# Hypoglycemia associated with concurrent use of commonly used sulfonylureas and warfarin, an observational analysis

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# Hypoglycemia associated with concurrent use of commonly used sulfonylureas and warfarin, an observational analysis

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## ABSTRACT

**Objective:** To determine whether warfarin use is associated with higher risk of serious hypoglycemic events among older individuals treated with glipizide or glimepiride.

**Design:** Retrospective cohort analysis of pharmacy and medical claims over 2006-2011.

**Setting:** 20% random sample of Medicare beneficiaries aged 65 years or older.

**Participants:** 465,918 beneficiaries with diabetes who filled a prescription for glipizide or glimepiride (4,355,418 person-quarters); 71,895 individuals (15.4%) also filled a prescription for warfarin (416,479 person-quarters with warfarin use)

**Main outcome measures:** ED visit or hospitalization with primary diagnosis of hypoglycemia.

**Results:** In quarters with sulfonylurea use, hospitalizations or ED visits for hypoglycemia were more common in person-quarters with concurrent warfarin use compared to quarters with sulfonylurea use alone (294/71533 vs. 1903/394385; adjusted odds ratio 1.22, 95% CI 1.05-1.42). Hypoglycemia risk associated with concurrent use was elevated among those using warfarin for the first time, as well as those age 65-74 years. Our findings were robust to sensitivity analyses, including a falsification test with concurrent statin use and longitudinal regressions of beneficiaries sometimes using warfarin.

**Conclusions:** Use of warfarin is associated with significantly higher rates of hospitalization and ED visits for hypoglycemia among older individuals treating with glipizide or glimepiride. Our findings suggest the possibility of a significant drug interaction between these medications.

## WHAT THIS PAPER ADDS

### Section 1: What is already known on this subject

- Antidiabetic and anticoagulant medications account for the majority of adverse drug events requiring emergency hospitalization among older Americans.
- Warfarin may potentiate hypoglycemic action of commonly prescribed sulfonylurea medications (glipizide and glimepiride) in individuals with type-2 diabetes.

### Section 2: What this study adds

- This study explores this potential drug interaction within the population of elderly Medicare beneficiaries.
- We find a substantial positive association between hypoglycemia hospitalization / ED visits and concurrent use of glipizide / glimepiride and warfarin, particularly among individuals initiating warfarin.
- Our findings suggest that clinicians should be aware of the potential increased risk for hypoglycemia among individuals concurrently receiving glipizide or glimepiride and warfarin, and closely monitor this population.

## INTRODUCTION

Older individuals are more than twice as likely to experience adverse drug events as the general population due to greater use of medications[1] and higher rates of frailty and renal insufficiency.[2-7] Each year, nearly 100,000 elderly U.S. residents are hospitalized for unintentional medication overdoses, adverse effects at recommended doses, and allergic reactions.[8,9] More than 40% of these hospitalizations are attributable to the anticoagulant warfarin[10] or to oral hypoglycemic agents such as sulfonylureas.[11,12] Sulfonylureas with a long duration of action have been deemed particularly inappropriate for older individuals according to expert consensus.[13,14]

Despite known interactions between warfarin and a number of medications[15] and the fact that both warfarin and oral hypoglycemic medications account for the plurality of adverse drug event hospitalizations, little is known about drug interactions between these two classes of medications. In particular, two clinical drug references advise that warfarin may potentiate the hypoglycemic effects of sulfonylureas,[16,17] but no large-scale empirical evidence exists to support this advisory. Rather, existing evidence for a potential drug-drug interaction between warfarin and sulfonylureas is based on pharmacokinetic theories related to displaced plasma protein binding and hepatic metabolism.[16] Consistent with this lack of firm evidence, other clinical databases report no interaction between warfarin and sulfonylureas.[18]

In light of limited evidence about a potential drug-drug interaction between warfarin and long-acting sulfonylureas, we analyzed rates of hospitalization and emergency department (ED) visits for hypoglycemia among a large national sample of Medicare beneficiaries aged 65 years or older with type 2 diabetes who were concurrently treated with warfarin plus the sulfonylureas glipizide or glimepiride compared to either of these sulfonylureas alone.

## METHODS

### Data sources and study sample

We used pharmacy and medical claims from a random 20% sample of Medicare beneficiaries during 2006-2011. The Chronic Conditions segment of the Master Beneficiary Summary File was used to identify Medicare beneficiaries aged 65 years or older with type 2 diabetes, derived from a validated algorithm using International Classification of Diseases, Ninth Revision (ICD-9) codes in inpatient and outpatient claims within a two-year window.[19] We restricted our analysis to individuals with at least one prescription fill for glipizide or glimepiride, identified in Medicare Part D pharmacy claims by the appropriate National Drug Codes.[20] The Medicare Provider Analysis and Review file was used to identify admissions to acute short-term hospitals for hypoglycemia based on ICD-9 primary diagnosis codes of 251.0, 251.1, or 251.2.[21] ED visits for hypoglycemia were identified based on appropriate revenue center codes within claims in the Medicare Outpatient file. The study was approved by the University of Southern California institutional review board.

### Primary outcomes

The unit of analysis was a person-quarter. Our primary outcome was whether an individual was hospitalized or treated in the ED for hypoglycemia in a given calendar quarter. We analyzed each of these outcomes separately and combined.

### Analysis

We identified all person-quarters in which there was a pharmacy claim for either glipizide or glimepiride. Within these person-quarters, we identified the association between warfarin use in that quarter (as identified by a pharmacy claim for warfarin in that quarter) and hospitalization or ED visit for hypoglycemia. We excluded those person-quarters in which the

individual did not have a prior medical claim for diabetes in any prior calendar quarter.[22] We also excluded person-quarters in which an individual was not enrolled in both Medicare Part A and Part B during each month he or she was alive during the quarter.

In our primary analyses, we estimated a multivariable logistic regression of the relationship between hospitalization or ED visit for hypoglycemia and use of warfarin among Medicare beneficiaries aged 65 years or older with type-2 diabetes treated with glipizide or glimepiride.[23,24] Regressions were estimated at the person-quarter level. Our model adjusted for age, sex, race, and 14 chronic comorbidities. Demographics were missing for 0.22% of beneficiaries; complete cases were analyzed. To address serial correlation in outcomes across quarters, the model included random effects at the person level.[25-27]

We estimated the association between hospitalization or ED visit for hypoglycemia and concurrent warfarin / sulfonylurea use according to several pre-specified subgroups: age above or below 75 years, male versus female, white versus non-white, comorbid conditions (higher versus less than median number), and whether a quarter was the first in which warfarin was prescribed. For the latter subgroup analysis, we hypothesized that hypoglycemia would be more common in the initial quarter of concurrent warfarin / sulfonylurea use when appropriate titration of warfarin dosing is most uncertain.[28]

**Additional analyses**

Among patients prescribed glipizide or glimepiride, those using warfarin may have unobserved characteristics that are associated with both warfarin use and the risk of hypoglycemia, which would confound the estimated association between warfarin use and risk of hospitalization or ED visit for hypoglycemia. We addressed this issue of confounding through several additional analyses. First, because unmeasured characteristics may differ between

individuals who do and do not use warfarin, we restricted our analysis to beneficiaries who used warfarin in at least one quarter. Among those patients who ever used warfarin, this approach therefore estimated the association between concurrent warfarin / sulfonylurea use and hypoglycemia by comparing hypoglycemia hospitalization and ED rates in those calendar quarters in which warfarin was used to those in which warfarin was not used. Second, we estimated a conditional fixed-effects logistic model that accounted for time invariant individual factors that are associated with warfarin use and risk of hypoglycemia. This approach essentially uses individuals as their own controls and identifies the association between concurrent warfarin / sulfonylurea use and hypoglycemia by comparing quarters of warfarin use to those of non-use within the same individual. This model was limited by design to the subsample of individuals who were observed over multiple quarters and whose warfarin use and outcomes varied across quarters.[29-32] Third, we conducted a falsification analysis to assess whether our findings were likely to be explained by unmeasured confounding.[33-35] Specifically, among patients prescribed glipizide or glimepiride, we estimated whether concurrent use of these sulfonylureas and statins was also associated with risk of hypoglycemia requiring hospitalization or ED visit. The intuition behind this approach is that if higher rates of hypoglycemia were also observed among patients using glipizide or glimepiride concurrently with another drug class for which no interaction with sulfonylureas is known, then any observed association between hypoglycemia risk and concurrent warfarin / sulfonylurea use would more likely reflect unobserved characteristics among patients using medications more generally as opposed to a specific effect of warfarin use.

All analyses were performed using Stata version 13 (StataCorp, College Station, TX). Hypothesis tests were conducted with a probability of 0.025 in each tail, or a P value of 0.05.

**Patient involvement**

There was no patient involvement in this study.

**RESULTS**

Over 2006-2011, the 20% Medicare database included 12,412,673 beneficiaries. Our analysis sample included a total of 465,918 elderly fee-for-service beneficiaries with type 2 diabetes who filled at least one prescription for either glipizide or glimepiride, of which 71533 (15.4%) used warfarin at some point during the study period (**Table 1**). Compared to beneficiaries who never used warfarin, those with at least one quarter of warfarin use concurrently with glipizide or glimepiride were older, were more likely to be male and white, and had higher rates of chronic comorbidities such as hypertension. Hospitalization and ED visits were rare but more common among patients who ever used warfarin compared to those who did not.

Our primary unit of observation in analysis was the person-quarter level. Out of 4,355,418 overall person-quarters, hospitalizations and ED visits without hospitalization for hypoglycemia occurred in 0.010% (442/4,355,418) and 0.040% (1755/4,355,418) of person-quarters, respectively (**Table 2**). Concurrent use of warfarin and glipizide or glimepiride was common, with 9.6% of person-quarters involving warfarin use (416,479/4,355,418). Hospitalizations and ED visits for hypoglycemia were more common in person-quarters in which warfarin was used compared to quarters in which it was not (77/416479, or 0.018%, hospitalizations for hypoglycemia in person-quarters with warfarin use versus 365/3938939, or 0.009%, hospitalizations in person-quarters without warfarin use, unadjusted odds ratio (OR) 2.36 (95% CI 1.74-3.21); 217/416479, or 0.052%, ED visits for hypoglycemia in person-quarters

with warfarin use versus 1538/3938939, or 0.039%, ED visits in person-quarters without warfarin use, unadjusted OR 1.36 (95% CI 1.17-1.58); unadjusted OR for combined hospitalization or ED visit 1.51, 95% CI 1.32-1.73).

**Multivariable analysis**

In multivariable analysis, hospitalization or ED visit for hypoglycemia (combined outcome) was more likely in person-quarters with concurrent warfarin / sulfonylurea use compared to quarters without warfarin use (adjusted OR, 1.22, 95% CI 1.05-1.42, as shown in **Figure 1**, with complete regression results in **Appendix Table 1**). Concurrent warfarin / sulfonylurea use was associated with higher rates of hospitalization for hypoglycemia (adjusted OR, 1.45, 95% CI 1.06-1.97) and a rate of ED visits without a subsequent hospitalization that trends toward significance (adjusted OR, 1.17, 95% CI 0.98-1.39).

**Subgroup analysis**

In sub-group analysis (**Figure 2**), the association between concurrent warfarin / sulfonylurea use and the combined outcome of hospitalization or ED visit for hypoglycemia was larger for person-quarters in which a patient first used warfarin (adjusted OR for first use 2.52, 95% CI 2.04-3.13, versus subsequent use 0.91, 95% CI 0.76-1.09, $p < 0.01$ for the difference), and for individuals age 65-74 years (adjusted OR for age 65-74 years, 95% CI 1.22-1.95, versus age 75 years and above, 1.08, 95% CI 0.89-1.86, $p=0.011$ for the difference).

**Additional analyses**

The estimated association between concurrent warfarin / sulfonylurea use and the combined outcome of hospitalization or ED visit for hypoglycemia was robust to additional analyses (**Figure 3**). For example, concurrent warfarin / sulfonylurea use was associated with higher rates of hospitalization for hypoglycemia when analysis was restricted only to those

beneficiaries who ever used warfarin (adjusted OR, 1.54, 95% CI 1.24-1.92) and in conditional fixed-effects analysis which compared hypoglycemia rates during periods of concurrent warfarin / sulfonylurea use and non-use within the same beneficiary over time (adjusted OR, 2.91, 95% CI 1.58-5.35). Our findings were also robust to a falsification analysis. Specifically, we found no association between the combined outcome of hospitalization or ED visit for hypoglycemia and concurrent use of sulfonylureas with statins.

## DISCUSSION

We found higher rates of hospitalization for hypoglycemia among a large national sample of Medicare beneficiaries aged 65 years or older with type 2 diabetes who were concurrently treated with warfarin plus the sulfonylureas glipizide or glimepiride compared to either of these sulfonylureas alone. The association was strongest in magnitude for those using warfarin for the first time and for individuals age 65-74 years. Our findings were robust to within-beneficiary analyses that compared hypoglycemia rates during quarters of concurrent warfarin / sulfonylurea use to quarters without warfarin use in the same beneficiary over time. We also found no relationship between hypoglycemia rates and concurrent use of sulfonylureas with statins. These sensitivity analyses suggest that the observed relationship between concurrent warfarin / sulfonylurea use and hypoglycemia risk may reflect an unexplored drug-drug interaction rather than unmeasured patient characteristics that are correlated with both warfarin use and hypoglycemia risk.

Although the underlying mechanism of action for this potential drug interaction is unclear, existing evidence suggests two possible mechanisms for increased hypoglycemia risk. The first is via displaced protein binding, as seen with first-generation sulfonylureas

(acetohexamide, chlorporpamide, tolazamide, and tolbutamide).[36] This interaction occurs when a second medication (in this case, warfarin) is added that displaces the sulfonylurea, thus increasing its plasma drug concentration and drug activity, leading to potentiation of hypoglycemia. However, it has been shown that changes in protein binding do not have meaningful pharmacodynamics or clinical effects.[37] The second possible mechanism is via competition for the CYP2C9 hepatic metabolic pathway.[36] Because glimepiride, glipizide, and warfarin are all primarily metabolized via CYP2C9, larger doses of warfarin may limit the rate at which the sulfonylurea can be metabolized. However, there is no empirical evidence to support this mechanism, and we can only hypothesize based on the drugs' pharmacokinetic characteristics.

Our study has a number of limitations. First, medication utilization was not directly measured. Warfarin dose and International Normalized Ratio (INR) levels are potentially informative but cannot be measured in pharmacy claims. Our use of prescription fills as a proxy for utilization allowed for a large and representative sample, but may have introduced measurement error into the analysis. Such measurement error could have led to attenuation bias in our estimates of the relationship between concurrent warfarin / sulfonylurea use and hypoglycemia risk. Second, our findings may be confounded by unmeasured patient characteristics that are correlated with both warfarin use and hypoglycemia risk. Although we cannot definitively rule out such confounding, our analyses were robust to several specifications intended to address this issue. Third, it is possible that our results would not generalize beyond the elderly population.

While readers should be mindful of these limitations, our study has several important potential implications. A number of clinical drug databases note that there may be an interaction

between warfarin and glipizide / glimepiride. However, evidence supporting these warnings has been limited. This study provides the first direct real-world evidence that warfarin may interact with commonly used sulfonylureas to produce the serious adverse event of hypoglycemia requiring hospital care. This potential interaction has not been widely appreciated and health care professionals are not routinely alerted when patients on sulfonylureas initiate treatment with warfarin.

Our study suggests a role for increased pharmacovigilance in individuals receiving both warfarin and the sulfonylureas glipizide or glimepiride, particularly among new users of warfarin who are on these sulfonylureas. For instance, in its development of ambulatory care medication quality measures, the National Quality Forum has endorsed a warfarin-specific measure that requires INR testing within 3 to 7 days of initiating anti-infective agents to lower the risk of major bleeding.[38] Similar measures may be expanded to include INR testing among patients on glipizide or glimepiride who are initiated on warfarin.

Medication therapy management (MTM) services may play an important role in monitoring patients concurrently using glipizide or glimepiride and warfarin.[39-41] MTM services focus on the evaluation and assessment of a patient's entire medication regimen. Within Medicare Part D prescription drug plans, certain enrollees with multiple chronic conditions are entitled to MTM services from a health care professional.[42] The American Pharmacists Association recommends that MTM services be considered for any individual with actual or potential medication-related problems, regardless of the number of medications, specific disease states, or health plan coverage.[43] In this particular context, the role of MTM in preventing hypoglycemic events could result in significant clinical and economic gains. The average length of stay among Medicare beneficiaries hospitalized with a principal diagnosis of hypoglycemia

was nearly four days during the period studied here.[44] With an average charge of $20,500 for these stays, there are substantial cost savings to be realized from prevention of these events.

In summary, concurrent use of warfarin and the second-generation sulfonylureas glipizide and glimepiride may increase the risk of significant hypoglycemic events in older individuals, with a pronounced effect when warfarin is first used. While these events are rare, clinicians should be aware of the potential increased risk for hypoglycemia among individuals concurrently receiving warfarin and glipizide or glimepiride, and closely monitor this population, especially patients who are newly initiated on warfarin.

## DECLARATIONS

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JAR, CG, and DG made substantial contributions to the conception and design of this project. JAR, CG, AJ, DG, BW and AP assisted with data acquisition, analysis, and interpretation of data for this manuscript. JAR, CG and AJ drafted the manuscript, and DG, BW and AP revised it critically for important intellectual content. JR is the guarantor of this work. All authors approved of the final version to be published.

All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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## Table 1: Characteristics of study population

| | Full sample | Patients with any warfarin use | Patients with no warfarin use | p value |
|---|---|---|---|---|
| No. persons | 465918 | 71533 | 394385 | - |
| Age, mean (sd) | 74.6 (7.5) | 75.9 | 74.4 | < 0.01 |
| Male, % | 42.2% | 45.5% | 41.6% | < 0.01 |
| White, % | 75.6% | 84.9% | 74.0% | < 0.01 |
| Comorbidities, % | | | | |
| Acute myocardial infarction or ischemic heart disease | 55.2% | 70.8% | 52.3% | < 0.01 |
| Alzheimer's disease or dementia | 14.2% | 14.2% | 14.2% | 0.871 |
| Asthma | 11.3% | 13.9% | 10.9% | < 0.01 |
| Atrial fibrillation | 13.8% | 49.6% | 7.3% | < 0.01 |
| Cancer (breast, colorectal, endometrial, lung or prostate) | 12.4% | 14.7% | 11.9% | < 0.01 |
| Chronic kidney disease | 23.5% | 29.8% | 22.3% | < 0.01 |
| Chronic obstructive pulmonary disease | 23.5% | 29.8% | 22.3% | < 0.01 |
| Congestive heart failure | 35.8% | 56.9% | 32.0% | < 0.01 |
| Depression | 24.6% | 26.5% | 24.2% | < 0.01 |
| Dyslipidemia | 76.8% | 80.1% | 76.2% | < 0.01 |
| Hypertension | 88.5% | 92.3% | 87.8% | < 0.01 |
| Osteoporosis | 12.3% | 12.6% | 12.2% | < 0.01 |
| Rheumatoid / Osteoarthritis | 44.4% | 50.8% | 43.2% | < 0.01 |
| Stroke / TIA | 16.4% | 23.2% | 15.1% | < 0.01 |
| Ever hospitalized for hypoglycemia, % | 0.092% | 0.144% | 0.083% | < 0.01 |
| Ever treated in ED for hypoglycemia but not admitted, % | 0.363% | 0.466% | 0.345% | 0.028 |
| Ever hospitalized or treated in ED for hypoglycemia, % | 0.453% | 0.603% | 0.426% | < 0.01 |

Notes: Age and comorbidities are measured at time of first appearance in sample. p values reflect comparison between patients with and without any warfarin use.

**Table 2: Hypoglycemia hospitalization or ED visit during periods of warfarin use**

| | Full sample | Person-quarters with warfarin use | Person-quarters without warfarin use | p value |
|---|---|---|---|---|
| Person-quarters, n | 4355418 | 416479 | 3938939 | - |
| Person-quarters with hospitalization for hypoglycemia, n (%) | 442 (0.010%) | 77 (0.018%) | 365 (0.009%) | < 0.01 |
| Person-quarters with ED visit for hypoglycemia but not admitted, n (%) | 1755 (0.040%) | 217 (0.052%) | 1538 (0.039%) | < 0.01 |
| Person-quarters with hospitalization or ED visit for hypoglycemia, n (%) | 2197 (0.050%) | 294 (0.071%) | 1903 (0.048%) | < 0.01 |

Note: p values reflect comparison between person-quarters with and without any warfarin use.

**Figure 1: Odds ratios for hypoglycemia hospitalization or ED visit in person-quarters with concurrent warfarin / sulfonylurea use**

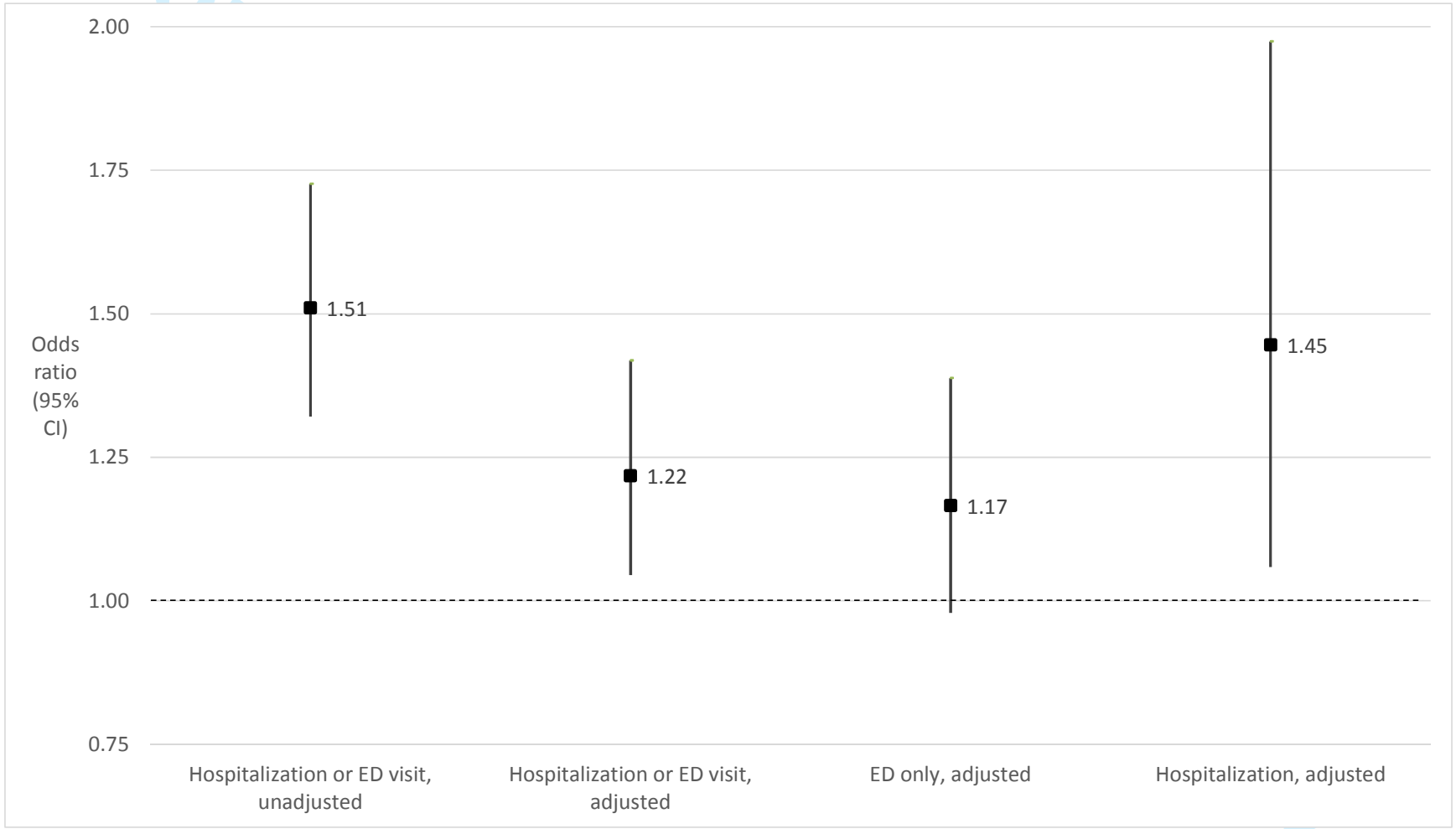
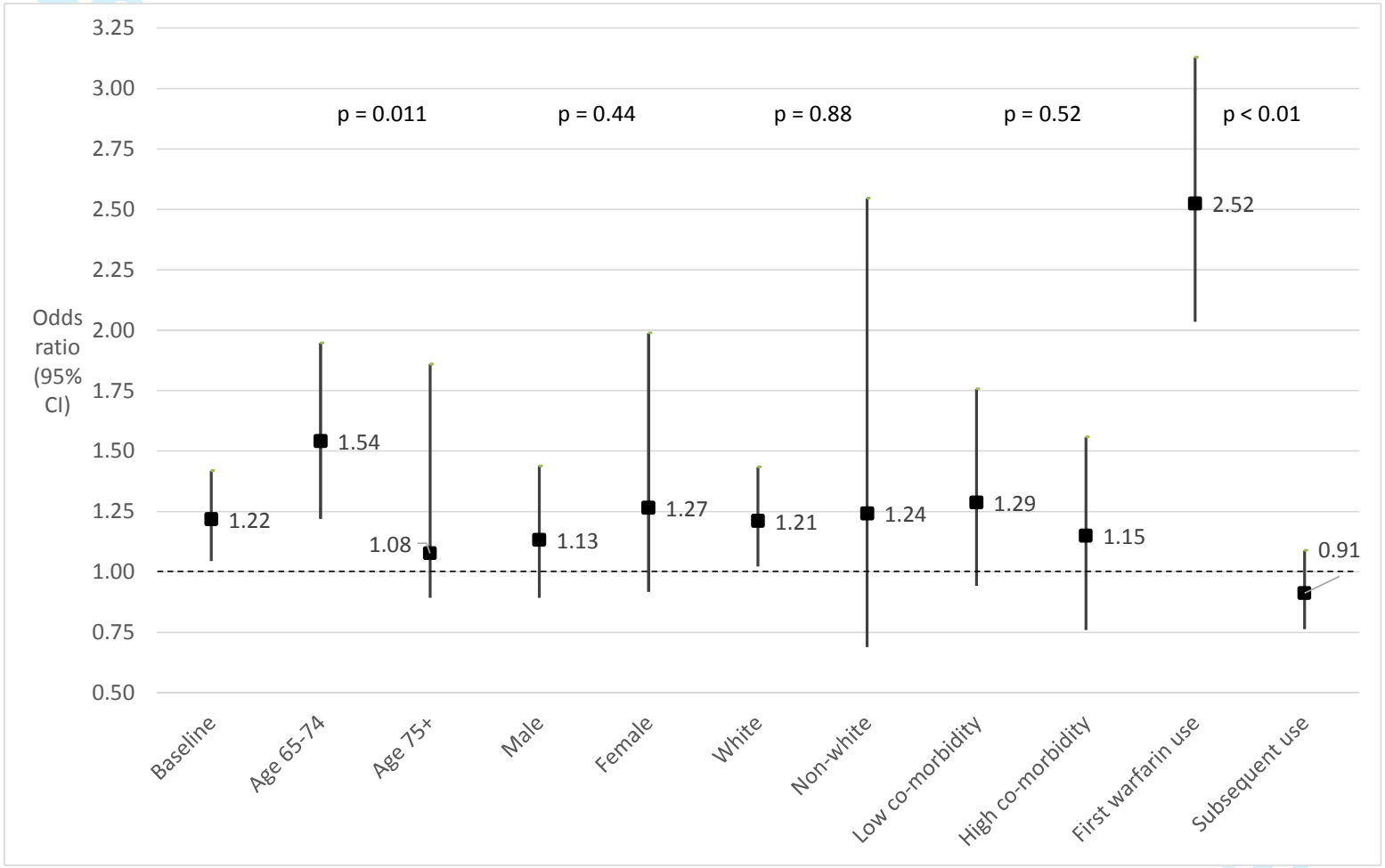
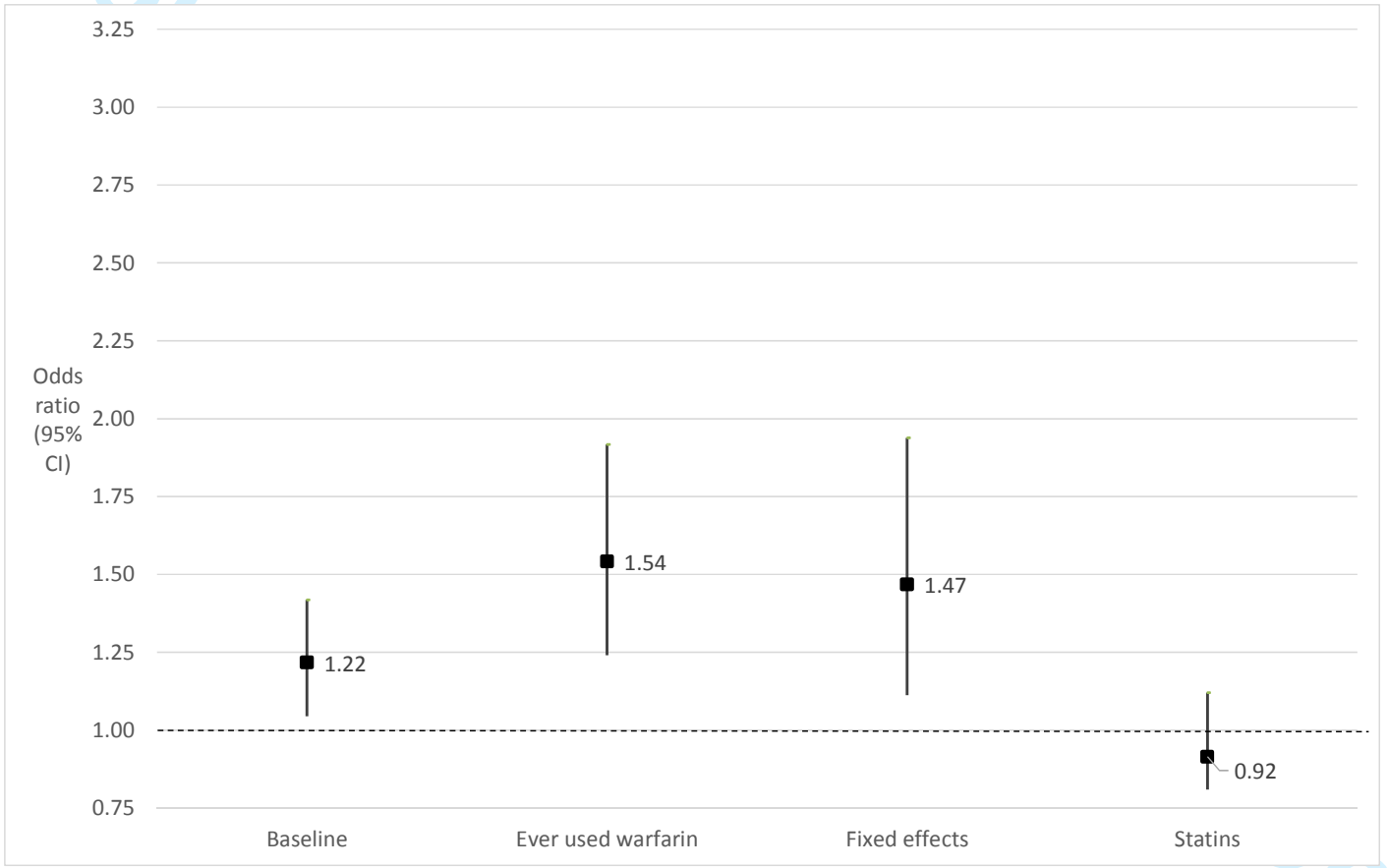


**Figure 2: Odds ratio for hypoglycemia hospitalization or ED visit in person-quarters with concurrent warfarin / sulfonylurea use, by subgroup**




Note: p values correspond to hypothesis tests of equal odds ratio. Low comorbidity was defined by having less than the median total number of combordities per individual in the sample.

**Figure 3: Odds ratio for hypoglycemia hospitalization or ED visit associated with concurrent warfarin / sulfonylurea use, sensitivity analysis**




Notes: *Ever used warfarin* analysis compares person-quarters with concurrent warfarin / sulfonylurea use to person-quarters without concurrent use within the subsample of patients who ever used warfarin. *Fixed effects* analysis compared hypoglycemia rates during periods of concurrent warfarin / sulfonylurea use and non-use within the same beneficiary over time. *Statin* analysis compares hypoglycemia rates according to concurrent sulfonylurea / statin use based on conditional fixed effects logistic specification.

**Appendix Table 1: Odds ratios for hypoglycemia hospitalization or ED visit, complete results**

| *Covariate* | *Odds ratio (95% CI)* |
|---|---|
| Constant | 6.81E-6 (3.61E-6 - 1.29E-5) |
| Warfarin use | 1.22 (1.04 - 1.42) |
| Age | 1.01 (1.01 - 1.02) |
| Female | 1.34 (1.21 - 1.49) |
| Non-white race / ethnicity | 1.69 (1.53 - 1.87) |
| Acute myocardial infarction or ischemic heart disease | 1.20 (1.06 - 1.35) |
| Alzheimer's disease or dementia | 1.82 (1.63 - 2.03) |
| Asthma | 0.85 (0.74 - 0.97) |
| Atrial fibrillation | 0.96 (0.84 - 1.10) |
| Cancer (breast, colorectal, endometrial, lung or prostate) | 0.92 (0.80 - 1.05) |
| Chronic kidney disease | 1.91 (1.73 - 2.10) |
| Chronic obstructive pulmonary disease | 1.33 (1.20 - 1.48) |
| Congestive heart failure | 1.45 (1.30 - 1.62) |
| Depression | 1.15 (1.04 - 1.27) |
| Dyslipidemia | 0.91 (0.79 - 1.04) |
| Hypertension | 1.39 (1.05 - 1.84) |
| Osteoporosis | 1.05 (0.93 - 1.18) |
| Rheumatoid / Osteoarthritis | 1.14 (1.03 - 1.26) |
| Stroke / TIA | 1.29 (1.16 - 1.44) |
| $\sigma$ | 1.93 (1.80 - 2.06) |
| $\sigma^2/(\sigma^2+\theta^2)$ | 0.53 (0.50 - 0.56) |
| *Other Statistics* | |
| Person-quarters, n | 4,355,418 |
| Persons, n | 465,918 |
| Log likelihood value | -18039.44 |

Notes: Age and comorbidities are measured as of beginning of each calendar-quarter analyzed. $\sigma$ is the standard deviation of beneficiary-level random effects; $\theta$ is the standard deviation of the idiosyncratic disturbance. Results correspond to *ED visit or admission, adjusted* in Figure 1.