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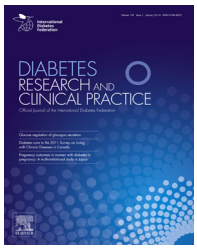

Comparative risk of severe hypoglycemia among concomitant users of thiazolidinedione antidiabetic agents and antihyperlipidemics

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ABSTRACT

We conducted high-dimensional propensity score-adjusted cohort studies to examine whether thiazolidinedione use with a statin or fibrate was associated with an increased risk of severe hypoglycemia. We found that concomitant therapy with a thiazolidinedione + fibrate was associated with a generally delayed increased risk of severe hypoglycemia.

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1. Introduction

Dyslipidemia is a major, yet modifiable, risk factor for cardiovascular disease. While glycemic control improves the lipid profile of persons with diabetes, treatment with antihyperlipidemics is often indicated. Co-prescribing of antidiabetic and antihyperlipidemic agents, though, may not be without risks. In particular, thiazolidinediones (TZDs)—peroxisome proliferator-activated receptor (PPAR) γ agonists which increase insulin sensitivity—are metabolized primarily by hepatic cytochrome P450 (CYP) 2C8 [1]. This isozyme can be inhibited by some antihyperlipidemics, most notably fibrates [2], leading to higher concentrations of TZDs. In addition, the PPAR α activity of fibrates may itself have effects on glucose homeostasis [3]. Some statins may also affect glucose metabolism [4]. These mechanisms might result in enhanced glucose lowering effects in concomitant users of TZDs and certain antihyperlipidemics. While these effects may be desirable for some patients, drug interactions might also increase the risk of severe hypoglycemia—a major clinical and public health problem. We therefore examined severe hypoglycemia risk among concomitant users of TZDs and antihyperlipidemics.

2. Methods

We conducted two high-dimensional propensity score-adjusted cohort studies of adult users of pioglitazone and rosiglitazone, respectively, using Medicaid data from five large states. Each cohort consisted exclusively of person-time concomitantly-exposed to the TZD plus one of eight antihyperlipidemics: atorvastatin; fenofibrate; fluvastatin; gemfibrozil; lovastatin; pravastatin; rosuvastatin; or simvastatin. The day on which the subject was first co-exposed served as the cohort entry date. Exposure was defined by the antihyperlipidemic active upon cohort entry. The primary outcome was a validated diagnosis-based algorithm for severe hypoglycemia within 30 days of cohort entry. Please see *Supplemental Materials* for details on: the data source; defining the study cohorts; exposure, covariate, and outcome ascertainment; and statistical analyses.

3. Results

3.1. Pioglitazone

Characteristics of pioglitazone users are presented in Table 1. Unadjusted and adjusted hazard ratios (HRs) for severe hypoglycemia within 30 days are presented in Table 2 and Fig. 1, respectively. Unadjusted and adjusted HRs for severe hypoglycemia within 180 days are presented in Table 2. Time-specific association measures for concomitant use of pioglitazone and fibrates are presented in Fig. 2. No time-course effects were evident for concomitant use with statins. See *Supplemental Materials* for results from sensitivity analyses.

3.2. Rosiglitazone

See *Supplemental Materials*.

4. Discussion

We examined potential drug–drug interactions between TZDs and antihyperlipidemics. While we found no increased risk of severe hypoglycemia during the first month of concomitant pioglitazone and antihyperlipidemic therapy, the risk was elevated and increased monotonically with time during later months of concomitant therapy with a fibrate. Pioglitazone + -fenofibrate was associated with an increased risk of severe hypoglycemia as much as 2.3-fold during 60–180d post-initiation of concomitant therapy, and pioglitazone + gemfibrozil as much as 2.6-fold during 30–180d. For rosiglitazone, we found no increased risk of severe hypoglycemia during the first 30d of concomitant use with a statin, but use of rosiglitazone + gemfibrozil was associated with a 1.6-fold increased risk. Subsequently, the risk of severe hypoglycemia peaked during 30–59d—1.8-fold for rosiglitazone + fenofibrate and 2.5-fold for rosiglitazone + gemfibrozil—and returned to the null by 180d.

This is first pharmacoepidemiologic investigation of these potential drug interactions. The presumptive mechanism underlying prior pharmacokinetic- and laboratory science-based work was that fibrates inhibited CYP2C8, the major metabolic pathway for TZDs. Yet, even if inhibition by fibrates significantly raises serum concentrations of TZDs, it is not generally thought that TZDs cause severe hypoglycemia [5]. However, we found that severe hypoglycemia occurs at a rate of ~2.5 per 100 p-y among TZD users even in the absence of concomitant insulin or sulfonylureas. Further, Bron et al. reported that TZDs are associated with a small but significant increased risk of moderate or severe hypoglycemia, especially within the first year of therapy [6]. This raises the possibility that TZDs, while clearly less associated with hypoglycemia than insulin or sulfonylureas, may cause severe hypoglycemia in certain circumstances. That being said, the mechanism seems more complex than elevated TZD serum concentrations caused by CYP2C8 inhibition. Arguments against a lone, major role for CYP2C8 inhibition include: some statins also inhibit CYP2C8 [7], yet we did not find elevated HRs for statins; and the inhibition and inactivation of CYP enzymes occurs rapidly [8], yet we generally found delayed rather than rapid-onset increases in the risk of severe hypoglycemia. This latter point could also be explained by the delayed onset of action of TZDs, whose effects may peak at one month [9,10].

A more plausible explanation for our findings may be driven by expected actions of fibrates. The PPAR α agonist effects of fibrates beneficially impact lipid and lipoprotein metabolism. Lipid and glucose homeostasis is interrelated [11] and lowering free fatty acids ameliorates insulin resistance [12,13] via protection of pancreatic islets [14]. Alternatively, or in addition, fibrates may induce fatty acid-binding protein and stimulate β-oxidation in skeletal muscles [15]. Regardless of potential mechanism, improvements in insulin resistance and glycemic control have been reported in users of gemfibrozil [16] and fenofibrate [13,17]. Further, some fibrates also act at PPAR γ [18], the site of action of TZDs. Of further interest are

Table 1 – Characteristics of pioglitazone users, by antihyperlipidemic exposure group.

Analyses examining 30-day time period post-cohort entry		Statins						Fibrates	
		Pravastatin	Atorvastatin	Fluvastatin	Lovastatin	Rosuvastatin	Simvastatin	Fenofibrate	Gemfibrozil
		% (Unless otherwise noted)							
Users, concomitant with pioglitazone		21,066	109,371	4,757	15,818	13,014	69,847	10,969	11,531
Person-years of follow-up		1709	8909	385	1282	1048	5662	829	891
Severe hypoglycemia events within 30 days of cohort entry		124	595	20	68	43	408	53	65
Cumulative incidence of severe hypoglycemia within 30 days of cohort entry (95% CI)		0.59% (0.49–0.70)	0.54% (0.50–0.59)	0.42% (0.26–0.65)	0.43% (0.33–0.54)	0.33% (0.24–0.44)	0.58% (0.53–0.64)	0.48% (0.36–0.63)	0.56% (0.44–0.72)
Demographics	Group	% (Unless otherwise noted)							
Age in years at cohort entry (continuous)	Median (Q1–Q3)	66.4 (56.0–74.1)	64.7 (54.3–73.0)	63.1 (52.4–72.5)	63.3 (51.0–72.8)	65.3 (54.5–73.1)	65.5 (55.1–73.6)	59.8 (48.5–70.4)	57.8 (47.7–68.9)
Sex	Female	66.5	65.0	68.4	64.2	64.4	64.8	56.8	53.7
Race	White	35.1	37.1	35.1	28.9	32.8	36.2	49.8	40.0
	Black	13.6	13.9	14.0	12.1	11.6	15.0	6.5	7.0
	Other/unknown	51.3	49.0	51.0	59.0	55.5	48.8	43.7	52.9
State of residence	CA	58.3	52.0	59.7	69.6	40.4	41.2	41.6	61.5
	FL	8.4	5.9	10.0	8.0	19.4	11.1	12.5	8.2
	NY	21.8	27.8	16.4	12.2	33.3	32.8	26.5	18.9
	OH	5.6	9.1	6.3	4.5	4.0	8.5	12.4	6.9
	PA	5.9	5.3	7.7	5.8	2.8	6.4	7.0	4.5
Calendar year of cohort entry	2000–2003	54.7	36.5	52.5	10.7	1.4	22.3	28.0	39.8
	2004	10.3	11.0	13.2	9.0	9.9	6.3	9.1	10.3
	2005	10.1	13.8	13.5	13.3	16.5	11.0	14.3	12.3
	2006	8.8	13.8	11.0	25.3	23.3	14.9	16.0	11.7
	2007	9.0	16.4	7.3	26.6	30.6	26.1	19.1	15.0
	2008	7.0	8.5	2.5	15.1	18.4	19.3	13.5	11.0
Medicare enrolled	Yes	66.2	62.2	58.5	60.5	61.5	64.5	59.6	52.8
Nursing home residence, ever during baseline	Yes	4.7	6.6	4.0	5.5	2.8	6.8	5.1	5.6
Healthcare utilization covariates, in baseline period*	Group	Measures of central tendency							
# prescriptions dispensed	Median (Q1–Q3)	57.0 (33.0–90.0)	58.0 (33.0–93.0)	52.0 (28.0–83.0)	44.0 (22.0–76.0)	58.0 (32.0–93.0)	58.0 (31.0–94.0)	65.0 (36.0–106)	57.0 (31.0–92.0)
# unique drugs dispensed	Median (Q1–Q3)	15.0 (10.0–22.0)	15.0 (9.0–21.0)	13.0 (8.0–20.0)	12.0 (7.0–18.0)	15.0 (9.0–22.0)	14.0 (9.0–21.0)	16.0 (10.0–23.0)	14.0 (9.0–21.0)
# outpatient diagnosis codes	Median (Q1–Q3)	47.0 (23.0–90.0)	47.0 (23.0–95.0)	36.0 (16.0–71.0)	27.0 (10.0–61.0)	43.0 (20.0–89.0)	44.0 (19.0–95.0)	50.0 (24.0–98.0)	40.0 (18.0–82.0)
# unique outpatient diagnosis codes	Median (Q1–Q3)	17.0 (10.0–26.0)	16.0 (9.0–26.0)	13.0 (7.0–23.0)	11.0 (5.0–20.0)	15.0 (9.0–25.0)	15.0 (8.0–26.0)	17.0 (10.0–27.0)	14.0 (8.0–23.0)

# outpatient CPT-4/HCPCS procedure codes	Median (Q1–Q3)	55.0 (28.0–103)	55.0 (27.0–104)	45.0 (22.0–85.0)	38.0 (16.0–75.0)	53.0 (26.0–102)	51.0 (22.0–103)	58.0 (30.0–107)	48.0 (24.0–93.0)
# unique outpatient CPT-4/HCPCS procedure codes	Median (Q1–Q3)	30.0 (17.0–48.0)	29.0 (16.0–49.0)	26.0 (14.0–41.0)	22.0 (10.0–39.0)	29.0 (16.0–48.0)	28.0 (14.0–48.0)	31.0 (18.0–49.0)	27.0 (15.0–45.0)
Other investigator pre-defined covariates, in baseline period	Group	%							
Prior severe hypoglycemia	Yes	3.4	3.4	2.7	2.4	2.0	3.5	2.7	3.4
Alpha-glucosidase inhibitor exposure	Yes	2.5	2.2	2.5	1.7	1.6	1.9	1.9	2.1
DPP-4 inhibitor exposure	Yes	0.7	1.1	0.4	1.1	3.2	2.1	1.9	0.7
GLP-1 inhibitor exposure	Yes	0.3	0.5	**	0.7	1.5	0.9	1.1	0.4
Insulin exposure	Yes	25.4	26.1	23.1	20.4	19.1	24.7	23.5	25.3
Meglitinide exposure	Yes	6.7	5.3	5.0	3.0	5.4	4.7	6.6	4.5
Metformin exposure	Yes	59.4	60.9	58.8	65.8	60.7	61.1	59.6	65.6
Sulfonylurea exposure: glipizide	Yes	22.7	23.9	25.5	26.6	18.9	22.8	19.3	26.0
Sulfonylurea exposure: glyburide	Yes	29.4	27.0	29.2	28.0	22.8	27.0	23.5	30.2
Sulfonylurea exposure: other agent	Yes	11.4	11.4	9.5	10.8	12.7	10.8	13.5	10.1

CI, confidence interval; CPT-4, Current Procedural Terminology-4; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HCPCS, Healthcare Common Procedure Coding System; Q, quartile.

* The following healthcare utilization covariates were excluded from the table, as the median values were zero: # inpatient International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes; # unique inpatient ICD-9 diagnosis codes; # inpatient ICD-9 procedure codes; # unique inpatient ICD-9 procedure codes; # inpatient CPT-4/HCPCS procedure codes; # unique inpatient CPT-4/HCPCS procedure codes; # outpatient ICD-9 procedure codes; # unique outpatient ICD-9 procedure codes; # other setting diagnosis codes; # unique other setting diagnosis codes; # other setting ICD-9 procedure codes; # unique other setting ICD-9 procedure codes.

** Omitted in compliance with Centers for Medicare & Medicaid Services privacy policy (i.e., underlying cell count <11 persons).

Table 2 – Summary of findings: pioglitazone + antihyperlipidemic and the risk of severe hypoglycemia.

Analyses examining 30-day time period post-cohort entry	Statins						Fibrates	
	Pravastatin	Atorvastatin	Fluvastatin	Lovastatin	Rosuvastatin	Simvastatin	Fenofibrate	Gemfibrozil
	Point estimates (95% CI) from primary analyses							
Unadjusted HR	Reference	0.92 (0.76–1.12)	0.72 (0.45–1.15)	**0.73 (0.54–0.98)**	**0.57 (0.40–0.80)**	0.99 (0.81–1.21)	0.88 (0.64–1.21)	1.00 (0.74–1.35)
Adjusted HR [see Fig. 1]		0.94 (0.77–1.14)	0.85 (0.53–1.37)	0.99 (0.73–1.35)	0.91 (0.63–1.30)	1.07 (0.87–1.32)	1.08 (0.78–1.49)	1.15 (0.85–1.56)
	Point estimates (95% CI) from sensitivity analyses							
Adjusted HR, excluding SU users*	Reference	1.17 (0.87–1.58)	1.20 (0.62–2.31)	1.15 (0.71–1.84)	1.05 (0.61–1.78)	1.23 (0.90–1.69)	0.91 (0.53–1.55)	1.23 (0.77–1.96)
Adjusted HR, excluding SU or insulin users**		1.62 (0.83–3.15)	2.09 (0.65–6.73)	2.05 (0.84–5.03)	1.91 (0.73–5.01)	1.64 (0.81–3.31)	1.32 (0.47–3.68)	1.62 (0.63–4.18)
Adjusted HR, excluding covariates from the PS strongly related to exposure but not outcome		0.94 (0.77–1.14)	0.84 (0.52–1.35)	1.00 (0.74–1.37)	0.92 (0.64–1.31)	1.07 (0.87–1.32)	1.07 (0.77–1.49)	1.14 (0.84–1.55)
Adjusted HR, excluding managed care enrollees		0.97 (0.77–1.22)	1.03 (0.60–1.75)	1.25 (0.84–1.87)	0.86 (0.56–1.31)	1.12 (0.89–1.43)	1.08 (0.74–1.58)	1.26 (0.89–1.79)
Analyses examining 180-day time period post-cohort entry	Point estimates (95% CI) from primary analyses							
Unadjusted HR	Reference	1.00 (0.88–1.13)	0.88 (0.67–1.17)	**0.74 (0.61–0.89)**	**0.62 (0.49–0.77)**	1.01 (0.89–1.16)	1.05 (0.86–1.29)	**1.34 (1.11–1.62)**
Adjusted HR		1.02 (0.90–1.15)	1.03 (0.78–1.37)	1.02 (0.83–1.25)	1.02 (0.81–1.28)	1.11 (0.97–1.27)	**1.33 (1.08–1.63)**	**1.60 (1.32–1.93)**
	Point estimates (95% CI) from sensitivity analyses							
Adjusted HR, excluding SU users*	Reference	1.10 (0.91–1.34)	1.20 (0.78–1.84)	0.98 (0.71–1.36)	1.14 (0.80–1.62)	1.13 (0.92–1.39)	1.05 (0.75–1.47)	**1.39 (1.03–1.88)**
Adjusted HR, excluding SU or insulin users**		1.20 (0.77–1.86)	**2.25 (1.07–4.76)**	1.12 (0.57–2.20)	1.30 (0.64–2.61)	1.19 (0.74–1.90)	0.96 (0.45–2.04)	1.52 (0.80–2.90)
Adjusted HR, excluding covariates from the PS strongly related to exposure but not outcome		1.02 (0.90–1.16)	1.03 (0.77–1.36)	1.02 (0.83–1.24)	1.01 (0.81–1.27)	1.11 (0.97–1.27)	**1.31 (1.07–1.61)**	**1.59 (1.31–1.92)**
Adjusted HR, excluding managed care enrollees		1.07 (0.92–1.24)	1.11 (0.80–1.55)	1.09 (0.83–1.43)	1.04 (0.80–1.36)	1.15 (0.99–1.34)	**1.36 (1.07–1.72)**	**1.57 (1.25–1.96)**

CI, confidence interval; HR, hazard ratio; PS, propensity score; SU, sulfonylurea.
Bolded values met the traditional threshold for statistical significance.
* If co-exposed within 60 days prior to cohort entry and censoring follow-up time if subsequently exposed to a SU.
** If co-exposed within 60 days prior to cohort entry and censoring follow-up time if subsequently exposed to a SU or insulin.

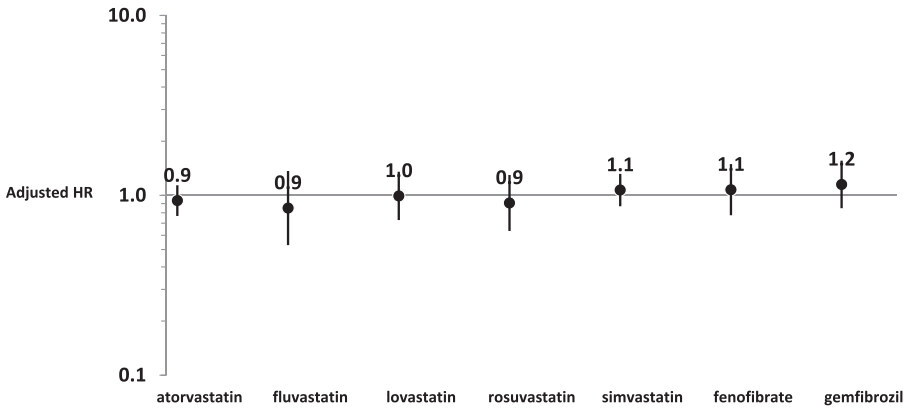

Fig. 1 – Adjusted hazard ratios (HRs) for the rate of severe hypoglycemia within 30 days of cohort entry among pioglitazone users, by antihyperlipidemic of interest (vs. pravastatin).

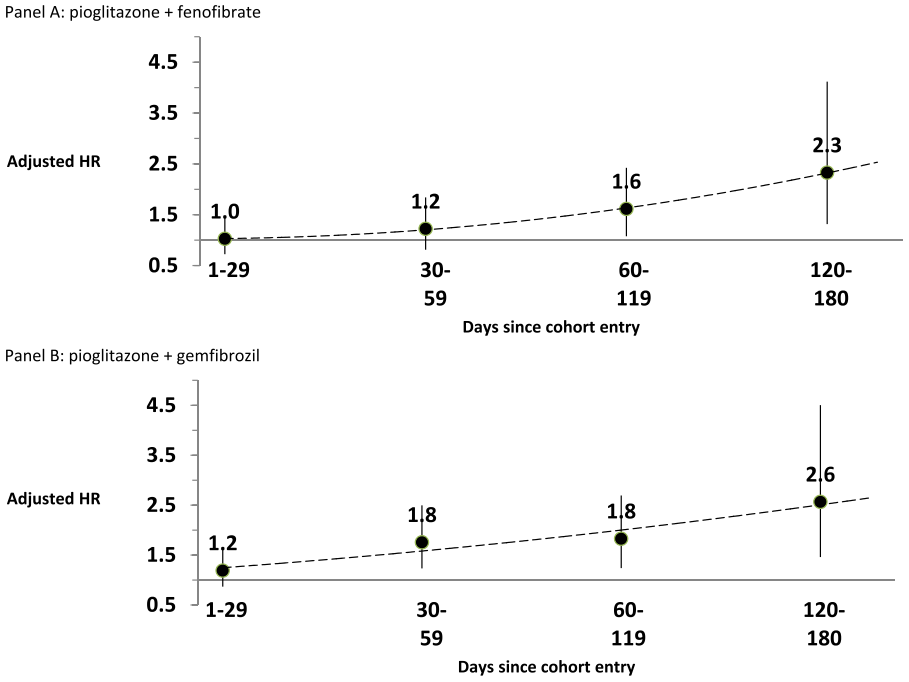

Fig. 2 – Adjusted hazard ratios (HRs) for the rate of severe hypoglycemia within 180 days of cohort entry among pioglitazone users, by fibrate of interest (vs. pravastatin), by time window.

differences between pioglitazone and rosiglitazone in the time-course of their interaction with fibrates—the former increasing monotonically with time (Fig. 2) and the latter having an inverted U-shape (Supplementary Figure 2). The sustained risk of severe hypoglycemia observed with pioglitazone + gemfibrozil or fenofibrate may be mediated by pioglitazone's more favorable effect on lipids compared to rosiglitazone [19]; pioglitazone significantly reduces fatty acids and triglycerides [20]. As discussed above, this may lead to less insulin resistance. The lack of a sustained risk with rosiglitazone + fibrate may be due to a sufficiently weaker interaction to which patients can develop compensatory behaviors or endocrine adaptations over time. Future studies should investigate the relative contributions of these and other potential mechanisms.

See *Supplemental Materials* for a discussion of this work's strengths and limitations.

5. Conclusion

We found that concomitant therapy with a TZD and fibrate is associated with an increased risk of severe hypoglycemia. The mechanism underlying this apparent drug-drug interaction needs further elucidation, but may involve fibrates' impact on glucose (i.e., a pharmacodynamic interaction mediated by PPAR $\alpha \pm \gamma$ effects). Clinicians should be attuned to both immediate- and delayed-onset hypoglycemia in their patients on this drug combination.

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Conflicts of interest

Charles Leonard:	None
Xu Han:	None
Warren Bilker:	None
James Flory:	None
Colleen Brensinger:	None
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Appendix A. Supplemental materials

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.diabres.2016.03.006.

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