SMASH-U
A Proposal for Etiologic Classification of Intracerebral Hemorrhage

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Background and Purpose—The purpose of this study was to provide a simple and practical clinical classification for the etiology of intracerebral hemorrhage (ICH).

Methods—We performed a retrospective chart review of consecutive patients with ICH treated at the Helsinki University Central Hospital, January 2005 to March 2010 (n=1013). We classified ICH etiology by predefined criteria as structural vascular lesions (S), medication (M), amyloid angiopathy (A), systemic disease (S), hypertension (H), or undetermined (U). Clinical and radiological features and mortality by SMASH-U (Structural lesion, Medication, Amyloid angiopathy, Systemic/other disease, Hypertension, Undetermined) etiology were analyzed.

Results—Structural lesions, namely cavernomas and armerovenous malformations, caused 5% of the ICH, anticoagulation 14%, and systemic disease 5% (23 liver cirrhosis, 8 thrombocytopenia, and 17 various rare conditions). Amyloid angiopathy (20%) and hypertensive angiopathy (35%) were common, but etiology remained undetermined in 21%. Interrater agreement in classifying cases was high (κ, 0.89; 95% CI, 0.82–0.96). Patients with structural lesions had the smallest hemorrhages (median volume, 2.8 mL) and best prognosis (3-month mortality 4%), whereas anticoagulation-related ICHs were largest (13.4 mL) and most often fatal (54%). Overall, median ICH survival was 5½ years, varying strongly by etiology (P<0.001). After adjustment for baseline characteristics, patients with structural lesions had the lowest 3-month mortality rates (OR, 0.06; 95% CI, 0.01–0.37) and those with anticoagulation (OR, 1.9; 1.0–3.6) or other systemic cause (OR, 4.0; 1.6–10.1) the highest.

Conclusions—In our patients, performing the SMASH-U classification was feasible and interrater agreement excellent. A plausible etiology was determined in most patients but remained elusive in one in 5. In this series, SMASH-U based etiology was strongly associated with survival. (Stroke. 2012;43:2592-2597.)

Key Words: amyloid angiopathy ■ anticoagulation ■ etiology ■ hypertension ■ ICH ■ stroke

Etiologic classifications help in evaluating patients, choosing purposeful diagnostic tests, predicting prognosis, and planning secondary preventive measures. Furthermore, uniform classification systems help in comparing patient populations across different series and in standardizing research. Several classifications exist for ischemic stroke according to infarct localization1 or etiology.2,3 However, an established etiologic classification for intracerebral hemorrhage (ICH) does not exist, but developing one has been recently acknowledged as a research priority.4 In the present work, we describe a novel classification system for ICH etiology using our consecutive single-center registry of 1013 patients with ICH and evaluate the validity and prognostic value of this classification.

Methods

This report is based on the Helsinki ICH Study, a retrospective analysis of all consecutive patients with ICH treated at the Helsinki University Central Hospital from January 2005 to March 2010. Helsinki University Central Hospital is the only university teaching hospital in the province of Uusimaa with a catchment population of 1.5 million and the only neurological emergency department with 24/7 service in the province.

We performed a retrospective chart review, including province-wide electronic patient records and imaging databases for all consecutive patients who at any time during their hospital stay or outpatient visit had a diagnosis of ICH, International Classification of Diseases, 10th Revision code I61, recorded. All patient records were retrieved. This study has been approved by institutional authorities. As a routine observational quality registry with no patient contact, consent for registration was not required by Finnish legislation.

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### Patient Selection and Etiologic Classification

Our classification rules were defined before data collection (Figure 1). We used the World Health Organization definition of stroke to differentiate between stroke ICH and nonstroke ICH: “rapidly developing clinical signs of focal or global disturbance of cerebral function leading to death or lasting more than 24 hours with no apparent cause other than a vascular one.”5 None of our patients were free of clinical signs and symptoms at 24 hours. We excluded as nonstrokes the patients with primary subdural/epidural hematoma or traumatic ICH or hemorrhage due to a tumor (nonvascular origin, n=18). Stroke due to primary subarachnoid hemorrhage with or without ICH and hemorrhagic transformation of a cerebral infarction with or without thrombolytic therapy (n=179)6,7 are not initially ICH and were excluded.

We included all other ICHs treated at any department of our hospital, whether primary, like with hypertensive or amyloid angiopathy, or secondary, either due to an underlying structural vascular pathology such as arteriovenous malformation or cavernoma, coagulopathy, anticoagulation, or other medication such as systemic thrombolysis of noncerebral thrombosis or any other vascular cause. Patients with previous ICH before the study period were included only if they had a new ICH during the study period. Patients with

### Figure 1. Classification scheme for the SMASH-U ICH etiology.

ICH indicates intracerebral hemorrhage; SMASH-U, Structural lesion, Medication, Amyloid angiopathy, Systemic/other disease, Hypertension, Undetermined.

**Figure 1. Classification scheme for the SMASH-U ICH etiology.**

**Table 1.**

<table>
<thead>
<tr>
<th>Structural Lesion</th>
<th>Medication</th>
<th>Amyloid Angiopathy</th>
<th>Hypertension</th>
<th>Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging or pathology confirmed structural vascular malformation diagnosed at ICH site</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic or other determined cause for ICH*, except for anticoagulation, hypertension or amyloid angiopathy</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin with INR≥2.0, novel oral anticoagulants within 3 days, full-dose heparin, or non-IS systemic thrombolysis</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lobar, cortical, or corticosubcortical hemorrhage and age ≥55</td>
<td>No</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Deep or infratentorial hemorrhage with pre-ICh hypertensionb</td>
<td>No</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>

*a* Liver cirrhosis implicated when known liver disease combined with spontaneously elevated INR or liver enzymes >3 x upper limit of the reference range, and thrombocytopenia when thrombocyte count <50 E9/L.

*b* Hypertension defined as: a) most recent pre-ICh blood pressure ≥160/100 mmHg, either on or off antihypertensive therapy or, when pre-ICh blood pressure was not known, either b) mention of pre-ICh elevated blood pressure by patient, relative, or medical records together with a left ventricular hypertrophy as a biomarker of hypertension, or c) any pre-ICh use of blood pressure medication.
multiple ICHs during the study period were included several times in the study only if there were >28 days between the 2 ICHs. No children aged <18 years were treated at our hospital.

Although many concomitant pathological processes lead to blood extravasation, we tried to provide rules for classifying the most likely cause for each patient assuming certain pathologies as causal and others merely as contributing factors. We preferred the risk factors that could be definitively demonstrated such as structural malformations, coagulation disorders, and anticoagulation to those that cannot: the hypertensive and amyloid angiopathies without pathology. We developed a strict definition for hypertensive etiology (Figure 1). For amyloid angiopathy, we used the Boston criteria 8 except for patients who had their stroke due to medication or other systemic disease. The etiologic classification was done by one of 3 stroke neurologists (A.M., D.S., J.P.) blinded to patients' 3-month outcome. A set of 100 patients was rated independently by 2 raters to test for interrater reliability.

Data Retrieval
All data were retrospectively retrieved from medical records. Every patient had been seen by a neurologist with accordingly diligent chart notes. The Glasgow Coma Scale was systematically registered for patients at the emergency department and the National Institutes of Health Stroke Scale for those presenting as thrombolytics candidates and reconstructed from chart notes for others. In intubated patients, the National Institutes of Health Stroke Scale and Glasgow Coma Scale were evaluated before intubation. Information on comorbidities and previous medications were retrieved from the province-wide hospital notes of all specialties and general practice referral notes. All scans were evaluated by neuroradiologists at our hospital, and we included all subsequent scans after the ICH in our analysis. Lesion volumes were estimated with the ABC/2 method. 9 We recorded the modified Rankin Scale at discharge but did not have systematic follow-up visits, wherefore functional outcome could not be evaluated after discharge. For this reason, we used mortality at 3 months as our primary outcome with date of death retrieved from Statistics Finland in October 2011 for all residents of our province.

Statistical Analyses
Due to nonnormal distribution of all continuous variables, median with interquartile range are reported. Groups were compared with the independent-samples Kruskal-Wallis test or the Pearson χ² test where appropriate with 2-sided statistical significance set at 0.05. Interrater agreement was evaluated using absolute agreement and nonweighted Cohen κ. Long-term survival is described as a Kaplan-Meier graph and difference in survival tested for with the log rank test. To test the independent prognostic value of the SMASH-U etiologic classification on 3-month mortality, a logistic regression model was constructed with the previously identified 10 covariates of intraventricular or infratentorial hemorrhage, sex, and, as continuous variables, age, arrival National Institutes of Health Stroke Scale, Glasgow Coma Scale, and baseline ICH volume. The relative significance of the model covariates was compared using the Wald statistic, and the overall performance of the model was analyzed with the receiver operating characteristic area under the curve. Analyses were performed on IBM SPSS 20 (IBM Corp, Armonk, NY).

Results
Between January 1, 2005, and March 31, 2010, a total of 1013 patients with ICH were treated at our hospital. Of these, 33 had a history of ICH before the study period, and 16 had more than one separate episodes of ICH during the study period. Overall, 25% of the patients had angiography performed (CT angiography, MR angiography, or digital subtraction angiography) and 6% had their ICH evacuated.

Structural lesions (n=50 [5%]), systemic disease (n=48 [5%]), and anticoagulation (n=143 [14%]) together constituted the ICH etiology in one fourth of our patients. Amyloid angiopathy (n=205 [20%]) and hypertension (n=354 [35%]) were common classifications, whereas 21% of our patients did not fulfill any of the definitions (n=213, of which 54 were cortical <55 years old and the rest deep with no known hypertension). Interrater reliability was high with 92 of 100 patients rated identically by 2 raters (κ, 0.89; 95% CI, 0.82–0.96; P<0.001). Baseline parameters, treatment, and outcome of the patients by SMASH-U class are presented in Table 1.

The identified structural lesions were either cavernomas (n=31) or arteriovenous malformations (n=19). The most common other defined etiologies were hepatopathy (n=23; 3-month mortality 48%) and thrombocytopenia (n=8 [75%]). Rare etiologies consisted of cerebral venous thrombosis (n=2), intravenous amphetamine use (n=2), coagulopathy due to carcinoma (n=2), and one patient each of hyperfusion syndrome after carotid endarterectomy, cerebral vasculitis without infarction, Staphylococcus aureus sepsis, hemorrhagic meningitis, Wernicke encephalopathy, reversible cerebral vasoconstriction syndrome, and presumably hereditary factor VII deficiency. None of these rare cases were fatal by 3 months. One patient with endocarditis and one with thalassemia-related ICH died as did one of the 2 patients with eclampsia included in our series.

Of the patients with anticoagulation-related ICH (n=143), 64 had warfarin within the therapeutic international normalized ratio (INR) range of 2.0 to 3.0 and a high 3-month mortality rate (52%), 56 had INR >3.0 (56%, P=0.58 compared with the therapeutic range), and the remaining 23 patients had full-dose low-molecular-weight heparin, standard heparin, or thrombolytic therapy for noncerebral thrombosis at the time of their ICH (52%). The 8 patients with subtherapeutic warfarin (INR <2.0) at baseline were not classified as anticoagulation-related and none died in 3 months.

Among the patients classified as ICH due to amyloid angiopathy (n=205), only 10 (5%) had definite cerebral amyloid angiopathy (CAA) according to the Boston criteria, a further 2 (1%) had pathology confirmed probable CAA, 36 (18%) had clinically probable CAA with multiple hemorrrhages, whereas in most (n=157 [77%]), the hemorrhage was single and without pathology. In the latter group, 58% had hypertension, representing a competing etiology. Hypertension was less common with cortical ICH than with ICH of any other location (56% versus 68%, P<0.001).

Etiology was classified as undetermined in 21% of patients based on the SMASH-U classification. If also patients with several risk factors for ICH would have been classified as undetermined, this would have increased to 58%.

Twenty-nine patients were lost to 3-month mortality follow-up due to nonresidence in Finland (n=14) or residence outside our province. The overall 3-month mortality rate was 32%. Long-term mortality after the acute phase was stable with median survival at 5.6 years. Survival strongly varied by SMASH-U etiology (Figure 2; P<0.001). In multivariable analysis, SMASH-U etiology was a strong predictor of 3-month mortality (Table 2; receiver operating characteristic area under the curve, 0.911). Based on the Wald statistic, SMASH-U etiology was a stronger predictor of mortality...
than either the patient’s age or ICH volume, next only to baseline National Institutes of Health Stroke Scale score. The variance in the mortality rates among different etiologies arose from the secondary ICH types only. Hypertensive, amyloid, and undetermined ICH 3-month mortality rates differed in univariate ($P=0.02$) but not in multivariable ($P=0.25$) analysis from each other.

### Discussion

We presented a simple highly reproducible etiologic classification for ICH in a large consecutive patient cohort. We classified 55% of ICH as due to hypertensive or amyloid angiopathy; one fourth secondary to underlying lesions, diseases, or medication; and finally one fifth as cryptogenic. This SMASH-U classification was strongly and independently associated with survival.

We applied the World Health Organization clinical definition of stroke solidly established since the 1970s. In ischemic stroke, modern imaging has provided tools to challenge the World Health Organization time-based definition with tissue-based ones, but with ICH, even the original World Health Organization definition has not been quite uniformly interpreted. A recent review of epidemiology of ICH concluded that among high-quality population-based studies (n=40), half did not define ICH in detail (n=17), whereas many excluded ICH due to trauma (n=15), or even arteriovenous malformation (n=3). The World Health Organization definition term “vascular cause” has been interpreted to exclude extracerebral intracranial ICH and ICH due to malignancy or trauma, as we did.

With inconsistency in classifying certain ICH as stroke or nonstroke, there has been even less consensus on defining...
ICH subtypes. It is known that hypertension, amyloid angiopathy, anticoagulation, and several other secondary causes are risk factors for ICH and often coexist. We aimed to develop a simple and practical etiology-oriented classification system that is easy to learn, quick to perform, and has high interrater agreement. For this purpose we preferred to avoid classifying patients as undetermined due to multiple possible etiologies, recognizing this as a practical simplification. In reality, few patients presented with a definite single cause of ICH. Should all risk factors be considered equal, 58% of our patients would have been of undetermined etiology and the classification less useful. Our preference of certain risk factors was based on presumption. Assuming an arteriovenous malformation at the ICH site to be causal, rather than coexisting hypertension, seems reasonable. Similarly, full anticoagulation may be more important than assumed angiopathy, although both may contribute.

Hypertension often exists with lobar hemorrhages, although less commonly than with deep ICH both in our series (56% versus 68%) and in others (48% versus 70%). The difference between assumed hypertensive and amyloid etiology is based on deep versus superficial hemorrhage location, as per the Boston criteria. In the absence of pathology, or even with it, solid differentiation between amyloid and hypertensive ICH is difficult. Indeed, 38% of patients with possible CAA by the Boston criteria show no pathological findings of CAA. Similarly, the distinction between hypertensive and undetermined etiology is vague and depends on the definition of hypertension. We, as have others, classified deep hemorrhages as hypertensive only when previous definite hypertension could be demonstrated.

Many studies have included anticoagulation-related ICH as “primary” ICH, not separating this subgroup. Based on our data, anticoagulation-related ICH, even when within the therapeutic range as was the case in most of our patients and those of other series, follows a much grimmer prognosis than other “primary” ICH. The Boston criteria may classify anticoagulation-related ICH as CAA when INR is up to 3.0. In our series, subtherapeutic INR <2.0 was not associated with increased mortality. Classifying patients with subtherapeutic INR as anticoagulation-related ICH, as many have done, might be incorrect for prognostic purposes.

Although secondary prevention of ICH is not determined by etiology as much as it is with ischemic stroke, ICH etiology has a strong prognostic value. Based on previous literature, prognosis of ICH related to arteriovenous malformation was known to be better and that of anticoagulation-related ICH worse than with other ICH. The ICH score developed by Hemphill and coworkers has been validated and used to evaluate the outcome of patients with ICH. In their small cohort of 152 patients, etiology defined as “impression of the treating physician” did not predict patient outcome. Prognostic factors included in our model have been previously prospectively validated to produce a good receiver operating characteristic area under the curve of 0.88. In our series, adding etiology produced an even more discriminatory model (receiver operating characteristic area under the curve, 0.91). Etiology seems to be a major determinant of mortality.

Our study has limitations. First, this is a retrospective analysis of consecutive patients with ICH in routine practice. Management and diagnostics varied, and there was no systematic follow-up for functional outcome. However, early death is common in ICH and the outcome of mortality robust. Second, our study is hospital-based and single-center. In Finland, a hospital-based approach imposes a smaller selection than in most countries with 97% of our patients with stroke treated as inpatients and 94% sensitivity of International Classification of Diseases, 10th Revision to capture population-based ICH. However, referral bias is possible with one third of the patients with ICH in our province being treated in other hospitals. Over the study period, the 3-month mortality rate of all patients with ICH in Finland was 35% and median survival 4½ years compared with our 32% and 5½ years. The difference may hint a selection bias or
simply reflect quality of care. Third, this classification was developed echoing our preconceived ideas of most likely etiologies. Lacking pathological verification, some true brain pathology and specific etiologies have certainly been misclassified. Finally, this etiologic classification has to be validated in an external data set preferably in a prospective series.

In summary, the SMASH-U classification for ICH etiology is practical to perform, has excellent interrater agreement, and was in our series strongly associated with patient outcome.

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Disclosures
Dr Meretoja has received compensation for consultancy from Boehringer-Ingeheim (modest). Dr Putaala has received travel expenses from Boehringer-Ingeheim and Genzyme and honoraria from Boehringer-Ingeheim (all modest). Dr Sairanen has received honoraria from Boehringer-Ingelheim for speaking and industry-funded travel for scientific meetings from Boehringer Ingelheim and Allergan (all modest). Dr Kaste has received honoraria and travel expenses for participating on the Steering Committee meetings of the Terutroban (all modest). Dr Kaste has received honoraria and travel expenses for speaking and industry-funded travel for scientific meetings from Boehringer Ingelheim for speaking and industry-funded travel for scientific meetings from Boehringer Ingelheim and Allergan (all modest). Dr Kaste has received honoraria and travel expenses for participating on the Steering Committee meetings of the Terutroban (all modest). Dr Kaste has received honoraria and travel expenses for participating on the Steering Committee meetings of the Terutroban (all modest).

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