FACULTY OF HEALTH SCIENCE; AARHUS UNIVERSITY

Trends in intracerebral haemorrhage epidemiology in Denmark between 2004 and 2012: Incidence, risk-profile and case-fatality

Research year report

Tobias Pilgaard Ottosen

Department of Clinical Epidemiology, Aarhus University Hospital

Supervisors

Søren Paaske Johnsen, Associate Professor, MD, PhD (main supervisor)
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Grethe Andersen, Professor, MD, DMSci (co-supervisor)
Department of Neurology
Aarhus University Hospital, Denmark

Morten Schmidt, MD, PhD-student (co-supervisor)
Department of Clinical Epidemiology
Aarhus University Hospital, Denmark

Marie Louise Schmitz, MD, PhD-student (co-supervisor)
Department of Neurology
Aarhus University Hospital, Denmark

Preface

This research year report is based on a study carried out during my research year at the Department of Clinical Epidemiology and the Department of Neurology, Aarhus University Hospital, from May 2013 to April 2014. During this year, I have been introduced to epidemiology, the methods used in the field and the daily work with clinical databases.

I am sincerely thankful to my main supervisor Søren Paaske Johnsen for giving me the opportunity to experience what health research can be like. It has been great to try *hands-on* how health research is conducted and I am honored by the trust you have shown me. Thank you for letting me disturb you at any time and always giving me positive and constructive feedback. Further I want to thank you for always having me in mind and letting me in, when projects regarding my area of interest and research field have been initiated. Finally, I want to thank you for not only being my supervisor, but also being a good friend.

Also, I would like to give a great thanks to Grethe Andersen, my primary clinical supervisor, for making it all possible and for believing in me from the beginning. Further, I want to thank you for always providing constructive feedback to my work and keeping me informed and updated among the clinical aspects in my study. I also want to thank you for the opportunity and support regarding presentation of my results, both in Denmark and overseas.

I want to thank my two co-supervisors Morten Schmidt and Marie Louise Schmitz for treating me as a colleague and always paying attention to how I was doing. Thank you for your guidance and answers to my questions regardless of how simple they might have been. I am grateful to statistician Heidi Hundborg and Jacob Bonde Jacobsen for the work with the creation of my datasets, statistical supervision and the analyses they have provided. I would also like to thank my colleagues and friends at the Department of Clinical Epidemiology and the Department of Neurology, for a friendly and inspiring work environment and for the help I have received throughout the year.

Finally, my warmest thanks to my girlfriend Anna Sophie Hjerrild for her unconditional support at all times.

Tobias Pilgaard Ottosen

Funding

This study was supported by grants from:

Trygfonden through their support of the Danish Stroke Centre

My conference participation was supported by grants from

American Heart Association / American Stroke Association

Eiler og Tatianas Fond

Oticon Fonden

Fonden af 1870

Linexfonden

European Stroke Conference

Danish Stroke Centre

Abbreviations

BMI	Body Mass Index
CCI	Charlson Comorbidity Index
CI	Confidence Interval
CT	Computed Tomography
DNRP	Danish National Registry of Patients
DSR	Danish Stroke Registry
DRP	Danish National Database of Reimbursed Prescriptions
HR	Hazard Ratio
ICD	International Classification of Disease
ICH	Spontaneus (non-traumatic) Intracerebral Haemorrhage
KI	Konfidens Interval
MRI	Magnetic Resonance Imagining

Content

Extract

Introduction

Intracerebral haemorrhage (ICH) remains the leading cause of stroke mortality although only accounting for approximately 10 percent of all stroke events and ICH is subsequently the most feared subtype of stroke.[1-3]

Within the last decades, the incidence and case-fatality of ischemic stroke have decreased, whereas less is known about current trends in the epidemiology of ICH.[2,4] However, the distribution of major modifiable risk factors for cardiovascular diseases, including ICH, changes rapidly in many populations emphasizing the need for updated data.[5] Intensified focus on comprehensive hypertension treatment, introduction of massive restrictions on smoking, introduction of new potent antithrombotic drugs and the increasing proportion of elderly in many populations may potentially have major implications for the epidemiology of ICH.

We therefore conducted a population-based study to examine national trends in first-time hospitalization due to ICH, the risk profile of the patients and subsequent short-term and long-term case-fatality between 2004 and 2012 in Denmark.

Materials and methods

This study is based on national Danish registries covering the entire population (approximately 5.6 million). The Danish National Health Service provides tax-financed health care to all Danish residents and unambiguous individual-level linkage between registries is enabled by a unique 10-digit civil registration number, which is assigned to every citizen and used in all registries.[6]
The study was approved by the Danish Data Protection Agency (ID 1-16-02-226-13). According to Danish law, ethical approval is not required for registry-based studies.

Study population
We identified all Danes (≥18 years) admitted with first-time acute spontaneous (non-traumatic) ICH from January 1, 2004 to December 31, 2012. Patients with multiple strokes during the study period were included only with their first admission.

The patients were identified in the Danish Stroke Registry (DSR). The DSR is a stroke specific clinical registry and reporting is mandatory for all hospital departments in Denmark treating

patients with acute stroke.[7] Almost all patients have computed tomography (CT) or magnetic resonance imagining (MRI) scans in the acute stroke phase (97 percent of all stroke patients). The sensitivity and positive predictive value of the registration of patients in the DSR is estimated to be >90 percent.[8]

In addition, in order to explore the robustness of our findings based on DSR data, we also identified an alternative study population for supplementary analyses. The alternative population consisted of patients registered with an ICH diagnosis in the Danish National Registry of Patients (DNRP). The DNRP is a hospital discharge registry, and contains data on admission and discharge from all Danish non-psychiatric hospitals since 1977. Each hospital visit is recorded in the registry with one primary diagnosis and one or more secondary diagnosis classified according to the International Classification of Diseases, 10th revision (ICD-10).[9] The overall validity of the registration of patients with acute stroke have been found to be lower in the DNRP compared with the DSR, however, the registry may capture some patients, who are potentially not captured by the DSR (i.e., patients who are moribund upon hospital arrival and die in the emergency room).[8]

Outcomes

- *Incidence:* Incidence of first-time hospitalization for ICH, according to the year of admission was assessed using the DSR and the DNRP, respectively.
- *Risk-profile:* Included hypertension and preadmission use of antithrombotic therapy (AT) (oral anticoagulant drugs and platelet inhibitors). Data were obtained from the DSR and the Danish National Database of Reimbursed Prescriptions (DRP).

The DRP encompasses records of all reimbursed drugs sold in Denmark since 2004. Patients, who had filled a prescription within 90 days before admission, were considered current users at the time of admission. Low dose aspirin is the only drug, that can be bought over-the-counter, but patients on long-term treatment, however, usually receive low-dose aspirin on prescription in order to receive financial reimbursement.[10]

Hypertension was defined as either current use of two or more blood pressure lowering drugs (beta-blockers, calcium antagonists, angiotensin converting enzyme inhibitors, angiotensin II antagonists or diuretics, (with the exception of loop-diuretics)) or as a hypertension diagnosis recorded in the DSR at the time of admission. This definition has previously been used and validated.[11] Preadmission use of AT was defined as one or more filled prescriptions for oral anticoagulant drugs and platelet inhibitors within 90 days before hospital admission with ICH.

- *30-day and 1-year case-fatality:* Case-fatality was assessed using information from the Danish Civil Registration System. The Danish Civil Registration System keeps daily updated electronic records on change of address, date of emigration, and changes in vital status.[12]

Covariates

The information obtained at the time of admission included sex, age, smoking habits, alcohol intake, previous or current history of atrial fibrillation or myocardial infarction, diabetes mellitus, body mass index and the Scandinavian Stroke Scale (SSS) score.

The SSS score reflect the severity of stroke at admission, and ranges from 0 (come with quadriplegia) to a total of 58 (intact neurological status).[13,14] Stroke severity was classified as very severe (0-14), severe (15-29) moderate (30-45) and mild (45-58). Diabetes mellitus was defined as either use of anti-diabetic drugs according to DRP, or a recording of diabetes in the DSR. Preadmission use of lipid-lowering drugs was obtained from the DRP. Finally, we computed the Charlson comorbidity index (CCI) score for each patient based on all discharge diagnosis recorded within the last 10 years before admission with ICH.[15] Because 4 of the disease categories included in the CCI score (cerebrovascular disease, hemiplegia and diabetes with and without end organ damage) were included as independent variables in our analysis, these were excluded from the CCI score.

Information on additional covariates was obtained during the ICH hospital admission: The quality of in-hospital care was assessed using a set of the guidelines recommended processes of care including early admission to a specialized stroke unit, early examination with CT or MRI, early assessment by a physiotherapist and an occupational therapist, and early nutritional risk assessment.[16]

Statistical analysis

We obtained information on the entire Danish population at risk between 2004 and 2012 from the Danish Civil Registration System.[6] We calculated and illustrated graphically the standardized incidence rate (SIR) of first-time ICH (standardized to the age of the Danish population in the year 2012) and subsequently 30-day and 1-year case-fatality using year 2004 as reference. Confidence intervals (CI) were calculated using the approximate bootstrap method.[17,18]

We followed all the patients until date of death, emigration or one year of follow-up whichever came first. We computed 30-day and 1-year unadjusted and adjusted hazard ratios (HR) for case-fatality using a Cox proportional hazards regression model. Two multivariable models were specified: Model 1 (M-1) contained the following variables: sex, age, diabetes mellitus, hypertension, use of platelet inhibitors, oral anticoagulant, and statins, CCI score and calendar year. Model 2 (M-2) in

addition to the M-1 variables also included the following variables: previous or current history of atrial fibrillation or myocardial infarction, smoking habits, alcohol intake, body mass index, early stroke unit admission, early CT or MRI, early assessment by physiotherapist, early assessment by occupational therapist, early nutritional risk assessment and the SSS score.

We used multiple imputation to impute the missing values among the covariates assuming that data were missing at random (Stata command: mi impute). [19] We created 5 dataset on the basis of aforementioned covariates. The outcome measures were averaged across the 5 imputations correcting for between- and within-imputation variation. We repeated the analysis with creation of respectively 20 and 100 imputations, to evaluate the results.

Finally, as supplementary analyses we repeated the analyses of incidence, risk-profile and case-fatality (except for the M-2 multivariable analysis, due to lack of information on the additional variables) on the alternative study population obtained from the DNRP.

All data analyses were performed using SAS 9.2 (SAS Institute INC, Cary NC) and STATA version 12.0 (StataCorp, College Station, TX).

Results

Characteristics

For patient characteristics, please see Table 1. We identified 7,850 patients with first-time hospitalization for ICH in the DSR. The median age was 74 years and men accounted for 52 percent. There were no changes in the age or sex distribution within the period. The median SSS score was 32 points (25/75 percentile: 10/49 points) and stable throughout the period (results not shown). Characteristics of the alternative study population obtained from the DNRP used for the supplementary analyses are shown in the supplementary Table 1.

Incidence

Figure 1 shows the crude and standardized incidence rates. The average SIR within the 9 years period was 21 per 100,000 person-years (95% CI: 20-22). Overall no clear trend was observed although it should be noted that the SIR in 2004 was 21 (95% CI: 19-22) per 100,000 person-years compared to 18 (95% CI: 17-20) in 2012. The incidence among men was in general higher as compared with women, but the SIR appeared stable for both sexes within the period. The average SIR found in the supplementary analysis on the DNRP population was 38 (95% CI: 35-41) per 100,000 person-years.

Overall, the incidence in the DNRP population showed a reduction of approximately 20 percent from 2004 to 2012 (See supplementary Figure 1).

Risk-profile

The changes in the risk-profile of the patients according to the year of diagnosis can be seen in Table 2 and Figure 2. The proportion of patients having hypertension and/or receiving preadmission AT increased from 55.6 percent in 2004 to 65.7 percent in 2012.

The primary increase was seen for patients having both hypertension and receiving AT where the proportion increased by 10.0 percent points from 2004 to 2012. Among the patients having both hypertension and receiving preadmission AT, those receiving platelet inhibitors as their AT, experienced an increase from 10.3 percent in 2004 to 16.1 percent in 2012, compared to those using oral anticoagulation therapy, where the increase was from 2.2 percent to 6.5 percent. For patients only having hypertension and not receiving preadmission AT there was an increase from 25.1 percent in 2004 to 28.1 percent in 2012. The proportion of patients using AT and not having hypertension decreased from 16.1 percent to 12.3 percent, when comparing the beginning of the period with the end.

The overall trends were the same in the supplementary analysis made on the DNRP population (see supplementary Table 2 and supplementary Figure 2). The changes in the risk-profiles were in both populations in particular observed in the age groups 65-74 and 75-84 years (data not shown).

Case-fatality

The case-fatality estimates according to the year of admission can be seen in Table 3. The absolute risk of 30-day and 1-year case-fatality varied from 38 to 42 percent and 47 to 51 percent across the years, respectively. No clear overall trends in 30-day and 1-year case-fatality was found, although a lower case-fatality was noted when focusing on the last year of the study period. When comparing the 30-day case-fatality rate among patients admitted in 2011/12 with patients admitted in 2004, we found an adjusted HR of 0.86 (95% CI: 0.74-1.00) when adjusting for the limited set of covariates (M-1). The adjusted HR remained virtually unchanged (0.84, 95% CI: 0.71-0.99) when adjusting for additional covariates (M-2).

Regarding 1-year case-fatality the adjusted HR (M-1) for 2011/12 was 0.85 (95% CI: 0.75-0.98) when compared with 2004. The corresponding fully adjusted HR (M-2) was 0.87 (95% CI: 0.75-1.01).

The supplementary analysis based on the alternative study population using M-1 confirmed the pattern of decline in both 30-day and 1-year case-fatality at the end of the study period. The estimates are shown in supplementary Table 3.

Discussion

No general trend towards lower incidence of ICH and subsequent case-fatality was observed in Denmark between 2004 and 2012, although there were indications of both lower incidence and in particular case-fatality when comparing 2011/2012 with 2004. The risk profile of patients hospitalized with ICH showed substantial changes with an increasing proportion of patients with hypertension and preadmission use of AT.

In 2010 a systematic review and meta-analysis on incidence and case-fatality among ICH patients was published.[2] The authors found overall no change in the incidence of ICH between 1980 and 2008. Their findings of no improvement within the period are much in line with our results based on updated data from a national stroke specific clinical registry, although we did observe a drop in the incidence rate in the very end of our study period (2011/12). In contrast, we found a 20 percent decline in incidence in our supplementary analyses based on a study population identified from an administrative hospital discharge registry. The declining incidence rate found in the supplementary analysis could be a consequence of better diagnostic work-up of patients and reorganization of the stroke care in Denmark with centralization to dedicated stroke units leading to less misclassification of the ICH diagnosis, instead of reflecting real changes in the incidence. The incidence rate of 21 per 100.000 person years found in our primary analyses was in the same range as the overall estimate of 25 per 100,000 person-years found in the systematic review by Van Asch *et al*.[2]

The changes in the risk-profile of the ICH patients in our study were remarkable, in particular since the study period was relatively short. This is, as far as we know, the first study to address the changes in the risk-profile since the publication by Lovelock et al.[20] in 2007. In line with their findings, we also found an increasing proportion of the patients receiving AT at the time of admission. Their observation of a change in the risk-profile from the early 80'ties to the beginning of the twenty-first century, seems to further progress according to our findings (e.g., we found an almost 3-fold increase in the proportion of hypertensive ICH patients receiving oral anticoagulation therapy within a 9 year observation period). This development is a major clinical concern since AT-associated ICH is associated with poorer outcomes, including a higher mortality, compared with non-AT-associated ICH.[21,22] In our study, we observed a particular increase in the proportion with a

combination of hypertension and AT use, which may be an adverse result of the intensified effort that has been put into preventing ischemic cardiovascular disease within the last 10 years. These patients represent a particular difficult clinical challenge, due to the shared risk factors and the limited possibilities to differentiate between their hemorrhagic and ischemic risk.

Several studies have reported on the short- and long-term case-fatality associated with ICH, all concluding that there has been no decrease between 1980 and 2011.[2,23,24] Our results showed some improvements in case-fatality when comparing 2004 with 2011/12, however, the improvements were modest and did not necessarily reflect a clear trend. In any case, the absolute case-fatality rates remain disturbingly high. This is not so surprising given the fact that no major breakthrough in the treatment of acute ICH has been done, despite several promising therapies both surgical and pharmacological have been tested.[24-26] Moreover the change in the risk-profile with more AT-related cases of ICH, may also be part of the explanation for the lack of improvement in case-fatality. Thus, at the moment, the primary way of reducing the disease burden caused by ICH on the individual patient and the community level remains to ensure implementation of effective primary prevention.[2,20]

The strengths of our study included the prospective and population-based design with complete follow-up, limiting the risk of bias. Furthermore, the total number of patients included in our study (n=7850) was comparable to the total number of patients (n=8145) included from 36 studies in the review published in 2010 [2], thus by far making it the largest single study ever performed on ICH patients.

Although we included a variety of well-known confounders, and use multiple imputation to generate the missing values, we cannot exclude the possibility that our results remain influenced by confounding factors because of the observational nature of the design. Finally, we used, 30-day and 1-year case-fatality as clinical outcomes. Other outcomes, in particular functional level after discharge (e.g. modified Rankin score), are also of major interest; however, such data were not available in our study population. Regarding changes in the risk-profile and case-fatality information on the location of the haemorrhage, information on cerebral amyloid angiopathy and values of international normalised ratio among those using oral anticoagulant therapy and information about the level of hypertension, would have been of interest, but unfortunately these data were unavailable.

Conclusion

In conclusion, despite intensified focus on prevention and early stroke care, no general trend towards lower incidence of ICH and subsequently short- and long-term case-fatality was observed in Denmark between 2004 and 2012. Together with a continuously increasing proportion of ICH patients with hypertension and preadmission use of AT, this underlines that ICH remains a major clinical challenge.

Dansk resumé

Baggrund og formål

Den epidemiologiske viden omkring patienter med intracerebrale blødninger (ICH) er kun blevet adresseret i ganske få studier det sidste årti. Distributionen af betydningsfulde risikofaktorer såsom rygning, forhøjet blodtryk og brugen af blodfortyndende behandling, har imidlertid ændret sig meget i den udviklede verden, og der er derfor behov for en opdatering af vores viden omkring patienter med ICH. Vi undersøgte udviklingstendenser i forekomsten af førstegangsindlæggelser, risiko-profilen samt dødeligheden blandt patienter med ICH i Danmark i perioden 2004 til 2012.

Metoder

Baseret på en række danske registre udførte vi et landsdækkende populationsbaseret studie. Patienterne blev identificeret i Dansk Apopleksi Register (DSR) og i Landspatientsregisteret (DNRP). Vi udregnede en alders-justeret standardiseret incidensrate (SIR) og estimerede en hazard ratio (HR) for 30-dags og 1-års dødeligheden under anvendelse af Cox regressionsmodel, med justering for velkendte risikofaktorer og med år 2004 som reference.

Resultater

Vi fandt 7.850 førstegangspatienter. SIR i 2004 og 2012 var henholdsvis 21 (95% CI: 19-22) og 18 (95% CI: 17-20) pr 100.000 person-år. Andelen af patienter med forhøjet blodtryk og/eller brug af blodfortyndende behandling før indlæggelsen steg fra 56 procent til 66 procent mellem 2004 og 2012. Den gennemsnitlige dødelighed efter 30-dage og 1 år var henholdsvis 31 procent og 40 procent. Den justerede HR for 30-dages og 1-års dødelighed var 0,86 (0,74-1,00) og 0,85 (0,75-0,98), når man sammenlignede 2011/12 med 2004.

Konklusion

Trods intensiveret fokus på forebyggelse og tidlig behandling af apopleksi patienter i Danmark gennem de seneste år er forekomsten af førstegangs ICH hospitaliseringer samt den efterfølgende korttids- og langtidsdødelighed uforandret. Imidlertid har risiko-profilen af ICH patienter ændret sig betydeligt, med en stigende andel der har forhøjet blodtryk og/eller modtog blodfortyndende behandling på indlæggelsestidspunktet, hvilket udgør en stor klinisk udfordring.

English summary

Background and Purpose

The distribution of major modifiable risk factors, particularly hypertension, smoking, and use of antithrombotic medications, changes rapidly in most populations, emphasizing the need for updated data on intracerebral haemorrhage (ICH) epidemiology. We examined trends in incidence and risk-profile of first-time hospitalization due to ICH and subsequent case-fatality in Denmark between 2004 and 2012.

Methods

Based on Danish medical registries we performed a nationwide population-based study. Age-adjusted standardized incidence rates (SIR) were calculated, and Cox regression was used to estimate the hazard ratio (HR) of death according to year of admission adjusted for potential confounding factors using 2004 as reference.

Results

We identified 7,850 incident patients. The SIRs in 2004 and 2012 were 21 (95% CI: 19-22) and 18 (95% CI: 17-20) per 100,000 person-years, respectively. The proportion of patients with hypertension and/or receiving antithrombotic therapy prior to their ICH increased from 56 percent to 66 percent between 2004 and 2012. The average 30-day and 1-year case-fatality was 31 percent and 40 percent, respectively. The adjusted HRs for 30-day and 1-year case-fatality were 0.86 (95% CI: 0.74-1.00) and 0.85 (95% CI: 0.75-0.98) when comparing 2011/12 with 2004.

Conclusions

Despite intensified focus on prevention and early stroke care in Denmark within recent years, both the incidence of first-time ICH hospitalizations and the subsequently short- and long-term case-fatality, have remained stable. However, the risk-profile of the patients have changed substantially with an increasing proportion of patients having hypertension and/or receiving antithrombotic therapy at the time of the ICH, which constitutes a major clinical challenge.

Supplementary information

This supplementary section provides additional information on the epidemiology of ICH including the risk-factors influencing this disease. This is followed by a presentation and discussion of some of the methodological considerations accompanying this study. In addition some of the supplementary analyses results are presented and finally a discussion of the results of this report and the clinical perspectives are provided.

Introduction

Stroke and intracerebral haemorrhage

Stroke is the second leading cause of dead worldwide and the main cause of long-term neurological disability in adults.[5] The two principal categories of stroke, ischemic and hemorrhagic, are in some ways opposite conditions. Ischemic stroke is characterized by too little blood to supply an adequate amount of oxygen and nutrients to a part of the brain, while hemorrhagic stroke is characterized by blood within the closed brain cavity. Each of these categories can be divided into subtypes that have somewhat different cause, clinical pictures, clinical courses, outcomes, and treatments strategies. This study focused on the hemorrhagic subtype spontaneous (non-traumatic) ICH, which involves bleeding directly into the brain tissue.[27]

ICH is the second most common cause of stroke and accounts for approximately 1 of 10 stroke episodes in Western societies.[4,28-30] The incidence of ICH, has in different studies, been reported to have both increased, decreased or stagnated during the last four decades.[2] The overall incidence of ICH has been reported to range from 12 to 31 per 100.000 person-years with highest rate of occurrence in Asians, intermediate in blacks and lowest in whites. [2,30]

The main risk-factors for development of ICH are hypertension, cerebral amyloid angiopathy (CAA) and use of antithrombotic therapy (AT). Hypertension is estimated to account for 50 percent of all cases of ICH [31,32], whereas use of antithrombotic therapy alone is estimated to account for 10 to 12 percent of all ICH events.[33]

Data from the United Kingdom suggests that the incidence of hypertensive ICH has declined since the early 1980s with improved control of hypertension, but the overall rates of ICH have remained stable, in part due to an increase in ICH associated with AT.[20] Aside from the UK data, very little is known about this possible change in the risk profile of the ICH patients, but in most Western

societies, the use of both antihypertensive and especially AT have increased within the last decades [34].

ICH is a disease with an extremely high morbidity and mortality rate, where about 35-52 percent of the patients die within the first 30-days after hospitalization and only about 12-39 percent of the discharged patients gain independent function after the event. [2,28,33,35] A systematic review and meta-analysis newly summarized data from the last three decades concerning patients with primary ICH, and concluded that the long-term survival did not appear to have changed within that time period.[23]

Whether the finding of lack of improvement in incidence and case-fatality for ICH patients is the same in updated data is unknown. Finally, whether there might have been a change in the risk-profile of ICH patients has not been investigated elsewhere since the publication from the United Kingdom in 2007.[20]

Methods

DSR versus DNRP

As described in the article extract of this report, patients with first-time hospitalization due to ICH were identified in a stroke-specific clinical registry, the DSR, and a hospital discharge registry, the DNRP. The purposes for using both registries was to identify possible differences in incidence and short- and long-term case-fatality of ICH between the patient populations identified from the different registries in an attempt to assess the possible risk of selection bias due to potential underreporting/misclassification.

The validity of a stroke diagnosis in the DSR and the DNRP have recently been reported.[8] The aim of the present study was not to validate the diagnosis of the ICH subtype of stroke, but to characterize the differences between the registries, and the hospital department destination for patients occurring in only one of the registries. In the ideal world, all patients registered as ICH patients in the DSR would also be found as ICH patients in the DNRP. However, in reality some patients were only registered in the DSR and vice versa.

Multiple imputation

The DSR is a stroke specific clinical registry, and the reporting is done by the relevant health personal treating the patient. As always, work done by human can be influenced by errors, failure to interpret the instructions for fulfilling the registration form, lack of knowledge about the patient regarding a specified area, or other reasons. In this case it would lead to that some of the registrations boxes are

left unanswered, leading to missing information. Missing information in this type of health registries is common, and needs to be handled appropriately, to reduce the influence on the analysis of the data.

To address the problem with missing data, researchers can choose only to include individuals with complete information on all study covariates. In this case the DSR population would then be reduced to include only 2,628 patients instead of 7,850. This method of analysis is referred to as complete case analysis; however, this method may lead to bias and to exclusion of a substantial proportion of the study population. At the end the loss of study outcomes may lead to loss of precision and power.[19]

Another way to address the problem with missing data is to use multiple imputation. Multiple imputation is a statistical technique designed to take advantage of the flexibility in modern computing to handle missing data. Multiple imputation consists of three steps [36]:

Imputation step: Multiple copies of the initial dataset are created and in our case we made respectively, 5, 20 and 100 datasets. Each missing value is then replaced with a set of plausible values, based on the other known characteristics of the patient and based on other individuals with the observed value. It is necessary to create 2 or more (often 5-20) datasets to reflect the uncertainty within the predicted values. By doing this the imputation procedure account for all uncertainty in predicting the missing values, by injecting appropriate variability into the multiple imputed values. The true value of the missing data can never be known, it can only be approximated by statistical methods based on the predictive variables.[19,37]

Completed-data analysis: Each imputed dataset is then analyzed using standard analytical techniques (in our case done by Cox regression). The estimates will differ in each of the imputed datasets, due to the variation introduced in the imputation of the missing values, and become only useful when averaged together to give overall estimated associations.[36]

Pooling step: The estimates are combined to obtain the overall risk estimates, variances and confidence intervals using Rubin's rules, incorporation both within-imputation variability and between-imputation variability.[19,36]

In order to use multiple imputation it is necessary to make the assumption that data were missing at random, meaning that the probability that a value is missing depends only on observed values and not on unobserved values. As an example from this database, it is not expected that patients missing a score regarding their severity of stroke do this, because of the unmeasured value of the score. This assumption is necessary to make because the imputation method require that the missing-data mechanism is ignorable, meaning that the process that causes missing data can be ignored. This

assumption cannot be tested directly, but rather approximated by including a relevant and sufficient set of predictive variables into the imputation model. It is sensible to include a wide range of variables in the imputation model and all the covariates used in an analysis model must be included to avoid bias.[37] The imputation model should include variables that are correlated to the imputed variable, variables that are associated with the missingness of the imputed variable, and outcomes variables.[37] The analysis were performed using multiple imputation by chained equations (the STATA "mi impute chained" command).[36,37]

The following covariates in the DSR population had missing values:

Covariate	*n, (percent of total population)*
BMI group	3,774 (48.1%)
Smoking status	2,621 (33.4%)
Alcohol consumption	2,204 (28.1%)
Severity of stroke	1,323 (16.9%)
Previous MI	916 (11.7%)
Atrial fibrillation	776 (9.9%)

As seen in the table above some of the covariates had a high proportion of missing values. Multiple imputation allows a high proportion of missing data when making a suitable model.[36]

The following table shows the number of missing covariate values per individual and the number of individuals having this specific number.

Number of missing values per individual	*n, (percentage of study population)*
0	2,628 (33.5%)
1	2,199 (28.0%)
2	1,172 (14.9%)
3	974 (12.4%)
4	413 (5.2%)
5	287 (3.7%)
6	177 (2.3%)

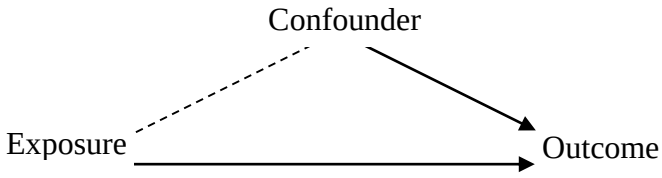
As showed above 6 covariates contained missing values. As it also can be seen, only a minority of the patients were missing more than 3 values at all. The following variables was therefore imputed*: BMI group, smoking status, alcohol consumption, severity of stroke, previous MI and atrial fibrillation*, using the following set of predictive variables: *sex, age group, smoking status, alcohol consumption, severity of stroke, previous MI and atrial fibrillation, body mass index, diabetes mellitus, hypertension, platelet inhibitors, anticoagulants, statins, early admission to a specialized stroke unit, early examination with CT or MRI, early assessment by a physiotherapist, early assessment by occupational therapist, early nutritional risk assessment , CCI score, admission year and case-fatality.*

Confounding

Confounding is defined as the confusion of effects. This definition implies that the effect of the exposure is mixed with the effect of another variable, leading to bias. When determining whether a variable is a confounder three criteria must be fulfilled:[38,39]

1) The variable must not be an effect of the exposure (not on the causal pathway between exposure and outcome).
2) The variable must be independently associated with the outcome as a cause (or as a proxy), but not as an effect of the outcome.
3) The variable must be associated with the exposure variable and imbalanced across exposure categories.

This relationship between exposure, confounder and outcome is illustrated below, in what is known to be the confounder-triangle.[38]



There are different types of confounding; residual confounding, unknown confounding, unmeasured confounding and confounding measured and adjusted for.

Residual confounding arises when a variable you have chosen to control for, is divided into broad categories. In this study an example of a covariate with possible residual confounding could be hypertension. It is known that the degree of hypertension is important, when characterizing the

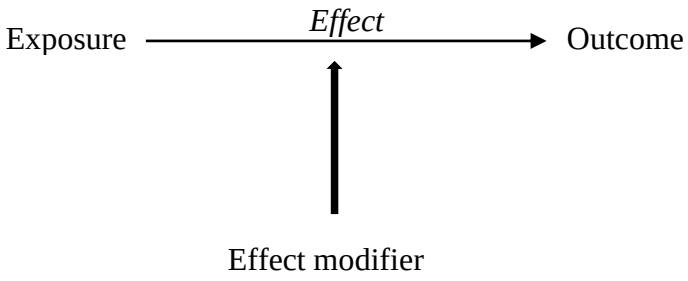
influence on case-fatality, but unfortunately the databases lack information about the specific blood pressure. Thereby hypertension becomes a proxy for the level of blood pressure, and includes some residual confounding do to the lack of level stratification. Normally it can be desirable to divide the data into more categories so that within category variance is diminished, to avoid residual confounding. However, dividing a variable into too many categories may result in too few events within each category and hence imprecise estimates.

Unknown confounding is due to not identified confounding variables, with lack of knowledge about. Unmeasured confounding is present when an identified confounder variable lacks information, making it impossible to adjust for. This is one of the reasons, that this study attach more attention to the results of DSR analysis than to the DNRP analysis, because the current knowledge about the influence of risk-factors, such as smoking, alcohol consumption, BMI and severity of stroke, on mortality, tell us, that when adjusting for these risk-factors, the estimates more accurately reflect the true value.[38,39]

In general confounding can be controlled in two different ways, either by the study design (restriction, matching or randomization) or by the analysis (standardization, stratification, or adjustment). Exploring the research aim of this study, confounding was chosen to be controlled for by multivariable adjustment in the regression analysis. By doing this, the arrow from the confounder to the outcome was removed by controlling for the effect of each confounder on the outcome. The inclusion of several variables results in a model in which each term is unconfounded by other terms in the model [39]. The analyses were adjusted for the following covariates in two different models, as specified in the article extract: *sex, age group, smoking status, alcohol consumption, severity of stroke, previous MI and atrial fibrillation, body mass index, diabetes mellitus, hypertension, platelet inhibitors, anticoagulants, statins, early admission to a specialized stroke unit, early examination with CT or MRI, early assessment by a physiotherapist, early assessment by occupational therapist, early nutritional risk assessment , CCI score and admission year.*

Effect measure modification

Effect measure modification is a situation in which another factor modifies the association between exposure and outcome. The term “measure” is included to emphasize the dependence of this phenomenon on the choice of effect measure. One cannot speak about effect measure modification without being specific about the details in the choice of effect measure. Effect measure modification is illustrated below:[38,39]



Effect measure modification is present when the exposure-outcome relationship differs within different levels of a variable which acts as an effect modifier. Hypertension and preadmission use of antithrombotic therapy was in this study investigated as possible effect modifications on the association between admission year with ICH and death. Additional analysis, restricting the population to patients with and without hypertension and preadmission use of AT, was therefore made.

Additional results

DSR versus DNRP

Merging the population from the DSR database together with the population from the DNRP database revealed 1,210 patients only to be found in the DSR, 6,753 patients only to found in the DNRP and 6,640 patients to be found in both registries. (See supplementary Figure 3)

Supplementary Table 4 shows the characteristics of the patients when dividing them according to whether they occurred in only one or both of the registries. As it can be seen in the supplementary Table 4, the number of patients only to be registered in DSR decreased from 167 in 2004 to 78 in 2012. In comparison the number of patients only to be registered in DNRP decreased from 942 to 724 within the same years, respectively. Otherwise, no major differences in the characteristics of the patients were found.

Regarding the destination for ICH patients when hospitalized, there were some differences in the pattern of departments receiving them. For the 6,753 patients only represented in the DNRP, 8 internal medicine, 5 neurosurgical and 4 neurological departments, accounted for handling 50 percent of these patients. For the 1,210 patients only to be registered in the DSR, 3 internal medicine and 6 neurological departments was accountable for handling 50 percent of the patients. All of these departments had a frequency above 80 patients within the period. The remaining

departments reporting to have hospitalized ICH patients had a cumulative frequency below 80 patients within the 9 years included, and most of them were internal medicine departments (Data not shown).

The results of the incidence, risk-profile and case-fatality analysis on the DNRP population have already been addressed in the article extract, and the results can be seen in the supplementary tables, but will not be further presented here.

The results of the case-fatality analysis on the DSR population using multiple imputation to take care of missing values, is included in the article extract as Table 2. The supplementary Table 5 shows the case-fatality rate according to the year of admission with 5, 20 and 100 imputations, respectively. To summarize the results of this comparison there were no differences in the case-fatality rate, when using 5, 20 or 100 imputations.

When restricting the case-fatality rate analysis to patients with and without hypertension, in the additional analysis of possible effect measure modification, the risk estimates for both 30-day and 1-year case-fatality was higher for patients receiving AT and having hypertension, compared to those without hypertension. As an example patients with hypertension receiving oral anticoagulant treatment had an adjusted HR of 30-day case fatality of 1.65 (95% CI: 1.38-1.97) compared to patients without hypertension and use of oral anticoagulant treatment. The corresponding adjusted HR for patients without hypertension using oral anticoagulant treatment was 1.39 (95% CI: 1.14-1.69). (Remaining results not shown)

Discussion

Strengths and limitations

The strengths of this study include the large study population consisting solely of spontaneous (non-traumatic) ICH patients. The equal access to health care provided to all Danish citizens minimized the risk of selection bias. Lack of information on non-hospitalized patients with ICH, including patients who died before reaching a hospital, could at least theoretically introduce selection bias, especially when characterizing the risk-profile of the patients and analyzing the influence of AT and hypertension on case-fatality, if patients with use of AT and/or hypertension were more (or less) likely not to be hospitalized when compared with those without hypertension and preadmission AT use. However, only few patients with stroke die early after start of symptoms, and there is a long tradition in Denmark for admitting almost all patients with acute stroke to hospital.[40] Further, as

described previously the inclusion of the two independent registries was also done to minimize the risk of selection bias.

Even though all this was done to ensure that all eligible patients were included, it is important to remember that our findings only reflect the incidence, risk-profile and case-fatality of patients with first-time hospitalization due to ICH and not the incidence rate of the disease or the risk-profile and case-fatality for all ICH patients.

Patients were identified using their diagnosis in DSR and DNRP, respectively. The diagnosis of the patients were defined by ICD-10 codes and coded as I61 in both registries. As described earlier, work done by human can be influenced by error. The diagnosis itself is not the disease, but an indicator of an assessment of the patient's illness.[38] This clinical assessment was at the clinical discretion of physicians and consequently can hold some misclassification. The differences between the registries included are important to note in this context. In the DSR the physician admitting the patient is the one to register the diagnosis, whereas it often is an unspecified physician that discharge the patient and obtain the diagnosis in the DNRP. Moreover, the DSR is restricted to specialized stroke units, typically with a high flow of ICH patients, making them experts in correct classification of this disease. In the DNRP all hospital departments are included, making the likelihood of misdiagnosis of ICH, more suspicious.

As described in the article extract the validity of the stroke diagnosis in the DSR and DNRP has recently been reported.[8] It was found that the sensitivity of the stroke diagnosis in DSR was 97 percent compared to 79 percent in DNRP and the positive predictive value was 90 percent in DSR compared to 79 percent in DNRP. This indicate that the completeness of our study population was high and that few false positive patients most likely were encountered in the DSR.

Although this study included detailed information about the patients and used multiple imputation to generate estimates, as close to the true value as possible, the possibility that the results remain influenced by confounding factors because of the observational nature of the study design cannot be excluded.

Clinical perspective

This study improves our knowledge regarding first-time hospitalized ICH patients in Denmark overall. The results are useful in several ways, as described in the following.

First, the difference in the population size between the registries, clarify the huge difference between a stroke specific clinical registry and a hospital discharge registry. The finding of ICH patients not to be registered in the DSR, but only in the DNRP, and especially the size of this

proportion of patients, clarify that our pre- and in-hospital identification of these patients can be improved. The current setting of acute stroke care in Denmark is constructed in such way, that patients with diffuse symptoms and blurred consciousness might be admitted to an emergency department, an internal medicine department or a neurosurgical department. Anyhow, stroke patients should be admitted to the specialized stroke units to guarantee guideline recommended treatment to this type of patients, and thereby optimize their hospitalization. If patients are admitted to e.g. an emergency department and then afterwards transferred to a specialized stroke unit, they would normally also be registered in the DSR, but according to our results, a substantial proportion of these patients seems never to reach a specialized stroke unit. Even though, as discussed in the article extract, some of this difference can be explained by misdiagnosis in the DNRP, further efforts seemed warranted to insure and improve, that ICH patients end up at a specialized stroke unit when hospitalized.

Secondly, our finding of no clear trend in improvement of incidence and case-fatality among ICH patients, points out the importance for further development of preventive strategies and treatment regimens to this specific patient group. The results also point out, that the reorganization of the stroke treatment within the recent years, have not yet had the same positive influence on ICH patients as seen among the ischemic patients, where both case-fatality and functional outcome have been improved.[35]

Thirdly, the changes in the risk-profile of the ICH patients that we found within the 9 year period, underlines the importance of being able to differentiate between patients who will, and will not, benefit from AT. The current scoring systems to determine whether patients with indication for AT patients are candidates for e.g. oral anticoagulant treatment (i.e. the CHA_2-DS_2-VASc score[41] to estimate the risk of stroke or systemic embolism, and the HAS-BLEED score[42] to estimate the risk of bleeding) are based on many identical risk factors, which makes it difficult to weight the value of these opposing systems against each other. To ensure that the thrombus versus haemorrhagic risk is balanced for every patient before prescription of AT drugs, we may well need to improve the available tools to identify the patients who will definitely not benefit from AT due to their risk of bleeding and make them easier to use in the clinical practice.

Overall, the results of this research project have clarified that there is much more work to be done within the research field of ICH, in order to reduce the incidence and to improve the outcome of the patients, especially when taking into account the progressive change in the risk-profile that we have observed.

Conclusion

In conclusion, this report found that despite intensified focus on prevention strategies and early in-hospital management of stroke within recent years, no improvements in incidence and case-fatality among ICH patients have been seen. Further the examination of this 9 year period revealed a substantial change in the risk-profile of ICH patients, with an increasing proportion having hypertension and receiving preadmission AT. This calls for further research into this specific group of patients, to manage the everyday challenge of handling ICH patients.

Tables and figures

Tables

Table 1. Characteristics of ICH patients in the DSR, n (%)

Characteristics	DSR (n=7850)
Age, mean (SD) (median)	71.52 (13.8) (73.85)
Age, distribution	
<35	99 (1.26)
35-44	235 (2.99)
45-54	694 (8.84)
55-64	1349 (17.18)
65-74	1810 (23.06)
75-84	2397 (30.54)
≥85	1266 (16.13)
Sex	
Men	3793 (51.68)
Comorbidity	
Hypertension	3831 (48.80)
Previous Myocardial Infarction	466 (5.94)
Diabetes Mellitus	807 (10.28)
Atrial Fibrillation	1062 (13.53)
Charlson comorbidity index	
No comorbidity, 0	4982 (63.46)
Moderate comorbidity, 1-2	2598 (33.10)
Severe comorbidity, ≥3	270 (3.44)
Body Mass Index, mean (SD)	25.25 (5.16)
Body Mass Index, distribution	
<18.5	257 (3.27)
18.5-<25	1894 (24.13)
≥25	1925 (24.52)
Missing	3774 (48.08)
Drinks per week	
≤14 women/≤21 for men	4952 (63.08)
>14 women/>21 for men	694 (8.84)
Missing	2204 (28.08)
Smoking	
Daily	1715 (21.85)
Former	1312 (16.71)
Never	2202 (28.05)
Missing	2621 (33.39)
Early nutritional risk assessment	
Not relevant	2888 (36.79)
Yes	3094 (39.41)
No	1868 (23.80)
Early occupational therapist assessment	

Not relevant	2839 (36.17)
Yes	3139 (39.99)
No	1872 (23.85)
Early physiotherapist assessment	
Not relevant	2850 (36.31)
Yes	3271 (41.67)
No	1729 (22.03)
Early CT or MRI	
Not relevant	166 (2.11)
Yes	6107 (77.80)
No	1577 (20.09)
Early stroke unit admission	
Not relevant	378 (4.82)
Yes	6442 (82.06)
No	1030 (13.12)
Antihypertensive drugs	1631 (20.78)
Antithrombotic therapy	
Oral anticoagulant treatment	827 (10.54)
Platelet inhibitors	2405 (30.64)
Lipid-lowering drugs	1096 (13.96)
Antidiabetic drugs	561 (7.15)
Scandinavian Stroke Scale Score	
45-58 point	2184 (27.82)
30-44 point	1248 (15.90)
15-29 point	1111 (14.15)
0-15 point	1984 (25.27)
missing	1323 (16.85)
Year of admission	
2004	824 (10.50)
2005	846 (10.78)
2006	866 (11.03)
2007	849 (10.82)
2008	859 (10.94)
2009	964 (12.28)
2010	924 (11.77)
2011	913 (11.63)
2012	805 (10.25)

ICH indicates intracerebral hemorrhage, DSR, Danish Stroke Registry.

Table 2. Changes in the risk-profile of patients with ICH. n, (%)

	2004	2005	2006	2007	2008	2009	2010	2011	2012
ICH events	824	846	866	849	859	964	924	913	805
No hypertension or use of antithrombotic therapy	366 (44.4)	348 (41.1)	333 (38.5)	304 (35.8)	265 (30.8)	326 (33.8)	288 (31.2)	299 (32.7)	276 (34.3)
Hypertension alone	207 (25.1)	200 (23.6)	248 (28.6)	223 (26.3)	246 (28.6)	268 (27.8)	271 (29.3)	237 (26.0)	226 (28.1)
Antithrombotic therapy alone	133 (16.1)	154 (18.2)	134 (15.5)	134 (15.8)	129 (15.0)	159 (16.5)	140 (15.2)	132 (14.5)	99 (12.3)
Anticoagulantia alone	13 (1.6)	22 (2.6)	25 (2.9)	18 (2.1)	19 (2.2)	30 (3.1)	17 (1.8)	22 (2.4)	13 (1.6)
Platelet inhibitors alone	111 (13.5)	125 (14.8)	101 (11.7)	105 (12.4)	97 (11.3)	112 (11.6)	112 (12.1)	106 (11.6)	73 (9.1)
Hypertension and antithrombotic therapy	118 (14.3)	144 (17.0)	151 (17.4)	188 (22.1)	219 (25.5)	211 (21.9)	225 (24.4)	245 (26.8)	204 (25.3)
Hypertension+OAC	18 (2.2)	25 (3.0)	36 (4.2)	33 (3.9)	38 (4.4)	45 (4.7)	42 (4.5)	46 (5.0)	52 (6.5)
Hypertension+platelet inhibitors	85 (10.3)	104 (12.3)	97 (11.2)	124 (14.6)	149 (17.3)	144 (14.9)	150 (16.2)	167 (18.3)	130 (16.1)
Hypertension+OAC+platelet inhibitors	15 (1.8)	15 (1.8)	18 (2.1)	31 (3.7)	32 (3.7)	22 (2.3)	33 (3.6)	32 (3.5)	22 (2.7)

OAT represents oral anticoagulant treatment, DSR, Danish Stroke Registry, ICH, intracerebral hemorrhage.

Table 3. Absolute risk, crude and mutually adjusted hazard ratios of 30-day and 1-year case-fatality among ICH patients.

	Year-groups	Absolute risk (%)	Crude HRs (95% CI)	Adjusted HRs M-1 (95% CI)	Adjusted HRs M-2 (95% CI)
0-30 days	2004	37.98	1.00	1.00	1.00
	2005/2006	42.30	1.11 (0.96-1.29)	1.06 (0.92-1.23)	0.96 (0.82-1.13)
	2007/2008	37.62	0.95 (0.82-1.11)	0.91 (0.78-1.06)	0.92 (0.79-1.09)
	2009/2010	42.02	1.03 (0.89-1.20)	0.98 (0.84-1.13)	1.00 (0.85-1.17)
	2011/2012	38.84	0.92 (0.79-1.07)	0.86 (0.74-1.00)	0.84 (0.71-0.99)
0-365 days	2004	46.86	1.00	1.00	1.00
	2005/2006	51.16	1.11 (0.97-1.26)	1.06 (0.93-1.21)	0.99 (0.86-1.14)
	2007/2008	47.83	0.99 (0.87-1.13)	0.96 (0.84-1.09)	0.99 (0.86-1.14)
	2009/2010	51.26	1.05 (0.92-1.20)	1.00 (0.88-1.14)	1.05 (0.92-1.21)
	2011/2012	47.11	0.91 (0.80-1.04)	0.85 (0.75-0.98)	0.87 (0.75-1.01)

CI indicates confidence interval, HRs, hazards ratios, M-1, multivariable model 1, M-2, multivariable model 2.

Supplementary Table 1. Characteristics of ICH patients obtained from the DNRP.

Characteristics	DNRP (n=13393)
Age, mean (SD) (median)	69.61 (15.4) (72)
Age, distribution, n (%)	
<35	355 (2.65)
35-44	614 (4.58)
45-54	1392 (10.39)
55-64	2424 (18.10)
65-74	3142 (23.46)
75-84	3638 (27.16)
≥85	1828 (13.65)
Sex, n (%)	
Men	6903 (51.54)
Charlson Comorbidity index, n (%)	
No comorbidity, 0	8155 (60.89)
Moderate comorbidity, 1-2	4713 (35.19)
Severe comorbidity, ≥3	525 (3.92)
Antihypertensive drug, n (%)	2847 (21.26)
Antithrombotic therapy, n (%)	
Oral anticoagulant treatment, n (%)	1336 (9.98)
Platelet inhibitors	4173 (31.16)
Lipid-lowering drugs, n (%)	1853 (13.84)
Antidiabetic drugs, n (%)	986 (7.36)
Year of admission, n (%)	
2004	1600 (11.95)
2005	1566 (11.69)
2006	1502 (11.21)
2007	1483 (11.07)
2008	1436 (10.72)
2009	1480 (11.05)
2010	1465 (10.94)
2011	1412 (10.54)
2012	1449 (10.82)

ICH indicates intracerebral hemorrhage, DNRP, Danish National Registry of Patients.

Supplementary table 2. Changes in the risk-profile of patients with ICH, obtained by the DNRP population. n, (%)

	2004	2005	2006	2007	2008	2009	2010	2011	2012
ICH events	1600	1566	1502	1483	1436	1480	1465	1412	1449
No hypertension or use of antithrombotic therapy	845 (52.8)	778 (49.7)	691 (46.0)	645 (43.5)	645 (44.9)	656 (44.3)	612 (41.8)	608 (43.1)	626 (43.2)
Hypertension alone	262 (16.4)	255 (16.3)	278 (18.5)	263 (17.7)	230 (16.0)	252 (17.0)	263 (18.0)	228 (16.1)	245 (16.9)
Antithrombotic therapy alone	237 (14.8)	249 (15.9)	245 (16.3)	234 (15.8)	211 (14.7)	231 (15.6)	222 (15.2)	224 (15.9)	185 (12.8)
Anticoagulantia alone	20 (1.3)	28 (1.8)	36 (2.4)	22 (1.5)	25 (1.7)	25 (1.7)	26 (1.8)	32 (2.3)	28 (1.9)
Platelet inhibitors alone	212 (13.3)	213 (13.6)	203 (13.5)	199 (13.4)	181 (12.6)	199 (13.4)	187 (12.8)	176 (12.5)	144 (9.9)
Hypertension and antithrombotic therapy	256 (16.0)	284 (18.1)	288 (19.2)	341 (23.0)	350 (24.4)	341 (23.0)	368 (25.1)	352 (24.9)	393 (27.1)
Hypertension+OAC	40 (2.5)	52 (3.3)	58 (3.9)	71 (4.8)	72 (5.0)	71 (4.8)	65 (4.4)	71 (5.0)	97 (6.7)
Hypertension+platelet inhibitors	177 (11.1)	193 (12.3)	194 (12.9)	225 (15.2)	222 (15.5)	227 (15.3)	245 (16.7)	243 (17.2)	244 (16.8)
Hypertension+OAC+platelet inhibitors	39 (2.4)	39 (2.5)	36 (2.4)	45 (3.0)	56 (3.9)	43 (2.9)	59 (4.0)	47 (3.3)	52 (3.6)

OAT represents oral anticoagulant treatment, DSR, Danish Stroke Registry, ICH, intracerebral hemorrhage.

Supplementary Table 3. Absolute risk, crude and mutually adjusted hazard ratios of 30-day and 1-year case-fatality among ICH patients, obtained from the DNRP.

	Year-groups	Absolute risk (%)	Crude HRs (95% CI)	Adjusted HRs M-1 (95% CI)
0-30 days	2004	37.31	1.00	1.00
	2005/2006	36.70	0.98 (0.89-1.08)	0.93 (0.85-1.03)
	2007/2008	34.46	0.91 (0.82-1.00)	0.86 (0.78-0.95)
	2009/2010	34.13	0.90 (0.81-0.99)	0.84 (0.76-0.93)
	2011/2012	31.67	0.82 (0.74-0.91)	0.75 (0.67-0.83)
0-365 days	2004	46.94	1.00	1.00
	2005/2006	45.93	0.97 (0.89-1.06)	0.93 (0.85-1.02)
	2007/2008	44.74	0.93 (0.85-1.02)	0.89 (0.81-0.98)
	2009/2010	44.11	0.91 (0.84-1.00)	0.86 (0.79-0.94)
	2011/2012	39.11	0.83 (0.76-0.91)	0.76 (0.69-0.83)

CI indicates confidence interval, HRs, hazards ratios, M-1, multivariable model 1, DNRP, Danish National Registry of Patients.

Supplementary Table 4. Characteristics of ICH patients according their appearance in the DSR and DNRP

Characteristics	DSR (n=1210)		DSR+DNRP (n=6640)		DNRP (n=6753)	
Age, mean (SD) (median)	73,8 (12,9) (76)		71,1 (13,9) (73)		68,2 (15,9) (70)	
Age, distribution, n (%)						
<35	9	(0.74)	96	(1.45)	259	(3.84)
35-44	22	(1.82)	231	(3.48)	383	(5.67)
45-54	82	(6.78)	630	(9.49)	762	(11.28)
55-64	175	(14.46)	1207	(18.18)	1217	(18.02)
65-74	278	(22.98)	1553	(23.39)	1589	(23.53)
75-84	414	(34.21)	1968	(29.64)	1670	(24.73)
≥85	230	(19.01)	955	(14.38)	873	(12.93)
Sex, n (%)						
Men	632	(52.23)	3425	(51.58)	3478	(51.50)
Comorbidity, n (%)						
Hypertension (yes)	584	(48.26)	3247	(48.90)	-	-
- Missing	-	-	-	-	-	-
Previous Myocardial Infarction (yes)	95	(7.85)	371	(5.59)	-	-
- Missing	182	(15.04)	734	(11.05)	-	-
Diabetes Mellitus (yes)	146	(12.07)	661	(9.95)	-	-
- Missing	-	-	-	-	-	-
Atrial Fibrillation (yes)	185	(15.29)	877	(13.21)	-	-
- Missing	171	(14.13)	605	(9.11)	-	-
Charlson Comorbidity index, n (%)						
No comorbidity, 0	677	(55.95)	4288	(64.58)	3867	(57.26)
Moderate comorbidity, 1-2	470	(38.84)	2145	(32.30)	2568	(38.03)
Severe comorbidity, ≥3	63	(5.21)	207	(3.12)	318	(4.71)
Body Mass Index, distribution, n (%)						
<18.5	26	(2.15)	231	(3.48)	-	-
18.5-<25	322	(26.61)	1572	(23.67)	-	-
≥25	296	(24.46)	1629	(24.53)	-	-
Missing	566	(46.78)	3208	(48.31)	-	-
Drinks/wk, n (%)						

≤14 women/≤21 for men	761	(62.89)	4191	(63.12)	-	-
>14 women/>21 for men	87	(7.19)	607	(9.14)	-	-
Missing	362	(29.92)	1842	(27.74)	-	-
Smoking, n (%)						
Daily	289	(23.88)	1426	(21.48)	-	-
Former	194	(16.03)	1118	(16.84)	-	-
Never	330	(27.27)	1872	(28.19)	-	-
Missing	397	(32.81)	2224	(33.49)	-	-
Antihypertensive drug, n (%)	247	(20.41)	1061	(15.98)	1132	(16.76)
Antithrombotic therapy, n (%)						
Oral anticoagulant treatment, n (%)	136	(11.24)	691	(10.41)	645	(9.55)
Platelet inhibitors	461	(38.10)	1946	(29.31)	2227	(32.98)
Lipid-lowering drugs, n (%)	216	(17.85)	877	(13.21)	976	(14.45)
Antidiabetic drugs, n (%)	95	(7.80)	418	(6.30)	489	(7.24)
Early nutritional risk assessment, n (%)						
Not relevant	437	(36.12)	2451	(36.91)	-	-
Yes	460	(38.02)	2634	(39.67)	-	-
No	313	(25.87)	1555	(23.42)	-	-
Early occupational therapist assessment, n (%)						
Not relevant	381	(31.49)	2458	(37.02)	-	-
Yes	506	(41.82)	2633	(39.65)	-	-
No	323	(26.69)	1549	(23.33)	-	-
Early physiotherapist assessment, n (%)						
Not relevant	385	(31.82)	2465	(37.12)	-	-
Yes	541	(44.71)	2730	(41.11)	-	-
No	284	(23.47)	1445	(21.76)	-	-
Early CT or MRI, n (%)						
Not relevant	43	(3.55)	123	(1.85)	-	-
Yes	854	(70.58)	5253	(79.11)	-	-
No	313	(25.87)	1264	(19.04)	-	-
Early stroke unit admission, n (%)						
Not relevant	49	(4.05)	329	(4.95)	-	-
Yes	978	(80.83)	5464	(82.29)	-	-
No	183	(15.12)	847	(12.76)	-	-

Scandinavian Stroke Scale Score, n (%)						
45-58 point	373	(30.83)	1,811	(27.27)	-	-
30-44 point	190	(15.70)	1058	(15.93)	-	-
15-29 point	137	(11.32)	974	(14.67)	-	-
0-15 point	254	(20.99)	1730	(26.05)	-	-
missing	256	(21.16)	1067	(16.07)	-	-
Year of admission, n (%)						
2004	167	(13.80)	657	(9.89)	942	(13.95)
2005	154	(12.73)	692	(10.42)	869	(12.87)
2006	158	(13.06)	708	(10.66)	791	(11.71)
2007	152	(12.56)	697	(10.50)	786	(11.64)
2008	155	(12.81)	704	(10.60)	728	(10.78)
2009	135	(11.16)	829	(12.48)	653	(9.67)
2010	119	(9.83)	805	(12.12)	665	(9.85)
2011	92	(7.60)	821	(12.36)	595	(8.81)
2012	78	(6.45)	727	(10.95)	724	(10.72)

ICH indicates intracerebral hemorrhage, DSR, Danish Stroke Registry, DNRP, Danish National Registry of Patients.

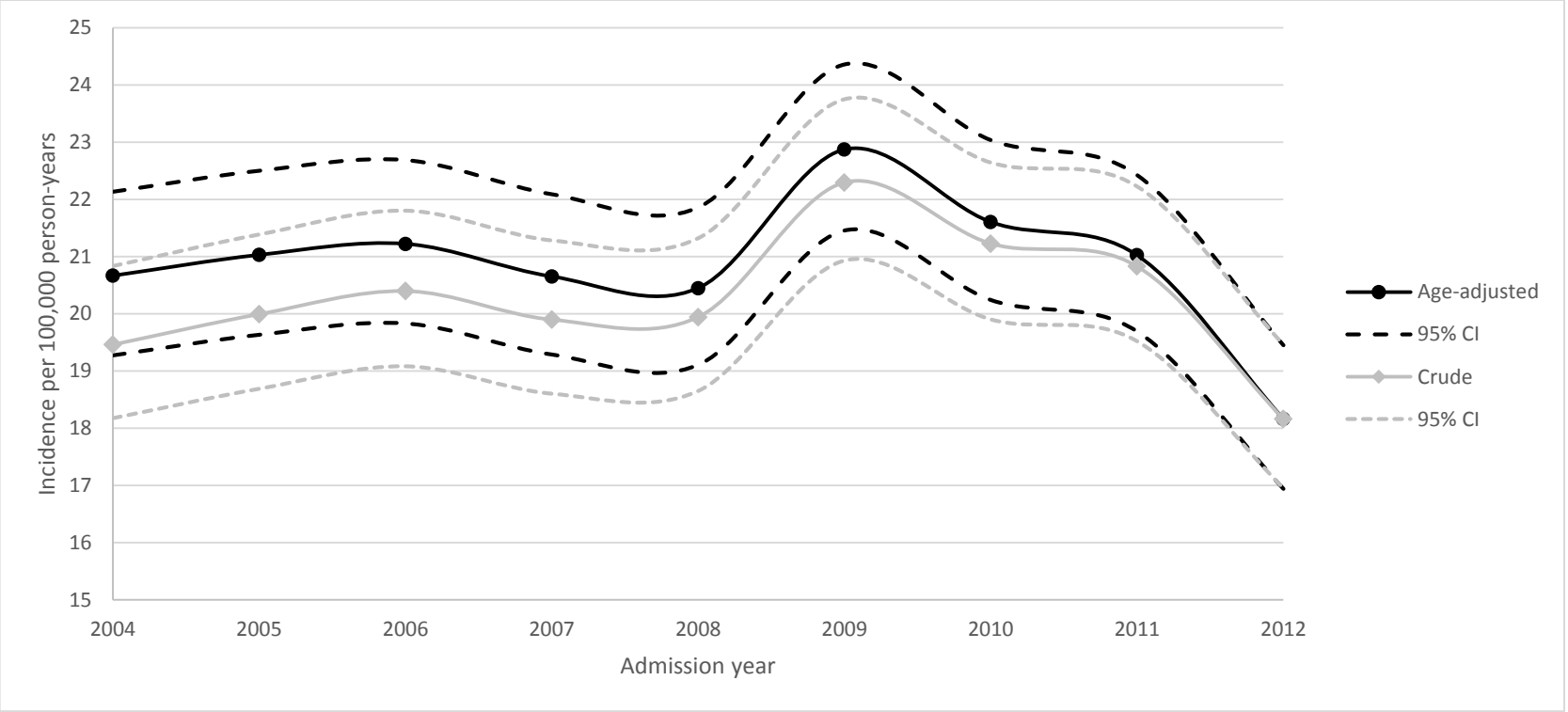
Supplementary table 5. Mutually adjusted hazard ratios (HRs) with 95% confidence interval (95% CI) of 30-day and 1-year case-fatality using different number of imputations.

		Multiple imputation x 5	**Multiple imputation x 20**	**Multiple imputation x 100**
	Year-groups	Adjusted HRs M-2 (95% CI)	Adjusted HRs M-2 (95% CI)	Adjusted HRs M-2 (95% CI)
0-30 days	2004	1.00	1.00	1.00
	2005/2006	0.96 (0.82-1.13)	0.97 (0.83-1.13)	0.97 (0.83-1.14)
	2007/2008	0.92 (0.79-1.09)	0.93 (0.79-1.09)	0.93 (0.79-1.09)
	2009/2010	1.00 (0.85-1.17)	1.00 (0.85-1.17)	1.00 (0.85-1.17)
	2011/2012	0.84 (0.71-0.99)	0.84 (0.71-1.00)	0.84 (0.71-1.00)
0-365 days	2004	1.00	1.00	1.00
	2005/2006	0.99 (0.86-1.14)	1.00 (0.87-1.15)	1.00 (0.87-1.15)
	2007/2008	0.99 (0.86-1.14)	0.99 (0.86-1.14)	0.99 (0.86-1.14)
	2009/2010	1.05 (0.92-1.21)	1.05 (0.91-1.21)	1.05 (0.91-1.21)
	2011/2012	0.87 (0.75-1.01)	0.88 (0.76-1.02)	0.88 (0.76-1.02)

CI indicates confidence interval, HRs, hazards ratios, M-2, multivariable model 2.

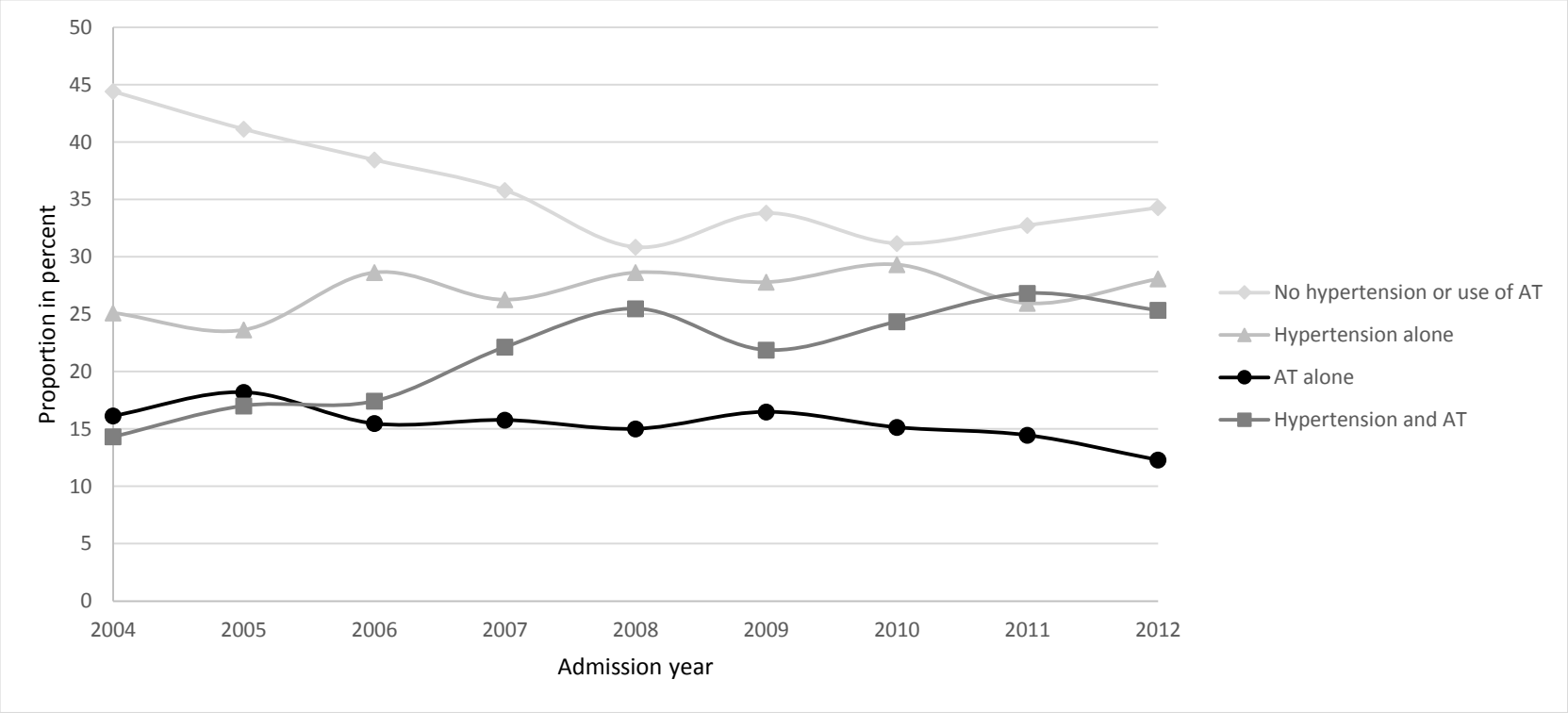
Figures

Figure 1. Crude and age-adjusted standardised incidence of ICH according to year of admission.



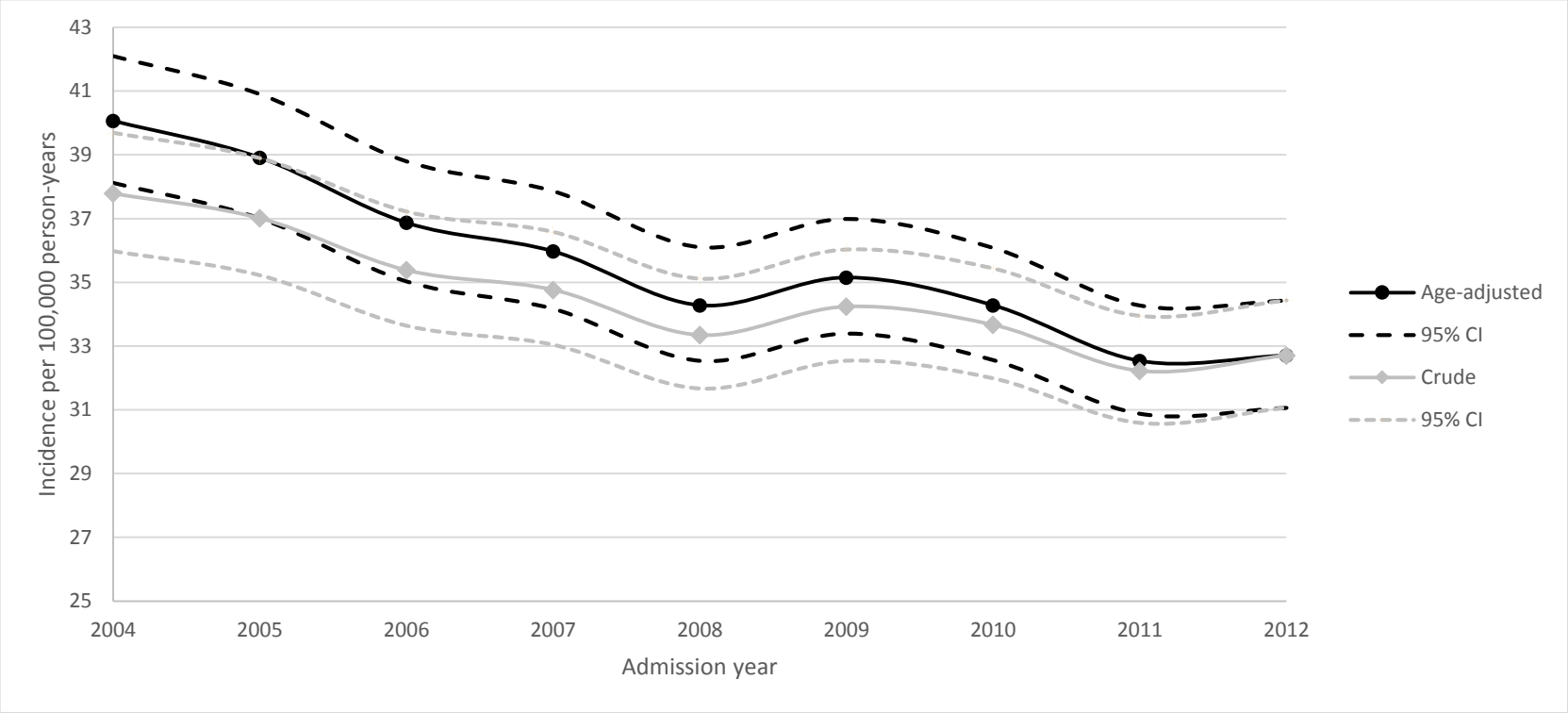
CI indicates confidence interval, ICH, intracerebral hemorrhage.

Figure 2. Changes in the risk-profile if ICH patients according to the prevalence of hypertension and use of preadmission AT.



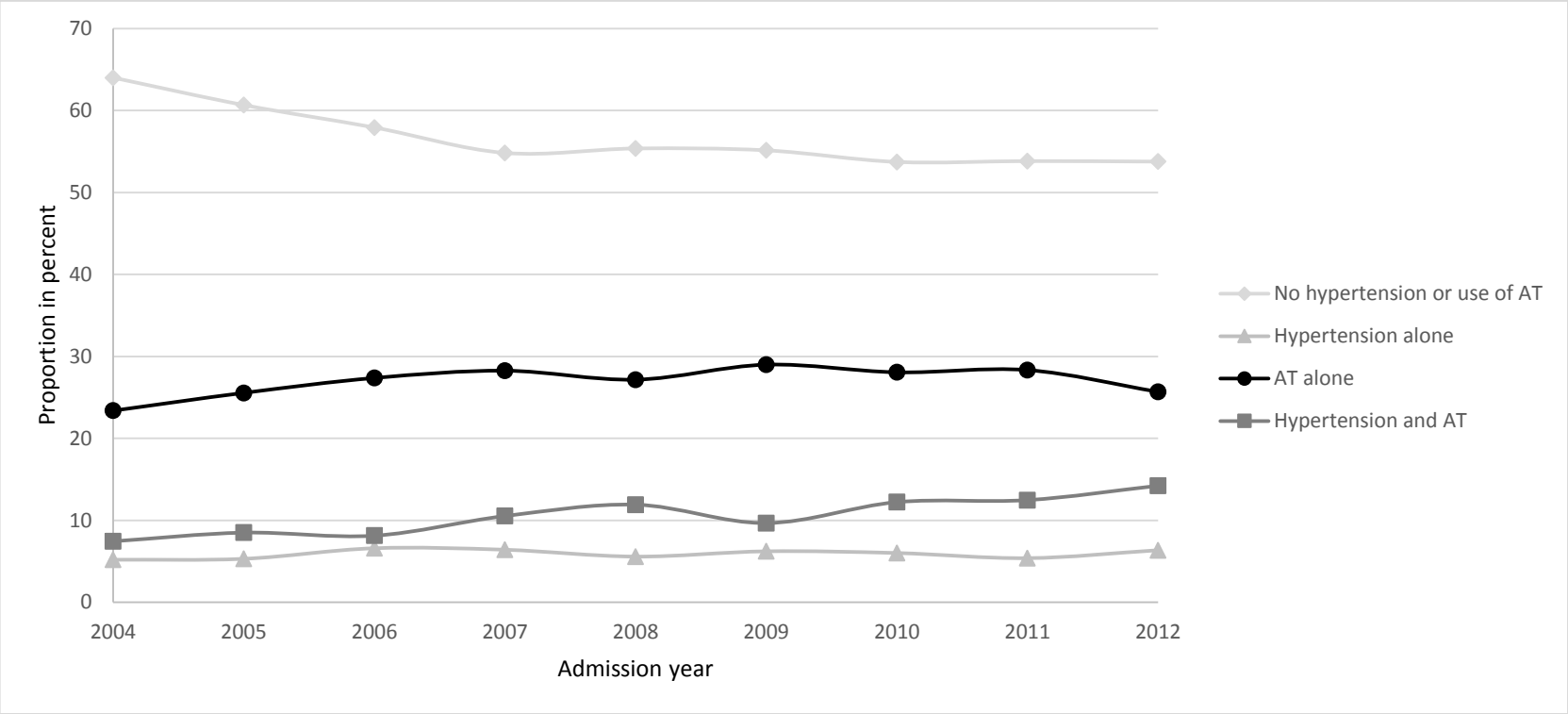
ICH indicates intracerebral hemorrhage, AT, antithrombotic therapy.

Supplementary Figure 1. Crude and age-adjusted standardised incidence of ICH according to year of admission. Patients identified from the Danish National Registry of Patients.



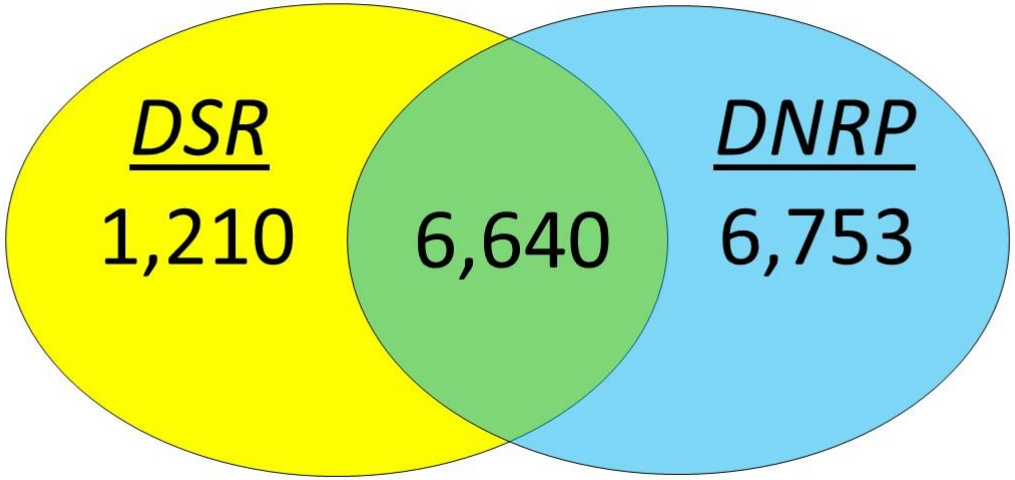
CI indicates confidence interval, ICH, intracerebral hemorrhage.

Supplementary Figure 2. Changes in the risk-profile of ICH patients according hypertension and use of preadmission AT. Patients identified from the Danish National Registry of Patients.



ICH indicates intracerebral hemorrhage, AT, antithrombotic therapy.

Supplementary Figure 3. Overview over patients identified in the DSR and the DNRP, respectively



DSR indicates Danish Stroke Registry, DNRP, Danish National Registry of Patients

References

(1) Donnan GA, Hankey GJ, Davis SM. Intracerebral haemorrhage: a need for more data and new research directions. Lancet Neurol. 2010;9:133-134.

(2) van Asch CJ, Luitse MJ, Rinkel GJ, van der Tweel I, Algra A, Klijn CJ. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. Lancet Neurol. 2010;9:167-176.

(3) Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet. 2009;373:1632-1644.

(4) Feigin VL, Lawes CM, Bennett DA, Barker-Collo SL, Parag V. Worldwide stroke incidence and early case fatality reported in 56 population-based studies: a systematic review. Lancet Neurol. 2009;8:355-369.

(5) Rothwell PM, Coull AJ, Giles MF, Howard SC, Silver LE, Bull LM, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet. 2004;363:1925-1933.

(6) Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol. 2014;29:541-549.

(7) Mainz J, Krog BR, Bjornshave B, Bartels P. Nationwide continuous quality improvement using clinical indicators: the Danish National Indicator Project. Int J Qual Health Care. 2004;16 Suppl 1:i45-50.

(8) Wildenschild C, Mehnert F, Thomsen RW, Iversen HK, Vestergaard K, Ingeman A, et al. Registration of acute stroke: validity in the Danish Stroke Registry and the Danish National Registry of Patients. Clin Epidemiol. 2013;6:27-36.

(9) Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health. 2011;39:30-33.

(10) Schmidt M, Hallas J, Friis S. Potential of prescription registries to capture individual-level use of aspirin and other nonsteroidal anti-inflammatory drugs in Denmark: trends in utilization 1999-2012. Clin Epidemiol. 2014;6:155-168.

(11) Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ. 2011;342:d124.

(12) Pedersen CB, Gotzsche H, Moller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. Dan Med Bull. 2006;53:441-449.

(13) Multicenter trial of hemodilution in ischemic stroke--background and study protocol. Scandinavian Stroke Study Group. Stroke. 1985;16:885-890.

(14) Lindenstrøm L, Boysen G, Christiansen LW, á Rogvi-Hansen B, Nielsen PW. Reliability of Scandinavian Neurological Stroke Scale. Cerebrovasc.Dis. 1991;1:103-107.

(15) Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40:373-383.

(16) Ingeman A, Pedersen L, Hundborg HH, Petersen P, Zielke S, Mainz J, et al. Quality of care and mortality among patients with stroke: a nationwide follow-up study. Med Care. 2008;46:63-69.

(17) Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. Third. ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.

(18) Swift M. A simulation study comparing methods for calculating confidence intervals for directly standardized rates. Computational Statistics & Data Analysis 2010;54:1103–8.

(19) Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009;338:b2393.

(20) Lovelock CE, Molyneux AJ, Rothwell PM, Oxford Vascular Study. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. Lancet Neurol. 2007;6:487-493.

(21) Rosand J, Eckman MH, Knudsen KA, Singer DE, Greenberg SM. The effect of warfarin and intensity of anticoagulation on outcome of intracerebral hemorrhage. Arch Intern Med. 2004;164:880-884.

(22) Saloheimo P, Ahonen M, Juvela S, Pyhtinen J, Savolainen ER, Hillbom M. Regular aspirin-use preceding the onset of primary intracerebral hemorrhage is an independent predictor for death. Stroke. 2006;37:129-133.

(23) Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry. 2014;85:660-667.

(24) Zahuranec DB, Lisabeth LD, Sanchez BN, Smith MA, Brown DL, Garcia NM, et al. Intracerebral hemorrhage mortality is not changing despite declining incidence. Neurology. 2014;82:2180-2186.

(25) Anderson CS, Heeley E, Huang Y, Wang J, Stapf C, Delcourt C, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368:2355-2365.

(26) Mendelow AD, Gregson BA, Rowan EN, Murray GD, Gholkar A, Mitchell PM, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial lobar intracerebral haematomas (STICH II): a randomised trial. Lancet. 2013;382:397-408.

(27) Caplan L editor. A Clinical Approach, Basic pathology, anatomy, and pathopysiology of stroke. 4th edition ed. Philadelphia: Saunders Elsevier; 2009.

(28) Flaherty ML. Anticoagulant-associated intracerebral hemorrhage. Semin Neurol. 2010;30:565-572.

(29) Rincon F, Mayer SA. The Epidemiology of Intracerebral Hemorrhage in the United States from 1979 to 2008. Neurocrit Care. 2012.

(30) Sacco S, Marini C, Toni D, Olivieri L, Carolei A. Incidence and 10-year survival of intracerebral hemorrhage in a population-based registry. Stroke. 2009;40:394-399.

(31) Sturgeon JD, Folsom AR, Longstreth WT,Jr, Shahar E, Rosamond WD, Cushman M. Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke. 2007;38:2718-2725.

(32) Ariesen MJ, Claus SP, Rinkel GJ, Algra A. Risk factors for intracerebral hemorrhage in the general population: a systematic review. Stroke. 2003;34:2060-2065.

(33) Steiner T, Rosand J, Diringer M. Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions. Stroke. 2006;37:256-262.

(34) Cervera A, Amaro S, Chamorro A. Oral anticoagulant-associated intracerebral hemorrhage. J Neurol. 2012;259:212-224.

(35) Schmidt M, Jacobsen JB, Johnsen SP, Botker HE, Sorensen HT. Eighteen-year trends in stroke mortality and the prognostic influence of comorbidity. Neurology. 2014;82:340-350.

(36) StataCrop. Stata statistical software: Release 12. College Station: Intro mi. 2013.

(37) White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med. 2011;30:377-399.

(38) Juul S. Epidemiologi og evidens. 2. udgave ed.: Munksgaard Danmark; 2010.

(39) Rothman K. Epidemiology - An introduction. 2nd edition ed.: Oxford University Press, Inc.; 2012.

(40) Thorvaldsen P, Davidsen M, Bronnum-Hansen H, Schroll M. Stable stroke occurrence despite incidence reduction in an aging population: stroke trends in the danish monitoring trends and determinants in cardiovascular disease (MONICA) population. Stroke. 1999;30:2529-2534.

(41) Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137:263-272.

(42) Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest. 2010;138:1093-1100.