Hemorrhagic and Ischemic Strokes Compared

Stroke Severity, Mortality, and Risk Factors

Klaus Kaae Andersen, MS, PhD; Tom Skyhøj Olsen, MD, PhD;
Christian Dehlendorff, MS; Lars Peter Kammersgaard, MD

Background and Purpose**—**Stroke patients with hemorrhagic (HS) and ischemic strokes were compared with regard to stroke severity, mortality, and cardiovascular risk factors.

Methods**—**A registry started in 2001, with the aim of registering all hospitalized stroke patients in Denmark, now holds information for 39 484 patients. The patients underwent an evaluation including stroke severity (Scandinavian Stroke Scale), CT, and cardiovascular risk factors. They were followed-up from admission until death or censoring in 2007. Independent predictors of death were identified by means of a survival model based on 25 123 individuals with a complete data set.

Results**—**Of the patients 3993 (10.1%) had HS. Stroke severity was almost linearly related to the probability of having HS (2% in patients with the mildest stroke and 30% in those with the most severe strokes). Factors favoring ischemic strokes vs HS were diabetes, atrial fibrillation, previous myocardial infarction, previous stroke, and intermittent arterial claudication. Smoking and alcohol consumption favored HS, whereas age, sex, and hypertension did not herald stroke type. Compared with ischemic strokes, HS was associated with an overall higher mortality risk (HR, 1.564; 95% CI, 1.441–1.696). The increased risk was, however, time-dependent; initially, risk was 4-fold, after 1 week it was 2.5-fold, and after 3 weeks it was 1.5-fold. After 3 months stroke type did not correlate to mortality.

Conclusion**—**Strokes are generally more severe in patients with HS. Within the first 3 months after stroke, HS is associated with a considerable increase of mortality, which is specifically associated with the hemorrhagic nature of the lesion. **(*Stroke*. 2009;40:2068-2072.)**

Key Words: cerebral infarct ■ intracerebral hemorrhage ■ mortality ■ risk factors ■ stroke recovery

Comparisons between hemorrhagic (HS) and ischemic stroke (IS) in respect to prognostic determinants are hampered by the disproportionate distribution of the 2 types of stroke, with IS being 10-times more frequent than HS in Western countries.[1–13] Even in large stroke cohorts absolute numbers of HS are low, rendering statistical validation of differences between the 2 types of stroke difficult.[1–13] Hence, our knowledge of this issue is still incomplete.

HS are considered to have a higher mortality risk than IS.[1–13] Previous studies have linked the excess mortality to the generally more severe strokes in patients with HS, whereas stroke type per se was not considered to be associated with mortality.[14,15] Numbers in these studies were, however, few.

Some risk factors are common for both HS and IS.[16–18] The association of atrial fibrillation, ischemic heart disease, and diabetes with IS seems well-established in comparative studies, but the relative role of risk factors such as hypertension, smoking, and alcohol consumption remains controversial.[14,16–21]

An ongoing nationwide Danish stroke registry was established in March 2001, with the aim of registering all patients hospitalized with acute stroke. In February 2007, the registry included 39 484 patients, of which 3993 had HS. Based on this large number of patients, we studied differences and similarities between patients with HS and IS with respect to risk factors, stroke severity, and survival.

Materials and Methods

The study is based on data collected in the Danish National Indicator Project (NIP).[22] NIP is expected to include information from all stroke admissions in Denmark. Coverage is now ≈80% of all stroke admissions. All Danish hospitals have committed to report a predefined set of data on all patients admitted to hospital with acute stroke including age, gender, admission stroke severity measured by the Scandinavian Stroke Scale (SSS),[23,24] and a predefined cardiovascular profile.

The SSS is a validated and widely used neurological stroke scale in Scandinavia that evaluates level of consciousness, eye movement, power in arm, hand, and leg, orientation, aphasia, facial paresis, and gait on a total score from 0 to 58 (lower scores indicate more severe strokes). A predefined set of cardiovascular risk factors was recorded on the basis of a standardized interview on admission and on evaluations during hospital stay. The cardiovascular profile included

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From Informatics and Mathematical Modelling (K.K.A., C.D.), Section for Statistics, Technical University of Denmark, Lyngby; The Stroke Unit (T.S.O., L.P.K.), Hvidovre University Hospital, Hvidovre, Denmark.

Correspondence to Tom Skyhøj Olsen, MD, PhD, The Stroke Unit, Dept. of Neurorehabilitation, Hvidovre University Hospital, Kettegaard Allé 30, DK-2650 Hvidovre, Denmark. E-mail skyhoj.olsen@dadlnet.dk

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Table. Univariate and Multivariate Analysis for Risk Factors

	HS	IS	Univariate Analysis OR (95% CI)	Multivariate Analysis OR (95% CI)
N and gender, female/male	N=3993 49.6%/50.4%	N=35 491 47.8%/52.2%	0.93 (0.87–0.99)	1.07 (0.97–1.18)
Alcohol intake, high/low	N=2813 9.8%/90.2%	N=29 660 8.2%/91.8%	0.82 (0.72–0.93)	0.80 (0.67–0.95)
Smoking, yes/no	N=2879 40.7%/59.3%	N=35 371 52.8%/47.2%	0.84 (0.79–0.90)	0.73 (0.66–0.81)
Diabetes, yes/no	N=3501 10.9%/89.1%	N=33 484 14.4%/85.6%	1.37 (1.23–1.53)	1.50 (1.28–1.77)
Atrial fibrillation, yes/no	N=3480 13.9%/86.1%	N=33 201 17.5%/82.5%	1.31 (1.19–1.45)	1.62 (1.40–1.89)
Previous myocardial infarction, yes/no	N=3429 7.8%/92.2%	N=32 816 10.3%/89.7%	1.35 (1.19–1.54)	1.72 (1.41–2.11)
Hypertension, yes/no	N=3382 47.1%/52.9%	N=32 687 48.7%/51.3%	1.06 (0.99–1.14)	0.95 (0.86–1.05)
Previous stroke, yes/no	N=3490 23.0%/77.0%	N=33 329 23.2%/76.8%	1.01 (0.93–1.10)	1.15 (1.02–1.30)
Intermittent arterial claudication, yes/no	N=3037 2.4%/97.6%	N=30 222 4.5%/95.5%	1.93 (1.52–2.45)	2.10 (1.52–2.90)

	HS	IS	*P*
Mean age (SD)	72.9 (12.1)	72.7 (12.2)	0.258
Mean SSS score (SD)	28.3 (19.9)	42.9 (15.7)	<0.001

Odds ratio (OR) of hemorrhagic stroke in the univariate analysis is obtained using all cases available for each risk factor. OR of hemorrhagic stroke in the multivariate analysis is obtained from multiple logistic regression analysis using complete cases including all risk factors, age, gender, and stroke severity. The OR is the increased risk of hemorrhagic stroke for the last factor level compared to the first factor level.

information about alcohol intake (high: >14 drinks per week in women and >21 drinks per week in men; low: ≤14 drinks per week in women and ≤21 drinks per week in men), smoking (current daily smoking, former smoking, never smoking), diabetes (diabetes known before admission or diagnosed during admission; no distinction between type 1 or type 2 diabetes was made), atrial fibrillation (atrial fibrillation [chronic or paroxystic] known before admission or diagnosed during admission), hypertension (known before admission or diagnosed during admission), previous myocardial infarction (known before admission or diagnosed during admission), previous stroke, and intermittent claudication (known before admission or diagnosed during admission). Diagnosis of diabetes, atrial fibrillation, arterial hypertension, previous myocardial infarction, previous stroke, and intermittent arterial claudication was made on current Danish standards.[22] Distinction between IS and primary HS was determined after CT/MR scan. HS was handled as 1 entity, without distinction between lobar and nonlobar hemorrhage. Hemorrhagic infarction was considered IS. Stroke was defined according to the WHO criteria.[25] For patients with multiple records (events), only the first event was included in the analysis. Patients with transient ischemic attacks or subarachnoid hemorrhages were not included in the study. Patients younger than age 40 years were not included in the study. Patients in whom CT/MR scan was not performed (1.8%) or unavailable (1.1%) were excluded from the study.

In Denmark, patients with acute stroke are exclusively treated and rehabilitated in public hospitals with a commitment to report all stroke admissions to the NIP registry. Also, in Denmark, patients are urged to seek hospital care immediately in case of symptoms of stroke regardless of age or severity of symptoms. Almost 90% of the patients registered in the NIP database are treated in a stroke unit within 2 days of arrival to hospital.[26]

Survival of the patients included in the NIP database was registered and followed through the Danish Registry of Persons. We studied all-cause mortality only. Inclusion of patients in NIP started on March 1, 2001, and end of the study follow-up (censoring date) was on February 15, 2007. Less than 0.2% of the patients were lost to follow-up, mainly because of emigration, and these patients were censored in the analysis. The study was approved by the board of NIP and by the Danish Data Protection Agency.

Statistical Analysis

First, a multiple regression model was used to obtain a risk profile with respect to HS vs IS. More specifically, this was performed using Generalized Additive Model[27] adjusting for age and stroke severity, and with a binomial response. Age and stroke severity score were modeled using smooth splines (penalized cubic regression spline, 4 degrees of freedom for each variable), because the effect of both covariates cannot be assumed linear.

Independent predictors of death were then identified using a Poisson regression model to the data in a time-split format. The Poisson approach was preferred over the Cox proportional hazard model because it is more practical in analyzing large data sets with complex and possible time-dependent hazard ratios.

In identifying the final model, only complete cases were included in the analysis. Significance of predictors was based on the likelihood ratio test. The fit of the model was evaluated using standard regression diagnostics tools.

Missing observations were analyzed for informative data being missing to justify list-wise deletion and, hence, that analysis of complete cases would lead to unbiased parameter estimates.

In all analyses, cardiovascular risk factors were kept in the model if significance was at a 5% level. The statistical software R[28] was used for the statistical analysis.

Results

Of the patients, 35 491 (89.9%) had IS whereas 3993 (10.1%) had HS. For patients with a complete data set, IS was the cause of stroke in 23 150 (92.1%) and HS was the cause in 1973 (7.9%) patients. Descriptive statistics for stroke subtype (IS/HS) related to gender, cardiovascular risk factors, age, and stroke severity appear in the Table. Higher proportions of patients with IS had diabetes, atrial fibrillation, previous myocardial infarction, and intermittent arterial claudication. Patients with HS had more severe strokes, more often had high alcohol intake, and more often were smokers. No difference in sex, age, and prevalence of hypertension was found between patients with IS and HS.

Initial Stroke Severity, Age, and Stroke Type

The association of SSS score and age with the probability of having IS, as opposed to HS, can be seen in Figure 1. The relative frequency of HS increased with increasing stroke severity from 2% in patients with the mildest strokes (SSS 58) to 30% in those with the most severe strokes (SSS 0). Age was of no clinical importance. Within the age range 40 to 60 years, the relative frequency of HS increased slightly with

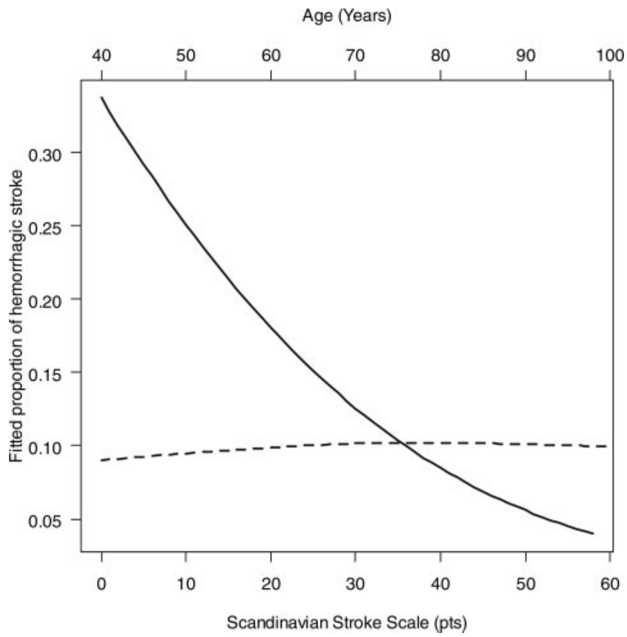

Figure 1. Fitted proportions (%) of hemorrhagic stroke vs stroke severity (solid line) and vs age (dotted line). The SSS measures stroke severity on a 0–58 scale (lower scores indicate more severe strokes).

increasing age (from 9% to 10%). After age 60 years, the relative frequency of HS remained constant (10%).

Risk Factors and Stroke Type

A multivariate logistic regression analysis was performed to determine the independent association of cardiovascular risk factors on stroke type (Table). Factors favoring IS as opposed to HS were diabetes, atrial fibrillation, previous myocardial infarction, previous stroke, and intermittent arterial claudication. High alcohol intake and smoking favored HS as opposed to IS. Neither sex nor hypertension favored either of the stroke types.

Survival and Stroke Type

Of the 3993 patients with HS, 1966 (49.2%) died during follow-up. In comparison, out of the 35 491 patients with IS, 9220 (25.9%) died during follow-up. Seven-, 30-, and 90-day unadjusted case fatality rates in patients with IS and HS were 1.8% vs 13.2%, 4.8% vs 19.8%, and 10.9% vs 25.0%, respectively.

In the multivariate survival analysis, adjusting for stroke severity, age, sex, and cardiovascular risk factors, we found that patients with HS had an overall (ie, proportional) higher risk of all cause death compared to patients with IS (HR, 1.564; 95% CI, 1.441–1.696; $P<0.001$). Other risk factors related to death were smoking, atrial fibrillation, previous myocardial infarction, previous stroke, older age, and low stroke score. We then proceeded to analyze the proportional hazard assumption of the model. Most interestingly, we found the risk between stroke subtypes was time-dependent, ie, the proportional hazard assumption was rejected. Figure 2 shows the time-dependent hazard ratio for HS. Striking changes in risk were observed within the first 3 months after stroke. Initially the excess mortality of patients with HS is 4-fold, after 1 week it is 2.5-fold, and after 3 weeks it is 1.5-fold. Thereafter, it gradually decreases, and after ≈3 months stroke subtype does not correlate to mortality after stroke.

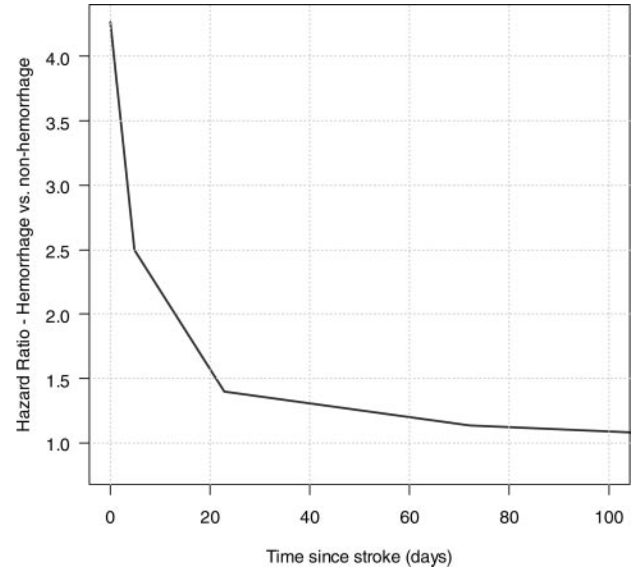

Figure 2. HR (RR) for patients with hemorrhagic stroke compared to ischemic stroke obtained from the Poisson survival model. It is seen that the HR is not constant but has a sharp decrease as a function of time since stroke.

Discussion

The major finding of this study was that HS per se is associated with a higher risk of death than IS, even after adjustment for age, sex, initial stroke severity, and relevant cardiovascular risk factors. The higher risk, initially 4-fold, gradually declines with time and equals that of infarction after 3 months.

Stroke in patients with HS are more severe than strokes in patients with infarcts. The relative frequency of HS is increasing, with increasing stroke severity being 2% in very mild strokes and 30% in the very severe strokes.

In stroke, diabetes, atrial fibrillation, previous myocardial infarction, previous stroke, and intermittent arterial claudication disfavors the diagnosis of HS. Smoking and high alcohol intake favors HS, whereas hypertension does not favor either stroke subtype.

Weaknesses and Strengths

Our study's strength is its large sample size allowing for sufficient statistical power. Second, we included patients without limitations on age (>40 years), gender, or stroke severity. Third, in our patients, stroke severity was measured on admission to hospital using a well-validated neurological stroke score. Fourth, all patients underwent a standardized risk factor evaluation. Finally, we had survival data on nearly all patients, with <0.2% lost to follow-up.

Although NIP is designed as a nation-wide registration of all patients admitted with acute stroke, coverage is not yet complete (presently ≈80%), and because of the large number of persons involved in a nation-wide registration, missing data are unavoidable. Of the 39 484 patients in our study, only 25 123 patients with a complete data set (age, sex, SSS, stroke subtype, and data on all cardiovascular risk factors) were included in our final survival analysis. We performed an analysis of the missing observations. Patients missing ≥1 risk factors were older (72.7 vs 71.4 years), had more severe strokes (41.4 vs 44.6 patients), and had higher mortality rates during follow-up (28.3% vs 21.5%). This difference was similar for the IS and HS groups. We cannot exclude the possibility of bias attributable to variables not recorded in the NIP database. However, we validated that measures of stroke type and cardiovascular risk factors are valid for all ages, both sexes, and the whole spectrum of stroke severities. Although we recorded mortality within the follow-up period, we have no information as to treatments or interventions that might have influenced survival, but we consider it unlikely that such information would change conclusions of this study.

Finally, HS was handled as 1 entity, without distinction between lobar and nonlobar hemorrhage. Although 2 recent studies[29,30] showed no statistical significant difference when comparing the risk factor profiles of patients with lobar and nonlobar hemorrhages, differences between these 2 subtypes (in comparison with stroke-free controls) were found in regard to diabetes and smoking.[29] Most studies, however, handle HS as 1 entity.[16,17,31]

Mortality

Patients with HS are generally considered to be at high risk for mortality compared to patients with infarcts.[1–13] This is amply demonstrated in this study. Previous studies have linked the excess mortality to the generally more severe strokes in patients with HS, whereas stroke type per se was considered of no influence on mortality—the extent of the injury and initial stroke severity was regarded decisive.[14,15]

The present study shows that the high fatality rate of patients with HS is the result of both more severe strokes and the stroke subtype per se. The period in which mortality of HS exceeds that of infarcts, all other things being equal, is confined to the first 3 months. Initially, the excess mortality is 4-fold, after 1 week it is 2.5-fold, and after 3 weeks it is 1.5-fold. Thereafter, it gradually decreases and after ≈3 months stroke subtype is not associated with poststroke mortality. This is a new finding. To our knowledge the literature contains no definite evidence of differential recovery between hemorrhagic and ischemic stroke. In a case-controlled study[15] of 120 patients with HS and IS matched for age, Glasgow coma scale, and Rankin scale, survival after 1 year did not differ between the 2 groups. In the Copenhagen Stroke Study[14] of 1000 unselected stroke patients, of whom 84 had HS, type of stroke per se was not associated with in-hospital mortality. Compared to our study, numbers in these studies are, however, small; in the latter study, multivariate survival analysis was not entertained. Thus, we conclude that outcome of stroke seems to be determined not only by its initial severity but also by the nature of the lesion as well. Hematoma expansions, edema formation, and intraventricular hemorrhage leading to increased intracranial pressure are likely contributors to the acute excess mortality.[16–18]

Stroke Severity

Strokes are generally more severe in patients with HS, and the ratio between HS and IS is closely related to stroke severity.[14] In our study the relation was almost linear on the probability scale. Of patients presenting with the mildest stroke (SSS 58), only 2% had HS, whereas in patients presenting with the most severe stroke (SSS 0), 30% had HS. Our study emphasizes that imaging is a must in stroke management. Even in patients presenting with very mild symptoms barely measurable in a stroke scale, HS continues to be an option, whereas in severe strokes HS is to be expected in 1 of 3 patients. Lesion size in patients with HS is generally larger than in patients with IS. In the Copenhagen Stroke Study,[14] the largest diameter of lesions in patients with HS was increased by 20% as compared to lesions in patients with IS.

Risk Factors

Knowledge on the relative role of risk factors in hemorrhagic vs ischemic strokes is still inconsistent. In the population-based case-controlled Perth study[19] (n=536), hypertension and diabetes favored IS and high alcohol intake favored HS, whereas smoking did not favor either of the stroke subtypes. In another population-based observational study[20] (n=1254) increasing age, previous stroke, and diabetes favored IS, whereas ischemic heart disease, atrial fibrillation, hypertension, alcohol intake, and smoking did not favor either of the stroke subtypes. In the hospital-based Copenhagen Stroke Study[14] (n=1000) diabetes and ischemic heart disease favored IS, whereas age, hypertension, alcohol consumption, atrial fibrillation, and smoking were not predictors of stroke type. In the hospital-based Lausanne Stroke registry[21] (n=3901) smoking, hypercholesterolemia, migraine, previous transient ischemic attack, atrial fibrillation, and heart disease favored IS, whereas hypertension was the only significant factor related to HS vs IS. In our study based on 39 484 patients, well-established risk factors and markers of atherosclerotic and occlusive arterial disease such as diabetes, atrial fibrillation, previous myocardial infarction, previous stroke, and intermittent arterial claudication were associated with IS rather than HS, smoking and high alcohol intake favored HS, whereas age, sex, and hypertension did not herald stroke type.

It appears that the presence of known risk factors for atherosclerotic cardiovascular disease in particular diabetes, atrial fibrillation, ischemic heart disease, and previous stroke disfavor HS as opposed to IS. Whether the presence of hypertension is in favor of either stroke subtype is unclear. Hypertension is a well-documented risk factor for both IS and HS. Recent studies show, however, that the gradient of the relationship between hypertension and HS is steeper than that for IS.[32,33] High alcohol intake is a well-established risk factor for HS.[16–18,34] Light or moderate drinking seems to have a protective effect on IS,[35] whereas heavy alcohol consumption is associated with elevated risk of IS. We found high alcohol intake to favor HS, but most other studies did not demonstrate any difference between HS and IS in relation to this risk factor. Although we found smoking to be highly in favor of HS as opposed to IS, there is no agreement in the literature regarding the relation between HS and smoking. In the Physicians Health Study,[36] the association of smoking with HS was approximately the same as that with IS. In a systematic review of 14 case-control and 11 cohort studies,[34] the relation was weak or not existent, whereas a recent pooled cohort of the Atherosclerosis Risk in Communities Study (ARIC) and Cardiovascular Health Study (CHS)[37] studies did not find any relation between HS and smoking.

Conclusion

The present comparative study shows high alcohol intake and smoking to be in favor of HS as compared to IS, whereas presence of diabetes, atrial fibrillation, previous myocardial infarction, previous stroke, and intermittent arterial claudication disfavors the likelihood of HS. Strokes are generally more severe in HS than in IS. Within the first 3 month after stroke, HS is associated with a considerable increase of mortality, which is specifically and independently associated with the hemorrhagic nature of the stroke lesion.

Disclosure

None.

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