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Original Article

The impact of anti-infective therapy on patients undergoing warfarin treatment

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Abstract

Introduction: The combination of antibiotics and warfarin is used frequently in clinical practice. However, the impact of this combination on the anticoagulant efficacy of warfarin remains uncertain, posing challenges to clinical decision-making. This study aimed to evaluate the influence of various antibiotics on the international normalized ratio (INR) values in hospitalized patients who were concurrently administered warfarin.

Methodology: This retrospective cohort study enrolled patients who received concomitant warfarin and antibiotic therapy at the Nanjing Drum Tower Hospital, between January 2013 and December 2022. The patients were categorized into 8 groups based on the type of antibiotics they were received. The demographic characteristics were recorded, and the clinical outcomes were focused on changes in INR values after combining antibiotics in warfarin users.

Results: A total of 623 patients were enrolled in this study. Based on analysis of covariance (ANCOVA), the maximum INR values of the combinations were as follows: 2.72 for oxazolidinones, 2.86 for β-lactams, 2.86 for carbapenems, 2.91 for glycopeptides, 2.91 for macrolides, 3.77 for quinolones, 4.13 for sulfonamides, and 4.37 for antifungal agents. Pairwise comparisons revealed that quinolones, sulfonamides, and antifungal agents manifested the most substantial elevation in INR values when co-administered with warfarin. β-lactams, glycopeptides, oxazolidinones, macrolides, and carbapenems demonstrated a comparatively weaker impact on INR values.

Conclusions: Co-administration of warfarin with antibiotics led to an elevation in INR values in patients. Quinolones, sulfonamides, and antifungal agents had the most pronounced impact.

Key words: warfarin; antibiotics; INR; interaction; overcoagulation.

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Introduction

Warfarin, widely employed as an anticoagulant drug, is used in the prevention and treatment of thrombotic diseases such as deep vein thrombosis, atrial fibrillation, and heart valves diseases [1]. It is known for its elevated bleeding risk and limited therapeutic range. Warfarin dosage adjustments are guided by international normalized ratio (INR) values to ensure optimal anticoagulation. INR values are susceptible to fluctuations due to factors such as medications, dietary variations, and diverse disease states. These play a pivotal role in influencing the anticoagulant efficacy of warfarin [2].

With the increase in the spectrum of modern diseases and elevated patient resistance, polypharmacy has become a common therapeutic option, especially for patients with multiple diseases such as concomitant infections and cardiovascular diseases. This tends to increase the risk of clinically relevant drug interactions and poses new challenges for therapeutic management. Drug-drug interactions usually trigger unintended pharmacological effects, which are beneficial in a few cases, increasing efficacy, decreasing toxicity, or minimizing resistance. However, the majority of drug-drug interactions are detrimental, and two possible situations may occur that are not conducive to efficacy of the single drug: (1) drug-drug interactions resulting

in efficacy that is lower than the therapeutic window, and (2) drug-drug interactions causing efficacy to exceed the therapeutic window, exposing patients to the risk of side effects and toxicity, or even worsening their physical condition. About 30% of adverse drug reactions have been reported to be associated with drug interactions, which lead to increased hospitalizations and emergency room visits. A statistical analysis showed that about 15% of older adults taking multiple medications may be at risk for serious drug interactions [3].

Cases of antibiotics affecting the anticoagulant effect of warfarin have been widely reported, but the interaction mechanism is still unclear. Possible mechanisms include: (1) disorder of intestinal flora caused by antibiotics affects the synthesis of endogenous vitamin K [4]; (2) regulation of hepatic microsomal enzyme activities, especially CYP2C9 and CYP3A4, by inhibition or induction [5]; and (3) antibiotics competing for the binding sites of warfarin protein, which affects its anticoagulant efficacy [6]. Antibiotics interactions with warfarin can increase the risk of bleeding complications in patients, ranging from minor bleeding, which may include rhinorrhea, gingival bleeding, ecchymosis of the skin and mucous membranes, and excessive menstruation; to severe bleeding, which may be characterized by macroscopic hematuria, gastrointestinal bleeding, and in the worst cases, intracranial hemorrhage [4]. Therefore, when patients require anti-infection treatment, clinicians should consider antibiotic susceptibility, interactions with warfarin, and the risk of bleeding which may increase the complexity of patient care.

The potential for interactions and intricacies of warfarin therapy can complicate the decision-making of physicians when selecting treatment options. Prior studies have examined limited types of antibiotics and comprehensive comparisons were lacking. Furthermore, there were a lack of studies with larger sample sizes among Asian populations, and the studies did not include all the common types of antibiotics. A thorough understanding of how interactions affect anticoagulant efficacy will enable precise drug administration, early prediction of effects, and timely dosage adjustments. The aim of this study was to investigate the extent to which various antibiotics affect INR values in warfarin users.

Methodology

Study design and patient selection

We conducted a retrospective cohort study involving 623 patients who were administered warfarin concomitantly with various antibiotics at Nanjing Drum Tower Hospital from January 2013 to December 2022. The study was approved by the Institutional Ethics Committees of Nanjing Drum Tower Hospital (Approval Number: 2021-198-03), and the study protocol met the ethical principles of Declaration of Helsinki.

The inclusion criteria were (1) patients with clear indications of infections who were prescribed antibiotics; (2) patients who took long-term oral warfarin before admission and the INR value was maintained between 2 and 3; (3) patients who had undergone at least two INR tests before antibiotic initiation, and the difference between the two INR values did not exceed 0.2; (4) patient age > 18 years.

The exclusion criteria were: (1) patients who received antibiotics before admission; (2) patients who received a combination of warfarin and antibiotics for less than 3 days; (3) patients received other drugs that affect the anticoagulant effect of warfarin according to the instructions, such as amiodarone, carbamazepine, etc.; (4) patients who received antibiotics by non-oral or non-intravenous means; and (5) patients who took two or more antibiotics at the same time.

The 623 patients were categorized into 8 groups based on the type of antibiotics used, comprising 119 cases in the β-lactam antibiotic group, 86 cases in the quinolone antibiotic group, 70 cases in the glycopeptide antibiotic group, 62 cases in the oxazolidinone antibiotic group, 55 cases in the macrolide antibiotic group, 53 cases in the carbapenem antibiotic group, 45 cases in the sulfonamide antibiotic group, and 53 cases in the antifungal agents group.

Data collection

The baseline INR value was the mean INR value measured within 3 days before starting treatment with antibiotics, and the maximum INR value was the highest INR value recorded during antibiotic administration. The data collected in this study included gender, age, indications for the application of warfarin and antibiotics, and combined use time. The difference between the maximum INR value and the baseline INR value for each patient was expressed as ΔINR.

Statistical analysis

The goal of this study was to evaluate the impact of concomitant antibiotic administration on warfarin INR values and to identify variations between the groups. Analysis of covariance (ANCOVA) was utilized to compare differences between the groups. INR change from baseline was evaluated with the ANCOVA model

that contained baseline INR, patients' age, and combined use time as covariates. The maximum INR value served as the dependent variable, with the antibiotic groups as independent variable. p value < 0.05 was considered significant. Statistical analysis was performed with R version 4.2.2 statistical software (The R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 623 patients were included in this study between January 2013 and December 2022. Table 1 summarizes the baseline characteristics of the study population. The mean age of the patients was 66.08 ± 16.87 years and 45.1% were males. Valvular heart diseases emerged as the most common indication for warfarin therapy (42.1%), followed by atrial fibrillation (27.8%), venous thromboembolic diseases (18.3%), and autoimmune disorders (8.2%). In terms of indications for antibiotics, respiratory infections accounted for 53.9% of patients and were the most common indication for antibiotics treatment. In addition, 26.5% indications were skin infections, 7.5% were abdominal infections, 5.0% were infective endocarditis, 3.2% were urinary system infections, 2.4% were bloodstream infections, and 1.5% were central nervous system infections. The average duration of warfarin and antibiotics combination therapy was 5.38 ± 2.71 days. The baseline INR value before starting combination therapy was 2.28 ± 0.28.

In the ANCOVA analysis, wherein adjustments were made for patients' age, time of combined medication and baseline INR values, the examination focused on the adjusted maximum INR values within each specified group. The results, as detailed in Table 2, revealed an elevation in the maximum INR values relative to the baseline INR values across all groups, albeit with varying magnitudes. Specifically, patients administered antifungal agents exhibited the most substantial increase in INR values, followed by those receiving sulfonamide antibiotics and quinolone antibiotics. The ANCOVA analysis revealed a statistically significant variance in the influence exerted by distinct antibiotics on INR values among patients on warfarin, following requisite adjustments ($p < 0.001$).

Table 1. Baseline characteristics of the patients.

Item	Overall
Gender (%)	
Female	342 (54.9)
Male	281 (45.1)
Age (years)	66.08 ± 16.87
Antibiotics (%)	
β-lactam	199 (31.9)
Quinolone	86 (13.8)
Glycopeptide	70 (11.2)
Oxazolidinone	62 (10.0)
Macrolide	55 (8.8)
Carbapenem	53 (8.6)
Sulfonamide	45 (7.2)
Antifungal	53 (8.5)
Warfarin indication (%)	
Valvular heart disease	262 (42.0)
Atrial fibrillation	173 (27.8)
Venous thromboembolic disease	114 (18.3)
Autoimmune disorders	51 (8.2)
Others	23 (3.7)
Antibiotic indication (%)	
Respiratory system	334 (53.9)
Skin	167 (26.5)
Abdominal infection	47 (7.5)
Infective endocarditis	31 (5.0)
Urinary system	20 (3.2)
Bloodstream	15 (2.4)
Central nervous system	9 (1.5)
Duration combined (d)	5.38 ± 2.71
Baseline INR	2.28 ± 0.28

INR: international normalized ratio.

We measured the INR values after coadministration of antibiotics in the patients who were included of the study and combined the obtained data in a scatter plot (Figure 1). According to the trend line, patients showed most significant increase in INR values after combining antifungal agents, followed by sulfonamides, and finally quinolones. The patients had the fastest rate of increase in INR values after coadministration of antifungal agents, resulting in the shortest time required to reach the maximum INR value, followed by sulfonamides and quinolones.

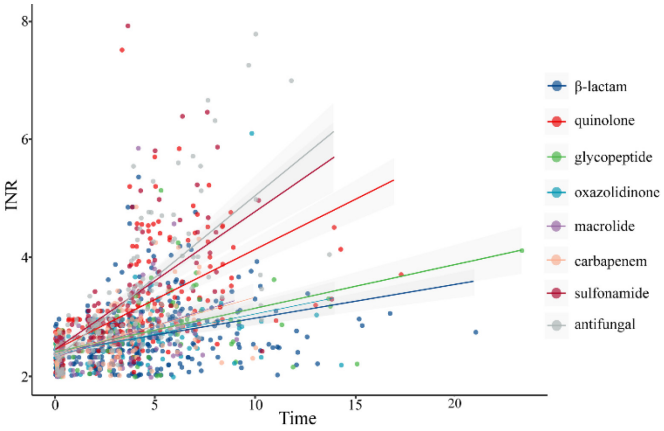
The results of the pairwise comparisons revealed that the maximum INR values of the quinolone, sulfonamides, and antifungal agents were higher than those of the other antibiotics, and the differences were

Table 2. The maximum INR values for each group after correction.

Group	Baseline INR	Maximum INR	95% CI
Oxazolidinone	2.28	2.72	2.54–2.90
β-lactam		2.86	2.76–2.96
Carbapenem		2.86	2.66–3.05
Macrolide		2.91	2.72–3.11
Glycopeptide		2.91	2.74–3.08
Quinolone		3.77	3.61–3.92
Sulfonamide		4.13	3.92–4.34
Antifungal		4.37	4.17–4.56

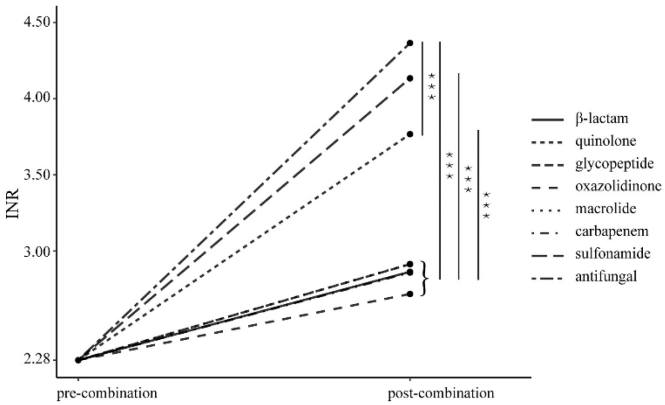
CI: confidence interval; INR: international normalized ratio.

Figure 1. Scatterplot of change in INR values after combining antibiotics in all patients.



INR: international normalized ratio.

Figure 2. Changes in INR values before and after combined use of various antibiotics and pairwise comparison results by ANCOVA analysis.



ANCOVA: Analysis of covariance; INR: international normalized ratio.

statistically significant (Table 3, Figure 2). Nevertheless, no statistically significant disparities were identified between quinolones and sulfonamides, nor between sulfonamides and the antifungal agents.

Discussion

The findings derived from our study elucidated that co-administration of antibiotics with warfarin was correlated with an elevation in INR values. Specifically, elevated INR values were most pronounced in patients receiving antifungal agents, sulfonamides, and quinolones; with antifungal agents exerting the most substantial influence on the elevation of INR. Moreover, β-lactam, glycopeptide, oxazolidinone, macrolide, and carbapenem antibiotics exhibited a relatively minimal effect on INR elevation, with no statistically significant distinctions between those antibiotics.

It has been reported that INR values exceeding 3.5 were correlated with an increased susceptibility to severe bleeding; and quinolones, sulfonamides, and antifungal agents were most likely to cause maximal INR values above 3.5 in the patients of our study [7]. Particularly, sulfonamides and antifungal agents induced maximum INR values, surpassing 4, thereby resulting in an increased risk of uncontrolled bleeding and potentially life-threatening conditions [3]. Antifungal agents and sulfonamide antibiotics emerged as entities with the highest proclivity for precipitating bleeding events [4]. Additionally, in a nested case-control study, antifungal agents and sulfonamide antibiotics demonstrated the highest association with the risk of gastrointestinal bleeding among the investigated antibiotics [8,9]. The augmented risk of bleeding associated with antifungal agents and sulfonamide antibiotics was attributable to a convergence of multiple mechanisms. Sulfonamide

Table 3. Groups with significant differences in pairwise comparisons.

Group1*	Group2	Difference	95% CI
Antifungal	Quinolone	0.60	0.22–0.98
Quinolone	Glycopeptide	0.85	1.20–0.50
Quinolone	Macrolide	0.85	1.23–0.47
Quinolone	β-lactam	0.90	0.62–1.18
Quinolone	Carbapenem	0.91	1.29–0.53
Quinolone	Oxazolidinone	1.05	1.41–0.69
Sulfonamide	Glycopeptide	1.22	0.81–1.64
Sulfonamide	Macrolide	1.22	0.78–1.66
Sulfonamide	β-lactam	1.27	0.91–1.63
Sulfonamide	Carbapenem	1.28	0.83–1.72
Sulfonamide	Oxazolidinone	1.42	0.99–1.84
Antifungal	Glycopeptide	1.45	1.06–1.85
Antifungal	Macrolide	1.45	1.03–1.87
Antifungal	β-lactam	1.50	1.17–1.84
Antifungal	Carbapenem	1.51	1.08–1.93
Antifungal	Oxazolidinone	1.65	1.24–2.06

*As reference. CI: confidence interval.

antibiotics, such as trimethoprim-sulfamethoxazole (TMP-SMX), interacted with warfarin through two discernible mechanisms. Firstly, it disrupted the intestinal flora, thereby diminishing vitamin K synthesis — a mechanism shared with other antibiotics [5]. Secondly, TMP-SMX exerted its effect through the inhibition of cytochrome CYP2C9, consequently influencing warfarin metabolism, similar to how antifungal agents impacted the efficacy of warfarin [10]. Hu *et al*. reported that fluconazole and voriconazole elevated the area under the S-warfarin concentration-time curve based on a vivo predictive modeling [11]. Itraconazole, a potent in vivo inhibitor of CYP3A4, lacked efficacy against other CYP enzymes, including CYP2C9 [10]. Although there were sporadic case reports of itraconazole elevating warfarin blood concentrations, the precise underlying mechanism remained elusive [12]. Furthermore, numerous potential interaction mechanisms between these antibiotics and warfarin, which have yet to receive comprehensive discourse, warranted consideration.

Cumulative evidence from diverse investigations suggested that quinolone antibiotics may disrupt vitamin K-producing intestinal flora or competitively bind to plasma proteins, thereby resulting in improved anticoagulant effect [4,13]. Nevertheless, the effect of distinct quinolone antibiotics on INR values have exhibited inconsistencies across various studies. For example, one study proposed that exposure to norfloxacin did not correlate with an increased bleeding risk in patients concurrently administered warfarin, whereas concomitant use of ciprofloxacin was associated with an elevated risk of bleeding [8]. Several retrospective studies have indicated that the use of levofloxacin was linked to increased INR values and a heightened risk of bleeding in warfarin users [14,15]. Systematic reviews appraising the effects of ciprofloxacin, levofloxacin, or moxifloxacin on warfarin have reported inconclusive outcomes across studies [16].

β-lactam antibiotics raised INR values modestly in patients who were concurrently administered warfarin. In contrast to our findings, a preceding retrospective study posited that patients utilizing penicillin and piperacillin-tazobactam did not undergo significant alterations in their warfarin dosage, thereby suggesting that warfarin dosage adjustments may not be necessary to maintain therapeutic INR values [17]. It was crucial to note that the limited sample size of that previous study necessitated cautious interpretation, and the conclusions required further investigation. Amoxicillin and potassium clavulanate, a potent β-lactamase inhibitor, constituted a commonly employed combination in clinical practice. Amoxicillin has been recognized for its capacity to influence the intestinal flora that is responsible for vitamin K production [6,21]. Moreover, the combination of potassium clavulanate with amoxicillin may significantly augment the likelihood of hepatotoxicity, potentially exacerbating the compromised hepatic synthesis of clotting factors [3]. Nevertheless, manifestations of this hepatotoxicity typically exhibited a delayed onset, rendering early diagnosis challenging [18]. A double-blind, crossover, placebo-controlled study reported that amoxicillin clavulanate potassium did not induce significant alteration in the anticoagulant effect of warfarin [19]. This suggested that the previously observed increases in INR values in these patients may not be exclusively attributed to drug interactions, emphasizing the imperative for further research to elucidate the underlying mechanisms. Furthermore, penicillin has been demonstrated to improve anticoagulation by inhibiting platelets [3]. Cephalosporins may influence the anticoagulant effect of warfarin through the inhibition of p-glycoprotein or alteration in intestinal flora [20]. Another interaction between cephalosporins and warfarin involved the N-methyl-thiotetrazole (MTT) side chain present in partial second-generation and third-generation cephalosporins, including cefmetazole, cefoperazone, cefotetan, and cefamandole [21]. In vitro, these side chains dissociated from the parent molecule and impeded clotting factor carboxylation, potentially intensifying the effect of warfarin [21]. Given the expansive spectrum of β-lactam antibiotics, the diversity of potential interactions necessitated further validation and comprehensive exploration.

The impact of glycopeptide antibiotics on the efficacy of warfarin primarily stemmed from their disruption of intestinal flora and high plasma protein binding rate. A retrospective study unveiled a significant increase in INR values when teicoplanin was co-administered with warfarin, displaying a notably higher increase in comparison to the vancomycin group [6]. Despite both drugs sharing a similar antibiotic spectrum and antimicrobial activity, the heightened plasma protein binding capacity of teicoplanin may contribute to increased free blood warfarin levels [6]. Furthermore, our study revealed that macrolide antibiotics had the capability to elevate INR values, albeit with a relatively modest increase. This effect was attributable to their inhibition of CYP3A4, impacting the metabolism of R-warfarin [5]. Significantly, a case-control study reported a comparatively low risk of

bleeding associated with macrolide antibiotics when contrasted with antifungal agents and TMP-SMX [4]. Nevertheless, a distinct investigation focusing on azithromycin specifically identified a two-fold increased risk of serious bleeding, underscoring the imperative for further exploration into the effects of macrolide antibiotics, particularly azithromycin [22].

Oxazolidinone antibiotics, notably linezolid, demonstrated the lowest maximum INR values among the eight antibiotics studied when co-administered with warfarin. Linezolid, a frequently utilized oxazolidinone antibiotic in clinical practice, underwent primarily non-enzymatic metabolism, distinct from the hepatic enzyme CYP2C9-mediated metabolism of warfarin. Linezolid exhibited a relatively low protein binding rate (31%) and did not affect the protein binding capacity of warfarin. Nevertheless, an earlier study reported an increase in INR from 3.74 to 4.06 following the concurrent use of linezolid in patients treated with warfarin [23]. Moreover, studies indicated that linezolid affected vitamin K synthesis [24].

Limitations

Our study has several limitations. Firstly, we were unable to assess the influence of factors such as fever associated with infections, which could potentially contribute to variations in INR values. Additionally, although we adjusted for potential confounders using ANCOVA, there remain unmeasured confounders, such as certain foods that may have an effect on INR values in warfarin users. Lastly, we categorized antibiotics by class, but did not examine the specific effect of individual drugs within those classes. Future prospective investigations, potentially encompassing larger multicenter cohort studies, are imperative to furnish a more exhaustive comprehension of the impacts of diverse antibiotics on INR values in warfarin users and to scrutinize potential differentiations among analogous antibiotics.

Conclusions

Antibiotics can elevate INR values in warfarin users, and different antibiotics have different effects on the INR values. Warfarin users taking high-risk antibiotics have a higher risk of over-anticoagulation. Therefore, physicians must exercise caution when prescribing antibiotics to patients on warfarin. Regular monitoring of INR values is essential in all cases to minimize the risk of over-anticoagulation, and more frequent monitoring of INR should be considered in patients at higher risk.

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References

1. Yagi T, Naito T, Kato A, Hirao K, Kawakami J (2021) Association between the prothrombin time-international normalized ratio and concomitant use of antibiotics in warfarin users: focus on type of antibiotic and susceptibility of *Bacteroides fragilis* to antibiotics. Ann Pharmacother 55: 157–164. doi: 10.1177/1060028020940728.
2. Greenblatt DJ, von Moltke LL (2005) Interaction of warfarin with drugs, natural substances, and foods. J Clin Pharmacol 45: 127–132. doi: 10.1177/0091270004271404.
3. Abdel-Aziz MI, Ali MA, Hassan AK, Elfaham TH (2016) Warfarin-drug interactions: an emphasis on influence of polypharmacy and high doses of amoxicillin/clavulanate. J Clin Pharmacol 56: 39–46. doi: 10.1002/jcph.583.
4. Baillargeon J, Holmes HM, Lin YL, Raji MA, Sharma G, Kuo YF (2012) Concurrent use of warfarin and antibiotics and the risk of bleeding in older adults. Am J Med 125: 183–189. doi: 10.1016/j.amjmed.2011.08.014.
5. Vega AJ, Smith C, Matejowsky HG, Thornhill KJ, Borne GE, Mosieri CN, Shekoohi S, Cornett EM, Kaye AD (2023) Warfarin and antibiotics: drug interactions and clinical considerations. Life (Basel) 13: 1661. doi: 10.3390/life13081661.
6. Nakano T, Nakamura T, Nakamura Y, Irie K, Sato K, Matsuo K, Imakyure O, Ogata K, Mishima K, Kamimura H (2017) [Effects of teicoplanin on the PT-INR controlled by warfarin in infection patients]. Yakugaku Zasshi 137: 909–916. [Article in Japanese]. doi: 10.1248/yakushi.17-00023.
7. Singer DE, Chang Y, Fang MC, Borowsky LH, Pomernacki NK, Udaltsova N, Go AS (2009) Should patient characteristics influence target anticoagulation intensity for stroke prevention in nonvalvular atrial fibrillation? The ATRIA study. Circ Cardiovasc Qual Outcomes 2: 297–304. doi: 10.1161/CIRCOUTCOMES.108.830232.
8. Fischer HD, Juurlink DN, Mamdani MM, Kopp A, Laupacis A (2010) Hemorrhage during warfarin therapy associated with cotrimoxazole and other urinary tract anti-infective agents: a population-based study. Arch Intern Med 170: 617–621. doi: 10.1001/archinternmed.2010.37.
9. Schelleman H, Bilker WB, Brensinger CM, Han X, Kimmel SE, Hennessy S (2008) Warfarin with fluoroquinolones, sulfonamides, or azole antifungals: interactions and the risk of hospitalization for gastrointestinal bleeding. Clin Pharmacol Ther 84: 581–588. doi: 10.1038/clpt.2008.150.
10. Yamamoto H, Habu Y, Yano I, Ozaki J, Kimura Y, Sato E, Shida A, Fukatsu S, Matsubara K (2014) Comparison of the effects of azole antifungal agents on the anticoagulant activity

of warfarin. Biol Pharm Bull 37: 1990–1993. doi: 10.1248/bpb.b14-00564.
11. Hu ZY, Parker RB, Laizure SC (2012) In vivo information-guided prediction approach for assessing the risks of drug-drug interactions associated with circulating inhibitory metabolites. Drug Metab Dispos 40: 1487–1494. doi: 10.1124/dmd.112.045799.
12. Miura M, Takahashi N, Kanno S, Kato S, Nara M, Itoh M, Saitoh H, Yoshioka T, Kameoka Y, Fujishima N, Tagawa H, Hirokawa M, Sawada K (2011) Drug interaction of (S)-warfarin, and not (R)-warfarin, with itraconazole in a hematopoietic stem cell transplant recipient. Clin Chim Acta 412: 2002–2006. doi: 10.1016/j.cca.2011.06.035.
13. Ji Y, Hokayem Y (2011) Moxifloxacin-warfarin interaction. J Community Hosp Intern Med Perspect 1. doi: 10.3402/jchimp.v1i4.11512.
14. Glasheen JJ, Fugit RV, Prochazka AV (2005) The risk of overanticoagulation with antibiotic use in outpatients on stable warfarin regimens. J Gen Intern Med 20: 653–656. doi: 10.1007/s11606-005-0113-5.
15. Mercadal Orfila G, Gracia García B, Leiva Badosa E, Perayre Badía M, Reynaldo Martínez C, Jodar Masanés R (2009) Retrospective assessment of potential interaction between levofloxacin and warfarin. Pharm World Sci 31: 224–229. doi: 10.1007/s11096-008-9265-9.
16. Carroll DN, Carroll DG (2008) Interactions between warfarin and three commonly prescribed fluoroquinolones. Ann Pharmacother 42: 680–685. doi: 10.1345/aph.1K605.
17. Chaudhuri A, Wade SL (2018) Flucloxacillin-warfarin interaction: an under-appreciated phenomenon. Intern Med J 48: 860–863. doi: 10.1111/imj.13944.
18. Andrade RJ, Tulkens PM (2011) Hepatic safety of antibiotics used in primary care. J Antimicrob Chemother 66: 1431–1446. doi: 10.1093/jac/dkr159.
19. Zhang Q, Simoneau G, Verstuyft C, Drouet L, Bal dit Sollier C, Alvarez JC, Rizzo-Padoin N, Bergmann JF, Becquemont L, Mouly S (2011) Amoxicillin/clavulanic acid-warfarin drug interaction: a randomized controlled trial. Br J Clin Pharmacol 71: 232–236. doi: 10.1111/j.1365-2125.2010.03824.x.
20. Bohm NM, Crosby B (2012) Hemarthrosis in a patient on warfarin receiving ceftaroline: a case report and brief review of cephalosporin interactions with warfarin. Ann Pharmacother 46: e19. doi: 10.1345/aph.1Q771.
21. Strom BL, Schinnar R, Gibson GA, Brennan PJ, Berlin JA (1999) Risk of bleeding and hypoprothrombinaemia associated with NMTT side chain antibiotics: using cefoperazone as a test case. Pharmacoepidemiol Drug Saf 8: 81–94. doi: 10.1002/(SICI)1099-1557(199903/04)8:2<81::AID-PDS411>3.0.CO;2-G.
22. Lane MA, Zeringue A, McDonald JR (2014) Serious bleeding events due to warfarin and antibiotic co-prescription in a cohort of veterans. Am J Med 127: 657–663.e652. doi: 10.1016/j.amjmed.2014.01.044.
23. Kinoshita S, Wada K, Matsuda S, Kuwahara T, Sunami H, Sato T, Seguchi O, Yanase M, Nakatani T, Takada M (2016) Interaction between warfarin and linezolid in patients with left ventricular assist system in Japan. Intern Med 55: 719–724. doi: 10.2169/internalmedicine.55.5756.
24. Moubareck C, Gavini F, Vaugien L, Butel MJ, Doucet-Populaire F (2005) Antimicrobial susceptibility of bifidobacteria. J Antimicrob Chemother 55: 38–44. doi: 10.1093/jac/dkh495.

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