The Heidelberg Bleeding Classification
Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy

Rüdiger von Kummer, DrMed; Joseph P. Broderick, MD; Bruce C.V. Campbell, MD; Andrew Demchuk, MD; Mayank Goyal, MD; Michael D. Hill, MD; Kilian M. Treurniet, MD; Charles B.L.M. Majoie, MD; Henk A. Marquering, PhD; Michael V. Mazya, MD; Luis San Román, MD; Jeffrey L. Saver, MD; Daniel Strbian, MD; William Whiteley, MD; Werner Hacke, DrMed

Intracranial hemorrhage is an important safety end point in clinical trials.1-6 Yet, not each intracranial hemorrhage detected by computed tomography (CT) or magnetic resonance imaging (MRI) worsens neurological symptoms and impairs outcomes. Consequently, intracranial hemorrhages after ischemic stroke and reperfusion therapy are classified by both imaging characteristics and the association with clinical worsening. Pure radiological classification uses the location, form, and extent of hemorrhage and its relation to ischemic injury to distinguish among hemorrhage subtypes that may differ in impairment of neurological function and prognosis. Mixed radiological–clinical classification adds clinical symptoms to the presence of radiological hemorrhage to classify intracranial hemorrhages as symptomatic or asymptomatic.

Historically, modern approaches to classifying hemorrhage after reperfusion therapy began with the emphasis of Pessin et al1 on the radiographic distinction between hemorrhagic infarction (HI) and parenchymatous hematoma (PH) after embolic stroke. They stated that HI refers to the pathological condition in which petechial or more confluent hemorrhages occupy a portion of an area of ischemic infarction. PH in an area of infarction; in contrast, is a solid clot of blood with mass effect, which displaces and destroys brain tissue.1 They later proposed that HI (in contrast to PH) could be more of a CT curiosity than a dreaded complication.2 Wolpert et al3,4 defined HI as areas of barely visible increased density with indistinct margins within an infarct or areas of increased density with indistinct margins and a speckled or mottled appearance or multiple areas of coalescent hemorrhage. A mass effect could be present because of the either edema or hemorrhagic component and PH (later named parenchymal hematoma)5 and as very dense, homogenous region(s) of circumscribed increased density usually with mass effect. Both HI and PH are presumably caused by the same postischemic pathophysiology, bleeding from damaged reperfused arteries, arterioles, capillaries, or venules.

Levy et al6 first used the term symptomatic intracranial hemorrhage (SICH) and distinguished intracerebral hematoma from hemorrhagic conversion by requiring either contemporaneous neurological worsening or a new mass effect on CT for intracerebral hematoma.

The European Cooperative Acute Stroke Study (ECASS) group graded each HI and PH into the CT grades 1 and 2 to evaluate with greater nuance the clinical relevance of intracranial hemorrhage as detected on CT after ischemic stroke.7 In agreement with histological findings,8,9 the ECASS protocol adapted pre-existing criteria10-13 to define HI 1 as small petechiae along the margins of the infarct, and HI 2 as more confluent petechiae within the infarcted area, but without space-occupying effect. PH 1 was defined as a clot not exceeding 30% of the infarcted area with some mild space-occupying effect. PH 2 represented dense blood clot(s) exceeding 30% of the infarct volume with significant space-occupying effect.9 Interobserver agreement on these categories was good although the justification for the 30%
Threshold between PH1 and PH2 was not clarified. Regardless, in the ECASS, only PH2, but not PH1 or HI, was associated with early deterioration and 3-month mortality. Consequently, the ECASS investigators did not report on SICH, but presented the bleeding categories as detected by CT in their trial populations. The National Institute of Neurological Disorders and Stroke (NINDS) recombinant tissue-type plasminogen activator (tPA) Stroke Study Group considered in their 2 trials an intracranial hemorrhage that occurred within 36 hours of treatment onset as symptomatic if it was not seen on a previous CT scan, and there had subsequently been either a suspicion of hemorrhage or any decline in neurological status. The protocol of the 2 NINDS studies required brain CT on day 1 and 7 after treatment. Without defining the type of brain hemorrhage and the severity of neurological symptoms associated with the CT finding, the NINDS investigators observed 12 of 168 patients (7%) with SICH after tPA and 2 of 165 patients (1%) after placebo. In ECASS II, the investigators categorized intracranial hemorrhages into HI1, HI2, PH1, and PH2 and defined SICH as blood at any site in the brain on the CT scan (as assessed by the CT reading panel, independently of the assessment by the investigator), documentation by the investigator of clinical deterioration, or adverse events indicating clinical worsening (eg, drowsiness and increase of hemiparesis) or causing an increase in the National Institutes of Health Stroke Scale (NIHSS) score of ≥4 points. A post hoc analysis of the ECASS II data confirmed PH2 as an independent variable associated with death at 3 months after ischemic stroke. The Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) defined symptomatic intracerebral hemorrhage as local or remote PH2 on 22- to 36-hour post-treatment imaging, combined with a neurological deterioration of ≥4 points on the NIHSS from baseline, from the lowest NIHSS value between baseline and 24 hours, or leading to death. The SITS-MOST investigators reported that 107 patients of 6444 treated patients (1.7%) fulfilled these criteria. The ECASS III investigators defined SICH as any hemorrhage with neurological deterioration, as indicated by an NIHSS score that was higher by ≥4 points than the value at baseline or the lowest value in the first 7 days or any hemorrhage leading to death. In addition, the hemorrhage must have been identified as the predominant cause of the neurological deterioration. They implemented for the first time a causal relationship between brain imaging findings and neurological deterioration in the definition, taking into account that other brain pathology than hemorrhage could impair neurological function. With this definition, the ECASS III investigators identified 10 patients with SICH among 418 alteplase-treated patients (2.4%) and 1 SICH patient among 403 placebo-treated patients (0.2%). When applying other SICH definitions for this study population, the incidences of SICH after tPA were 7.9% (NINDS), 5.3% (ECASS II), and 1.9% (SITS-MOST). Treatment with tPA increased the odds of SICH by an odds ratio of 2.4 (NINDS), 2.4 (ECASS II), 7.8 (SITS-MOST), and 9.9 (ECASS III). Subsequent studies confirmed that the NINDS definition of symptomatic hemorrhage was overly inclusive, capturing many cases in which the bleeding did not worsened final functional outcome. The NINDS investigators desired to select a definition that maximized the sensitivity to any risk related to bleeding associated with tPA, and the NINDS definition served this purpose well. However, as shown above, the definition of SICH used by ECASS III and SITS-MOST provided better discrimination between tPA and placebo as measured by odds ratio and better identification of bleeds associated with altered final clinical outcome.

In the International Stroke Trial-3 (IST-3), SICH was defined as a clinically significant deterioration or death within the first 7 days of treatment with evidence of either significant brain parenchymal hemorrhage (local or distant from the infarct) or significant hemorrhagic transformation (HT) of an infarct on brain imaging. This inclusive definition captured a similarly large group of patients as the NINDS Study definition (with an absolute risk of SICH of 6.8% [104 of 1515] by <7 days of randomization), although after taking account of stroke severity and age, there was no evidence that the relative risk of bleeding with alteplase was higher in IST-3 than in other trials. The risk of poor outcome in patients who had an SICH was high: by 6 months after randomization, few patients were independent in activities of daily living (8 of 104; 8%).

On the basis of this experience, we found that the adoption of a single classification scale for SICH is clearly needed. Moreover, the advent of neurothrombectomy devices mandated an expansion in the classification of hemorrhage after recanalization therapy for acute ischemic stroke. The intravenous thrombolysis trials had focused on parenchymal bleeds because HT of the ischemic brain is the predominant event after lytic treatment. However, subarachnoid hemorrhage (SAH) is a complication after neurothrombectomy because of perforating or dissecting injury by the device, guidewire, or catheter. The MERCI trial defined any SAH as symptomatic, but this definition was quickly recognized as overly inclusive because many minor SAHs occur without functional impact. A more contemporary approach was taken in the Solitaire With the Intent for Thrombectomy (SWIFT) trial, which recognized 7 types of intracranial hemorrhage, including the 4 types of hemorrhage within the infarct field delineated above (HT1, HT2, PH1, and PH2) plus SAH, intraventricular hemorrhage, and remote intracerebral hemorrhage. A more contemporary approach was taken in the Solitaire With the Intent for Thrombectomy (SWIFT) trial, which recognized 7 types of intracranial hemorrhage, including the 4 types of hemorrhage within the infarct field delineated above (HT1, HT2, PH1, and PH2) plus SAH, intraventricular hemorrhage, and remote intracerebral hemorrhage. A more contemporary approach was taken in the Solitaire With the Intent for Thrombectomy (SWIFT) trial, which recognized 7 types of intracranial hemorrhage, including the 4 types of hemorrhage within the infarct field delineated above (HT1, HT2, PH1, and PH2) plus SAH, intraventricular hemorrhage, and remote intracerebral hemorrhage.

### Table 1. Anatomic Description of Intracranial Hemorrhages

<table>
<thead>
<tr>
<th>Class</th>
<th>Type</th>
<th>Description</th>
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<tbody>
<tr>
<td>1</td>
<td>Hemorrhagic transformation of infarcted brain tissue</td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>HI1</td>
<td>Scattered small petechiae, no mass effect</td>
</tr>
<tr>
<td>1b</td>
<td>HI2</td>
<td>Confluent petechiae, no mass effect</td>
</tr>
<tr>
<td>1c</td>
<td>PH1</td>
<td>Hematoma within infarcted tissue, occupying &lt;30%, no substantial mass effect</td>
</tr>
<tr>
<td>2</td>
<td>Intracerebral hemorrhage within and beyond infarcted brain tissue</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>PH2</td>
<td>Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect</td>
</tr>
<tr>
<td>3</td>
<td>Intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>Parenchymal hematoma remote from infarcted brain tissue</td>
<td></td>
</tr>
<tr>
<td>3b</td>
<td>Intraventricular hemorrhage</td>
<td></td>
</tr>
<tr>
<td>3c</td>
<td>Subarachnoid hemorrhage</td>
<td></td>
</tr>
<tr>
<td>3d</td>
<td>Subdural hemorrhage</td>
<td></td>
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</table>

HI indicates hemorrhagic infarction; and PH, parenchymatous hematoma.
hemorrhage—any intraparenchymal hemorrhage remote from the ischemic field. Symptomatic hemorrhage was defined as any PH1, PH2, remote intracerebral hemorrhage, SAH, or IVH associated with a decline in NIHSS ≥4 within 24 hours of the end of the revascularization procedure.23

Properties of an Optimal Intracranial Hemorrhage Classification for Clinical Trials

1. It should capture and describe all types of intracranial hemorrhages.
2. It should differentiate between asymptomatic (which may be irrelevant for prognosis) and SICH.
3. It should help to assess the relatedness between intracranial hemorrhage and therapeutic intervention.
4. It should be simple to administer, reducing costs on trialists, researchers, and drug developers, and on clinicians and hospital systems.
5. It should have a high inter-rater reliability.
6. It should be easily understandable for clinicians and patients, to allow easy communication of risk.

Heidelberg Classification

We are proposing here the Heidelberg Bleeding Classification, developed during the XII Thrombolysis Symposium on Thrombolysis, Thrombectomy, and Ischemic Stroke Treatment held in Heidelberg/Mannheim, Germany, where the summary of this article was first discussed. Representatives from the Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times (ESCAPE), SWIFT Primary Endovascular Treatment for Acute Ischemic Stroke (PRIME), the Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial (EXTEND-IA), the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN), and the Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset (REVASCAT) trials have joined this initiative and contributed with their experience gained in recent trials on endovascular stroke treatment.24–28

A classification of bleeding events after reperfusion therapy for reporting in trials, registries, quality improvement
projects, and scientific articles should include both a pure radiological classification scheme and a combined radiological-symptomatic classification scheme. The pure imaging scheme provides an objective comparison among different series, based solely on radioanatomic features of the hemorrhage. Assessment of impact on the clinical course, in contrast, will inevitably be more variable across studies, depending on the intensity of monitoring for early neurological worsening and validity of functional outcome assessments. Such differences can be expected because of methodological differences between intensely regulated registration trials, national and multinational registries with potential audit, and single-center reports. Despite the greater variability of clinical assessment, a combined radiological–clinical schema incorporating a measure of functional impact of hemorrhage is desirable, as the symptomatic consequences of HT differentiate bleeding events with impact on neurological function and potentially on prognosis from pathological findings without clinical relevance. In addition, both types of classification schemes must be practical and feasible under trial and registry conditions.

The development of intracranial hemorrhage after ischemic stroke has been prospectively studied with serial CT and

Table 2. Recommended Procedural Reporting and Classification of Intracranial Hemorrhages and Their Relationship to Clinical Events in Trials and Registries

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
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| 1    | Brain imaging  
Scheduled according protocol within 48 h after treatment  
Unscheduled triggered by symptoms suggestive of intracerebral hemorrhage |
| 2    | Independent and blinded review of imaging |
| 3    | Anatomic description of intracranial hemorrhages (Table 1) |
| 4    | Adjudication of the cause of neurological deterioration in the presence of intracranial hemorrhage |
| 4a   | SICH: new intracranial hemorrhage detected by brain imaging associated with any of the item below:  
≥4 points total NIHSS at the time of diagnosis compared to immediately before worsening. Note that a 4 points change is not compared with the baseline admission NIHSS score but instead to the immediate predeterioration neurological status  
≥2 point in one NIHSS category. The rationale for this is to capture new hemorrhages that produce new neurological symptoms, making them clearly symptomatic but not causing worsening in the original stroke territory. For example, a new remote hemorrhage in the contralateral occipital lobe may cause new hemianopia that is clearly symptomatic but the patient will not have worsening of ≥4 points on the NIHSS score  
Leading to intubation/hemicraniectomy/EVD placement or other major medical/surgical intervention. |
| 4b   | aSICH: new hemorrhage that has no implications for prognosis or change in management, and there is no substantive change in the patient’s neurological status |
| 5    | Establishing the relatedness of deterioration and imaging findings  
In patients with neurological deterioration the relationship between clinical deterioration as defined in 4a and the hemorrhagic event is  
Definite: if any intracranial hemorrhage is the dominant brain pathology on imaging causal for deterioration  
Probable: in the presence of PH2, even if the ischemic infarct may have contributed to deterioration.  
Possible: in the presence of HI2, PH1, rPH, IVH, SAH, SDH, even if ischemic infarct may have contributed predominantly to the deterioration  
Unlikely: in the presence of HI1 |
| 6    | Categories for trial or registry reporting  
Definite and probable: hemorrhage shall be classified as symptomatic  
Possible and unlikely: hemorrhage shall be classified as asymptomatic |
| 7    | Adjudication of relatedness of intracranial hemorrhage (symptomatic and asymptomatic) to therapeutic intervention  
Relatedness is defined by  
Treatment with thrombolytic agents (IV or IA) within the last 24 h  
Area of hemorrhage compatible with endovascular complication (regional and temporal relationship)  
Documented complication of angiographic procedure  
Levels of certainty of relatedness  
Definite: observed procedural complication eg, perforation of intracranial artery  
Probable: treatment within last 24 h. PH, symptomatic or asymptomatic  
Possible: treatment within last 24 h. HI, symptomatic, or asymptomatic  
Unrelated: no therapeutic intervention during the last 24 h before detection of hemorrhage  
Hemorrhage is spontaneous. Any anatomic type, symptomatic or asymptomatic |

aSICH indicates asymptomatic intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale; EVD, external ventricular drain; HI, hemorrhagic infarction; IA, intraarterial; IV, intraventricular; rPH, remote from infarcted brain tissue; SAH, subarachnoid hemorrhage; and SDH, subdural hemorrhage.
MRI. HT is a natural consequence of ischemic blood–brain barrier breakdown that occurs mainly within 2 weeks of ischemic stroke.7 Because tPA has a short half-life and other reperfusion therapies including mechanical recanalization have a relatively rapid effect, intracranial hemorrhages within 24 hours of treatment are likely to be related to reperfusion therapy, whereas those beyond 1 week of treatment are likely to be a consequence of the pathophysiology of ischemic stroke.16,30

We recommend routine follow-up brain imaging with either CT or MRI at baseline and within 48 hours after reperfusion treatment and thereafter triggered by nausea, headache, impaired cognitive function, or neurological deterioration of ≥4 points NIHSS when compared with NIHSS at baseline or the lowest value thereafter before neurological deterioration (Table 2). A change in NIHSS by ≥4 points is widely accepted as a relevant change in neurological symptoms that can be reliably assessed.31

Intracranial hemorrhage after treatment of ischemic stroke can be subdural, subarachnoid, intracerebral, and intraventricular, and within and without ischemic brain tissue lesions (Table 1). Intracerebral hemorrhage should be categorized into HTs of ischemic brain tissue, categorized as HI type 1 (HI1), type 2 (HI2), or parenchymal hematoma type 1 (PH1) (Figure 1) and more extended parenchymal hematoma that may exceed the ischemic lesion (Figure 1D) or occur remote from it (Figure 2). Only larger hemorrhages (PH2) and co-occurring remote from infarcted brain tissue are associated with early deterioration and increased mortality and disability.10,13,32 We regard, therefore, PH2 as an entity distinct from hemorrhagic transformations: HI1, HI2, and PH1. The differentiation of PH2 from PH1 is hardly possible by comparing its volumes alone.33 The main feature of PH2 is that it occupies ≥30% of the infarcted tissue and often exceeds the borders of ischemic lesion being more than just a transformation of ischemic tissue (Figure 1D). Table 1 provides the main features that help to differentiate PH2 from PH1.

Identification of SICH

Symptomatic ICH is a clinical event caused by intracranial hemorrhage. Table 2 presents a procedural sequence for reporting of bleeding events in 7 steps. We expect that intracranial hemorrhage of relevant size may compress intact brain tissue causing neurological symptoms and an increase in the NIHSS score. We consider an increase by ≥4 points or an increase by ≥2 points of a NIHSS subcategory as a relevant change in neurological status, potentially associated with a worsened long-term prognosis. Therefore, all study patients should be followed closely with an NIHSS at least daily ≤5 days or day of discharge. Each increase in NIHSS by ≥4 points or ≥2 points NIHSS subcategory should trigger brain imaging with either CT or MRI (Table 2).

In patients with neurological deterioration, we recommend the approach outlined in Table 2 for adjudicating the causal relatedness between the hemorrhage and the early deterioration.

CT or MRI

CT and MRI are both sensitive for acute PH. MRI is more sensitive than CT in detecting HI, in particular, when gradient

References


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