Trends in the incidence and mortality of intracerebral hemorrhage, and the associated risk factors, in Denmark from 2004 to 2017

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Trends in incidence, risk factors, and mortality of intracerebral hemorrhage in Denmark 2004-2017

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ABSTRACT

Background: The distribution of major modifiable risk factors of intracerebral hemorrhage (ICH) changes rapidly. These changes call for contemporary data from large-scale population-based studies.

Aims: To examine trends in incidence, risk factors, and mortality of ICH patients from 2004-2017.

Methods: In a population-based cohort study, we calculated age- and sex-standardized incidence rates (SIR), incidence rates (IR) stratified by age and sex per 100,000 person-years, and trends in risk profile. We estimated absolute mortality risk, and Cox proportional-hazards regression multivariable adjusted hazard ratios of 30-day and 1-year mortalities.

Results: We included 16,902 patients (53% male; median age 75 years) from 2004-2017. The SIR of ICH decreased from 33 (95%CI: 32-34) in 2004/2005 to 28 (95%CI: 27-29) in 2016/2017. Among patients aged ≥70 years, the IR decreased from 137 (95%CI: 130-144) in 2004/2005 to 112 (95% CI: 106-117) in 2016/2017. The IR in patients aged <70 years was unchanged. From 2004-2017, the proportion of patients with hypertension increased from 49% to 66%, the use of oral anticoagulants increased from 7% to 18%, and the use of platelet inhibitors decreased from 40% to 28%. The adjusted hazard ratio for 30-day mortality in 2016/2017 was 0.94 (95%CI: 0.89-1.01) and 1-year mortality was 0.98 (95%CI: 0.93-1.04) compared with 2004/2005.

Conclusion: The incidence of spontaneous ICH decreased from 2004-2017 with no clear trend in mortality. The risk-profile of ICH patients changed substantially with increasing proportions of hypertension and anticoagulant treatment. Given the high mortality rate of ICH, further advances in prevention and treatment are urgently needed.

Non-standard abbreviations and Acronyms

CI, Confidence interval; DSR, The Danish Stroke Registry; HR, Hazard ratio; ICH, Intracerebral hemorrhage; IR, Incidence rate; NOAC, Non-Vitamin K antagonist oral anticoagulants; PY, Person-years; SIR, Age and sex-standardized incidence rate; VKA, Vitamin K antagonists.

INTRODUCTION

Although intracerebral hemorrhage (ICH) is the second most common type of stroke and associated with a high case-fatality and risk of severe functional impairment, controversy and uncertainty remains regarding the epidemiology of the condition, including contemporary changes in incidence and prognosis.(1-9)

Some studies have reported a decrease over time in ICH incidence,(7, 10, 11) whereas others have found either an unchanged or even an increase in the incidence.(1, 2, 6, 12) The reasons for these discrepancies are not entirely evident, however, differences in calendar periods, study periods, completeness of ICH registration, and underlying study populations may all have contributed.

Up-to-date information on the epidemiology of ICH is essential for research and for planning and prioritizing resources. Particularly in the current scenario with an ongoing demographic shift in many countries with aging populations, potentially increased physical inactivity due to modern sedentary lifestyle, and intensified use of antithrombotic therapy. These are all factors that may contribute to a higher incidence of ICH and an increasing absolute number of patients suffering from the adverse effect of brain injury. Hence, up-to-date data from large

scale population-based studies with high completeness and detailed information on patient risk factor profiles are required to fuel the research agenda in relation to prevention and treatment.

We hypothesized that changes in the distribution of risk factors of ICH in recent years have caused a change in the incidence of ICH and subsequent mortality. Specifically, the objective was to examine the time-trends in incidence, risk factors, and mortality in the Danish population between 2004 and 2017.

METHODS

Data sources

No informed written consent or permission from a scientific ethics committee is required for register-based studies in Denmark. According to the Danish General Data Protection Regulation, the study data cannot be shared publicly, even in a pseudonymized version.

This study was based on information from the following administrative nationwide registries:

- The Danish Stroke Registry (DSR) is a stroke-specific clinical registry based on mandatory reporting of all cases of stroke from all hospital departments in Denmark treating patients with acute stroke, as defined by WHO criteria.(13) The positive predictive value for spontaneous ICH has previously been estimated to be >85% in the DSR.(14)
- The Danish National Patient Registry contains information about all patients discharged from Danish non-psychiatric hospitals since 1977. Outpatients were included in the registry from 1995. Diseases are registered with the International Classification of Diseases eight revision until 1994 and then registration changed to tenth revision.(15)
- The Danish Civil Registration System provides basic personal information on all people residing in Denmark. All citizens or persons with residence permission in Denmark are given a unique 10-digit civil personal register number, which enabled unambiguous individual-based linkage between the different registries.(16)
- The Danish National Prescription Registry covers data about all prescription drugs dispensed at Danish pharmacies since 1994.(17)

Design, setting, and population

We conducted a nationwide population-based cohort study of Danish ICH patients. Our study included all patients from the age of 18 years who were registered in the DSR with a first-time hospitalization for acute spontaneous ICH between January 1, 2004, and December 31, 2017. We

excluded all patients with prior hospitalizations for ICH within 10 years before the study period based on information from the Danish National Patient Registry. The Danish population consists of approximately 5.7 million individuals, and the healthcare system is universal and founded on principles of free and equal access to healthcare for all citizens.(18) General taxes finance the majority of the services including healthcare for ICH patients.(18)

Risk profile of ICH

We examined the prevalence of a range of key modifiable risk factors of ICH: smoking, history of recognized hypertension, and use of antithrombotic therapy at the time of the diagnosis of ICH.(19) Information on smoking status was obtained from the DSR and classified as daily, former, or never. History of recognized hypertension was defined as at least two blood pressure-lowering drugs, which is in accordance with a validated algorithm,(20) or a diagnosis of hypertension in the DSR, or Danish National Patient Registry combined with at least one blood pressure-lowering drug. Use of antithrombotic therapy was defined as a redeemed prescription within 90 days before hospitalization for ICH. We categorized antithrombotic therapy as vitamin K antagonists (VKA), Non-Vitamin K antagonist oral anticoagulants (NOAC), and platelet aggregation inhibitors. The data about medications were retrieved from the Danish National Prescription Registry. The specific International Classification of Diseases and Anatomical Therapeutic Chemical codes are presented in the Appendix.

Covariates

To estimate the burden of chronic diseases, the Charlson Comorbidity Index was calculated based on discharge diagnoses recorded in the Danish National Patient Registry within the last 10 years prior to the admission with ICH.(21) Hypercholesterolemia was defined from Anatomical Therapeutic Chemical codes of use of lipid-lowering drugs. Information about sex, age, history of atrial fibrillation and myocardial infarction, and the Scandinavian Stroke Scale score at the time of admission was extracted from DSR.

We obtained information about the quality of in-hospital care from quality indicators in the DSR. We included data on nutritional risk assessment, assessment by a physiotherapist, and an occupational therapist, all within two days after admission. Furthermore admission to a specialized stroke unit and a computed tomography/magnetic resonance imaging scan on the day of

admission.(22) The specific International Classification of Diseases and Anatomical Therapeutic Chemical codes are presented in the Appendix.

Mortality

Thirty-day and 1-year mortality rates after the diagnosis of ICH were assessed. Information on vital status was obtained from the Civil Registration System.(16)

Statistical analysis

We calculated the average age- and sex-standardized incidence rate (SIR) within the 14-year study period per 100.000 person-years (PY) with the 95% confidence interval (CI). Statistics Denmark provided the total number of years at risk for the Danish population over the study period.(23) Hospitalization rate was used as a proxy for incidence rate.

We computed unadjusted incidence rates (IRs) and SIRs stratified by age and sex in calendar periods of two years to achieve a reasonable statistical precision. We assumed that the population size was constant throughout the individual calendar year so all individuals alive and residents in Denmark by January 1 contributed with one year of risk. SIRs were standardized to the age and sex distribution of the Danish population in the year 2017. Trend analyses were performed using meta-regression by random effects of aggregated data.(24)

We calculated the proportions of patients diagnosed with each risk factor separately and in combinations. We used Stata's p-trend command to calculate a chi-squared test to estimate temporal trends in risk profile.(25) The patients were censored when one of the following events occurred: death, emigration, or end of follow-up at 1-year, whichever came first. We calculated the 30-day and 1-year mortality risks.

We used Cox proportional-hazard regression to compute the hazard ratio (HR) as a measure of the mortality rate ratio associated with the two-year calendar period of diagnosis, using 2004/2005 as reference. We computed unadjusted estimates of 30-day and 1-year mortality as well as estimates adjusted for sex, age, hypertension, use of antithrombotic therapy, use of statins, Charlson Comorbidity Index, calendar year, previous or current history of atrial fibrillation, myocardial infarction, smoking habits, early stroke unit admission, early computed tomography/ magnetic resonance imaging scan, early assessment by physiotherapist, early assessment by occupational therapist, early nutritional risk assessment, and the Scandinavian Stroke Scale score. We used simple imputation to impute all missing data of covariates in the mortality analysis. We

generated 12,068 imputations. We were missing information about at least 1 variable in 6832 patients equivalent to 40% of the study population. The most frequent missing variable was smoking (n=5245). We calculated 95% CIs using the approximate bootstrap method. We repeated the analyses for the following subgroups: no hypertension or use of antithrombotic therapy, hypertension, antithrombotic therapy, and hypertension, and concomitant use of antithrombotic therapy.

RESULTS

Patient characteristics

Table 1 shows the characteristics of the study population by calendar years. Between 2004 and 2017, 16,902 patients encountered a first-time ICH. The median age at the diagnosis was 75 years (interquartile range: 64–84) and 53% of the patients were male. Over the calendar years, the Scandinavian Stroke Scale score at admission increased (less severe strokes) and the proportion of ICH patients with three or more comorbidities, prevalent hypertension, and atrial fibrillation, respectively, increased.

Incidence rates of ICH and temporal trend

During the 14-year study period, the overall SIR of a first-time hospitalization for ICH was 27.7 per 100.000 PY. The unadjusted IR and SIR decreased over time (Figure 1a). A decreasing linear temporal trend in SIR was observed from 2004-2017 ($p \leq 0.01$). In sex-stratified analyses, the IR decreased among men and women (Figure 1b). A temporal linear time trend was more noticeable for men ($p \leq 0.01$) than for women ($p=0.018$). In age-stratified analyses, the IR was higher among patients aged ≥70 years compared with patients aged <70 years (Figure 1c). Over the calendar years, the IR in patients aged <70 years was not markedly changed ($p=0.079$) for temporal linear time trend. Among patients aged ≥70 years, the IR decreased steadily over time ($p \leq 0.01$).

Temporal trends in risk profile

The risk factor profile of the ICH population is presented in Table 2. The proportion of patients with recognized hypertension both with ($p \leq 0.01$) and without concomitant use of antithrombotic therapy increased ($p \leq 0.01$).

The proportion of ICH patients only receiving antithrombotic therapy decreased from 18.0% to 9.7% during the study period, which was mainly driven by a reduction in treatment with platelet

inhibitors. In contrast, the proportion of ICH patients receiving anticoagulant medication increased from 7.4% to 17.8%. Following the introduction of NOAC, the proportion of ICH patients receiving NOAC increased substantially, however, the proportion of patients using vitamin K antagonists continued to increase.

Throughout the study period, the number of ICH patients who were smoking decreased from 23.7% to 16.4%.

Temporal trends in mortality

Table 3 presents the 30-day and 1-year mortality rates by year of admission. The absolute 30-day mortality ranged from 24% to 34% and 1-year mortality varied from 35% to 44%. The absolute mortalities were lowest in the most recent year of the study period. Both 30-day and 1-year mortality decreased during the study period. The adjusted 30-day mortality rate was lowest in 2016/2017 (adjusted HR 0.94, 95% CI: 0.89-1.01) and highest in 2008/2009 (adjusted HR 1.10, 95% CI: 1.04-1.16) when compared with 2004/2005. The adjusted 1-year mortality rate was lowest in 2016/2017 (adjusted HR 0.99, 95% CI: 0.93-1.04) and highest in 2008/2009 (adjusted HR 1.09, 95% CI: 1.04-1.14) when compared with 2004/2005.

The differences between crude and adjusted mortality rates were primarily explained by adjustment for changes over time in fulfilment of in-hospital care quality indicators and stroke severity.

Subgroup analyses

Subgroup analyses of mortality in patients with recognized hypertension, antithrombotic therapy, or a combination of both are presented in the Appendix. We did not observe any systematic time trends in the adjusted mortality rate in any of the examined subgroups.

DISCUSSION

We showed a declining trend in the incidence of first-time hospitalization for spontaneous ICH. The declining trend in incidence was similar between men and women. The decrease was observed among individuals aged ≥70 years but not among those aged <70 years.

We observed a tendency towards an increase in IR from 2014/15 to 2016/17. Although modest in size, the apparent increase is concern and underlines the need for continued population-based

monitoring of the ICH incidence in order to capture the possible adverse effects of temporal changes in the risk profile of the general population.

There was no clear temporal trend in mortality rates over calendar years.

Previous studies have reported unchanged IRs of ICH over three decades until 2010.(1-5) A systematic review of 36 studies showed no change in the IR between 1980-2008 with an overall IR of 24.6 per 100.000 PY.(1) However, pooling studies is often challenging due to dissimilarities in health systems, inclusion criteria, and characteristics of the study populations. In contrast to these previous findings, our study found a decrease in the IR from 2004-2017 and an overall IR in this period of 27.7 per 100.000 PY. There are also a number of previous studies, which have reported a similar reassuring trend of decreasing incidence,(6, 26, 27) but the use of different reference periods, different characteristic of the study population (e.g. genetical differences) and the relatively small number of ICH cases makes it difficult to directly compare the studies and provide definitive conclusions.

Zahuranec *et al.*(28) reported a decline of 31% in IR of ICH from 2000-2010 in Texas, USA, primarily driven by a reduction in IR in people aged > 74 years. The trend is in line with our findings of a 14.8% decrease in IR from 2004-2017. However, Zahuranec *et al.* only included patients above 44 years and the smaller IR reduction found in our study may therefore be attributed to the inclusion of younger patients aged >18 years, as the overall trend in reduction was less noticeable in the younger age group. This may be related to the age-related differences in etiology of ICH, *e.g.* cerebral arteriovenous malformations and cavernous bleeds as major risk factors among young, which are less amenable for pharmacological intervention, are more frequently found in younger patients.

A recent study from Framingham, USA, by Lioutas *et al.(6)* observed a decreasing incidence of ICH between 1987-1999 and 2000-2016. This finding is in accordance with our observation of a decreasing incidence of ICH between 2004 and 2017. However, in conflict with our finding, Lioutas *et al.* found an increase in ICH incidence among patients aged ≥75 years.(6) This difference may be related to variation in the use of primary prevention across health care systems and populations.

A study based on data from Australian hospitals also showed an average decline in IR of 1.6% per year across all age groups except those above 90 years of age between 2001-2009.(8) In our study, we found an average decrease in IR of 2.6% per two-year calendar period. The IR of

ICH in our study decreased every year except from 2014/2015 to 2016/2017 in which it increased 5.2%.

The declining IR of ICH may also to some extent reflect that improvements in the diagnostic tools and the centralization of the stroke care services in highly specialized stroke units result in less misclassification between ICH and other types of stroke. In that case, the observed reduced IR does not necessarily entirely reflect true changes.

A previous study by Lovelock *et al.*(12) from 2007 has also investigated changes in risk profile associated with ICH. Their observation of a change in risk-profile of ICH patients is in line with our finding of a substantial change over time. We found an increase in the prevalence of recognized hypertension among patients with first-time ICH from 2004-2017. Hypertension is known as a strong risk factor of ICH.(29) The definition of hypertension is dependent on the use of antihypertensive drugs. The increase in ICH patients with recognized hypertension therefore might well reflect a trend in the general population of more aggressive prevention and earlier detection of hypertension. This might explain a part of the reduction in ICH incidence despite the apparent increase in prevalence of hypertension.

Lioutas *et al*.(6) also observed substantial changes in risk profile of ICH. They found a threefold increase in the use of oral anticoagulant medication between 1987-1999 and 2000-2016. The increasing trend is in accordance with the findings by Lovelock *et al*. and our present study, and it reflects the general trend in the Danish population.(30) The trend could be a consequence of enhanced thromboprophylaxis in cardiovascular disease.(31) We observed an increase in the prevalence of atrial fibrillation during the study period, probably due to improved survival in patients with cardiovascular conditions predisposing to atrial fibrillation and enhanced detection. This is in accordance with the general trend in the Danish population.(32) Atrial fibrillation is one of the most common indications for oral anticoagulant therapy,(33) and the increase in atrial fibrillation prevalence could explain that more ICH patients were in anticoagulant therapy. In 2011, NOAC was approved for stroke prevention in patients with non-valvular atrial fibrillation in Denmark.(34) Clinical trials have documented a reduced incidence of ICH when comparing NOAC with VKA therapy in patients with atrial fibrillation.(35-38) This beneficial profile of NOAC has resulted in increased use.(39)

Overall, our findings show an improvement over time in the unadjusted mortality both after 30 and 365 days. This is encouraging for patients and other healthcare stakeholders and shows that patients admitted for ICH have a better prognosis today than what was observed at the start of the millennium. The improvement can besides changes in the risk profile and the increasing proportion of less severe strokes probably be attributed to admission of ICH patients to specialized stroke care units. Multidisciplinary teams with specialized knowledge about ICH are documented to reduce death and disability after ICH as compared to usual care.(40)

Furthermore, improvements in fulfilment of quality indicators of in-hospital care may have accounted for part of the improved mortality.

However, the fact that the absolute mortality remains high and that the adjusted HRs show no systematic improvements over time corresponds with other recent studies and indicates that further advances in treatment are urgently needed.[7-9]

Currently, the main strategy for reducing the disease burden of ICH is focused on prevention. Breakthrough clinical interventions with the potential for dramatically improving survival and functional outcome for a large proportion of patients with ICH is unfortunately still lacking, although the introduction of NOAC antidotes gives hope for a more rapid reversal of NOAC associated hemorrhage which is expected to improve case-fatality and functional outcome in ICH patients in NOAC therapy.

Limitations

Our study did not include patients that died of stroke before admission to the hospital. Given the Danish tradition of admitting almost all patients with acute stroke symptoms to hospital, virtually all acute stroke patients in Denmark are registered, even patients in nursing homes.(41) However, any missed cases of ICH may potentially have led to an underestimation of ICH incidence. Furthermore, despite the inclusion of a variety of patient characteristics, not all relevant variables were available in the study. Hence, we cannot elaborate on the location or volume of the haemorrhage. Neither could we comment on cerebral amyloid angiopathy which is a major cause of ICH in the elderly. This is an important limitation as both risk factor profile and mortality differs substantially according to subtype of ICH, e.g. hypertension is primarily associated with non-lobar ICH, whereas cerebral amyloid angiopathy is more common in lobar ICH.(19) Information on these pathophysiological characteristics would have strengthened the possibilities for a more in depth analysis of the impacts of changes in the risk factor profile of the ICH

population. In addition, we assessed use of antithrombotic therapy based on redeemed prescriptions (17) However, a minor part of low-dose aspirin is bought over the counter and is therefore not registered in the registry and thus not included in the study. Still, this part constituted less than 15% of the total use of low-dose aspirin in the study period.(42) Patients on long-term treatment with AT will typically have a prescription in order to receive financial reimbursement for the medication.(42) Finally, we used redeemed prescriptions partly paid out of the pocket by the patients as a proxy measure for actual drug use. Our results may not be directly generalizable to other European countries with another demographic profile, ICH risk factors distribution, and healthcare structure.

CONCLUSIONS

A declining trend in the incidence of first-time spontaneous ICH was observed in Denmark between 2004 and 2017, however, no clear trend was observed in the subsequent mortality. The risk-profile of the patients showed substantial changes with an increasing proportion of patients with recognized hypertension, a smaller proportion in antiplatelet therapy and a larger proportion in anticoagulant therapy. Together these findings underline that ICH remains a major clinical challenge.

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None

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Figure Legends

Table 1: Characteristics of patients with intracerebral hemorrhage by admission year. Danish Stroke Registry, 2004-2017

Table 2: Risk profile by admission year of patients with intracerebral hemorrhage according to antithrombotic therapy, hypertension, and smoking.

Table 3: 30-day- and 1-year mortality of patients with intracerebral hemorrhage

Figure 1a: Unadjusted and age- and sex standardized incidence rates according to admission year, 2004-2017

Figure 1b: Unadjusted and age standardized incidence rates stratified by sex according to admission year, 2004-2017

Figure 1c: Unadjusted and sex standardized incidence rates stratified age according to admission year, 2004-2017

Table 1: Characteristics of patients with intracerebral hemorrhage by admission year. Danish Stroke Registry, 2004-2017, n (%)

Admission year	2004/2005	2006/2007	2008/2009	2010/2011	2012/2013	2014/2015	2016/2017
All	2457 (100)	2403 (100)	2418 (100)	2390 (100)	2324 (100)	2335 (100)	2575 (100)
Demographics							
Age, Mean (median)	72.4 (74.9)	72.3 (74.7)	72.5 (74.6)	72.6 (74.9)	72.8 (74.5)	72.7 (74.8)	72.9 (74.8)
Male sex	1218 (49.6)	1245 (51.8)	1277 (52.8)	1253 (52.4)	1261 (54.3)	1271 (52.1)	1358 (52.7)
Comorbidity							
Hypertension	1191 (48.5)	1350 (56.2)	1438 (59.5)	1455 (60.9)	1456 (62.7)	1459 (62.5)	1702 (66.1)
Myocardial infarction	171 (7)	161 (6.7)	147 (6.1)	155 (6.5)	148 (6.4)	129 (5.5)	144 (5.6)
Diabetes Mellitus	232 (9.4)	233 (9.7)	251 (10.4)	278 (11.6)	256 (11)	278 (11.9)	287 (11.1)
Atrial fibrillation	304 (12.4)	345 (14.4)	395 (16.3)	387 (16.2)	397 (17.1)	450 (19.3)	533 (20.7)
Comorbidity burden†							
No (score 0)	41 (1.7)	40 (1.7)	55 (2.3)	45 (1.9)	42 (1.8)	36 (1.5)	83 (3.2)
Moderate (score 1-2)	1835 (74.7)	1727 (71.9)	1721 (71.2)	1628 (68.1)	1575 (67.8)	1562 (66.9)	1714 (66.6)
Severe (score ≥3)	581 (23.6)	636 (26.5)	642 (26.6)	717 (30)	707 (30.4)	737 (31.6)	778 (30.2)
Smoking							
Daily	583 (23.7)	533 (22.2)	539 (22.3)	449 (18.8)	449 (19.3)	410 (17.6)	423 (16.4)
Former	376 (15.3)	407 (16.9)	446 (18.4)	474 (19.8)	511 (22)	557 (23.9)	630 (24.5)
Never	673 (27.4)	586 (24.4)	620 (25.6)	706 (29.5)	729 (31.4)	730 (31.3)	826 (32.1)

Missing	825 (33.6)	877 (36.5)	813 (33.6)	761 (31.8)	635 (27.3)	638 (27.3)	696 (27)
Scandinavian Stroke Scale score							
45-58 points	603 (24.5)	586 (24.4)	645 (26.7)	658 (27.5)	751 (32.3)	748 (32)	906 (35.2)
30-44 points	401 (16.3)	364 (15.1)	423 (17.5)	406 (17)	403 (17.3)	442 (18.9)	508 (19.7)
15-29 points	349 (14.2)	307 (12.8)	330 (13.6)	345 (14.4)	389 (16.7)	397 (17)	450 (17.5)
0-14 points	639 (26)	624 (26)	626 (25.9)	681 (28.5)	650 (28)	584 (25)	592 (23)
Missing	465 (18.9)	522 (21.7)	394 (16.3)	300 (12.6)	131 (5.6)	164 (7)	119 (4.6)
Early nutritional risk assessment							
<2 days after admission	863 (39.8)	952 (44.3)	1098 (50.1)	1273 (57)	1345 (59.7)	1449 (64.9)	1693 (67.4)
No	1307 (60.2)	1199 (55.7)	1095 (49.9)	959 (43)	907 (40.3)	783 (35.1)	819 (32.6)
Early occupational therapist assessment							
<2 days after admission	1004 (43.9)	1148 (49.6)	1241 (54.4)	1302 (55.3)	1277 (55.4)	1327 (58.3)	1567 (61.5)
No	1285 (56.1)	1167 (50.4)	1042 (45.6)	1052 (44.7)	1030 (44.6)	950 (41.7)	981 (38.5)
Early physiotherapist assessment							
<2 days after admission	1094 (47.7)	1214 (52.1)	1273 (55.8)	1279 (54.4)	1274 (55.2)	1292 (56.6)	1543 (60.4)
No	1198 (52.3)	1115 (47.9)	1009 (44.2)	1071 (45.6)	1033 (44.8)	989 (43.4)	1011 (39.6)
Early computed tomography/ magnetic resonance imaging scan							
Same day as admission	1587 (65.6)	1785 (74.7)	1845 (77.6)	2099 (88)	2075 (89.3)	2128 (91.3)	2333 (90.8)
>1 day after admission	832 (34.4)	606 (25.3)	532 (22.4)	285 (12)	249 (10.7)	203 (8.7)	236 (9.2)

Early stroke unit admission							
Same day as admission	1784 (72.6)	1795 (74.7)	1778 (73.5)	1736 (72.6)	1770 (76.2)	1810 (77.5)	1996 (77.5)
>1 day after admission	673 (27.4)	608 (25.3)	640 (26.5)	654 (27.4)	554 (23.8)	525 (22.5)	579 (22.5)
Antihypertensive drugs ‡	948 (38.6)	1039 (43.2)	1079 (44.6)	1073 (44.9)	1092 (47)	1058 (45.3)	1189 (46.2)
Antidiabetic drugs	157 (6.4)	158 (6.6)	180 (7.4)	203 (8.5)	192 (8.3)	222 (9.5)	224 (8.7)
Lipid-lowering drugs	261 (10.6)	404 (16.8)	480 (19.9)	585 (24.5)	557 (24)	566 (24.2)	613 (23.8)
Antithrombotic therapy							
Oral anticoagulants	205 (8.3)	267 (11.1)	319 (13.2)	311 (13)	317 (13.6)	361 (15.5)	472 (18.3)
Platelet inhibitors	1008 (41)	987 (41.1)	1002 (41.4)	1005 (42.1)	875 (37.7)	827 (35.4)	740 (28.7)

† The comorbidity burden is based on Charlson Comorbidity Index

‡ Includes beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or non-loop diuretics

Table 2: Risk profile by admission year of patients with intracerebral hemorrhage according to antithrombotic therapy, hypertension, and smoking, n (%).

Year of admission	2004/2005	2006/2007	2008/2009	2010/2011	2012/2013	2014/2015	2016/2017
ICH event	2457	2403	2418	2390	2324	2335	2575
No hypertension or use of antithrombotic therapy	802 (32.6)	664 (27.6)	614 (25.4)	603 (25.2)	596 (25.6)	586 (25.1)	614 (23.8)
Hypertension without antithrombotic therapy	536 (21.8)	601 (25.0)	617 (25.5)	600 (25.1)	643 (27.7)	635 (27.2)	808 (31.4)

Antithrombotic therapy without hypertension	442 (18.0)	366 (15.2)	343 (14.2)	319 (13.3)	>244(>10.5) †	279 (12.0)	249 (9.7)
Anticoagulants	39 (1.6)	41 (1.7)	51 (2.1)	43 (1.8)	>36 (>1.5) †	60 (2.6)	70 (2.7)
NOAC	-	-	-	-	<5 (<1.0) †	11 (0.5)	37 (1.4)
Vitamin K antagonists	39 (1.6)	41 (1.7)	51 (2.1)	43 (1.8)	36 (1.5)	49 (2.1)	33 (1.3)
Platelet inhibitors	403 (16.4)	325 (13.5)	292 (12.1)	276 (11.5)	208 (9.0)	219 (9.4)	179 (7.0)
Hypertension and antithrombotic therapy	655 (26.7)	749 (31.2)	821 (34.0)	855 (35.8)	813 (35.0)	824 (35.3)	893 (34.7)
Hypertension and NOAC	-	-	-	-	18 (0.8)	66 (2.8)	157 (6.1)
Hypertension and VKA	72 (2.9)	110 (4.6)	134 (5.5)	139 (5.8)	151 (6.5)	160 (6.9)	184 (7.1)
Hypertension and platelet inhibitors	511 (20.8)	546 (22.7)	576 (23.8)	600 (25.1)	560 (24.1)	534 (22.9)	502 (19.5)
Hypertension and combinations of antithrombotic therapy	72 (2.9)	93 (3.9)	111 (4.6)	116 (4.9)	84 (3.6)	64 (2.7)	50 (1.9)
Smoking	583 (23.7)	533 (22.2)	539 (22.3)	449 (18.8)	449 (19.3)	410 (17.6)	423 (16.4)

† The exact value is not presented for reasons of discretion. ICH, intracerebral hemorrhage; NOAC, Non-vitamin K antagonists; VKA, Vitamin K antagonists

Table 3: 30-day- and 1-year mortality of patients with intracerebral hemorrhage

Follow-up	Calendar period	Mortality Risk (%)	Hazard ratio (95% confidence interval)	
			Crude	Adjusted†
0-30 days	2004/2005	32	1.00 (Ref)	1.00 (Ref)
	2006/2007	34	1.05 (0.95-1.15)	1.05 (1-1.11)
	2008/2009	33	1.01 (0.92-1.12)	1.10 (1.04-1.16)
	2010/2011	33	1.02 (0.92-1.12)	1.06 (1-1.12)
	2012/2013	30	0.92 (0.83-1.02)	1.00 (0.94-1.07)
	2014/2015	27	0.82 (0.74-0.91)	0.97 (0.91-1.04)
	2016/2017	24	0.74 (0.67-0.83)	0.94 (0.89-1.01)
0-365 days	2004/2005	43	1.00 (Ref)	1.00 (Ref)
	2006/2007	44	1.02 (0.94-1.12)	1.03 (0.98-1.08)
	2008/2009	44	1.03 (0.95-1.12)	1.09 (1.04-1.14)
	2010/2011	42	0.98 (0.90-1.07)	1.02 (0.98-1.07)
	2012/2013	41	0.95 (0.87-1.03)	1.02 (0.97-1.07)
	2014/2015	37	0.87 (0.80-0.95)	0.99 (0.93-1.04)
	2016/2017	35	0.83 (0.76-0.90)	0.98 (0.93-1.04)

† Adjusted for sex, age, hypertension, use of antithrombotic therapy, use of statins, Charlson Comorbidity Index, calendar year, previous or current history of atrial fibrillation, myocardial infarction, smoking habits, early stroke unit admission, early computed tomography/ magnetic resonance imaging scan, early assessment by physiotherapist, early assessment by occupational therapist, early nutritional risk assessment, and the Scandinavian Stroke Scale score.

FIGURES

Figure 1a: Unadjusted and age- and sex-standardized incidence rates according to admission year, 2004-2017

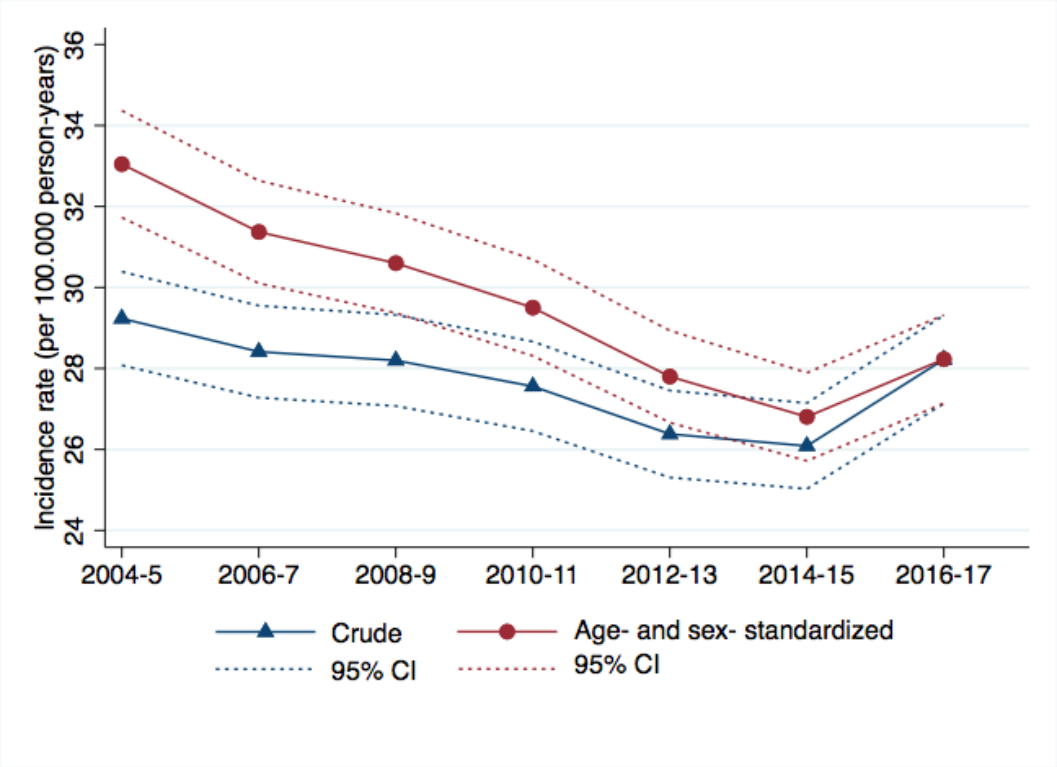
CI indicates confidence interval

Figure 1b: Age-standardized incidence rates stratified by sex according to admission year, 2004-2017

CI indicates confidence interval

Figure 1c: Sex standardized incidence rates stratified by age according to admission year, 2004-2017

CI indicates confidence interval



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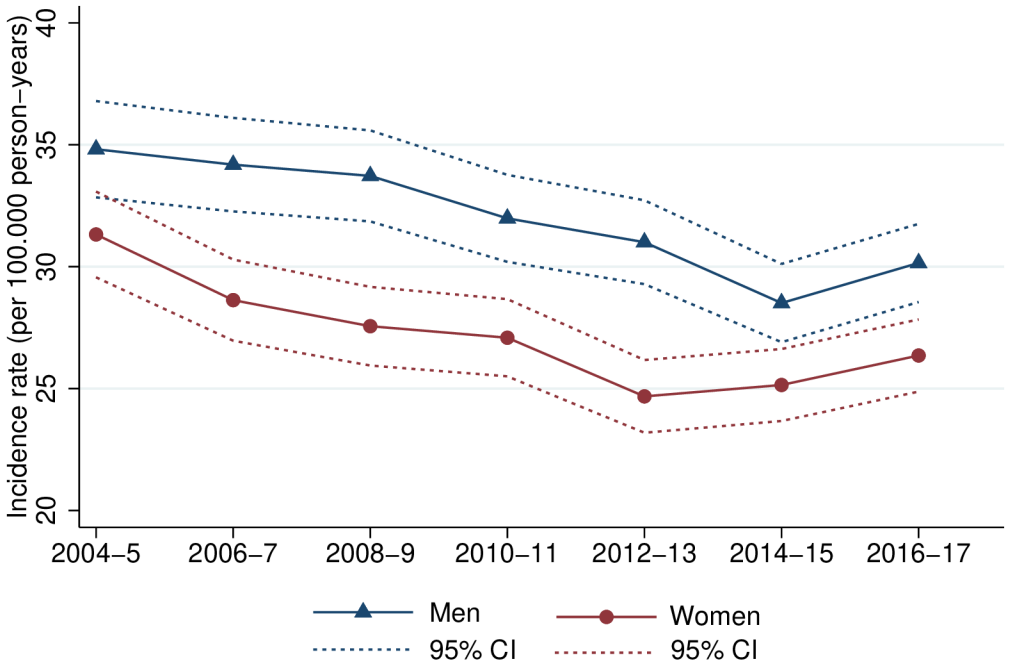

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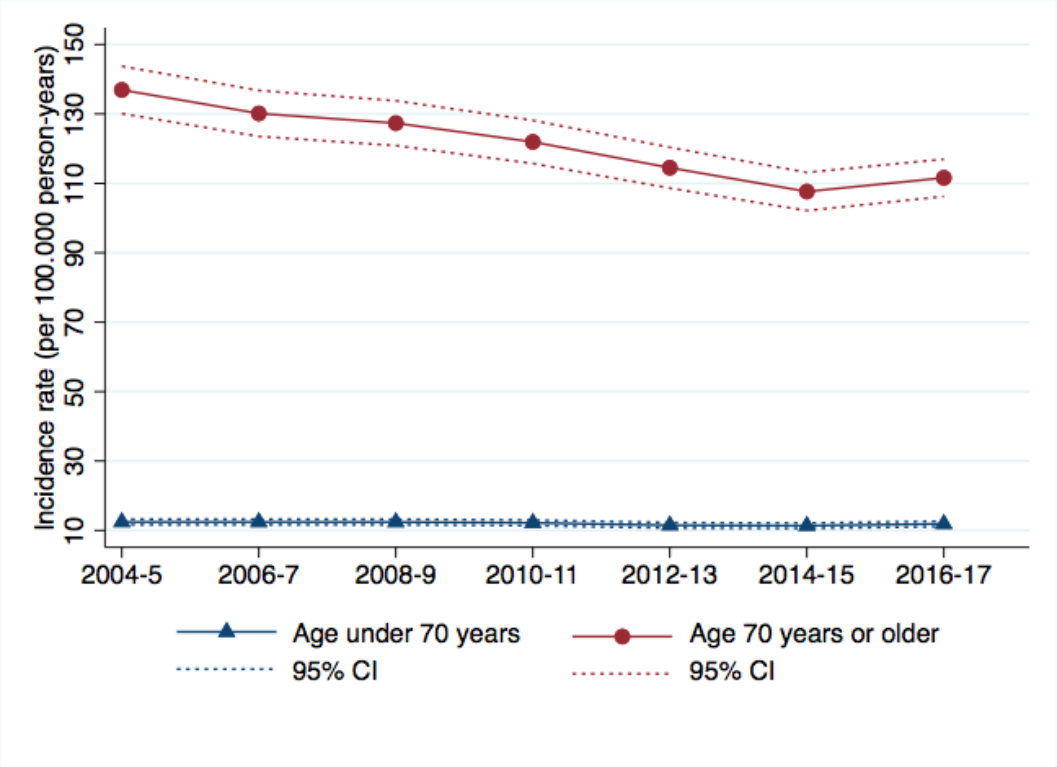

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