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Fibrate/Statin Initiation in Warfarin Users and Gastrointestinal Bleeding Risk

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Abstract

Purpose—To evaluate whether initiation of a fibrate or statin increases the risk of hospitalization for gastrointestinal bleeding in warfarin users.

Methods—We used Medicaid claims data (1999-2003) to perform an observational case-control study nested within person-time exposed to warfarin in those ≥ 18 years ($n=353,489$). Gastrointestinal bleeding cases were matched to 50 controls based on index date and state.

Results—Chronic warfarin users had an increased odds ratio of gastrointestinal bleeding upon initiation of gemfibrozil (1.88 [95% CI, 1.00-3.54] for the first prescription; 1.75 [95% CI, 0.77-3.95] for the second prescription); simvastatin (1.46 [95% CI, 1.03-2.07] for the first prescription; 1.60 [95% CI, 1.07-2.39] for the second prescription); or atorvastatin (1.39; [95% CI, 1.07-1.81] for the first prescription; 1.05 [95% CI, 0.73-1.52] for the second prescription). In contrast, no increased risk was found with pravastatin initiation (0.75; [95% CI, 0.39-1.46] for the first prescription; 0.90 [95% CI, 0.43-1.91] for the second prescription).

Conclusions—Initiation of a fibrate or statin that inhibits CYP3A4 enzymes, including atorvastatin, was associated with an increased risk of hospitalization for gastrointestinal bleeding. Initiation of pravastatin, which is mainly excreted unchanged, was not associated with an increased risk.

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Keywords

Pharmacoepidemiology; Drug-Drug Interactions

Introduction

Warfarin is highly efficacious at reducing the risk of thromboembolism, and with nearly 31 million dispensed outpatient prescription in 2004,[1] it is one of the top 20 medications prescribed in the US. A well recognized complication of warfarin therapy is the risk of potentially life-threatening bleeding, which results in approximately 29,000 emergency department visits per year.[1] Reducing this risk would have major clinical and public impact. Currently it is difficult to make definitive recommendations regarding the safety of coadministration of specific agents in patients receiving warfarin, because approximately 70% of the literature regarding warfarin-drug interactions consists of case reports.[2]

Nearly 30% of warfarin users are coprescribed an antihyperlipidemic agent.[3] Simvastatin (a CYP3A4 inhibitor[4]) is the third most commonly coadministered agent (about 13%[5]), even though coadministration of simvastatin can increase the International Normalized Ratio (INR) 1.27-fold in stable warfarin users,[6,7] and it is classified as an agent that could result in a major interaction with warfarin.[7,8] Fenofibrate (CYP3A4 inhibitor[9]) is classified as an agent that could result in a major interaction with warfarin, although this conclusion is based primarily on case reports.[8] Atorvastatin (CYP3A4 inhibitor[4]) is classified as an agent that does not interact with warfarin.[7,8] However, this conclusion seems to be based on only one study, which showed that coadministration of atorvastatin to 12 warfarin users did not result in a statistically significant increase in the INR after 15 days of treatment.[10] Another statin classified as non-interacting is pravastatin, which is not metabolized by CYP enzymes,[11] and might therefore be expected to be the least likely antihyperlipidemic agent to interact with warfarin. The evidence for other antihyperlipidemics is less clear, partly because the only available data for the interaction comes from product labels and case reports.[12-16]

The number of dispensed statin and warfarin prescriptions has nearly doubled over the last decade,[1,17] thereby increasing the opportunity for coadministration. Therefore, this study was designed to evaluate whether the risk of hospitalization for gastrointestinal (GI) bleeding is increased in persons receiving warfarin who are new initiators of a fibrate or statin. In addition, we wanted to assess the time course of any increased risk.

Methods

Setting and design

We performed an observational case-control study nested within the Medicaid programs of California, Florida, New York, Ohio, and Pennsylvania from 1999 to 2003. Medicaid is a series of state-run programs with joint federal-state funding that provide hospital, medical, and outpatient pharmaceutical coverage for certain categories of low-income and special-needs individuals. The claims data were obtained from the Centers for Medicare and Medicaid Services (CMS).[18] Because 15-17% of Medicaid beneficiaries are co-enrolled in Medicare, [19] we also obtained Medicare data on all dually-eligible persons. In total, the five states comprise about 13 million Medicaid enrollees, corresponding to about 35% of the US Medicaid population. A series of quality assurance analyses of the linked Medicaid and Medicare data found low rates of anomalies, suggesting that the data are of high quality.[20] This study was approved by the University of Pennsylvania's Committee on Studies Involving Human Beings, which granted waivers of informed consent and HIPAA authorization.

Eligible person-time in this case-control study

We included all person-time exposed to warfarin (outpatient prescriptions only) in those 18 years and older between January 1st, 1999 and December 1st, 2003. We assumed that the duration of a warfarin prescription (after combining warfarin prescriptions that were filled on the same day) was equivalent to the number of tablets dispensed, with a maximum duration of 30 days, since Medicaid prescriptions in California, Florida, New York, Ohio, and Pennsylvania are typically dispensed in 30-day increments. Both assumptions were confirmed by examining the frequency distribution of the number of pills dispensed and the number of days between subsequent prescriptions for the same enrollee. The observation period ended with either a hospitalization for GI bleeding or the end of the prescription period, whichever occurred first.

All warfarin users who filled an outpatient prescription for a fibrate or statin 90 days before or on the same day as their apparently first outpatient warfarin prescription were excluded, because the goal of this study was to examine the safety of new initiation of an antihyperlipidemic in patients already receiving warfarin.

Identification and validation of GI bleeding events

Cases consisted of all warfarin users who were hospitalized with an International Classification of Diseases, 9th edition (ICD-9) code for GI bleeding during eligible person-time exposed to warfarin. The hospital admission date was the index date for a case. The rationale for only including GI bleeding is that it is the most common type of major bleeding event in warfarin users.[21] Although CMS claims data are of good quality, it is well recognized that the validity of ICD-9 codes to identify specific outcomes of interest (in this case GI bleeding) generally needs to be assessed.[22] Therefore, we requested 150 hospital medical records of a (random) sample of inpatient GI bleeding events in our cohort of warfarin users. In total, we obtained 116 (77%) of the requested medical records. The medical records were reviewed by a trained researcher, and 10% of the samples were reviewed by a second reviewer (agreement = 100%). Three records were not evaluable because of missing data. The validation definition, a clinical verbatim diagnosis or statement of GI bleeding that originated in the outpatient setting, was met in 91 of the 113 charts (positive predicted value (PPV): 81% [95% confidence interval (CI): 72-87%]). The PPV was higher in GI bleeding cases who had a principal code (purportedly the diagnosis chiefly responsible for the hospital admission) for GI bleeding (PPV: 91% [95% CI, 80-97%]) than in persons with a non-principal code for GI bleeding (PPV: 71% [95% CI, 57-82%]) largely because some events with non-principal diagnoses originated in the hospital rather than the outpatient setting.

Identification of controls

Eligible controls consisted of all persons exposed to warfarin who had not been hospitalized with a diagnosis code for GI bleeding by the day of hospitalization of the GI bleeding case. We randomly selected up to 50 warfarin exposed controls for each case, matching on index date and state, using incidence density sampling.[23] The index date that was assigned to a control was the hospital admission date of the matched case.

Exposure to an antihyperlipidemic agent

We assumed that the average duration of an antihyperlipidemic prescription was 30 days, which was confirmed by examining the number of days between subsequent prescriptions for the same enrollee. We considered a warfarin user exposed to an antihyperlipidemic agent on the index date if a prescription for the antihyperlipidemic drug was filled 1 to 30 days prior to the index date.

For each person exposed to an antihyperlipidemic agent on the index date, we examined the time since initiation of the antihyperlipidemic agent. In particular, we classified each antihyperlipidemic-exposed warfarin user into the following categories based on the number of days since initiation of the antihyperlipidemic drug: 1 to 30 (1st antihyperlipidemic prescription), 31 to 60 (2nd antihyperlipidemic prescription), and 61 to 120 days (3rd or 4th antihyperlipidemic prescription). The rationale for this categorization is that we expected that the GI bleeding risk due to a drug-drug interaction would be highest during the first antihyperlipidemic prescription, and would decline subsequently because of depletion of susceptibles (i.e., patients who remain on the drugs are those who can tolerate them while those who are susceptible select themselves out of the population at risk).[24] We stopped follow-up time for each person if they had a gap of ≥ 180 days between consecutive antihyperlipidemic prescriptions.

The rationale for this stoppage is that we expected that antihyperlipidemic re-initiators might be less likely to experience a drug-drug interaction during the second course of antihyperlipidemic therapy. To avoid having an insufficient number of events in multivariable models, we did not examine any antihyperlipidemic drug with fewer than five exposed cases for any of the time categories.

To evaluate whether there was any remaining residual confounding, pravastatin was chosen as the reference drug. Pravastatin is mainly excreted unchanged, and therefore has the least potential of increasing the bleeding risk by a pharmacokinetic drug-drug interaction in warfarin users.

Ascertainment of potential confounding factors

All potential confounding factors are listed in Appendix 1. Potential confounding factors were identified with specific ICD-9 diagnostic codes for each of the disease confounders of interest using inpatient and outpatient claims data, and were ascertained based on the index date. We defined five types of potential confounding factors: demographic factors; chronic diseases, defined as diagnosis ever before the index date; current use of drugs that could potentially increase or decrease the bleeding risk, defined as a prescription in the 30 days prior to the index date; current use of drugs that could potentially interact with warfarin (class 1 and 2 of Drug Facts & Comparisons[8]), defined as a prescription in the 30 days prior to the index date; and current use of drugs that could potentially inhibit or induce CYP2C9, CYP3A4, and/or CYP1A2 enzymes, defined as a prescription in the 30 days prior to the index date (lists are available from the authors).

Statistical analysis

First, the incidence rate for the outcome of interest in our cohort of warfarin users was calculated. Conditional logistic regression was next used to estimate the matched odds ratios (ORs) and 95% CIs for the association between initiation of each antihyperlipidemic drug and hospital admission for GI bleeding in warfarin users. We then examined the need to retain the matching in the analysis, and because the matched and unmatched ORs were nearly identical, we did not retain the matching in subsequent analyses. Therefore, we used unconditional logistic regression to estimate the ORs of interest adjusting for age, sex, state, and race, referred to as the minimally adjusted model. Lastly, we examined each potential confounding factor individually; if a factor changed any of the ORs of interest by 10% or more, it was retained in the fully-adjusted model.[25] To determine whether a potential joint effect of confounding factors was missed, we compared the results of the fully adjusted model with the model that included all potential confounders.

We evaluated in secondary analyses whether the results differed between initiators and chronic warfarin users, defined as persons who had filled ≥ 3 warfarin prescription by the index date. The rationale for this secondary analysis is that chronic warfarin users are more likely to be on a stable warfarin dose and have less frequent INR measurements, and therefore may be more likely to experience bleeding complications due to a drug-drug interaction. In addition, we examined whether reducing the allowable gap time between consecutive antihyperlipidemic prescriptions from 180 to 90 days and excluding statins users with a gap of >180 days between consecutive warfarin prescriptions changed the results. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

In total, 353,489 warfarin users contributed a total of 304,661 person-years of observation. The incidence rate of GI bleeding was 4.84 per 100 person-years (95% CI, 4.76-4.92). We excluded 61,103 warfarin users (17%) who filled a prescription for an antihyperlipidemic drug in the 90 days before or on the same day as their first warfarin prescription. After this exclusion, 12,193 cases of hospitalization for GI bleeding remained. Table 1 presents the baseline characteristics of subjects by case-control status.

Table 2 presents the minimally and fully adjusted ORs for each antihyperlipidemic exposure period of interest, i.e. during the first, second, and third or fourth antihyperlipidemic prescription. The ORs for the primary time period expected for a warfarin-antihyperlipidemic interaction (i.e., 1st prescription) was 2.12 for gemfibrozil, 1.49 for fluvastatin, 1.47 for simvastatin, and 1.43 for atorvastatin in the minimally adjusted model. After adjusting for all factors that changed the OR of interest by $\geq 10\%$, the ORs were attenuated slightly, ranging from 1.29 to 1.96 but remained statistically significantly elevated, except for fluvastatin (Table 2). The OR for fluvastatin initiation was not statistically significantly elevated, most likely because there were few warfarin users who were coadministered fluvastatin. The OR for pravastatin (reference drug) was not elevated during the first prescription. There were insufficient numbers of exposed fenofibrate persons to obtain statistically reliable estimates. During second prescriptions all ORs were attenuated, except for pravastatin. During the third or fourth prescription, the fully adjusted ORs for fenofibrate, gemfibrozil, and simvastatin were even more attenuated, and ranged from 1.10 to 1.31. In contrast, atorvastatin initiators had a statistically significantly reduced odds ratio of hospitalization for GI bleeding during the third or fourth prescription compared to unexposed persons (OR=0.62 [95% CI, 0.46-0.85]). The results of the fully-adjusted model were not changed substantively compared to the model that included all variables shown in Appendix 1 (data not shown).

In a secondary analysis, we evaluated the odds of GI bleeding in chronic warfarin users, who are more likely to be on a stable warfarin dose (Figure 1). Consistent with a drug-drug interaction, the fully adjusted results were almost always higher in chronic warfarin than all warfarin users (Figure 1 and Table 2). In addition, among chronic warfarin users, the OR for GI bleeding was now statistically significantly elevated during the second simvastatin prescription (OR=1.60 [95% CI, 1.07-2.39]) and during the second fenofibrate prescription (OR=2.30 [95% CI, 1.01-5.22]). As expected, the GI bleeding OR in warfarin users who had filled only 1 or 2 warfarin prescription by the index day was close to 1 during the first simvastatin prescription (OR=0.99 [95% CI, 0.59-1.67]) and the first atorvastatin prescription (OR=1.03 [95% CI, 0.69-1.53]). The other antihyperlipidemic drugs had too few exposed cases to obtain reliable estimates. The ORs were slightly higher in the analysis with only events with a principal GI bleeding diagnosis versus the analysis including only events with a non-principal GI bleeding diagnosis (data not shown). Reducing the allowable gap time from 180 days to 90 day between consecutive antihyperlipidemic prescriptions and excluding warfarin users with

a gap of >180 days between consecutive warfarin prescription did not change the results substantively (data not shown).

Discussion

We undertook this study to evaluate whether initiation of particular fibrates or statins increases the risk of hospitalization for GI bleeding in subjects receiving warfarin. Our study is the first epidemiologic study to show that initiation of commonly used CYP3A4 metabolizing fibrates and statins (fenofibrate, gemfibrozil, fluvastatin, simvastatin, and atorvastatin[9,26]) increases the risk of clinically important GI bleeding in chronic warfarin users, especially during the first antihyperlipidemic prescription. A CYP3A4 inhibitor could potentially increase the bleeding risk by reducing the metabolism of the less potent form of warfarin (i.e., R-warfarin). As expected, no increased GI bleeding risk was seen with initiation of pravastatin, which is mainly excreted unchanged, and therefore should be least likely to inhibit warfarin metabolism.[27] Our results also support the hypothesis that the ORs for GI bleeding associated with initiation of antihyperlipidemic drugs are higher among chronic warfarin users than warfarin initiators, which might suggest that with increased INR monitoring, the risk of GI bleeding might be reduced.

Atorvastatin might appear to be less metabolized by CYP3A4 than simvastatin.[27] Our results are consistent with this observation, because the increased GI bleeding risk associated with statin initiation appears to subside sooner for atorvastatin than simvastatin, even though the ORs were similar during the first antihyperlipidemic prescription. In addition, there was a statistically significant reduction in GI bleeding odds with the third or fourth atorvastatin prescription. When we extended our window beyond 120 days of antihyperlipidemic exposure, there was a statistically significantly reduced odds for all statins examined, which was similar to the results of a prior study.[3] A possible explanation for this reduced odds compared to non-statin users, beside depletion of susceptibles,[24] is that persons using long-term statins may be more likely to be adherent to therapy and have regular INR measurements in general. Nevertheless, our results suggest that there is no need to switch long-term users of both warfarin and an antihyperlipidemic agent to a safer alternative.

This study has a number of potential limitations. The main limitation is the limited number of warfarin users initiating an antihyperlipidemic agent, which did not permit us to study all statins and fibrates. Because fewer warfarin users were exposed to fluvastatin than to atorvastatin or simvastatin, we were able to obtain less precise OR estimates for fluvastatin. It may be this imprecision, rather than absence of effect that was responsible for the lack of statistical significance, since fluvastatin is metabolized by CYP2C9 which inactivates the more potent form of warfarin and it had a higher point estimate. An additional limitation is that there might be unmeasured confounding by factors such as diet, laboratory measurements (such as INR measurements), indication for warfarin, adherence, alcohol use, and use of over the counter medication (e.g., NSAIDs). Further, since we did not have baseline hemoglobin levels to calculate the change in hemoglobin levels and missing endoscopies data, we were unable to evaluate whether the GI bleed was a major bleeding.

In conclusion, our results support the hypothesis that initiation of pravastatin is not associated with an increased GI bleeding risk in warfarin users. However, initiation of fibrates and statins that are metabolized by CYP3A4 appears to increase the risk of GI bleeding. This includes atorvastatin, which is currently classified as not having a clinically important interaction with warfarin.[7,8] The increased GI bleeding risk is most marked in chronic warfarin users and during the first antihyperlipidemic prescription. Therefore, warfarin users who initiate these agents may benefit from increased clinical vigilance, including enhanced INR monitoring, until their INR levels has stabilized.

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Appendix 1

Table 3

All potential confounding factors that were considered in this study

Demographic factors		
Age	Calendar year	Gender
Nursing home resident	Race	State
Chronic Diseases		
Chronic kidney disease	Diabetes	Liver disease
Obesity	Prior history of GI bleed	
Drugs that could potentially increase or decrease the bleeding risk		
Aspirin	Histamine H-2 antagonists	Proton pump inhibitors
NSAIDs		
Drugs that could potentially interact with warfarin [*]		
Acetaminophen	Amiodarone	Azathioprine
Azithromycin	Butalbital	Carbamazepine
Ciprofloxacin	Clarithromycin	Co-trimoxazole
Dexamethasone	Diltiazem	Doxycycline
Erythromycin	Fluconazole	Fluvoxamine
Gatifloxacin	Levofloxacin	Levothyroxine
Methimazole	Methylprednisolone	Metronidazole
Phenobarbital	Phenytoin	Prednisone
Primidone	Quinidine	Quinine
Sertraline	Troglitazone	Tetracycline
Trazodone	Zafirlukast	
Potential CYP2C9, CYP3A4, and/or CYP1A2 inhibitors or inducers [†]		
Nefazodone	Pioglitazone	Verapamil

^{*} Based on potentially interacting drugs according to Drug Facts and Comparison (Class 1 and 2 drugs)

[†] Only CYP2C9, CYP3A4, and/or CYP1A2 inhibitors or inducers that were not listed as drugs that could potentially interact with warfarin in Drug Facts and Comparison

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Figure 1.

Association between initiation of each antihyperlipidemic agent (exposed versus unexposed) and hospitalization for gastrointestinal bleeding in chronic warfarin users

Each diamond represents the OR of interest and the vertical line the 95% CI. The data is presented on the log scale. All analyses are adjusted for age, gender, race, state, prior GI bleed, diabetes, and number of prior warfarin prescriptions filled on the index date.

Table 1

Characteristics of cases and controls exposed to the precipitant drugs on the index date

Variable	Cases (12,193) N (%)	Controls (609,650) N (%)	Unadjusted OR and 95% CI
Fenofibrate *	39 (0.32%)	2,117 (0.35%)	0.92 (0.67-1.27)
Gemfibrozil *	67 (0.55%)	3,010 (0.49%)	1.11 (0.87-1.42)
Fluvastatin *	16 (0.13%)	1,835 (0.30%)	0.44 (0.27-0.71)
Simvastatin *	277 (2.27%)	14,909 (2.45%)	0.93 (0.82-1.05)
Atorvastatin *	499 (4.09%)	32,089 (5.26%)	0.77 (0.70-0.84)
Pravastatin *	113 (0.93%)	8,652 (1.42%)	0.65 (0.54-0.78)
Male sex	3,950 (32.40%)	203,916 (33.45%)	0.95 (0.92-0.99)
Race			
African-American	1,904 (15.62%)	81,290 (13.33%)	Reference
Caucasian	7,690 (63.07%)	393,017 (64.47%)	0.84 (0.79-0.88)
Other	2,599 (21.32%)	135,343 (22.20%)	0.82 (0.77-0.87)
Age			
<50 years	958 (7.86%)	90,597 (14.86%)	Reference
50-59 years	1,123 (9.21%)	74,015 (12.14%)	1.43 (1.32-1.56)
60-69 years	1,984 (16.27%)	103,406 (16.96%)	1.81 (1.68-1.96)
70-79 years	3,502 (28.72%)	154,803 (25.39%)	2.14 (1.99-2.30)
≥ 80 years	4,626 (37.94%)	186,829 (30.65%)	2.34 (2.18-2.51)
State			
California	3,239 (26.56%)	161,950 (26.56%)	Reference
Florida	2,431 (19.94%)	121,550 (19.94%)	1.00 (0.95-1.05)
New York	2,344 (19.22%)	117,200 (19.22%)	1.00 (0.95-1.06)
Ohio	2,368 (19.42%)	118,400 (19.42%)	1.00 (0.95-1.05)
Pennsylvania	1,811 (14.85%)	90,550 (14.85%)	1.00 (0.94-1.06)
Prior GI bleed ^{†‡}	4,165 (34.16%)	86,970 (14.27%)	3.12 (3.00-3.24)
Diabetes [†]	6,445 (52.86%)	249,325 (40.90%)	1.62 (1.56-1.68)
Liver disease [†]	2,653 (21.76%)	81,786 (13.42%)	1.79 (1.72-1.87)
Chronic kidney disease [†]	2,999 (24.60%)	68,633 (11.26%)	2.57 (2.47-2.68)
Number of prior warfarin prescriptions filled on the index date	7 (IQR: 2-19)	11 (IQR: 4-23)	0.99 (0.988-0.991)
Number of other potentially interacting medications *	1 (IQR: 0-2)	1 (IQR: 0-1)	1.28 (1.26-1.30)

IQR = Interquartile Range

* Currently exposed, defined as a prescription in the 30 days prior to the index date

[†] Ever in the past[‡] Either a outpatient diagnosis for GI bleeding during warfarin therapy before the index date and/or a hospital admission for GI bleeding prior to initiating warfarin therapy

Table 2

Association between initiation of an antihyperlipidemic agent (exposed versus unexposed) and hospitalization for gastrointestinal bleeding in patients receiving warfarin in case-control study

Model	1 to 30 days (1 st prescription) OR (95% CI)		31 to 60 days (2 nd prescription) OR (95% CI)		61-120 days (3 rd or 4 th prescription) OR (95% CI)	
	Minimally adjusted [*]	Fully adjusted [†]	Minimally adjusted [*]	Fully adjusted [†]	Minimally adjusted [*]	Fully adjusted [†]
Fenofibrate	No data [‡]	No data [‡]	2.14 (0.95-4.84)	2.07 (0.91-4.69)	1.42 (0.67-3.02)	1.31 (0.62-2.79)
Gemfibrozil	2.12 (1.29-3.50)	1.96 (1.19-3.24)	1.48 (0.66-3.33)	1.37 (0.61-3.10)	1.29 (0.64-2.59)	1.23 (0.61-2.48)
Fluvastatin	1.49 (0.70-3.15)	1.45 (0.68-3.09)	No data [‡]	No data [‡]	No data [‡]	No data [‡]
Simvastatin	1.47 (1.10-1.96)	1.33 (1.00-1.78)	1.35 (0.91-2.01)	1.26 (0.85-1.88)	1.16 (0.83-1.61)	1.10 (0.79-1.53)
Atorvastatin	1.43 (1.15-1.78)	1.29 (1.04-1.61)	0.98 (0.70-1.39)	0.96 (0.68-1.35)	0.66 (0.49-0.90)	0.62 (0.46-0.85)
Pravastatin	0.71 (0.41-1.22)	0.66 (0.38-1.14)	0.91 (0.47-1.75)	0.88 (0.45-1.71)	0.55 (0.29-1.02)	0.54 (0.29-1.01)

* Adjusted for age, gender, race, and state

[†] Adjusted for age, gender, race, state, prior GI bleed, diabetes, and number of prior warfarin prescriptions filled on the index date

[‡] Insufficient number of exposed cases to analyze