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High-risk Antimicrobial Prescriptions Among Ambulatory Patients on Warfarin

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Abstract

What is known—Warfarin is a potent anti-coagulant with many drug-drug interactions, including antimicrobials. There is limited data on the frequency of prescription of high-risk antimicrobials to patients on warfarin.

Objective—To examine the frequency of prescriptions for potentially interacting antimicrobials in ambulatory patients on warfarin, and the impact of warfarin on the prescription of high-risk antimicrobials.

Methods—A retrospective cohort study of patients with pharmacy benefits who had ≥ 1 claim for an oral antimicrobial between January 1, 2008 and December 31, 2008 was conducted, utilizing a pharmacy benefits database. Demographic data including age, gender, Chronic Disease Score (CDS), and geographic location were determined. Warfarin users were defined as any patient with ≥ 1 claim for warfarin during the follow-up period. Antimicrobials considered high-risk for potential interaction with warfarin based on existing literature included trimethoprim/sulfamethoxazole, levofloxacin, ciprofloxacin, metronidazole and fluconazole. Multivariate analysis was used to determine the impact of warfarin use and other factors on high-risk antimicrobial prescription.

Results and discussion—A total of 4,568,150 patients with ≥ 1 claim for antimicrobials during 2008 were analyzed. 110,192 (2.4%) also had one or more claims for warfarin. Among all antimicrobial prescriptions in warfarin users, 42.6% were for high-risk antimicrobials. The mean number of antimicrobial prescriptions was 3.0 in warfarin users vs. 2.4 in warfarin non-users (p-value <0.001). After adjusting for age, gender, CDS, and geography, the odds of exposure to high-risk antimicrobials was 42% lower (OR 0.58; p-value <0.001) in warfarin users compared to warfarin non-users.

What is new and conclusions—A high percentage (42.6%) of antimicrobial prescriptions among warfarin users were for high-risk antimicrobials which carry excess bleeding risk. While clinicians were somewhat less likely to prescribe high-risk antimicrobials to warfarin users compared to non-users, the incidence of co-prescription remains high.

Keywords

Warfarin; anticoagulation; antimicrobials; antibiotics; drug-drug interactions

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Introduction

Warfarin is a widely used oral anticoagulant that is used to treat and prevent thromboembolic events in patients with atrial fibrillation(1-4), venous thromboembolisms(5) and mechanical heart valves.(6) However, warfarin has a narrow therapeutic index and many drug-drug interactions, making its safe use difficult for clinicians. Warfarin use requires frequent monitoring in order to prevent potentially life-threatening adverse events due to under- and over-anticoagulation.

Over-anticoagulation carries the risk of significant bleeding events. The annual rate of major hemorrhage in patients treated with warfarin has been reported to be 1.2 – 7.0 episodes per 100 patients in different cohort studies.(7, 8) A meta-analysis of 4,374 patients showed a case fatality rate for major bleeding events of 13.4%.(9) Warfarin exerts its anticoagulant effect by competitively inhibiting the vitamin K dependent activation of the clotting factors, II, VII, IX and X.(10) Multiple foods and medications have interactions that complicate warfarin dosing.(11, 12) Antimicrobials including trimethoprim/sulfamethoxazole (TMP/SMX)(13, 14), metronidazole(15), fluconazole(16, 17), ciprofloxacin(18) and levofloxacin(13) have been shown to interact with warfarin. These drug-drug interactions carry the potential for causing significant adverse bleeding events.

In this study, we used pharmacy data from Express Scripts, Inc. (St. Louis, MO), a large, national pharmacy benefits manager with approximately 30 million members, to examine the frequency of prescriptions for potentially interacting antimicrobials in ambulatory patients on warfarin, and the impact of warfarin on the prescription of high-risk antimicrobials.

Methods

We conducted a retrospective cohort study of patients with pharmacy benefits managed by Express Scripts who had one or more claims for an oral antimicrobial agent between January 1, 2008 and December 31, 2008. Study cohort members included commercially insured clients of Express Scripts with integrated pharmacy benefits who were 18 years or older as of January 1, 2008, and continuously enrolled for no less than 90 days in 2008. Patients contributed patient-time to the cohort only for the period in which they were covered under the pharmacy benefit. Once an individual was no longer enrolled, they were considered lost to follow-up. Each patient's actual time enrolled in the pharmacy benefit plan was determined, and all analyses were weighted based upon their actual enrollment period.

An antimicrobial user was defined as an individual with one or more pharmacy claim for an antimicrobial with greater than 1 day supply during 2008. A warfarin user was defined as an individual with one or more pharmacy claims for at least a 30 day supply of warfarin during 2008. High-risk antimicrobials were analyzed separately because of their documented propensity to interact with warfarin. High-risk antimicrobials included TMP/SMX, ciprofloxacin, levofloxacin, metronidazole, and fluconazole. We conducted descriptive analyses of all antimicrobials and high-risk antimicrobials among warfarin users and non-users using t-tests for continuous variables and chi-squared tests for dichotomous variables.

We used logistic regression to estimate the odds of receiving a high-risk antimicrobial order adjusted for warfarin status, patient gender, age as of January 1st, 2008, quartile of chronic disease score (CDS)(19, 20), and US census region. The chronic disease score was calculated based upon 3 to 6 months of pharmacy claims depending upon the duration of eligibility of the patient during 2008. All analyses were conducted in SAS v9.2 (Cary, NC).

Results

There were 4,569,550 individuals with one or more orders for any antimicrobial agent, of whom 110,209 also had one or more claims for warfarin. A total of 17 patients who received both warfarin and an antimicrobial agent had one or more missing data points; these patients were excluded, leaving 110,192 patients who used both warfarin and antimicrobials during the study period. A total of 1,191 patients who were prescribed an antimicrobial but were not prescribed warfarin were excluded because they had at least one missing data point (Table 1). Among users of any antimicrobial, warfarin users were more likely to be male (52.9% vs 39.6%, $p < 0.001$), were older (mean ages: 65.4 years vs. 45.5 years, $p < 0.001$) and had a higher chronic disease score (7234 vs 2045, $p < 0.001$). Among warfarin users, 42.6% of all antimicrobial prescriptions were for high-risk antimicrobials. The average number of antimicrobial prescriptions and the average number of days on antimicrobial therapy during follow up were both higher in warfarin users than non-users. Among warfarin users, high-risk antimicrobials prescriptions were for levofloxacin (14,132 [30.1%]), TMP/SMX (12,827 [27.3%]), ciprofloxacin (12,087 [25.8%]), fluconazole (3,990 [8.5%]), and metronidazole (3,902 [8.3%]). Overall, warfarin users had slightly more prescriptions for and time on high-risk antimicrobials than non-users.

The unadjusted odds of high-risk antimicrobial utilization were 41% higher (OR=1.41, 95% CI: 1.39-1.43, $p < 0.001$) in warfarin users than non-users. After adjusting for gender, age, chronic disease score quartile and geography, the odds of exposure to high-risk antimicrobials was 43% lower (OR 0.57; 95% CI: 0.56-0.58, p -value < 0.001) in warfarin users than non-users (Table 2). Odds of co-prescription of warfarin with a high-risk antimicrobial increased with age and chronic disease score. Odds of co-prescription were lowest in New England (OR 1.00, referent) and the Mid-Atlantic region (OR 1.13), and were highest in the East South Central (OR 1.70) and West South Central (OR 1.59) regions.

Discussion

In this large cohort of ambulatory patients receiving warfarin, a very high percentage (42.6%) of antimicrobial prescriptions were for antimicrobials known to cause excess bleeding risk in warfarin users. Warfarin users received more high-risk antimicrobials per patient-year than non-users, potentially putting them at risk for over-anticoagulation and clinically important bleeding events. After adjusting for age, gender, comorbidities and geography, warfarin patients were less likely to receive high-risk antimicrobials than non-warfarin users. These findings demonstrate that, while clinicians are somewhat less likely to prescribe high-risk antimicrobials to warfarin users, the incidence of co-prescription remains high.

To our knowledge, no other studies have examined the frequency of prescriptions for these antimicrobials with known drug-drug interactions in warfarin users in the United States. Our adjusted data shows that although warfarin users are 43% less likely than non-users to receive high-risk antimicrobials, co-prescription with high-risk antimicrobials is very common, comprising 42.6% of all antimicrobial prescriptions. In a Dutch study utilizing the PHARMO Pharmacy Database, 47.6% of patients on coumarin anticoagulants (ie. acenocoumarol, phenprocoumon and warfarin) received a potentially interacting antimicrobial, including TMP/SMX and metronidazole, during the study period 1991-2003(21). The frequency of co-prescription in our study differs from this study due to our expanded list of high-risk antimicrobials, as well as our one-year study period.

Prior studies have shown that short-term use of antimicrobials has the potential to alter the International Normalized Ratio (INR), putting patients at risk for bleeding events. Among

27 patients in the US who were prescribed levofloxacin while on a stable warfarin dose, 9 (33%) patients had an elevation in INR beyond the therapeutic range. In this group, 19% of patients had an absolute INR ≥ 4 and 11% had an INR ≥ 5 . Additionally, 16 patients on stable warfarin doses were prescribed TMP/SMX. A mean increase in INR of 1.76 was seen among warfarin users who received TMP/SMX. Among warfarin users who received TMP/SMX, 69% had an elevation of the INR beyond the therapeutic range, with 44% of patients having an absolute INR ≥ 4 and 31% with an absolute INR ≥ 5 . In this small study, 13% of warfarin users who received TMP/SMX experienced an adverse bleeding event.(13) In a case control study, the risk of intracerebral hemorrhage doubled for every 1-point increase of the INR.(22)

In our study, multivariate modeling showed that increasing age was associated with a higher risk of receiving an antimicrobial with potential to interact with warfarin. Warfarin users ≥ 80 years old were 60% more likely to receive a high-risk antimicrobial than patients ≤ 50 years old. Prior studies have shown that increased age, particularly age ≥ 80 years is an independent risk factor for intracranial bleeding events.(22, 23) Our study suggests that patients who are at the greatest risk for intra-cranial hemorrhages are also most likely to receive antimicrobials that have potential to interact with warfarin.

Our study has several limitations. First, our study likely underestimates the frequency of prescriptions for interacting antimicrobials. Some commercial pharmacies in the United States offer discounted or free generic versions of the antimicrobials examined in this study. Medication claims may not be submitted for these prescriptions, under-representing the number of actual prescriptions and the frequency of this potential drug interaction. Second, we were unable to confirm actual concomitant utilization of warfarin and high-risk antimicrobials. Nevertheless, our data demonstrate potentially dangerous prescribing practices. Third, our data sources do not allow for identification of dose or therapy alterations that may have occurred in response to pharmacy drug interaction warning systems. It is possible that warfarin doses were proactively decreased in some warfarin users who were co-prescribed high-risk antimicrobials. Also, laboratory data, including INR, was not collected in this database. It is possible that clinicians increased the intensity of INR monitoring in order to mitigate some of the potential harm due to these drug-drug interactions.

Additionally, administrative diagnosis codes and other clinical data are not collected in this database, thus limiting our ability to control for certain comorbidities. Therefore, we used the pharmacy-based Chronic Disease Score as a marker for comorbidity burden in our population. This score has been shown to correlate with physician rated disease severity, patient-rated health status, mortality and hospitalization rates.(19, 24)

Future studies should examine prescriber knowledge of antimicrobial agents interacting with warfarin, prescriber knowledge of the clinical consequences of co-prescription, and reasons for co-prescription of high-risk antimicrobials. Also, additional data are needed in order to understand the comparative risk of bleeding events and other clinical outcomes attributable to each high-risk antimicrobial.

What is new and conclusions

This study highlights the high frequency of potentially serious drug-drug interactions among warfarin users in the United States. Although many pharmacies utilize warning systems to alert medical providers to drug interactions, a large percentage of warfarin users still receive antimicrobials that interact with warfarin, putting them at risk for serious bleeding events. Clinicians should choose alternate antimicrobials whenever possible. Future studies of co-

prescription of warfarin and antimicrobials are warranted to describe the clinical impact of these extremely common drug interactions.

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Table 2

Odds ratio estimates for high-risk antimicrobial exposure in the Express Scripts commercial pharmacy claims database between January 1, 2008 and December 31, 2008

	Point Estimate	95% Wald Confidence Limits
Warfarin use	0.57	0.56 - 0.58
Age group		
< 50	Referent	Referent
50 – 59	1.01	1.01 - 1.02
60 – 69	1.16	1.14 - 1.16
70 – 79	1.42	1.40 - 1.43
≥ 80	1.61	1.59 - 1.63
Female Gender	1.52	1.51 - 1.53
Region		
New England ^a	Referent	Referent
Middle Atlantic ^b	1.13	1.12 - 1.14
South Atlantic ^c	1.44	1.43 - 1.45
East South Central ^d	1.70	1.68 - 1.72
West South Central ^e	1.59	1.58 - 1.61
East North Central ^f	1.23	1.22 - 1.24
West North Central ^g	1.28	1.27 - 1.29
Mountain ^h	1.23	1.22 - 1.25
Pacific ⁱ	1.29	1.27 - 1.30
Chronic Disease Score		
Quartile 1 (0 -1478.4)	Referent	Referent
Quartile 2 (1478.4-1697.9)	1.44	1.43 - 1.46
Quartile 3 (1697.9-2567.9)	1.50	1.48 - 1.51
Quartile 4 (>2567.9)	1.62	1.60 - 1.63

^a CT, MA, ME, NH, RI, VT

^b NJ, NY, PA

^c DC, DE, FL, GA, MD, NC, SC, VA, WV

^d AL, KY, MS, TN

^e AR, LA, OK, TX

^f IL, IN, MI, OH, WI

^g IA, KS, MN, MO, ND, NE, SD

^h AZ, CO, ID, MT, NM, NV, UT, WY

ⁱ AK, CA, OR, WA