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RESEARCH ARTICLE

Thiazolidinedione use and risk of hospitalization for pneumonia in type 2 diabetes: population based matched case-control study [version 1; peer review: 2 approved with reservations]

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v1 First published: 27 Jun 2013, 2:145
<https://doi.org/10.12688/f1000research.2-145.v1>
 Latest published: 27 Jun 2013, 2:145
<https://doi.org/10.12688/f1000research.2-145.v1>

Abstract

Objective: Previous randomized clinical trials and their meta-analyses have raised the possibility that thiazolidinediones (rosiglitazone and pioglitazone) may increase the risk of pneumonia. We aimed to test the hypothesis that thiazolidinediones may increase the risk of pneumonia.

Design: Population based case-control study using a new user design.

Setting: A large administrative database in the United States from 2002 to 2008.

Population: Adults with type 2 diabetes aged 18-64; restricted to 6129 hospitalized pneumonia cases and 6129 controls without congestive heart failure matched on age, sex, enrollment pattern and diabetes complication severity index matched controls. Conditional logistic regression was used to analyse the data.

Results: Compared with controls, cases were more likely to have chronic obstructive pulmonary disease (COPD), tobacco use, cancer and have received influenza and pneumococcal vaccination. After adjusting for COPD, cancer, tobacco use, and receipt of influenza and pneumococcal vaccination, and exposure in other periods, neither recent exposure to pioglitazone (adjusted Odds Ratio [aOR], 1.15, 95% Confidence intervals 1.00 – 1.32) or rosiglitazone (aOR 1.09, 95% CI, 0.83 – 1.44) nor current exposure to pioglitazone within 60 days (aOR, 1.04, 95% CI, 0.60 – 1.79) was associated with a statistically significant odds of pneumonia. Current exposure to rosiglitazone was associated with a statistically significant reduction in the odds of pneumonia (aOR, 0.33, 95% CI 0.11-0.95).

Conclusion: In this study of US adults with type 2 diabetes we did not detect a significant increased risk of pneumonia with the

Open Peer Review

Approval Status **??**

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27 Jun 2013	view	view
1. Stephan F. Lanes , HealthCore, Inc., MA, USA		
2. Hans-Peter Hammes , University of Heidelberg, Mannheim, Germany		
Any reports and responses or comments on the article can be found at the end of the article.		

thiazolidinediones. The unusually large protective effect of current exposure to rosiglitazone reflects the healthy user effect or unmeasured confounding.

Keywords

Thiazolidinediones, pneumonia, type 2 diabetes, case-control study

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Competing interests: The authors have no competing interests. The dataset used in this study was created for a research project on the patterns of obesity care within selected BlueCross BlueShield health insurance plans. The original development of the dataset was funded by unrestricted research grants from Ethicon Endo-Surgery, Pfizer, and GlaxoSmithKline. Data and database development support were provided by the BlueCross BlueShield Association (Tennessee, Hawaii, Michigan, and North Carolina), Highmark (Pennsylvania), Independence BlueCross (Pennsylvania), and Wellmark BlueCross BlueShield (Iowa and South Dakota). The BlueCross BlueShield plans were invited to review the manuscript but they did not have any direct role in the design and conduct of the study, data management or analysis, interpretation of the data, or preparation of the manuscript.

Grant information: SS was supported by the Johns Hopkins Clinical Research Scholars Program. This publication was made possible by Grant Number 1KL2RR025006-03 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at <http://www.ncrr.nih.gov/>. Information on Re-engineering the Clinical Research Enterprise can be obtained from <http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp>. The design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript were independent of any other sources of funding. Dr Singh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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How to cite this article: Singh S, Yen Chang H, Richards T *et al.* **Thiazolidinedione use and risk of hospitalization for pneumonia in type 2 diabetes: population based matched case-control study [version 1; peer review: 2 approved with reservations]** F1000Research 2013, 2:145 <https://doi.org/10.12688/f1000research.2-145.v1>

First published: 27 Jun 2013, 2:145 <https://doi.org/10.12688/f1000research.2-145.v1>

Introduction

The thiazolidinediones, rosiglitazone and pioglitazone, are peroxisome proliferator-activated receptor γ (PPAR γ) agonists. These drugs effectively lower glycated hemoglobin levels among patients with type 2 diabetes¹. Both these agents have relatively similar efficacy, but may have different adverse effect profiles¹⁻⁸. Since regulatory approval, the thiazolidinediones have been associated with an increase in the risk of fractures in women, heart failure and, in the case of rosiglitazone, myocardial infarction¹⁻⁶. Certain immunological adverse effects such as increased risk of bladder cancer⁷, or acute cholecystitis⁹, are specific to pioglitazone.

Rosiglitazone is a PPAR γ agonist, whereas pioglitazone has both α and γ effects. PPAR γ activation may result in glucocorticoid like effects in the airways¹⁰⁻¹². These effects could induce susceptibility to pneumonia similar to the effect of glucocorticoids in chronic obstructive pulmonary disease¹³. In human macrophages the thiazolidinediones have off-target effects on PPAR δ at clinically relevant doses¹⁴⁻¹⁷. This augmentation of PPAR δ signaling by the thiazolidinediones may potentially exhibit proinflammatory activities such as pneumonia^{14,15}.

Patients with type 2 diabetes are known to be at a higher risk of pneumonia^{18,19}. A large, long term clinical trial⁷, and a meta-analysis of long term clinical trials raised the possibility that long term use (> one year) of the thiazolidinediones may increase the risk of pneumonia⁶. We aimed to test the hypothesis that the use of rosiglitazone or pioglitazone was associated with an increased risk of pneumonia in patients with type 2 diabetes.

Methods

Setting

We used administrative claims data from seven US Blue Cross and Blue Shield (BCBS) plans. These were the BCBS of Tennessee, Hawaii, Michigan, North Carolina; Highmark, Inc. of Pennsylvania, Independence Blue Cross of Pennsylvania and Wellmark, Inc. of Iowa and of South Dakota.

Study design and population

We assembled an incident cohort of all patients with type 2 diabetes who filled at least one prescription for any hypoglycemic agent between 2002 and 2008. To be eligible for inclusion, individuals had to be: a) between 18 and 64 years on their first date of diagnosis of diabetes; b) contribute at least 6 months of medical or pharmacy coverage in the calendar year of diabetes diagnosis; c) of known sex; d) without any claim for congestive heart failure. We restricted the analytical sample to cases of pneumonia without a history of diagnosis of congestive heart failure to reduce outcome misclassification because congestive heart failure is a known adverse effect of thiazolidinedione use and shares many clinical and radiographic similarities to pneumonia⁴. We determined eligibility for the study from computerized encounter

data including enrollment files for administrative data; benefits information to determine medical and pharmacy coverage; and inpatient, outpatient, and pharmacy claims records containing Common Procedural Terminology (CPT) codes, International Classification of Disease-9 Clinical Modification (ICD-9-CM) codes, and National Drug Codes (NDC) or Diagnosis Related Group (DRG) codes and costs and charges (submitted, allowed, and paid).

Selection of cases

Briefly, we identified presumptive cases by using an algorithm of ICD-9 codes for inpatient pneumonia ([Supplementary Table 1](#)). These were defined as individuals with an inpatient code for pneumonia. For people with multiple episodes of pneumonia, we included only the first episode.

Selection of controls

We selected one control for each case from the eligible source population matched on age (10 year intervals), sex, insurance plan site, and Diabetes Complication Severity Index (0, 1, and 2)^{20,21}, and enrollment pattern or duration of pneumonia-free follow-up (incidence density sampling). Pneumonia cases were not eligible to be resampled as controls.

Exposure definitions

Prescription data were used as an indicator of drug exposure using NDC codes. We obtained information about thiazolidinedione use from a computerized pharmacy database containing the date the prescription was filled and number of days supplied. We used these data elements to determine the dates a patient was exposed to the drug prior to the first observed diagnosis of pneumonia.

Drug exposure was defined as having filled a prescription on any day for rosiglitazone or pioglitazone prior to the first observed diagnosis of pneumonia. A first exposure after the index diagnosis of pneumonia with thiazolidinediones was counted as unexposed. We defined four categories of exposure. *Any users* were those with exposure to the thiazolidinediones after the diagnosis of diabetes before the index date of pneumonia. *Current users* were those who were exposed to the thiazolidinediones within 60 days prior to the index date of onset of pneumonia. *Recent users* were those with a claim for the thiazolidinediones from 61 days to 2 years prior to the index date of pneumonia. *Non-users* are defined as those for whom there was no thiazolidinedione prescription or a prescription more than 2 years prior to the index date of pneumonia. *Current users*, *recent users* and *non-users* were mutually exclusive categories of exposure. However, *any users* included *current* and *recent users*.

Statistical analysis

We calculated proportions for categorical variables and means or medians for continuous variables according to the case status.

We used conditional logistic regression to estimate the McNemar Odds Ratio for exposure to rosiglitazone or pioglitazone to account for the matching design of the study. We evaluated rosiglitazone and pioglitazone separately. However, we did not distinguish between single agent vs. combinations of the thiazolidinediones with other oral hypoglycemic agents. We conducted analyses for recent and current rosiglitazone and pioglitazone users and for any users in a series of statistical models. The most parsimonious model only took into account the matched design of the study (age, sex, enrollment pattern, and Diabetes Complication Severity Index). Subsequent statistical models adjusted for potential confounders specified *a priori* using a review of the literature including chronic obstructive pulmonary disease, tobacco use, receipt of influenza or pneumococcal vaccination, and an indicator of general morbidity level (the resource utilization band from the Johns Hopkins Adjusted Clinical Group case-mix system; [Supplementary Table 2](#))²³. The fully adjusted models adjusted for matching variable, confounders and recent and current exposure of both rosiglitazone and pioglitazone. We used SAS version 9.2 for analysis. Statistical significance was set at two sided $P=0.05$.

Results

Study population

We found 1,100,899 patients with type 2 diabetes who were potentially eligible during the study period. Within this group 5.8% of participants ($n=64,157$) experienced a first episode of inpatient pneumonia during the study period. After excluding participants above 64 or below the age of 18 years ($n=31,347$), participants with incomplete coverage ($n=24,402$), missing information on sex (1,761) a history of congestive heart failure (34,589) or a date of diabetes diagnosis later than or equal to date of pneumonia (14,150), 8883 cases of pneumonia remained eligible for inclusion. We removed two pairs of cases and controls for using both rosiglitazone and pioglitazone in the same study period. We restricted the analysis to 6129 cases of pneumonia without a history of congestive heart failure. 6129 controls matched for age, sex, and enrollment pattern and diabetes complication severity index were randomly selected from a pool of 428,826 potentially eligible controls. The flow of participants through the study is shown in [Figure 1](#).

Characteristics

The characteristics of the cases and controls are shown in [Table 1](#). The mean age of participants in the study was 52 years. Just over 50% of participants were male. Cases with pneumonia were more likely than controls to have chronic obstructive pulmonary disease, cancer, or be tobacco users, or to have received influenza and pneumococcal vaccination. More cases than controls were exposed to the thiazolidinediones during the study period (any exposure). The exposure of

cases and controls to rosiglitazone and pioglitazone in various exposure windows is shown in [Table 2](#).

Association between thiazolidinedione use and hospitalization for pneumonia

Our results for Model 1, Model 2, Model 3 and Model 4 are shown in [Table 3](#). After adjusting for COPD cancer, tobacco use, and receipt of influenza and pneumococcal vaccination, and exposure in other periods in the fully adjusted model, neither recent exposure to pioglitazone (adjusted Odds Ratio (aOR), 1.15, 1.27, 95% confidence intervals 1.00–1.32), rosiglitazone (aOR 1.09, 95% CI, 0.83–1.44) nor current exposure to pioglitazone within 60 days (aOR, 1.04, 95% CI, 0.60–1.79) was associated with statistically significant odds of pneumonia. Current exposure to rosiglitazone was associated with statistically significant reduction in the odds of pneumonia (aOR, 0.33, 95% CI 0.11–0.95).

Discussion

We did not find any evidence to support our initial hypothesis that either rosiglitazone or pioglitazone was associated with a statistically significant increased risk of hospitalization for pneumonia in a restricted sample of adult patients with type 2 diabetes without a history of congestive heart failure. We also noted some unexpected findings such as a statistically significant reduction in the risk of pneumonia with rosiglitazone of $\approx 70\%$. There is no biological evidence to support such a beneficial effect of rosiglitazone on infections such as pneumonia. Such post-hoc findings from observational studies should be noted with caution. It is also possible that some unmeasured confounders or potentially a healthy user effect could explain these results. We did not have access to clinical records to fully evaluate the healthy user effect.

Comparison with meta-analysis of randomized controlled trials

Our findings need to be interpreted in the context of other studies. The largest 4 year clinical trial of pioglitazone, the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) study [NCT00174993](#) reported a statistically significant increased risk of pneumonia reported as serious adverse events (Relative Risk (RR) 1.53, 95% CI 1.00–2.34; $P=0.047$) compared to placebo⁷. However a similar, large, long term clinical trial of rosiglitazone, the Rosiglitazone Evaluated for Cardiovascular outcomes in ORal agent combination therapy for type 2 Diabetes (RECORD) study did not detect a significantly increased risk of pneumonia with rosiglitazone as compared to metformin or sulfonylureas (RR 1.18, 95% CI 0.75–1.84; $P=0.56$)⁸. A previous meta-analysis of thirteen long-term (>1 year) randomized trials of the thiazolidinediones, which included the two long-term studies just mentioned, reported a $\approx 40\%$ increased risk of pneumonia or lower respiratory tract infection adverse events

Figure 1. Selection of cases and controls. BCBS – Blue Cross and Blue Shield; CHF – coronary heart failure; DCSI – Diabetes Complication Severity Index.

or serious adverse events with statistically significant RRs for pioglitazone (RR 1.63; 95% CI 1.09–2.46) but not for rosiglitazone (RR 1.26; 95% CI 0.90–1.76)⁶.

There are several possible reasons for the divergent findings between this observational study and the previous meta-analysis. It is possible that participants in the trials were different from this observational study. Some trials did not report on pneumonia events, and missing data are possible in both the trial and the observational study. Although chest X-rays were adjudicated in the largest trial for pioglitazone⁷, it is possible that the clinical trials reported more events of pneumonia associated with the thiazolidinediones because patients on the thiazolidinediones in the trials probably received more radiographic studies

to evaluate congestive heart failure associated with the thiazolidinedione (i.e. detection bias)²². In this study, we restricted our analysis to patients without congestive heart failure, which could have accounted for misclassification of outcomes.

Strengths of the study

The present study minimized the impact of the potential misclassification of congestive heart failure, a known adverse effect of thiazolidinedione use²⁵, by restricting the analysis to hospitalized patients with pneumonia and without congestive heart failure. We also used a new user design, which is important in studying the effects of drugs to remove prevalent user biases. In addition we were able to control for several available confounders.

Table 1. Characteristics of cases and controls.

	Cases	Controls
Number	6,129	6,129
Potential Confounder		
Influenza	10.20%	8.58%
Pneumococcal	8.11%	6.43%
COPD	25.06%	5.82%
Tobacco	14.44%	5.06%
Neoplasm	41.47%	29.52%
Resource Utilization Band (ACG)		
0	3.86%	3.22%
1	0.70%	0.72%
2	9.72%	5.74%
3	55.67%	43.60%
4	20.41%	23.76%
5	9.64%	22.97%
Diabetes Complication Severity Index		
Mean±SD	0.58±1.08	0.56±1.02
0	69.23%	69.23%
1	14.78%	14.78%
2	9.68%	9.68%
3+	6.31%	6.31%
Age		
Mean±S.D.	52.3±9.0	52.1±8.8
18–30	2.27%	2.27%
31–44	15.50%	15.50%
45–64	82.23%	82.23%
Sex		
Male	51.57%	51.57%
Length of observation: Date of pneumonia – date of diabetes/index date		
1 yr	21.70%	21.70%
2 yr	34.26%	34.26%
3 yr	25.55%	25.55%
4 yr	14.11%	14.11%
5 yr	4.37%	4.37%
6 yr	0.00%	0.00%

ACG = adjusted clinical group; SD = Standard deviation.

Limitations of the study

Our study has some limitations. Misclassification of exposure is possible because information on exposure was derived from pharmacy claims, and we cannot guarantee that the drugs were ingested. Differential misclassification of exposure ascertainment among cases and controls is unlikely but cannot be definitively ruled out. We did not impute for missing data. Although we restricted our analysis to participants without congestive heart failure to minimize potential differential misclassification of heart failure, we did not have access to the

Table 2. Exposure to pioglitazone and rosiglitazone among cases and controls.

	Cases	Controls
Number	6,129	6,129
Current Period		
Thiazolidinediones		
Recent exposure	11.24%	10.77%
Current exposure	0.59%	0.70%
Pioglitazone		
Recent exposure	9.45%	8.96%
Current exposure	0.52%	0.51%
Rosiglitazone		
Recent exposure	2.17%	2.20%
Current exposure	0.08%	0.29%

Values are percentages unless otherwise noted.

clinical records to confirm the diagnosis of pneumonia so potential outcome misclassification of congestive heart failure as pneumonia is still possible. Other database studies suggest that the positive predictive value of using a claims database to detect individuals with pneumonia is around 93%²⁴. Our findings are not generalizable to patients above the age of 65 who were excluded from the analysis. We were not able to evaluate dose-responsiveness of the association or the specific subtypes of pneumonia (viral or bacterial) and the subsequent outcomes from the pneumonia. Residual confounding is always possible in a database study as administrative databases are limited in their ability to identify occupational exposures and other risk-factors for pneumonia such as smoking. We did not adjust for inhaled corticosteroid use, which has been shown to increase the risk of pneumonia in patients with COPD to avoid over adjustment of proximal confounders¹³.

What is already known on this topic and what this study adds

Rosiglitazone and pioglitazone are used to lower glycated haemoglobin in patients with type 2 diabetes. Previous clinical trials and meta-analysis have raised the possibility that thiazolidinedione use may increase the risk of infections such as pneumonia. In this study of US adults with type 2 diabetes thiazolidinedione use was not associated with a statistically significant increased risk of pneumonia.

Unanswered questions and future research

Further studies with validation of pneumonia diagnosis with clinical and radiographic information are needed. Other methods, such as the use of instrumental variables, to control for confounding by indication may offer additional insight. Further studies are required to elucidate the role of PPAR agonists off-target and glucocorticoid effects in the development of serious infections such as pneumonia.

Table 3. McNemars odds ratio of hospitalization for pneumonia among pioglitazone and rosiglitazone users.

	Minimally adjusted Model 1 †	Model 2*	Model 3‡	Model 4#
No thiazolidinedione use	Referent	Referent	Referent	Referent
Thiazolidinediones				
<i>Recent exposure</i>	1.05 (0.94, 1.18)	1.14 (1.00, 1.29)	1.13 (1.00, 1.29)	
<i>Current exposure</i>	0.84 (0.54, 1.30)	0.89 (0.54, 1.45)	0.90 (0.55, 1.47)	
Pioglitazone				
<i>Recent pioglitazone</i>	1.06 (0.94, 1.20)	1.15 (1.00, 1.32)	1.15 (1.00, 1.32)	1.15 (1.00, 1.32)
<i>Current pioglitazone</i>	1.03 (0.63, 1.39)	1.02 (0.59, 1.76)	1.04 (0.60, 1.79)	1.04 (0.60, 1.79)
Rosiglitazone				
<i>Recent exposure</i>	0.99 (0.78, 1.25)	1.08 (0.82, 1.42)	1.08 (0.82, 1.42)	1.09 (0.83, 1.44)
<i>Current exposure</i>	0.28 (0.10, 0.75)	0.33 (0.11, 0.94)	0.33 (0.11, 0.94)	0.33 (0.11, 0.95)

† Adjusted for the matching design of the study [age, sex, enrollment pattern and diabetes complication severity index].

* Model 1 plus chronic obstructive pulmonary disease, tobacco use, cancer, pneumococcal and influenza vaccination and a general index of comorbidity Johns Hopkins adjusted clinical group case-mix index.

‡ Model 2 plus recent exposure and current exposure of rosiglitazone or pioglitazone.

Model 3 plus recent exposure and current exposure of both rosiglitazone and pioglitazone.

Bold signifies statistical significance.

Conclusions

Despite these limitations, our findings have implications. In this administrative database study of US adults with type 2 diabetes, we did not detect a significant increased risk of pneumonia with the thiazolidinediones. The unusually large protective effect of current exposure to rosiglitazone may reflect the healthy user effect or unmeasured confounding. Clinicians should carefully balance the benefits of thiazolidinediones on glycemic control against their known risks, after eliciting patient preferences for various outcomes in a shared decision making context.

Author contributions

Singh and Segal conceived and designed the study. Clark, Richardson and Segal acquired the data. Hsien-Yen, Singh and Richards analyzed the data and all authors interpreted the data. Singh drafted the initial manuscript and all authors critically revised the manuscript.

Competing interests

The authors have no competing interests. The dataset used in this study was created for a research project on the patterns of obesity care within selected BlueCross BlueShield health insurance plans. The original development of the dataset was funded by unrestricted research grants from Ethicon Endo-Surgery, Pfizer, and GlaxoSmithKline. Data and database development

support were provided by the BlueCross BlueShield Association (Tennessee, Hawaii, Michigan, and North Carolina), Highmark (Pennsylvania), Independence BlueCross (Pennsylvania), and Wellmark BlueCross BlueShield (Iowa and South Dakota). The BlueCross BlueShield plans were invited to review the manuscript but they did not have any direct role in the design and conduct of the study, data management or analysis, interpretation of the data, or preparation of the manuscript.

Grant information

SS was supported by the Johns Hopkins Clinical Research Scholars Program. This publication was made possible by Grant Number 1KL2RR025006-03 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCRR or NIH. Information on NCRR is available at <http://www.ncrr.nih.gov/>. Information on Re-engineering the Clinical Research Enterprise can be obtained from <http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp>.

The design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript were independent of any other sources of funding. Dr Singh had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Supplementary tables

Supplementary Table 1. Administrative codes used to identify inpatient diagnosis of pneumonia.

ICD-9	
480*	Viral pneumonia
481	Streptococcal pneumonia
482**	Other bacterial pneumonia
483*	Other specified organisms
484*	Pneumonia in infectious disease classified elsewhere
485	Bronchopneumonia
486	Pneumonia unspecified

* Denotes a digit that can be anything, even missing i.e. 482** could be 482 or 482.2 or 482.49.

ICD-9 = International Classification of Disease=9th revision.

Supplementary Table 2. Administrative and procedural codes used to identify confounders.

ICD-9	
428**	Congestive heart failure
	COPD
491**	Chronic bronchitis
492*	Emphysema
496	Chronic airway obstruction
	Tobacco
305.1	Tobacco use disorder
649*	Tobacco abuse during pregnancy
989.84	Toxic effect of tobacco
140. XX to 239.XX	Neoplasm
CPT Codes	Pneumococcal vaccination
4040F	
90669	
90670	
90732	
G0009	
G8115	
	Influenza vaccination
90668	
90667	
90666	
G0008	
4037F	
4274F	

* Denotes a digit that can be anything, even missing.

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Open Peer Review

Current Peer Review Status: ? ?

Version 1

Reviewer Report 09 May 2014

<https://doi.org/10.5256/f1000research.1534.r4687>

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The manuscript addresses the question whether PPAR- γ agonists can induce pneumonia as indicated by prior RCTs. The authors used administrative data sets and a new user design recruiting more than one million patients. Of these patients, a subgroup of > 6000 “cases” (i.e. age between 18 and 64, diabetes prior to pneumonia, one episode of pneumonia, no CHF) was matched with an identical number of diabetic patients without pneumonia “controls”.

Statistical analysis revealed a higher number of COPD patients in the pneumonia group (which is expected). After adjusting for important confounders of pneumonia (such as COPD, cancer, tobacco use and vaccination) the use of PPAR- γ agonists was not associated with higher incidence of pneumonia. In fact, a decreased odds ratio was found when current exposure of rosiglitazone was plotted against pneumonia. Overall, the authors conclude that there is no increased risk of pneumonia, when using PPAR- γ agonists.

In general, the paper is of high clinical relevance, only presently limited by the fact the TZDs are almost off market because the spectrum of side effects. There are a few points of possible amendments:

1. Introduction: the difference between the two TZDs is likely not relevant with regard to pneumonia development. This should be mentioned.
2. Introduction: reference 19 involves Type 1 diabetic patients – the pathogenesis of increased susceptibility is different, therefore a ref. restricted to type 2 diabetes is preferable.
3. M&M and result section: one of the most important determinants of infections in diabetic patients is metabolic control. Are there data on blood glucose, or HbA1c of the two groups to identify a possible additional confounder? Moreover, data on the current use of steroids would be helpful as the proportion of COPD is different between the two groups.
4. M&M and result section: important anthropometric data from both patient groups are lacking, such as age, known diabetes duration, and comorbidities. Are there any available data that could be incorporated?

5. Discussion section: specify the confounders that were explicitly addressed.
6. Future research: the current status of TZD approval with the FDA and EMA should be incorporated here.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 09 August 2013

<https://doi.org/10.5256/f1000research.1534.r1375>

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Thiazolidinedione use and risk of hospitalization for pneumonia in type 2 diabetes: population based matched case-control study. Review

Background

Results from a recent meta-analysis of randomized controlled trials suggest both drugs increase the risk of pneumonia ([Thorax 2011; 66:383-8](#)): Pioglitazone: RR=1.63; 95% CI 1.09, 2.46. Rosiglitazone: RR=1.26; 95% CI 0.90 1.76. An undue emphasis on statistical significance leads the authors to suggest these results are inconsistent, but both results show a large overlap in the confidence intervals in a range indicating an increased risk that is perhaps greater for pioglitazone than rosiglitazone. Package inserts on both pioglitazone and rosiglitazone carry warnings for heart failure and edema, along with increased risk of upper respiratory tract infection. Further, heart failure increases the risk of hospitalization for pneumonia ([Eur J Intern Med 2013 Jun; 24 \(4\): 349-53](#)) as does diabetes, especially with poor glycemic control ([Diabetes Care 2008 August; 31 \(8\): 1541-1545](#)).

Results

This study reports small increases in risk of hospitalization for pneumonia with recent exposure to pioglitazone (OR=1.15; 95% CI 1.00, 1.32) and pioglitazone (OR=1.09; 95% CI 0.83, 1.44), but not for current exposure to pioglitazone (OR=1.04; 95% CI 0.60, 1.79). Current exposure to rosiglitazone was associated with a reduced risk of pneumonia (OR=0.33; 95% CI 0.11, 0.95). The relatively higher rate of pneumonia with pioglitazone compared with rosiglitazone is consistent with the results from clinical trials, but the magnitudes of the effect estimates reported here are markedly

reduced, and recent exposure is associated with greater risk than current exposure. This pattern of results is puzzling and the authors offer no compelling explanation.

Methodology

The study description raises no obvious bias to account for a systematic reduction in risk estimates nor the greater risk with recent versus current exposure. There are, however, several uncertainties in the study methods that may have a bearing on validity:

1. The study is described as a new user design. The new user design was described by Ray ([Am J Epidemiol 2003; 158: 915–920](#)): *'A new-user design begins by identifying all of the patients in a defined population (both in terms of people and time) who start a course of treatment with the study medication. Study follow-up for endpoints begins at precisely the same time as initiation of therapy, or t0. The study is further restricted to patients with a minimum period of nonuse (washout) prior to t0. The study should include all patients in the study population meeting these criteria. Data for all patient characteristics are obtained at a time just before t0'*. The new user design is described for cohort studies, but can be adapted easily to a case-control study nested within a cohort of new users. Nevertheless, it is not clear that the current study follows the new user design described above by Ray. First, key to a new user design is that “new use” is defined by a drug dispensing following a period of minimum duration (e.g., 6 months or 1 year) with no dispensing of the drug. In the current study, the inclusion criteria as described do not include any minimal drug-free period. This raises a question of whether the study population truly comprises new users.
2. The current study indicates that the start of follow-up or index date corresponds to a diagnosis of type 2 diabetes (Table 1). This is also consistent with Figure 1, in which the cohort is defined by a diagnosis and without regard to therapy. However, the study methods indicate that therapy was required: “We assembled an incipient cohort of all patients with type 2 diabetes who filled at least one prescription for *any hypoglycemic agent* between 2002 and 2008” (emphasis added). The methods go on to list as an inclusion criterion that individuals had to “contribute at least 6 months of medical or pharmacy coverage in the calendar year of diabetes diagnosis.” This strategy is problematic in several respects.

First, the required therapy for cohort entry is any hypoglycemic agent and does not specify those medications which may be suitable therapeutic alternatives to glitazones. According to the new user design, the index date should be the first prescription of one of the glitazones or a therapeutic alternative (with analyses conditional on use of other medications).

Secondly, the six months of required observation time is not specified as occurring before the start of therapy or being drug-free. Instead, the required period is defined without regard to the date of initiation of therapy and only as occurring during the same calendar year as a diagnosis of type 2 diabetes (the apparent index date). This means that the six months of observation could occur before, after, or spanning the diagnosis date and putative start of follow-up. To the extent that the required observation time before the diagnosis was less than six months, even if it was a diagnosis-free and drug-free period, the probability is diminished that the patient was free of the diagnosis prior to inclusion and, therefore, that this is not a cohort of newly diagnosed patients. Further, to the extent that

the inclusion criteria require observation time after a diagnosis and start of follow-up, the corresponding follow-up time is “immortal” and represents a source of bias ([J Clin Oncol 2009; 27: e55-6](#)).

Finally, to detect diagnoses, patients would have to have medical coverage, and to detect prior therapy, patients would have to have pharmacy coverage. But the requirement of medical or pharmacy coverage does not ensure that either diagnosis or therapy would be detectable. If the patients had only medical coverage during this period, for instance, prescriptions of antidiabetic therapy would not be reimbursable and would not appear on the claims database. For this reason, claims database studies such as this one are typically restricted to patients having both medical and pharmacy benefits.

To summarize, the inclusion criteria do not define a cohort that is either newly diagnosed or newly treated. There are at least two potential concerns with the study as described. First, if it is not a new user design, then the cohort would include prevalent users of glitazone therapy. Prevalent users represent a “survivor” cohort of patients who have a good experience with therapy, by obtaining effectiveness and also by tolerating the therapy well; patients who did not do well are more likely to discontinue therapy. The inclusion criteria provide no assurance that the study cohort failed to exclude prevalent users. The new user design was developed in part to eliminate the “healthy user” effect, but this type of selection remains a concern with inclusion criteria described for this study. Another important feature of the new user design is that of defining a minimum drug-free period before the start of therapy (which should correspond to the start of follow-up), also defines the minimal baseline period during which risk factors (i.e., covariates) are identified as potential confounding variables. The current study does not describe the time period during which risk factors are identified. If the authors defined risk factors as occurring before the outcome (i.e., pneumonia) instead of before the start of glitazone therapy, then covariates such as the “Diabetes Complication Severity Index” and “enrolment pattern” occurred (at least in part) after initiation of glitazone therapy. It is not advisable to control for factors that occur after the study exposure because they could be a result of exposure and, therefore, in the causal pathway between exposure and outcome. Analytic control of such factors would inappropriately attenuate the true relation between the exposure and the endpoint.

3. The authors included patients “without any claim for congestive heart failure,” noting that heart failure shares similar clinical and radiographic findings as pneumonia. Their goal was to reduce outcome misclassification, presumably concerned that cases of heart failure could be confused with cases of pneumonia (and vice versa). I have two comments on this strategy. First, if the authors are concerned that claims data cannot accurately distinguish heart failure from pneumonia, then how did they exclude patients with heart failure? How do they know that patients with heart failure who were excluded did not have pneumonia? Secondly, including patients “without any claims for congestive heart failure” would exclude all patients with a claim of heart failure without regard to timing of the heart failure diagnosis. Specifically, cases of heart failure that occurred after initiation of glitazone therapy could be the result of glitazone therapy. Moreover, even if there was no misclassification, because heart failure increases the risk of hospitalization due to pneumonia ([Eur J Intern Med 2013 Jun; 24 \(4\): 349-53](#)), excluding cases of heart failure that occurred after the start of therapy would also exclude cases of pneumonia etiologically

related to glitazone therapy (because heart failure lies in a causal pathway). The impact would be to attenuate the relation between glitazone therapy and pneumonia.

4. The authors state that they matched controls to cases on duration of follow-up, according to the method of incidence density sampling. Actually, incidence density sampling stipulates that controls be in the cohort (and contributing person-time to the denominator of a theoretical incidence rate) at the time a case occurred, but does not require the control have the same duration of follow-up as the case (Am J Epidemiol 1982; 116; 547-53). Controls should be sampled to represent the exposure frequency in the entirety of person-time at risk, which includes people with any duration of follow-up (both longer than and shorter than the case's duration of follow-up). To the extent that glitazone therapy may be related to duration of follow-up, matching by duration of follow-up would have provided an exposure distribution that was not representative of the base population, creating a control selection bias.
5. A causal effect of an exposure is always measured relative to some alternative. A drug may cause an effect ($RR > 1$) compared with one drug, and prevent the same effect ($RR < 1$) when compared with another drug (that has an even stronger causal effect). These findings, especially that of a reduced risk for rosiglitazone, should be understood in terms of the reference category. The current study measures current and recent use of each glitazone relative to non-use of glitazones within two years. Non-use of glitazones is consistent with the absence of therapy, as well as many possible combinations of concomitant antidiabetic and other medications (some of which may be related to risk of pneumonia). It might be preferable to specify the comparator as a therapeutic alternative(s) to the glitazones. A related issue is that effects of other medications evidently were not controlled. Glycemic control has been related to risk of pneumonia. Although no direct measure of glycemic control is likely available in the claims database, data on the dispensing of and adherence to antidiabetic agents is available. The authors call for additional studies using other methods to better control for confounding, but it appears that better control of confounding is possible with the data used in this study.
6. The higher risk for recent exposure than current exposure is peculiar and seems to indicate an increased risk of recent discontinuation. Several explanations are possible, including an increased risk due to loss of glycemic control after discontinuation, or discontinuation due to early prodromal symptoms of adverse events that were diagnosed after discontinuation. If drug exposure caused the outcome, one would expect higher risks during exposure than after exposure. Further analyses aimed at identifying reasons for discontinuation would be of interest. In addition, duration of therapy might be important, and analyses of risk by duration of therapy might be illuminating.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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