Effect of oral antiplatelet agents on major bleeding in users of coumarins

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Summary

Treatment with vitamin K antagonists (coumarins) is associated with an increased risk of bleeding. In order to elucidate the bleeding risk of users of antiplatelet drugs among users of coumarins, we assessed the odds ratio of major bleeding associated with use of antiplatelet drugs in users of the coumarins acenocoumarol and phenprocoumon. We used data from a Dutch record linkage system, including pharmacy and linked hospitalization records for approximately two million subjects, to conduct a nested case control study in a cohort of new users of coumarins. Cases were patients who were hospitalized with a primary diagnosis of major bleeding while taking coumarin and were matched with up to four control subjects. Conditional logistic regression analysis was used to determine ORs and 95% confidence intervals (CI). We identified 1848 case patients who were matched to 5818 controls. Users of clopidogrel or aspirin showed a significantly increased risk of hospitalization because of major bleeding (OR 2.9, 95% CI 1.2–6.9 and OR 1.6, 95% CI 1.3–1.9, respectively), whereas users of dipyridamole and combinations of antiplatelet drugs showed a strong trend (OR 1.5, 95% CI 1.0–2.3 and OR 1.8, 95 % CI 1.0–3.3, respectively). In all cases, the risks were greater for upper gastrointestinal bleedings than for other bleedings. In conclusion, the use of any antiplatelet drug increases the risk of hospitalization for major bleeding among users of coumarins. Concurrent use of clopidogrel or dipyridamole and coumarins is probably not safer than concurrent use of aspirin and coumarins.

Keywords

Drug interaction, bleeding, coumarins, antiplatelet drugs

Thromb Haemost 2008; 100: 1076–1083

Introduction

Coumarins are effective drugs for the prevention of venous and arterial thromboembolism. The most common indication is atrial fibrillation for which the therapeutic superiority over aspirin alone or a combination of the antiplatelet agents aspirin and clopidogrel has been firmly established (1). The principal adverse effect of therapy with anticoagulants of the coumarin type is major bleeding, which can be fatal or disabling. Recently, the risk factors for increased bleeding in users of coumarins have been systematically reviewed (2, 3). This increased bleeding risk is an inevitable consequence of the pharmacodynamics of the coumarins, which affect the coagulation cascade by interfering with the activation of clotting factors II, VII, IX and X, ultimately inhibiting the formation of fibrin.

Antiplatelet drugs interfere with the activation of platelets and are of major importance in the prevention of atherothrombosis in patients suffering from atherosclerosis. There is ample evidence for the effectiveness of antiplatelet therapy in preventing recurrent vascular events in cerebrovascular disease, coronary artery disease and peripheral artery disease (4, 5).

With the increasing use of antiplatelet agents, the incidence of concurrent use with coumarin anticoagulants is expected to increase, for example in patients suffering from atrial fibrillation after coronary stent placement or after acute coronary syndromes. However, in daily practice aspirin is frequently added to a coumarin for associated stable vascular disease, although there is no evidence for benefit of such a combination, whereas it is plausible that it will be harmful (6). This underlines the need for reliable information on the bleeding risk of combined use of antiplatelet drugs and coumarins compared to coumarins alone.

Because of the different pathways along which coumarins and antiplatelet drugs affect haemostasis, an increased major bleeding risk with concurrent use compared with use of coumarins alone is conceivable for all antiplatelet drugs. For concurrent use of aspirin with coumarins such an increased bleeding risk has

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Received: May 7, 2008
Accepted after major revision: September 12, 2008

Prepublished online: November 13, 2008
doi:10.1160/TH08-05-0290

been convincingly demonstrated in several clinical trials (7–11), meta-analyses (12, 13) and population based observational studies (14–17). However, the effect of the newer antiplatelet drugs clopidogrel and dipyridamole on the bleeding risk among users of coumarins is unkown. For dipyridamole conflicting results have been described (18, 19), whereas to date no data have been reported on the risk of concurrent use of clopidogrel and coumarins. To establish the effect on the bleeding risk of clopidogrel and dipyridamole among users of coumarins, we conducted a population-based case-control study within a cohort of users of the coumarin antagonists acenocoumarol and phenprocoumon.

Materials and methods

Design and setting

We conducted a case-control study in a cohort of new users of acenocoumarol or phenprocoumon, the two coumarin anticoagulants licensed in The Netherlands. The setting of the study was the PHARMO record linkage system (Pharmo Institute, Utrecht, The Netherlands; available at htpp://www.pharmo.nl). This system includes the demographic details and complete medication histories from community pharmacies for more than two million community-dwelling residents in 25 geographic areas in The Netherlands from 1985 to the present day further linked to hospital admission records. Because virtually all patients in The Netherlands are registered with a single community pharmacy, pharmacy records are essentially complete insofar as the prescription drug use is concerned. For this study, drug prescribing data and hospitalization data were used. Drugs are coded according to the Anatomical Chemical Therapeutic Classification (ATC). The hospital admission and discharge codes are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Cohort and exposure to coumarins

In the cohort of new users of one of the coumarin anticoagulants, all patients aged 18 years and above who had received a first prescription for a coumarin between January 1, 1991 and December 31, 2004, and who did not have a history of hospital admission for major bleeding prior to coumarin start, were included. A patient was defined as a new coumarin user if none of these drugs had been dispensed before the first coumarin dispensing in the PHARMO database and if a medication history for at least one year before initiation of the coumarin anticoagulant was available. Patients were followed up until hospital admission for major bleeding, end of data collection (for example in case of removal of patient to an area outside the area of the PHARMO database), death or discontinuation of coumarin therapy, whichever occurred first.

Prescriptions for coumarin anticoagulants do not contain information about the dosage, which is variable and is frequently adjusted by anticoagulation clinics. As a result, the duration of coumarin use cannot be calculated from the number of dispensed units and the prescribed dosage. We assumed that treatment was

Table 1: General characteristics, current use of platelet inhibitors and relevant comedication and comorbities of cases and controls (N=7666), N,(%).

Characteristic	Cases (n=1848)	Controls (n=5818)
Male	993 (53.7)	3173 (54.5)
Age on index date, mean (SD)	72.7 (10.3)	72.9 (9.7)
Acenocoumarol on index date	1628 (88.1)	5302 (91.1)
Aspirin alone (30–100 mg)	165 (8.9)	381 (6.5)
Clopidogrel alone	11 (0.6)	11 (0.2)
Dipyridamole alone	34 (1.8)	85 (1.5)
Aspirin + clopidogrel	5 (0.3)	6 (0.1)
Aspirin + dipyridamole	12 (0.6)	30 (0.5)
Clopidogrel + dipyridamole	0	1
Nonsteroidal anti-inflammatory drugs	222 (12.0)	299 (5.1)
Glucocorticoids	113 (6.1)	176 (3.0)
Selective serotonine reuptake inhibitors	58 (3.1)	116 (2.0)
Gastroprotective agents (proton pump inhibitors, H2-antihistamines, misoprostol)	313 (16.9)	703 (12.1)
Inhibitors of coumarin metabolism (amiodarone, allopurinol, benzbromarone, cimetidine, miconazole, fluconazole, gemfibrozil)	153 (8.3)	385 (6.6)
Inducers of coumarin metabolism (carbamazepine, phenytoin, phenobarbitone, rifampicin)	21 (1.1)	66 (1.1)
Antibiotics	148 (8.0)	124 (2.1)
Diabetes mellitus	334 (18,1)	869 (14.9)
Thyroid disorders	104 (5.6)	336 (5.8)
Heart failure	581 (31.4)	1507 (25.9)
Malignancies	38 (2.1)	91 (1.6)

Table 2: Admission diagnosis of 1,848 patients within a cohort of users of acenocoumarol or phenprocoumon hospitalized with a first major bleeding event.

Bleeding localisation	No (%)
Gastrointestinal	605 (32.7)
Upper gastrointestinal	537 (29.0)
Lower gastrointestinal	68 (3.7)
Non-gastrointestinal	1243 (67.3)
Intracranial	318 (17.2)
Uterus	131 (7.1)
Urinary tract	115 (6.2)
Joint	34 (1.8)
Eye	20 (1.1)
Nose	161 (8.7)
Other*	464 (25.1)

*, Other bleedings: Haemoptysis, bleeding complicating a procedure, haemoperitoneum, spontaneous ecchymoses, bleedings NOS (NOS, not otherwise specified).

discontinued if more than 180 days had elapsed after the last recorded dispensing date of acenocoumarol or phenprocoumon. The period of 180 days has been estimated on the basis of experience in daily practice. Coumarin anticoagulants are usually dispensed in large quantities (several hundred defined daily dosages) and because daily dosages show large interindividual variation, 180 days could be an underestimation or an overestimation of the duration of use.

Cases and controls

Cases were all patients with a first hospitalization for major bleeding while being treated with a coumarin. To identify major bleeding we used International Classification of Diseased, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes, which cover the classification of major bleedings described by Fihn et al. for complications of anticoagulant treatment (20) (see Appendix Table 1) The date of first hospitalization for major bleeding was considered to be the index date. For each case patient, up to four nonhospitalized controls were randomly selected from the cohort by risk-set sampling. Control subjects were matched with case patients for sex, age (± 5 years), coumarin anticoagulant (acenocoumarol or phenprocoumon), time since initiation of coumarin therapy (± 90 days from dispensing date) and geographic region, and were assigned the same index date as the corresponding case patient.

Definition of exposure

We analyzed the following a priori chosen antiplatelet drugs: clopidogrel (ATC code B01AC04), dipyridamole (ATC code B01AC07) and low-dose aspirin (30–100 mg) (ATC codes B01AC06 and B01AC08). Since antiplatelet agents can be used concurrently (21–24), and since such combinations could carry a more increased bleeding risk (21–23), we separately analyzed use of aspirin, clopidogrel and dipyridamole alone or use of these drugs in combination (including the fixed combination of aspirin + dipyrimole, ATC code B01AC30). In the PHARMO database the duration of use of a dispensed drug is calculated by dividing the number of dispensed units by the prescribed number to be used per day. If the duration of use extended with 10% ended on or beyond the index date, this was considered to be the current use of the antiplatelet drug. If the duration of use extended with 10% from a dispensing date ended within 30 days or more than 30 days before the index date, it was considered as recent use or past use, respectively.

Potential confounders

As potentially confounding comedication we defined current use of non-steroidal anti-inflammatory drugs (NSAIDs) (selective COX-2-inhibitors were not included, because their association with bleeding is less clear than for nonselective COX-2-inhibitors), selective serotonin reuptake inhibitors (SSRIs), glucocorticoids, known inhibitors of coumarin metabolism (25–27) (amiodarone, allopurinol, benzbromarone, miconazole, fluconazole and gemfibrozil), known inducers of coumarin metabolism (25, 27) (carbamazepine, phenytoin, phenobarbitone and rifampicin) and antibiotics (as a proxy for intercurrent infections). Moreover, use of gastroprotective agents (proton pump inhibitors, H2 receptor antagonists and misoprostol) was defined as potentially confounding or effect modifying comedication for upper gastrointestinal bleeding. For current use of confounding or effect modifying comedication, we used the same definitions as for antiplatelet agents.

Any use before the index date of thyroid therapy, antidiabetic drugs, antineoplastic agents and a combination of ACE inhibitors or angiotensin II antagonists with loop diuretics were proxies for thyroid diseases, diabetes mellitus, malignancies and heart failure, respectively.

Statistical analysis

We compared the use of antiplatelet drugs between cases and controls. So, since the cohort consisted of users of coumarins, we compared concomitant use of coumarins and antiplatelet drugs in the case group with concomitant use of coumarins and antiplatelet drugs in the control group. We used conditional logistic regression models on the matched sets to estimate the risk of bleeding associated with current use of antiplatelet agents, expressed as odds ratios (ORs) with 95% confidence intervals (CIs).

We analyzed all major bleedings. Moreover, we stratified our analyses by upper gastrointestinal and non upper gastrointestinal bleedings (designated as 'other bleedings'), because these bleedings have different prognostic factors and because we expected that at least the use of aspirin would be more associated with upper gastrointestinal bleeding than with other bleedings. We separately analyzed clopidogrel, dipyridamole, low dose aspirin and all combinations of these antiplatelet agents.

Within the stratum of upper gastrointestinal bleedings we also analyzed whether an effect of antiplatelet agents was modified by gastroprotective drugs. We separately analyzed our results for users of acenocoumarol and phenprocoumon.

In sensitivity analyses we reanalyzed our results on the assumption that coumarin use ended a maximum of 30, 60 or 90 days (rather than 180 days) after the last dispensing date and for users who received more than one prescription for a coumarin anticoagulant. Moreover, we reanalyzed our results for bleeding events that occurred after the first 28 days of coumarin use, in-

creasing the chance that patients are more or less stabilized because the initiation phase can be associated with problems such as dose finding and severe overanticoagulation. We also analyzed our data for recent and past use of the examined drugs. All statistical analyses were performed using commercially available software (SPSS, version 12; SPSS Inc, Chicago, IL, USA).

Results

We identified 70,201 patients who were treated with a coumarin, for a total of 131,707 patient years. Within this cohort we identified 2403 cases of first bleeding requiring hospitalization (incidence rate 1.82 per 100 patient years). Of these, 555 could not be matched to control subjects, leaving 1848 cases available for analysis, who were matched with 5818 control subjects. The median follow-up time in patients until bleeding was 220 days (range: 1–4690 days). Mean age at the index date was 72.7 years, there were more men than women; and almost 90% of the patients used acenocoumarol (Table 1). The most frequently occurring bleeding was upper gastrointestinal bleeding (n=537), followed by intracranial bleeding (n=318) (Table 2).

Daily dosages of aspirin ranged from 30 to 100 mg for most patients (4 out of 536 aspirin users had a daily dosage of 160 mg). No patients used aspirin continuously in daily dosages higher than 160 mg. Daily dosages of dipyridamole ranged from 150 to 450 mg and the daily dosage of clopidogrel was 75 mg in all patients.

When major bleeding occurred (upper gastrointestinal and other bleedings taken together) the risks were significantly increased for clopidogrel alone and for aspirin alone, multivariate ORs being 2.9 (95% CI 1.2–6.9) and 1.6 (95% CI 1.3–1.9), respectively. The risks for dipyridamole and combinations of antiplatelet agents were also increased for all bleedings, although just not significantly, multivariate ORs being 1.5 (95% CI 1.0–2.3) and 1.8 (95% CI 1.0–3.3) (Table 3).

Use of all antiplatelet agents, including clopidogrel and dipyridamole, increased the risk of upper gastrointestinal bleeding. The point estimate was highest for clopidogrel, the effect showing a strong trend towards significance (OR 3.6, 95% CI 0.9–13.5) (Table 3). Use of gastroprotective drugs did not modify the effect of antiplatelet agents on the outcome upper gastrointestinal bleeding.

Use of antiplatelet drugs increased the risk of other bleedings to a lesser extent. The use of only aspirin was significantly associated with an increased risk of other bleedings. The use of dipyridamole resulted in a similar point estimate, whereas the point estimate for clopidogrel was greatest, as it was for upper gastrointestinal bleedings (Table 3).

Separate analysis of the most invalidating category of bleedings, the intracranial bleeding, resulted in not significantly increased risks for aspirin and dipyridamole, (adjusted ORs 1.2, 95% CI 0.7–2.0 and 1.6, 95% CI 0.6–4.2, respectively), point estimates being roughly similar to the point estimates for all non upper gastrointestinal bleedings. For users of clopidogrel or combinations of antiplatelet drugs numbers were too low for analysis.

Separate analysis for users of acenocoumarol resulted in similar point estimates as for the pooled analyses of users of acenocoumarol and phenprocoumon. Use of aspirin and dipyridamole resulted in somewhat higher point estimates in users of

Table 3: Association between current use of aspirin (30 and 80 mg), clopidogrel, dipyridamole and combinations of platelet inhibitors and hospitalization for all major bleedings, upper gastrointestinal bleedings and other bleedings.

	Cases, No (%)	Controls, No (%)	Crude OR (95 % CI)	P value	Adjusted OR* (95 % CI)	P value
All major bleedings	(N = 1848)	(N = 5818)				
Clopidogrel alone	11 (0.6)	11 (0.2)	3.4 (1.5–7.9)	0.005	2.9 (1.2–6.9)	0.018
Dipyridamole alone	34 (1.8)	85 (1.5)	1.3 (0.8–1.9)	0.30	1.5 (1.0–2.3)	0.078
Aspirin alone, all dosages	165 (8.9)	381 (6.5)	1.5 (1.3–1.9)	<0.001	1.6 (1.3–1.9)	<0.001
Concurrent use of platelet inhibitors†	17 (0.9)	37 (0.6)	1.7 (0.9–3.1)	0.080	1.8 (1.0–3.3)	0.051
Upper gastrointestinal bleedings	(N = 537)	(N = 1684)				
Clopidogrel alone	6 (1.1)	4 (0.2)	4.7 (1.3–17.0)	0.019	3.6 (0.9–13.5)	0.062
Dipyridamole alone	12 (2.2)	24 (1.4)	1.9 (0.9–3.9)	0.089	2.2 (1.1–4.6)	0.043
Aspirin alone, all dosages	56 (10.4)	105 (6.2)	1.9 (1.4–2.8)	<0.001	2.1 (1.5–3.1)	<0.001
Concurrent use of platelet inhibitors†	10 (1.9)	13 (0.8)	2.7 (1.1–6.3)	0.024	3.4 (1.4–8.4)	0.006
Other bleedings	(N = 1311)	(N = 4134)				
Clopidogrel alone	5 (0.4)	7 (0.2)	2.6 (0.8–8.3)	0.10	2.4 (0.7–8.0)	0.15
Dipyridamole alone	22 (1.7)	61 (1.5)	1.0 (0.6–1.8)	0.90	1.3 (0.8–2.1)	0.22
Aspirin alone, all dosages	109 (8.3)	276 (6.7)	1.4 (1.1–1.8)	0.007	1.4 (1.1–1.7)	0.012
Concurrent use of platelet inhibitors‡	7 (0.5)	24 (0.6)	1.1 (0.5–2.7)	0.78	1.2 (0.5–2.8)	0.71

OR, odds ratio; CI, confidence interval. * Adjusted for use of NSAIDs, antibiotics, SSRIs, glucocorticoids, inhibitors and inducers of coumarin metabolism, diabetes mellitus, heart failure, thyroid disorders and malignancies. For all major bleedings and upper gastrointestinal bleeding ORs were also adjusted for gastroprotective agents (proton pump inhibitors, H_2 antihistamines and misoprostol). † Aspirin + clopidogrel, 5 cases/0 controls; aspirin + dipyridamole, 5 cases/12 controls; clopidogrel + dipyridamole, 0 cases/1 control. ‡ Aspirin + clopidogrel, 0 cases/6 controls; aspirin + dipyridamole, 7 cases/18 controls.

phenprocoumon, although the ORs compared with users of coumarins alone were not statistically significant (OR 2.3, P-value 0.10 and 2.5, P-value 0.10, respecively). A risk estimate was not possible for clopidogrel (N=2).

Sensitivity analyses did not change the overall picture of our results, with the risks remaining higher for upper gastrointestinal than for other bleedings. For aspirin, the results for upper gastrointestinal and other bleedings are presented in Table 4. For other antiplatelet drugs the numbers became lower, resulting in wider confidence intervals without changing the picture of our main findings (data not shown).

Past use of all antiplatelet drugs did not show sustained increased bleeding risks (univariate ORs for all bleedings together 1.0, 1.0 and 1.2 for aspirin, clopidogrel and dipyridamole, respectively, point estimates being similar for upper gastrointestinal bleedings [data not shown]). Recent use showed a tendency for an increased bleeding risk in users of aspirin (OR 1.4, P-value 0.08 for all bleedings and OR 1.5, P-value 0.31 for gastrointestinal bleedings), while the numbers of recent users of clopidogrel (N=5) and dipyridamole (N=10) were too small for analysis.

Discussion

This study demonstrated for the first time that in users of coumarins clopidogrel increases the risk of major bleeding at least as much as aspirin. For dipyridamole we also found an increased risk approaching statistical significance.

The results of our study regarding aspirin are in agreement with the results of other population based studies (14–17) and with the findings of a recent meta-analysis by Salem et al., which assessed the therapeutic benefits and risks of combined use of aspirin and coumarins compared with use of coumarins alone (12), their OR for increased major bleeding risk (1, 43) being exactly the same as ours.

Although one study showed no effect of clopidogrel on INR among patients receiving long-term warfarin therapy (28), which suggests the absence of a pharmacokinetic interaction, a pharmacodynamic interaction between clopidogrel and coumarins is conceivable because of their differing effects on haemostasis. Clopidogrel is increasingly used as an antiplatelet agent, with one trial suggesting that it was more effective and caused significantly less gastrointestinal bleeding than low dose aspirin (325 mg daily) (29). However, in two studies among high risk patients with a history of upper gastrointestinal complications, clopidogrel was associated with a high incidence of upper gastrointestinal bleeding (30, 31). One of these studies even demonstrated that the combined use of aspirin and a proton pump inhibitor was superior to clopidogrel in the prevention of recurrent ulcer bleeding (30). In a Danish population-based case control study, clopidogrel alone was not associated with an increased risk of upper gastrointestinal bleeding, whereas the combination with aspirin increased the bleeding risk beyond the effect of aspirin alone (17). The findings of our study similarly suggest that clopidogrel adds to a further increased bleeding risk among users of coumarins and that clopidogrel is not safer than low dose aspirin when used in combination with coumarins, this suggestion being stronger for upper gastrointestinal bleedings than for other bleedings. Whilst it is not surprising that the combination therapy with warfarin, aspirin and clopidogrel was associated with a significantly increased risk of major bleeding compared to therapy with aspirin and clopidogrel (32), to our knowledge our study is the first to demonstrate an increased bleeding risk for the concurrent use of clopidogrel (without aspirin) and coumarins compared with coumarins alone.

Published data on the effect of dipyridamole on bleeding risk among users of coumarins are contradictory. Massel et al. reported an increased bleeding risk in a meta-analysis among patients with prosthetic heart valves for the combined use of dipyridamole and coumarins compared to coumarins alone (19), whereas Pouleur et al. did not find an increased risk in another meta-analysis (18) Our results are in agreement with the findings of Massel et al., who primarily analysed major bleedings as we did. Although dipyridamole, unlike aspirin, does not inhibit the synthesis of gastroprotecting prostaglandins (33), a Danish population-based observational study found a similarly increased risk of upper gastrointestinal bleedings in users of dipyridamole alone and low dose aspirin alone (17), which agrees with our finding that dipyridamole increases the risk of upper gastrointestinal bleedings to the same extent as low dose aspirin among users of coumarins.

Our results strongly suggest that all antiplatelet drugs increase the risk of upper gastrointestinal bleedings more than the risk of other bleedings. This was expected for aspirin because of its irreversible and unselective inhibition of cyclo-oxygenase-1 (COX-1), which has a role in the protection of the stomach mucosa (34). However, in users of coumarins the risk increasing effect of other antiplatelet drugs does not seem to be different from the risk increasing effect of low dose aspirin in the dosage range from 30–160 mg.

Table 4: Association between current use of aspirin alone and hospitalization for upper gastrointestinal bleedings and other bleedings for various assumptions of the maximal time between the last dispensing date of a coumarin and the index date, for users who received more than one prescription for a coumarin and for bleedings after the first 28 days of coumarin therapy.

	Multivariate Odds Ratios (95 % CI)				
	Last dispensing date – index date maximally 90 days	Last dispensing date – index date maximally 60 days	Last dispensing date – index date maximally 30 days	More than one prescription for a coumarin	Bleedings after the first 28 days of coumarin therapy
Upper gastrointestinal	2.5 (1.6–4.0)	2.5 (1.5–4.2)	2.2 (1.3–3.9)	2.0 (1.3–3.2)	2.1 (1.4–3.3)
Other	1.5 (1.1–2.0)	1.6 (1.2–2.2)	1.6 (1.1–2.3)	1.3 (1.0–1.8)	1.3 (1.0–1.7)

Appendix Table 1: List of the ICD-9-CM codes of the major bleeding events which were identified in cases.

Description	ICD-9-code	N
Gastrointestinal bleedings:		
Upper gastrointestinal		
Esophageal varices with bleeding	456.0	1
Gastric ulcer, acute with haemorrhage	531.0	6
Gastric ulcer, acute with haemorrhage and perforation	531.1	1
Gastric ulcer, chronic or unspecified with haemorrhage	531.4	80
Gastric ulcer, chronic or unspecified with haemorrhage and perforation	531.6	1
Duodenal ulcer, acute with haemorrhage	532.0	17
Duodenal ulcer, chronic or unspecified with haemorrhage	532.4	54
Duodenal ulcer, chronic or unspecified with haemorrhage and perforation	532.6	2
Peptic ulcer, acute with haemorrhage without obstruction	533.0	1
Gastrojejunal ulcer, chronic or unspecified with haemorrhage and perforation	534.4	1
Haematemesis	578.0	26
Melena	578.1	96
Haemorrhage of gastrointestinal tract, not otherwise specified	578.9	251
Lower gastrointestinal		
Haemorrhage of rectum or anus	569.3	68
Non-gastrointestinal bleedings:		
Intracranial		
Subarachnoidal haemorrhage	430	22
Intracerebral haemorrhage	431	218
Nontraumatic extradural haemorrhage	432.0	3
Subdural haemorrhage	432.1	65
Intracranial haemorrhage, not otherwise specified	432.9	10
Urinary tract		
Haemorrhage into bladder wall	596.7	3
Haematuria	599.7	102
Uterus		
Ovulation bleeding	626.5	1
Metrorrhagia	626.6	20
Disorder of menstruation or other abnormal bleeding, not otherwise specified	626.9	5
Premenopausal haemorrhage	627.0	1
Postmenopausal bleeding	627.1	104
Nose		
Epistaxis	784.7	161
Eye		
Haemophthalmos except current injury	360.43	1
Choroidal haemorrhage, unspecified	363.61	1
Hyphema	364.41	3
Conjunctival haemorrhage	372.72	2
Vitreous haemorrhage	379.32	13
Joint		
Hemarthrosis, site unspecified	719.10	1
Hemarthrosis, shoulder	719.11	4
Hemarthrosis, upper arm	719.12	1
Hemarthrosis, pelvic region and tigh	719.15	3
Hemarthrosis, lower leg	719.16	25
Other		
Haemoptysis	786.3	115
Haemoperitoneum	568.81	6
Spontaneous ecchymoses	782.7	1
Haemorrhage or hematoma complicating a procedure	998.1	210
Haemorrhage, unspecified	459.0	132

Our study has several limitations. First, there is the possibility of misclassification of users of coumarins, because we had to make assumptions regarding the duration of coumarin use. However, a reduction of the maximum time between the last dispensing date and the index date did not result in essentially different outcomes, suggesting that our assumptions were justified. A second limitation is that we did not have data on the intensity of anticoagulation (normal or high) or on diseases that we could not derive from drug therapy, such as liver and renal insufficiency, which are also risk factors for major bleeding (27, 35). A third limitation is that we could only evaluate a history of hospitalization for major bleeding from the moment patients were included in the PHARMO record linkage system, implicating that we could have missed information about earlier bleedings in patients. A forth potential limitation is that it is possible that use of confounding over-the-counter-drugs (OTC drugs, such as as-

What is known about this topic?
– The antiplatelet drug aspirin increases the risk of major bleeding in users of vitamin K antagonists.
– This pharmacodynamic interaction has been demonstrated in several studies, mainly for upper gastrointestinal bleedings.

What does this paper add?
– The other frequently used antiplatelet drugs clopidogrel and dipyridamole increase the risk of major bleeding in users of vitamin K antagonists to at least the same extent as low dose aspirin.
– All antiplatelet drugs affect the risk of upper gastrointestinal bleeding more than the risk of non-gastrointestinal bleeding in users of vitamin K antagaonists.
– Our results suggest that it is doubtful whether clopidogrel is a safer alternative to aspirin in users of vitamin K antagonists.

pirin or low dose NSAIDs) was not reliably recorded in the database. However, since most Dutch pharmacies record potentially interacting OTC drugs and since patients at anticoagulation clinics are clearly instructed not to use interacting OTC drugs, we do not think that lack of such information can have seriously confounded our results. Finally, the database contained neither information about the indications for use of coumarin anticoagulants, nor for the combined use with antiplatelet agents. We know from our other studies in Dutch populations that atrial fibrillation is the commonest indication for coumarins in outpatients (36, 37). However, we can only speculate on the reasons for combining a coumarin with an antiplatelet drug, which precludes a judgement on the potential appropriateness of combined use.

The results of our study give rise to some clinical considerations. Guidelines of the American College of Chest Physicians recommend adding dipyridamole or clopidogrel to warfarin in situations in which a combination of warfarin and an antiplatelet agent is indicated and patients are unable to take aspirin (38, 39). Of course, the desirability of combining coumarins and antiplatelet drugs is a matter of considerable debate and the benefit-risk ratio for applying such combinations is still unclear, even for situations in which combined use seems rational (6, 40). Anyhow, our findings do not support the view that adding clopidogrel or dipyridamole to coumarins is safer than adding low dose aspirin to coumarins.

In summary, our results suggest that next to aspirin, both clopidogrel and dipyridamole increase the risk of major bleeding among users of coumarins, and that this risk is more increased for upper gastrointestinal bleedings than for any other bleedings.

References

1. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006; 367: 1903–1912.
2. Hughes M, Lip G. Y. Stroke and thromboembolism in atrial fibrillation: a systematic review of stroke risk factors, risk stratification schema and cost effectiveness data. Thromb Haemost 2008; 99: 295–304.
3. Dahri K, Loewen P. The risk of bleeding with warfarin: a systematic review and performance analysis of clinical prediction rules. Thromb Haemost 2007; 98: 980–987.
4. Tran H, Anand SS. Oral antiplatelet therapy in cerebrovascular disease, coronary artery disease, and peripheral arterial disease. J Am Med Assoc 2004; 292: 1867–1874.
5. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324: 71–86.
6. Lip GY. Don't add aspirin for associated stable vascular disease in a patient with atrial fibrillation receiving anticoagulation. BMJ 2008; 336: 614–615.
7. van Es R. F., Jonker J. J., Verheugt F. W., Deckers J. W., Grobbee D. E. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002;360:109–13.
8. Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002; 347: 969–974.
9. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council's General Practice Research Framework. Lancet 1998; 351: 233–241.
10. Fiore LD, Ezekowitz MD, Brophy MT, et al. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. Circulation 2002; 105: 557–563.
11. Blackshear JL, Baker VS, Holland A, et al. Fecal hemoglobin excretion in elderly patients with atrial fibrillation: combined aspirin and low-dose warfarin vs conventional warfarin therapy. Arch Intern Med 1996; 156: 658–660.
12. Dentali F, Douketis JD, Lim W, et al. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease. Arch Intern Med 2007; 167: 117–124.
13. Larson RJ, Fisher ES. Should aspirin be continued in patients started on warfarin? J Gen Intern Med 2004; 19: 879–886.
14. Penning-van Beest F, Erkens J, Petersen KU, et al. Main comedications associated with major bleeding during anticoagulant therapy with coumarins. Eur J Clin Pharmacol 2005; 61: 439–444.
15. Johnsen SP, Sorensen HT, Mellemkjoer L, et al. Hospitalisation for upper gastrointestinal bleeding associated with use of oral anticoagulants. Thromb Haemost 2001; 86: 563–568.
16. Buresly K, Eisenberg MJ, Zhang X, et al. Bleeding complications associated with combinations of aspirin, thienopyridine derivatives, and warfarin in elderly patients following acute myocardial infarction. Arch Intern Med 2005; 165: 784–789.
17. Hallas J, Dall M, Andries A, et al. Use of single and combined antithrombotic therapy and risk of serious upper gastrointestinal bleeding: population based case-control study. Br Med J 2006; 333: 726.
18. Pouleur H, Buyse M. Effects of dipyridamole in combination with anticoagulant therapy on survival and thromboembolic events in patients with prosthetic heart valves. A meta-analysis of the randomized trials. J Thorac Cardiovasc Surg 1995; 110: 463–472.
19. Massel D, Little SH. Risks and benefits of adding anti-platelet therapy to warfarin among patients with prosthetic heart valves: a meta-analysis. J Am Coll Cardiol 2001; 37: 569–578.
20. Fihn SD, McDonell M, Martin DP, et al. Risk factors for complications of chronic anticoagulation. Ann Intern Med 1993; 118: 511–520.
21. Yusuf S, Zhao F, Mehta SR, et al. K. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001; 345: 494–502.
22. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation 2003; 108: 1682–1687.
23. Diener HC, Bogousslavsky J, Brass L, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004; 364: 331–337.
24. Halkes P. H, van Gijn J, Kappelle LJ, et al. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006; 367: 1665–1673.
25. Harder S, Thurmann P. Clinically important drug interactions with anticoagulants. An update. Clin Pharmacokinet 1996; 30: 416–444.
26. Harumi T, Teruki S, Yoshiaki S et al. Potentiation of anticoagulant effect of warfarin caused by enantioselective metabolic inhibition by the uricosuric agent benzbromarone. Clin Pharmacol Ther 1999; 66: 569–581.

27. Ansell J, Hirsh J, Poller L, et al. The pharmacology and management of the vitamin K antagonists: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126: 204S-233S.
28. Lidell C, Svedberg LE, Lindell P, et al. Clopidogrel and warfarin: absence of interaction in patients receiving long-term anticoagulant therapy for non-valvular atrial fibrillation. Thromb Haemost 2003; 89: 842–846.
29. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. Lancet 1996;348:1329–39.
30. Chan FK, Ching JY, Hung LC, et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. N Engl J Med 2005; 352: 238–244.
31. Ng FH, Wong SY, Chang CM, et al. High incidence of clopidogrel-associated gastrointestinal bleeding in patients with previous peptic ulcer disease. Aliment Pharmacol Ther 2003; 18: 443–449.
32. Khurram Z, Chou E, Minutello R, et al. Combination therapy with aspirin, clopidogrel and warfarin following coronary stenting is associated with a significant risk of bleeding. J Invasive Cardiol 2006; 18: 162–164.
33. Moncada S, Korbut R. Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin. Lancet 1978; 1: 1286–1289.
34. Vane JR, Botting RM. The mechanism of action of aspirin. Thromb Res 2003; 110: 255–258.
35. Landefeld CS, Beyth RJ. Anticoagulation-related bleeding: clinical epidemiology, prediction and prevention. Am J Med 1993; 95: 315–328.
36. Schalekamp T, Brasse BP, Roijers JF, et al. VKORC1 and CYP2C9 genotypes and acenocoumarol anticoagulation status: Interaction between both genotypes affects overanticoagulation. Clin Pharmacol Ther 2006; 80: 13–22.
37. Schalekamp T, Brasse BP, Roijers JF, et al. VKORC1 and CYP2C9 genotypes and phenprocoumon anticoagulation status: interaction between both genotypes affects dose requirement. Clin Pharmacol Ther 2007; 81: 185–193.
38. Salem DN, Stein PD, Al-Ahmad A, et al. Antithrombotic therapy in valvular heart disease--native and prosthetic: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126: 457S-482S.
39. Lip GY, Karpha M. Anticoagulant and antiplatelet therapy use in patients with atrial fibrillation undergoing percutaneous coronary intervention: the need for consensus and a management guideline. Chest 2006; 130: 1823–1827.
40. May AE, Geisler T, Gawaz M. Individualized antithrombotic therapy in high risk patients after coronary stenting. A double-edged sword between thrombosis and bleeding. Thromb Haemost 2008; 99: 487–493.