Risk of bleeding and antibiotic use in patients receiving continuous phenprocoumon therapy

A case-control study nested in a large insurance- and population-based German cohort

Sascha Abbas[1]; Peter Ihle[1]; Sebastian Harder[2]; Ingrid Schubert[1]

[1]PMV Research Group at the Department of Child and Adolescent Psychiatry and Psychotherapy, University of Cologne, Cologne, Germany; [2]Institute of Clinical Pharmacology, University Hospital Frankfurt am Main, Frankfurt am Main, Germany

Summary

There is major concern about coumarins interacting with various drug classes and increasing the risk of overanticoagulation. The aim of the study was to assess bleeding risk in patients with concurrent use of antibiotics and phenprocoumon, the most widely prescribed coumarin in many European countries. We conducted a nested-case-control study within a cohort of 513,338 incident and continuous phenprocoumon users ≥18 years of age using claims data of the statutory health insurance company AOK, covering 30% of the German population. Bleeding risk associated with current use of antibiotics for systemic use (antibacterials/antimycotics) was calculated using conditional logistic regression in 13,785 cases with a bleeding event and 55,140 risk-set sampling-matched controls. Bleeding risk associated with any antibacterial use in phenprocoumon users was significantly increased [odds ratio (OR) 2.37, 95% confidence interval (CI) 2.20–2.56]. The association was stronger for gastrointestinal than for cerebral bleeding (OR 2.09, 95% CI 1.84–2.38 and OR 1.34, 95% CI 1.03–1.74, respectively) and highest for other/unspecified bleeding (OR 2.92, 95% CI 2.62–3.26). Specific antibiotic classes were strongly associated with bleeding risk, e.g. cotrimoxazole (OR 3.86, 95% CI 3.08–4.84) and fluorquinolones (OR 3.13, 95% CI 2.74–3.59), among those highest for ofloxacin (OR 5.00, 95% CI 3.01–8.32). Combined use of phenprocoumon and antimycotics was not significantly associated with bleeding risk. Risk was not significantly modified by age (p_{int}=0.25) or sex (p_{int}=0.96). The association was stronger the closer the antibiotic exposure was to the bleeding event. Among continuous phenprocoumon users, antibiotics – particularly quinolones and cotrimoxazole – should be prescribed after careful consideration due to an increased bleeding risk. Close monitoring of international normalised ratio levels after prescription is recommended.

Keywords

Epidemiological studies, coagulation inhibitors, risk factors

Correspondence to:
Sascha Abbas
PMV Research Group
Department of Child and Adolescent Psychiatry and Psychotherapy
University of Cologne
Herderstr. 52, 50931 Köln, Germany
Tel.: +49 221 478 87613, Fax: +49 221 478 6766
E-mail: sascha.abbas@uk-koeln.de

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Introduction

Oral anticoagulants are commonly prescribed and widely used to prevent thromboembolic diseases. Whereas warfarin is the most widely used coumarin-type anticoagulant, common treatment in many European countries such as Germany and the Netherlands is conducted with phenprocoumon (1, 2). Both substances are vitamin K antagonists that inhibit vitamin K epoxide reductase and thus suppress the regeneration of the reduced form of vitamin K (1). However, they show substantially different pharmacokinetic and pharmacogenetic features (3, 4). In contrast to warfarin, phenprocoumon has a much longer half-life and longer onset of action (5) and is not completely metabolised but partly excreted as a parent compound (3, 6). Moreover, phenprocoumon is less dependent on the CYP2C9 clearance pathway and metabolism involves the CYP3A4 monooxygenase (3, 7). Besides the beneficial effects of coumarins, there is major concern about the increased risks of overanticoagulation and its enhancement by interactions with various drug classes, including antibiotics (8, 9). The mechanisms of interaction between antibiotics and coumarins are assumed to involve disruption of the intestinal flora, thus reducing vitamin K synthesis and inhibitory effects on the cytochrome P450 pathway – and thus on coumarin metabolism (10).

Several studies have reported on interactions of warfarin (11-18) or the combined group of phenprocoumon and acenocoumarol (19, 20) and antibiotic use with regard to bleeding risk or overanticoagulation. However, only one study so far assessed the association of bleeding risk and antibiotic use in phenprocoumon users (21). The authors reported significantly increased risks for quinolones, amoxicillin with clavulanic acid, cotrimoxazole and metronidazole, though case numbers were too small to detect potential effects in rarely described antibiotic subclasses. The present study is the largest so far assessing the risk of bleeding in patients with concurrent use of antibiotics (antibacterials/antimycotics)

and phenprocoumon. Due to the large sample size we were able to assess a) bleeding risk associated with infrequently prescribed antibiotic agents, b) risk estimates with regard to the localisation of bleeding and c) potential effect modification by age and sex.

Methods

Study base

The analysis is based on data of the statutory health insurance company AOK, which insures approx. 24 million persons, or around 30% of the German population. The following pseudonymous data were used for the present study: master data (i.e. age, sex, time insured), documented ICD-10 (22) coded diagnoses from out- and inpatient care and medication prescription data. Due to coding regulations, outpatient diagnoses are documented quarterly in each of the four quarters of a year; inpatient diagnoses are documented with reference to the respective hospital stay including date and length of hospitalisation. Outpatient diagnoses are also coded with a diagnostic modifier, i.e. "suspected", "ruled out", "assured" and "status post". Several health services research studies have been performed within this database (23-25).

Study design (cohort definition and nested case-control study)

A nested case-control study was performed within a cohort of incident continuous phenprocoumon users. Among all insurants insured within the AOK between 2007 and 2010 (N = 24.10 million insurants in 2010 (annual average)) for at least one day, we defined as incident phenprocoumon users all insurants above 17 years of age who received a prescription of phenprocoumon (ATC-code: B01AA04) within this time frame and no phenprocoumon therapy in the previous 365 days (N = 542,911). We further restricted the cohort population to those continuously insured in the 365 days before first prescription. The final cohort consisted of N = 513,338 incident phenprocoumon users.

Cohort entry was the date of the first phenprocoumon prescription. Cohort members were followed until either discontinuation of phenprocoumon therapy, death, hospitalisation due to a bleeding event or the end of the study period (December 31st, 2011), whichever came first. Discontinuation of therapy was defined as a gap of 14 or more days without phenprocoumon therapy. As the database does not include information on the prescribed daily dose we estimated the duration of each prescription and thus periods under phenprocoumon therapy by assuming a daily dose of 0.75 DDD (2.25 mg) phenprocoumon. This assumption was based on recent data on dosing requirements for phenprocoumon, which account for major genotype variations (26, 27), and approved by the calculation of the prescribed daily dose (PDD). In our data we calculated PDD as the sum of prescribed phenprocoumon (in DDD) in the first year of follow-up (excluding the last prescription) divided by the number of days between first and last prescription, resulting in a PDD of 0.81. Cases were defined as insurants with a hospitalisation with a discharge diagnosis of major bleeding (including gastrointestinal, cerebral and other/unspecified bleeding) during follow-up. ICD-10-codes and categorisation for bleeding types according to Jobski et al. (21) were used. We randomly selected four controls for each case according to a risk-set sampling strategy (28). All cohort members who did not become a case and were still under follow-up at hospital admission date of the respective case (index date), were eligible as potential controls. Controls were matched to the case by length of follow-up, i.e. the index date for the control was defined so that duration of follow-up was similar between the case and the matched control. Controls were further matched to the case according to sex, age at cohort entry (± 2 years) and start date of follow-up (± 183 days). Controls could be selected more than once for different cases; cases could be selected as controls before becoming a case (28).

Exposure definition

For each antibiotic/antimycotic agent for systemic use (ATC classification [29]: J01 and J02) prescription intake periods assuming a daily dose of one DDD were created. Current exposure was defined as at least one day under therapy in the last seven days before index date. Antibiotic classes, subclasses and active components presented here were selected a priori taking into account known or potential interactions with phenprocoumon or warfarin (publications, summary of product characteristics).

Variable definition

The following variables were defined for population description as well as adjustment in risk models. *Morbidity*: Morbidity the year before cohort entry was defined as a hospital discharge diagnosis in the four quarters before cohort entry or at least two quarters with a documented diagnosis from outpatient care (excluding diagnostic modifiers "ruled out" and "suspected"). *Indication for phenprocoumon use*: As potential indication for phenprocoumon use we defined selected diagnoses between the two quarters before and the quarter after cohort entry. Diagnosis validation (a hospital discharge diagnosis or at least two of four outpatient diagnosis quarters) was performed as described for morbidity above. *Polypharmacy*: In each of the four quarters the year before cohort entry five or more different prescriptions (ATC, 7-digits). *Charlson comorbidity index*: Each individual was assigned a Charlson comorbidity index (30, 31) according to their documented diagnoses the year before cohort entry.

Statistics

Risk of bleeding associated with antibiotic use was calculated using conditional logistic regression accounting for the matching factors. Three models were run to disentangle potential confounding effects (i.e. independent factors causing bleeding or interacting with phenprocoumon): a) unadjusted model; b) adjustment for specific antibiotic classes (yes/no), c) adjustment for a priori selected medication use [antiarrhythmics, class I and III (ATC-code [29]: C01B), antidepressants (N06A), anti-inflammatory and antirheumatic products, non-steroids incl. ASA (M01A, N02AA66,

N02BA01, N02BA51, N02BA71, R05XA02), fibrates (C10AB, C10BB), heparins (B01AB01, B01AB51, B01AX05, B05CX05, C05AX08, C05BA03, C05BA53), HMG CoA reductase inhibitors (C10AA, C10BA, C10BX), platelet aggregation inhibitors excl. heparin (B01AC), tramadol (N02AX02, N02AX52)] in the month before index date (yes/no), a priori selected co-morbidities [malignant neoplasms (ICD-10-code [22]: C00-C97), diabetes mellitus (E10-E14), diverticular disease of intestine (K57), heart failure (I50), hypertensive diseases (I10-I15), ischaemic heart diseases (I20-I25), diseases of liver (K70-K77), diseases of oesophagus, stomach and duodenum (K20-K31), renal failure (N17-N19, Z49, Z99.2), mental and behavioural disorders due to use of alcohol (F10), other chronic obstructive pulmonary disease (J44)] in the year before cohort entry (yes/no), amount of phenprocoumon prescription (in DDD) in the follow-up (cont.), hospital discharge diagnosis of bleeding in the year before cohort entry (yes/no) and a priori selected morbidities as indication for phenprocoumon use [pulmonary embolism (ICD-code: I26), atrial fibrillation (I48), ischaemic insult (I63, I64), phlebitis and thrombophlebitis (I80), presence of cardiac and vascular implants and grafts (Z95), others (I23.6, I25.3, I42, I51.7, I71, I72)] at first phenprocoumon prescription (yes/no). Effect modification by sex and age was analysed in age- and sex-stratified models. Test for interaction was evaluated using the Wald statistics for the respective interaction term. All tests were two-sided with a significance level of $p \leq 0.05$. Calculations were conducted with SAS 9.3 (SAS Institute, Cary, NC, USA).

Sensitivity analyses

We performed several sensitivity analyses to verify the results: a) assuming different daily doses of phenprocoumon, i.e. 0.25 DDD (0.75 mg) and 1.25 DDD (3.75 mg) [0.75 DDD (2.25 mg) in the main analysis] due to missing physicians' prescribed daily doses in the database and b) assuming different time windows of antibiotic exposure definition, i.e. antibiotic use within the last 14 and 21 days before index date (7 days in the main analysis) and c) adjusting for the Charlson comorbidity index and polypharmacy instead of a priori selected medications and co-morbidities.

Results

We identified 513,338 insurants with an incident phenprocoumon prescription and continuous insurance the year before first prescription. Total follow-up time was 354,807 person-years, resulting in a mean follow-up time of 252 days (standard deviation [SD] = 243). Mean age at cohort entry was 70.8 years (SD = 12.4), 15.9% were below 60 years of age, and 47.3% were male. During follow-up, insurants were censored for the following reasons: treatment discontinuation (n = 454,396 [88.5%]), death (n=17,485 [3.4%]) or end of the study period (n=27.672 [5.4%]). A total of 13,785 insurants (2.7%) were identified as being hospitalised with a bleeding discharge diagnosis. Among these, 40.1% were defined as having gastrointestinal bleeding, 13.2% as having cerebral bleeding and 46.7% as other/unspecified bleeding (►Table 1). To these cases we matched 55,140 controls in 1:4 matching. 51.9% of cases and controls were female. Mean follow-up time until bleeding event and respective index date of controls was 156 days. Mean age (SD) at cohort entry was 73.6 (10.3) in cases and 73.6 (10.2) in controls. ►Table 2 displays the descriptive characteristics of cases and controls. Cases had significantly more frequent co-morbid conditions the year before cohort entry, which is also reflected by the respective Charlson comorbidity index (36.2% and 28.2% ≥3 in cases and controls, respectively; $p < 0.01$). Due to the high case and control numbers, most differences between cases and controls were significant, although not always relevant (e.g. 74.8% and 73.4% with hypertensive diseases and 16.7% and 15.1% with malignant neoplasms in cases and controls, respectively; $p<0.01$). In addition, cases more frequently had a preceding hospitalisation due to a bleeding event (3.5% in cases vs 1.1% in controls) and used significantly more antidepressants, anti-inflammatory and antirheumatic products, HMG CoA reductase inhibitors as well as platelet aggregation inhibitors and tramadol. Selected morbidities as potential indication for phenprocoumon use were not considerably different between cases and controls (►Table 2).

Risk of bleeding was significantly associated with current use of antibacterials in phenprocoumon users (odds ratio [OR] 2.37, 95% confidence interval [CI] 2.20-2.56, $p<0.0001$; ►Table 3). The highest risk estimates were observed for the group of sulfonamides and trimethoprim (OR 3.71, 95% CI 2.97-4.62, $p<0.0001$) and quinolone antibacterials (OR 3.13, 95% CI 2.74-3.59, $p<0.0001$). Risk estimates for all antibiotic classes under investigation are displayed in ►Table 3. Antimycotics for systemic use were not significantly associated with bleeding risk (OR 1.11, 95% CI 0.52-2.34, $p = 0.792$).

We further distinguished bleeding events in gastrointestinal, cerebral and other/unspecified bleeding forms (►Table 4). Risk of bleeding associated with combined use of any antibacterial for systemic use and phenprocoumon use was stronger when focusing on gastrointestinal bleeding than on cerebral bleeding events (OR

Table 1: Types of bleeding[a] in cases within the cohort of incident phenprocoumon users.

	n	%
Gastrointestinal	5,528	(40.1)
Cerebral	1,823	(13.2)
Urogenital	1,438	(10.4)
Respiratory	1,441	(10.5)
Visceral	238	(1.7)
Ocular	262	(1.9)
Auricular	6	(0.0)
Other/Unspecified[b]	3,049	(22.1)

N = 13.785; a ICD-10 codes and categorisation of bleeding groups according to Jobski et al. (2011); b mainly including the ICD-code D68.3 "haemorrhagic disorder due to circulating anticoagulants".

Table 2: Characteristics of bleeding cases and controls in the cohort of incident phenprocoumon users.

	Cases (n=13,785)		Controls (n=55,140)		P-value[a]
	n	%	n	%	
Selected characteristics the year before cohort entry					
Charlson comorbidity index > 3	4,989	(36.2)	15,554	(28.2)	<0.01
Hospitalisation due to a bleeding event[b]	482	(3.5)	631	(1.1)	<0.01
Multimedication use	4,062	(29.5)	13,129	(23.8)	<0.01
Morbidity the year before cohort entry					
Malignant neoplasms	2,297	(16.7)	8,349	(15.1)	<0.01
Diabetes mellitus	5,148	(37.3)	18,978	(34.4)	<0.01
Diverticular disease of intestine	808	(5.9)	3,006	(5.5)	0.04
Heart failure	2,889	(21.0)	9,427	(17.1)	<0.01
Hypertensive diseases	10,318	(74.8)	40,464	(73.4)	<0.01
Ischaemic heart diseases	5,136	(37.3)	17,991	(32.6)	<0.01
Diseases of liver	1,616	(11.7)	5,725	(10.4)	<0.01
Diseases of oesophagus, stomach and duodenum	2,684	(19.5)	9,347	(17.0)	<0.01
Renal failure	1,836	(13.3)	4,722	(8.6)	<0.01
Mental and behavioural disorders due to use of alcohol	357	(2.6)	810	(1.5)	<0.01
Other chronic obstructive pulmonary disease	1,866	(13.5)	6,087	(11.0)	<0.01
Morbidity as potential indication for phenprocoumon use at cohort entry					
Atrial fibrillation	6,619	(48.0)	28,510	(51.7)	<0.01
Ischaemic insult	2,094	(15.2)	7,573	(13.7)	<0.01
Phlebitis and thrombophlebitis	1,971	(14.3)	8.177	(14.8)	0.09
Presence of cardiac and vascular implants and grafts	1,777	(12.9)	6,501	(11.8)	<0.01
Pulmonary embolism	1,513	(11.0)	5,598	(10.2)	<0.01
Others[c]	1,267	(9.2)	4,755	(8.6)	0.03
Medication use the year before cohort entry					
Antiarrhythmics, class I and III	901	(6.5)	3,652	(6.6)	0.93
Antidepressants	2,348	(17.0)	7,596	(13.8)	<0.01
Antiinflammatory and antirheumatic products, non-steroids incl. ASA	6,024	(43.7)	22,978	(41.7)	<0.01
Fibrates	215	(1.6)	871	(1.6)	0.96
Heparins	332	(2.4)	1,166	(2.1)	0.05
HMG CoA reductase inhibitors	5,171	(37.5)	19,493	(35.4)	<0.01
Platelet aggregation inhibitors excl. heparin	4,200	(30.5)	13,124	(23.8)	<0.01
Tramadol	1,437	(10.4)	4,278	(7.8)	<0.01

[a]Wald statistic based on univariate conditional logistic regression; [b]hospitalisation with a bleeding hospital discharge diagnosis; [c]including ICD-10-codes I23.6, I25.3, I42, I51.7, I71, I72 (see *Methods*).

Table 3: Risk of bleeding associated with current use of antibiotics[a] in phenprocoumon users.

Antibacterials/Antimycotics (ATC classification)	Cases		Controls		Model 1[b]		Model 2[c]		Model 3[d]	
	n	%	n	%	OR	95% CI	OR	95% CI	OR	95% CI
Antibacterials for systemic use (J01)	1,166	(8.5)	1,948	(3.5)	2.51	(2.33–2.71)	-	-	2.37	(2.20–2.56)
Tetracyclines (J01A)	84	(0.6)	201	(0.4)	1.68	(1.30–2.18)	1.62	(1.25–2.09)	1.56	(1.20–2.03)
Amphenicols (J01B)	0	(0.0)	0	(0.0)	-	-	-	-	-	-
Beta-lactam antibacterials, penicillins (J01C)	228	(1.7)	451	(0.8)	2.04	(1.74–2.40)	1.89	(1.61–2.23)	1.79	(1.52–2.12)
First-generation cephalosporins (J01DB)	4	(0.0)	12	(0.0)	1.39	(0.45–4.32)	1.32	(0.42–4.19)	1.31	(0.41–4.17)
Second-generation cephalosporins (J01DC)	114	(0.8)	259	(0.5)	1.72	(1.38–2.15)	1.63	(1.30–2.04)	1.53	(1.22–1.93)
Third-generation cephalosporins (J01DD)	42	(0.3)	68	(0.1)	2.37	(1.61–3.49)	2.27	(1.53–3.35)	1.98	(1.33–2.96)
Sulfonamides and trimethoprim (J01E)	169	(1.2)	173	(0.3)	3.96	(3.20–4.91)	3.79	(3.05–4.71)	3.71	(2.97–4.62)
Macrolides (J01FA)	112	(0.8)	214	(0.4)	2.07	(1.65–2.61)	1.81	(1.43–2.30)	1.75	(1.38–2.23)
Lincosamides (J01FF)	37	(0.3)	74	(0.1)	2.05	(1.37–3.05)	1.87	(1.25–2.80)	1.59	(1.06–2.40)
Aminoglycoside antibacterials (J01G)	4	(0.0)	8	(0.0)	1.83	(0.55–6.09)	1.48	(0.42–5.16)	1.41	(0.39–5.11)
Quinolone antibacterials (J01M)	413	(3.0)	498	(0.9)	3.41	(2.98–3.89)	3.28	(2.87–3.75)	3.13	(2.74–3.59)
Metronidazole (J01XD01, P01AB01)	12	(0.1)	34	(0.1)	1.44	(0.74–2.78)	0.98	(0.50–1.94)	0.99	(0.50–1.96)
Comb. for erradication of *H. pylori* (A02BD)	2	(0.0)	8	(0.0)	0.97	(0.20–4.58)	1.02	(0.22–4.81)	1.08	(0.22–5.17)
Expectorants and antibiotics (R05GB)	24	(0.2)	64	(0.1)	1.45	(0.91–2.33)	1.39	(0.86–2.23)	1.31	(0.81–2.13)
Antimycotics for systemic use (J02)	11	(0.1)	30	(0.1)	1.47	(0.72–2.98)	1.14	(0.55–2.36)	1.11	(0.52–2.34)

N (cases) = 13,785; N (controls) = 55,140; ATC= Anatomic Therapeutic Chemical; OR = odds ratio; CI = confidence interval; [a]at least one day under therapy in the last 7 days before index date assuming a daily dose of one DDD; [b]unadjusted conditional logistic regression; [c]as model 1 with additional adjustment for all other antibiotic/antimycotic classes in the table; [d]as model 2 (as model 1 for the J01-group) with further adjustment for selected morbidities the year before cohort entry, potential indication for phenprocoumon use, selected medication use the month before index date (see Table 2 for details), hospitalisation with discharge diagnosis of bleeding the year before cohort entry and amount of phenprocoumon prescription (DDD) during follow-up.

2.09, 95% CI 1.84-2.38, p<0.0001 and OR 1.34, 95% CI 1.03-1.74, p = 0.029 for gastrointestinal and cerebral bleeding, respectively). Highest risk estimates were observed for other/unspecified bleeding events including respiratory and urogenital bleeding and haemorrhagic disorder due to circulating anticoagulants (ICD D68.3) with an OR of 2.92 and 95% CI 2.62-3.26 (p<0.0001). The higher risk estimates for gastrointestinal bleeding than for cerebral bleeding was confirmed by the risk estimates in most of the antibiotic classes under investigation (►Table 4).

Results of the risk analyses of selected antibiotic subclasses and active components confirmed the results of the major classes presented in ►Table 3 (►Table 5). In the group of quinolones, the risk of bleeding associated with combined use of ofloxacin and phenprocoumon was five-fold increased (p<0.0001); by comparison, estimates for other active components under investigation (ciprofloxacin, levofloxacin, moxifloxacin) were three-fold increased (p<0.0001 for all of the three components). Cotrimoxazole was associated with an almost four-fold increased risk of bleeding (OR 3.86, 95% CI 3.08-4.84, p<0.0001).

We further assessed potential modifying effects of the association between overall bleeding and antibacterials from systematic use by sex or age. No significant effect modification was observed (p_{int} = 0.25 and 0.96 for age and sex, respectively).

In order to assess the influence of time of antibacterial exposure on bleeding risk we divided exposed individuals into three groups by duration between the date of latest antibacterial prescription before the index date and the index date: 0-3, 4-7 and ≥8 days (►Table 6). We observed the lowest association in individuals with their latest prescription far from the index date (≥8 days) (OR 1.58, 95% CI 1.39-1.79, p<0.0001), and an increase in risk the closer the latest antibacterial prescription was to the index date (OR 2.88, 95% CI 2.51-3.32, p<0.0001 and OR 3.25, 95% CI 2.85-3.70, p<0.0001 for 4-7 and 0-3 days, respectively).

Finally, we performed various sensitivity analyses in order to investigate the robustness of our results. First, we widened the time window of current antibiotic exposure into 14 and 21 days before the bleeding event, resulting in lower but still significantly increased risk estimates (OR 2.37, 95% CI 2.20-2.56, p<0.0001, OR 2.13, 95% CI 1.99-2.28, p<0.0001 and OR 1.96, 95% CI 1.84-2.09, p<0.0001 for 7, 14 and 21 days, respectively). Second, we repeated the analyses with different assumptions of the prescribed daily dose of phenprocoumon, i.e. 0.25 DDD (0.75 mg) and 1.25 DDD (3.75 mg phenprocoumon). Results were similar to the main analyses (OR 2.37, 95% CI 2.20-2.56, p<0.0001, OR 2.45, 95% CI 2.32-2.58, p<0.0001 and OR 2.18, 95% CI 1.97-2.41, p<0.0001 for 0.75, 0.25 and 1.25 DDD phenprocoumon, respectively). Finally

Antibacterials/Antimycotics (ATC classification)	Gastrointestinal bleeding				Cerebral bleeding				Other types of bleeding			
	Cases (n=5,528)	Controls (n=22,112)	OR	95% CI	Cases (n=1,823)	Controls (n=7,292)	OR	95% CI	Cases (n=6,434)	Controls (n=25,736)	OR	95% CI
Antibacterials for systemic use (J01)	431	780	2.09	(1.84–2.38)	88	249	1.34	(1.03–1.74)	647	919	2.92	(2.62–3.26)
Tetracyclines (J01A)	34	88	1.36	(0.89–2.06)	8	27	1.02	(0.46–2.29)	42	86	1.83	(1.25–2.67)
Amphenicols (J01B)	0	0	-	-	0	0	-	-	0	0	-	-
Beta-lactam antibacterials, penicillins (J01C)	91	173	1.84	(1.40–2.41)	18	49	1.38	(0.78–2.43)	119	229	1.89	(1.49–2.38)
First-generation cephalosporins (J01DB)	1	4	1.46	(0.16–13.40)	1	1	7.77	(0.46–130.57)	2	7	0.86	(0.16–4.53)
Second-generation cephalosporins (J01DC)	47	114	1.48	(1.04–2.13)	10	32	1.26	(0.59–2.67)	57	113	1.79	(1.28–2.50)
Third-generation cephalosporins (J01DD)	19	25	3.08	(1.64–5.77)	5	10	1.62	(0.52–5.03)	18	33	1.71	(0.94–3.10)
Sulfonamides and trimethoprim (J01E)	56	65	3.37	(2.32–4.90)	9	23	1.35	(0.60–3.02)	104	85	4.47	(3.31–6.04)
Macrolides (J01FA)	39	78	1.47	(0.97–2.23)	7	35	0.83	(0.33–2.10)	66	101	2.22	(1.60–3.08)
Lincosamides (J01FF)	15	26	1.90	(0.98–3.69)	4	10	1.00	(0.30–3.39)	18	38	1.58	(0.87–2.86)
Aminoglycoside antibacterials (J01G)	2	5	1.12	(0.19–6.71)	0	1	-	-	2	2	2.73	(0.35–21.31)
Quinolone antibacterials (J01M)	139	204	2.34	(1.86–2.94)	28	65	1.73	(1.08–2.76)	246	229	4.24	(3.51–5.13)
Metronidazole (J01XD01, P01AB01)	7	8	2.94	(1.02–8.47)	0	5	-	-	5	21	0.64	(0.23–1.77)
Comb. for erradication of *H. pylori* (A02BD)	2	1	9.49	(0.84–107.06)	0	2	-	-	0	5	-	-
Expectorants and antibiotics (R05GB)	6	28	0.96	(0.39–2.39)	2	9	0.75	(0.16–3.60)	16	27	1.92	(1.00–3.66)
Antimycotics for systemic use (J02)	6	10	2.18	(0.76–6.25)	2	1	4.06	(0.23–71.80)	3	19	0.34	(0.09–1.28)

ATC= Anatomic Therapeutic Chemical; OR = odds ratio; CI = confidence interval; [a]at least one day under therapy in the last 7 days before index date assuming a daily dose of one DDD; conditional logistic regression with adjustment for all other antibiotic/antimycotic classes in the table (except for the J01-group model) and further adjusted for selected morbidities the year before cohort entry, potential indication for phenprocoumon use, selected medication use the month before index date (see Table 2 for details), hospitalisation with discharge diagnosis of bleeding the year before cohort entry and amount of phenprocoumon prescription (DDD) during follow-up.

Table 4: Risk of bleeding associated with current use of antibiotics[a] in phenprocoumon users – by bleeding type.

we adjusted the risk models for a combined morbidity score (Charlson comorbidity index) and polypharmacy instead of adjusting for specific morbidities and medication use with no change in risk estimation (OR 2.37, 95% CI 2.20-2.56, p<0.0001 and OR 2.38, 95% CI 2.21-2.57, p<0.0001 in the main and sensitivity analyses, respectively).

Discussion

In this large population- and insurance-based nested case-control study in a cohort of continuous phenprocoumon users, concurrent use of antibiotics was associated with an increased risk of bleeding with higher risk estimates for gastrointestinal bleeding than for

Table 5: Risk of bleeding associated with current use of selected antibiotic subclasses / active components[a] in phenprocoumon users.

Antibacterials/Antimycotics (ATC classification)	Cases		Controls		Model 1[b]		Model 2[c]		Model 3[d]	
	N	%	N	%	OR	95% CI	OR	95% CI	OR	95% CI
Tetracyclines										
Doxycycline (J01AA02)	81	(0.6)	194	(0.4)	1.68	(1.29–2.18)	1.61	(1.24–2.10)	1.55	(1.19–2.03)
Beta-lactam antibacterials, penicillins										
Penicillins with extended sprectrum (J01CA)	119	(0.9)	265	(0.5)	1.82	(1.47–2.27)	1.65	(1.32–2.06)	1.59	(1.27–2.00)
Amoxicillin (J01CA04)	118	(0.9)	261	(0.5)	1.83	(1.47–2.28)	1.67	(1.33–2.08)	1.61	(1.28–2.02)
Amoxicillin and clavulanic acid (J01CR02)	50	(0.4)	74	(0.1)	2.74	(1.91–3.95)	2.56	(1.77–3.70)	2.33	(1.60–3.39)
Cloxacillin (J01CF02)	0	(0.0)	0	(0.0)	-	-	-	-	-	-
Cephalosporins										
Cefazolin (J01DB04)	0	(0.0)	0	(0.0)	-	-	-	-	-	-
Cefotaxime (J01DD01)	0	(0.0)	0	(0.0)	-	-	-	-	-	-
Cefpodoxime (J01DD13)	17	(0.1)	19	(0.0)	3.37	(1.74–6.52)	3.49	(1.80–6.76)	3.08	(1.58–6.03)
Ceftibuten (J01DD14)	4	(0.0)	10	(0.0)	1.74	(0.55–5.57)	1.63	(0.51–5.26)	1.45	(0.44–4.75)
Sulfonamides and trimethoprim										
Trimethoprim and derivates (J01EA)	4	(0.0)	11	(0.0)	1.53	(0.49–4.80)	1.33	(0.41–4.29)	1.42	(0.44–4.59)
Short-acting sulfonamides (J01EB)	0	(0.0)	0	(0.0)	-	-	-	-	-	-
Intermediate-acting sulfonamides (J01EC)	0	(0.0)	0	(0.0)	-	-	-	-	-	-
Long-acting sulfonamides (J01ED)	0	(0.0)	0	(0.0)	-	-	-	-	-	-
Cotrimoxazole (J01EE01)	165	(1.2)	162	(0.3)	4.12	(3.31–5.13)	3.96	(3.17–4.94)	3.86	(3.08–4.84)
Macrolides										
Erythromycin (J01FA01)	2	(0.0)	11	(0.0)	0.76	(0.17–3.42)	0.60	(0.13–2.81)	0.55	(0.11–2.70)
Quinolone antibacterials										
Fluorchinolones (J01MA)	413	(3.0)	498	(0.9)	3.41	(2.98–3.89)	3.28	(2.87–3.75)	3.13	(2.74–3.59)
Ofloxacin (J01MA01)	35	(0.3)	29	(0.1)	4.94	(3.00–8.14)	4.81	(2.90–7.95)	5.00	(3.01–8.32)
Ciprofloxacin (J01MA02)	217	(1.6)	261	(0.5)	3.39	(2.82–4.07)	3.15	(2.62–3.79)	3.02	(2.50–3.64)
Levofloxacin (J01MA12)	98	(0.7)	127	(0.2)	3.09	(2.37–4.03)	3.06	(2.35–4.00)	2.84	(2.17–3.73)
Moxifloxacin (J01MA14)	36	(0.3)	51	(0.1)	2.88	(1.87–4.44)	2.85	(1.85–4.40)	2.69	(1.73–4.18)
Other chinolones (J01MB)	0	(0.0)	0	(0.0)	-	-	-	-	-	-
Antimycotics for systemic use										
Imidazole derivates (J02AB)	0	(0.0)	2	(0.0)	-	-	-	-	-	-
Triazole derivates (J02AC)	11	(0.1)	27	(0.0)	1.60	(0.78–3.27)	1.23	(0.59–2.55)	1.20	(0.56–2.57)

N (cases) = 13,785; N (controls) = 55,140; ATC= Anatomic Therapeutic Chemical; OR = odds ratio; CI = confidence interval; [a]at least one day under therapy in the last 7 days before index date assuming a daily dose of one DDD; [b]unadjusted conditional logistic regression; [c]as model 1 with additional adjustment for all other antibiotic/antimycotic classes in Table 3; [d]as model 2 with further adjustment for selected morbidities the year before cohort entry, potential indication for phenprocoumon use, selected medication use the month before index date (see Table 2 for details), hospitalisation with discharge diagnosis of bleeding the year before cohort entry and amount of phenprocoumon prescription (DDD) during follow-up.

Duration between latest antibacterial prescription (ATC = J01) and index date	Cases		Controls		Model 1[b]		Model 2[c]	
	n	%	n	%	OR	95% CI	OR	95% CI
0–3 days	444	(3.2)	544	(1.0)	3.40	(2.99–3.86)	3.25	(2.85–3.70)
4–7 days	360	(2.6)	496	(0.9)	3.09	(2.69–3.55)	2.88	(2.51–3.32)
≥ 8 days	362	(2.6)	908	(1.6)	1.67	(1.48–1.89)	1.58	(1.39–1.79)

N (cases) = 13,785; N (controls) = 55,140; ATC= Anatomic Therapeutic Chemical; OR = odds ratio; CI = confidence interval; [a]at least one day under therapy in the last 7 days before index date assuming a daily dose of one DDD; those with current exposure were further divided into three groups according to time between latest prescription before the index date and index date (Reference = No use); [b]unadjusted conditional logistic regression; [c]adjustment for selected morbidities the year before cohort entry, potential indication for phenprocoumon use, selected medication use the month before index date (see Table 2 for details), hospitalisation with discharge diagnosis of bleeding the year before cohort entry and amount of phenprocoumon prescription (DDD) during follow-up.

Table 6: Risk of bleeding associated with current use of antibacterials[a] in phenprocoumon users according to time of exposure.

cerebral bleeding and a stronger association the closer the exposure was to the event.

Our results are in line with the only study so far assessing bleeding risk in phenprocoumon users (21). Jobski et al. reported significant associations between bleeding risk and the group of quinolones, cotrimoxazole and amoxicillin + clavulanic acid, which is comparable to the magnitude of the observed risk estimates in the present study. The authors also reported a significantly increased risk for metronidazole (21). We could, however, not confirm this result in our approximately five times larger case-control population. As already highlighted in a previous study (21), the observed drug interaction between phenprocoumon and quinolones is of special concern as it is listed neither in the summary of product characteristics of phenprocoumon in Germany nor in the 'Rote Liste', the German equivalent of the Physician's Desk Reference (32, 33). However, in the summary of the product characteristics for several quinolones potential interaction with anticoagulants are reported (34, 35).

Several population studies have reported significant increased risks of bleeding associated with concurrent use of the coumarin-type anticoagulant warfarin and antibiotics (11, 12, 15, 17, 18). In line with our results on phenprocoumon interactions, a systematic overview of warfarin interactions reported consistent interaction with macrolides and quinolones (9). By contrast, we could not repeat the reported increased risk of bleeding associated with use of azole antifungals in warfarin and the combined group of acenocoumarol and phenprocoumon users (9, 15, 36). Yet our results are in line with a recent large-scale case-control study nested in a cohort of a 5% sample of US Medicare beneficiaries reporting increased bleeding risks associated with concurrent use of quinolones, cotrimoxazole, as well as penicillins, macrolides, cephalosporins and warfarin (15). The authors also reported a weaker association between combined warfarin and antibiotic use for gastrointestinal bleeding than for non-gastrointestinal bleeding without distinguishing cerebral from other bleeding events. In the present study we could confirm that the risk of gastrointestinal bleeding is indeed lower than other/unspecified types of bleeding localisations, including urogenital and respiratory bleeding and an ICD-10-code specific for haemorrhagic disorders due to circulating anticoagulants (ICD D68.3) but higher than for cerebral bleeding risk.

We further observed a stronger association the closer the antibiotic exposure was to the bleeding event. Risk of bleeding associated with antibiotic use in phenprocoumon users was highest 0-3 days after the latest antibiotic prescription; it was less for 3-7 days and lowest for 8 days. Recently, Schelleman et al. specified a priori time windows of 0-5, 6-10, 11-15 and 16-20 days prior to the index date (11). Depending on the specific antibiotic drug class under observation, the authors reported stronger risks for days 0-5 (fluorquinolones), days 6-10 (cotrimoxazole) or days 11-15 (fluconazole) before the event. Indeed, these results and our observed higher bleeding risks the week after the latest antibiotic prescription raises the question of the latency from antibiotic exposure until the bleeding event. Clinical studies with international normalised ratio (INR) measurements after antibiotic exposure are necessary to study the effects of time until overanticoagulation as well as effects by dose and specific class of the antibiotic.

Pharmacokinetic and pharmacodynamic interaction mechanisms between antibiotics and coumarins that increase bleeding risk is only somewhat understood. One proposed mechanism is the disruption of the intestinal flora, which reduces vitamin K producing bacteria (10). Moreover, interaction via the cytochrome P450 is known to play a further role. Coumarin drug metabolism involves the cytochrome P450 enzyme CYP2C9 and CYP3A4 (3), the latter playing a major role as a catalyst in phenprocoumon hydroxylation (7). Both enzymes are also known to play a role as substrates (CYP3A4: macrolide antibiotics) or inhibitors (CYP3A4: macrolide antibiotics, ciprofloxacin, fluorquinolones, chloramphenicol; CYP2C9: azole antifungals, cotrimoxazole) of various antibiotic agents (37). With regard to cotrimoxazole, a further suggested mode of interaction is the expulsion of anticoagulants from plasma protein binding (38).

The study results may have been influenced by several limitations. We did not have information on potential confounders such as the

body mass index or life-style factors such as smoking, alcohol use or diet. However, a recent systematic review of risk factors for bleeding reported only malignancies and renal insufficiency as risk factors with moderate strength of evidence (39). In addition, a systematic review that was part of the UK NICE guidelines reported advanced age, concomitant use of other drugs such as antiplatelet agents and several co-morbid conditions as significant risk factors for bleeding (40). As we were able to adjust for several comorbidities and medications as well as a history of bleeding – factors with a potential of confounding the association – we feel confident that we did not miss any important confounding factors. Moreover, recent studies showed little changes in bleeding risk estimates associated with phenprocoumon or warfarin after additional confounder adjustment on lifestyle variables (41, 42). Confounding by indication of antibiotic use may also have biased our results, as fever or the underlying infection has been reported to be a risk factor for overanticoagulation (43). However, as elevated bleeding risks were found to be consistently associated with various antibiotic drug classes used for various infections confounding by indication is unlikely. Furthermore, we did not have any information on INR levels; rather, we used a documented hospital discharge diagnosis of bleeding as the outcome of interest. The accuracy of ICD codes for bleeding from Canadian administrative data has been proven with sensitivity, specificity, and positive and negative predictive values of around 90% of the gold standard in medical records (44). To our knowledge such a validation study has not been performed for insurance-based administrative data in Germany. However, a bleeding documented by a discharge diagnosis in hospital is a serious event, so coding quality can be regarded as high.

We did not have information on inpatient medication prescription, which may have led to a bias in the definition of discontinuation of phenprocoumon therapy. Missing over-the-counter medication is of minor concern as antibiotics as well as phenprocoumon require prescriptions. In addition, missing information on the prescribed daily dose and duration of prescription may have biased our definition of discontinuation of phenprocoumon therapy. For this reason, we ran sensitivity analyses assuming different daily doses of phenprocoumon therapy (i.e. 0.25, 0.75, 1.25 DDD; 1 DDD = 3 mg). These tests produced results similar to the main analyses. Further sensitivity analyses confirmed the robustness of our findings: e.g. the adjustment of a comorbidity index and polypharmacy instead of a priori selected co-morbid conditions and medications as well as the widening of the antibiotic exposure time window to 14 and 21 days before index date. Finally we were unable to focus on novel oral anticoagulants since data availability was from 2006 to 2011. Although safer with regard to drug-drug interactions (45), higher risks of gastrointestinal bleeding associated with novel anticoagulants compared with standard coumarins have been reported (46). Furthermore, as antibacterial agents adversely interfere with vitamin K synthesis, the resulting hypoprothrombinaemia (47, 48) might also contribute to bleeding risks with these compounds.

The main strength of our study is the large sample size, allowing us to assess risk estimates for rare antibiotic substances, for specific bleeding localization and for effect modification by age and sex. Another strength of this study is the inclusion of only incident users of phenprocoumon, thus ensuring comparability between cases and controls in terms of start and length of phenprocoumon therapy. Furthermore, recall and selection bias with regard to control selection can be mostly ruled out as information was routinely collected and the study nested in a defined cohort of incident phenprocoumon users. In addition, our study is based on real-life prescription practice, including patients irrespective of their physical or mental health condition.

In conclusion, among continuous phenprocoumon users, antibiotics – particularly fluorquinolones and cotrimoxazole – should be prescribed after careful consideration due to an increased risk of bleeding. Ideally, close monitoring of INR levels after prescription is necessary, particularly when further risk factors for bleeding such as multiple co-medications and co-morbid conditions (49) are present. In addition, the use of administrative and insurance-based data may help in identifying and monitoring populations at risk.

What is known about this topic?

- Combined use of coumarins and antibiotic agents is associated with increased risk of bleeding in several studies, yet there are few large-scale population-based studies on this topic.
- Most studies assess bleeding risk associated with antibiotic use in warfarin users. Only one study so far focuses on phenprocoumon, the most commonly prescribed coumarin in many European countries.

What does this paper add?

- Comprehensive data (> 500,000 incident phenprocoumon users) show that bleeding risk in incident and continuous phenprocoumon users is associated with use of specific antibacterial classes.
- Bleeding risk estimates by bleeding type indicate stronger associations for gastrointestinal bleeding than for cerebral bleeding.
- Effect modification analyses by time of antibiotic exposure reveal stronger associations the closer the antibiotic exposure was to the bleeding event.
- Bleeding risk associated with concurrent use of phenprocoumon and antibiotics is not modified by age or sex.

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Conflict of interest

Ingrid Schubert has received unrestricted grants for the PMV Research Group from health insurance providers (Federal Association of the AOK, AOK Hesse, AOK Baden-Württemberg), the Hessian Association of Statutory Health Insurance Physicians, and from the companies Abbott, Bayer, Lilly, Novo Nordisk, Sanofi and Schering. Sebastian Harder has received scientific grants from Merck KGaA and The Medicines Company and has received honoraria for lectures from Merck KGaA and LEO Pharmaceuticals. Peter Ihle has received honoraria for lectures from the ZI (Central Research Institute of Ambulatory Health Care in Germany) and Sanofi. Sascha Abbas has no conflicts of interest to declare.

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