

## Treatment and Outcome of Hemorrhagic Transformation After Intravenous Alteplase in Acute Ischemic Stroke A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

*The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.*

*The American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Cerebrovascular Section affirms the educational benefit of this document.*

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**Purpose**—Symptomatic intracranial hemorrhage (sICH) is the most feared complication of intravenous thrombolytic therapy in acute ischemic stroke. Treatment of sICH is based on expert opinion and small case series, with the efficacy of such treatments not well established. This document aims to provide an overview of sICH with a focus on pathophysiology and treatment.

**Methods**—A literature review was performed for randomized trials, prospective and retrospective studies, opinion papers, case series, and case reports on the definitions, epidemiology, risk factors, pathophysiology, treatment, and outcome of sICH. The document sections were divided among writing group members who performed the literature review, summarized the literature, and provided suggestions on the diagnosis and treatment of patients with sICH caused by systemic thrombolysis with alteplase. Several drafts were circulated among writing group members until a consensus was achieved.

**Results**—sICH is an uncommon but severe complication of systemic thrombolysis in acute ischemic stroke. Prompt diagnosis and early correction of the coagulopathy after alteplase have remained the mainstay of treatment. Further research is required to establish treatments aimed at maintaining integrity of the blood-brain barrier in acute ischemic stroke based on inhibition of the underlying biochemical processes. (*Stroke*. 2017;48:e343–e361. DOI: 10.1161/STR.000000000000152.)

**Key Words:** AHA Scientific Statements ■ stroke ■ therapeutics ■ thrombolytic therapy  
■ tissue plasminogen activator ■ treatment outcome

Intravenous alteplase improves outcome in selected patients with acute ischemic stroke when given within 4.5 hours from onset.<sup>1,2</sup> Despite its efficacy, the use of alteplase is limited by the risk of hemorrhagic complications, particularly

symptomatic intracranial hemorrhage (sICH). The risk of sICH varies on the basis of patient population and the definition of sICH used but generally ranges from 2% to 7%.<sup>3</sup> Treatment of alteplase-associated sICH is based on expert

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opinion and small case series, and the efficacy of such treatments is not well established. In this scientific statement, we aim to provide an overview of sICH with a focus on pathophysiology and treatment.

### Definitions of sICH

Classification of sICH after thrombolytic therapy is typically based on 2 main factors: the radiographic appearance of the hemorrhage and the presence of associated neurological deterioration. Radiographic classification of postthrombolytic intracranial hemorrhage (ICH) has traditionally distinguished between hemorrhagic infarction, which represents petechial hemorrhage into the area of infarction, and parenchymal hematoma, representing a sharply defined area of hemorrhage with or without mass effect (Figure 1).<sup>4</sup> Limitations of this radiological categorization scheme include the lack of explicit distinction between parenchymal hematomas within as opposed to remote from the area of infarction and the lack of clear criteria to categorize subarachnoid, subdural, or intraventricular hemorrhage. To address these issues, an expanded radiographic classification system, the Heidelberg Bleeding Classification, has recently been proposed (Table 1).<sup>5</sup> The integration of ICH and clinical neurological deterioration in the setting of alteplase is challenging given that variable definitions of neurological deterioration may be used and deterioration may occur for reasons other than ICH. A number of definitions of sICH have been used or proposed for use in clinical trials of thrombolytic therapy (Table 2). The choice of sICH definition has a dramatic impact on the reported sICH rate (see Incidence)<sup>2</sup>; therefore, comparison of sICH rates across studies must carefully consider the specific sICH

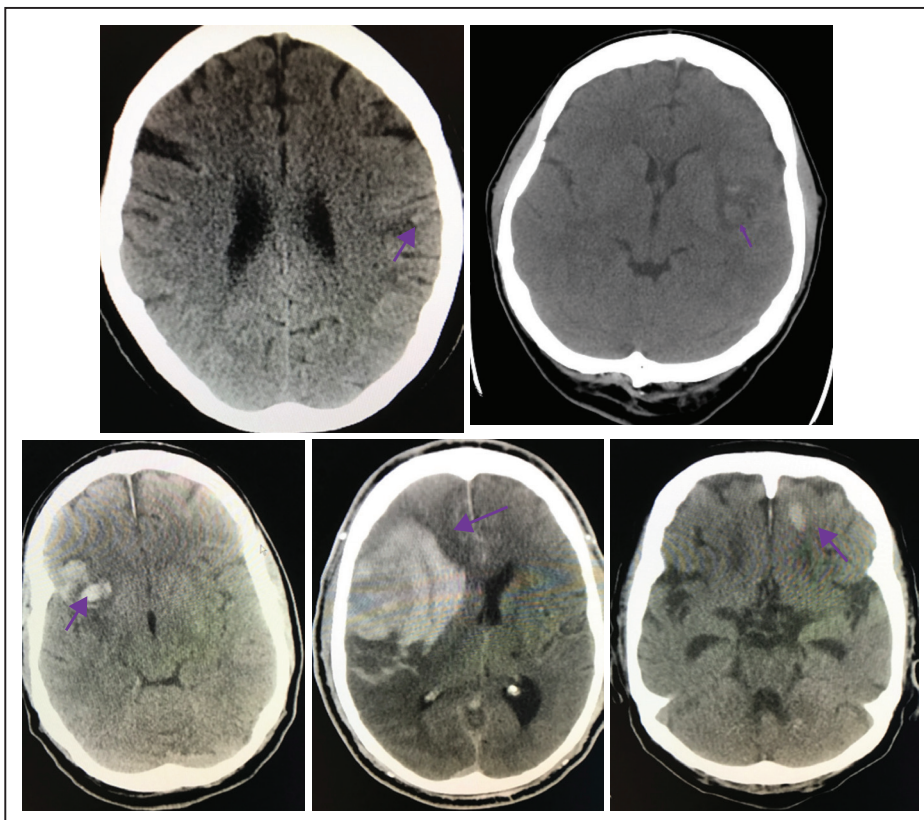
definition used. In addition, the interrater agreement for different definitions of sICH varies significantly, as does the correlation with clinical outcomes such as mortality.<sup>11</sup> Although the ECASS (European Cooperative Acute Stroke Study) II definition appears to have the highest interrater agreement,<sup>3,11</sup> the SITS-MOST (Safe Implementation of Thrombolysis in Stroke: Monitoring Study) definition correlates most strongly with mortality.<sup>3,11,12</sup>

In summary, the definitions of sICH used are widely variable, depending on the radiological classification of hemorrhage and degree of neurological deterioration, and this should be taken into account in the reporting and interpretation of sICH rates. To allow proper comparisons with clinical trial benchmarks, stroke centers should classify the appearance of hemorrhagic transformation according to radiographic criteria (hemorrhagic infarction [HI] type 1, HI-2, parenchymal hematoma [PH] type 1, PH-2, or remote ICH), assess the degree of neurological worsening by National Institutes of Health Stroke Scale (NIHSS) point change, and provide an attribution of causality for the worsening.

### Epidemiology of sICH

#### Incidence

Early-phase randomized trials of fibrinolytic therapy in acute myocardial infarction required dose reduction of concurrent intravenous heparin because of excessive risk of sICH (pooled rate, 1.56%; range, 0.92%–2.80%). Rates of sICH in the 7 major published randomized trials of patients with acute myocardial infarction treated with alteplase and low-dose heparin ranged from 0.64% to 0.94%.<sup>13</sup> Because of this feared complication, acute stroke clinical trials were designed to minimize



**Figure 1.** Radiographic classification of hemorrhagic transformation with the blue arrow in each figure showing the hemorrhage. **Top left,** Hemorrhagic infarction type 1. **Top right,** Hemorrhagic infarction type 2. **Bottom left,** Parenchymal hematoma type 1. **Bottom middle,** Parenchymal hematoma type 2. **Bottom right,** Extradural hematoma.

**Table 1. Radiographic Classification of Postthrombolysis Intracerebral Hemorrhage**

NINDS Trial Criteria		ECASS*		Proposed Heidelberg Classification Scheme†	
HI	Acute infarction with punctate or variable hypodensity/hyperdensity with an indistinct border within the vascular territory	HI-1	Small petechiae	1a	HI1, scattered small petechiae, no mass effect
PH	Typical homogeneous, hyperdense lesion with a sharp border with or without edema or mass effect	HI-2	More confluent petechiae	1b	HI2, confluent petechiae, no mass effect
		PH-1	<30% of the infarcted area with mild space-occupying effect	1c	PH1, hematoma within infarcted tissue, occupying <30%, no substantive mass effect
		PH-2	>30% of the infarcted area with significant space-occupying effect	2	Hematoma occupying ≥30% of the infarcted tissue with obvious mass effect
				3a	Parenchymal hematoma remote from infarcted brain tissue
				3b	Intraventricular hemorrhage
				3c	Subarachnoid hemorrhage
				3d	Subdural hemorrhage

ECASS indicates European Cooperative Acute Stroke Study; HI, hemorrhagic infarction; NINDS, National Institute of Neurological Diseases and Stroke; and PH, parenchymal hematoma.

\*HI: petechial infarction without space-occupying effect. PH: hemorrhage (coagulum) with mass effect.

†1: Hemorrhagic transformation of infarcted brain tissue. 2: Intracerebral hemorrhage within and beyond infarcted brain tissue. 3: Intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage.

this risk on the basis of previous acute myocardial infarction experience.

The incidence of sICH after alteplase in the modern era at the standard dose of 0.9 mg/kg administered over 1 hour with a 10% bolus varies from 2% to 7% in clinical trials and prospective stroke registries. This variation is likely the result of differences in study design, the populations treated, and the definitions of sICH.<sup>3</sup> Site of image adjudication, timing and type of required follow-up imaging, method of assessing and categorizing clinical worsening, and whether a causal relationship is required between imaging and clinical worsening have all varied across studies and definitions (Table 2).

Among 6756 patients pooled from 9 randomized trials,<sup>14</sup> the risk of sICH was greater with alteplase compared with placebo for several sICH definitions: ECASS III (6.8% versus 1.3%; odds ratio [OR] 5.55; 95% confidence interval [CI], 4.01–7.70), SITS-MOST (3.7% versus 0.6%; OR, 6.67; 95% CI, 4.11–10.84), and fatal hemorrhage (2.7% versus 0.4%; OR, 7.14; 95% CI, 3.98–12.79). In the NINDS (National Institute of Neurological Disorders and Stroke) trial cohort and using the definition from that trial, the sICH rate was also higher with alteplase compared with placebo (6.4% versus 0.6%; *P*<0.01).<sup>1</sup> Despite initial fears that excessive rates of sICH would eradicate the benefit of alteplase in clinical practice, large registries of postapproval use of alteplase demonstrated reassuringly low sICH rates ranging between 2% and 7% despite varying definitions.<sup>9,15</sup> An important limitation of these registry data, however, is the lack of central adjudication of imaging results or clinical worsening.

The risk of sICH resulting from the use of alteplase is likely to be related to the dose of alteplase used, with higher rates noted at doses >0.9 mg/kg.<sup>16,17</sup> A recent randomized trial conducted primarily in an Asian population showed a lower rate of sICH with low-dose tissue-type plasminogen activator (tPA; 0.6 mg/kg) compared with full-dose alteplase (1.0% versus 2.1%; *P*=0.01) but did not demonstrate noninferiority of the lower dose for the primary outcome (modified Rankin Scale score <2 at 90 days).<sup>18</sup>

In summary, rates of sICH vary widely across definitions, with a 2.5- to 5-fold variation in rates across studies. Clinical practice experience among centers with protocols and trained personnel suggests that rates of sICH are similar to those observed in the initial clinical trials.

**Risk Factors and Prediction Scores**

A number of clinical, laboratory, and radiographic factors associated with the risk of sICH after alteplase have been reported. The evidence supporting these associations is variable, with some evidence consistently demonstrated across multiple studies and other evidence shown only in small, single-center cohort studies. In a systematic review and meta-analysis of 55 studies, older age, greater stroke severity, higher baseline glucose, hypertension, congestive heart failure, renal impairment, diabetes mellitus, ischemic heart disease, atrial fibrillation, baseline antiplatelet use, leukoaraiosis, and visible acute infarction on brain imaging were all associated with increased risk of sICH, whereas current smoking was associated with a reduced risk.<sup>19</sup> Statin use was also associated with sICH in this meta-analysis based on a small number

**Table 2. Definitions of Symptomatic Intracerebral Hemorrhage After Alteplase**

Trial	Clinical	Radiographic	Causality of Neurological Deterioration	Time Frame
PROACT-2 <sup>6</sup>	Neurological deterioration defined as a $\geq 4$ -point increase in the NIHSS score or a 1-point deterioration in level of consciousness	Any hemorrhage on CT	Caused by hemorrhage	24 h
NINDS <sup>1</sup>	Any clinical suspicion of hemorrhage or any decline in neurological status	Any hemorrhage on CT	Regardless of causal relationship	CT required at 24 h and 7–10 d after stroke onset and with any clinical change suggestive of hemorrhage; primary analysis evaluated hemorrhage within 36 h
ECASS II <sup>7</sup>	Clinical deterioration or adverse events indicating clinical worsening (eg, drowsiness, increase of hemiparesis) or causing an increase in NIHSS score of $\geq 4$ points	Any hemorrhage on CT	Regardless of causal relationship	CT done at 22–36 h and 7 d after stroke onset
ECASS III <sup>2</sup>	Clinical deterioration defined by an increase of $\geq 4$ points in NIHSS score or that led to death	Any hemorrhage	Hemorrhage as the predominant cause of the neurological deterioration	CT/MRI required at 22–36 h after stroke onset
SITS-MOST <sup>9</sup>	Neurological deterioration indicated by an NIHSS score that was $\geq 4$ points higher than the baseline value or the lowest value between baseline and 24 h or hemorrhage leading to death	Local or remote PH-2	Regardless of causal relationship	CT/MRI 22–36 h after stroke onset
GWTC-S <sup>9</sup>	Any neurological deterioration	Any hemorrhage on CT	Causal	CT/MRI 24–36 h after onset
IST-3 <sup>10</sup>	Clinically important worsening of deficit measured on a valid stroke scale or the occurrence of a clinical syndrome suggesting recurrent stroke	Significant hemorrhage	Hemorrhage sufficient to have contributed to the deterioration	CT/MRI required at 24–48 h and with any clinical change; primary analysis evaluated hemorrhage within 7 d
Heidelberg classification scheme <sup>5</sup>	Clinical deterioration defined as increase of $\geq 4$ points in total NIHSS score at the time of diagnosis compared with immediately before worsening or $\geq 2$ points in 1 NIHSS category, or leading to intubation, hemicraniectomy, ventricular drain placement, or other major medical/surgical intervention	Any hemorrhage	Absence of alternative explanation for deterioration	24 h after intervention

CT indicates computed tomography; ECASS, European Cooperative Acute Stroke Study; GWTC-S, Get With The Guidelines–Stroke; IST, International Stroke Trial; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Diseases and Stroke; PH, parenchymal hematoma; PROACT, Prolyse in Acute Cerebral Thromboembolism; and SITS-MOST, Safe Implementation of Thrombolysis in Stroke: Monitoring Study.

of subjects but was not confirmed in a subsequent study of >20 000 patients.<sup>20</sup> Time from symptom onset to alteplase was not associated with sICH risk in this meta-analysis, a finding in line with other studies.<sup>14,21</sup> Microhemorrhages on pretreatment magnetic resonance imaging have also been associated with an increased risk of sICH after alteplase, although the absolute risk increase is relatively modest.<sup>22</sup>

Many factors associated with sICH are closely interrelated, and this limits the assessment of the independent additive risk of each factor, particularly in small studies that lack the power to perform sufficient multivariable analyses. For instance, atrial fibrillation, warfarin use (regardless of prothrombin time), age, and clinical stroke severity have all been found to increase risk of sICH, but each of these is generally correlated with the other factors.<sup>23</sup> Furthermore, the increase in absolute risk of sICH associated with each of these factors also varies widely; this is an important point to consider in the assessment of their clinical significance. Stroke severity as assessed

by NIHSS score is one of the factors most robustly associated with sICH risk. In a pooled analysis of 6756 patients from multiple randomized trials comparing alteplase with placebo, the absolute risk of fatal sICH in the alteplase arm increased from 1.6% with a baseline NIHSS score of 5 to 10 to 6.8% with an NIHSS score >21.<sup>14</sup>

These limitations have motivated attempts to create scoring systems integrating multiple factors to better predict risk of sICH in individual patients. At least 7 such risk prediction scores have been proposed (Table 3).<sup>9,24–29</sup> Validation studies comparing these scores in different populations of alteplase-treated patients have shown similar predictive values for the various scores (Table 3).<sup>30–37</sup> Although these scores generally are effective at estimating the incremental sICH risk facing individual patients, the upper range of absolute sICH risk predicted by the scores does not justify withholding thrombolytic therapy. Patients who may be at highest predicted risk for sICH are also likely to have very poor outcomes without

**Table 3. Postthrombolysis Symptomatic Intracerebral Hemorrhage Prediction Scores**

Score	Components	Receiver-Operating Characteristic Curve (C Statistics)
MSS <sup>24</sup>	Age, NIHSS score, glucose, platelets (0–4 points)	0.59–0.86
HAT <sup>25</sup>	NIHSS score, diabetes mellitus or glucose, early CT hypodensity (0–5 points)	0.59–0.79
SEDAN <sup>26</sup>	Age, NIHSS score, glucose, hyperdense middle cerebral artery sign, early CT hypodensity (0–5 points)	0.50–0.70
SITS-ICH <sup>27</sup>	Age, NIHSS score, glucose, weight, hypertension, antiplatelet therapy (none, aspirin, aspirin+clopidogrel), systolic blood pressure, onset-to-treatment time (0–12 points)	0.58–0.76
GRASPS GWTG <sup>9</sup>	Age, NIHSS score, glucose, systolic blood pressure, Asian vs non-Asian ethnicity, sex (0–101 points)	0.61–0.83
THRIVE <sup>28</sup>	Age, NIHSS score, hypertension, diabetes mellitus, atrial fibrillation (0–9 points)	0.6
SPAN-100 <sup>29</sup>	Age, NIHSS score (0–1 points)	0.55–0.57

CT indicates computed tomography; GRASPS, glucose at presentation, race (Asian), age, sex (male), systolic blood pressure at presentation, and severity of stroke at presentation (NIHSS); GWTG, Get With The Guidelines; HAT, Hemorrhage After Thrombolysis; MSS, Multicenter Stroke Survey; NIHSS, National Institutes of Health Stroke Scale; SEDAN, blood sugar, early infarct signs, hyperdense cerebral artery sign, age, NIHSS; SITS-ICH, Safe Implementation of Thrombolysis in Stroke–Intracranial Hemorrhage; SPAN, Stroke Prognostication Using Age and NIH Stroke Scale; and THRIVE, Total Health Risks in Vascular Events.

thrombolytic therapy. Indeed, the International Stroke Trial-3 showed the greatest benefit of alteplase versus placebo in the subgroup predicted to be at highest risk of sICH.<sup>37</sup>

Risk scores for sICH can be helpful for guiding patients' and their families' expectations and perhaps to inform the intensity of medical monitoring required for individual patients after alteplase administration. Patients at high risk of sICH based on prediction scores likely still have benefit from alteplase. Therefore, it is critical that sICH prediction scores and risk factors not be used to select patients for thrombolysis.

### Pathophysiology of Alteplase-Related Hemorrhagic Transformation

Alteplase, a recombinant tPA, is chemically identical to endogenous tPA but with a different spatial arrangement. The clearance of alteplase is best described as a 2-compartment model. The first consists of a plasma redistribution phase and hepatic clearance and is the dominant mode of elimination (ie, 85% of the area under the curve). The second consists of formation of a complex with plasminogen activator inhibitor-1

followed by hepatic clearance.<sup>38,39</sup> The half-life of alteplase is nearly 4 minutes, leading to 75% clearance within 8 minutes.

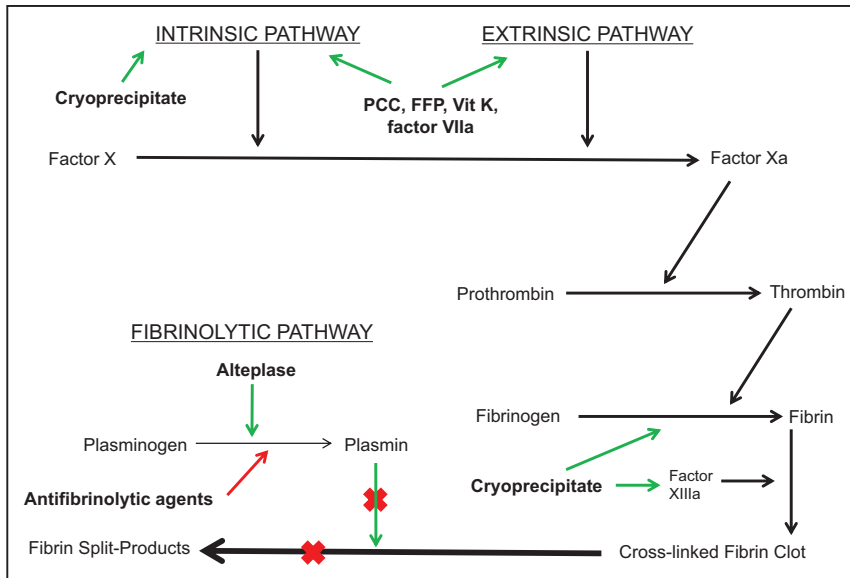
Like endogenous tPA, alteplase achieves clot lysis by converting inactive endogenous plasminogen to plasmin, mainly in the presence of fibrin. Plasmin, in turn, breaks fibrin into fibrin split products (Figure 2). Its relative fibrin specificity limits systemic fibrinolysis compared with other thrombolytic agents such as streptokinase.<sup>38</sup>

Despite the short half-life of alteplase in the bloodstream, its effect on the coagulation system persists for much longer.<sup>40</sup> The fibrinolytic activity of alteplase is associated with a consumptive coagulopathy, causing a reduction in fibrinogen levels<sup>41</sup> and prolongation of prothrombin and partial thromboplastin times. These abnormalities may last  $\geq 24$  hours after completion of the alteplase infusion.<sup>42,43</sup> Whether this effect may be magnified in patients on oral anticoagulants such as warfarin before receiving alteplase is controversial.<sup>44,45</sup> Although there are data showing elevations in both prothrombin and partial thromboplastin times after alteplase infusion, there are very limited data on whether alteplase results in the reduction of specific coagulation factors that are implicated in those laboratory parameters.

The degree of alteplase-related coagulopathy has been associated with sICH risk, with the most consistent associations with change in fibrinogen. A reduction in fibrinogen levels by  $\geq 200$  mg/dL from baseline within 6 hours of infusion is associated with a substantially increased risk of sICH, as is early hypofibrinogenemia (fibrinogen level  $< 200$  mg/dL at 2 hours after alteplase).<sup>42,46</sup> An early increase in fibrin degradation products has also been associated with increased risk of parenchymal hematoma.<sup>47</sup> Hypofibrinogenemia (fibrinogen level  $< 150$  mg/dL) at the time of sICH diagnosis has also been associated with hematoma expansion.<sup>48</sup>

The coagulopathy produced by alteplase is not the only determinant of hemorrhage occurring within an infarct (hemorrhagic infarct); it is also encountered even without the use of thrombolytic or anticoagulant agents. In a pooled analysis of thrombolytic clinical trials, radiographic evidence of hemorrhage occurred in 24.2% of placebo-treated patients and 32.5% of alteplase-treated patients<sup>49</sup>; most of these hemorrhages were considered asymptomatic. Thus, it is clear that hemorrhagic infarction occurs as part of the natural history of ischemic stroke.<sup>50</sup> In contrast to the common occurrence of hemorrhagic infarction, parenchymal hematoma is uncommon and occurs much more frequently in the setting of thrombolysis.<sup>4</sup> It has been suggested that hemorrhagic infarction is a result of multifocal red blood cell extravasation, whereas parenchymal hematoma is the result of a single bleeding site in the blood vessel damaged by ischemia and reperfusion.<sup>51</sup>

Reperfusion of injured brain tissue, related to recanalization of the affected artery,<sup>52</sup> provides the impetus for the development of hemorrhagic transformation. Recanalization of the affected artery, however, is not the only determinant of the risk of hemorrhagic transformation, which can also occur with persistent occlusion, as noted in autopsy and imaging studies.<sup>52,53</sup> Reperfusion injury may be exacerbated by or lead to elevated blood pressure.<sup>54,55</sup> In addition, postthrombolytic hemorrhage can occur in areas remote from the infarcted tissue,<sup>56</sup>



**Figure 2.** Mechanism of action of alteplase and various treatments in patients with thrombolysis-related hemorrhage. In green: Alteplase promotes plasmin activation, which in turn degrades cross-linked fibrin into fibrin split products and reversal agents, promoting various steps of the coagulation cascade. In red: The antifibrinolytic agents (aminocaproic acid and tranexamic acid) deactivate plasmin formation, which prevents the degradation of cross-linked fibrin. FFP indicates fresh-frozen plasma; and PCC, prothrombin complex concentrate.

lending support to the notion that thrombolytics can contribute to hemorrhage by mechanisms other than reperfusion. These seemingly remote hemorrhages may be in locations of additional ischemic injury in the setting of multifocal infarcts, or they may be in areas of underlying vulnerability in tissue. The development of postthrombolytic hemorrhagic transformation therefore requires a complex intersection of the biological processes underlying alteplase-associated coagulopathy, reperfusion injury, and disruption of the blood-brain barrier.<sup>57</sup>

Human imaging studies lend further evidence that breakdown of the blood-brain barrier is a critical component in the development of hemorrhagic transformation.<sup>58</sup> The presence of robust collateral circulation on vessel imaging is associated with a lower risk of sICH, which may in part be not only from smaller volumes of infarction but also collateral circulation, providing sufficient circulation for cerebral endothelial cells so that they do not undergo breakdown as a result of prolonged ischemia.<sup>59</sup> Permeability imaging, consisting of delayed acquisition perfusion imaging evaluating late-contrast extravasation into the brain parenchyma, is another predictor of sICH and requires the blood-brain barrier to be sufficiently disrupted to allow gadolinium entry.<sup>59,60</sup> Similarly, blood-brain barrier disruption occurs at a mean of 13 hours after onset when measured by cerebrospinal fluid gadolinium enhancement adjacent to an infarct, and this disruption is associated with increased rates of hemorrhagic transformation.<sup>61</sup> Serum biomarkers of breakdown in the blood-brain barrier, including tight junction proteins and neuronal markers, have also been associated with the risk of sICH.<sup>62,63</sup> An additional growing body of research suggests that subclinical cerebrovascular disease such as amyloid angiopathy or white matter hyperintensities, which may be associated with endothelial injury, is also associated with a higher risk of sICH.<sup>64,65</sup>

Ischemic injury to cerebral endothelial cells and the associated underlying components of the neurovascular unit leads to a series of biological processes resulting in breakdown of the blood-brain barrier. Animal models of ischemia and reperfusion demonstrate an association between hemorrhage and degradation of the basal lamina.<sup>66</sup> The process of breakdown in the blood-brain barrier is time dependent in that early in

the ischemic cascade there is activation of matrix metalloproteinases (MMPs), of which MMP-2 and MMP-9 are the most widely studied. MMPs are likely derived from leukocytes with subsequent breakdown of the tight junction proteins.<sup>67,68</sup> After the initial 24 hours of ischemic injury, further breakdown of the blood-brain barrier occurs from activation of inherent brain proteases,<sup>69</sup> although this process may not be as relevant to alteplase hemorrhages, which occur earlier. Tight junction proteins such as claudins, occluding, and junctional adhesion molecules lead to the ability of blood products to transverse the basement membrane and cross into brain parenchyma. These biological processes are accentuated with the time and volume of ischemia and may be accelerated by alteplase itself both at the endothelial cell level and in the adjacent proteins in the neurovascular unit.<sup>57,69,70</sup> Alteplase itself promotes activation of plasminogen and secretion of MMPs directly or indirectly through formation of free radicals, leading to degradation of the basal lamina,<sup>40,71,72</sup> blood-brain barrier disruption,<sup>66</sup> and injury to the neurovascular unit.<sup>73</sup> A clinical study demonstrated that baseline MMP-9 level predicted the occurrence of parenchymal hematoma after thrombolysis.<sup>72</sup> Degradation of the blood-brain barrier may be exacerbated by hyperglycemia,<sup>74</sup> which is an important predictor of sICH and has been shown to have therapeutic implications in animal models.<sup>75</sup> The processes underlying the breakdown of the blood-brain barrier and which pathways are amenable to pharmacological intervention require further research. To date, preventing the breakdown of the blood-brain barrier in patients with acute ischemic stroke has been less frequently a focus of “neuroprotectant” clinical trials.

In conclusion, the development of postthrombolytic hemorrhagic transformation requires multiple and interconnected pathological processes, including ischemic injury, coagulopathy, disruption of the blood-brain barrier, and reperfusion injury.

## Diagnosis of sICH

### Monitoring After Thrombolytic Therapy

In patients who receive intravenous alteplase for acute ischemic stroke, the American Heart Association (AHA)/American

Stroke Association guidelines recommend close monitoring during and for at least 24 hours after the infusion in an intensive care or acute stroke unit. The recommended monitoring includes blood pressure measurement and neurological examination every 15 minutes for the first 2 hours after the alteplase infusion, then every 30 minutes for the next 6 hours, and then every hour for the next 16 hours. Because an excessively high blood pressure may increase hemorrhagic complications, a blood pressure goal of <180/105 mm Hg is recommended for 24 hours after the infusion. In addition, an emergent brain computed tomography (CT) is recommended if headache, nausea, vomiting, or neurological worsening occurs because these symptoms may herald ICH. If patients develop these symptoms during the alteplase infusion, we suggest stopping the infusion temporarily and resuming if the emergent CT shows no ICH. Current AHA/American Stroke Association recommendations include avoiding antiplatelet agents or anticoagulants for 24 hours after the alteplase infusion (and after repeat neuroimaging confirms no asymptomatic blood products) to mitigate the risk of hemorrhagic complications.<sup>1,76</sup> Although some data suggest that the addition of antiplatelet agents to thrombolytic therapy is possibly safe,<sup>77</sup> a recent randomized trial definitively showed no net benefit from adding aspirin to alteplase and a trend toward increased hemorrhagic complications.<sup>78</sup> A subgroup of patients may be identified in the future who experience a net benefit from antiplatelet or anticoagulant agents within 24 hours after alteplase, but this requires testing in randomized trials. In addition, data from the SAINT trials (Stroke-Acute Ischemic NYX Treatment) showed that patients on antiplatelet agents before alteplase use versus those who were not were more likely to have symptomatic ICH and less likely to have asymptomatic ICH, suggesting that antiplatelet agents may convert asymptomatic hemorrhages into symptomatic hemorrhages.<sup>79</sup> Therefore, in patients with asymptomatic hemorrhage seen on the 24-hour image, the timing of the initiation of antiplatelet agents should be decided by weighing the risk of hematoma expansion against the risk of stroke recurrence.

### Timing of Postthrombolytic ICH

In early large trials of thrombolysis for myocardial ischemia, sICH occurred within 12 hours after thrombolytic therapy in 65% of patients, within 12 to 24 hours in 17%, within 24 to 48 hours in 9%, and after 48 hours in 9%.<sup>80</sup> In acute ischemic stroke, several studies have examined sICH timing but with variable time thresholds, thereby limiting comparability.<sup>3,7,81,82</sup> One recent review of stroke clinical trials found that the majority of sICHs occurred within 24 hours but that  $\approx 10\%$  to  $15\%$  occur after 24 hours.<sup>56</sup> In the NINDS trial, all fatal sICH events occurred within 24 hours, and 80% were within 12 hours.<sup>81</sup> Although any ICH can occur up to  $\geq 7$  days, the clear majority of sICHs occur within 36 hours. It is unlikely that sICH after 36 hours can be ascribed to an ongoing, treatable thrombolysis-associated coagulopathy.

Retrospective studies have reported median times from alteplase infusion to sICH ranging from 5 to 10 hours.<sup>48,83,84</sup> In 1 study of 128 alteplase-treated patients, nearly 80% of patients with sICH were diagnosed  $>2$  hours after the alteplase

infusion, and the median time from alteplase treatment to sICH diagnosis was nearly 8 hours.<sup>48</sup> Therefore, treating practitioners may consider extending the period of intensive (every 30 minutes) neurological and cardiovascular monitoring to 12 hours from the currently recommended 8 hours, particularly in patients with high risk for developing sICH. Larger prospective studies are needed to confirm the cost-effectiveness of this monitoring strategy.

In summary, sICH attributed to alteplase occurs within 36 hours from the infusion, with only half of the events being diagnosed by 5 to 10 hours from alteplase infusion. It is possible that extending the period of neurological and cardiovascular monitoring every 30 minutes from 8 to 12 hours may lead to an earlier diagnosis of sICH, particularly in high-risk patients, but this strategy requires assessment in larger prospective studies for cost-effectiveness.

### Detecting sICH

Regardless of the specific definition of postthrombolytic ICH, the diagnosis requires posttreatment brain imaging (CT or magnetic resonance imaging) showing acute hemorrhage.<sup>40</sup> Postthrombolysis monitoring protocols recommend follow-up brain imaging at 24 hours after intravenous alteplase to exclude hemorrhage before the initiation of antithrombotic agents.<sup>76</sup> Although recent studies have suggested that routine follow-up brain imaging at 24 hours in the absence of clinical deterioration rarely affects clinical management,<sup>85,86</sup> this remains controversial.<sup>87</sup> If clinical deterioration occurs, urgent repeat brain imaging to exclude hemorrhage is necessary. The degree of clinical deterioration needed to trigger follow-up imaging is not well established. In 1 study that used a cutoff of a 4-point decline in the NIHSS score, the incidence of early neurological deterioration after intravenous alteplase in acute ischemic stroke patients was nearly 7%, with only 2% being caused by sICH.<sup>88</sup> Using lesser degrees of neurological deterioration as a trigger for urgent brain imaging may potentially result in increased detection rates of hemorrhage that is not causative of the clinical decline. For instance, a  $\geq 4$ -point increase in the NIHSS score is more likely to be associated with parenchymal hematoma than hemorrhagic infarction.<sup>89</sup>

Because most hemorrhages after alteplase occur in already infarcted brain tissue, neurological deterioration may not occur at the onset of the hemorrhage.<sup>3,4</sup> New symptoms attributable to mass effect or increased intracranial pressure are typically detected in a delayed fashion. A recent multicenter retrospective study showed that patients diagnosed with sICH within the first 3 hours after alteplase infusion had significantly lower mean admission NIHSS scores than those diagnosed after 3 hours (median score, 11 versus 17;  $P=0.01$ ).<sup>48</sup> This likely reflects characteristics of the NIHSS score, with a “ceiling effect” such that at the upper range new neurological injury may not change the score. A lower clinical threshold to trigger urgent repeat imaging or even earlier routine brain imaging may be warranted in patients with severe ischemic strokes; this might allow earlier diagnosis and treatment. Large prospective studies are needed to test the cost-effectiveness of this approach.

In summary, neurological deterioration in the setting of sICH may be less pronounced with increasing stroke severity.

Therefore, a lower threshold to trigger emergent repeat imaging may be considered in patients with high NIHSS scores (eg, NIHSS score  $\geq 12$ ).

### Natural History and Outcome

The relationship between radiographic hemorrhage and clinical outcome has been most consistent with PH-2,<sup>49</sup> whereas the clinical relevance of HI-1, HI-2, and PH-1 is less clear.<sup>49</sup> Post hoc analysis of ECASS I data demonstrated an increased risk of early neurological deterioration and 3-month mortality after PH-2.<sup>50</sup> Compared with patients without radiographic hemorrhage, patients with PH-2 had a significantly increased risk of 24-hour deterioration (OR, 18.0; 95% CI, 6.0–56.0) and of 3-month mortality (OR, 11.4; 95% CI, 3.7–36.0). These findings were confirmed in a subsequent post hoc analysis of the ECASS II cohort and showed close to a 50% mortality with PH-2.<sup>89</sup> PH-1 compared with no hemorrhage was found to be associated with early neurological deterioration but not with worsened long-term outcome.<sup>89</sup> HI-1 and HI-2 were not associated with worsened outcomes.<sup>4,50,89</sup>

Quantifying the impact of postthrombolytic ICH on outcome is challenging. The main challenge lies in separating the impact of the ischemic event itself (with its natural sequelae) from the contribution of the hemorrhage. A retrospective analysis of a single-center stroke thrombolysis registry showed that the impact of previously recognized baseline prognosticators on poor outcome was larger than the effects of postthrombolytic sICH and depended on which sICH definition was used. Overall, in these analyses, sICH added limited predictive power for poor outcome regardless of specific sICH definitions (NINDS, ECASS II, SITS-MOST).<sup>56</sup>

In conclusion, the natural history of patients with sICH, particularly the PH-2 radiological subtype, is very poor, approaching 50% mortality and significant morbidity with survival. The relation between other radiological subtypes of hemorrhage and outcome is less clear; observed poor outcomes are more likely related to the combination of the sICH itself and the underlying ischemic event.

### Treatment of Postthrombolytic Hemorrhage

The general principles of treating patients with postthrombolytic hemorrhage in the setting of ischemic stroke are similar to those used in treating spontaneous intracerebral hemorrhage and include cardiovascular and respiratory support when needed, blood pressure management, monitoring for neurological deterioration, prevention of hematoma expansion, and treatment of elevated intracranial pressure and other complications that arise from the hemorrhage including seizures. These general principles can be found in the AHA/American Stroke Association guideline statement on the management of spontaneous intracerebral hemorrhage.<sup>90</sup>

### Indications for Reversal of Alteplase-Induced Coagulopathy

#### Risk of Hemorrhage Expansion

Once sICH is identified, the clinician needs to assess the risk for hematoma expansion on the basis of the presence of an ongoing alteplase-related coagulopathy. Although clinical

trials have not typically reported the risk of hemorrhage expansion, retrospective analyses have examined this risk in the setting of alteplase-related sICH. These studies are limited by a small sample size and variable timing of serial CT scans after diagnosis. However, clinically relevant hemorrhage expansion consistently occurred in 30% to 40% of patients diagnosed with sICH across these studies.<sup>48,83,84,91</sup>

#### Radiographic Appearance

It is unclear whether type of ICH (HI-1, HI-2, PH-1, PH-2, subarachnoid hemorrhage, or subdural hemorrhage) affects the risk of expansion. Existing studies of hemorrhage expansion after thrombolysis typically include only sICH and thus are weighted toward PH-2. Only 1 study considered radiographic type<sup>83</sup> and found that PH-2 represented  $\approx 64\%$  of sICH cases, but it could not clarify any differential risk of sICH expansion. Therefore, there is no evidence that different appearance of hemorrhage influences opportunity to benefit from treatment.

#### Symptomatic Versus Asymptomatic Hemorrhagic Infarction

Only 1 study detailed management of asymptomatic alteplase-associated hemorrhage, and that study included only PH-2.<sup>83</sup> Thus, it is unclear whether sICH is presaged by asymptomatic hemorrhage with a time window wide enough for both diagnosis and treatment to influence outcome. In theory, the risk of hemorrhage expansion may be greater for an asymptomatic hemorrhage in the setting of both alteplase and mechanical thrombectomy, especially if successful recanalization is achieved or the mechanism of hemorrhage involves blood vessel perforation or endothelial injury related to the neuro-interventional procedure. Further studies should evaluate both asymptomatic and symptomatic patients to determine the frequency and timing with which asymptomatic hematomas later become sICH.

#### Opportunity to Benefit

It seems unlikely that all patients with sICH have equal opportunity to clinically benefit from treatment. Once the diagnosis is made, predictors of death include poor neurological examination, large hematoma volume, and withdrawal of care.<sup>48,83,92</sup> It may be that small amounts of blood are not clinically relevant, and large hematoma volumes have such poor outcomes that treating any coagulopathy can offer no benefit.

Overall, currently available literature suggests that sICH within 24 hours of alteplase therapy or with hypofibrinogenemia might be a reasonable indication for treatment. Although very limited data are available to support treatment of asymptomatic bleeding, the use of reversal agents for any asymptomatic parenchymal hematoma occurring within 24 hours of alteplase infusion may be considered, particularly in the setting of an ongoing coagulopathy.

### Agents for Reversal of Coagulopathy

#### Cryoprecipitate

Suggestions for the use of various reversal agents are summarized in Table 4. Cryoprecipitate is derived from fresh-frozen plasma (FFP) and contains fibrinogen, which corrects dysfibrinogenemia; factor VIII, which helps activate the intrinsic pathway; factor XIII; and von Willebrand factor.<sup>93</sup> Previous

**Table 4. Suggestions for Reversal Agents That May Be Considered on the Basis of the Mechanisms of Action of the Agent and Alteplase in Patients With sICH Occurring Within 36 Hours After Alteplase Infusion**

Reversal Agent	Suggested Dose	Potential for Benefit	Adverse Effects
Cryoprecipitate	Consider sending a fibrinogen level immediately and empirically transfusing with 10 U cryoprecipitate, and anticipate giving more cryoprecipitate as needed to achieve a normal fibrinogen level of $\geq 150$ mg/dL (10 U cryoprecipitate increases fibrinogen by nearly 50 mg/dL)	Potential for benefit in all sICH	Transfusion reaction and transfusion-related lung injury
Platelets	2 donors (8–10 U)	Potential for benefit is unclear except in patients with thrombocytopenia (platelets $< 100\,000/\mu\text{L}$ ), who may possibly benefit	Transfusion reaction, transfusion-related lung injury, volume overload
FFP	12 mL/kg	Potential for benefit is unclear except in patients on warfarin, in whom FFP may be considered	Transfusion reaction, transfusion-related lung injury, volume overload
PCC	25–50 U/kg (based on INR level)	Potential for benefit is unclear except in patients on warfarin, in whom PCC may be considered and is the preferred adjunctive treatment	Thrombotic complications
Vitamin K	10 mg intravenously	Potential for benefit is unclear except in patients on warfarin, in whom vitamin K may be used as an adjunctive treatment	Anaphylaxis
rFVIIa	20–160 $\mu\text{g}/\text{kg}$	Potential for benefit is unclear	Thrombotic complications
Antifibrinolytic agents	Aminocaproic acid: 4 g IV during first hour followed by 1 g/h for 8 h Tranexamic acid: 10 mg/kg 3–4 times/d (adjustment based on kidney function may be necessary)	Potential for benefit in all patients with sICH, particularly when blood products are contraindicated or declined by patient/family or if cryoprecipitate is not available	Thrombotic complications

FFP indicates fresh-frozen plasma; INR, international normalized ratio; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa; and sICH, symptomatic intracranial hemorrhage.

guidelines have not specifically addressed the number of units of cryoprecipitate to administer, but 10 U is the standard dose in blood banks. There are limited data on increases of plasma fibrinogen levels that can be anticipated on the basis of cryoprecipitate doses in the stroke population. An estimate derived from a study of polytrauma patients reported that a mean infusion of 8.7 U led to an increase in fibrinogen level of  $55 \pm 24$  mg/dL.<sup>94</sup> Because fibrinogen is an acute-phase reactant, fibrinogen levels obtained in the acute stroke setting should be interpreted with caution; low levels should be not questioned, but normal-appearing levels may be misleading. Disadvantages of cryoprecipitate include the lack of pathogen inactivation, risk of transfusion-related lung injury, and delay in obtaining the solution because it requires thawing from its storage at  $-20^\circ\text{C}$ .<sup>40</sup>

Therefore, once sICH is diagnosed, treating physicians may consider immediately sending a fibrinogen level and empirically transfusing with 10 U cryoprecipitate and anticipate giving more cryoprecipitate as needed to achieve a fibrinogen level of  $\geq 150$  mg/dL. In addition, treating physicians may consider prioritizing cryoprecipitate infusion over other reversal agents. More studies are needed to support the benefit of this approach.

#### **Platelet Transfusion**

Platelet transfusion of 6 to 8 U is also routinely recommended for the treatment of alteplase-associated sICH.<sup>76</sup>

This recommendation is based on the theoretical concern that thrombolysis may lead to platelet inhibition through a variety of potential mechanisms, including an increase in both D-dimers and glycoprotein IIb/IIIa.<sup>95,96</sup> These theories originate from ex vivo studies with small sample sizes and primarily with patients receiving thrombolysis for myocardial infarction with thrombolytics other than alteplase. Although the mechanism of action is not well known, these studies have documented inhibition of platelet aggregometry.<sup>95,97</sup> It is not known whether infusion of platelets will correct this defect in platelet aggregometry or limit bleeding-related complications. In fact, in a small, limited, multicenter retrospective study of alteplase-associated sICH, platelet transfusion was associated with increased hematoma expansion compared with control subjects (50.0% versus 21.6%;  $P=0.01$ ).<sup>48</sup> However, this could be caused by a selection bias whereby patients who were given platelet transfusion were at high risk of hematoma expansion. More studies are needed to confirm this finding. Limitations of and adverse events caused by platelet transfusions are similar to those for cryoprecipitate.

The use of platelet transfusion for all patients with sICH is controversial. Exceptions include patients with thrombocytopenia (platelet count  $< 100\,000/\mu\text{L}$ ), in whom platelet transfusion should be considered.

**Prothrombin Complex Concentrate**

Prothrombin complex concentrates (PCCs) are concentrated forms of various vitamin K–dependent factors and can include factors II, VII, IX, and X, in addition to proteins C and S.<sup>98</sup> Different products are available in different countries, complicating the literature. The most widely available in the United States is a PCC containing all 4 factors. Combinations of these factors activate both the intrinsic and extrinsic coagulation pathways, resulting in the activation of factor X and thrombin, which in turn facilitates the conversion of fibrinogen into fibrin. PCCs are the first-line treatment in warfarin-related ICH, achieving reversal of warfarin-related coagulopathy in a median of 30 minutes from infusion without requiring large intravenous volumes.<sup>90</sup> The use of PCCs in the treatment of sICH may offer a rapid way to activate both the intrinsic and extrinsic pathways that facilitate the conversion of fibrinogen into fibrin, potentially reducing the risk of hematoma expansion. Because of the depletion of fibrinogen in patients with sICH, it may be necessary to replenish fibrinogen levels first to provide substrate for actions of the PCC. This treatment may be particularly beneficial in patients who received warfarin before alteplase and have a subtherapeutic but abnormal international normalized ratio (1.3–1.7); these patients are likely to have lower levels of coagulation factors that could be replenished by PCCs. The use of PCCs in patients with sICH, however, should be weighed against the risk of thrombotic events with such treatment.<sup>99</sup> This risk is 1% in the general population and may be elevated in the setting of an ischemic stroke.

The use of PCCs in most patients with sICH is controversial but may be considered as an adjunctive therapy to cryoprecipitate in those on warfarin treatment before alteplase administration.

**Fresh-Frozen Plasma**

FFP (thawed or unthawed) consists of plasma collected from blood donors and frozen at  $-18^{\circ}\text{C}$ . FFP contains all endogenous procoagulant and anticoagulant proteins that activate both the intrinsic and extrinsic pathways, leading to conversion of fibrinogen into fibrin in a fashion similar to PCCs. Unlike PCCs, however, FFP is administered slowly in large intravenous volumes to prevent volume overload and carries a risk for major transfusion reactions. Despite the fact that a standard dose of FFP can take up to 30 hours to reverse the warfarin-induced coagulopathy,<sup>100</sup> this effect may be faster in the setting of alteplase. The British Committee for Standards in Hematology, for example, recommended administering FFP 12 mL/kg in the setting of thrombolysis-related sICH.<sup>101</sup> To date, however, no studies have demonstrated the efficacy and safety of FFP in patients with sICH. Given that its mechanism of action is similar to that of PCCs, FFP may be considered in patients with factor deficiencies before thrombolysis such as those treated with warfarin when PCCs are not readily available.

The use of FFP in most patients with sICH is controversial but may be considered as an adjunctive therapy to cryoprecipitate in those on warfarin treatment before alteplase infusion when PCCs are not readily available.

**Vitamin K**

Vitamin K induces the synthesis of factors II, VII, IX, and X and proteins C and S in the liver. Nevertheless, vitamin K may

potentiate the effect of fibrinogen (after replenishment) by activating coagulation pathways, promoting the formation of fibrin, and stabilizing the growth of the hematoma,<sup>40</sup> with only a very small risk of anaphylaxis (1 in 3000).<sup>102</sup> Furthermore, vitamin K may be particularly useful in patients who were on warfarin with a subtherapeutic international normalized ratio before alteplase infusion. To date, however, we lack studies showing the efficacy of vitamin K in patients with sICH.

The use of vitamin K in most patients with sICH is controversial but may be considered as an adjunctive therapy in those on warfarin treatment.

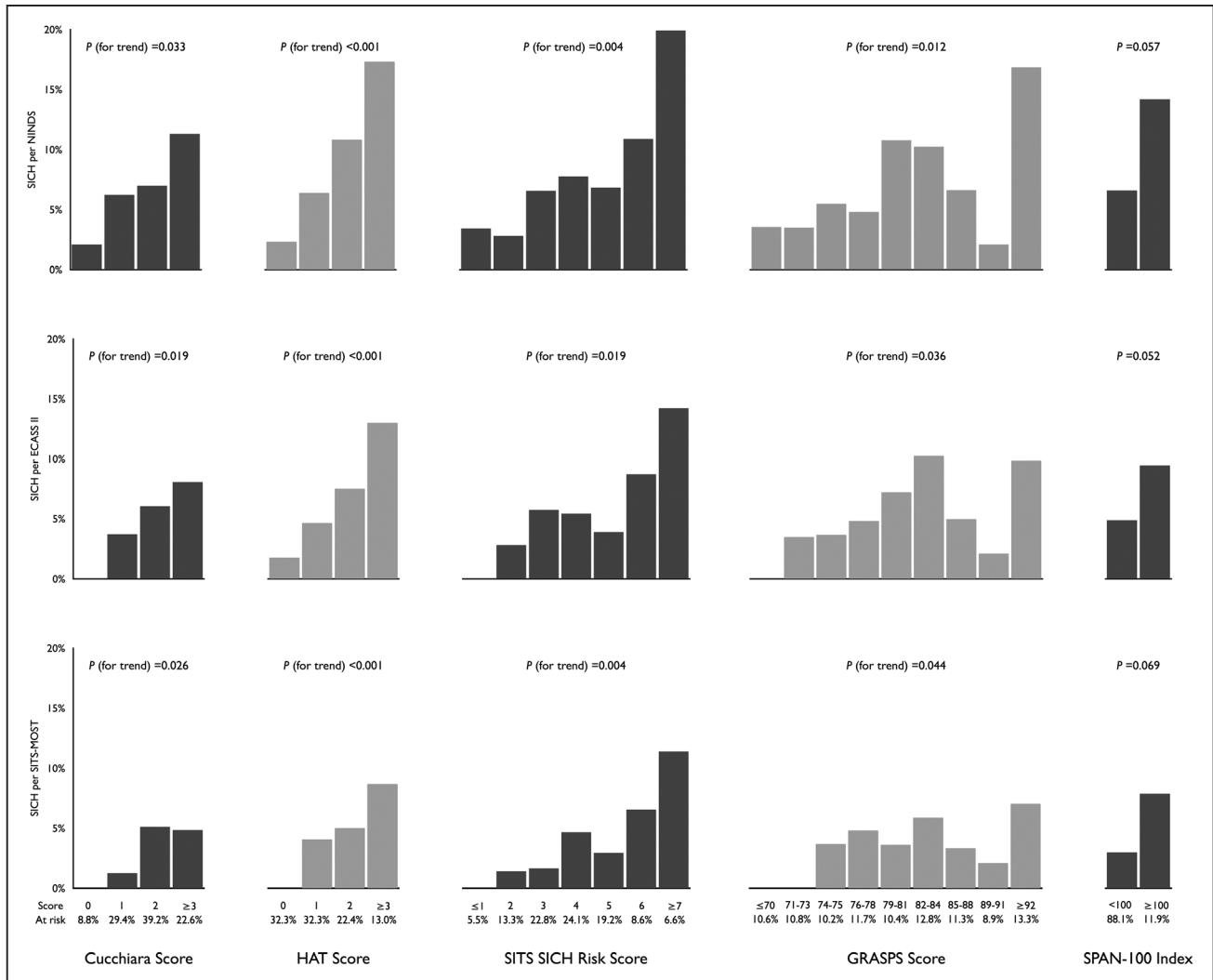
**Antifibrinolytic Agents ( $\epsilon$ -Aminocaproic Acid and Tranexamic Acid)**

Aminocaproic acid and tranexamic acid inhibit proteolytic enzymes such as plasmin, which are known to mediate the actions of alteplase (Figure 2). Because of their rapid onset in plasma activity, they are potentially appealing interventions. They are used in clinical practice in other conditions of uncontrolled bleeding such as cardiac surgery or hematologic disorders. They also are used in the neurological condition of aneurysmal subarachnoid hemorrhage during the time period when the aneurysm is still unsecured, although this remains highly controversial.<sup>103</sup> In the setting of sICH, the data are quite limited for both agents, with only individual or small-series case reports. In an AHA Get With The Guidelines–based analysis, 19 of 311 patients (6.1%) who received thrombolysis had sICH, and only 1 of the 19 received aminocaproic acid.<sup>91</sup> In a more recent multicenter retrospective analysis, 2 of 128 alteplase-treated patients with sICH received aminocaproic acid, neither of whom suffered in-hospital mortality or hematoma expansion.<sup>40</sup> Similar, limited reports are available for tranexamic acid treatment of sICH.<sup>104</sup> Guidelines from British Committee for Standards in Hematology suggest the use of antifibrinolytic agents for treating sICH in the setting of thrombolytic therapy. Because of their mechanism of action (Figure 3) and the fact that they are readily available and do not need to be thawed, antifibrinolytics may be an appealing treatment for sICH patients.

In conclusion, there are limited data on the safety and efficacy of antifibrinolytic agents in sICH. These agents, however, may be considered in all patients with sICH, particularly those who decline blood products.

**Activated Factor VII**

Recombinant factor VIIa (rFVIIa; Novoseven, Novo Nordisk) is a powerful procoagulant agent that, when given in pharmacological doses, activates the coagulation system and promotes hemostasis in the presence of exposed tissue factor or activated platelets.<sup>105</sup> rFVIIa is currently approved for the treatment of bleeding in patients with hemophilia who are resistant to factor VIII replacement therapy. Considerable evidence suggests that rFVIIa also enhances hemostasis in patients with normal coagulation systems. In phase II and III trials of spontaneous, noncoagulopathic ICH, rFVIIa was given in doses ranging from 20 to 160  $\mu\text{g}/\text{kg}$  within 4 hours of onset and reduced active bleeding on serial CT imaging in a dose-dependent fashion.<sup>106,107</sup> A consistent effect on clinical outcome could not be demonstrated, however, in a phase III study, and a 4% incremental risk of arterial thromboembolic events (stroke or myocardial infarction) was reported,



**Figure 3.** Rates of symptomatic intracerebral hemorrhage based on various prediction scores. ECASS II indicates European Cooperative Acute Stroke Study-2; GRASPS, glucose, race, age, sex, pressure, stroke severity; HAT, Hemorrhage After Thrombolysis; NINDS, National Institute of Neurological Disorders and Stroke; sICH, symptomatic intracranial hemorrhage; SITS-MOST, Safe Implementation of Thrombolysis in Stroke: Monitoring Study; and SPAN-100, Stroke Prognostication Using Age and NIH Stroke Scale. Reprinted from Sung et al.<sup>32</sup> Copyright © 2013, American Heart Association, Inc.

highlighting the ability of rFVIIa to trigger thrombosis in atherosclerotic vessels.<sup>108</sup>

rFVIIa has been reported to be effective as an off-label “rescue” therapy for life-threatening bleeding in the setting of hemorrhagic shock, uncontrolled surgical bleeding, disseminated intravascular coagulation, and other conditions.<sup>109</sup> It has also been successfully used to reverse coagulopathy and to allow safe placement of intracranial pressure monitors in patients with fulminant hepatic failure, and it has been reported to rapidly normalize the international normalized ratio in patients with acute intracranial bleeding on vitamin K antagonists such as warfarin.<sup>109</sup>

rFVIIa has yet to be rigorously evaluated as a potential emergency treatment for postthrombolytic hemorrhage, and its use is currently experimental. The only case report in the English literature described a patient given alteplase who experienced progressive intracerebral and subdural bleeding despite receiving 20 U cryoprecipitate and 6 U platelets. She was given 50 µg/kg rFVIIa and was taken to the operating

room for successful clot evacuation with good postoperative hemostasis.<sup>110</sup> This case shows the feasibility of using rFVIIa as a method for attaining hemostasis and allowing lifesaving neurosurgical intervention.

In conclusion, given the potential complications of rFVIIa, treating physicians should consider withholding it until more studies establish its safety in this setting.

### Prevention of Hematoma Expansion

Hematoma expansion is a major predictor of death and disability in patients with intracerebral hemorrhage.<sup>111–114</sup> Therefore, in addition to aggressive reversal of coagulopathy, other strategies for the prevention of hematoma expansion may be a therapeutic target in sICH. Elevated blood pressure has been shown to be associated with the risk of hematoma expansion in patients with spontaneous intracerebral hemorrhage.<sup>115–117</sup> In patients with spontaneous intracerebral hemorrhage, studies showed the relative safety of intensive systolic blood pressure lowering to a goal of <140 mm Hg,

but this measure lacked clear efficacy compared with a systolic blood pressure goal of <180 mm Hg.<sup>90,118</sup> In patients with sICH, blood pressure targets are unclear, but the goal is to achieve a balance between providing adequate blood flow to the ischemic territory and lowering the blood pressure to reduce the risk of hematoma expansion. For instance, patients with acute ischemic stroke receiving thrombolytic therapy or mechanical thrombectomy who achieve partial or no recanalization may be at risk of additional ischemia, especially in the setting of blood pressure reduction. In 1 study, a drop in mean arterial pressure by >40% was associated with poor neurological outcomes, although this study included only patients with periprocedural hypotension and results were not stratified by the presence of sICH.<sup>119</sup> Similar studies on the association of blood pressure after intravenous alteplase with outcomes and sICH are conflicting. For example, in a study of 1128 patients treated with thrombolysis in China, a systolic blood pressure of <140 mm Hg was associated with improved neurological outcomes and lower rates of sICH.<sup>120</sup> Among patients treated with thrombolysis in the ECASS II trial, a higher systolic blood pressure was also associated with worse functional outcomes and sICH, with no clear evidence that lower blood pressure in alteplase-treated patients led to worse functional outcomes.<sup>121</sup> Fewer data are available, however, on blood pressure treatment in the presence of hemorrhage after alteplase, particularly in PH-2 versus others. In the setting of alteplase-associated hemorrhage, healthcare providers should weigh the risk of worsening ischemia against the severity of sICH and expansion risk to decide on blood pressure goals. Among patients with HI-1 and HI-2 and incomplete recanalization, higher blood pressure targets may be necessary to maintain adequate collateral blood flow to the ischemic bed and to reduce the risk of infarct growth. In patients with full recanalization, stricter blood pressure control measures may be reasonable. Among patients with parenchymal hematoma who are at high risk for hematoma expansion, stricter blood pressure control is hypothesized to cause more benefit and perhaps less harm. The safety and efficacy of this approach after sICH development need further investigation.

In conclusion, healthcare providers should weigh the risk of worsening ischemia against the severity of hemorrhage and expansion risk to decide on blood pressure goals. In patients with incomplete recanalization, higher blood pressure targets may be necessary to maintain adequate blood flow to the ischemic bed and to reduce the risk of infarct growth. On the other hand, in patients with full recanalization, stricter blood pressure control measures may be reasonable. The safety and efficacy of this approach need further investigation.

### Neurosurgical Treatment

Surgical intervention is a challenge to organize into an evidence-based treatment algorithm because of the dearth of prospective data to guide when to treat and which surgical technique to implement.<sup>122</sup> Most surgical data in this setting are derived from observational studies and randomized trials in spontaneous intracerebral hemorrhage.<sup>90,122-125</sup> In practice, the risks and benefits of rapid surgical decompression versus iatrogenic injury must be carefully weighed.

The goal of surgery is to decompress the brain from mass effect, malignant edema, and toxic blood byproducts. Stable intracerebral hemorrhage can be surgically managed by  $\geq 1$  techniques. Bony decompressive craniectomy of the overlying skull with expansion duraplasty can reduce intracranial pressure and provide increased cranial volume to accommodate malignant edema. Open craniotomy and evacuation of hematoma can eliminate the mechanical effects of the hematoma in lobar, cerebellar, or surgically accessible basal ganglia hematomas >30 cm<sup>3</sup> in volume.<sup>91,122,126</sup> However, this requires an incision through the cortex and white matter tracts along the trajectory to the lesion. The clinical effectiveness of these interventions remains controversial.<sup>123,124,127</sup> Minimally invasive craniotomy and stereotactic or endoscopic evacuation of hematoma are currently under investigation for spontaneous intracerebral hemorrhage and may have a role in the surgical management of postthrombolytic hemorrhage. Smaller-volume hematomas are generally left untreated.<sup>124,126</sup> Deep-seated hemorrhages in areas such as the thalamus or brainstem are usually not evacuated. Immediate and delayed postoperative imaging is useful to track the effectiveness of decompression and to evaluate for any evidence of rehemorrhage. Current AHA/American Stroke Association guidelines on intracerebral hemorrhage indicate that, for most patients with supratentorial ICH, the benefit of surgery is unclear. Neurosurgical treatment is recommended, however, for patients with cerebellar hemorrhage with either brainstem compression or neurological deterioration. It may also be considered in patients with supratentorial ICH who exhibit neurological deterioration, coma, significant midline shift, or elevated intracranial pressure refractory to medical treatment.<sup>90</sup>

In a trial testing thrombolytic strategies of patients with myocardial infarction, retrospective analysis of neurosurgical evacuation of thrombolysis-related hemorrhage was associated with reduced mortality compared with no evacuation.<sup>128</sup> In patients with both ischemic stroke and thrombolysis-related hemorrhage, the benefit of surgery may be mitigated by the underlying ischemic cerebral injury. A recent multicenter, retrospective study across the United States showed that, in patients with sICH, there was a trend toward neurosurgical treatment (hematoma evacuation or decompressive hemicraniectomy) reducing mortality (OR, 0.58;  $P=0.10$ ).<sup>48</sup> Although this finding may be a result of selection bias, this effect may be similar to that in patients with large hemispheric ischemic strokes with malignant edema, such that neurosurgical treatment may reduce mortality by preventing herniation but still leave the patient with substantially disabling neurological deficits.<sup>129</sup> Furthermore, although isolated subdural hemorrhage is a very rare manifestation of sICH, certain patients with isolated subdural hemorrhage may possibly benefit from neurosurgical evacuation. When neurosurgical treatments are considered, they should be performed after coagulopathy reversal, and decisions should be balanced against the risk of hemorrhagic complications in the setting of alteplase-related coagulopathy. In addition, centers caring for patients with acute ischemic stroke treated with alteplase should have access to neurosurgical services in the event that sICH occurs.

In conclusion, neurosurgical treatment may be considered in select patients with sICH for whom surgery may improve

**Table 5. Summary of Suggestions for Each Section in This Document**

Section	Summary of Suggestions
Definition	The definitions of sICH used are widely variable, depending on the radiological classification of hemorrhage and degree of neurological deterioration, and these should be taken into account when sICH rates are interpreted and reported. To allow proper comparisons with clinical trial benchmarks, stroke centers should classify the appearance of hemorrhagic transformation according to radiographic criteria (HI-1, HI-2, PH-1, PH-2, or remote ICH), assess the degree of neurological worsening by NIHSS score point change, and provide an attribution of causality for the worsening.
Incidence	Rates of sICH vary widely across definitions, with a 2.5- to 5-fold variation in rates across studies. Clinical practice experience among centers with protocols and trained personnel suggests that rates of sICH are similar to those observed in the initial clinical trials.
Risk factors and prediction scores	Risk scores for sICH can be helpful for guiding patients' and their families' expectations and perhaps to inform the intensity of medical monitoring required for individual patients after alteplase administration. Patients at high risk of sICH on the basis of prediction scores likely still have benefit from alteplase; therefore, it is critical that sICH prediction scores and risk factors not be used to select patients for thrombolysis.
Pathophysiology	The development of postthrombolytic hemorrhagic transformation requires multiple and interconnected pathological processes, including ischemic injury, coagulopathy, disruption of the blood-brain barrier, and reperfusion injury.
Diagnosis and detection	sICH attributed to alteplase occurs within 36 h after the infusion, with only half of the events being diagnosed by 5–10 h after alteplase infusion. It is possible that extending the period of neurological and cardiovascular monitoring every 30 min from 8 h to 12 h may lead to an earlier diagnosis of sICH, particularly in high-risk patients, but this strategy requires assessment in larger prospective studies for cost-effectiveness. Neurological deterioration in the setting of sICH may be less pronounced with increasing stroke severity; therefore, a lower threshold to trigger emergent repeat imaging may be considered in patients with high NIHSS scores (eg, NIHSS score $\geq 12$ ).
Natural history and outcome	The natural history of patients with sICH, particularly the PH-2 radiological subtype, is very poor, approaching 50% mortality and significant morbidity with survival. The relation between other radiological subtypes of hemorrhage and outcome is less clear; observed poor outcomes are more likely related to the combination of the sICH itself and the underlying ischemic event.
Indications for treatment	Overall, currently available literature suggests that sICH within 24 h of alteplase therapy or with hypofibrinogenemia might be a reasonable indication for treatment. Although very limited data are available to support treatment of asymptomatic bleeding, the use of reversal agents for any asymptomatic PH occurring within 24 h of alteplase infusion may be considered, particularly in the setting of an ongoing coagulopathy.

**Table 5. Continued**

Section	Summary of Suggestions
Reversal of coagulopathy with various agents	<p><b>Cryoprecipitate:</b> Once sICH is diagnosed, treating physicians may consider immediately sending a fibrinogen level and empirically transfusing with 10 U cryoprecipitate and anticipate giving more cryoprecipitate as needed to achieve a fibrinogen level of <math>\geq 150</math> mg/dL. In addition, treating physicians may consider prioritizing cryoprecipitate infusion over other reversal agents. More studies are needed to support the benefit of this approach.</p> <p><b>Platelet transfusion:</b> The use of platelet transfusion for all patients with sICH is controversial. Exceptions include those with thrombocytopenia (platelet count <math>&lt; 100\,000/\mu\text{L}</math>), in whom platelet transfusion should be considered.</p> <p><b>PCC:</b> The use of PCCs in most patients with sICH is controversial but may be considered as an adjunctive therapy to cryoprecipitate in those on warfarin treatment before alteplase administration.</p> <p><b>FFP:</b> The use of FFP in most patients with sICH is controversial but may be considered as an adjunctive therapy to cryoprecipitate in those on warfarin treatment before alteplase infusion when PCCs are not readily available.</p> <p><b>Vitamin K:</b> The use of vitamin K in most patients with sICH is controversial but may be considered as an adjunctive therapy in those on warfarin treatment.</p> <p><b>Antifibrinolytic agents:</b> There are limited data on the safety and efficacy of antifibrinolytic agents in sICH. These agents, however, may be considered in all patients with sICH, particularly in patients who decline blood products.</p> <p><b>rFVIIa:</b> Given the potential complications of such therapy, treating physicians should consider withholding the use of rFVIIa until more studies establish its safety in this setting.</p>
Prevention of hematoma expansion	Healthcare providers should weigh the risk of worsening ischemia against the severity of hemorrhage and expansion risk to decide on blood pressure goals. In patients with incomplete recanalization, higher blood pressure targets may be necessary to maintain adequate blood flow to the ischemic bed and to reduce the risk of infarct growth. On the other hand, in patients with full recanalization, stricter blood pressure control measures may be reasonable. The safety and efficacy of this approach need further investigation.
Neurosurgical treatment	Neurosurgical treatment may be considered in select patients with sICH for whom surgery may improve outcome despite the ischemic injury. Careful consideration should be given to whether this potential benefit outweighs the risk of hemorrhagic complications in the setting of possible alteplase-associated coagulopathy.

FFP indicates fresh-frozen plasma; ICH, intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale; PCC, prothrombin complex concentrate; PH, parenchymal hematoma; rFVIIa, activated recombinant factor VII; and sICH, symptomatic intracranial hemorrhage.

(Continued)

outcome despite the ischemic injury. Careful consideration should be given to whether this potential benefit outweighs the risk of hemorrhagic complications in the setting of possible alteplase-associated coagulopathy.

### Conclusions and Future Directions

Symptomatic intracerebral hemorrhage is an uncommon but severe complication of systemic thrombolysis in acute ischemic stroke. The exact mechanisms by which alteplase and other thrombolytics lead to sICH are likely mediated by coagulopathy, reperfusion injury, and breakdown of the blood-brain barrier. Significant attention has been paid to risk factors and predictors of sICH. Despite the current quality reporting efforts and improved clinical algorithms, a small proportion of patients treated with alteplase within guidelines will develop sICH, and treatment options have been limited by studies with small sample sizes and heterogeneous practice patterns. Correction of the coagulopathy after alteplase has remained the mainstay of treatment, but no specific agent has been shown to be most effective. Data from other disease states, however, raise the possibility that certain agents

not routinely used may be effective, and they require further study. Treatment to correct coagulopathy will likely require early diagnosis before catastrophic expansion occurs and early administration of cryoprecipitate and other agents that can be rapidly administered with rapid time to take effect. Additional treatment modalities that require further research include neurosurgical evacuation of the hematoma. There is a significant avenue of research indicating the impact of breakdown of the blood-brain barrier in the pathogenesis of sICH, although these data have been limited mostly to rodent models of ischemic stroke. Further research is required to establish treatments aimed at maintaining the integrity of the blood-brain barrier in acute ischemic stroke on the basis of inhibition of the underlying biochemical processes. Whether other thrombolytics besides alteplase will be as effective in clinical trials with less impact on the coagulation cascade and blood-brain barrier remains to be established. The suggestions from this statement are summarized in Table 5.

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## Disclosures

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\*Modest.

†Significant.

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J. Claude Hemphill	UCSF	None	None	None	None	None	None	None
J. Mocco	Mount Sinai Hospital	FEAT: randomized trial (PI for a prospective randomized trial of 2 different methods of aneurysm treatment)*; POSITIVE: randomized trial of flow diversion versus coil embolization (co-PI for a prospective randomized trial of 2 different methods of delayed stroke treatment)*; COMPASS (co-PI for a prospective randomized trial of 2 different methods of stroke thrombectomy)*; INVEST (co-PI for a prospective randomized trial of 2 different methods of minimally invasive treatment of ICH)*	None	None	None	Neurvana†; TSP†; Cerebrotecht†; Endostream†; Rebound†; Synchron†; Apama†	None	None
Shyam Prabhakaran	Northwestern University	None	None	None	None	None	None	None

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\*Modest.

†Significant.

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## Treatment and Outcome of Hemorrhagic Transformation After Intravenous Alteplase in Acute Ischemic Stroke: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association

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