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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Drug-drug interactions with metronidazole and itraconazole in patients using acenocoumarol

Matthijs L. Becker[1,2] · Renate C.A.E. van Uden[1,2] · Thijs J. Giezen[1,2] · Karina Meijer[3] · Ilse Houtenbos[4] · Patricia M.L.A. van den Bemt[5]

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Abstract

Purpose Various population-based cohort studies have shown that antimicrobial agents increase the risk of overanticoagulation in patients using coumarins. In this study, we assessed this association in hospitalized patients.

Methods We included all patients hospitalized in the Spaarne Gasthuis (Haarlem/Hoofddorp, the Netherlands), who started using an antimicrobial agent during acenocoumarol treatment or vice versa between 1 January 2015 and 1 July 2019. Patients were followed from start of concomitant therapy until 48 h after termination of the concomitant therapy or discharge, whichever came first. We analyzed the association between the antimicrobial agents and the risk of overanticoagulation, defined as an interpolated INR above 6, using Cox regression analysis. We corrected for multiple testing with the Bonferroni correction. Patients who started using acenocoumarol and amoxicillin/clavulanic acid were used as reference group.

Results In the study population, sixteen antimicrobial agents were started frequently concomitantly with acenocoumarol treatment. We included 2157 interaction episodes in 1172 patients. Patients who started using the combination of co-trimoxazole (HR 3.76; 95% CI 1.47–9.62; $p = 0.006$), metronidazole (HR 2.55; 95% CI 1.37–4.76; $p = 0.003$), or itraconazole (HR 4.11; 95% CI 1.79–9.45; $p = 0.001$) concomitantly with acenocoumarol treatment had an increased risk of overanticoagulation compared with patients using acenocoumarol and amoxicillin/clavulanic acid concomitantly. The associations for metronidazole ($p = 0.045$) and itraconazole ($p = 0.015$) remained statistically significant after correction for multiple testing.

Conclusion Co-trimoxazole, metronidazole, and itraconazole increase the risk of overanticoagulation in patients using acenocoumarol. These combinations should be avoided if possible or otherwise acenocoumarol doses should be reduced and INR measured more frequently.

Keywords Drug interactions · Acenocoumarol · Antimicrobial drugs · Anticoagulants · Adverse effects

Introduction

Coumarins are widely used for the prevention of thromboembolic diseases. These drugs exert their anticoagulation effect by inhibition of the vitamin K epoxide reductase enzyme. This enzyme is involved in conversion of vitamin K to the active form and the production of coagulation factors II, VII, IX, and X. There is a wide intra- and

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✉ Matthijs L. Becker
mbecker@sahz.nl

[1] Pharmacy Foundation of Haarlem Hospitals, Boerhaavelaan 24, 2035 RC Haarlem, The Netherlands

[2] Department of Clinical Pharmacy, Spaarne Gasthuis, Haarlem / Hoofddorp, The Netherlands

[3] Department of Hematology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

[4] Department of Internal Medicine, Spaarne Gasthuis, Haarlem / Hoofddorp, The Netherlands

[5] Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

interindividual variation in the anticoagulation effect, and therefore, monitoring by international normalized ratio (INR) measurement is indicated. Too low doses of coumarins and INR levels below the therapeutic window are associated with an increased risk of thromboembolic events, while too high doses and INR levels above the therapeutic window are associated with an increased risk of bleeding [1]. The risk of hemorrhagic stroke increases with INR levels above four and sharply increases with INR levels above six [1, 2].

In the Netherlands, the coumarins acenocoumarol and phenprocoumon are in use, of which acenocoumarol is the most frequently used [3]. Factors that influence the anticoagulation effect are genetics, age, weight, dietary intake of vitamin K, fever, and co-prescribed drugs [4–9]. Drug-drug interactions between coumarins and antimicrobial drugs are a cause of overanticoagulation and an increased risk of bleeding [10]. In population-based cohort studies in the outpatient setting, co-trimoxazole is associated with a 20 to 24 times increased risk of overanticoagulation [10, 11] and a 3.7 to 6.2 times increased risk of bleeding compared with no antimicrobial drug use in coumarin users [12–15]. The risk of overanticoagulation and bleeding is already present in the first 3 days after initiation of the drug interaction and diminishes after 7 days [11, 12].

During hospital admission, antimicrobial agents are often started in patients on coumarin treatment. Within the hospital, coumarin is dosed by the treating physician, and alerts for drug-drug interactions are generated during order entry. If the combination of co-trimoxazole and a coumarin is prescribed, the alert recommends to avoid this combination. These alerts are subsequently reviewed by a pharmacist, who contacts the prescriber if there are adjustments to consider. Studies thus far have, to the best of our knowledge, never assessed the risk of overanticoagulation in hospitalized patients, although there are major differences with patients in the outpatient setting. In general, hospitalized patients treated with antimicrobial agents have more serious infections and comorbidities compared with ambulatory patients. During hospital admission, other antimicrobial agents are used, and antimicrobial agents are administered more often parenterally. Another difference is that INR measurements are more accessible to hospitalized patients, so they can be measured more frequently compared with ambulatory patients. In view of these differences, we performed a retrospective study in hospitalized patients using acenocoumarol and antimicrobial agents concomitantly to analyze the risk of overanticoagulation associated with these drug-drug interactions. Since acenocoumarol is the most frequently used coumarin in our hospital, we limited our study to acenocoumarol users.

Methods

Setting

Data for this retrospective study were obtained from the Spaarne Gasthuis (Haarlem/Hoofddorp, the Netherlands) in the time period between 1 January 2015 and 1 July 2019. In the Spaarne Gasthuis, the Hospital Information System Epic (Epic, Verona, WI) is used. Data acquisition was performed using Crystal Reports (Walldorf, Germany) to extract all relevant information from the Epic database. The medication administration data, age, sex, INR, alanine aminotransferase (ALAT), and admission and discharge data were extracted. All data were processed according to Dutch privacy legislation. This study was approved by the institutional review board of the Spaarne Gasthuis (Haarlem/Hoofddorp, the Netherlands).

Study cohort and procedures

All patients 18 years or older admitted to the hospital and using concomitantly acenocoumarol with an antimicrobial agent were included in the analysis. Drugs with the Anatomical Therapeutic Chemical (ATC) code that started with "J01" (antibacterials for systemic use) and "J02" (antimycotics for systemic use) were included in the analyses as antimicrobial agent. A treatment episode with acenocoumarol or antimicrobial agents started at the moment the drug was administered for the first time during an admission and ended at the moment of the last drug administration. For the antimicrobial agents, a treatment episode ended if the antimicrobial agent was not administered during two consecutive calendar days. For acenocoumarol, a treatment episode ended if it was not administered during three consecutive calendar days. In between two consecutive INR measurements during an admission, the INR was linearly interpolated [16]. INR values reported as "above 12" were analyzed as if they were 12.0. If the interpolated INR was above 3.0 at 0h00h of a day, a treatment episode with acenocoumarol was extended with two extra days, since acenocoumarol treatment can be interrupted until the INR is within therapeutic range. Concomitant use of acenocoumarol and an antimicrobial agent was defined as an interaction episode. If patients on acenocoumarol used multiple antimicrobial agents during an admission, multiple interaction episodes were included in the analysis.

Interaction episodes were excluded if the linearly interpolated INR at the moment of start of the concomitant use of acenocoumarol and antimicrobial agent was above 6.0. Interaction episodes that started with the concomitant use within 24 h after admission were excluded, because the treatment could have been started before admission. If acenocoumarol or the antimicrobial agent was administered

only once in an interaction episode, the interaction episode was excluded from the analysis, because single administrations will only have a minor impact on the pharmacokinetics.

Outcomes

The outcome parameter was the time from start of the concomitant use until the moment the interpolated INR was 6.0. Follow-up ended 48 h after stop of the concomitant use or at the moment of hospital discharge, whichever came first. A threshold of 6.0 was used for overanticoagulation, similar to other studies assessing the risk of overanticoagulation due to drug-drug interactions [10, 11, 17].

All antimicrobial agents with at least 25 interaction episodes were included in the analyses. We used amoxicillin with clavulanic acid as reference drug, because this antimicrobial agent was most frequently used and no drug-drug interactions with acenocoumarol have been described. We performed two subanalyses. In the first, we included only the first concomitant use of acenocoumarol and an antimicrobial agent during a hospital admission and ended follow-up at the moment a second antimicrobial agent was administered. In this subanalysis, we excluded all patients who started two or more antimicrobial agents simultaneously. In the second subanalysis, we included only the first episode of an antimicrobial agent per patient.

Statistical analysis

A Kaplan-Meier curve was constructed, and a Cox regression analysis was performed to analyze the difference in time until the interpolated or measured INR was above 6.0. We used two models to adjust for potential confounders. In the first model, sex, age, whether the ALAT was two times the upper limit of normal, concomitant administration of a Cytochrome P450 (CYP) 2C9 inhibitor, and concomitant administration of a CYP2C9 inducer were analyzed as co-factor and were entered into the Cox regression model. Acenocoumarol is metabolized by the CYP2C9 enzyme, and drugs that inhibit this enzyme increase the risk of overanticoagulation, while drugs that induce this enzyme will decrease the risk of overanticoagulation. The CYP2C9 inhibitors and inducers mentioned in the Flockhart table were used [18]. In the analysis of co-trimoxazole and metronidazole, respectively, these drugs were not considered as co-factors. In the second model, the parameters of the first model were used whether one or more administrations were given on the intensive care unit and whether one or more administrations were given parenterally. These latter parameters were included as proxies for severity of disease. The p values were corrected for multiple testing, using Bonferroni correction. For antimicrobial agents with a wide variation of prescribed doses, we analyzed whether the prescribed dose was associated with the risk of overanticoagulation. We compared patients who started acenocoumarol during treatment with antimicrobial agents with patients who started antimicrobial agents during acenocoumarol treatment. The analyses were performed using IBM SPSS Statistics for Windows software (IBM Corp., Version 24.0. Armonk, NY).

Results

Sixteen antimicrobial agents had at least 25 interaction episodes during the study period. We included 2157 interaction episodes during 1477 admissions in 1172 patients (Table 1). In 249 interaction episodes (11.5%), the interpolated INR was above 6.0 during follow-up.

The co-factors age (HR 1.02; 95% CI 1.01–1.04; $p = 0.001$), ALAT more than two times the upper limit of normal (HR 1.97; 95% CI 1.12–3.45; $p = 0.018$), CYP2C9 inhibitor use (HR 2.00; 95% CI 1.54–2.60; $p < 0.001$), intensive care unit (ICU) admission (HR 1.67; 95% CI 1.15–2.43; $p = 0.007$), and parenteral administration of antimicrobial agent (HR 1.58; 95% CI 1.19–2.11;$p = 0.002$) were significantly associated with an increased risk of overanticoagulation.

In the first model, concomitant use of acenocoumarol with ceftazidime (HR 2.22; 95% CI 1.10–4.50; $p = 0.027$), co-trimoxazole (HR 3.03; 95% CI 1.25–7.38; $p = 0.014$), metronidazole (HR 2.89; 95% CI 1.68–4.98; $p < 0.001$), and itraconazole (HR 4.51; 95% CI 1.19–17.0; $p = 0.027$) was significantly associated with an increased risk of overanticoagulation (Table 2).

In the second model, adjusting also for proxies for severity of disease, the associations with co-trimoxazole (HR 3.76; 95% CI 1.47–9.62; $p = 0.006$), metronidazole (HR 2.55; 95% CI 1.37–4.76; $p = 0.003$), and itraconazole (HR 4.11; 95% CI 1.79–9.45; $p = 0.001$) remained statistically significant. If we corrected for multiple testing with fifteen independent associations, using the Bonferroni correction, the associations with metronidazole ($p = 0.045$) and itraconazole ($p = 0.015$) remained statistically significant. The incidence ratios were one incident of overanticoagulation per 51.5, 19.3, 17.1, and 16.5 days for amoxicillin/clavulanic acid, co-trimoxazole, metronidazole, and itraconazole, respectively.

In the group of co-trimoxazole users, 9 patients received a daily dose of 480 mg or less, 19 patients received a daily dose between 960 and 1920 mg, and one patient received a daily dose of 5760 mg. The patients who received a daily dose of 480 mg or less had a nonsignificant lower risk of overanticoagulation compared with patients who received a daily dose of 960 mg or more (HR 0.29; 95% CI 0.033–2.47; $p = 0.26$).

For both co-trimoxazole and metronidazole, there was no difference whether acenocoumarol was added to co-trimoxazole (HR 1.12; 95% CI 0.14–9.33; $p = 0.92$) or

Table 1 Baseline table

Interaction episodes	2157
Male	1168 (54.1%)
Age (mean, SD)	79.9 (10.1) years
ALAT > 2x ULN*	58 (2.7%)
Concomitant CYP 2C9 inhibitor use	486 (22.5%)
Concomitant CYP 2C9 inducer use	34 (1.6%)
INR measurements per day	0.42
Follow-up (mean, SD)	4.6 (3.3) days
Antimicrobial agent added to acenocoumarol treatment	1127 (52.2%)
Acenocoumarol added to antimicrobial agent treatment	824 (38.2%)
Simultaneous start	206 (9.6%)
Admissions	1477
Admissions with 1 treatment episode	972
Admissions with 2 treatment episodes	377
Admissions with ≥ 3 treatment episodes	128
Patients	1172
Patients with 1 treatment episode	636
Patients with 2 treatment episode	310
Patients with ≥ 3 treatment episode	226

**ULN* upper limit of normal

metronidazole (HR 1.05; 95% CI 0.40–2.80; $p = 0.92$) treatment or vice versa. In all patients who used itraconazole, the itraconazole was added to acenocoumarol treatment.

The mean follow-up time of patients using amoxicillin/clavulanic acid (4.4 days) did not differ significantly from the mean follow-up times of patients using co-trimoxazole

Table 2 Risk of overanticoagulation, defined as a linearly interpolated INR > 6.0, during acenocoumarol treatment in hospitalized patients

	N	events	Unadjusted HR	Adjustedmodel 1[a] HR	95% CI	p	Adjusted model 2[a] HR	95% CI	p	Corrected *p* value[b]
Amoxicillin-clav	436	37	Ref.	Ref.			Ref.			
Amoxicillin	254	27	1.27	1.21	0.73–1.99	0.46	1.18	0.72–1.94	0.51	NA
Benzylpenicillin	43	8	1.71	1.92	0.85–4.37	0.12	1.56	0.65–3.74	0.32	NA
Flucoxacillin	120	12	1.04	1.12	0.58–2.18	0.73	0.99	0.51–1.95	0.98	NA
Cefuroxime	286	36	1.42	1.40	0.88–2.23	0.15	1.15	0.66–2.00	0.62	NA
Cefotaxime	28	1	0.39	0.47	0.06–3.51	0.46	0.26	0.03–2.19	0.22	NA
Ceftazidime	52	11	2.26	2.22	1.10–4.50	0.027*	1.77	0.82–3.86	0.15	NA
Ceftriaxone	202	25	1.33	1.20	0.71–2.03	0.50	1.00	0.54–1.84	0.99	NA
Meropenem	49	7	1.52	1.50	0.65–3.44	0.34	1.18	0.48–2.88	0.72	NA
Co-trimoxazole	29	6	2.47	3.03	1.25–7.38	0.014*	3.76	1.47–9.62	0.006*	0.090
Clindamycine	89	4	0.53	0.53	0.19–1.50	0.23	0.58	0.21–1.66	0.31	NA
Ciprofloxacin	347	41	1.41	1.46	0.94–2.29	0.096	1.67	1.04–2.67	0.034*	0.51
Vancomycin	26	3	1.22	1.27	0.39–4.20	0.69	1.07	0.31–3.66	0.92	NA
Metronidazole	90	21	2.82	2.89	1.68–4.98	< 0.001*	2.55	1.37–4.76	0.003*	0.045*
Nitrofurantoin	75	2	0.31	0.30	0.07–1.29	0.11	0.36	0.080–1.58	0.17	NA
Itraconazole	31	8	3.06	4.51	1.19–17.0	0.027*	4.11	1.79–9.45	0.001*	0.015*

[a] Adjusted for model 1, age, sex, ALAT > 2x upper limit of normal, CYP 2C9 inhibitor use, and CYP 2C9 inducer use, and model 2 as model 1 plus administration on ICU and parenteral administration

[b] Corrected for multiple testing with the Bonferroni correction

*$p < 0.05$

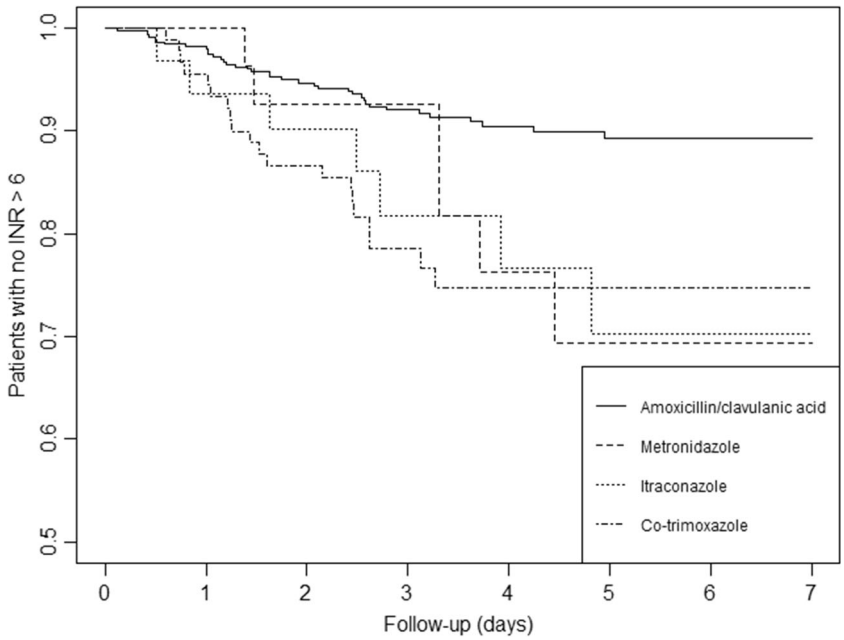

Fig. 1 Risk of overanticoagulation (INR > 6.0) during acenocoumarol treatment

(4.0 days), metronidazole (4.0 days), and itraconazole (4.3 days). Likewise, the mean number of INR measurements per day was similar for patients using amoxicillin/clavulanic acid (0.40 per day), co-trimoxazole (0.50 per day), metronidazole (0.43 per day), or itraconazole (0.45 per day).

In Fig. 1, the Kaplan-Meier curve for the incidence of an interpolated INR above 6.0 is given for amoxicillin/clavulanic acid, co-trimoxazole, metronidazole, and itraconazole. In the first subanalysis, including only the first interaction episode per admission, the association remained statistically significant for itraconazole (HR 5.62; 95% CI 1.16–27.2; $p = 0.032$), while the association for co-trimoxazole lost statistical significance (HR 2.93; 95% CI 0.57–15.1; $p = 0.20$), probably due to low numbers (appendix Table 1). Metronidazole was only prescribed six times as first antimicrobial agent during admission without co-prescription with other antimicrobial agents. In 62 patients, antimicrobial agent treatment was started with metronidazole, in 56 patients combined with one other antimicrobial agent and in six patients with two other antimicrobial agents. In these patients, metronidazole was most often co-prescribed with cefuroxime (31 times) and ceftriaxone (20 times). If we compared these 62 patients with patients starting with amoxicillin/clavulanic acid therapy during admission, the risk of overanticoagulation was statistically significantly increased (HR 2.32; 95% CI 1.02–5.30; $p = 0.046$). In the second subanalysis, including only the first episode of an antimicrobial agent per patient, the associations remained similar (appendix Table 2).

Discussion

In this study, we analyzed the risk of overanticoagulation in hospitalized patients using antimicrobial agents and acenocoumarol concomitantly. The use of co-trimoxazole, metronidazole, and itraconazole was significantly associated with an increased risk of overanticoagulation compared with amoxicillin/clavulanic acid use. The association with co-trimoxazole lost statistical significance after correction for multiple testing, probably due to low numbers. Since the drug-drug interaction between co-trimoxazole and acenocoumarol is established [10–15], correction for multiple testing is not indicated for confirmation of this result.

Previous studies that assessed the risk of overanticoagulation during concomitant use of coumarins and antimicrobial agents were performed in the general population and made comparisons with nonusers of the specific antimicrobial agent [10–15]. Our study was performed in hospitalized patients, and we compared this risk of overanticoagulation with patients using amoxicillin/clavulanic acid as reference group. We decided not to compare with patients using no antimicrobial agents, because all hospitalized patients are admitted because of a disease and patients using no antimicrobial agents during hospitalization are admitted for other diseases than infections. We decided to use amoxicillin/clavulanic acid as reference group, because this antimicrobial agent is most frequently used and no interactions with coumarins have been described in previous studies.

In population-based studies, the risk of overanticoagulation during concomitant use of co-trimoxazole and acenocoumarol

or phenprocoumon was 20 to 24 times higher, while in our study, the risk of overanticoagulation was 3.8 times higher. However, this difference is partly explained by the difference in population and reference group. Patients who are hospitalized have an acute illness and are at an increased risk of overanticoagulation irrespective of drug use. Moreover, in our study, we compared with patients using amoxicillin/clavulanic acid instead of patients using no antimicrobial agents. Patients using amoxicillin/clavulanic acid will have an increased risk of overanticoagulation, due to the underlying infection and accompanying fever, diminishing the hazard ratio for the association with co-trimoxazole. Other potential explanations are that INR is measured more frequently in hospitalized patients and acenocoumarol doses may be reduced to prevent overanticoagulation, since this is a well-known interaction.

To the best of our knowledge, we are the first to describe the drug-drug interaction between metronidazole and acenocoumarol. Similar to co-trimoxazole, metronidazole inhibits the CYP2C9 enzyme, and coumarins are metabolized by this enzyme, increasing the plasma levels of the coumarin [19]. A pharmacokinetic drug-drug interaction between metronidazole and warfarin has been described. The half-life of the enantiomorph S-warfarin increased significantly from 32 to 50 h after metronidazole administration [20]. This drug-drug interaction results in a significant 1.6 times increased risk of hemorrhage compared with warfarin monotherapy users [21], although in another study the association was not statistically significant [22]. In the study by Jobski et al., the odds ratio for major hemorrhage was 9.5 for the concomitant use of phenprocoumon and metronidazole, compared with 3.6 for the concomitant use of phenprocoumon and co-trimoxazole [13]. The two components of co-trimoxazole, sulfamethoxazole and trimethoprim, both inhibit the CYP2C9 enzyme activity [23]. Metronidazole reduces the expression of the CYP2C9 enzyme, instead of direct inhibition of the CYP2C9 enzyme. This suggests that the onset of CYP2C9 inhibition by metronidazole is later compared with co-trimoxazole. In the Kaplan-Meier curve, the curves for amoxicillin/clavulanic acid and metronidazole diverge after 3 days, although numbers were too small to draw definite conclusions.

An effect of itraconazole on the CYP2C9 enzyme has not been described, although itraconazole is a strong inhibitor of the CYP3A4 enzyme. In one population-based cohort study, a significantly increased risk of overanticoagulation in patients using both itraconazole and coumarins was found, although the authors mention that these results should be interpreted cautiously since it was based on just one case [17]. For warfarin, two case reports have been published. In one case report, a patient had an INR above eight and bleedings shortly after start of itraconazole during warfarin treatment [24]. In another case report, a seven-fold increased plasma level of S-warfarin was measured after initiation of itraconazole therapy, in a patient who also used co-trimoxazole [25].

In our study, we excluded patients if they had an interpolated INR level above 6.0 at the time of start of the interaction episode. It is possible that we have excluded patients who had a sharp increase in INR shortly after start of the combination of acenocoumarol and antimicrobial agent, while the actual INR at the time of start was below 6.0. Therefore, we may have missed cases of overanticoagulation shortly after start, and this may result in an underestimation of the hazard ratios during the first days.

Guidelines on the management of the drug interaction between co-trimoxazole and coumarins recommend to avoid the combination instead of managing the interaction by reducing the dose of the coumarin [26, 27]. For infections other than with *Pneumocystis jirovecii*, alternative antimicrobial agents are often available for co-trimoxazole treatment. If possible, the combinations of acenocoumarol and metronidazole and acenocoumarol and itraconazole should be avoided as well. Metronidazole has a spectrum that encompasses protozoans and anaerobic bacteria and is the mainstay drug for these infections. Therefore, alternative antimicrobial agents will often be less effective to cure these infections and not a suitable option. For itraconazole, switching to other antimycotics is often a suitable option. If the combinations cannot be avoided, preventive dose reductions of acenocoumarol and more frequent follow-up of the INR up to 7 days after initiation are indicated.

Our study has some potential strengths and limitations. Strengths of the current study are that we used the information registered in the hospital information system, with medication administration times and INR measurements available. Limitations in our study are that we could not differentiate between the effect of the antimicrobial agent and the effect of the underlying infection or accompanying fever. This may lead to confounding by indication, although the use of amoxicillin/clavulanic acid as reference drug may have partly overcome this limitation. If we adjusted in the analysis for administration on ICU unit and parenteral administration of the antimicrobial agent as proxy for severity of disease, the associations for co-trimoxazole, metronidazole, and itraconazole remained statistically significant. Meropenem is used as a reserve antimicrobial agent for severe infections, and no association was found for meropenem. For co-trimoxazole and metronidazole, there is a well-established mechanism that could result in an increased risk of overanticoagulation, making an effect of the infection or fever less likely. An association with itraconazole has been described in the literature before. Itraconazole was the only antimycotic, with sufficient numbers for analyses. Ideally, we would have compared itraconazole with other systemic antimycotics to rule out that the effect is present for all

antimycotics. In a previous study, no increased risk of overanticoagulation was found for oral fluconazole and oral terbinafine [17], suggesting that there is no such group effect. In the Netherlands, acenocoumarol is the most frequently used coumarin. The numbers of phenprocoumon users were too small to analyze, and warfarin is not marketed in the Netherlands. However, since all coumarins are mainly metabolized by the CYP2C9 enzyme and to a lesser extent by the CYP3A4 enzyme, we do not expect that the effect of antimicrobial agents on phenprocoumon or warfarin substantially differs from the effect on acenocoumarol. We used an INR above six as an outcome parameter for overanticoagulation, since numbers were too low to study clinically endpoints like major bleeding. We excluded patients who started with concomitant use of acenocoumarol and an antimicrobial agent within 24 h after admission, because the combination could have been initiated before admission. With this exclusion criteria, we have missed patients who started the concomitant therapy during the first 24 h of hospitalization. Since we included only hospitalized patients, the follow-up time of patients was rather short, and we did not have information before the admission and after the discharge. Therefore, we may have missed long-term effects occurring after discharge. The time from admission to start of concomitant therapy was too short to analyze differences with the acenocoumarol dose during concomitant therapy.

To conclude, the risk of overanticoagulation during acenocoumarol treatment is increased when used simultaneously with co-trimoxazole, metronidazole, and itraconazole. The use of these antimicrobial agents during acenocoumarol treatment should be avoided if possible, or otherwise acenocoumarol doses should be reduced and INR levels measured frequently during the first 7 days of the drug-drug interaction.

Authors' contributions M.L.B., R.C.A.E.v.U., and I.H. contributed to the study conception and design. Material preparation and data collection was performed by M.L.B., and analysis was performed by M.L.B., R.C.A.E.v.U., T.J.G., K.M., and P.M.L.A.v.d.B. The first draft of the manuscript was written by M.L.B., and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data and material The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interests K. Meijer reports travel support from Baxter; grants, travel support, and speaker fees from Bayer; grants and speaker fees from Sanquin; grants from Pfizer; speaker fees from Boehringer Ingelheim; speaker fees from BMS; speaker fees from Aspen; consulting fees from Uniqure; and grants from Federatie van Nederlandse Trombosediensten, all outside the submitted work. The other authors have no conflicts of interest.

Ethics approval Ethical approval was waived by the local Institutional Review Board of the Spaarne Gasthuis in view of the retrospective nature of the study, and all the procedures being performed were part of the routine care.

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