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

American Heart Association | American Stroke Association
science is why

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on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research

AHA/ASA STROKE COUNCIL

This slide presentation was developed by a member of the Stroke Council Professional Education Subcommittee

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Citation

Yaghi S, Willey JZ, Cucchiara B, Goldstein JN, Gonzales NR, Khatri P, Kim LJ, Mayer SA, Sheth KN, Schwamm LH; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. 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 [published online ahead of print x].

Stroke. doi x

Abbreviations

- AHA: American Heart Association
- BBB: blood-brain barrier
- ED: Emergency Department
- ICH: intracranial hemorrhage
- IV alteplase: intravenous tissue plasminogen activator
- NIHSS: NIH stroke scale
- sICH: symptomatic intracranial hemorrhage

Objectives

- Review definitions and epidemiology of sICH
- Review sICH pathophysiology, diagnosis, and natural history
- Review sICH treatments

Outline

- Introduction
- Definitions of symptomatic intracranial (sICH)
- Epidemiology of sICH
- Pathophysiology of alteplase related hemorrhagic transformation
- Diagnosis of sICH
- Natural history and outcome
- Treatment of post-thrombolysis hemorrhage
- Conclusion and future directions

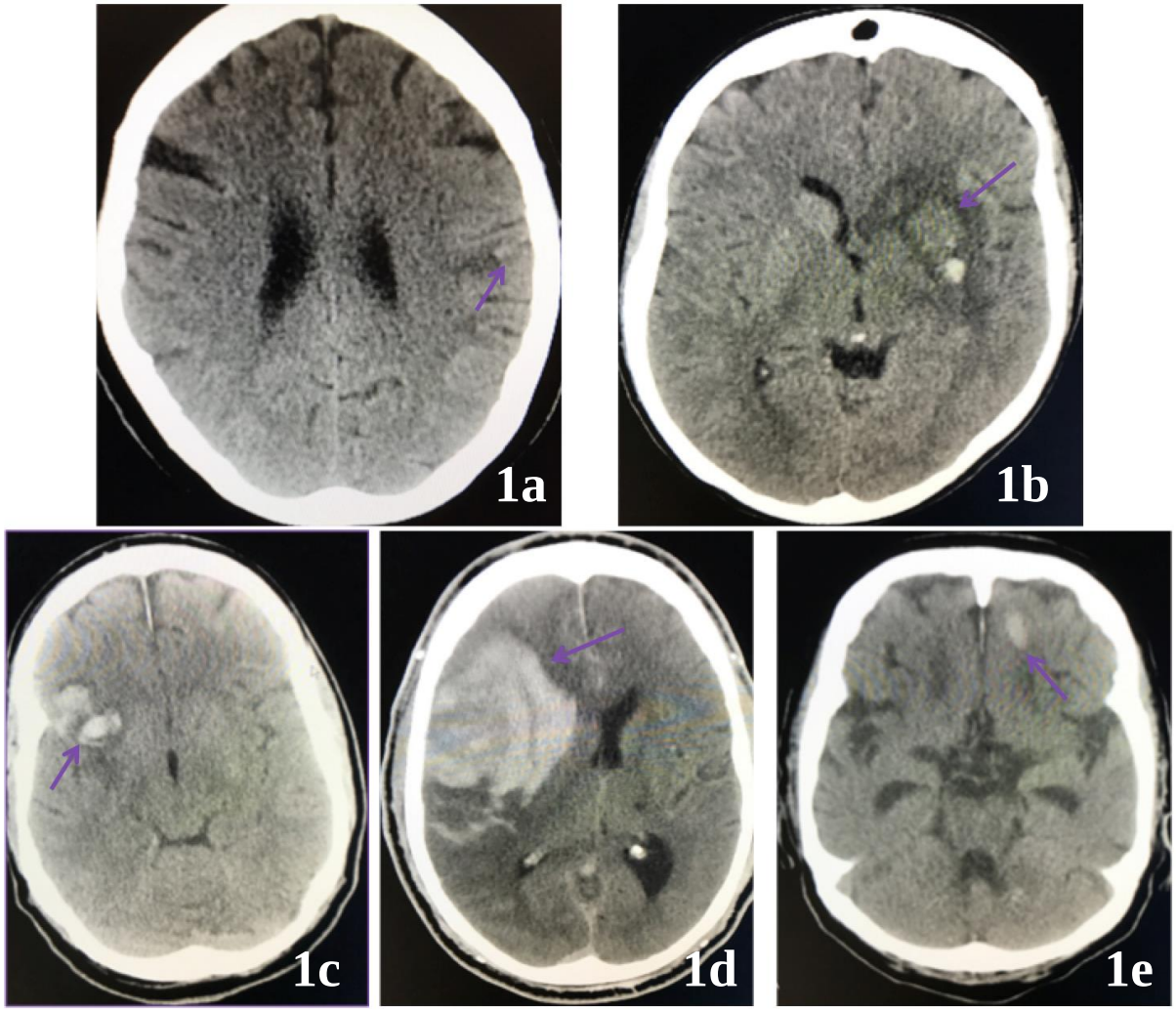
Introduction

- IV alteplase improves outcome in patients treated within 4.5 hours
- Alteplase is limited by risk of sICH (occurring in 2-7% of treated pts)
- Treatment of sICH is based on case series and expert opinion
- Efficacy of treatments is unclear

Definitions of Symptomatic ICH (sICH)

- 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 reporting and interpreting sICH rates.
- Classification dependent on
  - Radiographic appearance
  - Neurologic deterioration
- Hemorrhagic infarction (HI): petechial hemorrhage into the area of infarction
- Parenchymal hemorrhage (PH): sharply defined area of hemorrhage with or without mass effect

Radiographic Classification of Hemorrhagic Transformation



Legend:

1a. Hemorrhagic infarction type I.
1b. Hemorrhagic infarction type II.
1c. Parenchymal Hematoma Type I.
1d. Parenchymal Hematoma Type
1e. Extra-Ischemic hematoma

Definitions of symptomatic ICH

- Limitations to the HI/PH scheme
  - No way to differentiate hematoma within area of infarction vs extra-ischemic hematoma
  - No way to differentiate SAH, SDH, and IVH

- Expanded system (Heidelberg Bleeding Classification) recently proposed to address some of these limitations

Definitions of symptomatic ICH

*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% or more 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

*****
HI= hemorrhagic infarction; 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

Definitions of symptomatic ICH

- Choice of definition has an impact on sICH rates
  - ECASS 2: highest inter-rater agreement
  - SITS-MOST: strongest correlation with mortality
- Recommendations for stroke centers
  - Classify sICH according to radiographic criteria
  - Assess neurologic worsening via NIHSS score
  - Provide attribution of causality for worsening

Symptomatic ICH epidemiology

- Incidence
  - Rates vary across sICH definitions
  - Range between 2-7%
  - Clinical trials and prospective registries: similar results

Symptomatic ICH epidemiology

- Multiple studies have attempted to identify clinical, laboratory, and radiographic risk factors for sICH
- Evidence supporting these associations is variable
- sICH risk factors in a meta-analysis of 55 studies
  - Higher stroke severity
  - Older age
  - Higher baseline glucose
  - HTN
  - CHF
  - Renal impairment
  - Diabetes
  - Ischemic heart disease
  - Afib
  - Baseline antiplatelet use
  - Leukoaraiosis
  - Visible acute infarct on imaging

Symptomatic ICH epidemiology

- Prediction scores
  - Many of the factors associated with sICH are inter-related
  - At least 7 prediction scores have been proposed to integrate multiple risk factors
  - These scores have similar predictive value
  - Pts with higher scores are likely to have poor outcomes without thrombolysis
  - *These scores should not be used to select pts for thrombolysis*

Symptomatic ICH epidemiology

Score	Components	ROC curve
MSS	Age, NIHSS, glucose, platelets (0-4 pts)	0.59-0.86
HAT	NIHSS, diabetes or glucose, early CT hypodensity (0-5 pts)	0.59-0.79
SEDAN	Age, NIHSS, glucose, hyperdense middle cerebral artery sign, early CT hypodensity (0-5 pts)	0.50-0.70
SITS-ICH	Age, NIHSS, glucose, weight, hypertension, antiplatelet therapy (none, aspirin, aspirin+clopidogrel), systolic blood pressure, onset to treatment time (0-12 pts)	0.58-0.76
GRASPS GWTG	Age, NIHSS, glucose, systolic blood pressure, Asian vs. non-Asian ethnicity, gender (0-101 pts)	0.61-0.83
THRIVE	Age, NIHSS, hypertension, diabetes, atrial fibrillation (0-9 pts)	0.6
SPAN-100	Age, NIHSS (0-1 pts)	0.55-0.57

Pathophysiology of alteplase related hemorrhagic transformation

- sICH involves multiple connected pathologic processes
  - Coagulopathy
  - Ischemic injury
  - Reperfusion injury
  - BBB disruption

Pathophysiology of alteplase related hemorrhagic transformation

- Half-life of IV alteplase is 4 minutes
- Effect on coagulation lasts much longer because of a consumptive coagulopathy (up to 24 hours or more)
  - Reduced fibrinogen
  - Prolonged PT and PTT
- Most consistent association with sICH: reduced fibrinogen
  - Reduction by 200mg/dL within 6 hrs associated with sICH
  - Fibrinogen level <150mg/dL associated with hematoma expansion

Pathophysiology of alteplase related hemorrhagic transformation

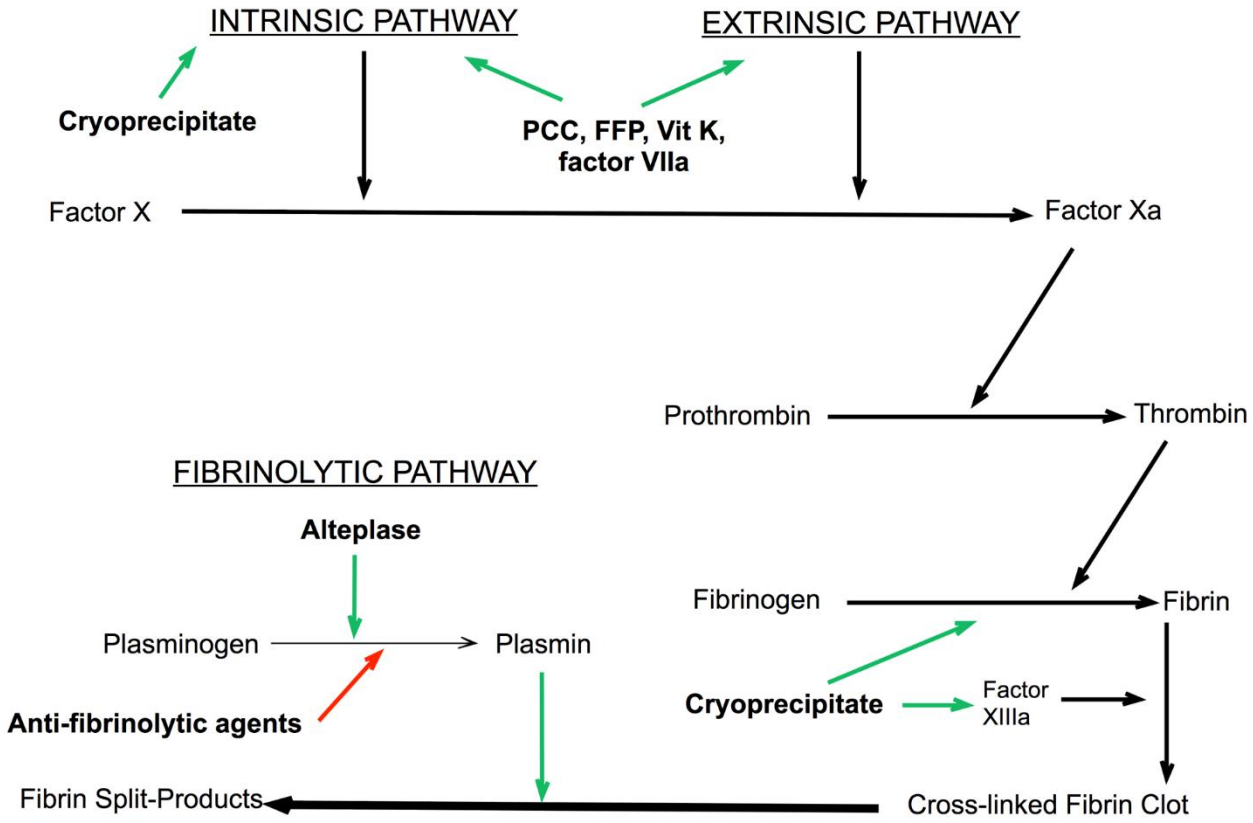


Figure 1. In green: Alteplase promotes plasmin activation which in turn degrades cross-linked fibrin into fibrin split-products and reversal agents promoting various steps of the coagulation cascade. In red: The anti-fibrinolytic agents (aminocaproic acid and tranexamic acid) deactivate plasmin formation which prevents the degradation of cross-linked fibrin.

Pathophysiology of alteplase related hemorrhagic transformation

- Hemorrhagic infarction occurs in ~25% of placebo pts
- Parenchymal hemorrhage, though, is mainly associated with thrombolysis
- Reperfusion of injured brain tissue can lead to sICH
  - But multiple mechanisms at work, as sICH can occur
    - In the setting of persistent occlusion
    - In areas remote from the infarcted tissue

Pathophysiology of alteplase related hemorrhagic transformation

- BBB disruption also associated with sICH development
  - Robust collaterals: associated with lower risk of sICH
  - Serum markers of BBB disruption (tight junction proteins and neuronal markers): associated with higher risk of sICH
  - Subclinical cerebrovascular disease also associated with sICH

Pathophysiology of alteplase related hemorrhagic transformation

- BBB disruption
  - Ischemic injury to brain endothelial cells
  - Time dependent, with activation of MMPs early
  - Tight junction breakdown
  - IV alteplase also promotes MMP secretion via free radical formation
- The processes underlying BBB disruption in IV alteplase-treated pts remain unclear
- Best pathway to target also requires more research

Diagnosis of symptomatic ICH

- Monitoring after IV alteplase
  - Guidelines recommend ICU or stroke unit care for 24 hours
    - Neurologic and BP monitoring (goal <180/105)
      Q15min for 2hrs, q30min for 6 hrs, then q60min for 16 hrs
    - Repeat imaging with HA, N/V, or neurologic worsening
  - If symptoms develop during infusion, consider stopping IV alteplase and obtaining an emergent head CT
  - If an asymptomatic hemorrhage is noted on 24 hour imaging, timing of antiplatelet initiation is dependent upon risk of recurrent stroke vs. risk of hematoma expansion

Diagnosis of symptomatic ICH

- Timing of post-alteplase sICH
  - sICH attributable to IV alteplase occurs within 36 hrs
  - NINDS: 80% fatal sICHs within 12 hrs and 100% within 24 hrs
  - Because many sICH occur more than 2 hrs from infusion, consider extending intensive monitoring of high-risk pts from 8 to 12 hrs

Diagnosis of symptomatic ICH

- Detecting sICH
  - Clinical deterioration should prompt imaging, but the degree of deterioration to trigger imaging is unclear
  - 4-point decline in NIHSS score is commonly used, but there might be a ceiling effect in those pts presenting with more severe strokes
  - Consider a lower threshold for emergent imaging in pts with more severe strokes (e.g. NIHSS ≥12)

Natural history and outcome

- Natural history is very poor in patients with PH-2 subtype compared with pts without radiographic hemorrhage
  - ECASS I
    - 24 hour deterioration: OR 32.3 (13.4-77.7)
    - 3-month mortality: OR 18.0 (8.05-40.1)
  - ECASS II: ~50% mortality
- Clinical relevance of HI-1, HI-2, and PH-1 is less clear
- Challenging to disentangle the impact of sICH from the underlying ischemic event on outcomes

Treatment of post-thrombolysis hemorrhage

- General principles similar to treatment of spontaneous ICH
- Identifying those patients most likely to benefit from reversal remains difficult
  - Unlikely that all patients with sICH have an equal opportunity to benefit
  - Current literature: sICH within 24 hrs or with hypofibrinogenemia might be reasonable to treat
  - Might be reasonable to treat pts within 24 hrs with ongoing coagulopathy even if bleeding is asymptomatic

Treatment of post-thrombolysis hemorrhage

- Cryoprecipitate
  - Contains fibrinogen, factor VIII, factor XIII, and von Willebrand factor
  - Consider sending a STAT fibrinogen level, empirically transfusing with 10 units of cryoprecipitate and anticipate giving more cryoprecipitate as needed to achieve a normal fibrinogen level of 150 mg/dL or more. (10 units of cryoprecipitate increases fibrinogen by nearly 50 dg/ml)
  - Disadvantages: no pathogen inactivation, Transfusion reaction and transfusion related lung injury (TRALI), time delay
  - Upon sICH diagnosis, consider
    - Sending an immediate fibrinogen level
    - Empiric 10 unit cryo infusion
    - Additional cryo to achieve fibrinogen >150mg/dL
  - *Consider prioritizing cryo over other reversal agents*

Treatment of post-thrombolysis hemorrhage

- Platelet transfusion
  - Transfusion of 6-8 units is routinely recommended, but efficacy unclear
  - Limitations similar to cryoprecipitate
  - Consider transfusion in pts with thrombocytopenia (platelet count <100K/microliter)
  - Transfusion for all sICH remains controversial
  - Transfusion reaction, transfusion related lung injury, volume overload

Treatment of post-thrombolysis hemorrhage

- Prothrombin complex concentrate (PCCs)
  - Various forms and can include factors II, VII, IX, X and proteins C and S
  - Activate both intrinsic and extrinsic pathways
  - Might need to replenish fibrinogen prior to PCC administration
  - 25-50 units/Kg (based on INR level)
  - Risk of thrombotic events is 1% in the general population
  - *PCCs are controversial in most pts, but possibly an adjunct to cryo in pts on warfarin prior to IV alteplase*
  - Thrombotic complications

Treatment of post-thrombolysis hemorrhage

- Fresh frozen plasma
  - Contains all proteins that activate both intrinsic and extrinsic pathways
  - Limitations: slow administration in large IV volumes to prevent volume overload, carries the risk for transfusion reactions
  - 12 ml/Kg
  - No safety or efficacy data in sICH
  - *FFP is controversial for most sICH pts, but possibly an adjunct to cryo in pts on warfarin prior to IV alteplase if PCCs are unavailable*
  - Transfusion reaction, transfusion related lung injury, volume overload

Treatment of post-thrombolysis hemorrhage

- Vitamin K
  - May potentiate effect of fibrinogen
  - 10 mg intravenously
  - No safety or efficacy data in sICH
  - *Vitamin K is controversial for most sICH pts, but possibly an adjunct to cryoprecipitate in pts on warfarin prior to IV alteplase*
  - Anaphylaxis

Treatment of post-thrombolysis hemorrhage

- Antifibrinolytic agents (aminocaproic acid and tranexamic acid)
  - Inhibit proteolytic enzymes like plasmin
  - Rapid onset
  - Aminocaproic acid: 4gIV during 1st hour followed by 1g per hour for 8 hours.
  - Transexamic acid: 10mg/Kg 3-4 times per day (adjustment based on kidney function may be necessary)
  - Commonly used in cardiac surgery, hematologic disorders, aneurysmal SAH
  - Limited safety and efficacy data (case reports)
  - *May be considered in all pts with sICH—particularly in pts who decline blood products*
  - Thrombotic complications

Treatment of post-thrombolysis hemorrhage

- Recombinant factor VIIa
  - Procoagulant well-studied in spontaneous ICH and hemophilia
  - Limitation: 4% incremental risk of stroke or MI in FAST trial
  - 20 to 160 µg/kg
  - Not yet rigorously studied in sICH
  - *Consider withholding factor VII in sICH until further safety data available*
  - Thrombotic complications

Treatment of post-thrombolysis hemorrhage

- Prevention of hematoma expansion
  - Optimal blood pressure target is unknown
  - Weighing worsened ischemia vs. hematoma expansion
    - If recanalization is complete, consider more strict BP control
    - If recanalization is incomplete, higher targets might help maintain adequate flow to the ischemic bed
    - If parenchymal hematoma and high risk of expansion, consider more strict BP control

Treatment of post-thrombolysis hemorrhage

- Neurosurgical treatment
  - Most data either from spontaneous ICH trials or observational studies
  - Rapid decompression weighed against iatrogenic injury
  - Neurosurgical treatments should be considered *after* coagulopathy reversal
  - *Neurosurgery may be considered in select cases*

Conclusion and future directions

- sICH is an uncommon but severe complication of systemic thrombolysis in acute ischemic stroke.
- Mechanisms include coagulopathy, reperfusion injury, and BBB breakdown
- Mainstay of treatment remains correction of coagulopathy, but the optimal agent is not yet clear
- Additional future research needed:
  - Earlier diagnosis before expansion
  - Role for neurosurgical intervention
  - Treatments for maintaining BBB integrity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