Background and Purpose—Subarachnoid hemorrhage (SAH) accounts for <7% of all strokes, but is an enormous individual and societal burden. We investigated the risk of SAH associated with prior use of antithrombotic drugs and their influence on 30-day case fatality.

Methods—We conducted a nested case–control study in a cohort of 13.4 million members of the German Pharmacoepidemiological Research Database. Ten controls were matched to each case hospitalized for SAH between July 2004 and November 2006 by health insurance, year of birth, and sex using risk set sampling. Exposure was assessed for the warfarin analog phenprocoumon, heparin, clopidogrel/ticlopidine, and acetylsalicylic acid. Multivariable-adjusted odds ratios (ORs) for SAH were estimated by conditional logistic regression. Risk factors for 30-day case fatality were assessed in patients with SAH by logistic regression.

Results—The nested case–control study included 2065 SAH cases and 20,649 matched controls. The risk of SAH was significantly increased for phenprocoumon (OR, 1.7; 95% confidence interval [CI], 1.3–2.3), clopidogrel/ticlopidine (OR, 1.7; 95% CI, 1.1–2.5), and for acetylsalicylic acid use (OR, 1.5; 95% CI, 1.2–2.0), but not for outpatient heparin use (OR, 1.2; 95% CI, 0.5–2.7). The early case fatality of 22.8% was associated with an age >70 years (OR, 2.3; 95% CI, 1.8–3.1) and arterial hypertension (OR, 1.3; 95% CI, 1.0–1.6), but not with any of the antithrombotic drugs.

Conclusions—Outpatient antithrombotic drug use was associated with an increased risk of SAH, but no association was observed with early case fatality. (Stroke. 2013;44:2422-2426.)

Key Words: anticoagulant ▪ coumarin ▪ phenprocoumon ▪ platelet aggregation inhibitors

Subarachnoid hemorrhage (SAH) causes only 5% to 7% of all incident strokes; however, treatment-related costs and loss in productivity are high.1,4,9 One in 2 affected persons is <55 years and dies rapidly or experiences severe disability.4

In 2000–2008, the risk of death within 30 days after onset was 25%,4,6 and 10% to 15% before reaching the hospital.5,6 Survivors often remain impaired with persistent SAH-related symptoms and experience a greatly reduced quality of life.7

A ruptured intracranial aneurysm accounts for 85% of SAH and is more frequent in patients with autosomal-dominant polycystic kidney disease.4,9,10 Despite genetic predisposition, intracranial aneurysm is usually not congenital, but develops throughout the course of life.4,9 Thus, modifiable risk factors, such as hypertension, smoking, and alcohol abuse, remain most important in the prevention of SAH.1,4,8,10

The influence of antithrombotic drugs on the risk of SAH has not been systematically studied, although these are widely used in the secondary prevention of thromboembolic diseases. In Germany, the warfarin analog phenprocoumon was the only vitamin K antagonist in use during the study period.11 It has the longest plasma half-life of the coumarins and is associated with high-dose variability.12 In previous studies, we showed an increased risk of serious bleeding from all causes in phenprocoumon users13,14 and also for intracerebral hemorrhage.15

The present study was conducted to assess the influence of antithrombotic drugs on the risk of SAH and on early case fatality within 30 days.

Methods

Study Design and Setting

We conducted a nested case–control study in a cohort of 13.4 million insurance members included in the German Pharmacoepidemiological Research Database who fulfilled the inclusion criteria defined below. This database contains data from 4 German statutory health insurances (SHIs) covering all regions in Germany and representing ≈20% of the German population. The study was based on data from the years 2004–2006 because more recent data were not available to us at the time of the analysis. The database included insurance members’ demographic characteristics, information on all hospitalizations, outpatient physician visits, and all refundable outpatient prescriptions. Death of insurance members can be identified (1) as reason for exit from the SHI or (2) as reason for discharge from the hospital for hospitalized patients. The hospital data contain information about the periods of time of the analysis.
diagnostic and therapeutic procedures. Claims of outpatient physician visits include outpatient treatments, procedures, and diagnoses. All diagnoses are coded according to the German modification of the International Classification of Diseases, Tenth Revision (ICD-10 GM).

Prescription data include the date of prescription and drug dispensation at the pharmacy, the amount of substance prescribed, and information on the prescribing physician. Prescription data are linked via the central pharmaceutical reference number to a pharmaceutical reference database, which contains information on the anatomic-therapeutic-chemical code, the defined daily dose, packaging size, strength, formulation, generic and trade name. Preliminary analyses on age and sex distribution, the number of hospital admissions, and drug use have shown the database to be representative for Germany.16

In Germany, the use of health insurance data for scientific research is regulated by the Code of Social Law. All involved SHIs, the Federal Ministry of Health (for federal SHI data), and the provincial health authority (for regional SHI data) approved the use of the data for this study. Informed consent was not required by law because the study was based on pseudonymous data.

Study Population and Outcome Assessment

All insured with 26 months of continuous insurance and no history of hospitalization for SAH during this period were included in the cohort. Cohort entry was defined as July 1, 2004, or the first day after 6 months of continuous enrollment in the SHI. Thereafter, data were collected from cohort entry onward until hospitalization for SAH, death, end of the insurance, or November 30, 2006. The latter was chosen to avoid incomplete data for hospitalizations spanning the end of the year.

Cases of SAH were identified from the main hospital discharge diagnosis (ICD-10 GM code of I60). To ensure that SAH was an acute event, a procedure code indicating imaging by computed tomography, MRI, or arteriography or documentation of other intracranial procedures was also required (codes available on request). The day of hospital admission was defined as the index date for the respective case. In a sensitivity analysis we also excluded all cases with head injuries (ICD-10 GM codes S00-S09) and those without MRI or computed tomography.

Ten controls were matched to each case by sex, year of birth, SHI, and time in cohort using risk set sampling.17 Thereby, the index date in each control was chosen with the same time of follow-up as for the corresponding case. Cohort members who were hospitalized on the index date of the case were excluded from the set of potential controls because they were not at risk of being admitted to hospital because of SAH at that time.

Early case fatality was defined as the proportion of all patients with SAH who died in the 30-day period after the index date. Information on death was obtained from the hospital discharge and insurance records. In addition, cases without any medical treatment or physician contacts beyond 30 days after the index date were presumed to have died.

Exposure Assessment

Exposure to the following anticoagulants was assessed: phenprocoumon, unfractionated or low molecular weight heparins, clopidogrel/ticlopidine, and low-dose acetylsalicylic acid (ASA). Exposure was defined as current if the last prescription overlapped with the 7-day period preceding the index date. The duration of a prescription was estimated by the amount of defined daily doses for all anticoagulants except for phenprocoumon where the defined daily dose could not be applied because of high interindividual dose variability. For phenprocoumon, the average daily dose was estimated for each patient by dividing the cumulative phenprocoumon dose until the last outpatient phenprocoumon prescription before the index date by the number of days corresponding to this period. The average daily dose was then used to estimate the duration of exposure for the last prescription preceding the index date. If there was only 1 prescription before the index date, the defined daily dose was used instead. Sensitivity analyses were conducted using fixed exposure assessment periods of 90, 180, and 270 days before the index date.

Confounder Assessment

The following comorbid conditions were assessed from hospital and outpatient diagnoses in the time period 6 months before cohort entry: diabetes mellitus, systemic hypertension, ischemic heart disease, ischemic cerebral infarction, cerebral aneurysm, brain tumor, epilepsy, liver and renal failure, polycystic kidney disease, alcohol dependence, history of bleeding events, and connective tissue disorders (Ehlers–Danlos syndrome, Marfan syndrome, neurofibromatosis, and fibromuscular dysplasia). Diabetes mellitus and alcohol dependency were identified from diagnoses and prescriptions of antidiabetic substances and disulfiram or acamprosate, respectively. Selective serotonin reuptake inhibitors were also considered in the analyses.

Statistical Methods

Incidence rates of SAH were calculated in the full cohort for different age groups stratified by sex. Corresponding 95% confidence intervals (CIs) were estimated by the substitution method assuming a Poisson distribution for the number of bleedings.18 In addition, incidence rates were standardized by age and sex to the 2006 European population19 using the direct method.20

On the basis of case–control data, crude odds ratios (ORs) were calculated using the Mantel–Haenszel estimator to account for matching. Multivariable conditional logistic regression analyses were conducted to estimate adjusted ORs and 2-sided 95% CI for SAH in subjects currently using phenprocoumon, heparin, or platelet aggregation inhibitors (ie, drugs of interest).

The preliminary multivariable model included known risk factors of SAH without interaction terms. Relevant covariates were selected by backward elimination using the Wald test (P<0.05) and forcing of all drugs of interest to stay in the model. Two-way interactions between sex or age, and other risk factors were only added to the model if they were significant at the 5% level. In addition, 2-way interactions between all considered antithrombotics were explored.

Predictors for 30-day case fatality were analyzed in subjects with SAH by logistic regression analysis including all considered risk factors. Backward selection was performed at a significance level of P<0.1 because of the small sample size.

Statistical analyses were performed using SAS/STAT software, version 9.2 of the SAS system for Windows (SAS Institute, Inc, Cary, NC).

Results

The cohort included 13.4 million insurants with a median follow-up time of 883 days. The average age was 39.9 years with a SD of 22.2 years, and 55% of cohort members were women. The overall crude incidence of SAH in this cohort was 7.1 (95% CI, 6.8–7.4) hemorrhages per 100,000 person-years. It was higher in women (8.39; 95% CI, 7.95–8.85 SAH per 100,000 person-years) than in men (5.42; 95% CI, 5.02–5.83 per 100,000 person-years) and rose with increasing age (Figure). The overall direct standardized incidence rate to the 2006 European population was 6.38 (95% CI, 6.10–6.65) per 100,000 person-years.

Within this cohort, we identified 2065 cases of SAH and 20,649 matched controls. Characteristics of the case–control sample are presented in Table 1. The final multivariable model included the drugs of interest and the covariables diabetes mellitus, arterial hypertension, cerebral aneurysm, epilepsy, polycystic kidney disease, alcohol dependence, and selective serotonin reuptake inhibitors. No interaction terms were added to the final multivariable model because either the main effect or the interaction term was not significant in the respective analysis.
Table 2 shows the crude and adjusted ORs based on the multivariable analysis model. The crude ORs were similar to those obtained from the multivariable model. Use of ASA, clopidogrel/ticlopidine, and phenprocoumon was associated with a small, but significantly increased risk of SAH. The risk was also increased for heparin; however, this increase was not significant. Among the other risk factors, high risks were observed for cerebral aneurysm and polycystic kidney disease. The adjusted ORs resulting from the full model, including all covariables and those of the sensitivity analysis excluding cases with head injuries, were similar to those obtained from the final model (results not shown). Similar results were also observed for the sensitivity analyses using fixed exposure assessment periods of 90, 180, and 270 days before the index date (results not shown).

A total of 470 subjects with SAH (22.8%) died within 30 days after hospitalization. Seventy percent of these were women and the average age was 60.5 (SD 15.8) years. A significantly increased risk was observed for ages >70 years (OR, 2.3; 95% CI, 1.8–3.1) and arterial hypertension (OR, 1.3; 95% CI, 1.0–1.6). Antithrombotic drug use was not found to be associated with increased 30-day case fatality.

Discussion
In our population-based nested case–control study, use of antithrombotics was associated with an increased risk of SAH, but not with early case fatality.

Our findings on phenprocoumon are in line with the results of a case–control study by Risselada et al,21 which investigated the risk of SAH for phenprocoumon, acenocoumarol, and platelet aggregation inhibitors with the Institute for Drug Outcomes Research database in the Netherlands. Only 1 study has investigated the risk of SAH in patients receiving warfarin.22 This was a population-based case–control study in Northern Denmark using data from the Danish National Registry of Patients. In contrary to our results, this study did not report an increased risk of SAH for vitamin K antagonist use (90% of patients used warfarin, only 10% had phenprocoumon prescribed). Overall vitamin K antagonist use in the Danish controls was with 1.3% similar to that in the controls of our study (1.6%); however, only 0.8% of the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=2065)</th>
<th>Controls (n=20649)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>56.3 (14.6)</td>
<td>56.3 (14.6)</td>
</tr>
<tr>
<td>Women</td>
<td>1354 (65.6)</td>
<td>13539 (65.6)</td>
</tr>
<tr>
<td>Antithrombotic and anticoagulant medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>72 (3.5)</td>
<td>488 (2.4)</td>
</tr>
<tr>
<td>Clopidogrel/ticlopidine</td>
<td>31 (1.5)</td>
<td>177 (0.9)</td>
</tr>
<tr>
<td>Heparin</td>
<td>8 (0.4)</td>
<td>50 (0.2)</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>55 (2.7)</td>
<td>326 (1.6)</td>
</tr>
<tr>
<td>Comorbid conditions before cohort entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>172 (8.3)</td>
<td>2083 (10.1)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>710 (34.4)</td>
<td>6308 (30.6)</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>219 (10.6)</td>
<td>2059 (10.0)</td>
</tr>
<tr>
<td>Ischemic cerebral infarction</td>
<td>47 (2.3)</td>
<td>371 (1.8)</td>
</tr>
<tr>
<td>Cerebral aneurysm</td>
<td>20 (1.0)</td>
<td>9 (&lt;0.1)</td>
</tr>
<tr>
<td>Brain tumor</td>
<td>14 (0.7)</td>
<td>68 (0.3)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>31 (1.5)</td>
<td>152 (0.7)</td>
</tr>
<tr>
<td>Liver failure</td>
<td>158 (7.7)</td>
<td>1475 (7.1)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>57 (2.8)</td>
<td>428 (2.1)</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>3 (0.1)</td>
<td>6 (&lt;0.1)</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>45 (2.2)</td>
<td>212 (1.0)</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>12 (0.6)</td>
<td>81 (0.4)</td>
</tr>
<tr>
<td>Connective tissue disorders*</td>
<td>2 (0.1)</td>
<td>6 (&lt;0.1)</td>
</tr>
<tr>
<td>Concomitant medication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>42 (2.0)</td>
<td>243 (1.2)</td>
</tr>
</tbody>
</table>

*Connective tissue disorders: Ehlers–Danlos syndrome, Marfan syndrome, neurofibromatosis, and fibromuscular dysplasia.
Danish cases had used vitamin K antagonists compared with 2.7% of the cases in our study. The age and sex distribution was nearly the same in both studies. Comorbidity of the study populations could not be well compared because the Danish study lacked outpatient diagnoses.

The increased risk observed for low-dose ASA is in line with the results of another Danish population–based nested case–control study, which reported a 2.5-fold risk of SAH associated with new use of low-dose ASA, whereas this study did not find an increased risk for long-term ASA use.21 Because of low numbers of clopidogrel users, this Danish study was inconclusive with respect to the risk of clopidogrel. In the study by Risselada et al,24 the use of platelet aggregation inhibitors was not associated with an increased risk of SAH. This study did, however, not differentiate between new or long-term use of platelet aggregation inhibitors or between ASA and clopidogrel.

In our study, heparin use resulted in a slight, but nonsignificant increase in the risk of SAH. Because only outpatient drug use was available to us for analysis, and this was rather low, our study had limited power to detect any increased risk. There are no other studies which have reported on the risk of heparin use.

We did not observe an increased risk for 30-day case fatality with any of the antithrombotic drugs used; however, power was limited for some of the antithrombotic exposures because of the small sample size for this analysis. Mortality was, however, significantly increased in patients >70 years and with arterial hypertension. Age has previously been shown to be a strong predictor for 60-day case fatality in a prognostic model presented by Risselada et al.24 This prognostic model was based on data from the randomized International Subarachnoid Aneurysm Trial which provided considerably more clinical detail for risk prediction than the health insurance data we had available for our study. Antithrombotic drug use and arterial hypertension were not considered as prognostic factors in the model reported by Risselada et al.24

Early case fatality (ie, within 30 days of the event) was 22.8% and is at the lower end of the estimates reported in a recent systematic review for high income countries (covering the period between 2000 and 2008, excluding Germany).5 Because of the advancement of diagnostic and treatment strategies for SAH, a constant decline of case fatality has been observed over time,5,6 which is in line with the rather low observed 30-day case fatality in our study.

Our results were consistent with previous research in terms of the crude incidence of SAH1 and the median age of patients with SAH.23 The standardized incidence rate was slightly lower than that provided in another study.25 Our study also confirmed several well-known risk factors for SAH, such as arterial hypertension,2,6 alcohol dependence,2,8,10 and autosomal-dominant polycystic kidney disease.10 Our findings also confirmed the reduced risk for diabetes mellitus reported for case–control studies.2 The reason for this association is not well understood, but it was suggested that patients with diabetes mellitus might have a higher risk of mortality because of other causes, reducing the chances of developing SAH compared with controls.2

### Strengths and Limitations

The study was conducted in a large database representative for Germany26,27 including >17 million subjects. It provides data on the practice of antithrombotic prescribing and the occurrence of SAH in a real-life setting on a population level. The large size of German Pharmacoepidemiological Research Database enabled us to also investigate single drugs and not only, for example, combined drug classes and rare diseases as risk factors for SAH. Because prescription data are available with the exact date of dispensal, there is low potential for misclassification of drug exposure when compared with field studies on the basis of interview data. Selection bias in the choice of controls is unlikely because this study was designed as a nested case–control study in a defined cohort providing both cases and controls. In addition, all information was recorded prospectively, thereby avoiding recall bias.

Cases of SAH were identified by the main hospital discharge diagnosis which provides the reason for the hospitalization. We did not consider secondary discharge diagnoses to avoid misclassifying prevalent as incident cases. Cases also had to have specific imaging and surgical procedures for SAH or one of the two to ensure an acute event. Because of the large amount of cases, but foremost because of restrictions of German data protection laws, we could not validate the cases on the basis of medical charts. However, with the case definition chosen, the incidence of SAH we observed was comparable with that of other studies.1,4,23 A sensitivity analysis excluding SAH cases with head injuries and cases without MRI or computed tomography corroborated the findings.

Because the database does not contain information on the prescribed dose and duration of use, the duration of exposure for phenprocoumon was estimated on the basis of average daily dose. Sensitivity analyses using fixed exposure assessment periods of 90, 180, and 270 days before the index date showed that our results were robust. Although we included information on many potential risk factors of SAH, we could not control for other potential confounders, such as smoking or over the-counter use of high-dose ASA because this information is

### Table 2. Crude and Adjusted Odds Ratios of Subarachnoid Hemorrhage for Antithrombotics and Risk Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Crude OR</th>
<th>Adjusted* OR</th>
<th>95% CI</th>
<th>PValue**</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antithrombotics medications</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>1.5</td>
<td>1.5</td>
<td>1.2–2.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Clopidogrel/ticlopidine</td>
<td>1.8</td>
<td>1.6</td>
<td>1.1–2.4</td>
<td>0.016</td>
</tr>
<tr>
<td>Heparin</td>
<td>1.6</td>
<td>1.2</td>
<td>0.6–2.8</td>
<td>0.604</td>
</tr>
<tr>
<td>Phenprocoumon</td>
<td>1.7</td>
<td>1.7</td>
<td>1.3–2.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Comorbid conditions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.8</td>
<td>0.7</td>
<td>0.6–0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>1.2</td>
<td>1.2</td>
<td>1.1–1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cerebral aneurysm</td>
<td>22.2</td>
<td>19.5</td>
<td>8.8–43.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>2.1</td>
<td>2.1</td>
<td>1.1–2.5</td>
<td>0.014</td>
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<tr>
<td>Polycystic kidney disease</td>
<td>5.0</td>
<td>4.8</td>
<td>1.2–19.4</td>
<td>0.026</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>2.2</td>
<td>2.0</td>
<td>1.4–2.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Concomitant medication</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake</td>
<td>1.8</td>
<td>1.7</td>
<td>1.2–2.3</td>
<td>0.003</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; and OR, odds ratio
*Adjusted for all other covariables.
**95% confidence intervals and Pvalues refer to the adjusted odds ratios.
not available in the database. However, whether a risk factor is truly a confounder depends on whether it is also associated with the exposure under study. Besides, the potential for confounding also depends on the magnitude of the risk of the potential risk factor. Smoking has been shown to be an important risk factor for SAH; however, the magnitude of the risk has varied between 1.23 and 2.2 in a systematic review of longitudinal studies.2 The association of smoking with oral anticoagulant exposure is probably weak, given that oral anticoagulation is prescribed for many conditions which seem rather unrelated to smoking. We, therefore, do not expect major confounding by lack of adjustment for smoking in our analyses. This is in line with the results of one of our previous studies on phenprocoumon use and serious bleeding where additional information on smoking obtained for a subsample of patients in a 2-phase analysis did not result in a relevant change of the risk estimate for phenprocoumon.13 Information on anticoagulation intensity is also lacking in the database. However, as it is a prerequisite that a confounder does not lie on the causal pathway between exposure and outcome, we are not concerned by this lack of information because we believe that high international normalized ratio values are on the causal pathway between phenprocoumon use and bleeding. Therefore, adjustment for anticoagulation intensity as a confounder in the statistical analysis is not appropriate. We could not provide information on the new generation of anticoagulants, such as rivaroxaban or dabigatran, as they had not yet been marketed during the study period.

Conclusions
We found that outpatient use of antithrombotic drugs increased the risk of SAH. We did not observe an increase in 30-day case fatality for the antithrombotic drugs under study; however, the power for this analysis was limited because of the small sample size for this analysis. Early case fatality was associated with an age >70 years and arterial hypertension.

Acknowledgments
We thank J. Böse who helped us with the preparation of the article.

Disclosures
Dr Garbe is running a department that occasionally performs studies for pharmaceutical industries with the full freedom to publish. Companies include Mundipharma, Bayer, Stada, SanofiAventis, SanofiPasteur, Novartis, Takeda, Celgene, and GlaxoSmithKline. Dr Garbe has been consulted to Bayer, Nycomed, Teva, GlaxoSmithKline, and Novartis unrelated to this work. The other authors report no conflict.

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Risk of Subarachnoid Hemorrhage and Early Case Fatality Associated With Outpatient Antithrombotic Drug Use
Edeltraut Garbe, Stefan H. Kreisel and Sigrid Behr

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