Association between use of warfarin with common sulfonylureas and serious hypoglycemic events: retrospective cohort analysis

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ABSTRACT

STUDY QUESTION

Is warfarin use associated with an increased risk of serious hypoglycemic events among older people treated with the sulfonylureas glipizide and glimepiride?

METHODS

This was a retrospective cohort analysis of pharmacy and medical claims from a 20% random sample of Medicare fee for service beneficiaries aged 65 years or older. It included 465 918 beneficiaries with diabetes who filled a prescription for glipizide or glimepiride between 2006 and 2011 (4 355 418 person quarters); 71 895 (15.4%) patients also filled a prescription for warfarin (416 479 person quarters with warfarin use). The main outcome measure was emergency department visit or hospital admission with a primary diagnosis of hypoglycemia in person quarters with concurrent fills of warfarin and glipizide/glimepiride compared with the rates in quarters with glipizide/glimepiride fills only, Multivariable logistic regression was used to adjust for individual characteristics. Secondary outcomes included fall related fracture and altered consciousness/mental status.

SUMMARY ANSWER AND LIMITATIONS

In quarters with glipizide/glimepiride use, hospital admissions or emergency department visits for hypoglycemia were more common in person quarters with concurrent warfarin use compared with quarters without warfarin use (294/416 479 *v* 1903/3 938 939; adjusted odds ratio 1.22, 95% confidence interval 1.05 to 1.42). The risk of hypoglycemia associated with concurrent use was higher among people using warfarin for the first time, as well as in those aged 65-74 years. Concurrent use of warfarin and glipizide/glimepiride was also associated with hospital admission or emergency department visit for fall related fractures (3919/416 479 *v* 20 759/3 938 939; adjusted odds ratio 1.47, 1.41 to 1.54) and altered consciousness/mental status (2490/416 479 *v* 14 414/3 938 939; adjusted odds ratio 1.22, 1.16 to 1.29). Unmeasured factors could be correlated with both warfarin use and serious hypoglycemic events, leading to confounding. The findings may not generalize beyond the elderly Medicare population.

WHAT THIS STUDY ADDS

A substantial positive association was seen between use of warfarin with glipizide/glimepiride and hospital admission/emergency department visits for hypoglycemia and related diagnoses, particularly in patients starting warfarin. The findings suggest the possibility of a significant drug interaction between these medications.

FUNDING, COMPETING INTERESTS, DATA SHARING

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Antidiabetic and anticoagulant drugs account for most adverse drug events requiring emergency hospital admission among older Americans

Warfarin may potentiate the hypoglycemic action of commonly prescribed sulfonylurea drugs (glipizide and glimepiride) in people with type 2 diabetes

WHAT THIS STUDY ADDS

A substantial positive association was seen between use of warfarin with glipizide/glimepiride and hospital admission/emergency department visits for hypoglycemia and related diagnoses, particularly in patients starting warfarin

Clinicians should be aware of the potential increased risk for serious hypoglycemic events among patients concurrently receiving glipizide or glimepiride and warfarin and should closely monitor this population

Introduction

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

Despite known interactions between warfarin and several drugs,[15] and the fact that both warfarin and oral hypoglycemic drugs account for the plurality of admissions for adverse drug events, considerable uncertainty exists about drug interactions between these two classes of drug. Two clinical drug references advise that warfarin may potentiate the hypoglycemic effects of the sulfonylureas glipizide and glimepiride,[16 17] but no large scale empirical evidence exists to support this advisory. Rather, existing evidence for a potential interaction of warfarin with 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 of warfarin with glipizide or glimepiride.[18] (One database advises that glyburide may increase the risk of bleeding from warfarin.[17])

In light of the limited evidence about a potential drug-drug interaction between warfarin and long acting

sulfonylureas, we analyzed rates of hospital admission and emergency department visits for hypoglycemia and related diagnoses among a large national sample of Medicare beneficiaries aged 65 years or older with type 2 diabetes who were concurrently treated with warfarin plus glipizide or glimepiride compared with 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 2006-11. We used the chronic conditions segment of the Master Beneficiary Summary file to identify Medicare beneficiaries aged 65 years or older with type 2 diabetes, derived from a validated algorithm using ICD-9 (international classification of diseases, 9th revision) codes in inpatient and outpatient claims within a two year window.[19] We restricted our analysis to people with at least one filled prescription for glipizide or glimepiride, identified in Medicare Part D pharmacy claims by national drug codes whose generic names included these medicines, in some cases in combination with others.[20] We used the Medicare Provider Analysis and Review file to identify admissions to acute short term hospitals; we identified emergency department visits on the basis of appropriate revenue center codes within claims in the Medicare Outpatient file.

Primary outcomes

The unit of analysis was a person quarter. Our primary outcome was whether a person was admitted to hospital or treated in the emergency department for hypoglycemia in a given calendar quarter. We analyzed each of these outcomes separately and in combination. In secondary analyses, we considered emergency department visits/hospital admissions for fall related fractures and altered consciousness/mental status, which have been linked to hypoglycemia.[21-23]

We identified hypoglycemia on the basis of ICD-9 principal diagnosis codes of 251.0, 251.1, or 251.2.[24] Identification of altered consciousness/mental status was based on any diagnosis code of 780.0, 780.02, 780.09, or 780.97. To identify fall related fractures, we followed the literature in identifying a diagnosis code for a fracture site likely to be caused by a fall (for example, hip), excluding cases with an external injury code for a cause other than a fall;[21] details are provided in appendix table 1.

Analysis

We identified all person quarters in which a pharmacy claim for either glipizide or glimepiride occurred. 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 hospital admission or emergency department visit for serious hypoglycemic events. We excluded those person quarters in which the person did not have a previous medical claim for diabetes in any previous calendar quarter.[25] We also excluded person quarters in which a person was not enrolled in both Medicare Part A and Part B during each month he or she was alive during the quarter.

In our main analyses, we estimated a multivariable logistic regression of the relation between hospital admission or emergency department visit and use of warfarin among Medicare beneficiaries aged 65 years or older with type 2 diabetes treated with glipizide or glimepiride.[26 27] Regressions were estimated at the person quarter level. Our model adjusted for age, sex, race, and 14 chronic comorbidities. Demographic data were missing for 0.22% (1042/466 960) of beneficiaries; we analyzed complete cases. To account for serial correlation in outcomes across quarters, the model included random effects at the person level.[28-30] This model was estimated for hypoglycemia, fall related fractures, and altered consciousness/mental status; for the latter two of these, we did an additional analysis that excluded person quarters with a hospital admission or emergency department visit for hypoglycemia.

We then estimated the association of our primary outcome with concurrent use of warfarin and glipizide/glimepiride 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), whether a quarter was the first in which warfarin was prescribed (excluding a person's first quarter with glipizide/glimepiride if warfarin was also filled), and concurrent use of a β blocker. We hypothesized that hypoglycemia would be more common in the initial quarter of concurrent use of warfarin and glipizide/glimepiride, when appropriate titration of warfarin dosing is most uncertain.[31] We also hypothesized that concurrent use of a β blocker could mask any effect from warfarin use.

Additional analyses

Among patients treated with glipizide or glimepiride, those using warfarin may have characteristics that are associated with both warfarin use and the risk of hypoglycemia, which could confound the estimated association between warfarin use and risk of hospital admission or emergency department visit for hypoglycemia. We tackled this problem of confounding through several additional analyses. Firstly, we replaced each person's current comorbidities with the previous year's risk score from the CMS Hierarchical Condition Categories model (version 21, 2010 clinical revision, community enrollee specification).[32] Secondly, we adjusted for concurrent fills of several diabetes drugs (insulin, thiazolidinediones, metformin, meglitinides, and glyburide), which could affect (or proxy for) risk of hypoglycemia. Thirdly, because unmeasured characteristics may differ between people 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 use of warfarin with glipizide/glimepiride and hypoglycemia by comparing rates of hospital admission and emergency department visits for hypoglycemia in those calendar

quarters in which warfarin was used with those in which warfarin was not used.

Fourthly, 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 use of warfarin with glipizide/glimepiride and hypoglycemia by comparing quarters of warfarin use with those of non-use within the same person. This model was limited by design to the subsample of people who were observed over multiple quarters and whose warfarin use and outcomes varied across quarters.[33-36] Fifthly, we did a falsification analysis to assess whether our findings were likely to be explained by unmeasured confounding.[37-39] Specifically, among patients treated with glipizide or glimepiride, we estimated whether concurrent use of these sulfonylureas and statins was also associated with risk of hypoglycemia requiring hospital admission or emergency department 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 use of warfarin with glipizide/glimepiride would more likely reflect unobserved characteristics among patients using drugs more generally as opposed to a specific effect of warfarin use (of note, statins do not themselves interact with sulfonylureas).[40 41]

Finally, we analyzed risk of hypoglycemia when warfarin was used concurrently with other diabetes drugs. Warfarin could appear to interact with glipizide/glimepiride only because it does interact with several foods,[15] resulting in dietary changes that increase (or decrease) hypoglycemia risk. An apparent interaction with low risk drugs (such as metformin and thiazolidinediones[42]) would be inconsistent with a real interaction with glipizide/glimepiride. Similarly, we would not expect to detect an interaction with high risk drugs for which no evidence of a warfarin interaction exists—in particular, insulin and glyburide.[42]

We used Stata version 13 for all analyses. Hypothesis tests were conducted with a probability of 0.025 in each tail, or a P value of 0.05.

Patient involvement

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design and implementation of the study. There are no plans to involve patients in the dissemination of results.

Results

Over 2006-11, the 20% Medicare database included 12 412 673 beneficiaries. Our analysis sample included a total of 465 918 fee for service beneficiaries aged 65 or over with type 2 diabetes who filled at least one prescription for either glipizide or glimepiride, of whom 71 533 (15.4%) used warfarin at some point during the study period (table 1). Compared with 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. Hospital admission and emergency department visits were rare but more

Table 1 | Characteristics of study population. Values are numbers (percentages) unless stated otherwise

Characteristics	Full sample (n=465 918)	Any warfarin use (n=71 533)	No warfarin use (n=394 385)	P value*
Mean (SD) age†, years	74.6 (7.5)	75.9 (7.3)	74.4 (7.5)	<0.01
Male sex	196 758 (42.2)	32 552 (45.5)	164 206 (41.6)	<0.01
White ethnicity	352 409 (75.6)	60 731 (84.9)	291 678 (74.0)	<0.01
Comorbidities†:				
Acute myocardial infarction or ischemic heart disease	257 018 (55.2)	50 678 (70.8)	206 340 (52.3)	<0.01
Alzheimer's disease or dementia	66 026 (14.2)	10 151 (14.2)	55 875 (14.2)	0.871
Asthma	52 754 (11.3)	9914 (13.9)	42 840 (10.9)	<0.01
Atrial fibrillation	64 214 (13.8)	35 458 (49.6)	28 756 (7.29)	<0.01
Cancer (breast, colorectal, endometrial, lung, or prostate)	57 565 (12.4)	10 509 (14.7)	47 056 (11.9)	<0.01
Chronic kidney disease	109 280 (23.5)	21 337 (29.8)	87 943 (22.3)	<0.01
Chronic obstructive pulmonary disease	118 254 (25.4)	24 189 (33.8)	94 065 (23.9)	<0.01
Congestive heart failure	166 988 (35.8)	40 675 (56.9)	126 313 (32.0)	<0.01
Depression	114 473 (24.6)	18 964 (26.5)	95 509 (24.2)	<0.01
Dyslipidemia	357 962 (76.8)	57 326 (80.1)	300 636 (76.2)	<0.01
Hypertension	412 322 (88.5)	66 007 (92.3)	346 315 (87.8)	<0.01
Osteoporosis	57 094 (12.3)	8999 (12.6)	48 095 (12.2)	<0.01
Rheumatoid arthritis/osteoarthritis	206 651 (44.4)	36 320 (50.8)	170 331 (43.2)	<0.01
Stroke/transient ischemic attack	76 271 (16.4)	16 611 (23.2)	59 660 (15.1)	<0.01
Ever admitted to hospital for hypoglycemia	430 (0.092)	103 (0.144)	327 (0.083)	<0.01
Ever treated in ED for hypoglycemia but not admitted	1693 (0.363)	333 (0.466)	1360 (0.345)	0.028
Ever admitted or treated in ED for hypoglycemia	2111 (0.453)	431 (0.603)	1680 (0.426)	<0.01

ED=emergency department.
*For comparison between patients with and without any warfarin use.
†Measured at time of first appearance in sample.

Table 2 | Hospital admissions or emergency department (ED) visits for hypoglycemia during periods of warfarin use. Values are numbers (percentages) unless stated otherwise

Person quarters	Full sample (n=4 355 418)	Person quarters with warfarin use (n=416 479)	Person quarters without warfarin use (n=3 938 939)	P value*
With hospital admission for hypoglycemia	442 (0.010)	77 (0.018)	365 (0.009)	<0.01
With ED visit for hypoglycemia but not admitted	1755 (0.040)	217 (0.052)	1538 (0.039)	<0.01
With hospital admission or ED visit for hypoglycemia	2197 (0.050)	294 (0.071)	1903 (0.048)	<0.01

*For comparison between person quarters with and without any warfarin use.

common among patients who ever used warfarin than among those who did not.

Our primary unit of observation in the analysis was the person quarter level. Of 4 355 418 overall person quarters, hospital admissions and emergency department visits without admission for hypoglycemia occurred in 0.010% (442/4 355 418) and 0.040% (1755/4 355 418) of person quarters, respectively (table 2). Overall, 2111 people had an emergency department visit or admission for hypoglycemia, of whom 78 had multiple events. Concurrent use of warfarin and glipizide or glimepiride was common, with 9.6% (416 479/4 355 418) of person quarters involving warfarin use. Hospital admissions and emergency department visits for hypoglycemia were more common in person quarters in which warfarin was used than in quarters in which it was not (77/416 479 (0.018%) admissions for hypoglycemia in person quarters with warfarin use versus 365/3 938 939 (0.009%) in person quarters without warfarin use, unadjusted odds ratio 2.36 (95% confidence interval 1.74 to 3.21); 217/416 479 (0.052%) emergency department visits for hypoglycemia in person quarters with warfarin use versus 1538/3 938 939 (0.039%) in person quarters without warfarin use, unadjusted odds ratio 1.36 (1.17 to 1.58); unadjusted odds ratio for combined hospital admission or emergency department visit 1.51, 1.32 to 1.73).

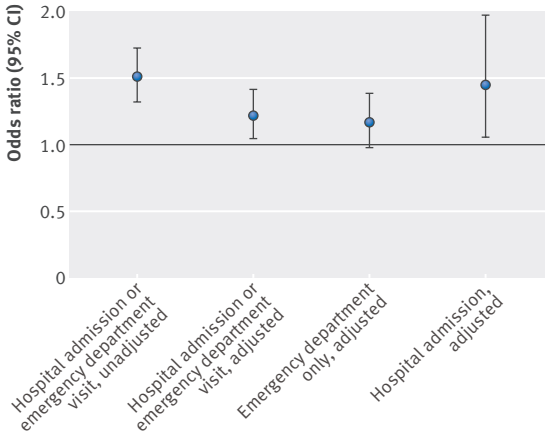

Fig 1 | Odds ratios for hospital admission or emergency department visit for hypoglycemia in person quarters with concurrent use of warfarin and glipizide/glimepiride

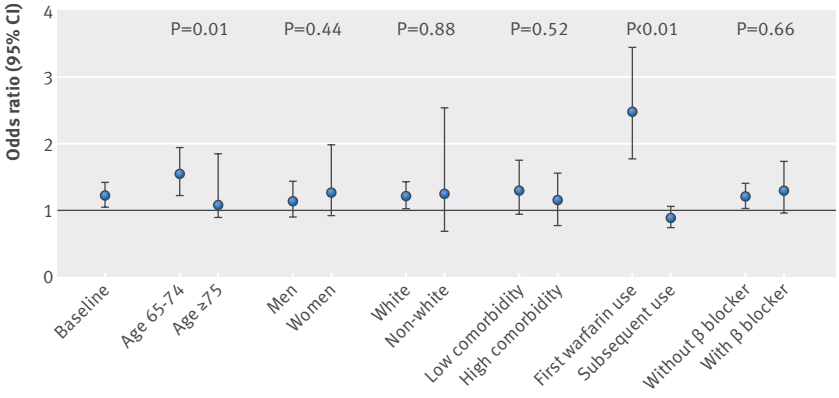

Fig 2 | Odds ratio for hospital admission or emergency department visit for hypoglycemia in person quarters with concurrent use of warfarin and glipizide/glimepiride, by subgroup. P values correspond to hypothesis tests of equal odds ratios. Low comorbidity is defined by having less than median total number of comorbidities per patient in sample

Multivariable analysis

In multivariable analysis, hospital admission or emergency department visit for hypoglycemia (combined outcome) was more likely in person quarters with concurrent use of warfarin and glipizide/glimepiride than in quarters without warfarin use (adjusted odds ratio 1.22, 1.05 to 1.42, as shown in figure 1, with complete regression results in appendix table 2). Concurrent use of warfarin and glipizide/glimepiride was associated with a higher rate of hospital admission for hypoglycemia (adjusted odds ratio 1.45, 1.06 to 1.97) and a rate of emergency department visits without a subsequent admission that trends toward significance (adjusted odds ratio 1.17, 0.98 to 1.39).

Subgroup analysis

In subgroup analysis (fig 2), the association between use of warfarin with glipizide/glimepiride and the combined outcome of hospital admission or emergency department visit for hypoglycemia was larger for person quarters in which a patient first used warfarin (adjusted odds ratio 2.47 (1.77 to 3.45) for first use versus 0.88 (0.74 to 1.05) for subsequent use; P<0.01 for the difference) and for patients aged 65-74 years (adjusted odds ratio 1.54 (1.22 to 1.95) for age 65-74 years versus 1.08 (0.89 to 1.86) for age 75 years and above; P=0.011 for the difference).

Additional analyses

The estimated association between use of warfarin with glipizide/glimepiride and the combined outcome of hospital admission or emergency department visit for hypoglycemia was robust to several sensitivity analyses (fig 3). Under an alternative approach to risk adjustment, the adjusted odds ratio was 1.19 (1.04 to 1.36), and

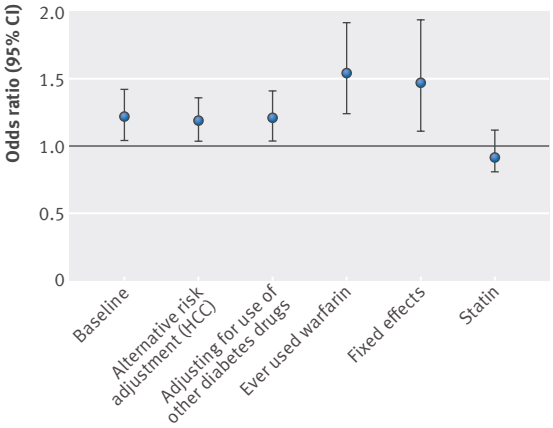

Fig 3 | Odds ratio for hospital admission or emergency department visit for hypoglycemia associated with concurrent use of warfarin and glipizide/glimepiride, sensitivity analysis. Alternative risk adjustment uses hierarchical condition categories (HCC), as described in methods section. Adjusting for use of other diabetes drugs includes concurrent fills in analysis. Ever used warfarin analysis compares person quarters with concurrent warfarin/sulfonylurea use with person quarters without concurrent use within subsample of patients who ever used warfarin. Fixed effects analysis compares hypoglycemia rates during periods of concurrent warfarin/sulfonylurea use and non-use within same beneficiary over time. Statin analysis compares hypoglycemia rates according to concurrent sulfonylurea/statin use based on conditional fixed effects logistic specification

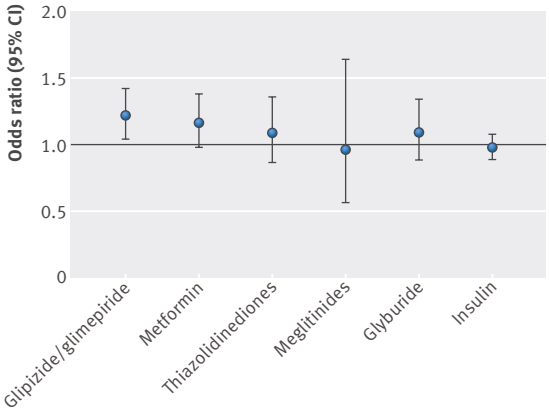

Fig 4 | Odds ratio for hospital admission or emergency department visit for hypoglycemia associated with concurrent use of warfarin and various diabetes drugs. For each analysis, the sample includes person quarters with filled prescription of relevant diabetes drug

it was 1.21 (1.04 to 1.41) when we adjusted for concurrent use of other drugs (whose use is characterized in appendix table 3). Furthermore, use of warfarin with glipizide/glimepiride was associated with higher rates of hospital admission for hypoglycemia when analysis was restricted to only those beneficiaries who ever used warfarin (adjusted odds ratio 1.54, 1.24 to 1.92) and in conditional fixed effects analysis that compared hypoglycemia rates in periods of concurrent use with rates in periods without warfarin use for the same beneficiary over time (adjusted odds ratio 2.91, 1.58 to 5.35). Our findings were also robust to a falsification analysis. Specifically, we found no association between the combined outcome of hospital admission or emergency department visit for hypoglycemia and concurrent use of glipizide/glimepiride with statins.

For other diabetes drugs, concurrent use of warfarin was not associated with the combined outcome of hospital admission or emergency department visit for hypoglycemia (fig 4). For example, the adjusted odds ratio was 1.08 (0.86 to 1.36) for thiazolidinediones and 0.98 (0.89 to 1.08) for insulin. Additional detail on these analyses is reported in appendix table 4.

Use of warfarin with glipizide/glimepiride was associated with other hypoglycemia related diagnoses. For fall related fractures, hospital admissions and emergency department visits were more common in person quarters in which warfarin was used than in quarters in which it was not (3919/416 479 (0.941%) in person quarters with warfarin use versus 20 759/3 938 939 (0.527%) in person quarters without (table 3). In multivariable analysis (fig 5), the adjusted odds ratio was 1.47 (1.41 to 1.54). For altered consciousness/mental status, the adjusted odds ratio was 1.22 (1.16 to 1.29). Results were similar when person quarters with an admission or emergency department visit for hypoglycemia were excluded, as shown in appendix figure 1.

In absolute terms, the probability of the combined outcome of hospital admission or emergency department visit for a fall related fracture is predicted to increase with concurrent warfarin use from 0.318% to 0.467% per quarter (these calculations are described in appendix note 1). For hypoglycemia and altered consciousness/mental status, the risk per quarter increases by 0.002% and 0.038%, respectively. For any of the three diagnoses, the adjusted odds ratio of a hospital admission or emergency department visit with concurrent use of warfarin and glipizide/glimepiride was 1.38 (1.33 to 1.42) (fig 5).

Discussion

We found higher rates of hospital admission and emergency department visits for hypoglycemia and related diagnoses 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 sulfonylurea glipizide or glimepiride, compared with either of these sulfonylureas alone. The association was strongest in magnitude for people using warfarin for the first time and for those aged 65-74 years. Our findings were robust to an alternative measure of risk and to adjustment for use of other diabetes drugs. Our findings were also robust to a comparison within individuals of quarters with concurrent use versus quarters without warfarin use. We found no association of rates of hypoglycemia with concurrent use of statins with glipizide/glimepiride or with use of warfarin and other diabetes drugs. These analyses suggest that the observed relation between use of warfarin with glipizide/glimepiride and risk of hypoglycemia may reflect a drug-drug interaction rather than unmeasured characteristics of

Table 3 | Incidence of fall related fractures and altered consciousness/mental status. Values are numbers (percentages) unless stated otherwise

Person quarters with hospital admission or ED visit	Full sample (n=4 355 418)	Person quarters with warfarin use (n=416 479)	Person quarters without warfarin use (n=3 938 939)	P value
Fall related fracture	24 678 (0.567)	3919 (0.941)	20 759 (0.527)	<0.001
Altered consciousness/mental status	16 904 (0.388)	2490 (0.598)	14 414 (0.366)	<0.001

Corresponds to adjusted analysis in fig 5.
ED=emergency department.

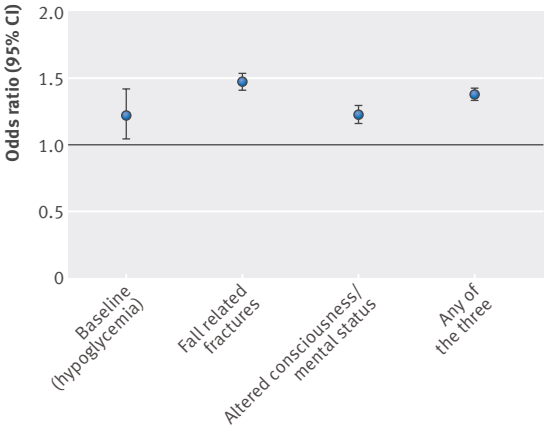

Fig 5 | Odds ratio for hospital admission or emergency department visit for hypoglycemia related diagnoses associated with concurrent use of warfarin and glipizide/glimepiride

patients that are correlated with both warfarin use and hypoglycemia risk.

Comparison with other studies

Existing evidence on the incidence of adverse drug events offers perspective on our findings. For example, Gurwitz and colleagues analyzed Medicare managed care beneficiaries treated at a multispecialty group practice in 1999-2000 and found a rate of 8.0 events per thousand person years, which were serious to fatal (including fall with fracture) and preventable (having been caused by an error or otherwise avoidable).[43] More recently, Budnitz and colleagues estimated that unintentional drug overdoses, adverse effects at recommended doses, and allergic reactions led to 265 802 hospital admissions and emergency department visits among older US residents in 2010, implying a rate of 6.6 events per thousand person years.[8] Among older Medicare beneficiaries using glipizide/glimepiride, our analysis indicates that the concurrent use of warfarin is associated with approximately 8.8 adverse events per thousand person years, in terms of hospital admission or an emergency department visit for hypoglycemia, fall related fracture, or altered consciousness/mental status.

Potential mechanisms

Although the underlying mechanism of action for an interaction between warfarin and glipizide/glimepiride is unclear, existing evidence suggests two possible mechanisms for increased risk of hypoglycemia. The first is through displaced protein binding, as seen with first generation sulfonylureas (acetohexamide, chlorpropamide, tolazamide, and tolbutamide).[44] This interaction occurs when a second drug (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, changes in protein binding have been shown not to have meaningful pharmacodynamics or clinical effects.[45] The second possible mechanism is through competition for the CYP2C9 hepatic metabolic pathway.[44] Because glimepiride, glipizide, and warfarin are all primarily metabolized by CYP2C9, larger doses of warfarin may limit the rate at which the sulfonylurea can be metabolized. However, no empirical evidence exists to support this mechanism, and we can only hypothesize on the basis of the drugs' pharmacokinetic characteristics.

Limitations of study

Our study has some limitations. Firstly, drug use was not directly measured. Warfarin dose and international normalized ratio values are potentially informative but cannot be measured in pharmacy claims. Our use of prescription fills as a proxy for use allowed for a large and representative sample but may have introduced measurement error into the analysis. Also, some patients may have first used warfarin concurrently with glipizide/glimepiride before enrollment in Medicare. Such sources of measurement error could have led to attenuation bias in our estimates of the relation between use of warfarin with glipizide/glimepiride and risk of hypoglycemia. Secondly, our findings may be confounded by unmeasured characteristics of patients 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 minimize this problem. Thirdly, our results may not be generalizable beyond the elderly population.

Conclusions and policy implications

Although readers should be mindful of the above limitations, our study has several important potential implications. Several clinical drug databases note that an interaction may occur 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 or

related outcomes requiring hospital care. This potential interaction has not been widely appreciated, and healthcare professionals are not routinely alerted when patients on sulfonylureas start treatment with warfarin.

Our study suggests a role for increased pharmacovigilance in people receiving both warfarin and the sulfonylurea glipizide or glimepiride. In its development of ambulatory care drug quality measures, the National Quality Forum has endorsed a warfarin specific measure that requires international normalized ratio testing within three to seven days of starting anti-infective agents to lower the risk of major bleeding.[46] It has also endorsed a measure of the rate of severe hypoglycemia following administration of glipizide, glimepiride, and other antidiabetic drugs within a hospital.[46] Such measures may be expanded to include glycemic monitoring among patients taking glipizide or glimepiride who start warfarin in an ambulatory setting. A workgroup of the American Diabetes Association and American Endocrine Society has emphasized the importance of clinical surveillance and glucose monitoring and noted that older people are particularly vulnerable to harm from hypoglycemia.

Medication therapy management (MTM) services may play an important role in monitoring patients concurrently using glipizide or glimepiride and warfarin.[47-49] MTM services focus on the evaluation and assessment of a patient's entire drug regimen. Within Medicare Part D prescription drug plans, certain enrollees with multiple chronic conditions are entitled to MTM services from a healthcare professional.[50] The American Pharmacists Association recommends that MTM services be considered for any patient with actual or potential drug related problems, regardless of the number of drugs, specific disease states, or health plan coverage.[51] It is noteworthy that warfarin treatment guidelines have called for lower initial dosing among people aged 75 or older to mitigate the risk of bleeding[52]; our findings suggest that lower dosing may also be appropriate for those aged 65-74 who start warfarin while taking glipizide/glimepiride to treat diabetes.

In this particular context, the role of MTM in preventing hypoglycemic events could result in important clinical and economic gains. For example, the average length of stay among Medicare beneficiaries admitted to hospital with a principal diagnosis of hypoglycemia was nearly four days during the period studied here.[53] With an average charge of $20 500 (£13 400; €19 200) for these stays, there are substantial cost savings to be realized from prevention of hypoglycemia and related events. Likewise, treatment of medical conditions related to falls has been estimated to cost $12 300 (in 2002 dollars) per hospital stay.[54]

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

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Data sharing: No additional data available.

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