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SEVERE HYPOGLYCEMIA IN USERS OF SULFONYLUREA ANTIDIABETIC AGENTS AND ANTIHYPERLIPIDEMICS

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Abstract

Background—Drug-drug interactions causing severe hypoglycemia due to antidiabetic drugs is a major clinical and public health problem. We assessed whether sulfonylurea use with a statin or fibrate was associated with severe hypoglycemia.

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CONFLICT OF INTEREST DISCLOSURE

The following authors have no conflicts to declare: Dr. Leonard; Dr. Bilker; Ms. Brensinger; Dr. Han; Dr. Flory; and Dr. Flockhart.

AUTHOR CONTRIBUTIONS

C.E.L., W.B.B., C.M.B., X.H., J.H.F., D.F., J.J.G., S.C., and S.H. wrote the manuscript; C.E.L., W.B.B., J.H.F., D.F., J.J.G., S.C., and S.H. designed the research; C.E.L., W.B.B., C.M.B., X.H., J.H.F., and S.H. performed the research; W.B.B. and C.M.B. analyzed the data; W.B.B., C.M.B., and J.J.G. contributed new reagents/Analytical Tools.

Methods—We conducted cohort studies of users of glyburide, glipizide, and glimepiride plus a statin or fibrate within a Medicaid population. The outcome was a validated, diagnosis-based algorithm for severe hypoglycemia.

Results—Among 592,872 persons newly-exposed to a sulfonylurea+antihyperlipidemic, the incidence of severe hypoglycemia was 5.8/100 person-years. Adjusted hazard ratios (HRs) for sulfonylurea+statins were consistent with no association. Most overall HRs for sulfonylurea +fibrate were elevated, with sulfonylurea-specific adjusted HRs as large as 1.50 (95% confidence interval (CI): 1.24–1.81) for glyburide+gemfibrozil, 1.37 (95% CI: 1.11–1.69) for glipizide +gemfibrozil, and 1.63 (95% CI: 1.29–2.06) for glimepiride+fenofibrate.

Conclusions—Concomitant therapy with a sulfonylurea and fibrate is associated with an often delayed increased rate of severe hypoglycemia.

Keywords

cohort studies; drug interactions; fibric acids; hydroxymethylglutaryl-CoA reductase inhibitors; hypoglycemia; Medicaid; pharmacoepidemiology; propensity score; sulfonylurea compounds

INTRODUCTION

By the year 2050, approximately one-third of the United States (US) population is predicted to have diabetes mellitus.(1) While pharmacologic approaches to normalize blood glucose can delay diabetes onset and minimize micro- and macrovascular complications, hypoglycemia from antidiabetic drug regimens is a major barrier to glycemic control.(2) Severe hypoglycemia can result in dementia, seizures, coma, major adverse cardiovascular events and death,(3–5) and is feared by persons with diabetes and their relatives.(6) Therefore, it is not surprising that the US Department of Health & Human Services named antidiabetic drug-induced hypoglycemia as one of three high-priority targets in reducing adverse drug events, and called for research to close knowledge gaps to facilitate its prevention.(7)

The American Diabetes Association currently recommends a sulfonylurea (SU) as one of three classes of highly efficacious add-on treatments to metformin in persons with type 2 diabetes, if metformin monotherapy fails to achieve the glycosylated hemoglobin target by three months.(8) In persons intolerant or with a contraindication to metformin, SUs may be used as monotherapy. Given these guidelines and the drug class' historic use as a first-line agent, SU use remains very common.(9) Hypoglycemia is an expected, dose-related adverse effect of SU therapy, occurring in up to 20% of users over six months of treatment.(10) While severe hypoglycemia accounts for a small proportion of these events, it can result in death in up to 7.5% who experience it.(11) For those surviving, hospitalization tends to be prolonged.(12)

Drug interactions with SUs may potentiate hypoglycemia risk via inhibition of hepatic cytochrome P450 (CYP) enzymes responsible for their metabolism. In particular, antihyperlipidemic drugs—frequently co-prescribed with antidiabetic agents—may inhibit CYP3A and CYP2C9, both of which are responsible for the inactivation of glyburide(13) and the latter of which for glipizide(14) and glimepiride(15). Further, antihyperlipidemic

fibrates and statins themselves may affect glucose homeostasis.(16,17) Such mechanisms might result in enhanced glucose lowering effects in concomitant users of SUs and certain antihyperlipidemics. While these effects may be desirable for some patients, such effects might also increase the risk of severe hypoglycemia.

We therefore quantified the rates of severe hypoglycemia among concomitant users of SUs and individual antihyperlipidemics.

RESULTS

Cohort characteristics and outcome frequency

We identified 224,821, 239,151 and 128,900 concomitant users of antihyperlipidemics with glyburide, glipizide and glimepiride, respectively. Characteristics of glyburide users, stratified by antihyperlipidemic exposure are presented in Table 1. Users of glipizide (Appendix Table 1) and glimepiride (Appendix Table 2) had characteristics similar to glyburide users. Users of antihyperlipidemics with glyburide, glipizide and glimepiride contributed 52,180, 57,013 and 30,824 person-years (p-y) of concomitant exposure, during which we identified 3,201, 2,898 and 1,953 severe hypoglycemia events (unadjusted incidence rates = 6.1 [95% confidence interval (CI): 5.9–6.4], 5.1 [4.9–5.3] and 6.3 [6.1–6.6] per 100 p-y). In subcohorts of persons treated with a SU as antidiabetic monotherapy, the unadjusted rates of severe hypoglycemia were 5.7 (5.3–6.1), 3.7 (3.4–4.0) and 5.4 (4.8–5.9) per 100 p-y, respectively. By comparison, the unadjusted rate in users of metformin as antidiabetic monotherapy was 0.8 (0.7–0.9) per 100 p-y.

Measures of association: primary and secondary analyses

The high-dimensional propensity score (hdPS) algorithm identified 614, 586 and 632 covariates for inclusion in the multinomial propensity score (PS) models for glyburide, glipizide and glimepiride, respectively (Appendix Table 3). Among these, 23, 13 and 42 variables occurred very infrequently ($N < 10$ for ≥ 1 of the antihyperlipidemic exposure groups) and were excluded to avoid model instability. Therefore, the multinomial PS models included 591, 573 and 590 empirically-identified covariates, respectively; each model also included as many as 35 predefined covariates (Appendix Table 4). Crude hazard ratios (HRs) are presented in Appendix Figure 1; PS-adjusted HRs are presented in Figure 1. Time-specific association measures for concomitant use of each SU are presented for fenofibrate in Figure 2 and for gemfibrozil in Figure 3. No time-course effects were evident for concomitant use with statins (data not shown).

Measures of association: sensitivity analyses

PS-adjusted HRs for concomitant users of antidiabetic monotherapy and antihyperlipidemics are presented in Table 2. These results generally reflected the same pattern as analyses not restricted to antidiabetic monotherapy (except for metformin) presented in Figure 1, although the estimates are less precise because of fewer subjects. Among antihyperlipidemic-triggered persons in the overall cohorts, we identified 3.9%, 5.2% and 5.2% of users with an increase in glyburide, glipizide and glimepiride dose, respectively, during follow-up. After their exclusion, our findings remained unchanged. PS-adjusted HRs

for glyburide, glipizide and glimepiride with fenofibrate were 1.33 (1.06–1.67), 1.23 (0.95–1.59) and 1.62 (1.28–2.05), respectively. PS-adjusted HRs for glyburide, glipizide and glimepiride with gemfibrozil were 1.48 (1.22–1.79), 1.37 (1.10–1.70) and 1.57 (1.21–2.03), respectively. PS-adjusted HRs of an analysis limited to new SU users concomitantly exposed to an antihyperlipidemic are presented in Appendix Figure 2; these findings are similar to our overall findings presented in Figure 1, although the estimates are less precise because of fewer subjects.. Results from the sensitivity analysis that excluded covariates from the PS strongly related to exposure, but not outcome, were similar to our overall findings (data not shown).

DISCUSSION

We examined severe hypoglycemia associated with potential drug-drug interactions between SUs and antihyperlipidemics. The incidence of severe hypoglycemia among concomitant SU and antihyperlipidemic users was about 5–6 per 100 p-y. The rate was lowest among glipizide users, consistent with prior findings that glipizide causes less hypoglycemia than glyburide.(18,19) Interestingly, the rate was highest among glimepiride users, contrary to predictions that this third generation SU with a lower affinity for the pancreatic β-cell receptor may carry a lower risk of hypoglycemia.(20) As approximately 3% of each of glyburide, glipizide, and glimepiride users had a severe hypoglycemia event during the baseline period (Table 1, Appendix Table 1, Appendix Table 2), this seems unlikely to be responsible for this difference. To further contextualize our findings, rates among users of an SU as antidiabetic monotherapy were about seven times as large as those among metformin antidiabetic monotherapy users.

We found an increased rate of severe hypoglycemia during the first six months of concomitant use of a SU and either fenofibrate or gemfibrozil. There was no corresponding increased rate among concomitant users of SUs and a statin. SU + fenofibrate was associated with a 20%–60% increased rate of severe hypoglycemia overall, with rate increasing as much as 2.5-fold in users of glimepiride during the third and fourth months of concomitant use. SU + gemfibrozil was associated with a 40%–60% increased rate of severe hypoglycemia overall, with rate increasing as much as 2.4-fold in users of glipizide during the fifth and sixth months of concomitant use. Unexpectedly, metformin + fenofibrate was associated with a 60% increased rate of severe hypoglycemia overall, with rate increasing as much as 90% during the third and fourth months of concomitant use, although the metformin findings did not meet the conventional threshold for statistical significance.

The potential role of hepatic CYP inhibition in this drug interaction has been examined previously, but studies examining clinical relevance are scant. Niemi *et al* reported that gemfibrozil increases glimepiride's plasma concentrations by 23%, presumably via CYP2C9 inhibition.(15) Appel *et al* reported that fluvastatin and simvastatin (examined separately) increased glyburide's plasma concentrations by about 20%, yet concluded that such a change was not clinically relevant.(21) Prior models found that predicted CYP2C9- and CYP3A4-based area under the curve ratios (a measure of the change in systemic exposure to a drug in the presence of an inhibitor) for SUs with fibrates or statins were near 1.0, suggesting that a CYP-based interaction is unlikely.(22)

Our findings of an increased rate of severe hypoglycemia among concomitant users of glyburide and fibrates are consistent with our prior work in this area, the only previous study to examine the health effects of this potential interaction.(22) Our current studies build upon this prior work by: 1) overcoming the previously underpowered findings for glipizide, by including nearly 60% more data; 2) including persons entering the cohort as antidiabetic-triggered (Figure 4); 3) including glimepiride and metformin users; 4) reducing residual confounding by use of hdPS methods; and 5) examining time-specific associations measures soon after and more distant from cohort entry.

Taken together, our prior and current findings suggest that the apparent drug interaction between SUs and fibrates is unlikely mediated primarily by CYP2C9 inhibition. Evidence for this conclusion is as follows. First, concomitant use of rosuvastatin, an inhibitor of CYP2C9, was not associated with an increased rate of severe hypoglycemia. Second, the increases in hypoglycemia rate with concomitant use of fibrates were delayed, and interactions involving enzymatic inhibition are usually rapid-onset interactions.(23) Finally, there was a suggestion of an increased rate of severe hypoglycemia among users of metformin + fenofibrate, and metformin is not hepatically metabolized and only rarely causes hypoglycemia. Future work should elucidate the mechanism(s) underlying this apparent drug interaction. Inhibition by fibrates of organic anion transporter polypeptides (OATPs) involved in the hepatic uptake and resultant reduced clearance of SUs may contribute to this potential interaction. Arguing against this mechanism is the observation that OATP inhibition has been attributed to both statins and fibrates, and concomitant use of SUs and statins was not associated with an increased rate of severe hypoglycemia. Another potential mechanism involves peroxisome proliferator-activated receptor (PPAR) α agonist effects of fibrates, which can beneficially impact lipid and lipoprotein metabolism. Lipid and glucose homeostasis is interrelated and lowering free fatty acids ameliorates insulin resistance via protection of pancreatic islets.(24) Alternatively, or in addition, fibrates may induce fatty acid-binding protein and stimulate β-oxidation in skeletal muscles.(25) Regardless of potential mechanism, improvements in insulin resistance and glycemic control have been reported in users of gemfibrozil(26) and fenofibrate.(27) Further, some fibrates also act at PPAR γ,(28) the site of action of TZDs. In fact, bezafibrate—a pan-PPAR fibrate available outside of the US—has been shown to delay type 2 diabetes onset (and progression) in persons with impaired fasting glucose.(29,30)

Our studies have important strengths. They are the largest to date to examine the association between second generation SUs and severe hypoglycemia, the first to examine the association in users of a third generation SU, and the first to quantify the rate of severe hypoglycemia among metformin users. Our use of an active comparator, hdPS methods, and sensitivity analyses serves to mitigate confounding. Further, our large sample sizes allow for the examination of the time-course of the interactions. Finally, our algorithm to identify severe hypoglycemia has a very good positive predictive value.

These studies also have limitations. First, we did not have access to biosamples and were therefore unable to examine CYP polymorphisms. Second, we lacked data on adherence to prescribed antidiabetic and antihyperlipidemic therapies. Third, administrative databases may poorly capture some lifestyle behaviors and nonprescription therapies that may modify

hypoglycemia risk. Regardless, such factors seem unlikely to differ substantially by antihyperlipidemic exposure. Fourth, despite the high positive predictive value of our outcome definition, some events may be misclassified. Such misclassification is likely non-differential by antihyperlipidemic exposure and therefore effect estimates may biased toward the null. Finally, our results may not be generalizable beyond a US Medicaid population. Nevertheless, this population was specifically chosen because of its inherent vulnerability and inclusion of large numbers of women and minorities—groups typically understudied. Biological associations identified in Medicaid populations are often replicated in commercially insured populations and *vice versa*.(31)

Managing drug-drug interactions is regarded as a cornerstone of antidiabetic therapy.(23) By far the most important consequence of such interactions is severe hypoglycemia, an outcome of significant clinical and public health concern that is feared by patients and their relatives.(6) We found that concomitant therapy with a SU and fibrate is associated with an increased rate of emergency department presentation or hospitalization for hypoglycemia. The mechanism underlying this apparent drug-drug interaction needs further elucidation, but is unlikely to solely involve a pharmacokinetic interaction mediated by CYP2C9 inhibition. Clinicians should be attuned to both immediate- and delayed-onset hypoglycemia in their patients on this drug combination.

METHODS

Overview and study population

We conducted three hdPS-adjusted retrospective cohort studies of adult users of glyburide, glipizide and glimepiride. Each cohort consisted exclusively of person-time concomitantly-exposed to the SU plus one of the following antihyperlipidemics: atorvastatin; fenofibrate; gemfibrozil; lovastatin; pravastatin; rosuvastatin; or simvastatin. Study data included that of the Medicaid programs of California, Florida, New York, Ohio, and Pennsylvania from 1999–2009.(32) Findings from 1999–2003 for a subset of the pairs examined herein using different methods have been reported earlier.(22) These states comprise about 38% of the US Medicaid population, with the 11-year dataset recording the experience of over 59 million cumulative enrollees and nearly 180 million p-y of observation. Because a proportion of Medicaid beneficiaries are co-enrolled in Medicare, we also obtained Medicare claims to ascertain a more complete picture of enrollees' healthcare.(33) To contextualize our SU findings, we conducted a fourth hdPS-adjusted cohort study among concomitant users of metformin (which causes hypoglycemia only rarely) and an antihyperlipidemic.

Defining the study cohorts

We defined new users as those with ≥12 months of Medicaid enrollment before their concomitant antidiabetic + antihyperlipidemic use. The day on which users were first co-exposed defined cohort entry. The 12-month period immediately preceding cohort entry served as the baseline period. Use of a fixed baseline period is standard in studies utilizing hdPS methods. Persons entered the cohort as combination triggered, antidiabetic triggered, or antihyperlipidemic triggered (Figure 4).

Persons were excluded if <18 or ≥100 years of age. Persons with exposure to a non-SU antidiabetic drug during the baseline period were not excluded from the SU cohorts, as SUs are often used as second-line therapy; however, prior use of non-SU antidiabetic drug classes were pre-specified covariates in the PS. Persons with exposure to a non-metformin antidiabetic drug during the baseline period were excluded from the metformin cohort, as it was intended to be an antidiabetic monotherapy cohort with a low rate of antidiabetic-induced hypoglycemia. Severe hypoglycemia during the baseline period was not an exclusion criterion, as hypoglycemia is often recurrent, but was a pre-specified variable in the PS.

Follow-up began upon cohort entry and continued until the first occurrence of the following: a) outcome of interest (defined below); b) death, as ascertained from linkage to the Social Security Administration Death Master File (National Technical Information Service: Alexandria, VA); c) the 181st day of follow-up; d) >15-day gap in either antidiabetic or antihyperlipidemic therapy; e) prescription for a sulfonylurea or antihyperlipidemic different than that upon cohort entry (i.e., indicative of switching to an alternate therapy); f) prescription for any non-metformin antidiabetic agent or antihyperlipidemic different than that upon cohort entry (for the metformin antidiabetic monotherapy cohort alone); g) loss of Medicaid eligibility; or h) the end of the dataset. Follow-up time occurring during a period of hospitalization was excluded, although hospitalization did not serve as a censoring event. This exclusion served to minimize immeasurable time bias.

Exposure and covariate ascertainment

Exposure was defined by the antihyperlipidemic active on the day of cohort entry. The following antihyperlipidemics were excluded because of minimal use: cerivastatin; clofibrate; fluvastatin; and pitavastatin. Pravastatin served as the reference exposure, as it is a negligible inhibitor of CYP isozymes(34) which are involved in the metabolism of SUs.(35) Therefore, pravastatin would not be expected to interact pharmacokinetically with SUs. Further, pravastatin has minimal-to-no effect on fasting plasma glucose(36–39) or daylong plasma glucose.(40) Therefore, it alone would not be expected to have an inherent hypoglycemic effect.

Potential confounders included pre-specified variables and those identified via empiric methods, both of which informed the PS. Pre-specified variables included demographics, baseline measures of intensity of healthcare utilization, baseline drug exposures, and baseline comorbidities (Table 1). Empiric covariates included those identified during baseline via a high-dimensional approach(41,42) which ranks and selects potential confounders (or proxies thereof) based on their empirical associations with exposure and outcome (see specifications in Appendix Table 5).

Outcome ascertainment

The outcome was severe hypoglycemia (i.e., resulting in emergency department treatment or hospitalization) within 181 days of cohort entry—operationally defined by one of the following International Classification of Diseases 9th Revision Clinical Modification discharge diagnosis codes in any position on an emergency department claim or the principal

position on an inpatient claim: a) 251.0 (hypoglycemic coma); b) 251.1 (other specific hypoglycemia); c) 251.2 (hypoglycemia, unspecified); or d) 250.8X (diabetes with other specified manifestations), as long as it did not co-occur with ≥1 exclusionary diagnosis suggesting manifestations other than hypoglycemia (Appendix Table 6). The emergency department and inpatient components of this algorithm have positive predictive values of 89%(43) and 78%,(44) respectively.

Statistical analysis

We calculated descriptive statistics for baseline variables and calculated incidence and unadjusted association measures, the latter via Cox proportional-hazards models. We utilized the hdPS approach to reduce the impact of potential confounders. However, as we wished to compare multiple antihyperlipidemic drugs to a common pravastatin comparison group, matching on PS was not an option, and the hdPS algorithm has so far been developed only for pairwise comparisons.(42,45) As described below, we therefore used pairwise hdPS to identify potential confounders for each antihyperlipidemic drug versus pravastatin and included all such empirically-identified variables (plus pre-specified variables) in a multinomial PS model. We first used the hdPS program(42,45) to identify the 200 most prevalent diagnosis, procedure and drug codes (excluding drug codes indicative of SU or antihyperlipidemic prescribing) in each of nine data dimensions, to assess their associations with the antihyperlipidemic of interest versus pravastatin, and to assess their associations with the outcome. We then used these associations to select the top 500 codes with the largest potential for causing confounding. Because of the large number of variables in the final multinomial PS model, empirically-identified covariates did not include measures of frequency (i.e., sporadic, frequent) as generated by the hdPS program. Then, the union of all confounders arising from the seven sets of 500 hdPS-identified variables (one for each antihyperlipidemic versus pravastatin) were included in the multinomial PS. The following pre-specified covariates were also included in the multinomial PS model: age; sex; race; state of residence; calendar year of cohort entry; Medicaid-Medicare dual-enrollment status; nursing home residence status; prior severe hypoglycemia; measures of the intensity of healthcare utilization; and prior use of other antidiabetic drugs, by pharmacologic class. The multinomial PSs were modeled using multinomial logistic regression,(46) generating for each subject the predicted probability of receiving each antihyperlipidemic drug. These PSs were then included in the outcome model as continuous covariates;(47) this adjustment approach (compared to the use of matching or weighting) would likely result in minimal bias.(48,49) PS-adjusted HRs and 95% CIs were calculated via Cox proportional-hazards regression. Refer to the Appendix Methods Addendum for more detail on PS methodology. Association measures were examined overall within the first 181 days of follow-up and also stratified as four pre-specified, mutually exclusive time periods. A polynomial trend line was generated to graphically depict trends across time periods.

A pre-specified secondary analysis examined persons treated with a SU as antidiabetic monotherapy (i.e., no other antidiabetic drug dispensed in the 60 days prior to cohort entry and censored upon dispensing of any other antidiabetic therapy). Pre-specified sensitivity analyses: a) excluded persons with an increase in SU dose from pre-to-post cohort entry, among those entering the cohort as antihyperlipidemic triggered (Figure 4); and b) excluded

empirical covariates from the PS thought to be strong correlates of exposure but not associated with the outcome,(41) as their inclusion in the PS can increase standard error and bias.(50) A *post hoc* sensitivity analysis examined persons devoid of baseline SU use, i.e., new SU users concomitantly exposed to an antihyperlipidemic. PSs were re-estimated for all secondary and sensitivity analyses. Statistical analyses were conducted using SAS v9.4 (SAS Institute Inc.: Cary, NC). This research was approved by the institutional review board of the University of Pennsylvania.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STUDY HIGHLIGHTS

What is the current knowledge on this topic?

Drug interactions with sulfonylureas may potentiate hypoglycemia risk via inhibition of hepatic cytochrome P450 (CYP) enzymes responsible for their metabolism.

What question did this study address?

Given that dyslipidemia is common in persons with diabetes mellitus, we examined the rates of severe hypoglycemia among concomitant users of sulfonylureas and individual antihyperlipidemics.

What does this study add to our knowledge?

Concomitant use of a sulfonylurea plus either fenofibrate or gemfibrozil is associated with severe hypoglycemia. The increase in rate among users of either fenofibrate or gemfibrozil is most notable beginning *after* the first month of concomitant use, but in some instances also elevated within the first month. The pattern of this apparent interaction is generally similar to that seen among concomitant users of metformin and a fibrate. The apparent sulfonylurea-fibrate drug interaction seems unlikely mediated by CYP2C9 inhibition.

How might this change clinical pharmacology and therapeutics?

Clinicians should be attuned to both immediate- and delayed-onset hypoglycemia in their patients on this drug combination.

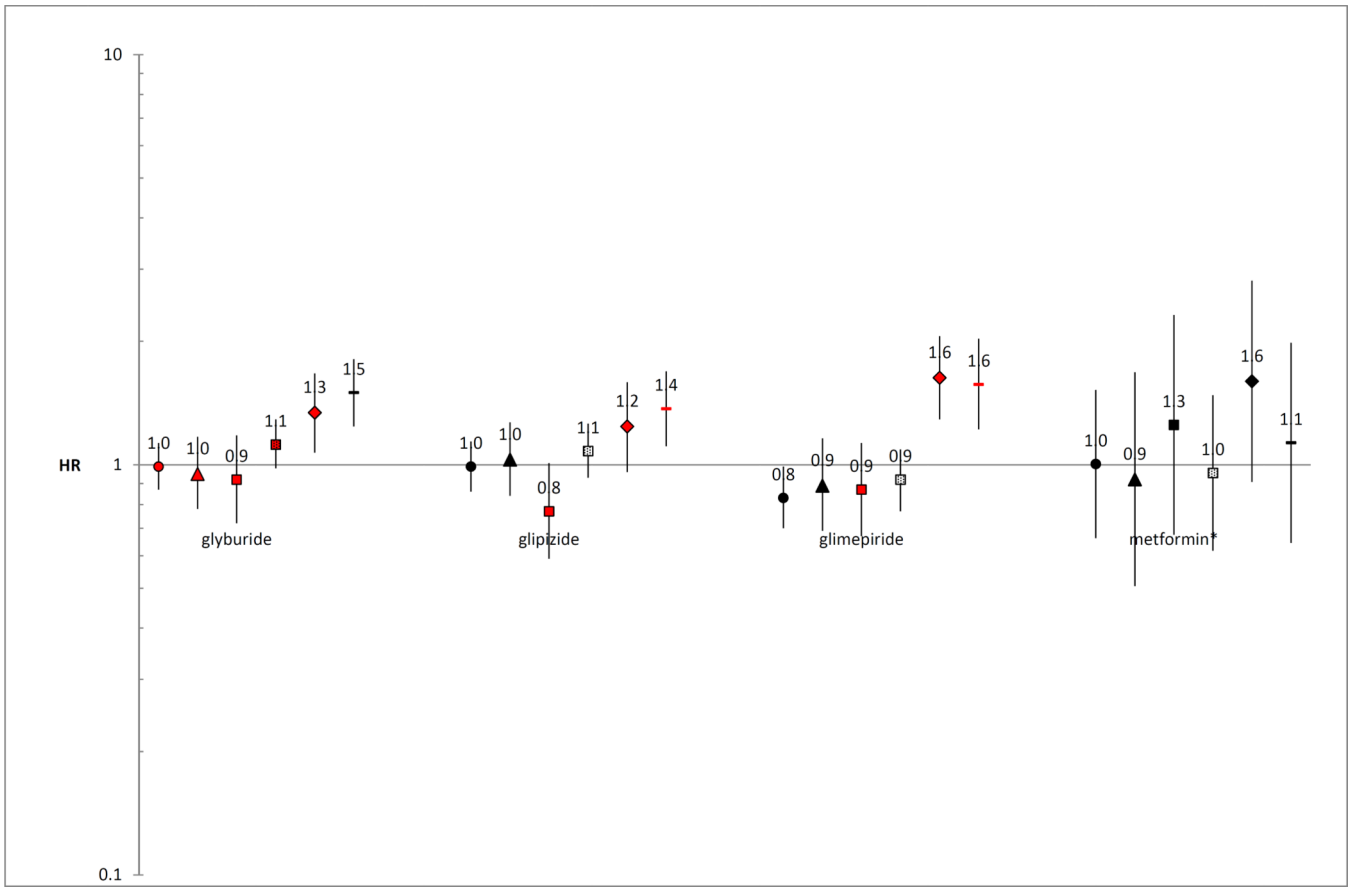

Figure 1.

Propensity score-adjusted hazard ratios (HRs) for association between antidiabetic + antihyperlipidemic drug (vs. pravastatin) and severe hypoglycemia within 181 days of cohort entry

● atorvastatin ▲ lovastatin ▉ rosuvastatin ▮ simvastatin ♦ fenofibrate ▬ gemfibrozil

Red coloring indicates that antihyperlipidemic precipitant drug inhibits hepatic metabolism of antidiabetic object drug (Neuvonen et al. *CPT* 2006;80., Wen et al. *Drug Metab Dispos* 2001;29., and Schelleman et al *BJCP* 2014;78).

* monotherapy cohort

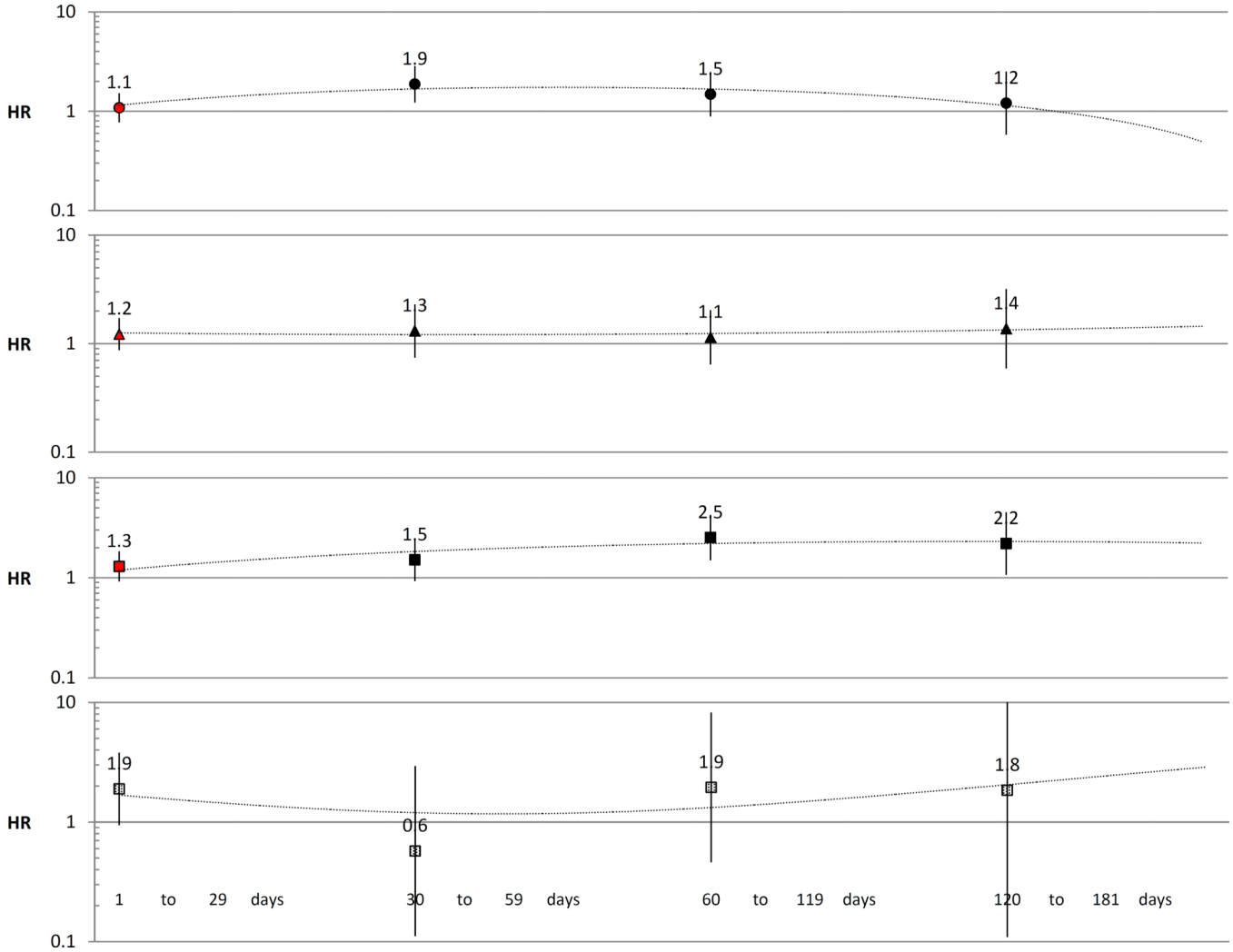

Figure 2.

Propensity score-adjusted hazard ratios (HRs) for association between antidiabetic + FENOFIBRATE (vs. pravastatin) and severe hypoglycemia—by antidiabetic, by time since cohort entry

● glyburide ▲ glipizide ▮ glimepiride ▮ metformin*

Red coloring indicates that antihyperlipidemic precipitant drug inhibits hepatic metabolism of antidiabetic object drug (Neuvonen et al. *CPT* 2006;80., Wen et al. *Drug Metab Dispos* 2001;29., and Schelleman et al *BJCP* 2014;78).

* monotherapy cohort

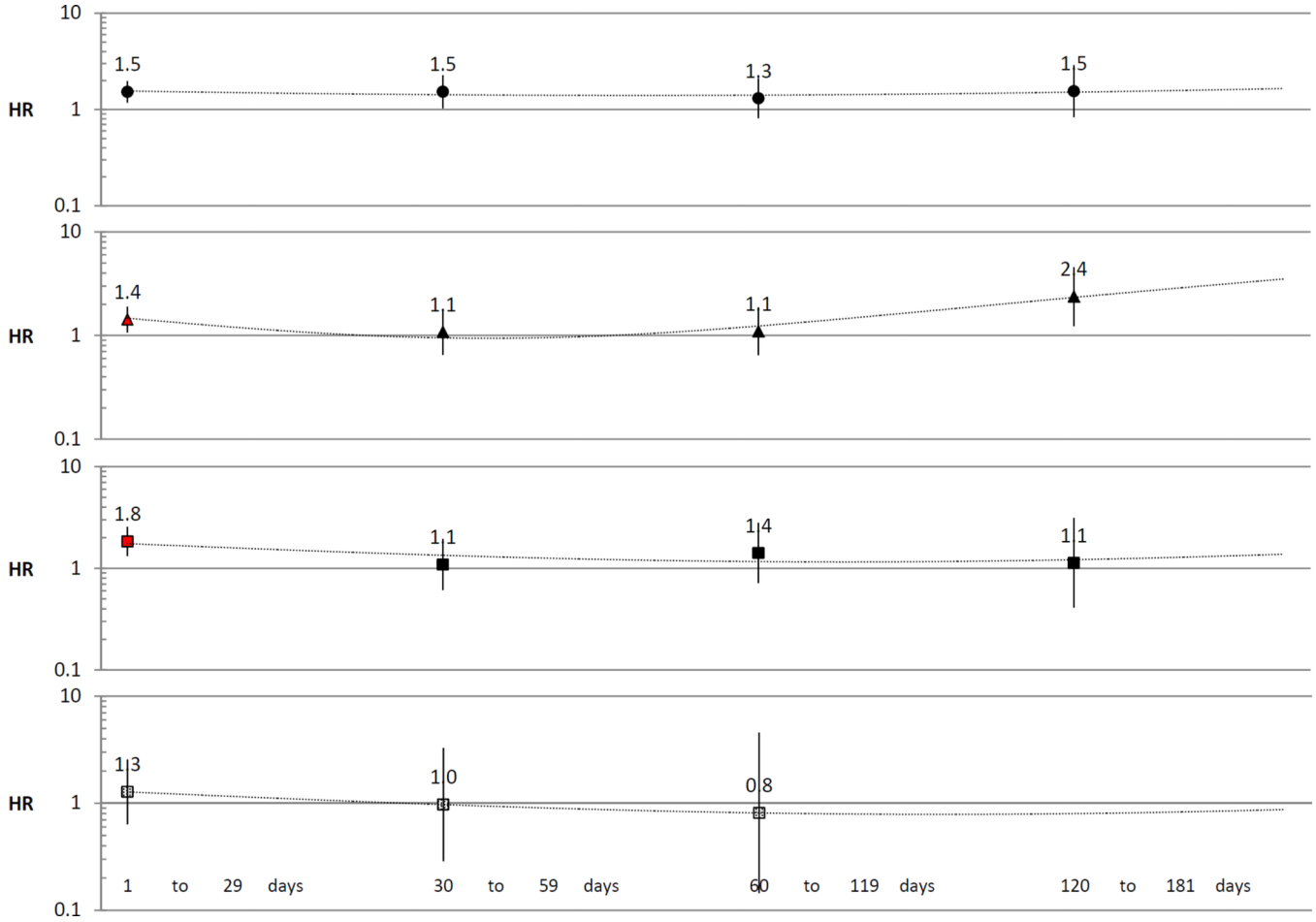

Figure 3.

Propensity score-adjusted hazard ratios (HRs) for association between antidiabetic + GEMFIBROZIL (vs. pravastatin) and severe hypoglycemia—by antidiabetic, by time since cohort entry

● glyburide ▲ glipizide ▮ glimepiride ▮ metformin*

Red coloring indicates that antihyperlipidemic precipitant drug inhibits hepatic metabolism of antidiabetic object drug (Neuvonen et al. *CPT* 2006;80., Wen et al. *Drug Metab Dispos* 2001;29., and Schelleman et al *BJCP* 2014;78).

* monotherapy cohort

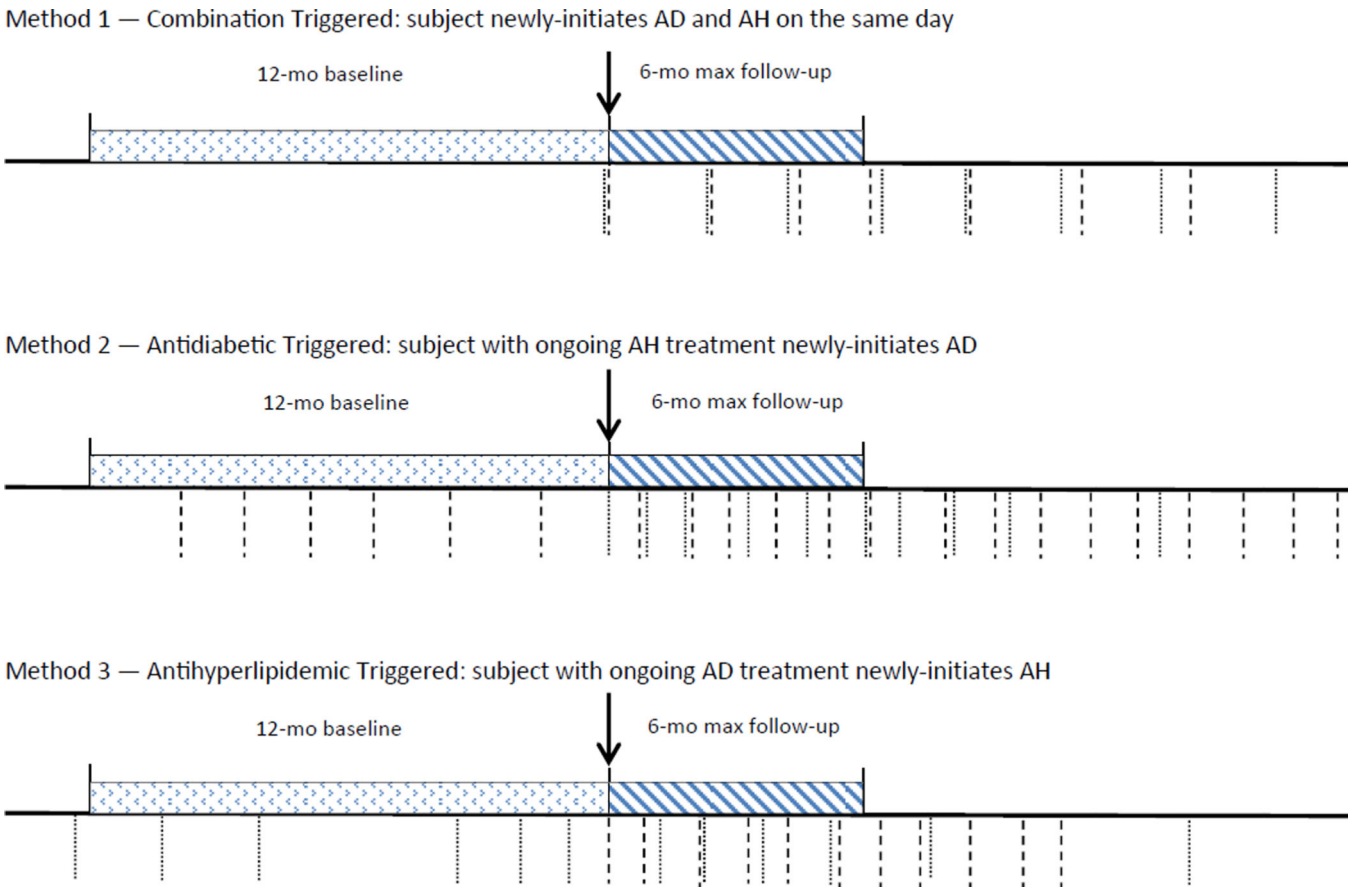

Figure 4.

Methods by which concomitant antidiabetic (AD) and antihyperlipidemic (AH) users could enter a study cohort

↓ cohort entry begins

antihyperlipidemic prescription dispensing

antidiabetic prescription dispensing

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Table 1

Characteristics of glyburide users, by antihyperlipidemic exposure group

		Statins					Fibrates	
		pravastatin	**atorvastatin**	**lovastatin**	**rosuvastatin**	**simvastatin**	**fenofibrate**	**gemfibrozil**
		Ns						
Users, concomitant with glyburide		21,802	92,974	16,490	9,042	63,081	7,660	13,772
Person-years of follow-up		4,986	22,199	3,933	1,999	14,646	1,613	2,804
Severe hypoglycemia events within 181days of cohort entry		282	1,310	160	91	1,060	111	187
		Measures of Association						
Unadjusted hazard ratio (95% confidence interval)		1.00 (reference)	1.06 (0.93–1.20)	0.73 (0.60–0.88)	0.80 (0.63–1.01)	1.29 (1.13–1.47)	1.20 (0.96–1.49)	1.15 (0.95–1.38)
Adjusted hazard ratio (95% confidence interval)		1.00 (reference)	0.99 (0.87–1.13)	0.95 (0.78–1.17)	0.92 (0.72–1.18)	1.12 (0.98–1.29)	1.34 (1.07–1.67)	1.50 (1.24–1.81)
Demographics	**Group**	% (unless otherwise noted)						
Event triggering concomitant use (see Figure 4)	combination triggered	28.8	27.1	30.4	29.7	29.3	22.9	29.2
	antidiabetic triggered	34.7	37.2	31.2	35.5	36.2	36.5	32.2
	antihyperlipidemic triggered	36.5	35.8	38.5	34.8	34.5	40.6	38.6
Age in years at cohort entry, continuous	Median (Q1–Q3)	66.2 (55.2–73.8)	65.1 (54.1–73.4)	66.6 (52.4–74.8)	65.7 (54.9–73.7)	65.7 (54.7–73.8)	60.7 (49.0–71.3)	57.5 (46.8–69.3)
Sex	female	65.6	63.7	62.8	62.8	62.6	55.5	53.0
Race	white	30.7	34.1	27.6	28.6	33.1	46.2	33.6
	black	15.4	15.4	13.2	13.3	17.6	7.7	7.8
	other/unknown	54.0	50.6	59.2	58.1	49.4	46.2	58.7
State of residence	CA	56.3	50.8	65.4	33.6	40.3	36.2	62.9
	FL	10.2	7.7	15.0	25.5	13.3	16.5	11.0
	NY	24.1	29.2	11.0	35.2	33.8	28.6	18.1
	OH	4.2	7.5	3.3	3.2	7.1	10.9	4.8
	PA	5.2	4.8	5.3	2.5	5.6	7.8	3.2
Calendar year of cohort entry	2000–2003	62.8	46.0	13.6	1.6	27.3	31.9	46.1
	2004	9.2	11.8	11.6	10.7	6.8	9.2	9.8
	2005	7.5	12.5	14.0	14.6	9.4	12.2	9.6

		Statins					Fibrates	
		pravastatin	**atorvastatin**	**lovastatin**	**rosuvastatin**	**simvastatin**	**fenofibrate**	**gemfibrozil**
		Ns						
	2006	7.0	13.2	31.5	25.1	14.0	14.5	12.0
	2007	4.1	8.1	13.6	16.8	14.7	11.5	8.8
	2008	4.2	4.9	8.0	11.3	13.0	9.7	6.8
	2009	5.1	3.5	7.7	19.9	14.8	11.1	7.0
Medicare enrolled	Yes	62.9	60.4	64.4	60.6	62.3	59.6	50.3
Nursing home residence, ever during baseline	Yes	4.4	7.0	6.0	3.5	7.6	6.3	4.8
Healthcare utilization intensity measures, in baseline period *	**Group**	Measures of Central Tendency						
# prescriptions dispensed	Median (Q1–Q3)	43.0 (20.0–74.0)	45.0 (21.0–78.0)	28.0 (10.0–60.0)	49.0 (22.0–85.0)	45.0 (19.0–79.0)	55.0 (26.0–94.0)	40.0 (16.0–74.0)
# unique drugs dispensed	Median (Q1–Q3)	13.0 (7.0–19.0)	13.0 (7.0–20.0)	10.0 (5.0–16.0)	13.0 (8.0–20.0)	12.0 (7.0–19.0)	14.0 (8.0–21.0)	12.0 (6.0–18.0)
# outpatient diagnosis codes	Median (Q1–Q3)	39.0 (17.0–79.0)	41.0 (19.0–85.0)	19.0 (3.0–48.0)	37.0 (16.0–83.0)	38.0 (15.0–88.0)	44.0 (20.0–90.0)	30.5 (12.0–67.0)
# unique outpatient diagnosis codes	Median (Q1–Q3)	14.0 (8.0–24.0)	15.0 (8.0–25.0)	8.0 (2.0–17.0)	14.0 (7.0–25.0)	14.0 (7.0–25.0)	15.0 (8.0–25.0)	12.0 (6.0–21.0)
# outpatient CPT-4/HCPCS procedure codes	Median (Q1–Q3)	46.0 (21.0–92.0)	48.0 (22.0–95.0)	28.0 (7.0–62.0)	47.0 (20.0–99.0)	44.0 (17.0–95.0)	52.0 (25.0–101)	38.0 (16.0–78.0)
# unique outpatient CPT-4/HCPCS procedure codes	Median (Q1–Q3)	26.0 (13.0–45.0)	27.0 (15.0–46.0)	17.0 (4.0–34.0)	27.0 (14.0–47.0)	26.0 (12.0–46.0)	29.0 (16.0–47.0)	23.0 (11.0–40.0)
Other investigator pre-defined covariates, in baseline period	**Group**	%						
Prior severe hypoglycemia	Yes	2.7	2.8	1.9	1.8	3.0	2.3	2.2
Alpha-glucosidase inhibitor exposure	Yes	1.6	1.4	0.9	1.2	1.3	1.3	1.3
DPP-4 inhibitor exposure	Yes	0.4	0.7	0.7	3.5	1.9	2.0	0.5
GLP-1 inhibitor exposure	Yes	0.2	0.2	0.2	0.7	0.5	0.7	0.2
Insulin exposure	Yes	13.8	14.8	11.5	14.2	16.0	15.1	13.1
Meglitinide exposure	Yes	3.6	3.0	1.5	3.3	2.8	3.9	2.1
Metformin exposure	Yes	58.0	57.2	56.4	64.1	58.3	62.0	56.5
Thiazolidinedione exposure	Yes	27.2	28.3	23.6	32.8	26.7	30.3	20.2

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 their 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 ICD-9 diagnosis codes; # unique other setting ICD-9 diagnosis codes; # other setting ICD-9 procedure codes; # unique other setting ICD-9 procedure codes

Table 2

Propensity-score adjusted hazard ratios for severe hypoglycemia within 181 days of cohort entry among concomitant users of antidiabetic monotherapy and an antihyperlipidemic

	Antidiabetic agent (N = severe hypoglycemia events among antidiabetic monotherapy users)			
	glyburide (N = 685)	**glipizide (N = 629)**	**glimepiride (N = 354)**	**metformin (N = 359)**
Antihyperlipidemic	**Hazard ratio (95% confidence interval)**			
atorvastatin	1.07 (0.80–1.43)	0.91 (0.68–1.21)	0.66 (0.46–0.96)	1.00 (0.66–1.52)
lovastatin	0.92 (0.59–1.43)	0.91 (0.60–1.39)	0.80 (0.42–1.50)	0.92 (0.51–1.68)
pravastatin	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
rosuvastatin	0.97 (0.53–1.78)	0.61 (0.32–1.15)	0.86 (0.49–1.50)	1.25 (0.68–2.32)
simvastatin	1.13 (0.84–1.53)	0.92 (0.68–1.24)	0.76 (0.52–1.10)	0.96 (0.62–1.48)
fenofibrate	1.69 (1.02–2.82)	0.69 (0.35–1.35)	1.75 (1.05–2.89)	1.60 (0.91–2.81)
gemfibrozil	1.52 (1.01–2.29)	1.63 (1.08–2.47)	1.58 (0.89–2.80)	1.13 (0.65–1.99)