PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2016
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4058

ORIGINAL REPORT

Subdural hematoma cases identified through a Danish patient register: diagnosis validity, clinical characteristics, and preadmission antithrombotic drug use

Frantz Rom Poulsen[1], Bo Halle[1], Anton Pottegård[2], Luis Alberto García Rodríguez[3], Jesper Hallas[2] and David Gaist[4]*

[1]*Department of Neurosurgery, Odense University Hospital, Odense, Denmark*
[2]*Clinical Pharmacology and Pharmacy, Department of Public Health, University of Southern Denmark, Odense, Denmark*
[3]*Centro Español Investigación Farmacoepidemiológica (CEIFE), Madrid, Spain*
[4]*Department of Neurology, Odense University Hospital & Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark*

ABSTRACT

Purpose This study aimed to assess the usefulness of Danish patient registers for epidemiological studies of subdural hematoma (SDH) and to describe clinical characteristics of validated cases.

Methods Using a patient register covering a geographically defined area in Denmark, we retrieved hospital contacts recorded under SDH International Classification of Diseases version 10 codes S065 and I620 in 2000–2012. Neurosurgeons reviewed medical records of all potential cases. Based on brain scan results, verified cases were classified by SDH type (chronic SDH (cSDH) or acute SDH (aSDH)). Thirty-day mortality and preadmission antithrombotic drug use were established through linkage to population-based registers. We calculated the positive predictive value of the SDH code and compared mortality and preadmission antithrombotic drug use of cSDH with those of aSDH (age-adjusted and sex-adjusted odds ratio (OR), 95% confidence interval (95%CI)).

Results We verified the diagnosis in 936 of 1185 identified patients. The positive predictive value was highest for hospital contacts with principal discharge diagnosis code S065 (96%) but was low for other contact types under code S065 (25–54%), and only moderate for patients recorded under code I620 (62%). cSDH represented 57% of verified cases, and aSDH the remaining 43%. cSDH differed markedly from aSDH with regard to a number of clinical characteristics, including a much lower mortality (OR 0.2, 95%CI 0.1–0.3). However, preadmission antithrombotic drug use did not vary by SDH type (OR 0.9, 95%CI 0.6–1.2).

Conclusions Danish patient registers are a useful resource for SDH studies. However, choice of International Classification of Diseases code markedly influences diagnostic validity. Distinction between cSDH and aSDH is not possible based on SDH diagnosis codes only.

KEY WORDS—subdural hematoma; antithrombotics; validity; pharmacoepidemiology

Received 17 February 2016; Revised 18 May 2016; Accepted 07 June 2016

INTRODUCTION

Subdural hematoma (SDH), an intracranial bleed localized under the dural membrane and above the surface of the brain, can be classified into acute SDH (aSDH) and chronic SDH (cSDH).[1] aSDH is usually clinically evident within 72 hours of hematoma accumulation, and the blood clot is readily identifiable on unenhanced brain CT scan. A history of head trauma is frequent in patients with SDH. aSDH is often the result of severe acute trauma, while for patients with cSDH the trauma, if present, has usually occurred several days to weeks prior to manifestation and is often relatively modest.[2] Advanced age and other factors leading to reduced brain volume, for example, alcohol overuse, increase an individual's risk of cSDH. Use of antithrombotic drugs, mainly vitamin K antagonists (VKAs), has also been associated with increased risk of cSDH.[3–7] However, more recent epidemiologic studies focusing on the risk of cSDH associated with the use of antithrombotic drugs are scarce.[8] As the

*Correspondence to: D. Gaist, Department of Neurology, Odense University Hospital, Sdr Boulevard 29, 5000 Odense C, Denmark, Email: dgaist@health.sdu.dk

incidence of SDH is low, 8–14 per 100 000 person-years for cSDH,[9,10] large population-based registers are necessary for studies of the epidemiology of SDH. Denmark, with its array of nationwide medical registers,[11] offers a highly favorable setting for such studies. We conducted the present study to investigate whether Danish patient registers can be used to validly identify incident cases of SDH. Our study material comprised combined data on cSDH and aSDH in a population-based setting, which also allowed us to quantify the effect of known risk factors on subtypes of SDH, that is, cSDH versus aSDH.

METHODS

Setting

We conducted a descriptive study of incident cases of SDH in former Funen County, a geographically well-defined area (484 346 inhabitants in 2009) that holds one of five neurosurgery departments in Denmark and has previously been used by us for this type of research.[12] The regional approach made it possible to collect detailed clinical data, which are not routinely collected in the nationwide automated data sources, and furthermore enabled us to ascertain the validity of the SDH diagnosis codes.

Data sources

Using a regional administrative patient register, we identified all residents of the area admitted under SDH diagnostic codes International Classification of Diseases version 10 (ICD-10) S065 (traumatic SDH —principal code (i.e., main diagnosis) or secondary code (i.e., secondary diagnoses)—any hospital contact (i.e., discharges, outpatient—or emergency room contacts)) and I620 (acute non-traumatic—principal discharge code) at any hospital in the catchment area in 2000–2012. We classified patients that had received both discharge codes (i.e. S065 and I620) under the code S065 ($n = 81$). We restricted potential cases to subjects aged 20–89 years at the time of admission. Two neurosurgeons (F. R. P. and B. H.) ascertained the diagnosis based on medical record information. For verified cases, the neurosurgeons also abstracted data from the medical records on the following: the manifestation of SDH (symptoms and signs), history of head trauma (including timing in relation to admission and severity), and type of operation performed (burr hole or craniotomy). In patients who were not operated on, the reasons for abstaining from surgery were recorded. Based on brain scan results, patients with verified SDH were classified into aSDH or cSDH cases by the study neurosurgeons. Patients with brain scans revealing both aSDH and cSDH changes ("acute-on-chronic") were classified as cSDH. Digitalized brain imaging information was also used to assess SDH laterality (unilateral or bilateral), thickness of SDH in millimeter, and presence of displacement of midline structures. To collect this information, the study neurosurgeons inspected the original brain scan images and performed the aforementioned measurements. If brain scan images were unavailable, the information was abstracted from radiologist descriptions.

Using a regional prescription register,[13] we classified prehospital use of antithrombotic drugs in all patients. In Denmark, low-dose aspirin is mainly prescribed. Thus, only 9% of the total quantity of low-dose aspirin was sold over the counter in 2015 according to national statistics (www.medstat.dk/en). All other antithrombotic drugs available in Denmark are prescription only. For each subject, we identified all prescriptions redeemed within 180 days prior to the index date. Based on prescriptions of low-dose aspirin ($\leq$150 mg) or other antiplatelet drugs dispensed during this interval, study subjects were classified as current users (one or more prescription) or non-users (no prescription) of low-dose aspirin or clopidogrel. We applied the same principles for anticoagulant drugs, which were classified into VKAs and non-vitamin K oral anticoagulants. Finally, we retrieved international normalized ratio (INR) results on study subjects from a regional register, which holds the results of all blood tests completed at hospitals in the catchment area. For patients using VKA, we identified the highest INR value in the period 7 days before to 1 day after the SDH admission and categorized this information as follows: $<$2.0, 2.0–2.9, $\geq$3.0, and missing information. We used the highest INR value in the time interval, because physicians would be likely to attempt to revert INR values, that is, prior to surgery or if the values were above therapeutic limits. Using the most recent INR value prior to the index date might therefore provide results biased towards lower INR values. Also, in recognition of the possibility of some diagnostic delay, we extended the time window to 1 day after the index date.

Finally, in order to compare our data with nationwide figures, we used the Danish National Patient Register[14] to identify all first-ever admissions with principal discharge diagnosis SDH code (ICD-10 S065) in Denmark, 2000–2012. We did not include secondary S065 codes or code I620 in the nationwide data because the validity of these codes in the regional data was found to be low (Results section). For each patient, the date of the first hospital contact under a principal SDH diagnosis was identified (index date). We excluded cases with

DOI: 10.1002/pds

SDH diagnoses prior to 2000. Notably, the regional and national patient registers collect and record data in a highly similar fashion, and data from the regional register are fed into the national register.

Statistical analyses

Results were reported in numbers and percentages for categorical data and median and interquartile ranges for continuous variables. For group comparisons, we used the χ^2 test, Fisher's exact test, and Mann–Whitney *U*-test when appropriate. Probability results below 0.05 were considered statistically significant.

We calculated the positive predictive value (PPV) of the diagnostic codes and used Wilson's score method to estimate 95% confidence intervals (CIs). We stratified verified cases by type of SDH and compared the distribution of patients with regard to various characteristics, including history of alcoholism, preadmission trauma and trauma severity, preadmission use of antithrombotic drugs, and 30-day case fatality rate. We used unconditional logistic regression to calculate age-adjusted and sex-adjusted odds ratios (aORs) and 95%CIs of exposure to the aforementioned variables in patients with cSDH compared with aSDH. The case fatality rate was computed after linking the data to the Danish Civil Registration System that records continuously updated information on residency and vital status of all residents of Denmark.[15] We also calculated aORs and 95%CIs in subjects who were classified as VKA users upon admission, where we compared exposure to high INR values (≥3.0) in cSDH versus aSDH and in patients with head trauma versus non-trauma patients. Finally, we compared the age and sex distribution of admitted patients recorded under principal discharge S065 codes in the regional data with the corresponding numbers in the nationwide data.

RESULTS

We verified the diagnosis in 936 of 1185 patients identified with first-ever hospital contacts with codes for SDH (Figure 1). For discharge codes, the PPV of the diagnosis varied by ICD code, that is, 84% (95%CI 82–86%) with code S065 (principal or secondary code) and 62% (95%CI 48–75%) for the more rarely used code I620 (principal code; used exclusively in 45 patients) (Figure 1 and Table 1). For discharges under code S065, the position of the code had a major impact on the PPV, that is, 96% (95%CI 94–97%) for the principal code and 54% (95%CI 48–59%) for the secondary code. The PPV was low (25%, 95%CI 17–35%) for patients with contacts to outpatient units or emergency rooms only (i.e., no recorded admission for SDH).

In all, 69% of patients were admitted to the neurosurgery department (76% of patients with the principal S065 discharge code). The PPV of the principal discharge code S065 was high with some variation according to type of ward, that is, 98% (95%CI 96–99%) for the neurosurgery department and 88% (95%CI 82–92%) for non-neurosurgery departments. The SDH diagnosis could not be verified in 249 patients. A high proportion of these patients (40%) represented presumptive diagnoses; that is, they had received the diagnosis due to clinically suspected SDH, even though a subsequent brain scan ruled out the disorder. A further 16% had suffered an ischemic stroke, and 14% a spontaneous or traumatic

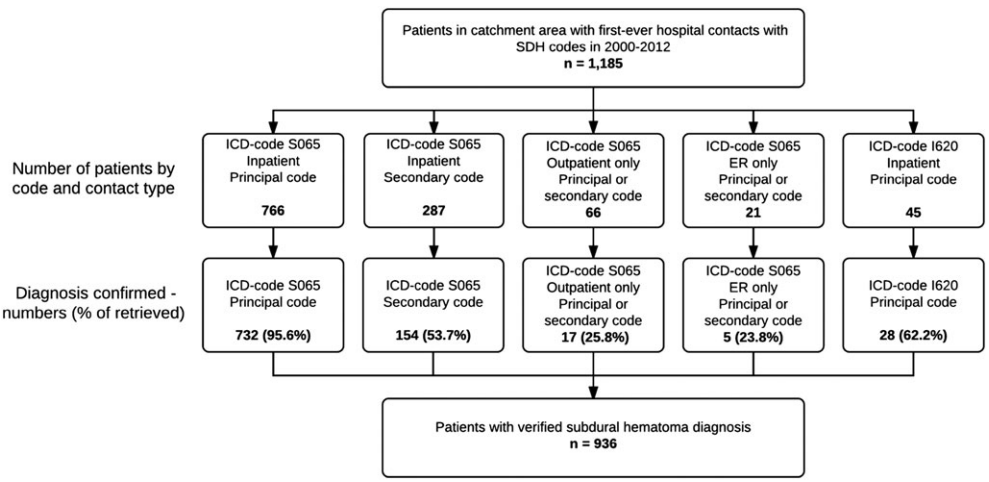

Figure 1. Number of patients identified and number (percentage) of verified diagnoses by subdural hematoma code and type of contact. ER, emergency room; ICD, International Classification of Diseases; SDH, subdural hematoma

DOI: 10.1002/pds

Table 1. Positive predictive value of register codes for SDH and underlying diagnoses in non-verified cases in a Danish patient register

	S065*—"traumatic SDH"			I620*—"acute non-traumatic SDH" only[†]
	Admitted		Outpatient only or emergency room only[‡]	Admitted
	Principal code ($n = 766$)	Secondary code[§] ($n = 287$)	Principal or secondary code ($n = 87$)	Principal code ($n = 45$)
SDH diagnosis verified				
Number	732	154	22	28
Positive predictive value (95%CI)	96 (94–97)	54 (48–59)	25 (17–35)	62 (48–75)
SDH diagnosis not verified[¶], no. (%)				
Intracerebral hemorrhage	5 (14.7)	1 (0.8)	3 (4.6)	4 (23.5)
Subarachnoid hemorrhage**	9 (26.5)	10 (7.5)	6 (9.2)	9 (52.9)
Brain contusion or epidural hematoma	2 (5.9)	6 (4.5)	2 (3.1)	0
Ischemic stroke	2 (5.9)	29 (21.8)	8 (12.3)	0
SDH clinically suspected, not present	10 (29.4)	56 (42.1)	33 (50.8)	2 (11.8)
Other[††]	6 (17.6)	25 (18.8)	12 (18.5)	1 (5.9)
Information missing	0	6 (4.5)	1 (1.5)	1 (5.9)

CI, confidence interval; SDH, subdural hematoma.
*International Classification of Diseases version 10 codes. Corresponding text in Danish version in inverted commas.
[†]Subjects with concurrent I620 and S065 codes during the same episode of care were classified as S065.
[‡]No recorded admission for SDH.
[§]Diagnosis code in position other than principal.
[¶]Underlying diagnosis in cases where SDH code was not verified.
**Spontaneous or traumatic.
[††]"Other" ($n = 44$), underlying conditions: various symptoms that probably gave rise to clinical suspicion of SDH, although not noted as such in medical records (gait difficulties, confusion, fall/trauma, etc.) ($n = 18$), concussion (8), subarachnoid hemorrhage suspected, not confirmed (4), intraspinal extramedullary hemorrhage (2), seizures (2), headache (2), erroneous code (3), brain tumor (1), eye disorder (1), cranial deformity (1), porencephalic cyst (1), alcohol withdrawal symptoms (1).

subarachnoid hemorrhage. The underlying diagnoses for patients with unverified SDH diagnosis are presented in Table 1. We chose not to exclude a small number of patients with hygroma ($n = 8$) diagnosed in connection with surgical procedures, because we cannot rule out that these cases suffered an SDH at an earlier stage that later liquefied to form a hygroma.[16]

Based on the results of brain scan imaging, 531 patients were classified as cSDH and 405 as aSDH. cSDH represented 56% of cases recorded under code S065 (64% of S065—principal code), and 54% of cases recorded exclusively under code I620. The proportion of SDH that was classified as cSDH increased with age from 25% in those aged less than 50 years to 65% in those aged 70–89 years at the time of diagnosis. Compared with aSDH patients, those who suffered an cSDH were older; were more frequently male; had less frequently suffered head trauma, which was less frequently severe; and manifested less frequently with coma and markedly decreased level of consciousness, or seizures, but more frequently with headache, unilateral signs (hemiparesis, hemianopsia, and hemiataxia) or aphasia, confusion/memory problems, or gait and balance problems (Table 2). Timing of head trauma also differed markedly between SDH types. In all, 46% of cSDH patients with a verified head trauma history experienced this event at least 15 days prior to admission (range 15–240 days), while this only held true for 1.2% of aSDH patients (range 15–35 days). History of alcohol overuse did not differ significantly among cSDH compared with that among aSDH (Figure 2). There were marked differences in brain scan findings in the two types of SDH. Patients with cSDH more frequently had bilateral SDH, their SDHs were wider, and a larger fraction of patients had midline structure deviations, compared with aSDH patients. While 74% of cSDH patients underwent surgery, this was only the case for 30.1% of aSDH patients, with "too mild symptoms" (47%) being the most frequent reason for abstaining from surgery in this group (Table 2). Burr hole was the most commonly used operative technique in cSDH and craniotomy in aSDH. Thirty-day case fatality was markedly lower in patients with cSDH compared with that in aSDH patients. Preadmission use of antiplatelet and antithrombotic drugs did not vary by SDH type (Table 2 and Figure 2). In comparisons stratified by SDH type, antithrombotic use did not vary substantially in patients with head trauma history compared with patients with no head trauma (Table 3). Exceptions were VKA use in aSDH and clopidogrel use in cSDH; use of both drugs was less common among SDH patients with a history of trauma compared with patients with no trauma (Table 3). However, it should be noted that these comparisons were not age and sex adjusted and that clopidogrel estimates were based on small numbers. In analyses

DOI: 10.1002/pds

Table 2. Odds ratios of clinical characteristics, preadmission antithrombotic drug use, and case fatality rate in subacute/chronic subdural hematoma compared with acute subdural hematoma in 936 patients hospitalized with the disorder in 2000 to 2012

Characteristic	All ($n = 936$)	Subdural hematoma type		
		Subacute/chronic* ($n = 531$)	Acute* ($n = 405$)	Age-adjusted and sex-adjusted odds ratio (95% confidence interval)
Sex—male	613 (65.5)	368 (69.3)	245 (60.5)	1.7 (1.3–2.3)
Age, years—median (interquartile range)	72 (58–81)	75 (63–82)	66 (50–78)	Not applicable
Age (years)				
<50	134 (14.3)	33 (6.2)	101 (24.9)	1 (reference)
50–69	295 (31.5)	167 (31.5)	128 (31.6)	4.0 (2.5–6.3)
70–89	507 (54.2)	331 (62.3)	176 (43.5)	6.3 (4.0–9.7)
Time period of admission				
January 2000 to June 2006	430 (45.9)	236 (44.4)	194 (47.9)	1 (reference)
July 2006 to December 2012	506 (54.1)	295 (55.6)	211 (52.1)	1.1 (0.8–1.4)
Manifestation†				
Coma or markedly decreased consciousness level	186 (19.9)	35 (6.6)	151 (37.8)	0.1 (0.08–0.2)
Headache	293 (31.3)	215 (40.5)	78 (19.3)	3.7 (2.6–5.2)
Hemiparesis, hemianopsia, hemiataxia, or aphasia	320 (34.2)	269 (50.7)	51 (12.6)	7.3 (5.1–10.4)
Confused or memory problems	260 (27.8)	160 (30.1)	100 (24.7)	1.1 (0.8–1.5)
Seizure	76 (8.1)	29 (5.5)	47 (11.6)	0.6 (0.3–0.9)
Gait or balance problems	110 (11.8)	94 (17.7)	16 (4.0)	4.5 (2.6–7.9)
One or more of above	843 (90.1)	490 (92.3)	353 (87.2)	1.9 (1.2–3.0)
Head trauma				
History of head trauma				
Yes	683 (73.0)	334 (62.9)	349 (86.2)	0.3 (0.2–0.5)
No‡	87 (9.3)	67 (12.6)	20 (4.9)	1 (reference)
Not documented§	166 (17.7)	130 (24.0)	36 (8.9)	1.0 (0.5–1.8)
Timing of head trauma, days prior to admission¶				
0–2	345 (50.5)	54 (16.2)	291 (83.4)	1 (reference)
3–14	127 (18.6)	90 (27.0)	37 (10.6)	13 (7.8–22)
15+**	159 (23.3)	155 (46.4)	4 (1.2)	309 (92–1033)
Information missing	52 (7.6)	35 (10.5)	17 (4.9)	9.1 (4.6–18)
Severity of head trauma¶				
No trauma	87 (9.3)	67 (12.6)	20 (4.9)	1 (reference)
Mild	17 (2.5)	15 (4.5)	2 (0.6)	2.3 (0.5–11.7)
Moderate	414 (60.6)	240 (71.9)	174 (49.9)	0.4 (0.2–0.7)
Severe	219 (32.1)	61 (18.3)	158 (45.3)	0.1 (0.08–0.3)
Information missing or insufficient	33 (4.8)	18 (5.4)	15 (4.3)	0.7 (0.08–5.1)
Alcohol overuse,‡‡ current or past	155 (16.6)	76 (14.3)	79 (19.5)	0.8 (0.5–1.2)
Brain scan findings				
Subdural hematoma laterality§§				
Unilateral	728 (77.8)	377 (71.0)	351 (86.7)	1 (reference)
Bilateral	180 (19.2)	145 (27.3)	35 (8.6)	3.4 (2.3–5.2)
Subdural hematoma width,¶¶ mm—median (interquartile range)	14 (8–20)	18 (11–22)	8 (5–15)	Not applicable
Midline structure deviation present***	511 (54.6)	324 (61.0)	187 (46.2)	2.5 (1.8–3.4)
Operation performed				
Yes, performed	514 (54.9)	392 (73.8)	122 (30.1)	6.4 (4.7–8.8)
No, not performed	397 (42.4)	135 (25.4)	262 (64.7)	1 (reference)
Reasons for not performing operation				
Prognosis too poor†††	77 (8.2)	15 (2.8)	62 (15.3)	Not applicable
Mild symptoms	308 (32.9)	119 (22.4)	189 (46.7)	Not applicable
Other reasons‡‡‡	12 (1.3)	1 (0.2)	11 (2.7)	Not applicable
Information missing	25 (2.7)	4 (0.8)	21 (5.2)	Not applicable
Type of operation performed§§§				
Craniotomy	167 (32.5)	53 (13.5)	122 (93.4)	1 (reference)
Burr holes	346 (67.3)	338 (86.2)	8 (6.6)	83 (37–183)
30-day mortality¶¶¶	119 (12.7)	30 (5.7)	89 (22.0)	0.2 (0.1–0.3)
Preadmission antithrombotic drug use****				
Aspirin, low dose	256 (27.4)	153 (28.8)	103 (25.4)	0.8 (0.6–1.1)
Clopidogrel	23 (2.5)	13 (2.5)	10 (2.5)	0.8 (0.4–2.0)
Vitamin K antagonist				
All	125 (13.4)	73 (13.8)	52 (12.8)	0.8 (0.5–1.2)
By international normalized ratio level††††				
<2.0	25 (2.7)	19 (3.6)	6 (1.5)	1.9 (0.7–4.8)
2.0–2.9	40 (4.3)	26 (6.4)	14 (3.5)	1.0 (0.5–2.0)
3.0–3.9	31 (3.3)	15 (2.8)	16 (4.0)	0.5 (0.2–1.1)

(*Continues*)

DOI: 10.1002/pds

Table 2. (Continued)

Characteristic	All ($n = 936$)	Subdural hematoma type: Subacute/chronic* ($n = 531$)	Subdural hematoma type: Acute* ($n = 405$)	Age-adjusted and sex-adjusted odds ratio (95% confidence interval)
Unknown	29 (3.1)	13 (2.5)	16 (4.0)	0.5 (0.2–1.0)
Non-vitamin K oral anticoagulant	2 (0.2)	1 (0.2)	1 (0.3)	Not applicable
Any of above	338 (36.1)	208 (39.2)	130 (32.1)	0.9 (0.6–1.2)

Univariate analyses, adjusted for age and sex.
*Classified according to brain scan imaging (computed tomography in 923 patients and magnetic resonance imaging in 12 patients).
†Numbers do not add to 100%; subjects may be classified under more than one manifestation (symptom or sign).
‡Physician asked patient or carers, who specifically denied head trauma.
§No documentation in medical record of whether physician asked about history of head trauma.
¶Patients where history of head trauma was not documented in medical records were not included. Odds ratio for each type of severity compared separately using no trauma as reference.
**Patients in this group reported experiencing a head trauma on average of 57 days (range 15–240 days) for chronic subdural hematoma and 22 days (range 15–35 days) for acute subdural hematoma prior to their admission for subdural hematoma.
††Trauma type exemplified to neurosurgeons who extracted medical record data as follows: *severe*, for example, traffic accident victim, fell down flight of stairs; *moderate*, for example, patient fell flat and hit head; *mild*, for example, hit head against cupboard door.
‡‡Referred to as alcoholic, current or past, in medical record.
§§Missing information on 28 patients (19 acute and 9 subacute/chronic).
¶¶Measured at widest diameter by radiologist or study neurosurgeons. If bilateral, the thickest subdural hematoma was measured. Information not available in 223 cases (105 acute and 118 subacute/chronic).
***Information not available for 172 patients (70 acute and 102 subacute/chronic).
†††Patient too sick, or heavy comorbidity burden.
‡‡‡Inaccessible for surgery, patient not interested, and miscellaneous other reasons.
§§§Nine patients received both burr hole surgery and craniotomy. These were classified as craniotomy. Information on operation type missing in one patient. Only operated patients included.
¶¶¶Date of death obtained from nationwide continuously updated Civil Registration Register.
****Based on Prescription Register data. Odds ratios calculated adjusted for other antithrombotic drug use; for example, low-dose aspirin estimates were adjusted for use of vitamin K agonist and clopidogrel.
††††Highest value measured 7 days before admission date to 1 day after admission date. Non-users of vitamin K agonist are the reference group.

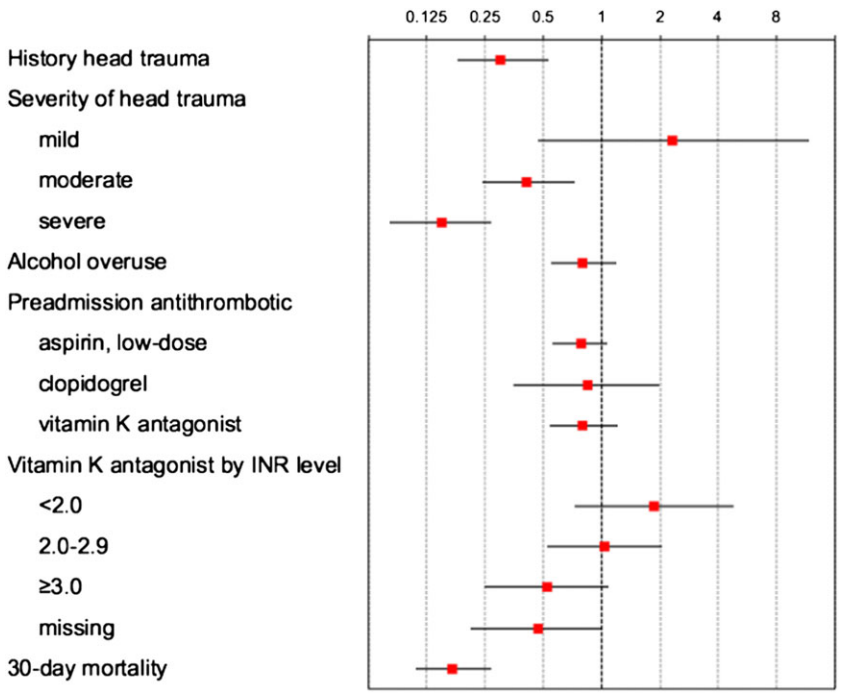

Figure 2. Age-adjusted and sex-adjusted univariate odds ratio of history of head trauma, alcohol overuse, preadmission antithrombotic drug use, and 30-day mortality in patients with subacute/chronic subdural hematoma compared with patients with acute subdural hematoma. For a given characteristic, odds ratio >1 indicates a higher prevalence in chronic subdural hematoma, while odds ratio <1 indicates a higher prevalence in acute subdural hematoma. Bars indicate 95% confidence intervals. INR, international normalized ratio

DOI: 10.1002/pds

Table 3. Preadmission antithrombotic drug use stratified by subdural hematoma type and history of head trauma

Preadmission antithrombotic drug use*	Subacute/chronic subdural hematoma				Acute subdural hematoma			
	Head trauma history			*P* value§	Head trauma history			*P* value§
	No†	Yes	Not documented‡		No†	Yes	Not documented‡	
Vitamin K antagonist								
Yes	10 (14.9)	46 (13.8)	17 (13.1)		7 (35.0)	35 (10.0)	10 (27.8)	
No	57 (85.1)	288 (86.2)	113 (86.9)	0.9	13 (65.0)	314 (90.0)	26 (72.2)	<0.001
Low-dose aspirin								
Yes	21 (31.3)	91 (27.3)	41 (31.5)		6 (30.0)	84 (24.1)	13 (36.1)	
No	46 (68.7)	243 (72.8)	89 (68.5)	0.6	14 (70.0)	265 (75.9)	23 (63.9)	0.3
Clopidogrel								
Yes	5 (7.5)	4 (1.2)	4 (3.1)		1 (5.0)	8 (2.3)	1 (2.8)	
No	62 (92.5)	330 (98.8)	126 (96.9)	0.01	19 (95.0)	341 (97.7)	35 (97.2)	0.4
Any of the aforementioned drugs¶								
Yes	28 (41.8)	126 (37.7)	54 (41.5)		9 (45.0)	104 (29.8)	19 (52.8)	
No	39 (58.2)	208 (62.3)	76 (58.5)	0.7	11 (55.0)	245 (70.2)	17 (47.2)	0.046

*Prescription for drug presented within 180 days of admission. Drug use ascertained through prescription register.
†Physician asked patient or carers, who specifically denied head trauma.
‡No documentation in medical record of whether physician asked about history of head trauma.
§Chi-squared or Fisher's exact test. Testing whether the distribution of "yes"/"no"/"not documented" to head trauma history varies according to preadmission antithrombotic use.
¶Also includes two patients treated with non-vitamin K agonist drugs (one with chronic subdural hematoma and one with acute subdural hematoma).

using patients with no preadmission VKA use as reference and stratifying patients on VKA treatment by their recently measured INR values, patients with cSDH had INR values of ≥3.0 less frequently, compared with patients with aSDH (aOR 0.5, 95%CI 0.2–1.1) (Table 2 and Figure 2).

We also looked at the relationship between trauma severity and antithrombotic drug use in analyses restricted to patients with a history of head trauma (Table 4). Preadmission antithrombotic drug use was more prevalent among patients with moderate/mild head trauma, compared with patients with severe trauma (VKA: 14.6% vs. 6.4%, aOR 1.7, 95%CI 0.9–3.1; low-dose aspirin: 32.3% vs. 14.2%, aOR 1.8, 95%CI 1.1–2.9). This association was most pronounced among patients with aSDH (VKA: 15.9% vs. 3.2%, aOR 3.4, 95%CI 1.2–9.5; low-dose aspirin: 34.7% vs. 12.7%, aOR 2.3, 95%CI: 1.2–4.5).

The regional data on the age and sex distribution of patients with first ever recorded principal discharge code S065 ($n = 766$) were generally similar to nationwide data ($n = 8926$) for the same period (Figure 3).

Table 4. Preadmission use of antithrombotic drugs by trauma severity in patients with subdural hematoma and history of head trauma ($n = 683$)

Severity of trauma	Preadmission antithrombotic drug use*					
	Vitamin K antagonist		Age and sex adjusted	Low-dose aspirin		Age and sex adjusted
	Yes	No	OR (95%CI)	Yes	No	OR (95%CI)
Subdural hematoma, any type						
Severe	14	205	1 (reference)	31	188	1 (reference)
Moderate/mild†	63	368	1.7 (0.9–3.1)	139	292	1.8 (1.1–2.9)
Not documented	4	29	1.5 (0.5–5.1)	5	28	0.7 (0.2–2.1)
Subacute/chronic SDH						
Severe	9	52	1 (reference)	11	50	1 (reference)
Moderate/mild	35	220	0.8 (0.4–1.8)	78	177	1.7 (0.8–3.6)
Not documented	2	16	0.6 (0.1–3.2)	2	16	0.5 (0.1–2.4)
Acute SDH						
Severe	5	153	1 (reference)	20	138	1 (reference)
Moderate	28	148	3.4 (1.2–9.5)	61	115	2.3 (1.2–4.5)
Not documented	2	13	4.2 (0.7–26.5)	3	12	1.4 (0.3–6.5)

SDH, subdural hematoma; OR, odds ratio; CI, confidence interval.
*Prescription for drug presented within 180 days of admission. Drug use ascertained through prescription register.
†Categories moderate and mild head trauma collapsed into a single category because of low number of patients in the mild category (SDH any type: 17 with mild head trauma, of whom four were exposed to vitamin K antagonist, and five to low-dose aspirin).

DOI: 10.1002/pds

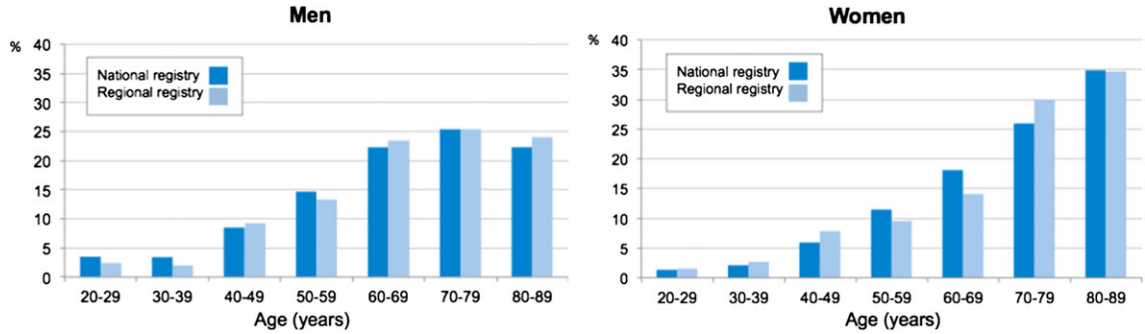

Figure 3. Age and sex distribution of patients with first-time ever discharge code for subdural hematoma (principal diagnosis International Classification of Diseases version 10 code S065) in a national ($n = 8924$) versus a regional ($n = 766$) patient register in Denmark, 2000–2012

However, in those aged 50+ years, certain differences between regional and national data were observed among women (regional versus national): 50–59 years, 11.5% vs. 9.6%; 60–69 years, 18.2% vs. 14.0%; and 70–79 years, 25.9% vs. 29.9%. In men of the same age groups, only those aged 80–89 years differed by more than 1.5% in regional (24%) compared with national (22.3%) data (Figure 3).

DISCUSSION

Validation of coding accuracy

We found that the PPV of SDH diagnosis codes in a Danish regional patient register varied considerably by type of ICD-10 code used (i.e., S065 versus I620), whether the code was principal or secondary, and by type of hospital contact (i.e., inpatient, outpatient, or emergency room). Principal discharge diagnosis S065 had a very high PPV (96%), and although this code only represented 65% of all SDH hospital contacts, it captured 78% of verified SDH cases, indicating an acceptable sensitivity. Furthermore, the age and sex distribution of patients with inpatient contacts with principal discharge code S065 in the regional register was similar to corresponding data from the national register. This provides indirect evidence for the generalizability of our findings regarding the PPV of code S065 principal discharge diagnosis and also indicates comparable coding practices at regional and national levels in Denmark. We therefore believe that our findings are applicable to the Danish National Patient Register. Our large study of 1185 patients provides evidence that enables valid use of Danish patient register data for epidemiological studies of SDH.

Studies of the validity of administrative ICD codes for SDH are scarce and mostly limited to grouped diagnoses (e.g., "major bleeding") in selected patient groups.[17,18] We are only aware of a single previous study that validated SDH discharge codes in a defined population. In this small study from Northern Wales, 49 patients with chronic SDH codes were identified (ICD code not reported), and the diagnosis could be verified in 40 based on medical records reviews.[10] Although direct comparisons are difficult because of design differences, we note that our results are in line with this study.

Our study also demonstrated that ICD-10 SDH codes in a Danish setting cover both cSDH and aSDH. Although the fraction of patients with cSDH increased with age in our study, a significant proportion of patients suffered aSDH even in the oldest age group, for example, 35% of patients aged 70–89 years. Distinguishing between cSDH and aSDH based on ICD-10 codes for SDH alone is not possible. Administrative patient registers in Denmark may therefore be of more limited interest to researchers interested in particular SDH types, unless algorithms incorporating supplementary data beyond the SDH diagnosis code can be developed to differentiate between aSDH and cSDH.

Descriptive baseline data and clinical management of chronic subdural hematoma and acute subdural hematoma

Because of its heterogeneous manifestations, cSDH has been dubbed "the great imitator."[19] While the distribution of manifestations in our study is not unlike that observed by others,[20–22] we note that compared with more recently prospectively collected data,[23] we found a higher frequency of hemiform manifestations (i.e., hemiparesis, hemianopsia, hemiataxia, or aphasia) and a lower frequency of gait disturbance and balance problems. These discrepancies are in all likelihood due to design differences, including the retrospective nature of our data, and the selected nature of other studies, for example, randomized clinical trial data.[23]

Chronic SDH is seen mostly in the elderly, frequently after trivial injury, while aSDH generally

DOI: 10.1002/pds

occurs in younger adults and is often caused by severe head trauma.[21] Our data reproduce these well-known associations between SDH and head trauma, including the severity and timing of trauma in the two SDH types. We also found a high prevalence of history of alcohol overuse, another known risk factor of SDH.[21,24] Burr hole is the preferred surgical procedure for cSDH, a condition where bilateral SDH is far more frequent than in aSDH.[24] The reported short-term mortality after cSDH varies widely in the literature[21] and depends on several factors we did not take account of in our analyses, for example, the patients' neurological condition and surgical treatment.[25] In spite of these limitations, we believe our simple 30-day mortality analysis highlights the strikingly different short-term mortality in cSDH compared with aSDH, which was still present after adjusting for age and sex.

Previous studies of antithrombotic use in patients with SDH are mostly from single centers and restricted to surgically treated patients[26–28] or patients admitted to neurointensive care units.[29] This is in contrast to our study, where all hospital contacts coded as SDH in a geographic area were included. Straightforward comparisons with other study results are therefore not possible. We note that a previous single-center study in Denmark, comprising 284 patients with surgically evacuated cSDH (mean age, 71.8 years), reported preadmission antithrombotic treatment in 44% of patients,[28] a proportion similar to that found in our study. Aspegren *et al*. also reported a higher prevalence of antithrombotic drug use in cSDH patients without head trauma (63%) compared with patients with head trauma (42%),[28] a finding we could not corroborate. However, we found that preadmission antithrombotic drug use was inversely related to trauma severity for SDH overall and aSDH in particular. Our data also suggest that intensity of anticoagulation possibly contributes more to aSDH than to cSDH. Our results should be interpreted cautiously, as data on trauma history were collected retrospectively and without use of a validated instrument to assess trauma severity. Furthermore, some of our results on trauma and preadmission antithrombotic use were based on small numbers, which influenced the statistical precision and limited our options with regard to multivariate adjustments (i.e., we only adjusted for sex and age). Finally, our data on INR values were limited. We did not have access to all INR values for cases (e.g., we lacked results of blood tests by general practitioners), and we had no information on INR values of non-hospitalized users of VKA (e.g., controls) to compare our cases with. Bearing these caveats in mind, we infer that for patients predisposed to SDH owing to some degree of brain shrinkage (e.g., due to age or alcohol overuse), a mild to moderate head trauma may represent a sufficient causal event to produce an SDH, but this risk can be further enhanced by the use of antithrombotic drugs. Severe head trauma, on the other hand, appears to be a sufficient cause of SDH per se, irrespective of antithrombotic drug use.

We conclude that Danish administrative patient registers are a useful resource for SDH research. These registries can be simply and unambiguously linked to Danish prescription registries,[13] a possibility we will utilize in future pharmacoepidemiological studies of antithrombotic drug use and risk of SDH. We furthermore believe that our findings may be applicable to other settings with similar healthcare systems and registers, for example, other Scandinavian countries.

CONFLICT OF INTEREST

Drs. Frantz Rom Poulsen, Bo Halle, Jesper Hallas, and Mr. Anton Pottegård report no conflicts of interest. Dr. Luis A. García Rodriguez works at CEIFE, which has received research grants from Bayer Pharma AG, Germany. Dr. García Rodríguez has also served as an advisory board member for Bayer Pharma AG, Germany. Dr. David Gaist received honoraria from AstraZeneca (Sweden) for participation as a co-investigator in a research project.

KEY POINTS

- Among 1185 patients recorded under subdural hematoma (SDH) diagnosis codes in an administrative patient register in Denmark the principal discharge code S065 had the highest PPV (96%) and correctly identified 78% of all verified SDH cases.
- ICD-10 SDH codes do not differentiate between acute and subacute/chronic SDH. The two SDH types, while different with respect to several clinical characteristics, were similar with regard to preadmission antithrombotic drug use.
- Danish administrative medical registers can be a useful resource for pharmacoepidemiological studies of SDH.

ETHICS STATEMENT

The study was approved by the Danish Data Protection Agency and the Danish National Board of Health. According to Danish law, approval from an ethics board is not required for register studies.

DOI: 10.1002/pds

REFERENCES

1. Laviv Y, Rappaport ZH. Risk factors for development of significant chronic subdural hematoma following conservative treatment of acute subdural hemorrhage. *Br J Neurosurg* 2014; **28**: 733–738. doi:10.3109/02688697.2014.918578.
2. Ivamoto HS, Lemos HP, Atallah AN. Surgical treatments for chronic subdural hematomas: a comprehensive systematic review. *World Neurosurg* 2016; **86**: 399–418. doi:10.1016/j.wneu.2015.10.025.
3. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med* 1994; **120**: 897–902.
4. Fang MC, Go AS, Chang Y, *et al.* Death and disability from warfarin-associated intracranial and extracranial hemorrhages. *Am J Med* 2007; **120**: 700–705. doi:10.1016/j.amjmed.2006.07.034.
5. Hart RG, Diener H-C, Yang S, *et al.* Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. *Stroke J Cereb Circ* 2012; **43**: 1511–1517. doi:10.1161/STROKEAHA.112.650614.
6. Connolly BJ, Pearce LA, Kurth T, Kase CS, Hart RG. Aspirin therapy and risk of subdural hematoma: meta-analysis of randomized clinical trials. *J Stroke Cerebrovasc Dis Off J Natl Stroke Assoc* 2013; **22**: 444–448. doi:10.1016/j.jstrokecerebrovasdis.2013.01.007.
7. Connolly BJ, Pearce LA, Hart RG. Vitamin K antagonists and risk of subdural hematoma: meta-analysis of randomized clinical trials. *Stroke J Cereb Circ* 2014; **45**: 1672–1678. doi:10.1161/STROKEAHA.114.005430.
8. De Bonis P, Trevisi G, de Waure C, *et al.* Antiplatelet/anticoagulant agents and chronic subdural hematoma in the elderly. *PLoS One* 2013; **8** e68732.. doi:10.1371/journal.pone.0068732.
9. Cousseau DH, Echevarría Martín G, Gaspari M, Gonorazky SE. Chronic and subacute subdural haematoma. An epidemiological study in a captive population. *Rev Neurol* 2001; **32**: 821–824.
10. Asghar M, Adhiyaman V, Greenway MW, Bhowmick BK, Bates A. Chronic subdural haematoma in the elderly—a North Wales experience. *J R Soc Med* 2002; **95**: 290–292.
11. Thygesen LC, Ersbøll AK. When the entire population is the sample: strengths and limitations in register-based epidemiology. *Eur J Epidemiol* 2014; **29**: 551–558. doi:10.1007/s10654-013-9873-0.
12. Pottegård A, García Rodríguez LA, Poulsen FR, Hallas J, Gaist D. Antithrombotic drugs and subarachnoid haemorrhage risk. A nationwide case–control study in Denmark. *Thromb Haemost* 2015; **114**. doi:10.1160/TH15-04-0316.
13. Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997; **44**: 445–448.
14. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011; **39**: 30–33. doi:10.1177/1403494811401482.
15. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011; **39**: 22–25. doi:10.1177/1403494810387965.
16. Mayer S, Rowland L. Head injury. In Merritt's Neurology (10th edn), Rowland L (ed.). Lippincott Williams & Wilkins: Philadelphia, 2000; 483–501.
17. Arnason T, Wells PS, van Walraven C, Forster AJ. Accuracy of coding for possible warfarin complications in hospital discharge abstracts. *Thromb Res* 2006; **118**: 253–262. doi:10.1016/j.thromres.2005.06.015.
18. Al-Ani F, Shariff S, Siqueira L, Seyam A, Lazo-Langner A. Identifying venous thromboembolism and major bleeding in emergency room discharges using administrative data. *Thromb Res* 2015; **136**: 1195–1198. doi:10.1016/j.thromres.2015.10.035.
19. Potter JF, Fruin AH. Chronic subdural hematoma—the "great imitator.". *Geriatrics* 1977; **32**: 61–66.
20. Luxon LM, Harrison MJ. Chronic subdural haematoma. *Q J Med* 1979; **48**: 43–53.
21. Adhiyaman V, Asghar M, Ganeshram KN, Bhowmick BK. Chronic subdural haematoma in the elderly. *Postgrad Med J* 2002; **78**: 71–75.
22. Borger V, Vatter H, Oszvald Á, Marquardt G, Seifert V, Güresir E. Chronic subdural haematoma in elderly patients: a retrospective analysis of 322 patients between the ages of 65–94 years. *Acta Neurochir (Wien)* 2012; **154**: 1549–1554. doi:10.1007/s00701-012-1434-x.
23. Santarius T, Kirkpatrick PJ, Ganesan D, *et al.* Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. *Lancet Lond Engl* 2009; **374**: 1067–1073. doi:10.1016/S0140-6736(09)61115-6.
24. Kolias AG, Chari A, Santarius T, Hutchinson PJ. Chronic subdural haematoma: modern management and emerging therapies. *Nat Rev Neurol* 2014; **10**: 570–578. doi:10.1038/nrneurol.2014.163.
25. van Havenbergh T, van Calenbergh F, Goffin J, Plets C. Outcome of chronic subdural haematoma: analysis of prognostic factors. *Br J Neurosurg* 1996; **10**: 35–39.
26. Baechli H, Nordmann A, Bucher HC, Gratzl O. Demographics and prevalent risk factors of chronic subdural haematoma: results of a large single-center cohort study. *Neurosurg Rev* 2004; **27**: 263–266. doi:10.1007/s10143-004-0337-6.
27. Lindvall P, Koskinen L-OD. Anticoagulants and antiplatelet agents and the risk of development and recurrence of chronic subdural haematomas. *J Clin Neurosci Off J Neurosurg Soc Australas* 2009; **16**: 1287–1290. doi:10.1016/j.jocn.2009.01.001.
28. Aspegren OP, Åstrand R, Lundgren MI, Romner B. Anticoagulation therapy a risk factor for the development of chronic subdural hematoma. *Clin Neurol Neurosurg* 2013; **115**: 981–984. doi:10.1016/j.clineuro.2012.10.008.
29. Bershad EM, Farhadi S, Suri MFK, *et al.* Coagulopathy and inhospital deaths in patients with acute subdural hematoma. *J Neurosurg* 2008; **109**: 664–669. doi:10.3171/JNS/2008/109/10/0664.