

Association of Antithrombotic Drug Use With Subdural Hematoma Risk

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 Supplemental content

IMPORTANCE Incidence of subdural hematoma has been reported to be increasing. To what extent this is related to increasing use of antithrombotic drugs is unknown.

OBJECTIVES To estimate the association between use of antithrombotic drugs and subdural hematoma risk and determine trends in subdural hematoma incidence and antithrombotic drug use in the general population.

DESIGN, SETTING, AND PARTICIPANTS Case-control study of 10 010 patients aged 20 to 89 years with a first-ever subdural hematoma principal discharge diagnosis from 2000 to 2015 matched by age, sex, and calendar year to 400 380 individuals from the general population (controls). Subdural hematoma incidence and antithrombotic drug use was identified using population-based regional data (population: 484 346) and national data (population: 5.2 million) from Denmark. Conditional logistic regression models were used to estimate odds ratios (ORs) that were adjusted for comorbidity, education level, and income level.

EXPOSURES Use of low-dose aspirin, clopidogrel, a vitamin K antagonist (VKA), a direct oral anticoagulant, and combined antithrombotic drug treatment.

MAIN OUTCOMES AND MEASURES Association of subdural hematoma with antithrombotic drug use, subdural hematoma incidence rate, and annual prevalence of treatment with antithrombotic drugs.

RESULTS Among 10 010 patients with subdural hematoma (mean age, 69.2 years; 3462 women [34.6%]), 47.3% were taking antithrombotic medications. Current use of low-dose aspirin (cases: 26.7%, controls: 22.4%; adjusted OR, 1.24 [95% CI, 1.15-1.33]), clopidogrel (cases: 5.0%, controls: 2.2%; adjusted OR, 1.87 [95% CI, 1.57-2.24]), a direct oral anticoagulant (cases: 1.0%, controls: 0.6%; adjusted OR, 1.73 [95% CI, 1.31-2.28]), and a VKA (cases: 14.3%, controls: 4.9%; adjusted OR, 3.69 [95% CI, 3.38-4.03]) were associated with higher risk of subdural hematoma. The risk of subdural hematoma was highest when a VKA was used concurrently with an antiplatelet drug (low-dose aspirin and a VKA: 3.6% of cases and 1.1% of controls; adjusted OR, 4.00 [95% CI, 3.40-4.70]; clopidogrel and a VKA: 0.3% of cases and 0.04% of controls; adjusted OR, 7.93 [95% CI, 4.49-14.02]). The prevalence of antithrombotic drug use increased from 31.0 per 1000 individuals from the general population in 2000 to 76.9 per 1000 individuals in 2015 ($P < .001$ for trend). The overall subdural hematoma incidence rate increased from 10.9 per 100 000 person-years in 2000 to 19.0 per 100 000 person-years in 2015 ($P < .001$ for trend). The largest increase was among older patients (>75 years; $n = 4441$) who experienced an increase from 55.1 per 100 000 person-years to 99.7 per 100 000 person-years ($P < .001$ for trend).

CONCLUSIONS AND RELEVANCE In Denmark, antithrombotic drug use was associated with higher risk of subdural hematoma; and the highest odds of subdural hematoma was associated with combined use of a VKA and an antiplatelet drug. The increased incidence of subdural hematoma from 2000 to 2015 appears to be associated with the increased use of antithrombotic drugs, particularly use of a VKA among older patients.

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Subdural hematoma, which is an intracranial hemorrhage localized under the dural membrane and above the brain surface, can be classified into 2 categories: acute subdural hematoma and subacute or chronic hematoma. Both subdural hematoma types are typically traumatic. Acute subdural hematoma is more frequently associated with severe trauma and usually becomes clinically apparent within 72 hours, whereas subacute or chronic subdural hematoma is most often seen weeks to months after relatively modest trauma (eg, low-impact falls among elderly individuals).¹

Since the 1980s, studies with data on subacute or chronic subdural hematoma have reported an increase in the incidence of this disorder in both Europe and the United States.^{2,3} Subacute or chronic subdural hematoma incidence is predicted to further increase due to the aging population.² Use of antithrombotic drugs has been associated with increased subacute or chronic subdural hematoma risk. In meta-analyses of controlled trials, use of a vitamin K antagonist (VKA) was associated with a pooled odds ratio (OR) of 3.0 for subacute or chronic subdural hematoma compared with antiplatelet therapy, and use of low-dose aspirin compared with no antithrombotic treatment was associated with a pooled OR of 1.6, which was not statistically significant.^{4,5}

However, epidemiological data on the association of antithrombotic drug use with subdural hematoma risk are limited, particularly with regard to antiplatelet drug use⁶ and use of a direct oral anticoagulant, and in relation to more aggressive regimens of multiple antithrombotic drugs, which are increasingly common.⁷ The purpose of this study was to provide updated estimates of subdural hematoma risk associated with antithrombotic drug use and to explore recent trends in antithrombotic drug use in relation to subdural hematoma occurrence.

Methods

Case-control analyses and descriptive analyses were performed on Danish national and regional population-based data. The study was approved by the Danish Data Protection Agency and the Statens Serum Institut. According to Danish law, approval from an ethics board and informed consent are not required for register studies.⁸

Cases

Cases were patients aged 20 to 89 years with a first-ever principal discharge code of subdural hematoma from 2000 to 2015 according to Danish National Patient Register⁹ data (discharge, outpatient, procedure, and medication codes appear in eTable 1 in the [Supplement](#)). The date of admission was used as the index date. Cases with any history of subdural hematoma recorded before 2000 and individuals with residency in Denmark for less than 10 consecutive years were excluded.

Controls

Using risk set sampling¹⁰ and applying the same eligibility and exclusion criteria as for cases, 40 controls from the Danish general population were sampled to each case via use of the Danish

Key Points

Question Are changes in subdural hematoma incidence related to antithrombotic drug use?

Findings In this observational study with 10 010 subdural hematoma cases and 400 380 controls, subdural hematoma risk was significantly associated with antithrombotic drug use, in particular use of a vitamin K antagonist (adjusted odds ratio, 3.69). An observed increase in antithrombotic drug use was related to an increase in subdural hematoma incidence from 10.9 per 100 000 person-years in 2000 to 19.0 per 100 000 person-years in 2015.

Meaning The increased incidence of subdural hematoma was associated with increased use of antithrombotic drugs, especially use of a vitamin K antagonist.

Civil Registration System.¹¹ Controls were matched by birth year and sex to their index case and were assigned an index date identical to the event date of their corresponding case.

Assessment of Antithrombotic Drug Exposure, Potential Confounders, and Short-term Mortality

Data on filled prescriptions were retrieved from the Danish National Prescription Registry.¹² For each prescription, the date the drug was dispensed and a full account of the dispensed product (including the Anatomical Therapeutic Chemical code) were recorded.¹³ The indication and prescribed dose are not available in the prescription registry.

Based on prescriptions dispensed from 1995 up to 1 day prior to the index date, cases and controls were classified as ever users (≥ 1 prescription) or never users (no prescription) of low-dose aspirin (only available in doses of ≤ 150 mg in Denmark), clopidogrel, other adenosine diphosphate inhibitors (prasugrel and ticagrelor), or dipyridamole. The same principles were applied for an oral anticoagulant drug classified as a VKA (warfarin or phenprocoumon) and a direct oral anticoagulant (dabigatran etexilate, rivaroxaban, or apixaban). The assessment of drug exposure is further detailed in the eMethods in the [Supplement](#).

National register data (population: 5.2 million) were used to classify individuals with regard to a number of disorders that were potential confounders, which are listed in the statistical analyses section (codes appear in eTable 1 in the [Supplement](#)). As proxies for socioeconomic status, individuals were classified by highest education level attained (years of education: 7-10 years, 11-12 years, ≥ 13 years, or missing) and by income level (low, middle, and high according to tertiles of individual incomes in the control group).^{8,14} Register data from the continuously updated Danish Civil Registration System¹¹ were used to ascertain 30-day fatality rates for cases.

Regional Data

Information on certain factors of potential interest (eg, subdural hematoma type, trauma severity) is not routinely collected in Danish registers. Therefore, information was gathered on the subset of patients with subdural hematoma who were from the Funen area (population: 484 346 in 2009), which has 1 of the 5 facilities with a neurosurgery department in Denmark.¹²

Patients with verified subdural hematoma (cases) were classified as having acute subdural hematoma or subacute or chronic subdural hematoma based on brain scan results analyzed by 2 neurosurgeons, who also evaluated the presence and severity of the head trauma according to medical record information (eMethods in the Supplement).¹⁵ Use of an antithrombotic drug by the validated cases and their general population controls was assessed for the period from 2000 to 2012 when data were available.

Statistical Analyses

Conditional logistic regression was used to compute adjusted ORs and 95% CIs for subdural hematoma associated with use of low-dose aspirin, clopidogrel, a VKA, and a direct oral anticoagulant. Because use of other adenosine diphosphate receptor inhibitors (prasugrel and ticagrelor) was limited during the study period, analyses restricted to this drug class were not performed.

The analyses were adjusted for (1) the presence of chronic obstructive pulmonary disease (as a marker of smoking), disorders indicative of high intake of alcohol, chronic hepatic diseases, chronic renal failure, diabetes, myocardial infarction, angina, unstable angina, peripheral artery disease, coagulopathy, hypertension, epilepsy, dementia, or stroke; (2) use of nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, statins, hypnotics and sedatives (including benzodiazepines), postmenopausal hormone replacement therapy, or oral corticosteroids; and (3) highest education level attained and income level as proxies for socioeconomic status.

Analyses focusing on any use or use of a single antiplatelet drug were further adjusted for current use of any oral anticoagulant. Similarly, analyses for use of a single anticoagulant were adjusted for current use of any antiplatelet drug. Furthermore, because low-dose aspirin is often prescribed with clopidogrel or dipyridamole, analyses for these drugs were adjusted for current use of low-dose aspirin and vice versa. We tested whether the ORs for the different antithrombotic regimens differed by using a likelihood ratio test, which compared 2 models: one model in which the main exposure variable was use of any antithrombotic regimen and another model in which the individual antithrombotic regimens were specified. Differences in strength of association between subgroups or between different outcomes were evaluated using the 2-sample Wald test. A 2-sided limit of .05 was used as the significance threshold.

Using the regional data, the association of antithrombotic drug use with subdural hematoma stratified by type of subdural hematoma and head trauma history was assessed. Using cases only, the association between use of a VKA or use of low-dose aspirin and imaging characteristics (subdural hematoma width, midline structure deviation), surgical treatment, and 30-day mortality, stratified by subdural hematoma type was studied. Age and sex were adjusted for using linear regression (continuous outcomes) or logistic regression (categorical outcomes). The annual incidence rate of subdural hematoma was estimated using census data from Statistics Denmark,¹⁶ standardized (age and sex) to the popu-

lation in 2008 and tested for trend (linear regression; eMethods in the Supplement).

Regional data on antithrombotic prescriptions for the period from 2000 to 2015 were retrieved.¹² For each antithrombotic regimen, the number of regional residents who were users of that regimen on a given date was calculated, according to the exposure definition used in the main study. Using census data, the user prevalence proportion for this regimen for a given day was estimated and hence an average prevalence proportion for an entire calendar year. These analyses were restricted to the same age population as in the main analyses (ie, aged 20-89 years).

Probability results of 2-tailed tests less than .05 were considered statistically significant. All analyses were performed using Stata SE version 14.1 (StataCorp).

Results

A total of 10 010 incident cases of subdural hematoma (3462 women [34.6%]) were identified in Denmark during the study period with a mean age of 69.2 years (median, 72 years [interquartile range, 60-81 years]) and 47.3% were taking antithrombotic medications. The 30-day mortality of patients with subdural hematoma was 16.1%.

Compared with 400 380 matched controls, cases had higher levels of comorbidity for the disorders included in the present analyses, especially illnesses indicative of high intake of alcohol (17.6% of cases vs 4.6% of controls), but also regarding a history of hypertension (54.0% vs 46.3%), stroke (14.2% vs 6.8%), epilepsy (6.6% vs 1.8%), dementia (5.8% vs 2.7%), chronic renal insufficiency (2.9% vs 1.5%), chronic hepatic disease (2.6% vs 1.0%), and coagulopathy (0.5% vs 0.2%) (Table 1). Cases had less frequently completed 13 or more years of education (16.1% vs 17.9% of controls) and less frequently had high income levels (22.8% vs 33.3% of controls) (Table 1). All abovementioned comparisons were statistically significant ($P < .001$).

With the exception of oral corticosteroids and postmenopausal hormone therapy, preadmission medication use was more prevalent among cases than controls for the drugs included in the analyses and for the use of antithrombotic drugs (Table 1; $P < .001$ for both comparisons). The risk of subdural hematoma was higher with current use of low-dose aspirin (cases: 26.7%, controls: 22.4%; adjusted OR, 1.24 [95% CI, 1.15-1.33]), clopidogrel (cases: 5.0%, controls: 2.2%; adjusted OR, 1.87 [95% CI, 1.57-2.24]), a direct oral anticoagulant (cases: 1.0%, controls: 0.6%; adjusted OR, 1.73 [95% CI, 1.31-2.28]), and a VKA (cases: 14.3%, controls: 4.9%; adjusted OR, 3.69 [95% CI, 3.38-4.03]; Table 2 and Table 3). For low-dose aspirin, subdural hematoma risk was inversely related to duration of current use; eg, for a duration of less than 1 month (cases: 1.8%, controls: 0.8%; adjusted OR, 2.66 [95% CI, 2.20-3.22]) compared with a duration of more than 3 years (cases: 8.1%, controls: 7.9%; adjusted OR, 0.99 [95% CI, 0.88-1.10]) (Table 2).

A similar relationship was not observed for clopidogrel, for which the subdural hematoma risk remained fairly constant (adjusted OR range, 1.46-2.18) and was independent of the duration of current use (Table 2). The risk of subdural hematoma

Table 1. Characteristics of Cases With Incident Subdural Hematoma and General Population Controls

	No. (%) ^a		P Value ^b
	Cases With Subdural Hematoma (n = 10 010)	Controls (n = 400 380)	
Sex			
Men	6548 (65.4)	261 920 (65.4)	
Women	3462 (34.6)	138 460 (34.6)	
Age, median (IQR), y	72 (61-81)	72 (61-81)	
Age group, y			
20-64	3166 (31.6)	126 620 (31.6)	
65-74	2403 (24.0)	96 120 (24.0)	
75-89	4441 (44.4)	177 640 (44.4)	
30-d Case fatality rate	1608 (16.1)	NA	
Admitted to neurosurgery department	7352 (73.4)	NA	
Type of surgical procedure performed			
Burr hole	3912 (39.1)	NA	
Craniotomy	1495 (14.9)	NA	
None	4603 (46.0)	NA	
Index period			
2000-2005	2971 (29.7)	118 828 (29.7)	
2006-2010	3168 (31.6)	126 720 (31.6)	
2011-2015	3871 (38.7)	154 832 (38.7)	
Medication use			
Low-dose aspirin ^c	2676 (26.7)	89 502 (22.4)	<.001
Clopidogrel ^c	500 (5.0)	8755 (2.2)	<.001
Other adenosine diphosphate inhibitors ^c	25 (0.2)	392 (0.1)	<.001
Dipyridamole ^c	505 (5.0)	12 222 (3.1)	<.001
Vitamin K antagonist ^c	1427 (14.3)	19 659 (4.9)	<.001
Warfarin	1367 (13.7)	18 679 (4.7)	<.001
Phenprocoumon	74 (0.7)	1102 (0.3)	<.001
Direct oral anticoagulant ^c	100 (1.0)	2525 (0.6)	<.001
Dabigatran	46 (0.5)	1482 (0.4)	.16
Rivaroxaban	36 (0.4)	707 (0.2)	<.001
Apixaban	26 (0.3)	412 (0.1)	<.001
Non-aspirin NSAIDs ^d	2041 (20.4)	72 786 (18.2)	<.001
Selective serotonin reuptake inhibitors ^d	1728 (17.3)	30 664 (7.7)	<.001
Hypnotics and sedatives ^d	2724 (27.2)	64 950 (16.2)	<.001
Statins ^d	2504 (25.0)	85 886 (21.5)	<.001
Oral corticosteroids ^d	606 (6.1)	24 082 (6.0)	.86
Hormone replacement therapy ^d	585 (5.8)	22 025 (5.5)	.14

(continued)

Table 1. Characteristics of Cases With Incident Subdural Hematoma and General Population Controls (continued)

	No. (%) ^a		P Value ^b
	Cases With Subdural Hematoma (n = 10 010)	Controls (n = 400 380)	
Comorbidity			
Hypertension	5408 (54.0)	185 272 (46.3)	<.001
Stroke	1420 (14.2)	27 311 (6.8)	<.001
Epilepsy	664 (6.6)	7131 (1.8)	<.001
Dementia	582 (5.8)	10 855 (2.7)	<.001
Chronic obstructive pulmonary disease	759 (7.6)	25 027 (6.3)	<.001
Diabetes	1264 (12.6)	36 548 (9.1)	<.001
Chronic renal insufficiency	292 (2.9)	5932 (1.5)	<.001
Chronic hepatic disease	256 (2.6)	3913 (1.0)	<.001
Coagulopathy	53 (0.5)	746 (0.2)	<.001
High intake of alcohol	1762 (17.6)	18 382 (4.6)	<.001
Myocardial infarction	856 (8.6)	27 630 (6.9)	<.001
Unstable angina	335 (3.3)	9486 (2.4)	<.001
Other angina	1303 (13.0)	41 467 (10.4)	<.001
Peripheral artery disease	251 (2.5)	7962 (2.0)	<.001
Education level, y			
7-10	4073 (40.7)	154 584 (38.6)	<.001
11-12	3529 (35.3)	143 705 (35.9)	.19
≥13	1611 (16.1)	71 609 (17.9)	<.001
Missing	797 (8.0)	30 482 (7.6)	.19
Income level^e			
Low	4832 (48.3)	133 455 (33.3)	<.001
Middle	2892 (28.9)	133 467 (33.3)	<.001
High	2286 (22.8)	133 458 (33.3)	<.001

Abbreviations: IQR, interquartile range; NA, data not provided because not relevant; NSAID, nonsteroidal anti-inflammatory drug.

^a Data are expressed as No. (%) unless otherwise indicated. Data are from Denmark from 2000 through 2015.

^b Calculated using the χ^2 test. Values not provided for age, sex, and index year because cases were matched to controls for these variables.

^c Use of drug at index date.

^d Use of drug between 1 year and 1 month prior to index date.

^e Median annual income among controls was kr 69 342 (IQR, kr 29 654-kr 98 372) in the low income level, kr 157 418 (IQR, kr 141 850-kr 172 563) in the middle income level, and kr 268 155 (IQR, kr 224 700-kr 341 543) in the high income level. One krone equals approximately US \$0.15.

associated with current use of a direct oral anticoagulant or a VKA did not vary substantially by duration (Table 3). Limiting the analyses to individuals with current use of a single antithrombotic drug and no use of other antithrombotic drugs within the last 12 months (to exclude patients who had switched from other antithrombotic drugs) produced risk estimates similar to those of the main analyses (eg, low-dose aspirin: adjusted OR, 1.19 [95% CI, 1.10-1.19]; clopidogrel: adjusted OR, 1.61 [95% CI, 1.30-1.98]) (eTable 2 in the Supplement).

Furthermore, limiting the analyses to individuals with first-time use of antithrombotic drugs (definition appears in the eMethods in the Supplement) resulted in an adjusted OR of 1.39 (95% CI, 1.26-1.52) for low-dose aspirin and an adjusted OR of 1.68 (95% CI, 1.31-2.16) for clopidogrel (eTable 3 in the Supplement). These estimates did not change notably when first-time use was further restricted to single use of the drug in question (ie, no concomitant use of other antithrombotic drug) and corresponded to an adjusted OR of 1.37 (95% CI, 1.24-1.52) for low-dose aspirin and an adjusted OR of 1.60 (95% CI, 1.21-2.12) for clopidogrel. For oral anticoagulant drugs, limiting analyses to first-time use was related to association estimates comparable with those found in the main analyses (eTable 3 in the Supplement).

The risk of subdural hematoma associated with concurrent use of antithrombotic drugs varied across regimens. The lowest risk was associated with concurrent use of low-dose aspirin and dipyridamole (cases: 4.2%, controls: 2.6%; adjusted OR, 1.17 [95% CI, 0.99-1.38]), whereas the risk of subdural hematoma was highest when a VKA was used concurrently with an antiplatelet drug (low-dose aspirin and a VKA: 3.6% of cases and 1.1% of controls; adjusted OR, 4.00 [95% CI, 3.40-4.70]; clopidogrel and a VKA: 0.3% of cases and 0.04% of controls; adjusted OR, 7.93 [95% CI, 4.49-14.02]) (likelihood ratio test for overall difference in effect estimates, $P < .001$; Figure 1).

The observed associations between use of antithrombotic drugs and subdural hematoma were stronger among women than men for use of low-dose aspirin ($P = .004$) and a VKA ($P < .001$) (eTable 4 in the Supplement). Associations did not vary substantially within age groups with use of clopidogrel, a VKA, and a direct oral anticoagulant, whereas the association increased with use of low-dose aspirin from an adjusted OR of 1.08 (95% CI, 0.90-1.30) for those aged 20 to 64 years to an adjusted OR of 1.46 (95% CI, 1.33-1.60) for those aged 75 to 89 years ($P = .003$; eTable 4 in the Supplement).

In addition, antithrombotic use carried a greater risk for fatal (died within 30 days of diagnosis) than nonfatal subdural

Table 2. Use of Antiplatelet Drugs and Risk of Subdural Hematoma in Denmark, 2000-2015

	No. (%)		Adjusted OR (95% CI) ^a	Adjusted OR (95% CI) ^b
	Cases With Subdural Hematoma (n = 10 010)	Controls (n = 400 380)		
Never use of any antithrombotic drug	5013 (50.1)	252 593 (63.1)	1 [Reference]	1 [Reference]
Low-dose aspirin use ^c				
Ever ^d	4204 (42.0)	132 727 (33.2)	1.83 (1.75-1.92)	1.20 (1.13-1.27)
Current	2676 (26.7)	89 502 (22.4)	1.72 (1.63-1.82)	1.24 (1.15-1.33)
Recent	228 (2.3)	5170 (1.3)	2.43 (2.10-2.80)	1.39 (1.15-1.68)
Past	295 (2.9)	7239 (1.8)	2.34 (2.06-2.65)	1.14 (0.94-1.38)
Distant	1005 (10.0)	30 816 (7.7)	1.86 (1.73-2.01)	1.03 (0.93-1.14)
Duration of current use				
<1 mo	185 (1.8)	3127 (0.8)	3.44 (2.93-4.03)	2.66 (2.20-3.22)
≥1-≤3 mo	217 (2.2)	6142 (1.5)	2.01 (1.74-2.32)	1.41 (1.17-1.68)
>3-≤12 mo	695 (6.9)	21 135 (5.3)	1.84 (1.69-2.00)	1.26 (1.12-1.41)
>1-≤3 y	767 (7.7)	27 423 (6.8)	1.59 (1.46-1.73)	1.09 (0.98-1.22)
>3 y	812 (8.1)	31 675 (7.9)	1.50 (1.38-1.63)	0.99 (0.88-1.10)
Clopidogrel use ^c				
Ever ^d	890 (8.9)	21 694 (5.4)	2.45 (2.26-2.66)	1.75 (1.50-2.04)
Current	500 (5.0)	8755 (2.2)	3.46 (3.11-3.84)	1.87 (1.57-2.24)
Recent	29 (0.3)	654 (0.2)	2.39 (1.62-3.53)	1.53 (0.77-3.05)
Past	48 (0.5)	1589 (0.4)	1.66 (1.23-2.23)	1.13 (0.60-2.13)
Distant	313 (3.1)	10 696 (2.7)	1.76 (1.55-1.99)	1.26 (0.92-1.71)
Duration of current use				
<1 mo	28 (0.3)	455 (0.1)	3.65 (2.42-5.49)	1.46 (0.70-3.05)
≥1-≤3 mo	71 (0.7)	909 (0.2)	4.47 (3.43-5.81)	2.18 (1.37-3.47)
>3-≤12 mo	176 (1.8)	3047 (0.8)	3.46 (2.93-4.09)	1.78 (1.36-2.32)
>1-≤3 y	157 (1.6)	2919 (0.7)	3.18 (2.67-3.80)	1.71 (1.32-2.22)
>3 y	68 (0.7)	1425 (0.4)	2.85 (2.20-3.71)	1.49 (1.05-2.13)

Abbreviation: OR, odds ratio.

^a Adjusted for age, sex, and calendar period (year) by design.

^b Adjusted for age, sex, and calendar period (by design) and based on register data for presence of hypertension, stroke, epilepsy, dementia, chronic obstructive pulmonary disease, high intake of alcohol, chronic hepatic disease, chronic renal insufficiency, diabetes, myocardial infarction, angina, unstable angina, peripheral artery disease; use of an oral anticoagulant, nonsteroidal anti-inflammatory drug, selective serotonin reuptake inhibitor, hypnotic and sedative, hormone replacement therapy, or oral corticosteroid drug; and

socioeconomic status (education level and income level). Analyses for low-dose aspirin were adjusted for current use of clopidogrel and vice versa.

^c Based on the most recent treatment episode prior to the index date (date of diagnosis for cases and date of selection for controls), exposure was divided into current use (at index date), recent use (treatment episode ending 1-90 days before index date), past use (91-365 days before index date), and distant use (>365 days before index date).

^d Previous or concurrent use of other antiplatelet drugs included.

hematoma. This pattern was most pronounced with use of a direct oral anticoagulant (fatal subdural hematoma: adjusted OR, 3.87 [95% CI, 1.84-8.13] vs nonfatal subdural hematoma: adjusted OR, 1.44 [95% CI, 1.05-1.96]; $P = .01$) and a VKA (fatal: adjusted OR, 6.30 [95% CI, 5.04-7.88] vs nonfatal: adjusted OR, 3.33 [95% CI, 3.02-3.67]; $P < .001$) (eTable 4 in the Supplement).

The regional data from the Funen area comprised 936 validated cases with a median age of 72 years (interquartile range, 59-81 years) and 34.5% females. Based on visual assessment of brain imaging studies, 55% of validated subdural hematoma cases were classified as subacute or chronic subdural hematoma and 45% as acute subdural hematoma.¹⁵ Results of analyses of associations with antithrombotic drug use based exclusively on these validated cases and their 18 689 controls were highly similar to estimates derived from the nationwide data (eTable 5 in the Supplement).

Current use of low-dose aspirin was not associated with risk of subacute or chronic subdural hematoma (adjusted OR, 1.10

[95% CI, 0.83-1.45]), whereas there was a higher risk of acute subdural hematoma (adjusted OR, 1.47 [95% CI, 1.04-2.08]; eTable 6 in the Supplement). In contrast, current use of a VKA was associated with higher risk of both subacute or chronic subdural hematoma (adjusted OR, 2.59 [95% CI, 1.88-3.55]) and acute subdural hematoma (adjusted OR, 4.72 [95% CI, 3.31-6.72]).

Analyses limited to 650 cases with trauma of known severity (definition of trauma severity appears in eMethods in the Supplement) showed that current use of antithrombotic drugs was associated with subdural hematoma in the low to moderate trauma severity group (low-dose aspirin: adjusted OR, 1.41 [95% CI, 1.04-1.92]; a VKA: adjusted OR, 3.51 [95% CI, 2.51-4.89]). In the severe trauma group, use of a VKA presented the strongest association with risk of subdural hematoma (adjusted OR, 2.49 [95% CI, 1.31-4.73]), whereas low-dose aspirin was not associated with higher risk of subdural hematoma (adjusted OR, 0.93 [95% CI, 0.53-1.63]; eTable 7 in the Supplement).

Table 3. Use of an Oral Anticoagulant and Risk of Subdural Hematoma in Denmark, 2000-2015

	No. (%)		Adjusted OR (95% CI) ^a	Adjusted OR (95% CI) ^b
	Cases With Subdural Hematoma (n = 10 010)	Controls (n = 400 380)		
Never use of any antithrombotic drug	5013 (50.1)	252 593 (63.1)	1 [Reference]	1 [Reference]
Direct oral anticoagulant use ^c				
Ever	170 (1.7)	4423 (1.1)	2.34 (1.96-2.79)	1.88 (1.51-2.32)
Current	100 (1.0)	2525 (0.6)	2.50 (1.99-3.13)	1.73 (1.31-2.28)
Recent	8 (0.008)	241 (0.1)	2.01 (0.97-4.18)	2.00 (0.83-4.78)
Past	16 (0.2)	470 (0.1)	2.08 (1.24-3.50)	1.91 (0.98-3.70)
Distant	46 (0.5)	1187 (0.3)	2.39 (1.74-3.28)	2.69 (1.85-3.92)
Duration of current use				
<1 mo	16 (0.2)	234 (0.1)	4.22 (2.43-7.33)	2.41 (1.07-5.44)
≥1-≤3 mo	22 (0.2)	391 (0.1)	3.49 (2.19-5.56)	2.98 (1.69-5.27)
>3-≤12 mo	33 (0.3)	956 (0.2)	2.20 (1.51-3.20)	1.41 (0.89-2.22)
>1-≤3 y	25 (0.2)	815 (0.2)	2.00 (1.31-3.06)	1.61 (1.01-2.56)
>3 y	4 (0.004)	129 (0.003)	1.66 (0.59-4.68)	0.81 (0.19-3.49)
Vitamin K antagonist use ^c				
Ever	1890 (18.9)	33 431 (8.3)	3.42 (3.21-3.64)	2.83 (2.61-3.06)
Current	1427 (14.3)	19 659 (4.9)	4.43 (4.13-4.75)	3.69 (3.38-4.03)
Recent	85 (0.8)	1320 (0.3)	3.62 (2.86-4.58)	2.71 (2.01-3.67)
Past	88 (0.9)	1966 (0.5)	2.67 (2.13-3.35)	1.57 (1.12-2.20)
Distant	290 (2.9)	10 486 (2.6)	1.64 (1.44-1.86)	1.18 (0.97-1.43)
Duration of current use				
<1 mo	75 (0.7)	938 (0.2)	4.42 (3.43-5.71)	3.18 (2.27-4.45)
≥1-≤3 mo	165 (1.6)	1804 (0.5)	5.25 (4.39-6.27)	4.59 (3.65-5.78)
>3-≤12 mo	378 (3.8)	4923 (1.2)	4.58 (4.06-5.16)	3.70 (3.16-4.32)
>1-≤3 y	368 (3.7)	4979 (1.2)	4.26 (3.78-4.80)	3.42 (2.94-3.99)
>3 y	441 (4.4)	7015 (1.8)	3.87 (3.46-4.32)	3.28 (2.85-3.77)

Abbreviation: OR, odds ratio.

^a Adjusted for age, sex, and calendar period (year) by design.

^b Adjusted for age, sex, and calendar period (by design) and based on register data for presence of hypertension, stroke, epilepsy, dementia, chronic obstructive pulmonary disease, high intake of alcohol, chronic hepatic disease, chronic renal insufficiency, diabetes, myocardial infarction, angina, unstable angina, peripheral artery disease; use of antiplatelet drugs, nonsteroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, hypnotics

and sedatives, hormone replacement therapy, or oral corticosteroid drugs; and socioeconomic status (education level and income level).

^c Based on the most recent treatment episode prior to the index date (date of diagnosis for cases and date of selection for controls), exposure was divided into current use (at index date), recent use (treatment episode ending 1-90 days before index date), past use (91-365 days before index date), and distant use (>365 days before index date).

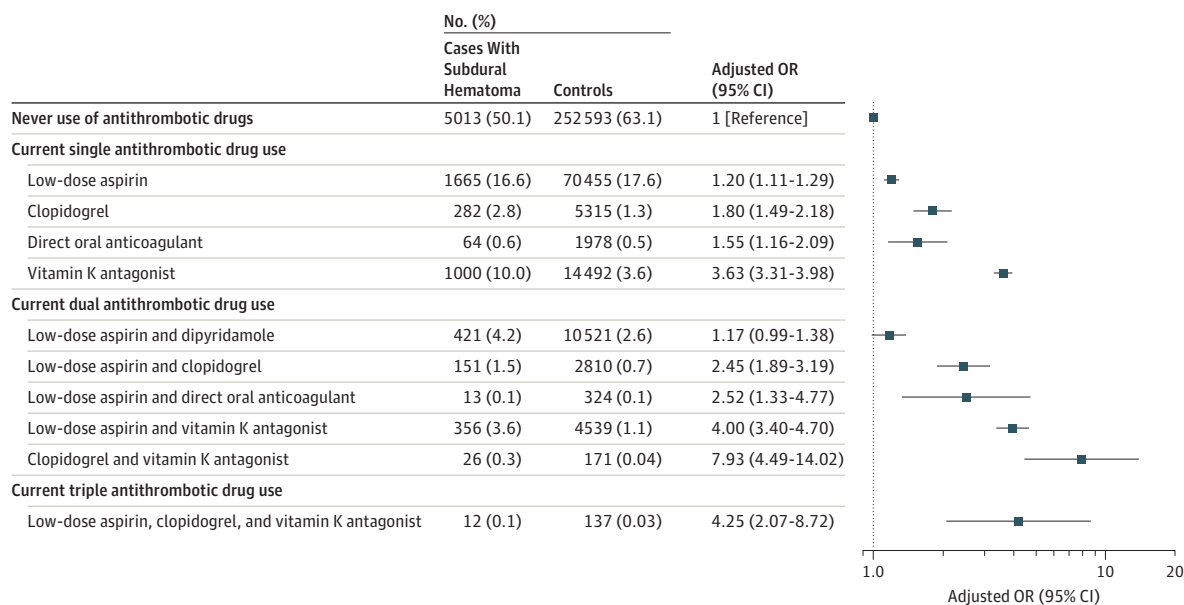
Analyses restricted to validated cases revealed that current users of VKAs were more likely to exhibit midline structure deviation on their brain scan (subacute or chronic subdural hematoma: OR, 3.29 [95% CI, 1.14-9.51]; acute subdural hematoma: OR, 2.80 [95% CI, 1.18-6.60]; eTable 8 in the Supplement) and had higher 30-day mortality (subacute or chronic subdural hematoma: OR, 2.77 [95% CI, 0.94-8.18]; acute subdural hematoma, 1.33 [95% CI, 0.62-2.89]; eTable 9 in the Supplement) compared with never users of anticoagulants. Current low-dose aspirin use resulted in far less marked differences with regard to these outcomes (eTable 8 and eTable 9 in the Supplement).

The incidence of subdural hematoma increased during the study period from 10.9 per 100 000 person-years (95% CI, 9.9-12.0 per 100 000 person-years) in 2000 (441 cases in 4 036 965 person-years) to 19.0 per 100 000 person-years (95% CI, 17.8-20.4 per 100 000 person-years) in 2015 (819 cases in 4 301 391 person-years) ($P < .001$ for trend). The largest increase in the incidence of subdural hematoma occurred among older pa-

tients (aged 75-89 years; $n = 4441$) and went from 55.1 per 100 000 person-years (191 cases in 346 529 person-years) to 99.7 per 100 000 person-years (382 cases in 383 030 person-years) ($P < .001$ for trend). The corresponding incidence trend among men aged 75 to 89 years increased from 77.9 per 100 000 person-years (95% CI, 63.5-94.6 per 100 000 person-years) in 2000 (102 cases in 130 899 person-years) to 135.5 per 100 000 person-years (95% CI, 118.3-154.6 per 100 000 person-years) in 2015 (222 cases in 163 778 person-years) ($P < .001$; Figure 2 and eTable 10 in the Supplement).

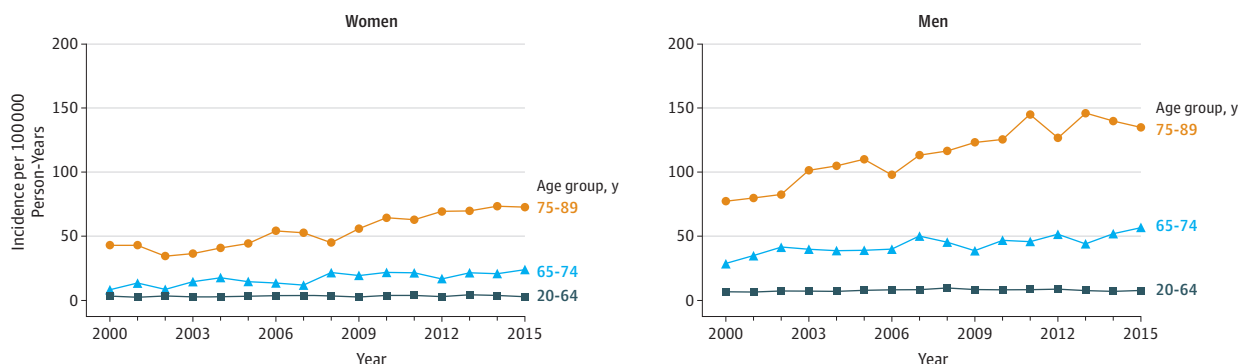
The regional analyses revealed increases in antithrombotic drug use during the study period both as single drug regimens (average prevalence proportion of 31.0 per 1000 inhabitants from the general population in 2000 vs 76.9 per 1000 inhabitants in 2015; $P < .001$ for trend) and concurrent drug use regimens (average prevalence proportion of 2.6 per 1000 inhabitants in 2000 vs 17.3 per 1000 inhabitants in 2015, $P < .001$; Figure 3). Any use of a VKA increased from 7.4 per 1000 inhabitants in 2000 to 16.7 per 1000 inhabitants in 2015 ($P < .001$).

Figure 1. Current Use of Antithrombotic Drugs and Risk of Subdural Hematoma



Error bars indicate 95% CIs; OR, odds ratio. The data were adjusted for age, sex, calendar period, comorbidity, education level, and income level.

Figure 2. Incidence Rate of Subdural Hematoma by Sex and Age Group in Denmark, 2000-2015



Thirty-day mortality after subdural hematoma diagnosis declined during the study period from 17.9% in 2000-2004 (432 of 2414 patients died) to 13.1% in 2013-2015 (314 of 2395 patients died). However, the decline in 30-day mortality over time was only observed for patients aged 20 to 64 years and aged 65 to 74 years ($P < .001$ for trend for both age groups), whereas the 30-day mortality remained stable for patients aged 75 to 89 years ($P = .40$ for trend; eFigure 1 in the Supplement). Neither this measure of short-time mortality, nor the annual incidence rate estimates were materially changed after age and sex standardization (eFigure 2 in the Supplement).

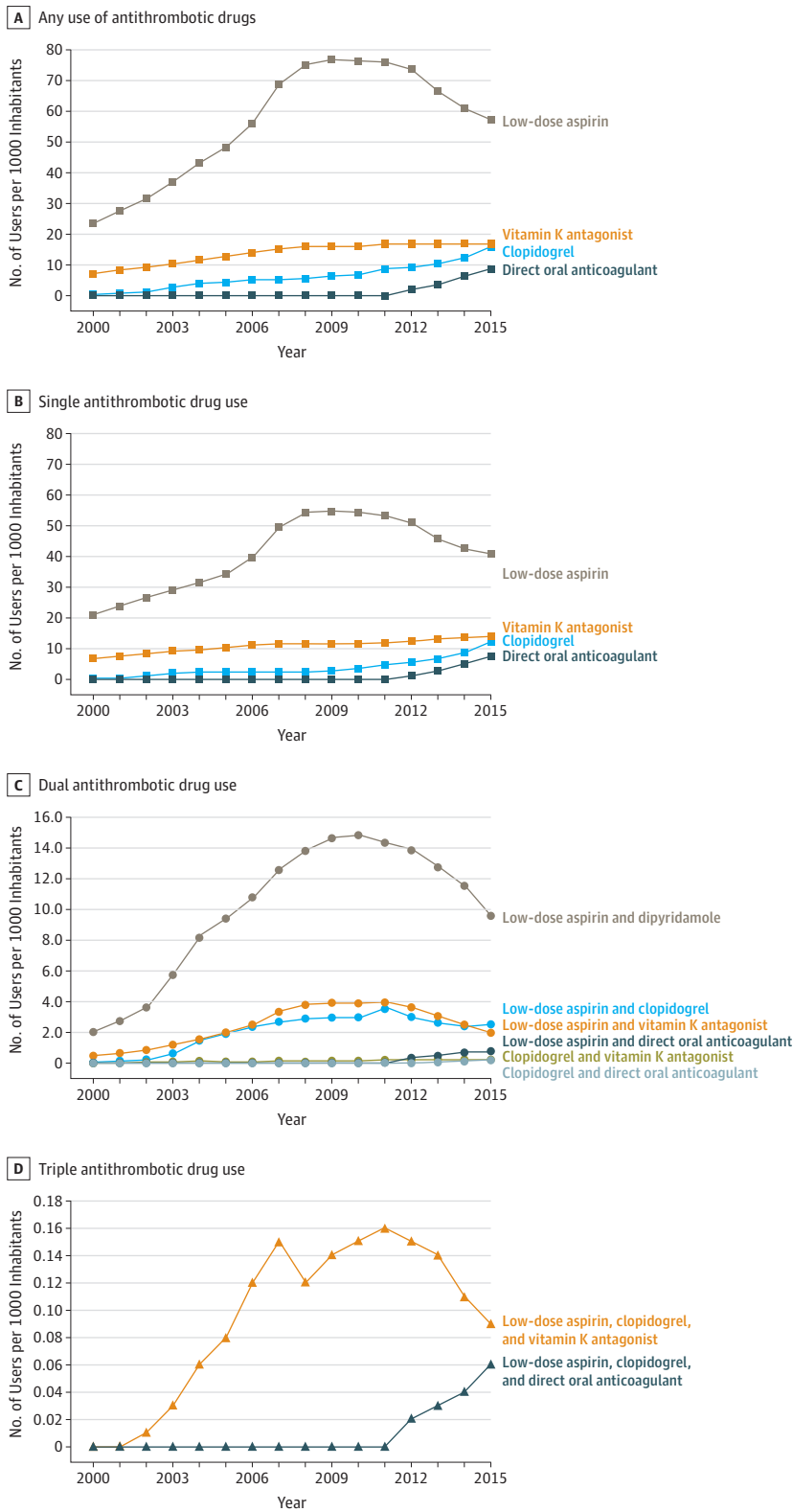
Discussion

In this case-control study that included 10 010 patients with subdural hematoma, low-dose aspirin was associated with a

small risk, use of clopidogrel and a direct oral anticoagulant with a moderate risk, and use of a VKA with a higher risk of subdural hematoma. With the exception of low-dose aspirin combined with dipyridamole, which was associated with a risk similar to low-dose aspirin monotherapy, concomitant use of more than 1 antithrombotic drug was related to substantially higher subdural hematoma risk, which was particularly marked for combined treatment of clopidogrel with a VKA. Antithrombotic drug use was found to be associated with higher relative risks of subdural hematoma in women than in men, and fatal subdural hematoma was more strongly associated with antithrombotic drug use than nonfatal subdural hematoma.

Incidence of subdural hematoma, particularly among older patients (aged 75-89 years), increased within the 16-year study period. This observation appears to be temporally related to a major increase in the use of antithrombotic drugs and in particular in the use of a VKA. The present data add 1 more piece

Figure 3. Use of Antithrombotic Regimens per 1000 Inhabitants in a Geographically Well-Defined Part of Denmark



Only those aged 20 to 89 years (n = 363 000) were included.

of evidence to the complex risk-benefit equation of antithrombotic drug use. It is known that these drugs result in net benefits overall in patients with clear therapeutic indications.¹⁷⁻¹⁹ Furthermore, the present results are in line with previous studies indicating a lower risk of intracranial hemorrhage in association with use of a direct oral anticoagulant compared with use of a VKA.^{20,21}

Although use of antithrombotic drugs has long been recognized as a risk factor for subdural hematoma, previous studies were either based exclusively on patients with subdural hematoma (ie, with no comparison group)²²⁻²⁵ or focused exclusively on patients treated with an anticoagulant.^{26,27} In a case-control study from Italy with 345 cases of subacute or chronic subdural hematoma collected from a single hospital and matched to 138 786 emergency department attendees, antithrombotic drug use increased subacute or chronic subdural hematoma risk (anticoagulant use: OR, 2.46 [95% CI, 1.66-3.64]; antiplatelet drug use: OR, 1.42 [95% CI, 1.07-1.89]).⁶ Meta-analyses of randomized clinical trials reported similar, albeit slightly higher estimates of the risk of subdural hematoma conferred by use of a VKA or low-dose aspirin.^{4,5} Despite differences in setting and design, the present results are thus in line with previous studies.

In a nationwide Swedish register-based study spanning the period of 1987 to 2010, subdural hematoma was the most frequent traumatic intracranial injury (excluding concussion), and the proportion of patients with subdural hematoma increased substantially over time.³ A study from the United States also showed an increase in the incidence rates of subacute or chronic subdural hematoma, and the researchers predicted that subacute or chronic subdural hematoma will become the most common cranial neurosurgical condition among adults in 2030.² Steep increases in incidence rates of subdural hematoma among older patients (aged 75-89 years) were found in the present study.

Furthermore, the present results emphasize that the major shifts in patterns of antithrombotic drug treatment for older individuals,²⁸ and the increasing use of more aggressive antithrombotic regimens, have already had a major effect on subdural hematoma incidence. The present results may partly be driven by increasingly rapid and easier access to brain imaging. However, if this was predominantly the case, a decrease in short-term mortality over time would have been expected as a consequence of less severe cases being detected in more recent years. Indeed, this seems to be the case for patients aged 20 to 74 years.

However, the 30-day mortality rate remained stable in patients aged 75 to 89 years, which is the age group with use of antithrombotic drugs that was markedly more prevalent than that of younger age groups. Increasing surveillance is unlikely to explain the increasing incidence rates of subdural hematoma other than for a fraction of the present findings. A lower threshold for scanning patients who are taking antithrombotic drugs could also result in higher detection rates of less severe subdural hematoma cases and bias the results. However, based on the present study data on imaging characteristics, treatment, and outcome among validated cases, this scenario is unlikely.

The notion that trauma events could modify the effect of antithrombotic use⁶ is supported by the present results based on regional data. Risk estimates for preadmission antithrom-

botic drug use were higher among patients with low to moderate severity trauma compared with those with severe trauma. Although based on small numbers, these results are compatible with antithrombotic drugs playing a greater role in predisposed patients (eg, due to age-related brain atrophy) with a history of mild to moderate head trauma compared with patients experiencing a severe head trauma for whom there is little role left for additional risk factors. This finding is important from a public health perspective because the risk of experiencing a small to moderate head trauma exceeds the probability of experiencing a severe head injury.

The present study has a number of strengths. The study was performed in Denmark, a setting with free access to health services, independent of income level. Population-based registers were used with complete coverage and continuously collected data on all Danish residents, an approach that eliminated recall bias and minimized selection bias. It has previously been shown that the subdural hematoma code used to identify cases in this study is highly valid with a positive predictive value of 96%.¹⁵

This study has several limitations. Even though the approach used in this study enabled the identification of subdural hematoma incident cases with minimal misclassification, it probably resulted in incomplete coverage. Based on the results from a previous validation study, the incidence rates are probably underestimated by approximately 22%.¹⁵ Also, the small numbers prevented the assessment of the association of individual types of direct oral anticoagulants drugs, or of other adenosine diphosphate receptor inhibitor use with subdural hematoma risk. Low-dose aspirin is the only antiplatelet drug in Denmark that is available over-the-counter. Because the coverage of the prescription registry for low-dose aspirin is in the order of 91%,²⁹ misclassification of exposure caused by over-the-counter use of this drug is believed to be of minor significance. Other potential limitations of the present study include the lack of data on international normalized ratio and alcohol consumption.

Among patients using a VKA, subdural hematoma risk is known to be associated with international normalized ratio levels.³⁰ Information on this factor was lacking, and the effect of the international normalized ratio on subdural hematoma risk could therefore not be assessed. Alcohol overuse, and its negative effect on brain volume and associated increased risk of trauma, predisposes individuals to subdural hematoma. In the nationwide study, register-based information was used to assess this effect modifier and possible confounder, which may have led to considerable misclassification. It is noted, however, that the estimate of patients with subdural hematoma and high alcohol intake in the nationwide sample (17.6%) in the present study was comparable with the fraction of patients with subdural hematoma classified with alcoholism (16.6%) in the validation study.¹⁵

Furthermore, a higher frequency of other disorders predisposing individuals to brain atrophy and associated with an increased risk of falling (eg, dementia) was found among cases compared with controls in the present study. Although adjusted for in multivariate analyses, residual confounding by these and other potential confounders cannot be ruled out.

Conclusions

In Denmark, antithrombotic drug use was associated with higher risk of subdural hematoma; and the highest odds of sub-

dural hematoma was associated with combined use of a VKA and an antiplatelet drug. The increased incidence of subdural hematoma from 2000 to 2015 appears to be associated with the increased use of antithrombotic drugs, particularly use of a VKA among older patients.

ARTICLE INFORMATION

Author Contributions: Drs Gaist and Pottegård had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Gaist.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Gaist, Hallas, Pottegård.

Administrative, technical, or material support: Hallas, Pottegård.

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