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Serious Bleeding Events due to Warfarin and Antibiotic Co-prescription In a Cohort of Veterans

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Abstract

Background—Antibiotics may interact with warfarin, increasing the risk for significant bleeding events.

Methods—Retrospective cohort study of veterans prescribed warfarin for ≥ 30 days without interruption through the VA between October 1, 2002 and September 1, 2008. Antibiotics considered to be high-risk for interaction with warfarin include: trimethoprim/sulfamethoxazole (TMP/SMX), ciprofloxacin, levofloxacin, metronidazole, fluiconazole, azithromycin, and clarithromycin. Low-risk antibiotics include: clindamycin and cephalexin. Risk of bleeding event within 30 days of antibiotic exposure was measured using Cox proportional hazards regression, adjusted for demographic characteristics, comorbid conditions and receipt of other medications interacting with warfarin.

Results—A total of 22,272 patients met inclusion criteria with 14,078 and 8,194 receiving high- and low-risk antibiotics, respectively. There were 93 and 36 bleeding events in the high- and low-risk groups, respectively. Receipt of a high-risk antibiotic (HR 1.48, 95% CI 1.00-2.19) and azithromycin (HR 1.93, 95% CI 1.13-3.30) were associated with increased risk of bleeding as a primary diagnosis. TMP/SMX (HR 2.09, 95% CI 1.45-3.02), ciprofloxacin (HR 1.87, 95% CI 1.42-2.50), levofloxacin (HR 1.77, 95% CI 1.22-2.50), azithromycin (HR 1.64, 95% CI 1.16-2.33), and clarithromycin (HR 2.40, 95% CI 1.16-4.94) were associated with serious bleeding as a primary or secondary diagnosis. INR alterations were common; 9.7% of patients prescribed fluconazole had INR value >6. Patients who had INR performed 3-14 days of co-prescription were at a decrease risk of serious bleeding (HR 0.61, 95% CI 0.42-0.88).

Conclusions—Warfarin users who are prescribed high-risk antibiotics are at higher risk for serious bleeding events. Early INR evaluation may mitigate this risk.

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Keywords

Warfarin; antibiotics; drug interactions; patient safety; pharmacoepidemiology; bleeding

Introduction

Warfarin is a widely used anticoagulant with indications for the prevention and treatment of thromboembolic events in patients with atrial fibrillation[1-4], mechanical heart valves[5] and venous thromboembolisms.[6] Warfarin has a narrow therapeutic index, requiring frequent laboratory monitoring to prevent life-threatening complications due to under- and over-anticoagulation.[7, 8]

Warfarin produces its anticoagulant effect by inhibiting the vitamin K-dependent activation of clotting factors II, VII, IX and X.[9] A wide variety of factors including genetic factors[10, 11], dietary factors[12], drug interactions[13] and comorbidities[7] can produce significant variability in an individual's dose-response to warfarin. Co-prescribed medications may alter the metabolism of warfarin by inducing or inhibiting cytochrome P450-2C9, resulting in a decrease or increase in anticoagulant effect.[14] Interactions between warfarin and antibiotics including trimethoprim/sulfamethoxazole (TMP/SMX),[15, 16] metronidazole,[17] fluconazole,[18, 19] ciprofloxacin[20], levofloxacin[15], azithromycin [21, 22], and clarithromycin[23] have been described. In addition to interacting with warfarin via cytochrome P450-2C9, these antibiotics may also eliminate vitamin K-producing bacteria in the intestines to further alter INR.[24, 25] Conversely, cephalexin and clindamycin are believed to have only minimal interactions with warfarin. Prior studies have demonstrated that warfarin users are commonly prescribed antibiotics with known interactions.[26]

In this study, we used the Department of Veterans' Affairs (VA) national databases to characterize the risk of serious bleeding events that require hospitalization among warfarin users who receive antibiotics. We have utilized VA pharmacy, administrative and laboratory databases to identify risk factors for serious bleeding events.

Methods

This study was approved by the institutional review boards of the participating institutions.

Data Sources

Inpatient and outpatient International Classification of Diseases, Version 9, Clinical Modification (ICD-9-CM) diagnosis codes, encounter data and patient demographic data were obtained from the VA's Austin Information Technology Center, a repository for VA administrative data. Pharmacy data for all study subjects, including both inpatient and outpatient medications, were obtained from the VA's Pharmacy Benefits Management program.

Study Population

The study included all veterans who were prescribed warfarin for ≥ 30 days without interruption from a VA between October 1, 2002 and September 1, 2008. Subjects were required to have had ≥ 2 international normalized ratio (INR) lab results while receiving warfarin to demonstrate utilization of the VA for ongoing healthcare.

Subject-time in cohort

Subject-time began 30 days after the date of the first warfarin prescription, in order to establish a stable warfarin regimen and exclude the initial dose-finding period during which bleeding risk may be elevated. Since prescription length for warfarin is 30 days, subject-time continued while warfarin prescriptions continued, allowing lapses of up to 30 days between subscriptions. Subject-time ended 30 days after the last projected warfarin pill (last prescription date plus duration of prescription). Subjects contributed more than one continuous treatment course of warfarin if they were treated with warfarin on multiple occasions with greater than 30 day lapse during the study period.

Antibiotic exposure

Subjects were considered to be receiving an antibiotic from the date of prescription plus the number of days prescribed. Antibiotic prescriptions lasting less than 3 days were excluded. Antibiotics were grouped based upon what is known about their degree of interaction with warfarin. Antibiotics which are known to interact in a way which may increase bleeding risk were considered “high-risk.” High-risk antibiotics included trimethoprim/sulfamethoxazole (TMP/SMX), ciprofloxacin, levofloxacin, metronidazole, fluconazole, azithromycin and clarithromycin. Low-risk antibiotics included clindamycin and cephalexin. For patients receiving two high-risk antibiotics, outcomes were attributed to each medication equally. Outcomes that occurred among patients receiving high- and low-risk antibiotics wereattributed to the high-risk antibiotic.

Primary outcome

The primary outcome was hospitalization for serious bleeding event. A hospitalization was considered to be caused by a serious bleeding event if an ICD-9-CM code found in Appendix 1 occurred in the field designating primary reason for hospitalization. ICD-9-CM codes for serious bleeding event are a modification of a previously described group of codes.[27] A bleeding event that occurred during subject-time was attributed to an antibiotic if it occurred within 30 days of the last prescribed dose of the antibiotic.

Secondary outcomes

Secondary outcomes included elevations in INR >4, and serious bleeding events coded in secondary diagnosis fields of a hospitalization.

Data analysis

For descriptive and bivariate analysis, chi-square test was used for dichotomous variables. Continuous variables were analyzed using student's t-test. A two-sided p-value of ≤ 0.05 was considered statistically significant. Risk of outcomes was described using hazard rations and

95% confidence intervals. Cox proportional hazards regression was performed for time to event analysis. Regression models were adjusted for age, gender, race, comorbid diagnosis, indication for anticoagulation and coprescription of other medications known to interact with warfarin. Each drug was modeled separately and adjusted as described. Because patients living further from a VA hospital are more likely to seek care at a non-VA facility in case of emergency, the model was adjusted for proximity to the nearest VA hospital based upon zip code data. Patients residing in zip codes where the mean distance was > 20 miles from the nearest VA hospital were considered to be distant to a VA hospital. Maximum INR values within 30 days of antibiotic exposure were analyzed by antibiotic. During data analysis, INR values from two VA hospitals were found to have a disproportionate number of values > 12. After closer evaluation, these values likely represented a systematic error (entry of prothrombin times instead of INR into the INR field), and reported INR values from these facilities were excluded from analysis. All analyses were performed using SAS software version 6.12 (SAS Institute, Cary, NC).

Validation

Fifty patients who were hospitalized for a bleeding event and 50 patients not hospitalized for a bleeding event at a single center during the study period were randomly identified by ICD-9-CM codes. All medical records, including admission histories, discharge summaries, and daily notes were reviewed by two physicians (M.A.L and J.R.M). Hospitalization was classified as “for a bleeding event” or “not for a bleeding event” by each reviewer based on their interpretations of primary reason for hospitalization. Consensus was achieved between the 2 reviewers in all cases. Adjusted sensitivity and specificity were calculated by extrapolating the validation results over the entire study population.

Results

There were a total of 22,272 veterans on warfarin for ≥ 30 days who were also prescribed an included antibiotic during the study period (Table 1). There were 8,194 patients who received a low-risk antibiotic and 14,078 patients who received a high-risk antibiotic. Patients receiving a high-risk antibiotic were slightly older and were more likely to have a malignancy or chronic lung disease. Diabetes mellitus, hypertension and alcohol dependence were slightly less common among those receiving a high-risk antibiotic. Those receiving a high-risk antibiotic were less likely to be receiving anticoagulation for heart valve replacement compared to warfarin users who received low-risk antibiotics. Patients prescribed a high-risk antibiotic were also more frequently receiving other medications known to interact with warfarin when compared to those receiving a low-risk antibiotic. More patients receiving a high-risk antibiotic lived > 20 miles from the nearest VA when compared to those receiving low-risk antibiotics. Additionally, more patients receiving a high-risk antibiotic had an INR test within 3-14 days of antibiotic prescription when compared to those who were prescribed a low-risk antibiotic.

There were 36 and 93 bleeding events among patients receiving a low- and high-risk antibiotic, respectively (Table 2). The demographic characteristics between those who had a serious bleeding event and those that did not were largely similar. Malignancy (HR 1.89,

95% CI 1.33-2.70) and renal failure (HR 2.53, 95% CI 1.74-3.68) were associated with an increased risk of serious bleeding events. Co-prescription of other interacting medications increased the risk of serious bleeding events (HR 2.29, 95% CI 1.01-5.19). Early INR evaluation, occurring within 3-14 days of antibiotic co-prescription, reduced the risk of serious bleeding events (HR 0.61, 95% CI 0.42-0.88). Receipt of a high-risk antibiotic also increased the risk of serious bleeding when compared to receipt of a low risk antibiotic (HR 1.48, 95% CI 1.00-2.19). Of the individual high-risk antibiotics, azithromycin was associated with an increased risk of serious bleeding event when compared to the low-risk antibiotics (HR 1.93, 95% CI 1.13-3.30). When ICD-9-CM codes for serious bleeding events in either the primary or secondary diagnosis position were considered, diabetes mellitus (HR 1.25, 95% CI 1.01-1.56), malignancy (HR 1.56, 95% CI 1.27-1.97) and renal failure (HR 2.07, 95% CI 1.64-2.60) were associated with an increased risk for serious bleeding events. Early INR evaluation was associated with a similar reduction in risk of bleeding as seen in the primary outcome measure. Gastrointestinal bleeding events accounted for 57% of all serious bleeding events among patients receiving high-risk antibiotics, followed by bleeding in the genitourinary system (24.7%).

In the secondary outcomes analysis examining ICD-9-CM codes for serious bleeding seen in either primary or secondary coding position , TMP/SMX (HR 2.09, 95% CI 1.45-3.02), ciprofloxacin (HR 1.87, 95% CI 1.42-2.50), levofloxacin (HR 1.77, 95% CI 1.22-2.55), azithromycin (HR 1.64, 95% CI 1.16-2.33) and clarithromycin (HR 2.40, 95% CI 1.16-4.94) were associated with increased risk of serious bleeding when compared to the low risk antibiotics. Alterations in INR were common among warfarin users receiving antibiotics (Figure 3). Among those prescribed a high-risk antibiotic, 7.8% had INR elevations >4 - ≤ 6. Among individual antibiotics, metronidazole (10.1%), fluconazole (13.9%), and receipt of two or more high-risk antibiotics (11.1%) was associated with elevations of INR >4 - ≤ 6. When compared to those prescribed a low-risk antibiotic, significant INR elevations ≥ 6 were seen in 9.7% (p<.0001) and 4.9% (p<.0001) of patients receiving fluconazole and metronidazole, respectively. There were no substantial differences in types of bleeding events between antibiotic groups (data not shown).

The medical records of 50 patients identified by ICD-9-CM codes as being hospitalized for a bleeding event and 50 patients not hospitalized for a bleeding event were reviewed. Bleeding events were confirmed in 48 patients, resulting in a positive predictive value of the administrative data to identify a hospitalization for bleeding of 96%. There were 5 hospitalizations for bleeding among the 50 patients identified as not having a bleeding event during the study period. The sensitivity and specificity of the ICD-9 codes to identify a bleeding event was 91% and 96%, respectively. The kappa was 0.86, indicating excellent agreement between the code and our gold standard.

Discussion

In this large cohort of warfarin users in the VA healthcare system, we describe the risk of and risk factors for serious bleeding events following prescription of selected antibiotics. We demonstrated excellent validity of our outcome measure using electronic medical records. We have shown that patients receiving high-risk antibiotics are at increased risk for serious

bleeding events compared to those receiving low-risk antibiotics. Warfarin users who received azithromycin had nearly twice the risk of hospitalization for serious bleeding compared to low-risk antibiotics. When ICD-9-CM codes for serious bleeding were permitted in the primary or secondary reasons for admission, TMP/SMX (HR 2.09, 95% CI 1.45 – 3.02), ciprofloxacin (HR 1.87, 95% CI 1.42 – 2.50), levofloxacin (HR 1.77, 95% CI 1.22 - 2.55), azithromycin (HR 1.64, 95% CI 1.16 – 2.33), clarithromycin (HR 2.40, 95% CI 1.16 – 4.94) all increased the risk for serious bleeding events.

Bleeding events were the primary reason for admission in 0.6% of all patients included in this study. A study utilizing a 5% national sample of Medicare beneficiaries with Part D benefits, 2.9% of warfarin users met the case definition of a serious bleeding event. However, differences in study methodology may account for the difference in frequency of bleeding events. In the Medicare study, 78.7% all warfarin users who had a bleeding event were not exposed to antibiotics prior to the bleeding event. Our study includes only those patients who are prescribed warfarin and an antibiotic concurrently based on VA pharmacy data. Additionally, this Medicare study includes bleeding events occurring >60 days after antibiotic exposure, whereas our study includes those within 30 days of co-prescription.[28] A study of 19,935 new users of coumarin anticoagulants in the Netherlands found a 4 to 7-fold increased risk of bleeding related to antibiotics.[29] However, the study did not control for potential confounders. Additionally, patients included in the study were incident users of coumarin anticoagulants. Prior studies have shown significantly higher rates of serious bleeding events in the period immediately after initiation of anticoagulation.[30-33] We excluded the early period after initiation in order to estimate the rate of complications during stable long-term use.

We found that exposure to high-risk antibiotics increases the risk of serious bleeding events as primary diagnosis by nearly 50% when compared to low-risk antibiotics. Azithromycin nearly doubled the risk of serious bleeding event. When primary and secondary diagnosis codes were included, nearly all high-risk antibiotics increased the risk for bleeding. TMP/SMX was associated with a >2-fold increased risk for bleeding. Other studies have also found that TMP/SMX [28, 34, 35], fluoroquinolones[28] and macrolides[28] significantly increase the risk for serious bleeding. Prior studies have found a significant increased risk of serious bleeding among warfarin users who received fluconazole.[28, 35] However, only 3 patients who received fluconazole in our study had a bleeding event, and thus we are likely underpowered to show a clinically significant interaction. Likewise, there were only 5 warfarin users who were prescribed metronidazole and had a bleeding event. Infection may cause elevations in INR independent of antibiotic use.[36] However, our results suggest infection alone does not alter the bleeding risk among warfarin users. All patients in our cohort received antibiotics for an infection, but only those who received a high-risk antibiotic were at increased risk of serious bleeding events.

Anticoagulation intensity, as measured by INR, has been associated with increased risk of serious bleeding.[8, 37-40] Risk of intracranial hemorrhage has been shown to increase significantly at INR values > 3.5.[8, 41] Many studies demonstrating INR alterations after antibiotic administration have been relatively small. Among 27 patients on stable warfarin regimens who were co-prescribed levofloxacin, 11% had an elevation of INR ≥5. Among 16

patients prescribed TMP/SMX, 31% had an elevation of INR ≥5. [15] In our study, elevations in INR were seen among all high-risk antibiotics. Notably, 4.9% of patients receiving metronidazole and 9.7% of those prescribed fluconazole had a peak INR >6, putting these patients at significant risk for harm. Prior studies suggest infection may independently cause elevations in INR.[36] It is possible some of the alterations in INR are due to the underlying infection. In our multivariate analysis, INR evaluation within 3-14 days of antibiotic coprescription reduced the risk of serious bleeding event by 39%. This finding strongly supports early INR check after coprescription.

Our study has several limitations that may influence the results. This study relies on the accuracy of ICD-9-CM codes to identify bleeding events. Evaluations of the ICD-9-CM codes used in this study have demonstrated the ability to accurately identify serious bleeding events. [2742] Additionally, our validation demonstrated excellent agreement between the ICD-9-CM code definition and the electronic medical records (kappa = 0.86). However, it is possible that some serious bleeding events were misclassified. In order for us to identify an outcome, a subject must have utilized a VA healthcare facility for their health care needs. We attempted to limit the impact of this by only including patients who have ≥ 2 INR values checked in the VA system prior to outcome, to indicate utilization of the VA for healthcare services. Additionally, our multivariate models included distance to the nearest VA hospital to control for the higher likelihood of seeking non-VA care for a bleeding event in subjects residing further from the nearest VA facility. In addition to antibiotics, multiple medications interact with warfarin. We included interacting medications as a dichotomous variable in our models, but did not assess the impact of individual medications. However, given the complex nature of these multiple drug interactions, this approach may approximate real-world clinical practice. Additionally, we were unable to assess patient adherence to antibiotic therapy which could alter our estimate of the interaction effect.

Although warfarin is effective in the prevention and treatment of thromboembolic events, its narrow therapeutic index and multiple drug interactions put patients at risk for serious bleeding events. In this study we have used national VA administrative data to demonstrate an increased risk for serious bleeding events among warfarin users who receive high-risk antibiotics. Our findings suggest that when possible, clinicians should choose antibiotics with low potential to interact with warfarin. Our data strongly supports INR monitoring after co-prescription as a means to decrease risk of hospitalization for serious bleeding.

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Appendix 1: Current Procedural Terminology (CPT) and International Classification of Diseases, Ninth Revision (ICD-9) Codes Used

	CPT Codes
36430	Transfusion, blood or blood components (nonspecific)
	ICD-9 Codes
99.03	Transfusion of blood (whole) NOS (nonspecific)
99.04	Transfusion of packed cells (nonspecific)
285.1	Acute post-hemorrhage anemia (nonspecific)
287.9	Hemorrhagic diathesis (nonspecific)
360.43	Eye hemorrhage (Ocular)
362.81	Retinal hemorrhage (Ocular)
363.61	Choroid hemorrhage (Ocular)
364.41	Iris/ciliary body hemorrhage (Ocular)
376.32	Orbital hemorrhage (Ocular)
379.23	Vitreous hemorrhage (Ocular)
430	Subarachnoid hemorrhage (CNS)
431	Intracerebral hemorrhage (CNS)
432x	Other and unspecified intracranial hemorrhage (CNS)
456.0, .20	Esophageal varices with bleeding (GI)
459.0	Hemorrhage, unspecified/spontaneous hemorrhage (nonspecific)
530.21	Esophageal ulcer with bleeding (GI)
530.82	Esophageal hemorrhage (GI)
531.0x	Gastric ulcer – acute with hemorrhage (GI)
531.2x	Gastric ulcer – acute with hemorrhage and perforation (GI)
531.4x	Gastric ulcer – chronic or unspecified with hemorrhage (GI)
531.6x	Gastric ulcer – chronic or unspecified with hemorrhage and perforation (GI)
532.0x	Duodenal ulcer – acute with hemorrhage (GI)
532.2x	Duodenal ulcer – acute with hemorrhage and perforation (GI)
532.4x	Duodenal ulcer – chronic or unspecified with hemorrhage (GI)
532.6x	Duodenal ulcer – chronic or unspecified with hemorrhage and perforation (GI)
533.0x	Peptic ulcer, site unspecified – acute with hemorrhage (GI)
533.2x	Peptic ulcer, site unspecified – acute with hemorrhage and perforation (GI)
533.4x	Peptic ulcer, site unspecified – chronic or unspecified with hemorrhage (GI)
533.6x	Peptic ulcer, site unspecified – chronic or unspecified with hemorrhage and Perforation (GI)
534.0x	Gastrojejeunal ulcer – acute with hemorrhage (GI)
534.2x	Gastrojejeunal ulcer – acute with hemorrhage and perforation (GI)
534.4x	Gastrojejeunal ulcer – chronic or unspecified with hemorrhage (GI)
534.6x	Gastrojejeunal ulcer – chronic or unspecified with hemorrhage and perforation (GI)
535.01	Acute gastritis with hemorrhage (GI)
535.11	Atrophic gastritis with hemorrhage (GI)
535.21	Gastric mucosal hypertrophy with hemorrhage (GI)
535.31	Alcoholic gastritis with hemorrhage (GI)
535.41	Other gastritis with hemorrhage (GI)
535.51	Unspec gastritis with hemorrhage (GI)

535.61 Duodenitis with hemorrhage (GI)

535.71 Eosinophilic gastritis with hemorrhage (GI)

537.83 Gastric angiodysplasia with hemorrhage (GI)

537.84 Hemorrhagic dieulafoy lesion of stomach/duodenum (GI)

562.02 Small intestine diverticulosis with hemorrhage (GI)

562.03 Small intestine diverticulitis with hemorrhage (GI)

562.12 Colonic diverticulosis with hemorrhage (GI)

562.13 Colonic diverticulitis with hemorrhage (GI)

568.81 hemoperitoneum – non-traumatic (GI)

569.3 Hemorrhage of the rectum and anus (GI)

569.85-6 angiodysplasia with hemorrhage, dieulafoy lesion (hemorrhagic)(GI)578 GI hemorrhage (GI)

578.0 Hemetemesis (GI)

578.1 Blood in the stool (melena) (GI)

578.9 Hemorrhage GI tract, unspecified (GI)

595.0 Hemorrhagic cystitis (GU)

596.7 Hemorrhage into bladder wall (GU)

599.7 Hematuria (GU)

626.2 Excessive menstruation (GU)

626.6 Metrorrhagia (GU)

719.1x Hemarthrosis (other)

784.7 Epistaxis (other)

784.8 Hemorrhage from throat (other)

786.3 Hemoptysis (pulmonary)

Bleeding event by system:

CNS:

430 Subarachnoid hemorrhage

431 Intracerebral hemorrhage

432x Other and unspecified intracranial hemorrhage

Ocular:

360.43 Eye hemorrhage (Ocular)

362.81 Retinal hemorrhage (Ocular)

363.61 Choroid hemorrhage (Ocular)

364.41 Iris/ciliary body hemorrhage (Ocular)

376.32 Orbital hemorrhage (Ocular)

379.23 Vitreous hemorrhage (Ocular)

GI:

456.0, .20 Esophageal varices with bleeding (GI)

530.21 Esophageal ulcer with bleeding (GI)

530.82 Esophageal hemorrhage (GI)

531.0x Gastric ulcer – acute with hemorrhage (GI)

531.2x Gastric ulcer – acute with hemorrhage and perforation (GI)

531.4x Gastric ulcer – chronic or unspecified with hemorrhage (GI)

531.6x Gastric ulcer – chronic or unspecified with hemorrhage and perforation (GI)

532.0x Duodenal ulcer – acute with hemorrhage (GI)

532.2x	Duodenal ulcer – acute with hemorrhage and perforation (GI)
532.4x	Duodenal ulcer – chronic or unspecified with hemorrhage (GI)
532.6x	Duodenal ulcer – chronic or unspecified with hemorrhage and perforation (GI)
533.0x	Peptic ulcer, site unspecified – acute with hemorrhage (GI)
533.2x	Peptic ulcer, site unspecified – acute with hemorrhage and perforation (GI)
533.4x	Peptic ulcer, site unspecified – chronic or unspecified with hemorrhage (GI)
533.6x	Peptic ulcer, site unspecified – chronic or unspecified with hemorrhage and Perforation (GI)
534.0x	Gastrojejeunal ulcer – acute with hemorrhage (GI)
534.2x	Gastrojejeunal ulcer – acute with hemorrhage and perforation (GI)
534.4x	Gastrojejeunal ulcer – chronic or unspecified with hemorrhage (GI)
534.6x	Gastrojejeunal ulcer – chronic or unspecified with hemorrhage and perforation (GI)
535.01	Acute gastritis with hemorrhage (GI)
535.11	Atrophic gastritis with hemorrhage (GI)
535.21	Gastric mucosal hypertrophy with hemorrhage (GI)
535.31	Alcoholic gastritis with hemorrhage (GI)
535.41	Other gastritis with hemorrhage (GI)
535.51	Unspec gastritis with hemorrhage (GI)
535.61	Duodenitis with hemorrhage (GI)
535.71	Eosinophilic gastritis with hemorrhage (GI)
537.83	Gastric angiodysplasia with hemorrhage (GI)
537.84	Hemorrhagic dieulafoy lesion of stomach/duodenum (GI)
562.02	Small intestine diverticulosis with hemorrhage (GI)
562.03	Small intestine diverticulitis with hemorrhage (GI)
562.12	Colonic diverticulosis with hemorrhage (GI)
562.13	Colonic diverticulitis with hemorrhage (GI)
568.81	hemoperitoneum – non-traumatic (GI)
569.3	Hemorrhage of the rectum and anus (GI)
569.85-6	angiodysplasia with hemorrhage, dieulafoy lesion (hemorrhagic)(GI)
578	GI hemorrhage (GI)
578.0	Hemetemesis (GI)
578.1	Blood in the stool (melena) (GI)
578.9	Hemorrhage GI tract, unspecified (GI)
GU:	
595.0	Hemorrhagic cystitis (GU)
596.7	Hemorrhage into bladder wall (GU)
599.7	Hematuria (GU)
626.2	Excessive menstruation (GU)
626.6	Metrorrhagia (GU)
Nonspecific:	
36430	Transfusion, blood or blood components (nonspecific)
99.03	Transfusion of blood (whole) NOS (nonspecific)
99.04	Transfusion of packed cells (nonspecific)
285.1	Acute post-hemorrhage anemia (nonspecific)
287.9	Hemorrhagic diathesis (nonspecific)
459.0	Hemorrhage, unspecified/spontaneous hemorrhage (nonspecific)

Pulmonary:	
786.3	Hemoptysis
Other:	
719.1x	Hemarthrosis (other)
784.7	Epistaxis (other)
784.8	Hemorrhage from throat (other)

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Clinical Significance

- Patients who receive warfarin and a high-risk antibiotic are at increased risk for significant bleeding events.
- Alterations in the INR are common among patients who receive antibiotics
- INR evaluation within 3-14 days of antibiotic prescription may reduce the risk of serious bleeding events among patients receiving warfarin.

Table 1
Demographic and Clinical Characteristics

	Total	Low-Risk Antibiotic[1]	High-Risk Antibiotic[2]	P-value
N	22,722	8,194	14,078	
Mean Age (SD)	69.5 (10.8)	68.8 (11.1)	69.8 (10.7)	<**.0001**
Gender (% male)				
Race (%)				
White	19,631 (88.1)	7,323 (89.4)	12,308 (87.4)	<**.0001**
Black	1,803 (8.1)	568 (6.9)	1,235 (8.8)	<**.0001**
Other	838 (3.8)	303 (3.7)	535 (3.8)	0.7
Comorbidities (%)				
Diabetes Mellitus	9,930 (44.6)	3,739 (45.6)	6,191 (44.0)	**0.02**
Hypertension	19,592 (88.0)	7,268 (88.7)	12,324 (87.5)	**0.01**
Heart Failure	9,701 (43.6)	3,518 (42.9)	6,183 (43.9)	0.2
Malignancy	6,676 (30.0)	2,369 (28.9)	4,307 (30.6)	**0.008**
Chronic Lung Disease	11,170 (50.2)	3,610 (44.1)	7,560 (53.7)	<**.0001**
Renal Failure	3,501 (15.7)	1,301 (15.9)	2,200 (15.6)	0.6
Liver Disease	930 (4.2)	335 (4.1)	595 (4.2)	0.6
Ischemic Heart Disease	14,745 (66.2)	5,395 (65.8)	9,350 (66.4)	0.4
Valvular Heart Disease	5,663 (25.4)	2,135 (26.1)	3,528 (25.1)	0.1
Alcohol Dependence	1,624 (7.3)	643 (7.9)	981 (7.0)	**0.02**
None of the Above	423 (1.9)	170 (2.1)	253 (1.8)	0.1
Indication for Anticoagulation (%)				
Heart Valve Replacement	4,325 (19.4)	1,672 (20.4)	2,653 (18.9)	**0.005**
Other	19,113 (85.8)	7,028 (85.8)	12,085 (85.8)	0.9
Interacting Medications (%)	19,555 (87.8)	6,872 (83.9)	12,085 (85.8)	<**.0001**
Distance > 20 miles (%)	12,288 (55.2)	4,415 (53.9)	7,873 (55.9)	**0.003**
Early INR Check *(%)	9,770 (43.8)	3,504 (42.8)	6,266 (44.5)	**0.01**

[1] Low-Risk Antibiotics: clindamycin, cephalexin

[2] High-Risk Antibiotics: trimethoprim/sulfamethoxazole (TMP/SMX), ciprofloxacin, levofloxacin, metronidazole, fluconazole, azithromycin and clarithromycin

Table 2
Multivariate Predictors of Bleeding Event as Primary Diagnosis

	(+) Bleeding Event	(-) Bleeding Event	HR (95% CI)
N	129	22,143	-
Mean Age (SD)	71.2 (9.8)	69.5 (10.8)	1.00 (0.99 – 1.02)
Gender (% male)	123 (95.4)	21,579 (97.5)	0.5 (0.22 – 1.13)
Race (%)			
White	120 (93.0)	19,511 (88.1)	Referent
Black	6 (4.7)	1,797 (8.1)	0.47 (0.21 - 1.10)
Other	3 (2.3)	835 (3.8)	0.61 (0.19 - 1.94)
Comorbidities (%)			
Diabetes Mellitus	67 (51.9)	9,866 (44.6)	1.07 (0.74 -1.55)
Hypertension	124 (96.1)	19,470 (87.9)	2.15 (0.87 - 5.31)
Heart Failure	78 (60.5)	9,629 (43.5)	1.21 (0.82 - 1.80)
Malignancy	64 (49.6)	6,619 (29.9)	**1.89 (1.33 - 2.70)**
Chronic Lung Disease	81 (62.8)	11,095 (50.1)	1.16 (0.80 - 1.68)
Renal Failure	50 (38.8)	3,458 (15.6)	**2.53 (1.74 - 3.68)**
Liver Disease	12 (9.3)	920 (4.2)	1.61 (0.86 - 3.00)
Ischemic Heart Disease	99 (76.7)	14,648 (66.2)	0.83 (0.60 - 1.44)
Valvular Heart Disease	55 (42.6)	5,611 (25.3)	1.34 (0.90 - 1.98)
Alcohol Dependence	13 (10.1)	1,611 (7.3)	1.47 (0.82 - 2.63)
None of the Above	0 (0.0)	423 (1.9)	Referent
Indication for Anticoagulation			
Heart Valve Replacement	51 (39.5)	4,275 (19.3)	**2.12 (1.43 - 3.14)**
Other	116 (89.9)	19,000 (85.8)	1.30 (0.71 - 2.38)
Interacting Medications (%)	123 (95.4)	19,436 (87.8)	**2.29 (1.01 - 5.19)**
Distance > 20 miles (%)	74 (57.4)	12,216 (55.2)	1.15 (0.80 - 1.64)
Early INR Check *(%)	48 (37.2)	9,714 (43.9)	0.61 (0.42 - 0.88)
High-Risk Antibiotic (%)	93 (72.1)	13,988 (63.2)	**1.48 (1.00 - 2.19)**
TMP/SMX	14 (10.9)	1,964 (8.9)	1.79 (0.97 - 3.32)
Ciprofloxacin	30 (23.3)	4,349 (19.6)	1.42 (0.87 - 2.31)
Levofloxacin	11 (8.5)	2,521 (11.4)	1.30 (0.66 - 2.55)
Metronidazole	5 (3.9)	755 (3.4)	1.63 (0.61 - 4.39)
Fluconazole	3 (2.3)	287 (1.3)	2.11 (0.60 - 7.34)
Azithromycin	33 (25.6)	5,725 (25.9)	**1.93 (1.13 - 3.30)**
Clarithromycin	2 (1.6)	481 (2.3)	1.71 (0.45 - 6.57)
Co-prescribed High-risk	8 (6.2)	991 (4.5)	1.75 (0.79 - 3.89)
Co-prescribed High- and Low- risk	8 (6.2)	1,162 (5.2)	1.35 (0.61 - 2.99)
Low-Risk Antibiotic (%)	36 (27.9)	8,155 (36.8)	Referent
Clindamycin	11 (8.5)	1,862 (8.4)	0.58 (0.31 - 1.09)
Cephalexin	34 (26.4)	6,561 (29.6)	0.07 (0.48 - 1.04)

INR = International Normalized Ratio

TMP/SMX = Trimethoprim/Sulfamethoxazole

* INR evaluation within 3-14 days of antibiotic co-prescription

Table 3
Alterations in INR Following Antibiotic Administration

	Total	≤ 4	Peak INR >4 - ≤ 6	> 6
High-risk Antibiotic (%)	22,381	20,061 (89.6)	1,748 (7.8)	572 (2.6)
TMP/SMX	2,828	2,538 (89.7)	227 (8.0)	63 (2.2)
Ciprofloxacin	6,844	6,195 (90.5)	514 (7.5)	135 (2.0)
Levofloxacin	3,343	2,972 (88.9)	279 (8.4)	92 (2.8)
Metronidazole	1,003	853 (85.0)	101 (10.1)	49 (4.9)
Fluconazole	381	291 (76.4)	53 (13.9)	37 (9.7)
Azithromycin	9,331	8,526 (91.4)	649 (7.0)	156 (1.6)
Clarithromycin	584	521 (89.2)	46 (7.9)	17 (2.9)
Co-prescribed High-risk	1,357	1,153 (85.0)	151 (11.1)	53 (4.0)
Co-prescribed High- and Low-risk	2,401	2,089 (87.0)	226 (9.4)	86 (3.6)
Low-risk Antibiotic (%)	12,973	11,799 (91.0)	931 (7.2)	243 (2.9)

INR = International Normalized Ratio

TMP/SMX = Trimethoprim/Sulfamethoxazole