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Original article

Keywords drug interactions, oral anticoagulants, phenprocoumon, German Pharmacoepidemiological Research Database, nested case-control study

Abstract

Purpose Phenprocoumon is the most frequently used vitamin K antagonist in Germany. Aim of this study was to estimate the risk of serious bleeding as a result of use of drugs with potential interaction with phenprocoumon.

Methods We conducted a nested case-control study in a cohort of 246,220 phenprocoumon users in the German Pharmacoepidemiological Research Database. Cases were patients hospitalised for haemorrhage of different kinds. Ten controls were matched to each case by health insurance, birth year and sex using incidence density sampling. Odds ratios (OR) with 95% confidence intervals (CI) of the risk of serious bleeding associated with combined use of phenprocoumon and potentially interacting drugs versus phenprocoumon alone were estimated using conditional logistic regression analysis. Our analyses considered multiple risk factors such as bleeding history, other comorbidities or co-medication.

Results Our study included 2,553 cases and 25,348 matched controls. An increased risk of bleeding was observed for the combined use of phenprocoumon and clopidogrel vs. phenprocoumon use alone (OR: 1.83, 95% CI: 1.41-2.36). Antibiotic drugs associated with an increased risk of haemorrhage in the population of phenprocoumon users included the group of quinolones with ORs ranging from 2.74 (95% CI: 1.80-4.18) for ciprofloxacin to 4.40 (95% CI: 2.45-7.89) for levofloxacin, amoxicillin plus clavulanic acid (OR: 2.99, 95% CI: 1.39-6.42) and cotrimoxazole (OR 3.57, 95% CI: 2.36-5.40). Among non-steroidal anti-inflammatory drugs (NSAIDs), ketoprofen and naproxen were associated with the highest risks.

Conclusion Significantly elevated risks of major bleeding were mainly observed for drugs with known pharmacodynamic interaction with phenprocoumon, and less for drugs with possible pharmacokinetic interaction.

Introduction

Coumarin-type anticoagulants are widely used for the treatment and prevention of thromboembolic diseases. However, their use is complicated by a large inter-individual and intra-individual variability and a narrow therapeutic margin, which necessitates frequent monitoring of the anticoagulant effect and dosage adjustments. The most serious complication of treatment with vitamin K antagonists is an increased risk of bleeding. Major or life-threatening haemorrhage during anticoagulant therapy with coumarins occurs at an estimated rate of 1.2–3.5 per 100 patient-years [1-5]. Several studies examining hospital admission because of adverse drug reactions found that coumarins were an important cause [6-8].

In Germany, oral anticoagulation with coumarins is usually conducted with phenprocoumon. 325.7 million defined daily doses (DDD) were prescribed in 2008, compared to 3.1 million DDDs of warfarin [9]. Despite the similar chemical structure of the coumarins, there are substantial differences in their pharmacokinetic profile [10]. Compared to warfarin and acenocoumarol, phenprocoumon metabolism is less dependent on the polymorphic CYP2C9 enzyme, while it may be more liable to CYP3A4-mediated drug interactions [11-13]. About 40% of an oral dose of phenprocoumon is excreted unchanged, whereas warfarin and acenocoumarol are almost completely metabolized [13]. S- and R-acenocoumarol have very short half-lives of approximately 2 and 8 hours, followed by S- and R-warfarin with half-lives of approximately 32 and 43 hours. The half-life of racemic phenprocoumon ranges from 156 to 172 hours [14].

A main aspect of the safety of coumarins is their sensitivity to drug interactions [15-17]. However, the large majority of studies investigating overanticoagulation or bleeding as a result of interactions with coumarins refer to warfarin [1, 18-21] or the combined group of acenocoumarol and phenprocoumon [22-25]. Due to the described pharmacokinetic differences, results of these studies cannot automatically be extrapolated to potential drug interactions with phenprocoumon.

We conducted a nested case-control study within a phenprocoumon user cohort to investigate which drug interactions result in an increased risk of major bleeding during anticoagulant therapy with phenprocoumon.

Methods

Data Source

Data were obtained from the German Pharmacoepidemiological Research Database (GePaRD). This database consists of claims data from four German statutory health insurances (SHI) and includes more than 14 million insurants covering all German regions. It provides demographic information as well as information on hospital admissions, outpatient physician visits, and outpatient prescriptions. Hospital data include the dates of admission and discharge with their corresponding diagnoses, and information on inhospital diagnoses and procedures. Claims on outpatient physician visits contain diagnoses, ambulatory diagnostic procedures and nondrug treatments. Since these claims are reimbursed on a quarterly basis, ambulatory diagnoses can only be allocated to a quarter of the year and not to an exact date. All diagnoses are coded according to the German modification of the International Classification of Diseases (ICD-10 GM). Prescription data contain the prescribed drugs, characterized by the central pharmaceutical number (PZN), the dates of prescription and dispensation, and information on the prescribing physician. They are available for all outpatient prescriptions which are reimbursed by the SHIs. Prescription data are linked to a pharmaceutical reference database which adds information on the Defined Daily Dose (DDD), the anatomical-therapeutic-chemical (ATC) code, strength, packaging size, generic and brand name. The study was based on data from 2004 – 2006 which were available at the time of the analysis. In preliminary analyses regarding age and sex distribution, the number of hospital admissions and drug use, the database was found to be representative for Germany [26, 27]. The observed stability of patients' memberships makes long term follow-up studies feasible [26]. The GePaRD has been used successfully to study haemorrhagic complications of phenprocoumon treatment [28]. In Germany, the utilization of health insurance data for scientific research is regulated by the Code of Social Law (SGB X). This study was conducted with permission from the Federal Ministry of Health. Since it was based on pseudonymous data, informed consent was not required by law.

Study design

We conducted a case-control study nested in a cohort of phenprocoumon users who had to be continuously enrolled for at least 6 months prior to cohort entry. Cohort entry was defined as the first prescription of phenprocoumon (ATC-code B01AA04) between July 1, 2004 and November 30, 2006, after 6 months of continuous insurance. All patients were followed from their first phenprocoumon prescription in the study period until either discontinuation of phenprocoumon, hospitalisation for bleeding, death, or the end of the study period, whichever occurred first. The end of the study period in November 2006 was set to avoid incomplete hospital data spanning the turn of the year.

As phenprocoumon dosages depend on several patient-specific factors and the database does not include information on the prescribed daily dose, we estimated the duration of each prescription by assuming that a patient's daily dose was one DDD (3mg phenprocoumon), allowing a grace period of 7 days between two phenprocoumon prescriptions. In case of no consecutive prescription of phenprocoumon within this time frame, we defined that treatment was discontinued. Patients were only followed during their first period of continuous phenprocoumon exposure. Due to large inter- and intra-individual differences in phenprocoumon dose requirements we performed two sensitivity analyses, assuming that the daily dose of phenprocoumon was 1.5mg phenprocoumon and 4.5mg phenprocoumon, respectively.

Since the initiation phase is supposed to be associated with a higher risk of bleeding [1, 29], we distinguished between incident and prevalent use of phenprocoumon. Incident use was

defined as use during the first 90 days following start of phenprocoumon treatment and no prescriptions of phenprocoumon in the 6 months preceding cohort entry. All other use was defined as prevalent use.

Definition of cases and controls

Cases were defined as phenprocoumon users hospitalised with a main discharge diagnosis of bleeding. Since the main discharge diagnosis in Germany according to the coding rules reflects the main reason for hospital admission, patients in whom bleeding developed in hospital are not included in this definition. Bleeding included gastrointestinal, cerebral, urogenital or intraocular haemorrhage, haemorrhage from respiratory passages and other bleeding conditions. The list of ICD-10-GM codes used to define these outcomes is available upon request. The hospital admission day was defined as the index day of the case.

From the cohort of continuous phenprocoumon users, we randomly selected ten controls for each case, matching for sex, patient age (birth year), and SHI, using incidence-density sampling. An index day was assigned to each control that resulted in the same time of follow-up as for the corresponding case. We excluded cohort members who were hospitalised at the index day of the case from the set of potential controls, since information on drug use in hospital is not available in the GePaRD. In accordance with epidemiological principles, before becoming a case, a case patient could serve as a control for a different case, and controls could be used more than once [30].

Exposure to drugs with potential clinically relevant interaction with phenprocoumon

Potentially interacting drugs were obtained from the Summary of Product Characteristics (SPC) and the "Rote Liste" (a national compendium with abridged information from the SPC), which are important sources of reference information concerning drug interactions for German physicians [12, 31, 32] as well as from Drugdex [16]. Additionally we included important inhibitors of the CYP isozymes 2C9, 2C8 and 3A4 involved in phenprocoumon metabolism [33]. Potentially interacting drugs are presented in Table 1. All oral formulations of these drugs were taken into account in our statistical analyses of potentially interacting drugs. We considered only current exposure of these drugs which was defined as a drug supply which overlapped with the index date or ended in the 7-day period before the index date. Categorisation of current exposure was based on the date of the prescription of a potentially interacting drug and its assumed duration. The duration was estimated by multiplying the number of tablets prescribed with their strength and dividing this by the DDD of the respective drug, assuming full compliance.

Assessment of potential confounders

Potential confounders were ascertained from ambulatory and hospital care in the six-month continuous enrolment period before cohort entry. We assessed the following conditions as potential confounders: arterial hypertension, heart failure, ischaemic heart disease, diabetes, chronic obstructive pulmonary disease, diverticular disease of the intestine, upper gastrointestinal (GI) diseases including ulcers and diseases of the oesophagus, all types of cancer, hepatic failure**,** renal failure, alcohol dependence, cerebral amyloid angiopathy / aneurysm, and a prior ambulatory or hospital diagnosis of bleeding. ICD 10-GM codes for potential confounders are available on request. Additionally, we included as potential confounders use of proton pump inhibitors or H2-receptor antagonists as surrogate information for GI problems as well as heparins at the index date or ending in the 7-day period before the index date.

Statistical Analyses

We calculated incidence rates of hospitalisation for bleeding stratified by sex for different age groups and in another analysis stratified by incident and prevalent phenprocoumon use. Odds ratios (ORs) of hospitalisation for bleeding associated with current use of each potentially interacting drug were calculated by conditional logistic regression analysis using the SAS procedure PHREG (SAS 8.2, SAS Institute Inc., Cary, NC). For each analysis, the reference category was the absence of current use of the respective potentially interacting drug at the index date. All regression models controlled for relevant confounders and interacting medications selected in a backward selection procedure. Covariates were removed from the model step by step in case the Wald test was not significant ($p>0.05$). A p-value lower or equal 0.05 in the two-tailed test was considered significant, and 95% confidence intervals (CIs) were calculated for all ORs.

Results

During the study period 13,397,148 insurants met the criterion of being insured for at least six months. Among these we identified 246,220 patients who were treated with phenprocoumon. These patients were followed for a total of 91,520 patient-years resulting in a mean follow-up time of 136 days (standard deviation (STD): 102 days) per patient. The mean age at cohort entry was 67.6 years (STD: 12.5 years). Fifty-six percent of cohort members were male. Within this cohort, we identified 2,553 cases of first bleeding requiring hospitalisation resulting in an overall incidence rate of 2.79 (95% CI: 2.68-2.90) hospitalisations for bleeding per 100 patient-years. Gastrointestinal bleeding was the most frequent cause of hospitalisation for bleeding with 33.5%, followed by other bleedings including "haemorrhagic disorder due to circulating anticoagulants" (32.7%), cerebral bleeding (13.6%), and bleeding from the respiratory (8.8%) and genitourinary tract (8.2%). The incidence rate of hospitalisation for bleeding was higher with incident (3.66, 95% CI: 3.47-3.85 per 100 patient-years) than with prevalent phenprocoumon use (2.15, 95% CI: 2.02-2.28 per 100 patient-years). The incidence of hospitalisations for bleeding increased gradually with rising age from 1.24 (95% CI: 1.03-1.48) hospitalisations for bleeding per 100 patient-years in phenprocoumon-users younger than 50 years of age to 4.98 (95% CI: 4.60-5.39) hospitalisations for bleeding per 100 patient-years in those who were older than 80 years. Incidence rates of major haemorrhage under treatment with phenprocoumon stratified by age group and sex are shown in Figure 1.

The case-control analysis was based on 2,553 cases and 25,348 matched controls. Less than ten matched controls were found for 36 cases which were either very old or very young. Table 2 shows the characteristics of cases and controls. We observed elevated risks for several co-morbid conditions including alcohol dependence (adjusted OR: 2.38, 95% CI: 1.71-3.30), renal failure (adjusted OR: 1.67, 95% CI: 1.46-1.90), and a history of bleeding (adjusted OR: 2.29, 95% CI: 2.03-2.59). We also found increased adjusted odds ratios for the concomitant use of proton pump inhibitors (OR: 1.56, 95% CI: 1.40-1.74) used as a proxy measure for GI problems and for concomitant use of heparins (OR: 2.66, 95% CI: 2.33-3.03).

Table 3 displays the risks of major bleeding for drugs which showed a significant interaction with phenprocoumon in the adjusted statistical analysis. Drugs from table 1 which did not show a significant interaction are not further shown here. Ibuprofen and diclofenac, the most frequently used NSAIDs in this study, were associated with similar risks with an OR of 1.63 (95% CI: 1.26-2.11) for ibuprofen and 1.60 (95% CI: 1.33-1.91) for diclofenac, respectively. For ketoprofen and naproxen which were used by only few patients, the ORs were substantially higher, however, with wide confidence intervals. The combined use of antibiotics and phenprocoumon increased the ORs of bleeding 2- to 10-fold compared to phenprocoumon use alone. High ORs were observed for several antibiotics, including quinolones such as ciprofloxacin (adjusted OR: 2.74, 95% CI: 1.80-4.18) or levofloxacin (adjusted OR: 4.40, 95% CI: 2.45-7.89). The concomitant use of phenprocoumon and clopidogrel resulted in an elevated OR of 1.83 (95% CI: 1.41-2.36).

Table 4 displays odds ratios for drugs with a possible pharmacokinetic interaction with phenprocoumon through inhibition of CYP3A4. None of these drugs was associated with a significant risk. Prevalence of exposure at the index date was low for several of these drugs. Table 5 shows the results of the sensitivity analyses with the respective number of cases and controls assuming an average daily dose of 1.5 or 4.5 mg phenprocoumon. The increased risk estimates observed in the main analysis remained elevated in both sensitivity analyses.

Discussion

Drug interactions with warfarin are generally considered hazardous. In a US Top Ten list of dangerous drug-drug interactions in long-term care, warfarin was involved in half of the drug combinations [34]. Data on the relevance of drug interactions with phenprocoumon are sparse, since most epidemiological studies investigating the relevance of drug interactions have been conducted in warfarin-treated patients [1, 21, 35]. Studies of possible drug interactions with phenprocoumon have so far also included users of acenocoumarol and not differentiated between both drugs [22-25, 36]. To our knowledge, this large nested case-control study is the first to study the risk of drug interactions with phenprocoumon alone. Our study shows that several frequently prescribed drugs were associated with an increased risk of major bleeding when taken concomitantly with phenprocoumon. We observed significantly elevated risks for drugs with a possible pharmacodynamic interaction with coumarins such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors and antibiotics. A similar spectrum of interacting drug groups has been described in a Dutch cohort study. In this study, ninety-five percent of the coumarin use was conducted with acenocoumarol [23].

A pharmacodynamic interaction between NSAIDs and other coumarins is well known and attributed to injury caused by NSAIDs to the GI mucosa. An increased risk of major haemorrhage was observed in several studies when NSAIDs were co-administered with warfarin [18, 19, 37] or phenprocoumon and acenocoumarol [23, 38]. Our results concur with these findings, revealing similar risks for concomitant use of phenprocoumon with diclofenac and ibuprofen, the two NSAIDs mainly used in Germany.

Our study demonstrated an elevated risk of major haemorrhage when clopidogrel was co-administered with phenprocoumon. Several studies reported similarly increased risks of haemorrhage when drugs that impair platelet function, such as acetylsalicylic acid or clopidogrel were given to patients treated with warfarin [18, 39, 40] or other coumarins [41]. Two recently published Danish cohort studies comparing different antithrombotic regimens recommended that the combination of clopidogrel and a vitamin K antagonist or an antithrombotic triple therapy should be considered very carefully [42, 43].

Co-administration of antibiotics from different groups increased the risk of bleeding in phenprocoumon-treated patients. Assumed pharmacodynamic interaction mechanisms are a reduction of the intestinal flora that produces vitamin K or a direct inhibition of vitamin K–dependent coagulation factors by antibiotic therapy [17, 22]. Additionally the underlying indication as well as illness-related factors are supposed to increase the anticoagulant effect [24, 35, 44]. This is supported by a Dutch nested case-control which found fever and diarrhoea to be risk factors for overanticoagulation with coumarins [45]. Beyond that, some antibiotic drugs may also inhibit the hepatic metabolism of coumarins. This applies for example to cotrimoxazole which is known to be a strong inhibitor of CYP2C9 [33]. Our results are in line with several studies that reported an increased risk of bleeding when cotrimoxazole was administered concomitantly with a coumarin [22-24, 46]. The elevated risk of haemorrhage we observed when phenprocoumon-treated patients were prescribed quinolones is worth a comment. Their frequent concomitant use with phenprocoumon might be explained by the fact that none of these drugs is listed as potential interaction in the German SPC or “Rote Liste” of phenprocoumon products [12, 32]. For warfarin, there have been discrepant findings regarding an interaction with quinolones [47]. Numerous case

reports and case series [48-52] as well as population-based studies [35, 46] have indicated that quinolones may potentiate the anticoagulant effect of warfarin and increased the risk of bleeding. In contrast, a large Canadian nested case-control study conducted in a cohort of chronic warfarin users did not find an elevated risk of hospitalisation for haemorrhage within 14 days after initiation of levofloxacin [53]. However, this study compared levofloxacin against use of cefuroxim and not against no use.

In summary, the spectrum of interacting drugs observed in our study with phenprocoumon is comparable to that reported for the other coumarins. Since interaction of the coumarins with these drugs is mainly through a pharmacodynamic mechanism, this could have been anticipated. Some additional pharmacokinetic interactions of phenprocoumon with CYP3A4 inhibitors might have been expected, since phenprocoumon metabolism is more dependent on the CYP3A4 isozyme than the other coumarins [11-13]. However, none of the investigated CYP3A4 inhibitors was associated with an increased risk of bleeding. In the case of azole antimycotics or protease inhibitors, the low exposure prevalence did not permit statistical analyses with sufficient statistical power. However, many phenprocoumon-treated patients received concomitant prescriptions of the CYP3A4 inhibitors verapamil or diltiazem, but our results did not indicate an elevated risk for these drugs either.

In the last years, two new oral anticoagulants, dabigatran and rivaroxaban were launched to market, offering future alternatives to coumarins. Besides their practical advantages such as fixed doses and no need of coagulation monitoring, they are hoped to be less prone to drug interactions. While one would expect pharmacodynamic interactions with NSAIDs or platelet inhibitors also for these agents, they will probably be less affected by interaction with antibiotics, if this interaction is caused by antibiotic-induced alterations of the gut flora and diminished vitamin K production and if it is not result of the underlying disease for which antibiotics are administered. Regarding pharmacokinetic interactions, both drugs are substrates for P-glycoprotein, which is involved in the transport of many drugs. In case of rivaroxaban also caution is required when combined with strong CYP3A4 inhibitors [54-56].

Our study confirmed several well known risk factors of major bleeding such as increasing age, a previous history of bleeding [57, 58], alcohol use [18, 59], or renal failure [18, 60]. The high odds ratios we found for the concomitant use of heparins and phenprocoumon might reflect the bridging period of overlapping use of both drugs until phenprocoumon reaches its therapeutic effect. This period has been reported to be associated with a high risk of haemorrhage [61, 62]. We also observed a substantially higher risk of bleeding in the beginning of phenprocoumon treatment which concurs with findings from other studies [4].

Our study had several limitations. Although we included a large number of risk factors in our statistical analysis, we lacked information on several others such as the International Normalized Ratio (INR) [63], diet [64] or body mass index [18, 65]. The association between INR and haemorrhage is not perfect, since the INR level may increase as a consequence of bleeding and therefore INR data are needed for the time period just preceding or at the time of bleeding which is often not available even in prospective studies [66]. We also did not have information on drugs bought over the counter such as high dose acetylsalicylic acid. Since low dose acetylsalicylic acid is not always prescribed but sometimes bought over the counter in Germany, we might have underestimated concomitant use of this drug. The same applies for low dose ibuprofen and low dose diclofenac. The resulting misclassification of exposed patients as unexposed is supposed to be non-differential and thus will lead to an attenuation of the risks observed for ibuprofen and diclofenac, i.e. the observed increased risks for these drugs may actually be higher. We also did not have information on the duration of phenprocoumon use, but calculated the duration of use based on the Defined Daily Dose. We therefore cannot exclude some misclassification in phenprocoumon exposure due to the large inter- and intra-individual differences in phenprocoumon dose requirements [67]. Sensitivity

analyses based on 1.5mg or 4.5mg phenprocoumon, respectively, for the calculation of duration, however, showed our main results to be robust.

A main strength of our study is its large size which allows the investigation of rare, but clinically important events such as hospitalisation for bleeding as well as the investigation of less frequent exposures. Because our study was designed as a nested case-control study in a defined cohort providing both cases and controls, selection bias in the choice of controls is unlikely. All information was recorded prospectively so that recall bias can be ruled out. Our study was population-based and unlike randomized clinical trials reflects clinical practice.

In conclusion, several frequently prescribed drugs were associated with an increased risk of major bleeding when taken concomitantly with phenprocoumon. Among these, co-administration of antibiotics may be particularly hazardous, since antibiotics are mainly used as short-time medications and are often prescribed by a specialist and not by the general practitioner who mostly monitors anticoagulation therapy. Our results concerning drug interactions between phenprocoumon and quinolones warrant further attention, since these are not labelled in Germany [12, 32]. Overall, we found the spectrum of interacting drugs to be quite similar for phenprocoumon and the other coumarins, despite their different pharmacokinetic profiles. Significantly increased risks of major haemorrhage were mainly observed for drugs with known pharmacodynamic interaction with phenprocoumon and less for those with possible pharmacokinetic interaction.

Acknowledgement:

The authors are grateful to all SHIs that provided data for this study. Three of these are the Allgemeine Ortskrankenkasse (AOK) Bremen/Bremerhaven, the Deutsche Angestellten-Krankenkasse (DAK), and the Handelskrankenkasse (HKK).

Conflict of interest

The authors declare that they have no conflict of interest.

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Table 1 Drugs with potential clinically relevant interaction with phenprocoumon [a]

Antibiotics
- Penicillins
  - Amoxicillin
  - Amoxicillin + clavulanic acid
  - Phenoxymethylpenicillin
  - Sultamicillin
  - Penicillins (other)
- Cephalosporins
  - Cephalosporins listed as potential interaction[b]
  - Cephalosporins (other)
- Tetracyclines
- Macrolides
  - Azithromycin
  - Clarithromycin
  - Erythromycin
  - Roxithromycin
  - Macrolides (other)
- Clindamycin
- Sulfonamides and trimethoprim
  - Cotrimoxazole
  - Trimethoprim
  - Sulfonamides (other)
- Quinolones
  - Ciprofloxacin
  - Levofloxacin
  - Moxifloxacin
  - Norfloxacin
  - Ofloxacin
  - Quinolones (other)
- Chloramphenicol
- Antibiotics (other)

Imidazoles and triazoles
- Fluconazole
- Itraconazole
- Ketoconazole
- Metronidazole
- Voriconazole

NSAIDs
- Diclofenac
- Ibuprofen
- Indometacin
- Ketoprofen
- Naproxen
- Oxicam derivatives
- COX-2 inhibitors
- Phenylbutazone
- NSAIDs (other)

Antithrombotics
- Acetylsalicylic acid
- Ticlopidine
- Clopidogrel
- Antithrombotics (other)

Antiarrhythmic drugs
- Amiodarone
- Propafenone
- Quinidine

Fibrates
- Fenofibrate
- Gemfibrozil
- Fibrates (other)

Protease inhibitors
- Indinavir
- Nelfinavir
- Ritonavir
- Saquinavir

Statins
- Lovastatin
- Fluvastatin
- Statins (other) [c]

SSRIs [d]
- Citalopram
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline

Other drugs
- Allopurinol
- Capecitabine
- Diltiazem
- Disulfiram
- Glitazones
- Leflunomide
- Tamoxifen
- Thyroid hormones
- Tricyclic antidepressants
- Verapamil

[a] all drugs listed in this table were considered in the statistical analyses
[b] listed as potential interaction in the German SPC of phenprocoumon (cefazoline, cefpodoximproxetil, cefotaxime, ceftibuten)
[c] i.e. artovastatin, pravastatin, simvastatin
[d] selective serotonin reuptake inhibitors

Table 2 Characteristics of cases and matched controls

	Cases N= 2,553	Controls N= 25,348	Crude odds ratio [a]	Adjusted odds ratio [b]	95% confidence interval [b]
Age, Mean (Std) [c]	71.20 (11.10)	71.07 (10.90)			
Male sex [c]	1,348 (52.80%)	13,383 (52.80%)			
Co-morbid conditions [d]					
Arterial hypertension	1,292 (50.61%)	10,501 (41.43%)	1.46	1.23	1.12-1.34
Heart failure	503 (19.70%)	3,582 (14.13%)	1.51	1.34	1.19-1.50
Ischemic heart disease	733 (28.71%)	6,038 (23.82%)	1.30	1.07	0.97-1.18
Diabetes	562 (22.01%)	4,202 (16.58%)	1.43	1.26	1.13-1.40
COPD	208 (8.15%)	1,386 (5.47%)	1.54	1.10	0.94-1.31
Diverticular disease of intestine	93 (3.64%)	595 (2.35%)	1.57	1.40	1.12-1.75
Upper GI diseases	181 (7.09%)	1,010 (3.98%)	1.85	1.17	1.00-1.40
Cancer	317 (12.42%)	2,476 (9.77%)	1.32	1.11	0.97-1.26
Hepatic failure	168 (6.58%)	1,285 (5.07%)	1.33	1.07	0.90-1.28
Renal failure	347 (13.59%)	1,759 (6.94%)	2.15	1.67	1.46-1.90
Alcohol dependence	48 (1.88%)	217 (0.86%)	2.25	2.38	1.71-3.30
Cerebral amyloid angiopathy / aneurysm	2 (0.08%)	2 (0.01%)	10.03	2.35	0.82-6.71
Bleeding history	334 (13.08%)	1,759 (6.94%)	2.01	2.29	2.03-2.59
Concomitant use of … [e]					
Proton pump inhibitors [f]	523 (20.49%)	2,930 (11.56%)	1.99	1.56	1.40-1.74
H2-receptor antagonists [f]	52 (2.04%)	397 (1.57%)	1.30	1.28	0.95-1.73
Heparins	368 (14.41%)	1,417 (5.59%)	2.98	2.66	2.33-3.03

[a] Obtained from univariate conditional logistic regression model
[b] Adjusted for all other covariates included in the table
[c] Birth year and sex are matching variables
[d] Assessed in the 6 months before cohort entry
[e] Drug supply which overlapped with the index date or ended in the 7 day period before the index date
[f] Used as surrogate for upper GI problems

Table 3 Crude and adjusted odds ratios and 95% confidence intervals for major haemorrhage associated with current use of potentially interacting drugs

	Cases N= 2,553	Controls N= 25,348	Crude odds ratio [a]	Adjusted odds ratio [b]	95% confidence interval [b]
Concomitant use of …[c]					
Amoxicillin	28 (1.10%)	140 (0.55%)	2.01	1.56	1.01-2.40
Amoxicillin + clavulanic acid	12 (0.47%)	23 (0.09%)	5.22	2.99	1.39-6.42
Cephalosporins (other)	20 (0.78%)	73 (0.29%)	2.73	2.16	1.28-3.63
Cotrimoxazole	35 (1.37%)	92 (0.36%)	3.80	3.57	2.36-5.40
Ciprofloxacin	37 (1.45%)	91 (0.36%)	4.08	2.74	1.80-4.18
Levofloxacin	19 (0.74%)	40 (0.16%)	4.80	4.40	2.45-7.89
Moxifloxacin	13 (0.51%)	31 (0.12%)	4.15	3.51	1.77-6.96
Ofloxacin	6 (0.24%)	14 (0.06%)	4.29	3.60	1.30-10.00
Metronidazole	6 (0.24%)	4 (0.02%)	14.98	9.49	2.44-37.00
Diclofenac	158 (6.19%)	927 (3.66%)	1.74	1.60	1.33-1.91
Ibuprofen	78 (3.06%)	434 (1.71%)	1.81	1.63	1.26-2.11
Ketoprofen	6 (0.24%)	9 (0.04%)	6.67	8.06	2.74-23.75
Naproxen	3 (0.12%)	6 (0.02%)	4.60	4.29	1.03-17.95
Clopidogrel	85 (3.33%)	360 (1.42%)	2.42	1.83	1.41-2.36
Statins (other) [d]	525 (20.56%)	5,370 (21.19%)	0.97	0.88	0.79-0.98

[a] Obtained from univariate conditional logistic regression model

[b] Adjusted for all other covariates included in the table as well as for arterial hypertension, heart failure, diabetes, diverticular disease of the intestine, renal failure, alcohol dependence, a prior ambulatory or hospital diagnosis of bleeding (assessed in the 6 months before cohort entry), and a drug supply with proton pump inhibitors or heparins which overlapped with the index date or ended in the 7 day period before the index date

[c] Drug supply which overlapped with the index date or ended in the 7 day period before the index date

[d] i.e. artovastatin, pravastatin, simvastatin

Table 4 Odds ratios [a] and 95% confidence intervals for major haemorrhage associated with concomitant use of CYP3A4 inhibitors

	Cases N= 2,553	Controls N= 25,348	Odds ratio [a]	95% confidence interval [a]
Concomitant use of … [b]				
Clarithromycin	4 (0.16%)	39 (0.15%)	1.03	0.37-2.87
Erythromycin	0	9 (0.04%)	-	-
Norfloxacin	4 (0.16%)	24 (0.09%)	1.67	0.58-4.80
Azole antimycotics [c]	1 (0.04%)	10 (0.04%)	1.00	0.13-7.81
Amiodarone	87 (3.41%)	732 (2.89%)	1.19	0.95-1.49
Protease inhibitors [d]	0	0	-	-
Fluvoxamine	0	12 (0.05%)	-	-
Diltiazem	19 (0.74%)	207 (0.82%)	0.91	0.57-1.45
Verapamil	158 (6.19%)	1,612 (6.36%)	0.97	0.82-1.15

[a] Obtained from univariate conditional logistic regression model, since only significant drugs or covariates were included in the multivariate model building

[b] Drug supply which overlapped with the index date or ended in the 7 day period before the index date

[c] i.e. fluconazole, ketoconazole, itraconazole, voriconazole

[d] i.e. indinavir, nelfinavir, ritonavir, saquinavir

Table 5 Adjusted odds ratios (OR) and 95% confidence intervals (CI) for major haemorrhage associated with concomitant use of potentially interacting drugs assuming different daily doses of phenprocoumon (PPC)

	Sensitivity analysis 1 (daily dose = 1.5mg PPC) **Cases N = 6,107 Controls N = 60,820**	**Main analysis** (daily dose = 3mg PPC) **Cases N = 2,553 Controls N = 25,348**	**Sensitivity analysis 2** (daily dose = 4.5mg PPC) **Cases N = 1,669 Controls N = 16,541**
	OR (95% CI) [a]	**OR (95% CI) [a]**	**OR (95% CI) [a]**
Concomitant use of …[b]			
Amoxicillin	1.74 (1.31-2.29)	1.56 (1.01-2.40)	1.89 (1.10-3.23)
Amoxicillin + clavulanic acid	2.99 (1.69-5.31)	2.99 (1.39-6.42)	2.03 (0.87-4.74)
Cephalosporins (other)	1.92 (1.35-2.74)	2.16 (1.28-3.63)	1.79 (0.93-3.44)
Cotrimoxazole	3.58 (2.67-4.81)	3.57 (2.36-5.40)	4.00 (2.43-6.57)
Ciprofloxacin	3.02 (2.28-4.00)	2.74 (1.80-4.18)	2.14 (1.27-3.60)
Levofloxacin	2.94 (1.89-4.56)	4.40 (2.45-7.89)	5.51 (2.64-11.50)
Moxifloxacin	2.64 (1.62-4.32)	3.51 (1.77-6.96)	2.69 (1.11-6.53)
Ofloxacin	3.27 (1.76-6.10)	3.60 (1.30-10.00)	4.99 (1. 80-13.87)
Metronidazole	5.95 (2.14-16.60)	9.49 (2.44-37.00)	5.32 (1.45-19.54)
Diclofenac	1.80 (1.60-2.02)	1.60 (1.33-1.91)	1.81 (1.45-2.26)
Ibuprofen	1.84 (1.57-2.16)	1.63 (1.26-2.11)	1.61 (1.18-2.20)
Ketoprofen	3.99 (1.76-9.05)	8.06 (2.74-23.75)	4.20 (0.80-22.21)
Naproxen	3.66 (1.68-7.99)	4.29 (1.03-17.95)	3.79 (0.75-19.29)
Clopidogrel	1.78 (1.47-2.16)	1.83 (1.41-2.36)	1.92 (1.44-2.56)
Statins (other) [c]	0.94 (0.88-1.00)	0.88 (0.79-0.98)	0.91 (0.80-1.03)

[a] Adjusted for all other covariates included in the table as well as for arterial hypertension, heart failure, diabetes, diverticular disease of the intestine, renal failure, alcohol dependence, a prior ambulatory or hospital diagnosis of bleeding (assessed in the 6 months before cohort entry), and a drug supply with proton pump inhibitors or heparins which overlapped with the index date or ended in the 7 day period before the index date

[b] Drug supply which overlapped with the index date or ended in the 7 day period before the index date

[c] i.e. artovastatin, pravastatin, simvastatin

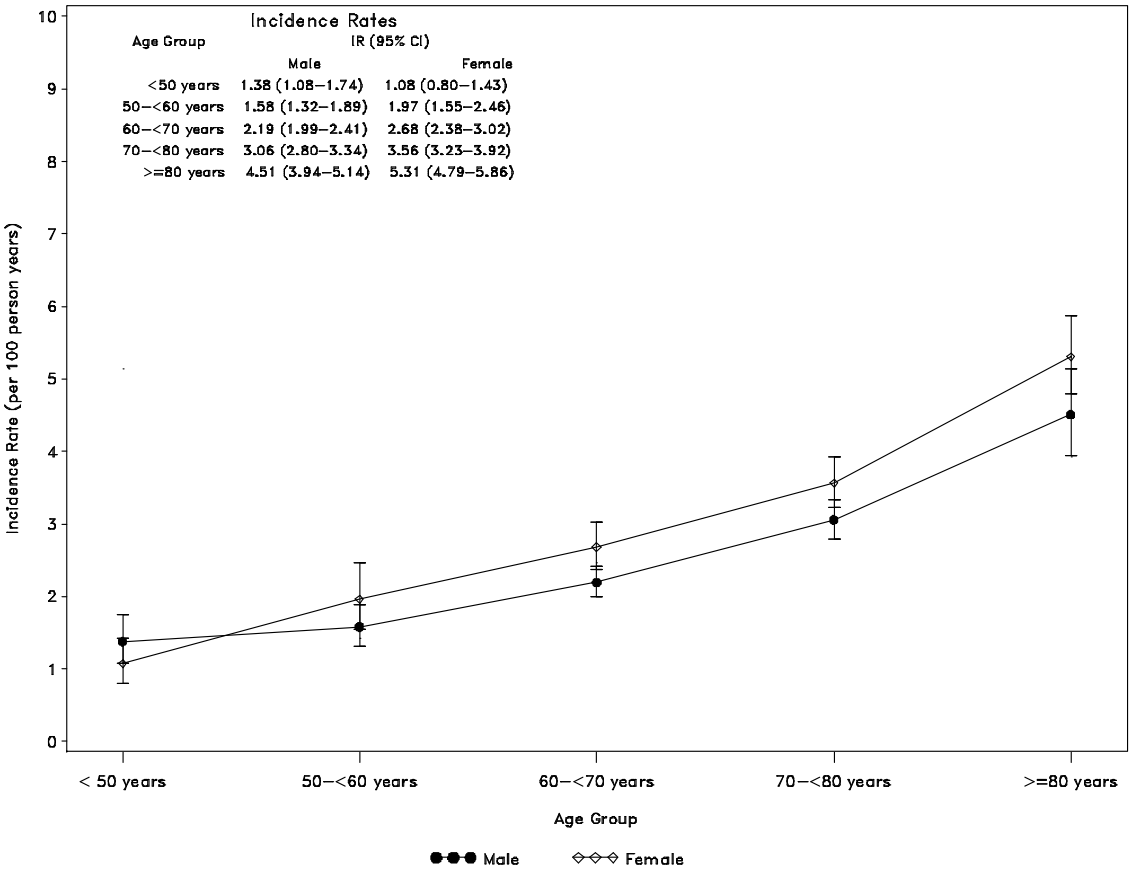

Figure 1 Incidence rates of major haemorrhage under treatment with phenprocoumon by age group and sex