Long-term use of thiazolidinediones and the associated risk of pneumonia or lower respiratory tract infection: systematic review and meta-analysis

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ABSTRACT

Introduction The peroxisome proliferator-activated receptor-γ agonists rosiglitazone and pioglitazone activate glucocorticoid receptors and have an immunomodulatory effect. The authors aimed to systematically determine the risk of pneumonia or lower respiratory tract infections associated with thiazolidinediones.

Methods Systematic searches of MEDLINE, EMBASE, regulatory documents and trial registries were carried out for randomised controlled trials of thiazolidinediones with no date restrictions through March 2010. The authors selected long-term (≥1 year) randomised controlled trials of thiazolidinediones versus a placebo, metformin or sulfonylurea control for prevention or treatment of type 2 diabetes that reported on pneumonia or lower respiratory tract infection adverse events or serious adverse events (hospitalisation, disability or death). Relative risks (RRs) were estimated using a fixed-effects meta-analysis, and statistical heterogeneity was assessed using the I^2 statistic.

Results Thirteen trials (n=17 627, including 8163 patients receiving thiazolidinediones and 9464 patients receiving control therapy) with a duration of follow-up of 1—5.5 years were included after a detailed screening of 58 studies. Thiazolidinediones were associated with a statistically significantly increased risk for any pneumonia or lower respiratory tract infection (n=130/8163 vs 100/9464; RR 1.40; 95% CI 1.08 to 1.82; p=0.01; I^2=0%) and serious pneumonia or lower respiratory tract infection (n=111/7391 vs 87/8692; RR 1.39; 95% CI 1.05 to 1.83; p=0.02; I^2=0%).

Interpretation Long-term thiazolidinedione use is associated with a modestly increased risk of any pneumonia or lower respiratory tract infection and serious pneumonia or lower respiratory tract infection in patients with type 2 diabetes.

INTRODUCTION

Thiazolidinediones (rosiglitazone and pioglitazone) are peroxisome proliferator-activated receptor (PPAR)-γ agonists. Rosiglitazone is a PPARγ agonist whereas pioglitazone has both α and γ effects. PPAR activation has anti-inflammatory and immunomodulatory effects in the lung.[1] Thiazolidinediones act as partial agonists at the glucocorticoid receptor.[2] Rosiglitazone significantly improved lung function compared with inhaled beclometasone in a recent randomised controlled trial (RCT) in people who smoke and have asthma.[3] Pioglitazone is as effective as dexamethasone in reducing airway hyper-responsiveness and pulmonary inflammatory mediators in animal studies.[4] There is considerable optimism about the potential of the thiazolidinediones to favourably affect the course of asthma and chronic obstructive pulmonary disease.

The long-term effects of thiazolidinediones, however, are unpredictable, resulting in unusual toxicities. There have been concerns about an increased risk of myocardial infarction associated with rosiglitazone.[5—7] Thiazolidinediones are associated with an increased risk of congestive heart failure,[6—8] fractures (in women),[9] and possibly macular oedema.

It is possible that these immunomodulatory and glucocorticoid-like properties of the thiazolidinediones could potentially induce susceptibility to lung infections, similar to glucocorticoids in chronic obstructive pulmonary disease.[10] A signal for an increased risk of pneumonia in patients with type 2 diabetes was reported in a long-term trial of pioglitazone.[11] Another long-term trial of rosiglitazone reported a non-significant increase in pneumonia adverse events.[6] However, the exact risk of rare, serious adverse events such as pneumonia cannot always be conclusively determined from a single trial because of inadequate statistical power. The authors aimed to systematically determine the risk of pneumonia or lower respiratory tract infection adverse events associated with thiazolidinedione therapy in long-term clinical trials of patients with type 2 diabetes.

METHODS

Selection of trials with pneumonia or lower respiratory tract infection adverse event data

Our specific inclusion criteria were as follows: a study design consisting of parallel group RCTs of any thiazolidinedione (rosiglitazone or pioglitazone) with a treatment duration of at least 12 months; study participants with type 2 diabetes mellitus; control treatment which could be placebo, metformin or sulfonylurea, with the only difference between the treatment groups being thiazolidinedione exposure among participants; studies that reported data on 'pneumonia' or 'lower respiratory tract infection' adverse events or serious adverse events (including 0 events).

Active oral hypoglycaemic agents (metformin or sulfonylurea) were used as active comparators because metformin and sulfonylurea are not known to increase the risk of pneumonia. The recently approved incretin mimetics have been linked to an increase in the risk of infections.[12] The analysis was restricted to RCTs of at least 12 months' duration to evaluate the risk of pneumonia associated with long-term use of thiazolidinediones.

Search strategy

The authors evaluated all the RCTs identified from the database searches (MEDLINE, EMBASE, Cochrane Controlled Trials Register) in their previous systematic reviews.[7–9] The authors (YKL and SS) conducted an updated search of MEDLINE and EMBASE (Ovid SP from June 2008 to March 2010) for RCTs of rosiglitazone and pioglitazone. Trial reports were evaluated of all phase 3 and 4 published or unpublished trials of the GlaxoSmithKline clinical trials register, the Takeda clinical trials register and the Clinical Study Results Database for additional RCTs. Existing systematic reviews and the bibliographies of the studies that were included were checked. The search was limited to English-language articles, and included pre-approval and unpublished studies from regulatory documents and trial registries. The updated search strategy is outlined in online appendix S1.

Study selection

Trials were identified and subjected to inclusion and exclusion criteria. Two reviewers (SS and YKL) independently and in duplicate scanned all titles and abstracts that indicated the study was an RCT evaluating the use of thiazolidinediones among patients with type 2 diabetes. After obtaining full reports of potentially relevant trials, the same reviewers independently assessed eligibility from full-text articles.

Study characteristics

A prespecified protocol was used to record the location and duration of the RCT (in years), the inclusion and exclusion criteria, the dose and frequency of thiazolidinedione and control interventions, mean age and sex of participants, and mean glycated haemoglobin levels at baseline.

Risk of bias assessment

The Cochrane Toolkit was used for the assessment of bias in evaluating each trial for the reporting of sequence generation, allocation concealment, the use of blinding of participants and personnel, and information on loss to follow-up or withdrawal rates.[13] In accordance with the Cochrane handbook of systematic reviews, the authors assessed the strength of adverse events data by noting how the investigators monitored and recorded adverse events.[13]

Outcome measures

The primary prespecified outcomes measures were any pneumonia or lower respiratory tract infection adverse event (irrespective of severity), and pneumonia or lower respiratory tract infection reported as serious adverse events. Serious adverse events are life-threatening, require hospitalisation, or lead to significant disability or death.

Data abstraction

Two reviewers (SS and YKL), independently and as a team, assessed the eligibility and quality of studies for reporting of adverse events. They separately extracted data (including 0 events) on the proportion of patients with any pneumonia or lower respiratory tract infection among tabulated listings of adverse events for each study. Published reports were reconciled with trials in the clinical trials register when possible to avoid potential duplication. If there were multiple reports available for a particular study, data on pneumonia were extracted from the latest version.

Two reviewers (SS and YKL) were independently involved in all stages of study selection, data extraction and quality assessment. Any discrepancies were resolved through discussion. The reviewers achieved consensus on inclusion of studies and data extraction.

Data synthesis

Review Manager (RevMan), version 5.024 (Nordic Cochrane Center, Copenhagen, Denmark) was used to conduct a meta-analysis of the pooled relative risks (RRs), with 95% CI, using the fixed-effects model for dichotomous outcomes. The fixed-effects Mantel—Haenszel model is the appropriate method for meta-analysis of rare events because the random effects model lacks statistical power.[14] A continuity correction of 0.5 was used when there were zero events in one intervention arm. All reported p values are two sided, with significance set at $p < 0.05$. Statistical heterogeneity was assessed using the I^2 statistic.[15] A substantial level of heterogeneity is indicated by I^2 values of 50% or more.[15]

Prespecified sensitivity analyses were conducted to determine the influence of statistical models (use of Peto odds ratio which has been recommended for analysis of rare events, or the random effect which has less power)[14] on effect size. A subgroup analysis was also conducted to evaluate for intraclass differences in the risk of pneumonia between rosiglitazone and pioglitazone. Publication bias was assessed by visual inspection for funnel plot asymmetry,[13] and evaluation of effect sizes in published studies versus data obtained from unpublished studies. The fail-safe number using the Rosenberg method was estimated to assess the potential impact of missing data in the meta-analysis (ie, the number of additional negative trials that would be required to reverse a significant finding in the meta-analysis).[16]

The number needed to harm (and 95% CI) was estimated by applying the pooled RR from the meta-analysis to the average control event rate in different populations. The number needed to harm is the number of patients with type 2 diabetes who need to be treated with a thiazolidinedione, rather than with placebo or comparators, for one additional patient to have pneumonia or a lower respiratory tract infection.

RESULTS

The selection of trials is shown in figure 1 (online). The authors identified 280 potentially relevant citations, and after a detailed review of 58 studies, selected 10 datasets involving 13 trials of 17 627 patients that reported on pneumonia or lower respiratory tract infections.[6 11 17–32]

Trial characteristics are shown in table 1. In the trials 8163 participants received thiazolidinediones and 9464 received control therapy. Nine RCTs evaluated thiazolidinediones against active controls,[6 17–21 27–32] while four RCTs evaluated them against placebo.[11 22–26] The RCTs ranged in duration from 1 year to 5.5 years[6] and the sample size ranged from as low as 57[26] to 5238.[11] Thiazolidinedione-exposed participants had similar glycated haemoglobin at baseline to the control patients. Eight RCTs evaluated rosiglitazone.[6 17–27] Five RCTs evaluated pioglitazone, including one large RCT (the Prospective Pioglitazone Clinical Trial in Macrovascular Events, PROactive)[11] and another dataset,[28] which reported a pooled analysis among older patients with diabetes from four pioglitazone trials.[29–32]

Trial quality was generally satisfactory (online table S1). All the RCTs were double blind except for the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycaemia in Diabetes (RECORD) trial, which was open label.[6] Four trials had inadequate reporting of allocation concealment, sequence generation or loss to follow-up.[21 30–32] Eight RCTs were judged to be at low risk of bias (adequate

Table 1 Characteristics of long-term randomised controlled trials of thiazolidinedione use included in the analysis of pneumonia and lower respiratory tract infection adverse events

Source	Location	Participants	Inclusions	Exclusions	Duration (years)	Drug and daily dose	Male (%)	Age, mean (SD) (years)	Median HbA1c (SD)
Rosiglitazone									
Kahn et al (2006)[17] GSK 49653/048[18]	Multicentre, North America and Europe	Type 2 diabetes	Diagnosed in last 3 years and treated with diet and exercise	Hepatic disease, renal impairment, anaemia, lactic acidosis or UA or CHF, uncontrolled HTN, requiring steroid	4	Rosiglitazone 8 mg / Glibenclamide 15 mg / Metformin 2000 mg	55.7 / 58.0 / 59.4	56.3 (10) / 56.4 (10.2) / 56.9 (9.9)	7.36 (0.92) / 7.36 (0.93) / 7.35 (0.93)
Gerstein et al (2010)[19] GSK AVD 100521[20]	Multicentre, Europe, Asia and America	Type 2 diabetes	>1 atherosclerotic plaque with 1–2 OHAs	MI, CABG, CHF, renal and liver disease	1.5	Rosiglitazone 4 mg / Glipizide 5 mg	70.4 / 65.6	61.8 (8.38) / 60.2 (9.05)	7.10 (0.84) / 7.20 (0.91)
GSK 049653/020 (2004)[21]	Multicentre, Europe	Type 2 diabetes	C- peptide level>0.80 ng/ml and FPG>126 mg/dl and <270 mg/dl	Diabetic complications, serious renal, hepatic or haematological impairment	1	Rosiglitazone 4 mg / Rosiglitazone 8 mg / Glibenclamide	68.2 / 57.7 / 70.4	60.4 (8.23) / 60.6 (9.27) / 60.1 (8.34)	8.07 (1.29) / 8.21 (1.44) / 8.15 (1.26)
Dargie et al (2007)[22] GSK 49653/211[23]	Multicentre, Europe	Type 2 diabetes	Symptomatic CHF and FPG>126 mg/dl or <216 mg/dl	BMI>35 kg/m^2, significant hepatic, renal disease or anaemia	1	Rosiglitazone 4 mg / Placebo	84.3 / 79	64.3 (8.8) / 63.9 (8.6)	7.7 (1.3) / 7.8 (1.3)
Hedblad et al (2007)[24] GSK 49653/334[25]	Single centre, Sweden	Type2 diabetes insulin resistance	HOMA IR>1.80 for women and >2.12 for men	UA, CHF, required insulin, history of ketoacidosis, 2 or more OHAs	1	Rosiglitazone 4 mg / Placebo	44.8 / 47.6	67.7 (5.3) / 67.3 (6.3)	6.31 (0.76) / 6.28 (0.78)
GSK 049653/351[26]	Single centre, UK	Type 2 diabetes	HBAIC <10%, treated with OHA, vascular disease	2 or more OHAs or required insulin	1	Rosiglitazone 8 mg / Placebo	77.8 / 79.3	62.2 (8.2) / 65.6 (6.1)	NA / NA
GSK AVM 100264 (2006)[27]	Multicentre, Europe, Mexico	Type 2 diabetes	HBAIC >7 and <10 on Met	OHAs other than metformin, renal, hepatic disease or CHF NYHA I–IV	1	Rosiglitazone 4–8 mg / Sulfonylurea	52.7 / 52.5	58.5 (9.6) / 59.3 (9.2)	8.04 (0.89) / 7.99 (0.96)
Home et al (2009)[6]	364 centres in Europe and Australasia	Type 2 diabetes	BMI>25 kg/m^2 on Met or SU with HBAIC 7–9%	Hospitalisation for major CV event 3 months prior, planned intervention, CHF	5.5	Rosiglitazone 4–8 mg (+Met) / Rosiglitazone 4–8 mg (+SU) / Metformin 2550 mg (+SU) / Glibenclamide 15 mg (+Met)	53.8 / 49 / 52.9 / 50.6	57.0 (8.0) / 59.8 (8.3) / 57.2 (8.1) / 59.7 (8.2)	7.8 (0.7) / 8.0(0.7) / 7.8 (0.7) / 8.0 (0.7)
Pioglitazone									
Dormandy et al (2005)[11]	Multicentre	Type 2 diabetes	HBAIC>6.5% treated with diet or oral agents and extensive macrovascular disease	Type 1 diabetes, coronary or peripheral revascularisation, NHYA II and above CHF, haemodialysis or elevated liver enzymes	3.5	Pioglitazone15–45 mg / Placebo	67 / 66	61.9 (7.6) / 61.6 (7.8)	7.8 (NA) / 7.9 (NA)
Schernthaner et al (2004)[29] *	167 centres in 12 European countries	Type 2 diabetes	Poorly controlled type 2 diabetes with HBAIC between 7.5% and 11%, age >65	Type 1 diabetes, ketoacidosis, MI, TIA or stroke in last 6 months, NYHA I–IV CHF, cancer or substance abuse	1	Pioglitazone 30–45 mg / Metformin 850 mg once a day to three times a day	52.1 / 44.7	69.5 (2.93) / 69.1 (2.92)	8.58 (0.93) / 8.83 (1.01)
Charbonnel et al (2005)[30] *	206 centres in Europe	Type 2 diabetes	Poorly controlled type 2 diabetes with HBAIC between 7.5% and 11%, age >65	Type 1 diabetes, ketoacidosis, MI, TIA or stroke in last 6 months, NYHA I–IV CHF, cancer or substance abuse	1	Pioglitazone 30–45 mg / Gliclazide 80–160 mg twice a day	52.1 / 56.3	69.5 (2.93) / 69.5 (2.85)	8.58 (0.95) / 8.58 (0.95)
Hanefeld et al (2004)[31] *	91 centres in Europe and Canada	Type 2 diabetes	Poorly controlled type 2 diabetes with HBAIC between 7.5% and 11%, age >65	Type 1 diabetes, ketoacidosis, MI, TIA or stroke in last 6 months, NYHA I–IV CHF, cancer or substance abuse	1	Pioglitazone 14–45 mg / Metformin 850 mg once a day to three times a day	53.3 / 49.5	69.8 (2.7) / 69.3 (3.12)	8.79 (0.79) / 8.75 (1.01)
Matthews et al (2005)[32] *	75 centres in Europe and Australia	Type 2 diabetes	Poorly controlled type 2 diabetes with glycated haemoglobin between 7.5% and 11%, age >65	Type 1 diabetes, ketoacidosis, MI, TIA or stroke in last 6 months, NYHA I–IV CHF, cancer or substance abuse	1	Pioglitazone 15–45 mg / Gliclazide 80–160 mg twice a day	50.8 / 33.3	69.5 (2.79) / 69.3 (2.75)	8.58 (0.97) / 8.50 (0.82)

*Post hoc pooled safety analysis on a subgroup of older participants from four randomised controlled trials (Rajagopalan et al 2006).[28]
BMI, body mass index; CABG, coronary artery bypass graft; CHF, congestive heart failure; CV, cardiovascular; FPG, fasting plasma glucose; GSK, GlaxoSmithKline; HOMA IR, homeostatic model assessment insulin resistance; HBAIC, glycated haemoglobin; HTN, hypertension; Met, metformin; MI, myocardial infarction; NA, not available; NYHA, New York Heart Association; OHA, oral hypoglycemic agents; TIA, transient ischaemic attack; UA, unstable angina; SU, sulfonylurea.

sequence generation, allocation concealment and double blinding, and clear reporting of loss to follow-up or withdrawal rates), whereas the remaining five RCTs were at unclear risk of bias.[6 21 30–32]

Because pneumonia and lower respiratory tract infection have not previously been linked to thiazolidinedione therapy, detection in these trials occurred via routine monitoring of adverse events or serious adverse events because it is not possible to prespecify diagnostic criteria for unexpected adverse events. Accordingly, none of the included RCTs had objective pneumonia definitions, or reported the proportion of patients that had radiographic confirmation of pneumonia. Thus the methods for diagnosing pneumonia and lower respiratory tract infection possibly varied between trials (clinical vs radiographical). Seven trials reported pneumonia or lower respiratory tract infection to be a serious adverse event,[6 11 17–23] whereas six trials reported lower respiratory tract infection as an adverse event.[26–32] Approximately 86% of pneumonia and lower respiratory tract infection events in our meta-analysis were classified as serious adverse events leading to hospitalisation, disability or death. Although six trials did not report on cause-specific mortality,[6 11 28–32] available information on fatal adverse events from seven rosiglitazone trials[17] reported no deaths due to pneumonia or lower respiratory tract infection associated with rosiglitazone. Thus it is possible that most of these serious adverse events caused by pneumonia or lower respiratory tract infection stemmed from hospitalisation.

Risk of pneumonia or lower respiratory tract infection
Thiazolidinediones were associated with a significantly increased risk of pneumonia or lower respiratory tract infection compared with controls in a meta-analysis of 13 RCTs involving 17 627 participants (n=130/8163 vs 100/9464; 1.59% vs 1.06%; RR 1.40; 95% CI 1.08 to 1.82; p=0.01); there was no statistical heterogeneity among the included trials ($I^2=0\%$) (figure 2).[6 11 17–32]
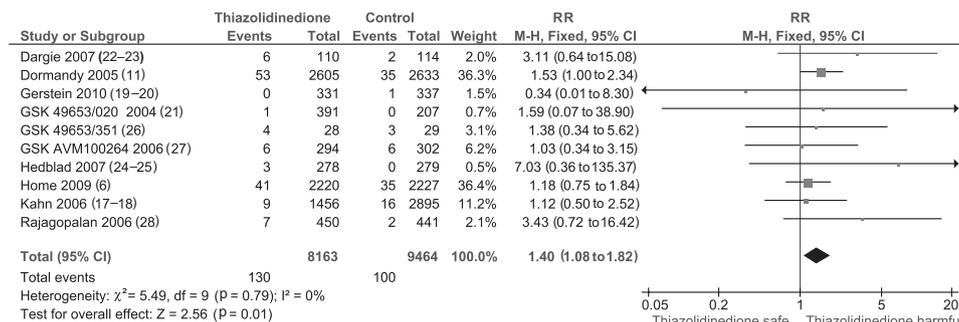
Risk of pneumonia or lower respiratory tract infection as serious adverse events
Thiazolidinediones were associated with a significantly increased risk of serious adverse events caused by pneumonia or lower respiratory tract infections compared with controls in a meta-analysis of seven trials involving 16,083 patients (RR 1.39; 95% CI 1.05 to 1.83; p=0.02); there was no statistical heterogeneity among the included trials ($I^2=0\%$) (figure 3).[6 11 17–23]

Sensitivity analysis
The sensitivity analysis using the Peto odds ratio yielded estimates similar to those of the fixed-effects model for the risk of any pneumonia or lower respiratory tract infection associated with the thiazolidinediones (RR 1.42; 95% CI 1.09 to 1.84; p=0.009; $I^2=0\%$).[6 11 17–32]

The sensitivity analysis using a random-effects model yielded estimates similar to those of the fixed-effects model for the risk of any pneumonia or lower respiratory tract infection associated with the thiazolidinediones (RR 1.38; 95% CI 1.06 to 1.79; p=0.02; $I^2=0\%$).[6 11 17–32]

The direction of effect for both the thiazolidinediones showed a similar increased risk, with the RRs for pioglitazone achieving statistical significance (RR 1.63; 95% CI 1.09 to 2.46; p=0.02) in a meta-analysis of five trials involving 6129 patients.[11 28–32] The RRs for rosiglitazone did not reach statistical significance (RR 1.26; 95% CI 0.90 to 1.76; p=0.23) in a meta-analysis of eight trials involving 11 498 patients, but a clinically significant excess risk could not be ruled out.[6 17–27] The test for homogeneity of effects across the two thiazolidinediones pioglitazone and rosiglitazone did not demonstrate a statistically significant difference between the two agents (p=0.32). However, these subgroup analyses should be interpreted for the direction of effect, rather than the magnitude of statistical significance, because subgrouping or removal of specific studies can render the meta-analysis underpowered to detect differences.

Assessment of publication bias and missing data
Visual inspection of the funnel plot did not reveal any evidence of asymmetry (online figure S1). The RR for pneumonia from unpublished data was 1.38 (95% CI 0.82 to 2.30), which was similar to that of the published studies (RR 1.40; 95% CI 1.05 to 1.90). To reverse the significantly increased risk of pneumonia or lower respiratory tract infection shown in our meta-analysis, 11 negative studies with an average sample size of 1400 participants would be required.[23]
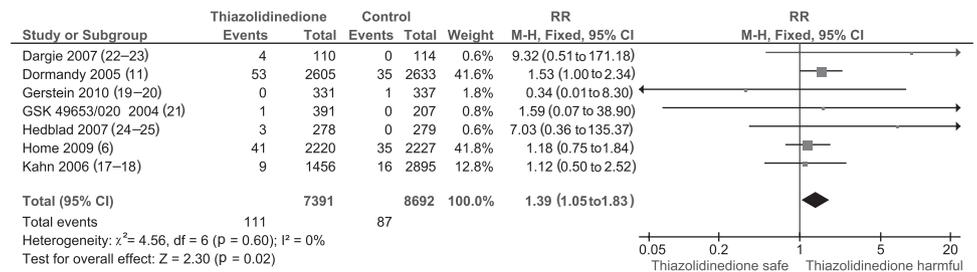
Estimated number needed to harm
Using estimates of the incidence of pneumonia of 4919/100 000 person-years from a population-based study (mean age 61 years, 51.7% male) in patients with type 2 diabetes in Ontario,[33] the number needed to harm for pneumonia or lower respiratory tract infection associated with thiazolidinedione use was estimated to be 55 (95% CI 28 to 269). Treatment of 55 patients with thiazolidinediones for 3.7 years would result in one extra case of pneumonia or lower respiratory tract infection based on the event rate in population-based studies. Based on the average control event rate in the trials, the estimated number needed to harm for any pneumonia or lower respiratory tract infection associated with thiazolidinedione use is 239 (95% CI 117 to 1191).

DISCUSSION
Our meta-analysis of 17 627 patients raises serious concern about a significant association between long-term thiazolidinedione use and pneumonia or lower respiratory tract infection leading to adverse events or serious adverse events among

Figure 2 Fixed-effects meta-analysis of long-term randomised controlled trials of pneumonia or lower respiratory tract infection with thiazolidinediones versus controls.

Study or Subgroup	Thiazolidinedione Events	Total	Control Events	Total	Weight	RR M-H, Fixed, 95% CI
Dargie 2007 (22–23)	6	110	2	114	2.0%	3.11 (0.64 to 15.08)
Dormandy 2005 (11)	53	2605	35	2633	36.3%	1.53 (1.00 to 2.34)
Gerstein 2010 (19–20)	0	331	1	337	1.5%	0.34 (0.01 to 8.30)
GSK 49653/020 2004 (21)	1	391	0	207	0.7%	1.59 (0.07 to 38.90)
GSK 49653/351 (26)	4	28	3	29	3.1%	1.38 (0.34 to 5.62)
GSK AVM100264 2006 (27)	6	294	6	302	6.2%	1.03 (0.34 to 3.15)
Hedblad 2007 (24–25)	3	278	0	279	0.5%	7.03 (0.36 to 135.37)
Home 2009 (6)	41	2220	35	2227	36.4%	1.18 (0.75 to 1.84)
Kahn 2006 (17–18)	9	1456	16	2895	11.2%	1.12 (0.50 to 2.52)
Rajagopalan 2006 (28)	7	450	2	441	2.1%	3.43 (0.72 to 16.42)
Total (95% CI)		8163		9464	100.0%	1.40 (1.08 to 1.82)
Total events	130		100			

Heterogeneity: $\chi^2=5.49$, df=9 (P=0.79); $I^2=0\%$
Test for overall effect: Z=2.56 (P=0.01)

Thiazolidinedione safe ← → Thiazolidinedione harmful
(0.05 0.2 1 5 20)

Figure 3 Fixed-effects meta-analysis of long-term randomised controlled trials of serious pneumonia or lower respiratory tract infection with thiazolidinediones versus controls.

Study or Subgroup	Thiazolidinedione Events	Total	Control Events	Total	Weight	RR M-H, Fixed, 95% CI
Dargie 2007 (22–23)	4	110	0	114	0.6%	9.32 (0.51 to 171.18)
Dormandy 2005 (11)	53	2605	35	2633	41.6%	1.53 (1.00 to 2.34)
Gerstein 2010 (19–20)	0	331	1	337	1.8%	0.34 (0.01 to 8.30)
GSK 49653/020 2004 (21)	1	391	0	207	0.8%	1.59 (0.07 to 38.90)
Hedblad 2007 (24–25)	3	278	0	279	0.6%	7.03 (0.36 to 135.37)
Home 2009 (6)	41	2220	35	2227	41.8%	1.18 (0.75 to 1.84)
Kahn 2006 (17–18)	9	1456	16	2895	12.8%	1.12 (0.50 to 2.52)
Total (95% CI)		**7391**		**8692**	**100.0%**	**1.39 (1.05 to 1.83)**
Total events	111		87			

Heterogeneity: χ²= 4.56, df = 6 (p = 0.60); I² = 0%
Test for overall effect: Z = 2.30 (p = 0.02)

patients with type 2 diabetes (RRs ≈ 40% increased risk). The absence of statistical heterogeneity, the consistency in the direction of effect, and the robustness of risk estimates for pneumonia or lower respiratory tract infection of varying severity suggest that this concern deserves detailed investigation. Any potential accentuation of risk with thiazolidinediones is of particular concern given that several recent epidemiological studies have reported an increased risk of pneumonia in patients with type 2 diabetes.[33]

The exact mechanisms by which thiazolidinediones increase the risk of pneumonia or lower respiratory tract infection are uncertain. Thiazolidinediones have glucocorticoid-like effects in the airways.[3] [4] These effects could induce susceptibility to pneumonia or lower respiratory tract infection, similar to the effect of glucocorticoids in chronic obstructive pulmonary disease.[10] Thiazolidinediones have off-target effects on PPARδ at clinically relevant doses.[34] Thiazolidinediones may exhibit proinflammatory activities in a PPARγ and PPARα independent manner by augmenting PPARδ signalling.[34] Pioglitazone was also associated with an increased risk of hospitalisation for acute cholecystitis in a pooled analysis of 1526 patients (12 cases vs one for placebo).[35] Further studies are required to elucidate the role of PPARs off-target and glucocorticoid effects in the development of serious infections such as pneumonia.

LIMITATIONS

The study has potential limitations, which mainly reflect the quality of reported data. The estimates are imprecise because of the low event rates in the trials. In the absence of patient-level data, we could not determine whether pneumonia or lower respiratory tract infection associated with thiazolidinedione use is immediate or there is a lag time to harm. Another possibility is that congestive heart failure events, a known harmful effect of thiazolidinedione use, were misclassified as pneumonia or lower respiratory tract infection. However, congestive heart failure was studied in several long-term trials.[6] [11] [19] [20] [22] [23] In the PROactive study, post-hoc adjudication of congestive heart failure and pneumonia outcomes reclassified only three pneumonia events—one in the pioglitazone arm (0.04%) and two in the placebo arm (1%).[11] The effect of any potential misclassification on the meta-analysis is likely minimal because all trials (except RECORD) were double blind. Any misclassification of pneumonia or lower respiratory tract infection would be non-differential, and would bias our estimates towards the null. The absence of specific mortality data for pneumonia or lower respiratory tract infection from some of the included trials, and the low event rates prevent conclusions being drawn on the prognostic outcome of pneumonia or lower respiratory tract infection associated with thiazolidinediones.

Despite their limitations, the findings warrant further investigation. Individual patient data analysis could yield further information on the risk of pneumonia or lower respiratory tract infection with long-term use of thiazolidinediones. Stratified analysis ought to be conducted to determine any differences in the risk among people who smoke, people with chronic obstructive pulmonary disease, or those vaccinated with the influenza or pneumococcal vaccine. Clinical trials of thiazolidinediones among patients with type 2 diabetes, and ongoing trials in patients with obstructive lung disease, should monitor the risk of pneumonia using objective definitions with radiological and microbiological confirmation. The safety concern for long-term thiazolidinedione use needs to be replicated in carefully conducted epidemiological studies.

CONCLUSION

Long-term thiazolidinedione use is associated with a modestly increased risk of pneumonia or lower respiratory tract infection, and serious pneumonia or lower respiratory tract infection in patients with type 2 diabetes.

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