte D, Semenkovich CF, Smith S, Young LH, Kahn R: Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and American Diabetes Association. *Diabetes Care* 27:256–263, 2004
10. The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368:1096–1105, 2006
11. Aronson JK, Ferner RE. Joining the DoTS: New approach to classifying adverse drug reactions. *BMJ* 327:1222-1225, 2003
12. Wald NJ, Morris JK. Teleanalysis: Combining data from different types of study. *BMJ* 327:616-618, 2003
13. Chiquette E, Ramirez G, Defronzo R: A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. *Arch Intern Med.* 164:2097-2104, 2004
14. Berlie HD, Kalus JS, Jaber LA: Thiazolidinediones and the risk of edema: A meta-analysis. *Diabetes Res Clin Pract* 76:279-289, 2007
15. Glaxo smith Kline. Clinical trial register-rosiglitazone studies. Available from: <http://ctr.gsk.co.uk/Summary/rosiglitazone/studylist.asp>. Accessed Mar 27 2007
16. Canadian adverse drug reaction monitoring program (CADRMP) adverse reaction database Canada: Health Canada. 2006 Available from: [http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/agreement\\_accord\\_e.html](http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/agreement_accord_e.html). Accessed March 27, 2007
17. Glaxo Smith Kline. Study no 049653/211 A 52- week double blind study of the effect of rosiglitazone on cardiovascular structure and function in subjects with type 2 diabetes and congestive heart failure. [Article online] Available from: [http://ctr.gsk.co.uk/Summary/Rosiglitazone/IV\\_49653\\_211.pdf](http://ctr.gsk.co.uk/Summary/Rosiglitazone/IV_49653_211.pdf). Accessed 27 March 2007

18. The PROactive Investigators: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macro Vascular Events): a randomised controlled trial. *Lancet* 366:1279–1289, 2005
19. Hartung DM, Touchette DR, Bultemeier NC, Haxby DG: Risk of hospitalization for heart failure associated with thiazolidinedione therapy: A medicaid claims-based case-control study. *Pharmacotherapy* 25:329-36, 2005
20. Karter AJ, Ahmed AT, Liu J, Moffet HH, Parker MM. Pioglitazone initiation and subsequent hospitalization for congestive heart failure. *Diabet Med* 22:986-993, 2005
21. Inzucchi SE, Masoudi FA, Wang Y, Kosiborod M, Foody JM, Setaro JF, Havranek EP, Krumholz HM: Insulin-sensitizing antihyperglycemic drugs and mortality after acute myocardial infarction: insights from the National Heart Care Project. *Diabetes Care* 28:1680–1689, 2005
22. 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* 26:2983-2989, 2003
23. 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* 111:583-590, 2005
24. Rajagopalan R, Rosenson RS, Fernandes AW, Khan M, Murray FT: Association between congestive heart failure and hospitalization in patients with type 2 diabetes mellitus receiving treatment with insulin or pioglitazone: A retrospective data analysis. *Clin Ther* 26:1400-10, 2004
25. Richter B, Bandeira-Echtler E, Bergerhoff K, Clar C, Ebrahim SH. Pioglitazone for type 2 diabetes mellitus. *Cochrane Database Syst Rev* (4):CD006060, 2006
26. Maru S, Koch GG, Stender M, Clark D, Gibowski L, Petri H, White AD, Simpson RJ Jr: Antidiabetic drugs and heart failure risk in patients with type 2 diabetes in the U.K. primary care setting. *Diabetes Care* 28:20-26, 2005
27. Iribarren C, Karter AJ, Go AS, Ferrara A, Liu JY, Sidney S, Selby JV: Glycemic control and heart failure among adult patients with diabetes. *Circulation* 103:2668-2673, 2001
28. Mudaliar S, Chang AR, Henry RR: Thiazolidinediones, peripheral edema, and type 2 diabetes: Incidence, pathophysiology, and clinical implications. *Endocr Pract* 9:406-16, 2003
29. St. John Sutton M, Rendell M, Dandona P, Dole JF, Murphy K, Patwardhan R, Patel J, Freed M: A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. *Diabetes Care* 25:2058–2064, 2002
30. 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.* 102:9406-9411, 2005
31. Avandia Rosiglitazone [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2005.
32. Actos Pioglitazone [package insert]. Lincolnshire, IL: Takeda Pharmaceuticals America, Inc. and Indianapolis, IN: Eli Lilly and Company; 2004.

33. Karalliedde J, Buckingham R, Starkie M, Lorand D, Stewart M, Viberti G: Effect of various diuretic treatments on rosiglitazone-induced fluid retention. *J Am Soc Nephrol* 2006 17:3482-3490, 2006

**Table 1 Randomized Controlled Trials of Thiazolidinediones that evaluated heart failure outcomes**

<b>STUDY</b>	<b>Heart Failure rates in Treatment Arm</b>	<b>Heart Failure rates in Control Arm</b>	<b>Participants</b>	<b>Drug &amp; Daily Dosage</b>	<b>Duration of treatment</b>	<b>Case Ascertainment and Definition</b>
<b>DREAM 06 (10)</b>	14 / 2635	2 / 2634	Impaired glucose tolerance and/ or fasting glucose, not on hypoglycaemic medication. Patients with heart failure excluded.	Rosiglitazone 8mg	3 yrs median	Active surveillance. Confirmed heart failure was secondary outcome adjudicated by blinded independent monitoring committee. Prespecified definition was patient requiring acute treatment plus 2 of 3 criteria from: (i) typical signs/symptoms, (ii) radiologic findings, (iii) use of diuretics, vasodilators, or inotrope
<b>ProActive 05 (18)</b>	281 / 2605	198 / 2633	Type 2 diabetics with vascular disease. Less than one- third on insulin. Excluded if >NYHA Class II.	Pioglitazone titrated from 15 to 45 mg	34.5 months	Active surveillance, but no independent monitoring. We extracted data on all reported heart failure events. Post-hoc independent blinded adjudication using clinical, radiologic and laboratory criteria confirmed accuracy of original diagnoses.
<b>GSK 211;(17)</b>	19 / 110	10 / 114	Type 2 diabetics with NYHA Class I or II; single-blinded. No information on concomitant medications	Rosiglitazone titrated from 4-8 mg	12 months	Active surveillance – worsening heart failure a prespecified secondary outcome. We extracted data on all investigator reported cardiac failure events. No information on diagnostic criteria or adjudication.

**Table 2 Observational studies of thiazolidinedione exposure and association with heart failure**

ID	Study Type and Data Source	Study Population	Outcome Ascertainment	Key findings
<b>Hartung 05(19)</b>	Case-control. Oregon Medicaid insurance claims database.	Diabetic patients - 288 cases and 1652 controls - with prescription claims data for OHAs within 60 days of hospital admission.	ICD codes used to verify cases with first hospital admission due to heart failure. Controls had admission for other reasons.	59/229 cases of heart failure had been exposed, while 216/1436 controls exposed
<b>Karter 05(20)</b>	Retrospective cohort. Kaiser Permanente Northern California Diabetic registry.	23,440 patients initiating diabetic medication, ('new user'), with no history of heart failure.	ICD codes used to identify admissions for heart failure	Heart failure rates in exposed: 67/3556 vs. unexposed : 253/19884
<b>Inzucchi 2005(21)</b>	Retrospective cohort. Medicare National Heart Care Project.	Diabetic patients with recent admission for myocardial infarction discharged on hypoglycemic agents.	Readmission events (including heart failure) recorded for up to one year after discharge.	Heart failure rates in exposed: 402/819 as compared to in 3294/ 7914 unexposed.
<b>Delea 2003(22)</b>	Retrospective cohort, based on Pharmetrics Insurance database.	Diabetic patients with pharmacy claim for oral hypoglycaemic drugs. Patients with existing heart failure excluded.	Follow-up data for 43 months to diagnose new heart failure cases. Verification through ICD codes for claims	Heart failure rates in exposed: 126/5441 vs unexposed : 397/28103

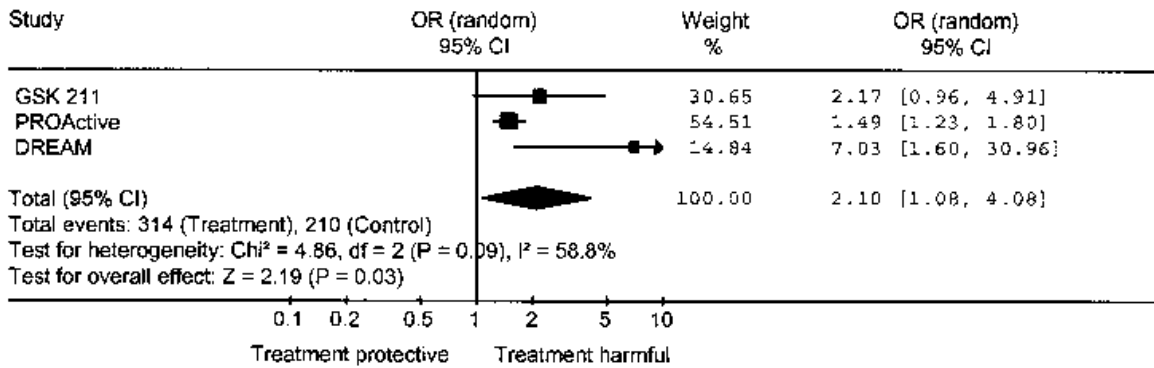
**Table 2 (b) Observational Studies excluded from the meta-analysis**

<b>Masoudi 2005(23)</b>	Retrospective cohort. From a Medicare database.	16,417 diabetic patients with a pre-existing history of hospital admission for heart failure.	One year follow-up to estimate risk of readmission for heart failure.	Heart failure rates in exposed: 1505/2226 vs. unexposed : 8912/13930
<b>Rajagopalan 2004(24)</b>	Retrospective cohort. Pharmetrics insurance database in US.	1668 matched pairs initiating pioglitazone or insulin between Jan 1999 – Dec. 2001. Those with existing heart failure were excluded.	Follow-up data of at least 3 months, using ICD codes for claims arising from heart failure.	Heart failure rates in those on pioglitazone: 33/2226 as compared to 66/ 1668 in those on insulin

**Figure 1**

**Meta-analysis of risk of heart failure in patients exposed to thiazolidinediones**

Review: Randomized controlled trials of thiazolidinediones  
 Comparison: Thiazolidinedione versus placebo  
 Outcome: All Heart Failure Adverse Events



Review: Observational studies of thiazolidinediones and heart failure  
 Comparison: Thiazolidinedione exposure versus no exposure  
 Outcome: Heart Failure

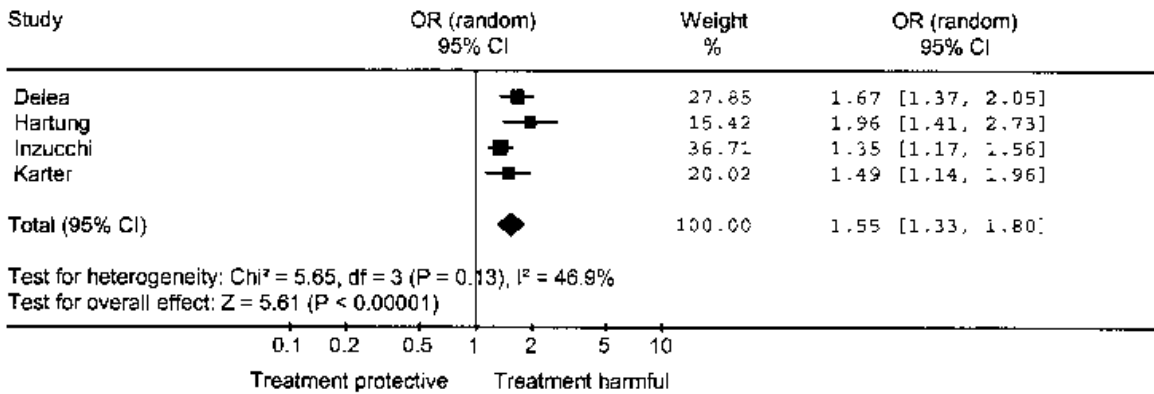
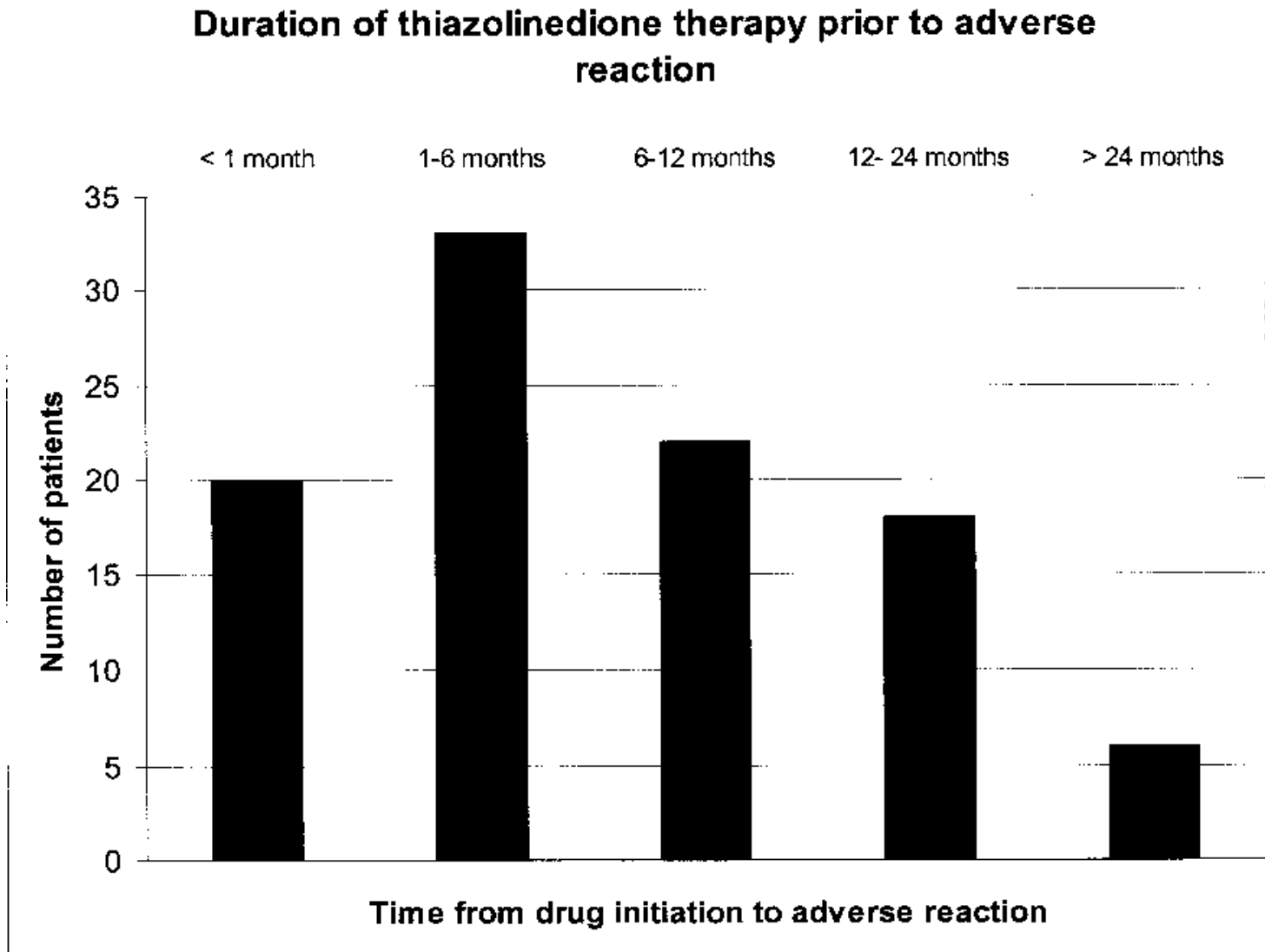


Figure 2



**Figure 3**

Dose and duration of thiazolidinedione therapy prior to occurrence of heart failure

