Antithrombotic drugs and subarachnoid haemorrhage risk

A nationwide case-control study in Denmark

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Summary

The study objective was to investigate the relationship between use of antithrombotic drugs and subarachnoid haemorrhage (SAH). We identified patients discharged from Danish neurosurgery units with a first-ever SAH diagnosis in 2000 to 2012 (n=5,834). For each case, we selected 40 age-, sex- and period-matched population controls. Conditional logistic regression models were used to estimate odds ratios (aOR), adjusted for comorbidity, education level, and income. Low-dose aspirin (ASA) use for <1 month was associated with an increased risk of SAH (aOR 1.75, 95% confidence interval [CI] 1.28–2.40). This aOR decreased to 1.26 (95%CI: 0.98–1.63) with 2–3 months of ASA use, and approached unity with use for more than three months (1.11, 95%CI 0.97–1.27). Analyses with first-time users confirmed this pattern, which was also observed for clopidogrel. ASA treatment for three or more years was associated with an aOR of SAH of 1.13 (95%CI: 0.86–1.49). Short-term use (<1 month) of vitamin K–antagonists (VKA) yielded an aOR of 1.85 (95%CI 0.97–3.51) which dropped after 3+ years to 1.24, 95%CI: 0.86–1.77. The risk of SAH was higher in subjects in dual antithrombotic treatment (aOR 2.08, 95%CI: 1.26–3.44), and in triple antithrombotic treatment (aOR 5.74, 95%CI: 1.76–18.77). In conclusion, use of aspirin,clopidogrel and VKA were only associated with an increased risk of SAH in the first three months after starting treatment. Long-term aspirin use carried no reduced SAH risk. Results should be interpreted cautiously due to their observational nature.

Keywords

Anticoagulants, aspirin, clopidogrel, platelet aggregation inhibitors, subarachnoid haemorrhage

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Introduction

Subarachnoid haemorrhage (SAH), in 80–90% of cases due to rupture of an intracranial aneurysm, occurs at all ages, but strikes primarily in middle age (1). The consequences of SAH are often devastating: a high proportion of patients admitted to hospital die within one month (2) and more than one third of survivors have severe disability (1).

Cigarette smoking, hypertension, and family history are among the most consistently observed risk factors for SAH (3). Whether use of antithrombotic drugs influences the risk of SAH has been the focus of a limited number of epidemiological studies with inconsistent results (4–7). Use of low-dose aspirin has in one study been reported to increase SAH risk in the short-term only (5), not to be associated with this stroke type in another (6), and, in more recent studies, to potentially confer a protective effect against SAH when used long-term (7, 8). Data on vitamin K–antagonist (VKA) use and SAH risk are also conflicting (4, 6, 7). Given the widespread use of antithrombotic drugs, establishing the magnitude and direction of their association with SAH risk is of interest from both a clinical and a public health perspective. We therefore conducted the present study with the aim to investigate the relationship between use of antiplatelet drugs and VKA and SAH in the general population, using nationwide Danish registries.

Materials and methods

This study was designed as a nationwide case-control study based on information from population-based Danish registries. Cases were persons with incident SAH and controls were selected randomly from the Danish source population. Subjects' previous exposure to drugs was assessed through prescription data.

Cases

Cases were patients with a first-ever primary diagnosis code of SAH in the period 2000–2012 according to the Danish National

Patient Register (Patient Registry) (9) data and ages 20–89 years. The registry codes used to identify patients with SAH and their characteristics and endovascular or surgical treatment, as well as covariates including drug use and medical history, are provided in the Appendix. For each patient, the date of the first hospital contact under a primary diagnosis of SAH was identified (index date). We identified the specialty of all departments the patient was admitted to within seven days following the index date, as we considered such contacts to belong to the same episode. Based on this information, we identified patients admitted or transferred to neurosurgery departments, where the validity of the SAH code has previously been shown to be high (10). Cases were furthermore classified according to aneurysm interventions into a procedure group (codes compatible with endovascular therapy using detachable coils, or surgery, i.e. clipping, ligation, or trapping) and a non-procedure group (no procedure codes recorded). We excluded cases fulfilling the following criteria: (i) SAH diagnoses recorded before 2000; (ii) concurrent or previous diagnoses compatible with arteriovenous malformations or fistulas recorded at any time prior to the index date, or up to seven days hereafter; (iii) residency in Denmark for less than 10 consecutive years at the time of the index date.

Validity of SAH-related codes

To assess the validity of SAH-related codes we used data from the former Funen County, a geographically well-defined area of Denmark (484,346 inhabitants in 2009), holding one of five neurosurgery departments in Denmark. Using a regional Patient Registry, we identified all area residents admitted under primary SAH diagnostic codes to any of the hospitals in the catchment area, including the aforementioned neurosurgery department, in 2000 to 2012. Using the same criteria as in the main study, we classified patients by department type and procedure and retrieved a random sample of 200 patients; 100 admitted at the neurosurgical department, and further 100 patients admitted to non-neurosurgery departments. A neurosurgeon ascertained the diagnosis and procedures based on medical record information. We calculated the positive predictive value (PPV) of an SAH diagnosis code and the PPV and negative predictive value (NPV) of procedure codes. For patients with SAH we further calculated the proportion in which the work-up disclosed an aneurysm as the source of the bleed.

Controls

Using risk set sampling (11) and applying the same eligibility and exclusion criteria as for cases, we sampled 40 birth year- and sex matched controls from the Danish population for each case using the Danish Civil Registration System (12). Controls were assigned an index date identical to the date of diagnosis of the corresponding cases.

Assessment of antiplatelet and anticoagulant drug exposure

From the Danish National Prescription Registry (Prescription Registry) (13), we retrieved all available prescriptions redeemed by study subjects. Based on prescriptions of low-dose aspirin (ASA; only available in doses of 150 mg or less in Denmark) or other antiplatelet drugs dispensed during the period from 1995 up to one day prior to the index date, study subjects were classified as ever users (≥1 prescription) or never users (no prescription) of low-dose ASA, clopidogrel, or dipyridamole. We applied the same principles for anticoagulant drugs, which were classified into vitamin K antagonists (VKA) and newer oral anticoagulants (NOACs).

To calculate duration of use of each prescription, we set each prescription to last a number of days corresponding to the number of pills dispensed (divided by 2 for dipyridamole) plus a grace period of 30 days (to allow some degree of non-compliance or irregular dispensing). Based on the most recent continuous treatment prior to the index date, we divided exposure into current use (0–30 days before index-date), recent use (31–90 days), past use (91–365 days), and distant use (>365 days before index-date). Similar to a previous study (7), current use was further subdivided by the duration of the current treatment episode: <1 month, ≥1 to <3 months, ≥3 to <12 months, ≥1 to <3 years, ≥3 years. A continuous treatment period lasted for as long as consecutive prescriptions were presented with no gap, i.e. presented within the time-window defined by the coverage of the preceding prescription.

Some subjects switch between antiplatelet drugs. To analyse the effect of individual antiplatelet drugs we therefore repeated the above analyses in subjects that used ASA only, or clopidogrel only, defined as never use of other antiplatelet drugs. We did not analyse the effect of dipyridamole only (with no concurrent use of ASA), since, in accordance with Danish guidelines on stroke prevention, this drug is only recommended in combination with ASA (14). Accordingly, we only studied the combination ASA/dipyridamole.

For low-dose ASA, we calculated an estimated daily dose defined as the most frequently prescribed tablet strength during the last five years in the exposure period. This was categorised as a 'low' (≤100 mg) or 'high' (150 mg) daily dose of low-dose ASA.

Finally, for low-dose ASA and clopidogrel, we performed analyses restricted to first time users of the drug. First time users were defined as subjects presenting prescriptions for any antiplatelet drug for the first time ever in the time period from four years to one day before index date.

Potential confounders

We used data from the Patient Registry, the Prescription Registry, or both to classify subjects with regard to the following disorders (see Appendix): hypertension, chronic obstructive pulmonary disease (COPD, as a marker of smoking), high alcohol consumption, diabetes, myocardial infarction (MI), angina, unstable angina, peripheral artery disease, and use of nonsteroidal anti-inflammatory

(NSAID) drugs, hormone replacement therapy (HRT), or oral corticosteroid drugs. As proxies for socioeconomic status, we furthermore classified subjects by highest education attained (years of schooling: 7–10, 11–12, 13+, or missing) and by income (low, middle, and high according to tertiles of individual incomes in the control-group) based on nationwide registry data (15, 16).

Statistical analyses

The nationwide study setting provided the opportunity to compute population-based descriptive epidemiologic measures of SAH. We calculated annual incidence rates (overall, and sex- and age-specific) with the Danish population as the denominator (aggregated population data retrieved from Statistics Denmark www.dst.dk). The 30-day case fatality rate was computed after linking our data to information on vital status according to the National Danish Civil Registry (12). Ninety-five percent confidence intervals were computed under the assumption of a Poisson distribution.

We used conditional logistic regression to compute adjusted odds ratios (ORs) (and 95% confidence intervals [CIs]) for SAH associated with low-dose ASA or other antiplatelet drug use and anticoagulants, respectively. We adjusted for all factors listed under potential confounders. In the analyses focusing on antiplatelet drug use we furthermore included ever use of anticoagulants as a potential confounder. All analyses were performed both for the entire sample and restricted to cases admitted to neurosurgery units. The latter group was further stratified according to whether the cases had had procedures performed (endovascular treatment or surgery for aneurysm). We also computed the risk of SAH associated with concomitant exposure of dual, or triple antithrombotic therapy.

We performed a number of supplementary analyses to address: (i) the presence of potential effect measure modification of age and sex by stratifying analyses according to these variables; (ii) the influence of varying the grace period for gaps between prescriptions (90 days instead of 30 days) and lag-time (period with omitted prescriptions before index-date; 30 days instead of 1 day).

All analyses were performed using Stata SE 13 (StataCorp, College Station, TX, USA). The study was approved by the Danish Data Protection Agency and the Statens Serum Institut. According to Danish law, approval from an ethics board is not required for register studies (16).

Results

We identified a total of 7,278 incident cases of SAH in Denmark in the years 2000 to 2012 (►Table 1 and ►Figure 1). This corresponds to an incidence rate of SAH of 13.6 per 100,000 person-years (95% CI 13.3–13.9). When limited to subjects admitted to neurosurgery department, i.e. diagnoses with highest validity, the incidence rate was 10.9 per 100,000 person-years (95% CI 10.6–11.2). The age and sex distribution of the 80.2% cases admitted to neurosurgical departments was as expected for SAH cases (►Figure 1B). Conversely, cases exclusively admitted to non-neurosurgery units had a distribution of age and sex markedly different from the one among cases admitted to neurosurgical departments, which questions the validity of these diagnoses (►Figure 1C). We therefore only included patients from the neurosurgery group (n=5,834) in further analyses.

Characteristics of cases from neurosurgery departments

Out of the 5,834 cases in the neurosurgery group, 54.7% were also coded for aneurysm procedure (neurosurgery and procedure group), while 45.3% did not receive such codes (no procedure group) (►Table 1). The proportion of patients treated with endovascular therapy increased considerably in the study period, and this was paralleled by a decrease in the proportion of patients who underwent surgery. Thus, the annual proportion of patients treated with either procedure (endovascular therapy or surgery) remained relatively stable during the study period (►Figure 2).

The median age of cases admitted to neurosurgery departments was 57 years (interquartile range [IQR] 47–66), 61.3% were women and the age-and sex adjusted 30-day case fatality rate in this group was 24.9%. However, patients subjected to aneurysmal procedures were younger (median age 55 years), more frequently female (69.2%) and had a lower adjusted 30-day case fatality rate (14.5%) compared with patients from the no procedure group (median age 58 years, 51.7% female, adjusted case fatality rate 36.4%) (►Table 1 and ►Figure 3). Prevalence of hypertension, previous stroke, and high alcohol intake was higher in cases compared with their controls from the general population, and these differences were more pronounced in the no procedure group compared with the aneurysmal procedure group (►Table 1). Similar patterns were observed for prevalence of COPD and use of drugs for treatment of nicotine dependency. Furthermore, high education level and high income were less prevalent among cases compared with controls, and these differences were most pronounced in the aneurysm procedure group. Other characteristics, including use of various medications, are presented in ►Table 1.

Risk of SAH associated with antithrombotic drug use

The crude OR of SAH associated with current use of aspirin was 1.26 (95% CI 1.15–1.39) (adjusted OR 1.20, 95% CI 1.07–1.36), while that associated with distant use was 1.28 (95% CI: 1.11–1.47) (adjusted OR: 1.15, 95% CI 0.97–1.35) (►Table 2). Similar results for current use were found among the subgroup with and without procedure. In analyses by duration of current use an increase in the risk of SAH was only observed in those with duration of low-dose aspirin use of less than one month (neurosurgery, all: 1.75, 95% CI 1.28–2.40) and to a lesser extent in subjects with 2–3 months of current low-dose ASA use (neurosurgery, all: 1.26, 95% CI 0.98–1.63). Current use of low-dose aspirin with a duration exceeding three months was not associated with increased risk of SAH (OR 1.11, 95% CI 0.97–1.27). Similar patterns were observed in analyses restricted to the neurosurgery and pro-

Table 1: Characteristics of cases with incident subarachnoid haemorrhage and their general population controls, Denmark 2000–2012. Cases identified through hospital discharge codes and classified by hospital department type and aneurysm procedure (endovascular or surgery).

	All departments		Neurosurgery, all		Neurosurgery & aneurysm procedure		Neurosurgery, no aneurysm procedure	
	cases	controls	cases	controls	cases	controls	cases	controls
All	(n=7,278)	(n=291,109)	(n=5,834)	(n=233,349)	(n=3,189)	(n=127,555)	(n=2,645)	(n=105,794)
Women	4,356 (59.9)	174,229 (59.9)	3,575 (61.3)	142,989 (61.3)	2,207 (69.2)	88,275 (69.2)	1,368 (51.7)	54,714 (51.7)
Age, median (IQR)	58 (48–69)	58 (48–69)	57 (47–66)	57 (47–66)	55 (47–64)	55 (47–64)	58 (48–69)	58 (48–69)
30-day case fatality rate	2,014 (27.7)	NA	1,378 (23.6)	NA	445 (14.0)	NA	933 (35.3)	NA
30-day case fatality, standardised %	27.7	NA	24.9	NA	14.5	NA	36.4	NA
Aneurysm procedure performed								
Surgery	1,570 (21.6)	NA	1,570 (26.9)	NA	1,570 (49.2)	NA	0 (0.0)	NA
Endovascular therapy	1,619 (22.2)	NA	1,619 (27.8)	NA	1,619 (50.8)	NA	0 (0.0)	NA
None	4,089 (56.2)	NA	2,645 (45.3)	NA	0 (0.0)	NA	2,645 (100.0)	NA
Index year								
2000–2006	4,002 (55.0)	160,071 (55.0)	3,301 (56.6)	132,031 (56.6)	1,767 (55.4)	70,675 (55.4)	1,534 (58.0)	61,356 (58.0)
2007–2012	3,276 (45.0)	131,038 (45.0)	2,533 (43.4)	101,318 (43.4)	1,422 (44.6)	56,880 (44.6)	1,111 (42.0)	44,438 (42.0)
Medications								
Low-dose aspirin[1]	933 (12.8)	30,415 (10.4)	587 (10.1)	20,039 (8.6)	249 (7.8)	9,152 (7.2)	338 (12.8)	10,887 (10.3)
Clopidogrel[1]	79 (1.1)	1,739 (0.6)	54 (0.9)	1,189 (0.5)	16 (0.5)	581 (0.5)	38 (1.4)	608 (0.6)
Dipyridamol[1]	197 (2.7)	4,042 (1.4)	120 (2.1)	2,685 (1.2)	55 (1.7)	1,184 (0.9)	65 (2.5)	1,501 (1.4)
Newer oral anticoagulants[1]	(n<3)	47 (0.0)	(n<3)	30 (0.0)	(n<3)	11 (0.0)	(n<3)	19 (0.0)
Vitamin K–antagonists[1]	250 (3.4)	5,623 (1.9)	117 (2.0)	3,543 (1.5)	28 (0.9)	1,515 (1.2)	89 (3.4)	2,028 (1.9)
Non-aspirin NSAIDs[2]	1,508 (20.7)	53,265 (18.3)	1,217 (20.9)	42,817 (18.3)	674 (21.1)	23,610 (18.5)	543 (20.5)	19,207 (18.2)
Statins[2]	823 (11.3)	32,228 (11.1)	593 (10.2)	23,777 (10.2)	280 (8.8)	12,228 (9.6)	313 (11.8)	11,549 (10.9)
Oral corticosteroids2	357 (4.9)	13,050 (4.5)	273 (4.7)	9,860 (4.2)	145 (4.5)	5,232 (4.1)	128 (4.8)	4,628 (4.4)
Hormone replacement therapy[2]	566 (7.8)	24,642 (8.5)	466 (8.0)	20,310 (8.7)	285 (8.9)	12,467 (9.8)	181 (6.8)	7,843 (7.4)
Nicotine dependency treatment[2]	55 (0.8)	1,445 (0.5)	49 (0.8)	1,188 (0.5)	36 (1.1)	685 (0.5)	13 (0.5)	503 (0.5)
Comorbidity								
Hypertension	2,377 (32.7)	84,809 (29.1)	1,686 (28.9)	61,556 (26.4)	843 (26.4)	31,864 (25.0)	843 (31.9)	29,692 (28.1)
Stroke	487 (6.7)	9,732 (3.3)	278 (4.8)	6,264 (2.7)	110 (3.4)	2,806 (2.2)	168 (6.4)	3,458 (3.3)
COPD	327 (4.5)	9,409 (3.2)	211 (3.6)	6,481 (2.8)	115 (3.6)	3,194 (2.5)	96 (3.6)	3,287 (3.1)
Diabetes	345 (4.7)	15,978 (5.5)	205 (3.5)	11,735 (5.0)	66 (2.1)	5,984 (4.7)	139 (5.3)	5,751 (5.4)
High alcohol intake	533 (7.3)	11,428 (3.9)	392 (6.7)	9,510 (4.1)	159 (5.0)	5,017 (3.9)	233 (8.8)	4,493 (4.2)
Myocardial infarct	279 (3.8)	9,487 (3.3)	170 (2.9)	6,164 (2.6)	71 (2.2)	2,636 (2.1)	99 (3.7)	3,528 (3.3)
Unstable angina	101 (1.4)	3,289 (1.1)	63 (1.1)	2,211 (0.9)	16 (0.5)	1,025 (0.8)	47 (1.8)	1,186 (1.1)
Other angina	446 (6.1)	16,000 (5.5)	295 (5.1)	11,097 (4.8)	111 (3.5)	5,364 (4.2)	184 (7.0)	5,733 (5.4)
Peripheral artery disease	74 (1.0)	2,288 (0.8)	52 (0.9)	1,460 (0.6)	20 (0.6)	696 (0.5)	32 (1.2)	764 (0.7)
Schooling, years								
7–10	2,839 (39.0)	102,107 (35.1)	2,201 (37.7)	79,697 (34.2)	1,238 (38.8)	42,714 (33.5)	963 (36.4)	36,983 (35.0)
11–12	2,657 (36.5)	108,905 (37.4)	2,230 (38.2)	90,373 (38.7)	1,203 (37.7)	49,449 (38.8)	1,027 (38.8)	40,924 (38.7)
13+	1,252 (17.2)	62,275 (21.4)	1,059 (18.2)	52,723 (22.6)	565 (17.7)	30,168 (23.7)	494 (18.7)	22,555 (21.3)
Missing values	530 (7.3)	17,822 (6.1)	344 (5.9)	10,556 (4.5)	183 (5.7)	5,224 (4.1)	161 (6.1)	5,332 (5.0)
Income, tertiles								
Low	2,427 (33.3)	95,624 (32.8)	1,738 (29.8)	70,218 (30.1)	898 (28.2)	36,733 (28.8)	840 (31.8)	33,485 (31.7)
Middle	2,469 (33.9)	95,588 (32.8)	2,085 (35.7)	80,072 (34.3)	1,240 (38.9)	45,941 (36.0)	845 (31.9)	34,131 (32.3)
High	2,212 (30.4)	95,839 (32.9)	1,869 (32.0)	80,201 (34.4)	968 (30.4)	43,535 (34.1)	901 (34.1)	36,666 (34.7)

Numbers (%) unless otherwise specified. [1]Use of drug 1 month to 1 day before index date. [2]Use of drug between 1 year and 1 month prior to index date.

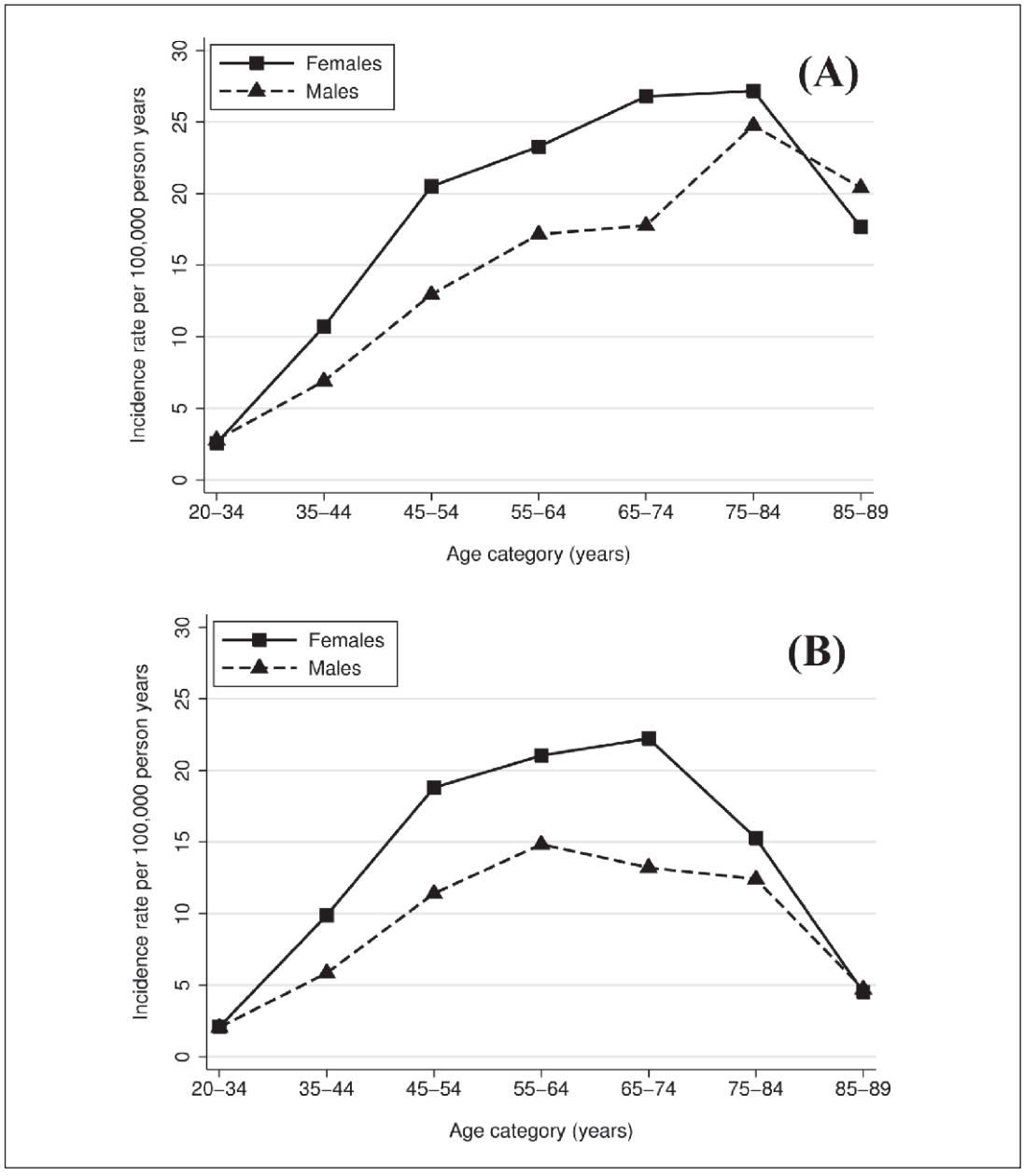

Figure 1: Incidence rate of first-ever subarachnoid haemorrhage coded admissions by department type, Denmark 2000–2012. A) All departments; B) Neurosurgery departments; and C) Non neurosurgery departments.

cedure group and the no procedure group (▶Table 2). Long-term use of low-dose ASA (3+ years) was not associated with a reduction in the risk of SAH in analyses based on the neurosurgery-all group (OR 1.13, 95% CI 0.86–1.49) or in the subgroups based on procedure status. Analyses of the use of clopidogrel revealed a similar overall pattern, although with lower statistical precision due to smaller numbers (▶Table 2).

In analyses restricted to first-time users of low-dose ASA, we also observed higher risks associated with short-term use in the neurosurgery group (≤1 month OR 1.98, 95%CI 1.35–2.92; 2–3 months: OR 1.61, 95%CI: 1.19–2.16), while use exceeding three months did not present an increased risk (OR 1.09, 95%CI: 0.92–1.29) (▶Table 3). However, the short-term risk of SAH associated with low-dose ASA use was higher in the no procedure group (≤1 month 2.75, 95%CI: 1.70–4.45; 2–3 months: 1.75, 95%CI 1.18–2.61) compared with the procedure group (1.22; 95%CI: 0.61–2.42 and 1.43, 95%CI 0.91–2.25, respectively). Similar patterns were observed with new users of clopidogrel, although these analyses were based on small numbers.

The indication for VKA use could be established in the majority of subjects, based on information from the Patient Registry: atrial fibrillation (65.6%), venous thromboembolism (17.2%), or mechanical prosthetic heart valves (5.2%). Current use of VKA was associated with a slight increase in the risk of SAH (1.22, 95%CI 1.00–1.48). In subjects with current use of ≤1 month duration, the OR was 1.85 (95%CI 0.97–3.51). The OR was 1.24

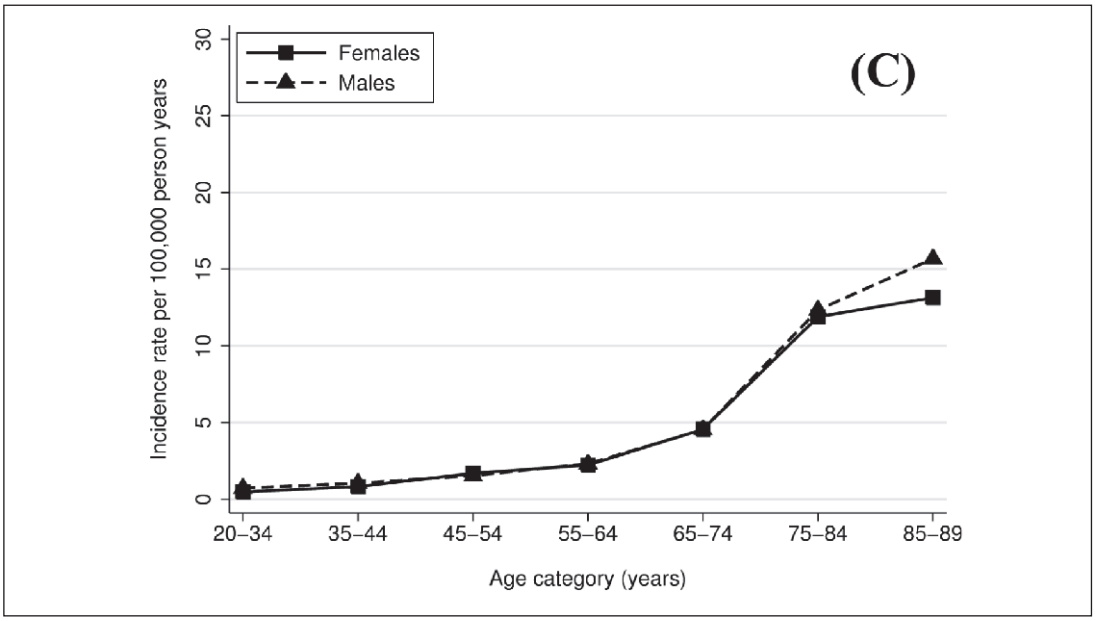

Figure 1: continued

(95%CI 0.86–1.77) in those with long-term use of the drug (►Table 4). Dual antithrombotic treatment increased the risk of SAH further, and this risk was even higher in subjects with triple concurrent antithrombotic treatment (OR 3.50, 95% CI 1.19–10.28)) (►Table 5, ►Figure 4). However, in these analyses, due to relatively small numbers, we did not calculate the effect according to treatment duration.

The sensitivity analyses produced results similar to the main analyses (data not presented).

Validity of SAH diagnosis and procedure codes

We could verify the SAH diagnosis in 94 patients admitted to the neurosurgery unit (PPV for SAH code: 94%, 95% CI 87%-98%) and in 45 patients admitted to non-neurosurgery units according to our classification (PPV 45%, 95%CI 35%-55%). In patients with verified SAH, an aneurysm could be detected in 85% of cases. In patients with aneurysm (n=118), procedures were performed in 72 cases (61%). In 46 patients with aneurysm, a procedure had not been performed, primarily due to a dismal prognosis (83%) or because the procedure was deemed too risky/not possible (13%).

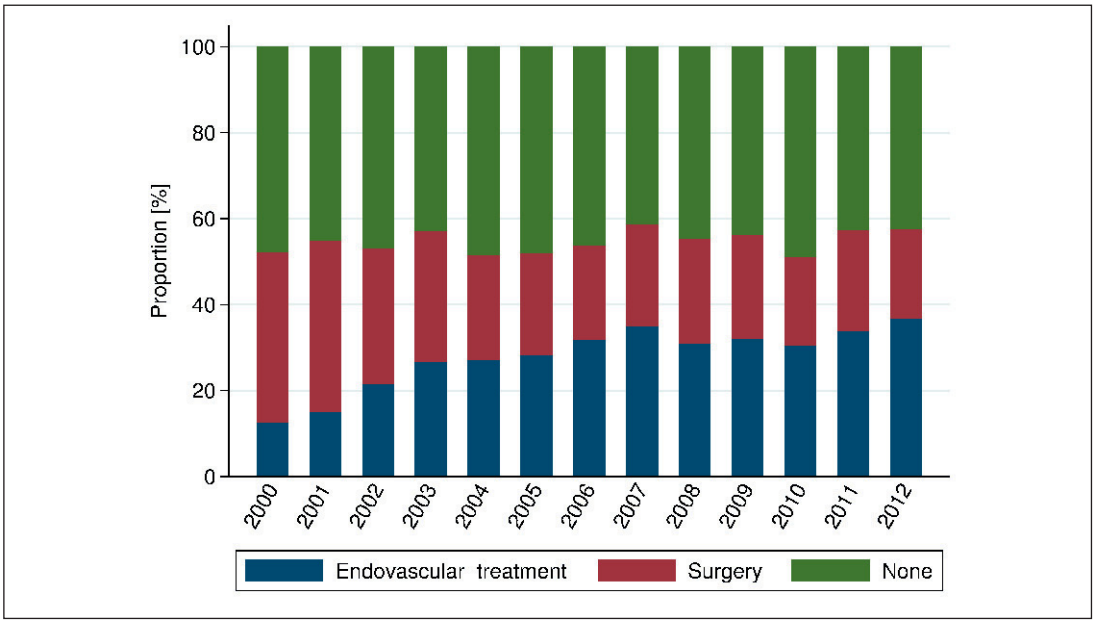

Figure 2: Annual distribution of aneurysm procedure codes (endovascular treatment, surgery, or none) in patients admitted with subarachnoid haemorrhage at neurosurgery departments, Denmark 2000–2012.

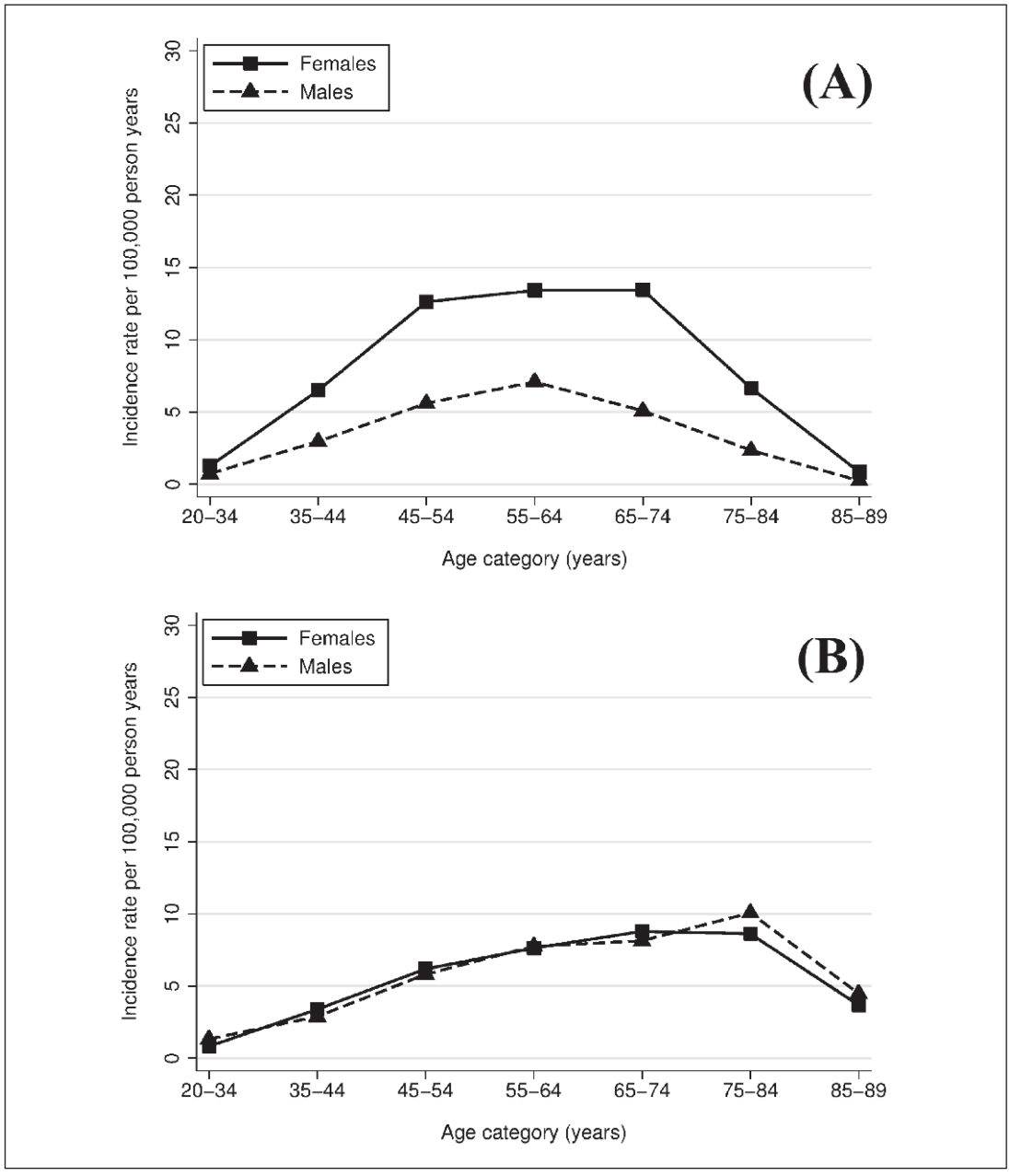

Figure 3: Incidence rate of subarachnoid haemorrhage stratified by procedure (surgery or endovascular), Denmark 2000–2012. A) Neurosurgery department & procedure and B) Neurosurgery department, no procedure.

The majority of the patients found to be too poor for procedures (28 out of 38) belonged to the non-neurosurgery group. Among patients admitted to the neurosurgery department, 64 cases had had procedures performed according to the medical records. Procedure codes were registered in 58 of these cases, while in six patients the procedure had been performed but not coded. This corresponded to a PPV for procedure codes of 100% (94%-100%), and a NPV for procedure codes of 86% (71%-95%).

Eight patients classified by us as belonging to the non-neurosurgery group had been admitted to the neurosurgery department according to the medical records. This misclassification of department type occurred due to use of erroneous diagnostic codes at the neurosurgery department (n=5), or because the time from first admission for SAH to transfer to neurosurgery ward exceeded the seven-day limit imposed in our algorithm (n=3).

The SAH diagnosis could not be verified in six patients admitted to the neurosurgery department (3 subdural haemorrhage (SDH), 2 traumatic SAH, 1 missing medical record), and 55 patients admitted to non-neurosurgery departments (19 traumatic SAH, 12 intracerebral haemorrhage (ICH), 5 SDH, 3 cavernous haemangioma, 1 ischaemic stroke, 1 sinus thrombosis, 6 SAH suspected but not verified, 6 non-neurological diagnosis, 2 missing records). Thus, among patients admitted to non-neurosurgery units where the SAH diagnosis code could not be verified, the correct diagnosis was another type of non-traumatic cerebrovascular

Table 2: Use of antiplatelet drugs and risk of subarachnoid haemorrhage in Denmark, 2000–2012.

	Neurosurgery, all			Neurosurgery & aneurysm procedure[1]			Neurosurgery, no aneurysm procedure[1]		
	cases	controls	adjusted OR[2]	cases	controls	adjusted OR[2]	cases	controls	adjusted OR[2]
Never use of any antiplatelet drug	4,842	200,353	1.00 (ref.)	2,743	112,139	1.00 (ref.)	2,099	88,214	1.00 (ref.)
Low-dose aspirin									
Recency of use									
Current use	587	20,039	1.20 (1.07–1.36)	249	9,152	1.19 (1.00–1.42)	338	10,887	1.22 (1.04–1.44)
Recent use	43	1,374	1.20 (0.85–1.68)	21	662	1.40 (0.86–2.26)	22	712	1.02 (0.63–1.64)
Past use	116	3,540	1.25 (0.99–1.57)	52	1,704	1.27 (0.91–1.77)	64	1,836	1.26 (0.91–1.74)
Distant use	226	7,509	1.15 (0.97–1.35)	114	3,631	1.40 (1.12–1.74)	112	3,878	0.95 (0.75–1.21)
Duration of current use									
≤1 month	54	1,200	1.75 (1.28–2.40)	22	568	1.59 (1.00–2.55)	32	632	1.87 (1.22–2.87)
2–3 months	80	2,562	1.26 (0.98–1.63)	34	1,174	1.24 (0.85–1.82)	46	1,388	1.27 (0.90–1.78)
3–12 months	212	7,609	1.09 (0.92–1.29)	86	3,508	1.01 (0.78–1.31)	126	4,101	1.15 (0.91–1.45)
1–3 years	166	5,951	1.10 (0.91–1.34)	74	2,653	1.18 (0.89–1.57)	92	3,298	1.03 (0.78–1.34)
>3 years	75	2,717	1.13 (0.86–1.49)	33	1,249	1.20 (0.80–1.79)	42	1,468	1.07 (0.73–1.57)
>3 months	453	16,277	1.11 (0.97–1.27)	193	7,410	1.11 (0.91–1.35)	260	8,867	1.12 (0.93–1.34)
Clopidogrel									
Recency of use									
Current use	54	1,189	1.67 (1.15–2.41)	16	581	1.30 (0.70–2.41)	38	608	1.92 (1.20–3.09)
Recent use	3	148	0.67 (0.20–2.23)	3	59	2.08 (0.60–7.27)	(n<3)	89	NA
Past use	14	507	1.18 (0.63–2.20)	3	230	0.75 (0.22–2.53)	11	277	1.35 (0.63–2.92)
Distant use	48	1,835	0.96 (0.62–1.47)	23	826	1.51 (0.82–2.78)	25	1,009	0.63 (0.34–1.18)
Duration of current use									
≤1 month	9	96	2.33 (1.02–5.35)	(n<3)	58	1.29 (0.29–5.65)	7	38	3.92 (1.37–11.22)
2–3 months	11	168	2.40 (1.20–4.81)	5	87	2.78 (0.99–7.80)	6	81	2.13 (0.83–5.48)
3–12 months	20	548	1.49 (0.88–2.54)	9	253	1.95 (0.89–4.26)	11	295	1.19 (0.57–2.49)
1–3 years	11	295	1.40 (0.71–2.75)	(n<3)	142	NA	11	153	2.53 (1.20–5.34)
>3 years	3	82	1.15 (0.35–3.84)	(n<3)	41	NA	3	41	1.80 (0.48–6.75)
>3 months	34	925	1.43 (0.93–2.20)	9	436	1.05 (0.49–2.25)	25	489	1.64 (0.95–2.81)

[1]Codes for aneurysm endovascular or surgery treatment. [2]Adjusted for age and sex (by design) and the following based on register data: hypertension, chronic obstructive pulmonary disease, high alcohol consumption, diabetes, myocardial infarct, angina, unstable angina, peripheral artery disease, use of anticoagulants, nonsteroidal anti-inflammatory drugs, hormone replacement therapy, or oral corticosteroid drugs, and socioeconomic status (education level and income).

disorder in 22 of 55 patients, most frequently another type of intracranial haemorrhage, e.g. ICH or SDH.

Discussion

We found that use of antithrombotics, i.e. low-dose aspirin, clopidogrel and VKA, are not associated with an increased risk of SAH, except within a short time-window of three months after initiation of treatment, during which time-period the relative risk of this rare cerebrovascular event is slightly to moderately increased.

Use of antiplatelet drugs and SAH risk was investigated in a previous smaller register-based Danish study. In this study, a total of 1,186 cases of non-traumatic SAH were identified through admissions to neurosurgery and neurology wards and their drug use was compared with 11,840 controls using prescription data (5). Current use of low-dose aspirin did not increase the risk of SAH (OR 1.13, 95% CI 0.89–1.42). However, the authors observed an

Table 3: First-time use of low-dose aspirin or clopidogrel and risk of subarachnoid haemorrhage in Denmark, 2000–2012.

	Neurosurgery, all			Neurosurgery & aneurysm procedure[1]			Neurosurgery, no aneurysm procedure[1]		
	cases	controls	adjusted OR[2]	cases	controls	adjusted OR[2]	cases	controls	adjusted OR[2]
Never use of any antiplatelet drug	4,842	200,353	1.00 (ref.)	2,743	112,139	1.00 (ref.)	2,099	88,214	1.00 (ref.)
Low-dose aspirin	286	9,060	1.24 (1.07–1.44)	115	4,316	1.10 (0.88–1.38)	171	4,744	1.36 (1.11–1.66)
Duration of current use									
≤1 month	34	629	1.98 (1.35–2.92)	9	311	1.22 (0.61–2.42)	25	318	2.75 (1.70–4.45)
2–3 months	53	1,328	1.61 (1.19–2.16)	23	639	1.43 (0.91–2.25)	30	689	1.75 (1.18–2.61)
>3 months	199	7,103	1.09 (0.92–1.29)	83	3,366	1.02 (0.79–1.33)	116	3,737	1.14 (0.90–1.44)
Clopidogrel	26	667	1.32 (0.81–2.14)	9	338	1.19 (0.56–2.53)	17	329	1.44 (0.77–2.71)
Duration of current use									
≤1 month	6	60	2.14 (0.74–6.14)	(n<3)	37	NA	5	23	5.04 (1.37–18.48)
2–3 months	7	102	2.44 (1.04–5.75)	3	54	2.56 (0.70–9.34)	4	48	2.40 (0.76–7.56)
>3 months	13	505	0.92 (0.50–1.72)	5	247	0.98 (0.37–2.58)	8	258	0.89 (0.40–2.02)

[1]Codes for aneurysm endovascular or surgery treatment. [2]Adjusted for age and sex (by design) and the following based on register data: hypertension, chronic obstructive pulmonary disease, high alcohol consumption, diabetes, myocardial infarct, angina, unstable angina, peripheral artery disease, use of anticoagulants, nonsteroidal anti-inflammatory drugs, hormone replacement therapy, or oral corticosteroid drugs, and socioeconomic status (education level and income).

increased risk of SAH associated with current new use of low-dose aspirin (OR 2.52, 95% CI 1.37–4.62). Duration of new use was not estimated in this study and risk-estimates on clopidogrel were not reported, probably due to small numbers. In a study from the Netherlands comprising 1,004 cases of SAH, and employing three different analytical approaches, the authors concluded that the slight increase in SAH risk associated with overall antiplatelet use (risks were not reported for individual drugs) observed in the case-control analysis (OR 1.32, 95% CI: 1.02–1.70) was due to residual confounding (6). In a population-based study based on data

Table 4: Use of oral anticoagulant drugs and risk of subarachnoid haemorrhage in Denmark, 2000–2012.

	Neurosurgery, all			
	cases	controls	crude OR	adjusted OR[1]
Never use of vitamin K antagonist[2] (VKA)	5,642	226,592	1.00 (ref.)	1.00 (ref.)
VKA use				
Recency of use				
Current use	117	3,543	1.34 (1.11–1.62)	1.22 (1.00–1.48)
Recent use	12	225	2.16 (1.20–3.88)	2.00 (1.11–3.60)
Past use	15	661	0.92 (0.55–1.53)	0.84 (0.50–1.41)
Distant use	48	2,328	0.84 (0.63–1.12)	0.77 (0.57–1.03)
Duration of current use				
≤1 month	10	192	2.09 (1.10–3.95)	1.85 (0.97–3.51)
2–3 months	12	363	1.30 (0.73–2.31)	1.18 (0.66–2.10)
3–12 months	30	1,012	1.19 (0.83–1.72)	1.08 (0.75–1.56)
1–3 years	32	992	1.30 (0.91–1.86)	1.19 (0.83–1.70)
>3 years	33	984	1.36 (0.96–1.93)	1.24 (0.86–1.77)

[1]Adjusted for age and sex (by design) and the following based on register data: hypertension, chronic obstructive pulmonary disease, high alcohol consumption, diabetes, myocardial infarct, angina, unstable angina, peripheral artery disease, nonsteroidal anti-inflammatory drugs, hormone replacement therapy, or oral corticosteroid drugs, and socioeconomic status (education level and income). [2]A total of 6 cases and 149 controls exposed to NOAC were not included.

Table 5: Concurrent use of antithrombotics and risk of subarachnoid haemorrhage in Denmark, 2000–2012.

Type of antithrombotic drug	Neurosurgery, all			Neurosurgery & procedure[1]			Neurosurgery, no procedure[1]		
	cases	controls	adjusted OR[2]	cases	controls	adjusted OR[2]	cases	controls	adjusted OR[2]
No antithrombotic drug use	4,761	197,264	1.00 (ref.)	2,716	110,653	1.00 (ref)	2,045	86,611	1.00 (ref.)
Dual antithrombotic treatment									
Low-dose aspirin & clopidogrel	33	675	1.90 (1.19–3.03)	11	341	1.64 (0.78–3.45)	22	334	2.08 (1.13–3.81)
Low-dose aspirin & dipyridamole	108	2,309	1.64 (1.22–2.21)	49	1,004	1.54 (1.00–2.37)	59	1,305	1.73 (1.15–2.60)
Low-dose aspirin & VKA	30	755	1.58 (1.04–2.39)	6	309	0.80 (0.34–1.87)	24	446	2.08 (1.26–3.44)
Triple antithrombotic treatment[3]	4	50	3.50 (1.19–10.28)	0	24	NA	4	26	5.74 (1.76–18.77)

VKA = Vitamin K–antagonist. [1]Aneurysm endovascular or surgery treatment. [2]Adjusted for age and sex (by design) and the following based on register data: hypertension, chronic obstructive pulmonary disease, high alcohol consumption, diabetes, myocardial infarct, angina, unstable angina, peripheral artery disease, nonsteroidal anti-inflammatory drugs, hormone replacement therapy, or oral corticosteroid drugs, and socioeconomic status (education level and income). [3]Low-dose aspirin & dipyridamole & VKA, or low-dose aspirin & clopidogrel & VKA.

from general practitioners in the UK, neither current use of low-dose aspirin (OR 0.82, 95% CI: 0.67–1.00), nor clopidogrel (OR 1.16, 95% CI:0.70–1.94) were associated with increased risk of SAH (7). However, in this study comprising 1,340 SAH cases, short-term risk of antiplatelet drugs of less than three months was associated with an increased risk, although the results were not statistically significant (low-dose aspirin OR 1.32, 95% CI: 0.71–2.47; clopidogrel OR 2.82, 95% CI: 0.70–11.40). Although methodological issues hinder straightforward comparisons, our results based on more than 5,000 cases of SAH, seem in line with those of previous population-based studies of the risk of SAH in association with antiplatelet use.

The influence of long-term use of antiplatelet drugs on SAH risk was also of interest to us, since a small number of studies indicate that long-term use of low-dose aspirin (ASA) may have a protective effect on aneurysm rupture. Thus, a small study nested within the International Study of Unruptured Intracranial aneurysms reported a protective effect of ASA taken at least three times weekly (risk ratio [RR] 0.27; 95% CI, 0.11–0.67) (8). Inflammation has been suggested to be a key factor in the process of intracranial aneurysm formation and rupture (17). The walls of ruptured human intracranial aneurysms have recently been reported to have higher immunohistochemical staining for cyclooxygenase-2 and microsomal prostaglandin E2 synthase 1, both of which are inhibited by aspirin (18). Furthermore, aspirin use attenuated inflammation in the wall of intracranial aneurysms in a small randomised trial (19). In concert, the abovementioned studies pointed towards the intriguing possibility that long-term use of aspirin may have a beneficial effect on the risk of SAH. In a recent large case-control study, we found an inverse association between long-

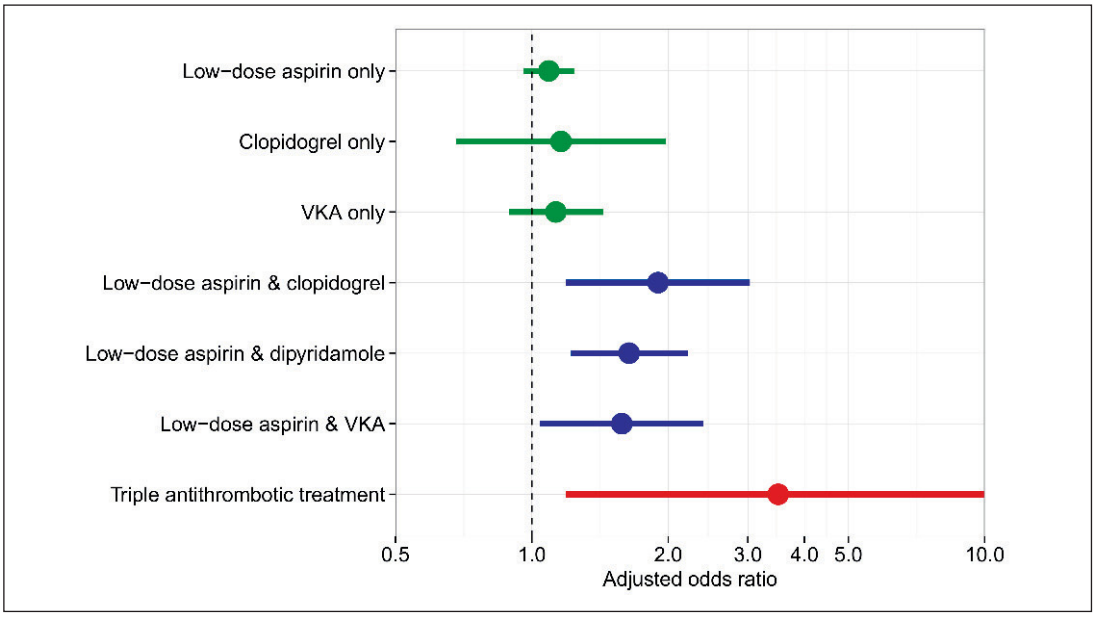

Figure 4: Use of antithrombotic drugs and risk of subarachnoid haemorrhage.

term use (≥3 years) of low-dose aspirin and SAH (RR 0.63, 95% CI 0.45–0.90) compared with no antiplatelet therapy (7). However, in the present study, which is the largest to date, we found no protective effect of long-term use of low-dose aspirin on SAH risk.

Only three previous population-based studies examined the association between VKA use and risk of SAH (4, 6, 7). In the previous Danish study by Olsen et al., current use of VKA was not associated with SAH risk (OR 0.80; 95% CI: 0.37–1.74), although this estimate was based on nine exposed cases only. In the previously mentioned study from the Netherlands, VKA were reported to confer a slight to moderate increase in SAH risk (OR 1.29 to 2.46, depending on analytical approach) (6). The study based on data from the UK reported an OR of 1.65 (95% CI 1.17–2.33) of SAH associated with current use of warfarin (7). However, this study also clearly demonstrated that warfarin-associated SAH risk depends on the level of the international normalized ratio (INR), with risk of SAH increasing with INR levels. Although our results are in line with those of some of the aforementioned studies we find that our lack of data on INR prevents us from drawing firm conclusions on VKA and risk of SAH.

Concurrent use of two antiplatelets drugs has previously been reported to increase SAH risk (5, 7). Our study lends support to these findings and indicates that triple antithrombotic treatment substantially increases SAH risk compared to use of single use of low-dose ASA . For how long the risk remains elevated among users of dual or triple antithrombotic drugs remains unanswered, since sample size limitations prevented us from addressing this question.

Our study has a number of strengths. Our study was performed in a setting with free access to health services independent of income. We used nationwide registries with complete coverage and continuously collected data on all Danish residents, which allowed us to perform the largest study of its kind to date. Our approach furthermore eliminated recall bias. Our novel approach of defining subgroups of SAH patients by the presence of procedure codes, which enabled us to identify patients with aneurysmal SAH with a high degree of certainty, allowed us to ensure that the risk of aneurysmal SAH associated with antithrombotic drug use did not differ from that of the overall sample, neither in the short-term, nor in the long-term.

Potential limitations of our study should also be considered. Cases were identified through the Danish Patient Registry, which could raise concern as to the validity of the diagnosis. However, we ensured high diagnosis validity by limiting the sample to patients admitted to neurosurgery departments. The soundness of this approach was confirmed by the results of our own validation study. In spite of imposing this restriction, our material seems fairly complete, as indicated by the estimate of SAH incidence based on patients admitted to neurosurgery departments being similar to previously published population-based incidence rate estimates (20). We find the fraction of SAH patients in our study that were admitted to neurosurgery departments and did not receive procedures rather high (45.3%). This high rate, which remained stable during the study period (►Figure 2), may be due to a number of reasons, e.g. surgeons not coding the procedures, or procedures being withheld due to dismal prognosis, as indicated by the high mortality rate in this group. Although our validation study indicates that incorrect diagnosis coding was only a minor problem, we cannot exclude that some patients in this group received an incorrect SAH diagnosis code, particularly since our validation study only included data from a single neurosurgical centre, and may therefore not have captured variations in coding practice across centres. We note, however, that such misclassification, if present, had little bearing on our study results, since the main results for patients not receiving procedures were similar to the results for treated patients, a patient group where we find little reason to doubt the high validity of the SAH diagnosis. Classifying the material by the type of department the patient was admitted to and whether procedures were performed, also imposed a potential risk of selection bias. Indeed, our validation study indicates that such a problem may exist, since the majority of patients where a procedure was not performed due to dismal prognosis were from the non-neurosurgery group, i.e. prognosis may have influenced the chances of transferal of patients to a neurosurgery department. It is therefore reassuring, that in post-hoc analyses we performed including all cases (also those exclusively admitted to non-neurosurgery departments), the risk estimates of SAH associated with antithrombotic drug use showed similar patterns and magnitudes to those reported in the present study for short- and long-term use of low-dose aspirin and clopidogrel. In these analyses, the risk associated with current use of VKA was somewhat higher (OR 1.6 to 2.1 depending on exposure time-window), although this could be due to contamination of the sample by patients with ICH and SDH, which, according to our validation study, were common underlying diagnoses in patients admitted to non-neurosurgery departments with an SAH diagnosis code that was not verified. The prescription register data offered complete coverage on the use of reimbursed drugs by all subjects. Low-dose aspirin is the only antiplatelet also available over the counter. However, the coverage of the Prescription Registry for low-dose aspirin is in the order of 90% (21). Finally, our datasources did not include sufficiently detailed or complete information on well-known risk factors for SAH, e.g. smoking and hypertension. Although we attempted to adjust for the effect of such potential confounders by means of surrogate measures, e.g. use of antihypertensive drugs, we cannot exclude that our results, at least to some extent, are due to inadequately measured or unmeasured confounders. Although there is also the theoretical possibility of confounding by indication, e.g. that aspirin was given to treat the excruciating headache associated with SAH, we find this scenario unlikely, since aspirin doses used for preventive purposes (75–150 mg) are entirely sub-optimal for headache treatment, and other antithrombotics are not used to treat headache in Denmark.

We conclude that use of antithrombotic drugs does not influence the risk of SAH with the exception of a brief period of a few months after treatment initiation. For this period, our results indicate a possible increased risk, which, if causal, is minimal in absolute terms. Lack of INR levels prevented quantification of SAH risk in relation to intensity of VKA anticoagulation.

What is known about this topic?

- Few population-based studies have focused on antithrombotic drug use and risk of subarachnoid haemorrhage (SAH), and results are conflicting.
- Recent studies indicate a protective effect of long-term aspirin on aneurysm rupture, the most frequent cause of SAH.

What does this paper add?

- In this large nationwide study in Denmark, anti-thrombotic drug use was only associated with an increased risk of SAH during the first three months after treatment initiation.
- Long-term use of low-dose aspirin was not associated with a lower risk of SAH.
- While our results underscore the safety of using antiplatelet treatment with regard to SAH risk, they also indicate that long-term low-dose aspirin use is not associated with a reduced risk of aneurysm rupture.

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Conflicts of interest

A. Pottegard reports grants paid to his institution from AstraZeneca, outside the submitted work. L. A. G. Rodriguez reports grants paid to his institution from Bayer Pharma AG, outside the submitted work. J. Hallas reports grants paid to his institution from Takeda-Nycomed, outside the submitted work. D. Gaist reports personal fees from Astra Zeneca (Sweden) for participation as a co-investigator in a research project, outside the submitted work. F. Poulsen reports no conflicts of interest.

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