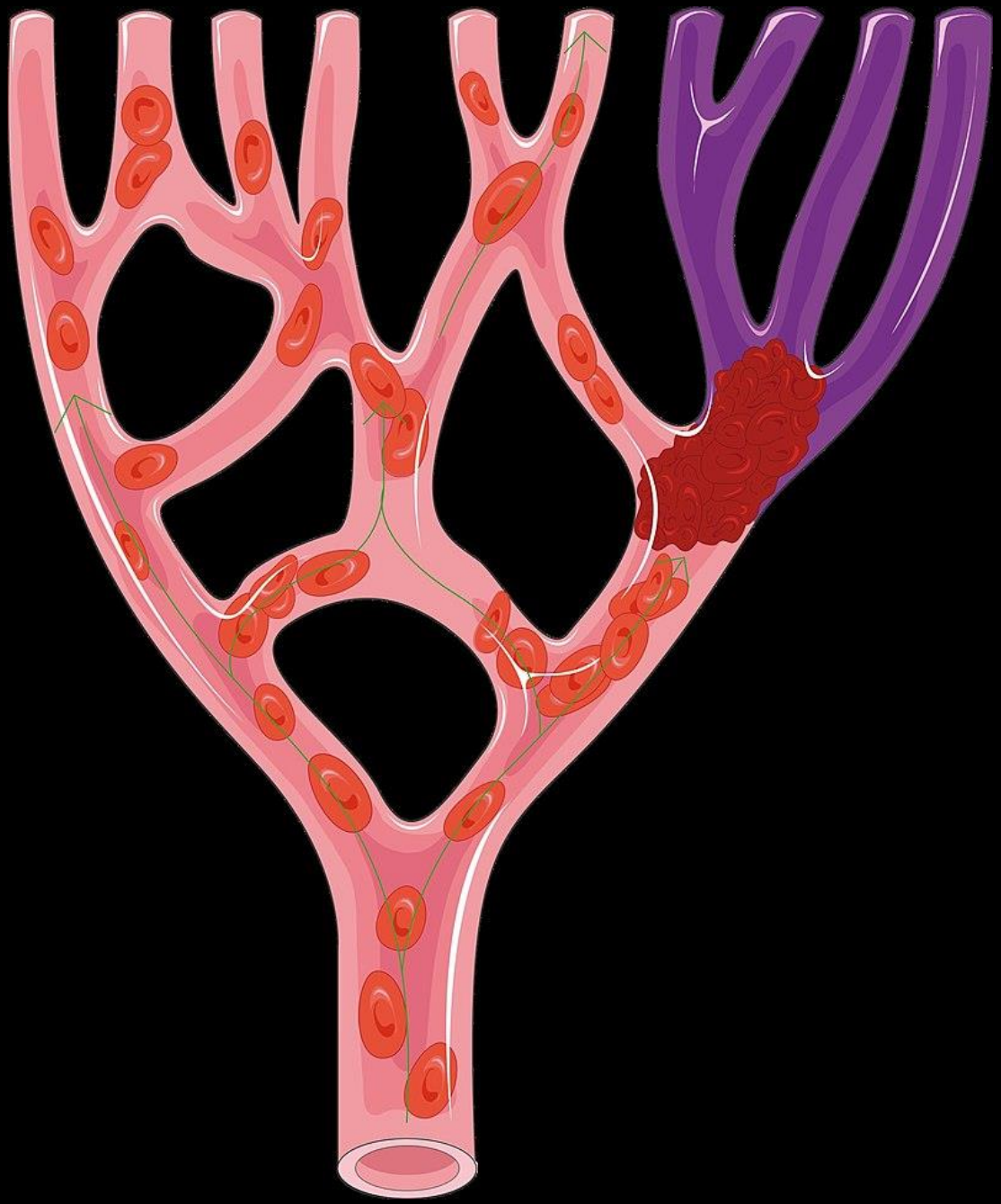


ALTEPLASE COMPLICATIONS

Dr. A Sharifi-Razavi

- The most feared complication of thrombolytic therapy is :
- Symptomatic intracerebral hemorrhage.

Others:

- Asymptomatic intracerebral hemorrhage,
- Systemic bleeding,
- Angioedema

ANGIOEDEMA

- Orolingual angioedema after thrombolysis is an even less common complication than SICH, but since it is also potentially life threatening, it is important to recognize it quickly and have a treatment algorithm in place.
- It is estimated that orolingual angioedema occurs in approximately 1.3% to 5% of patients with stroke receiving IV r-tPA.
- It usually presents as a transient, self-limited swelling of the tongue and lips but can potentially cause airway obstruction and respiratory compromise requiring emergent intubation or cricothyrotomy.
- CT of the tongue can distinguish hematoma from angioedema in this setting

- The exact mechanism of action underlying the development of orolingual angioedema has not been elucidated.
- Patients taking angiotensin-converting enzyme (ACE) inhibitors are at increased risk of developing this rare complication, but it has also been reported in patients not taking these medications.
- It appears that the incidence of r-tPA-related orolingual angioedema is higher in caucasians than in Asians, and the use of ACE inhibitors prior to stroke also significantly increases the risk of orolingual angioedema in Asians.

ANGIOEDEMA ASSOCIATED WITH THROMBOLYSIS FOR ISCHEMIC STROKE

Ischemic stroke

Thrombolytic therapy

Angioedema

Cheeks **8%**

Lips **49%**

Tongue **64%**

Pharynx **6%**

Incidence: 2,1% to 7,9%

Demographics

Risk X3

If asymetric, 2/3 contralateral to the stroke location

Risk X6

JIM Journal of Internal Medicine

- Orolingual angioedema following thrombolysis can be bilateral or unilateral.
- If it is unilateral, it is usually contralateral to the affected hemisphere.
- Risk of developing orolingual angioedema was associated with
- (1) prior use of ACE inhibitors (relative risk [RR] 13.6; 95% confidence interval [CI]: 3.0-62.7)
- (2) ischemic strokes involving the insular and frontal cortex (RR 9.1; 95% CI: 1.4-30.0).
- Orolingual angioedema occurs in patients of all ages with no gender predilection.


tPA-Associated Angioedema
REBELEM

- Since orolingual angioedema can appear quickly and unexpectedly after thrombolysis, we recommend close monitoring and examination of the patient with stroke, especially toward the end of the r-tPA infusion, as this is when it is more likely to occur.
- The patient with angioedema near or involving the tongue, uvula, soft palate, or larynx must be immediately assessed for signs of airway compromise. If intubation is necessary, the airway should be managed by the most experienced person available, because intubation in the presence of laryngeal angioedema can be difficult due to distortion of the normal anatomy.
- Angioedema of the lips or mouth sometimes spreads to involve the throat, and frequent monitoring of airway patency is critical throughout treatment.

Specific management recommendations for orolingual angioedema include the following

:

- Endotracheal intubation may not be necessary if edema is limited to anterior tongue and lips.
- Edema involving larynx, palate, floor of mouth, or oropharynx with rapid progression (within 30 minutes) poses higher risk of requiring intubation.
- Awake fiberoptic intubation is optimal.
- Nasotracheal intubation may be necessary but is associated with a risk of epistaxis after treatment with IV alteplase.
- Emergency cricothyrotomy is rarely needed and is also problematic after IV alteplase treatment, but in a life-threatening circumstance the need to establish an airway supersedes this concern.

- Discontinue alteplase infusion and hold angiotensin converting enzyme inhibitor

Give in rapid sequence:

- IV methylprednisolone 125 mg
- IV diphenhydramine 50 mg
- IV famotidine 20 mg
- If there is further increase in angioedema, give epinephrine (0.1 percent) 0.3 mL subcutaneously or 0.5 mL by nebulizer, but note that epinephrine has a theoretical risk of blood pressure elevation and hemorrhage.

- Finally, a short course of maintenance, corticosteroids, and antihistamines should be considered for those patients who are intubated or for those patients with extensive edema not responding to the initial doses of medications.
- Additional treatment options for refractory angioedema include icatibant and plasma-derived C1 inhibitor concentrate, which have been used to treat hereditary angioedema and angiotensin converting enzyme inhibitor-related angioedema .

SYSTEMIC BLEEDING

- Mild systemic bleeding usually occurs in the form of oozing from intravenous catheter sites, ecchymoses (especially under automated blood pressure cuffs), and gum bleeding; these complications do not require cessation of treatment.
- More serious bleeding, such as from the gastrointestinal or genitourinary system, may require discontinuation of alteplase depending on the severity.
- Rarely, patients who suffer stroke after a recent myocardial infarction can develop bleeding into the pericardium, resulting in life-threatening tamponade.
- Consequently, patients who become hypotensive after alteplase should be evaluated with urgent echocardiography.

SYMPTOMATIC ICH

- Symptomatic ICH After Thrombolysis The risk of SICH is roughly 6% in patients with stroke treated with IV r-tPA.
- The risk of SICH after intra-arterial (IA) thrombolysis with or without IV r-tPA is approximately 10%.

- Differences exist in the criteria used to define SICH following IV thrombolysis in clinical trials, cohort studies, and stroke registries.
- SICH was defined as computed tomography (CT) or magnetic resonance imaging-documented hemorrhage associated with clinical deterioration, defined as an increase in the National Institute of Health Stroke Scale (NIHSS) score of 4 points or more and was determined to be the cause of the neurological deterioration or if the hemorrhage resulted in death.

- ‘‘minor’’ symptomatic hemorrhage :
- ‘‘major’’ symptomatic hemorrhage/; patients with a 4-point increase in their NIHSS.
- Finally, it is important to emphasize that there is no definitive consensus as to what time period constitutes a clinically relevant SICH attributable to thrombolysis.
- SICH were considered attributable to thrombolysis when they occurred within 36 hours of receiving r-tPA.

- Risk Factors for SICH and Pathophysiology There are several patient characteristics that are thought to increase the probability of developing SICH after thrombolysis.
- Some studies have suggested that advanced age may increase the risk of postthrombolysis SICH.
- Patients older than 80 years of age were 2.87 times more likely to experience an SICH within 36 hours of IV tPA compared to younger patients.
- We must remember advanced age is associated with worse outcomes and higher numbers of comorbidities regardless of thrombolysis-related complications, and traditionally most trials have excluded patients older than the age of 80.
- Stroke severity has been identified as an independent risk factor for SICH after IV or IA thrombolysis.

- Additionally, many studies suggest that hyperglycemia on admission and history of diabetes increases the risk of thrombolysis-associated SICH.
- The majority of patients presenting with acute ischemic stroke have elevated blood pressure, and this places them at risk of ICH post thrombolysis. There is a higher rate of SICH post thrombolysis in patients presenting with uncontrolled hypertension compared to those without uncontrolled hypertension, 26% versus 12%, with elevated systolic blood pressure (SBP) in the first 24 hours post treatment further associated with increased risk of SICH.

- There is also suggestion that dual antiplatelet therapy places patients at a higher risk of SICH than those patients on single therapy or no antiplatelet therapy, but data are inconclusive and even in the studies with higher rates of SICH, there does not appear to be an effect on outcome.
- There are limited data to suggest that renal impairment is associated with a higher risk of SICH after administration of IV r-tPA, but larger prospective studies are needed to determine whether or not this observation is true.

Risk Factors for SICH After Thrombolysis

- CT hypodensity (early ischemic changes >1/3 of MCA territory)
- Elevated serum glucose or history of diabetes mellitus
- Symptom severity
- Time to treatment
- High systolic blood pressure
- Low platelets
- Advanced age

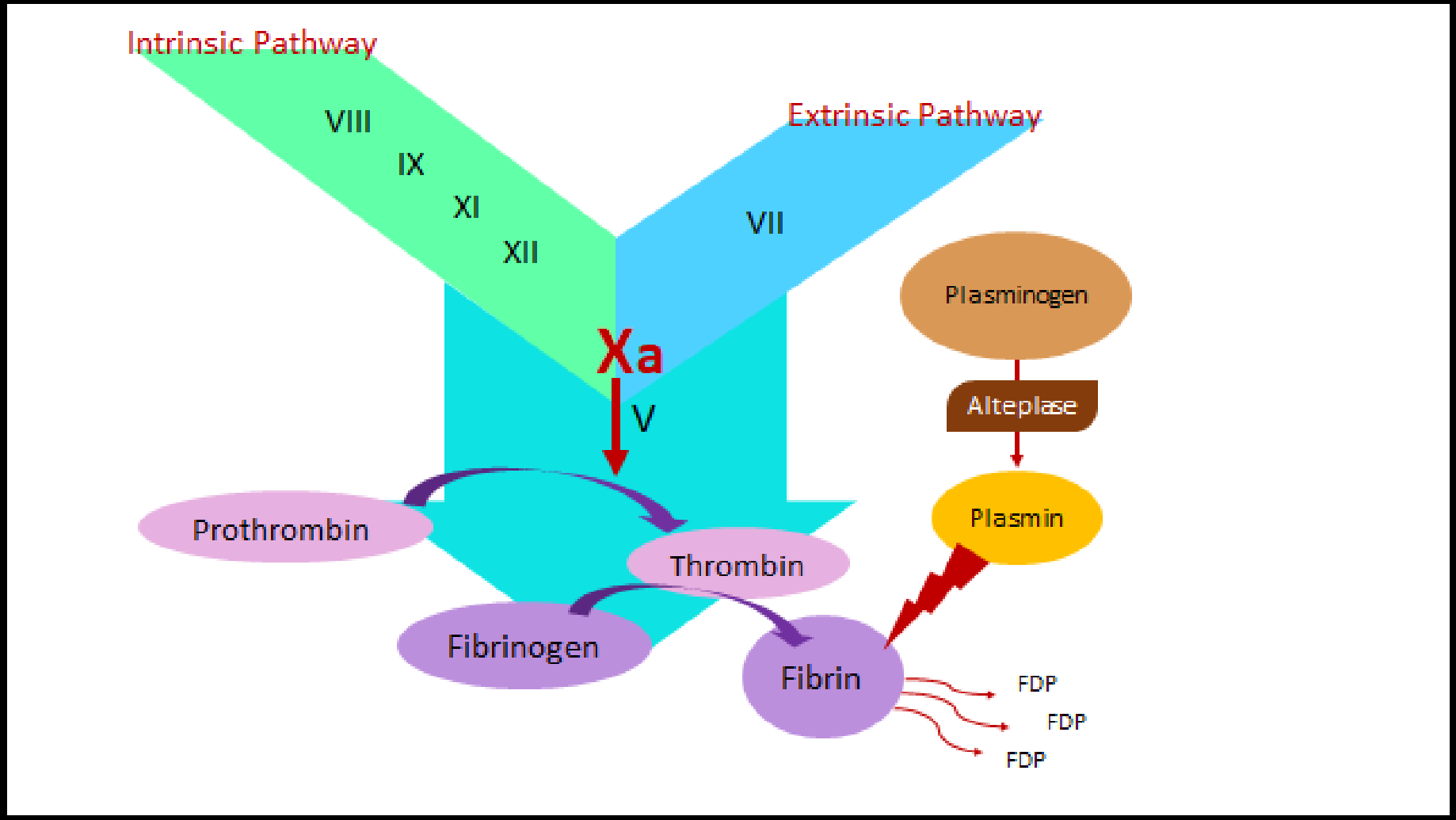
- The underlying mechanism by which rt-PA leads to ICH is complex.

It was initially thought to be due to

1)the breakdown of vessel walls caused by free radical production upon reperfusion

2) the effects of fibrinogen depletion

3) platelet dysfunction due to circulating fibrin degradation products.


Intrinsic Pathway
VIII
IX
XI
XII
Extrinsic Pathway
VII
Xa
V
Plasminogen
Alteplase
Plasmin
Prothrombin
Thrombin
Fibrinogen
Fibrin
FDP
FDP
FDP

- More recently, it has been discovered that r-tPA may also be associated with disruption of the blood–brain barrier, as it has pleiotrophic effects on signaling cascades inducing expression of matrix metalloproteinase, which is responsible for the breakdown of the extracellular matrix and subsequent vascular permeability.
- Animal models have discovered that by inhibiting activation of metalloproteinase or oxygen free radical formation, the incidence of SICH is decreased, thus further supporting this underlying mechanism of action.

- Thrombolysis-related ICH usually occurs at the site of ischemic brain tissue though can present at a distant, unrelated site .
- Remote post thrombolysis cerebral hemorrhages can be solitary or multiple and by definition appear in brain regions without visible ischemic damage.
- Traditionally, the risk of remote cerebral hemorrhage post thrombolysis has been reported as occurring in approximately 1.3% to 3.7% of patients.
- However, the recent Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register (SITS-ISTR) study, which included 45 079 patients treated with IV r-tPA, discovered that remote parenchymal hematomas made up one-third of all parenchymal hematomas after IV thrombolysis.

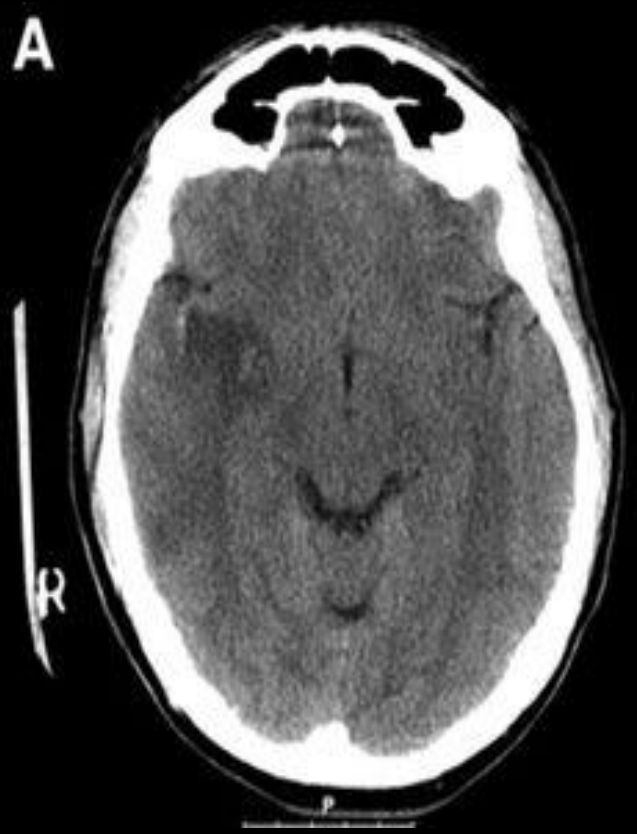
- Patients with remote hematomas post thrombolysis were more likely to be female, with a higher median age, and have a history of previous non recent stroke (>3 months) compared to patients with local/intra ischemic parenchymal hemorrhage.
- They were also less likely to have severe strokes, early infarct signs, and hyperdense cerebral artery signs (HCAS) on baseline CT head, which were all characteristics more commonly found in patients with local/ intraischemic hemorrhage.

- Additionally, patients with remote hemorrhages had a lower frequency of atrial fibrillation (AF) and diabetes compared to patients with local/intra ischemic hemorrhage.
- Small-vessel disease was rarely found in either hemorrhage type.
- This raises the possibility that the risk factor profile differs between the different types of SICH seen post thrombolysis, with local/intra ischemic hemorrhage more often seen in association with large-vessel occlusion (higher NIHSS, AF, and HCAS) and remote hemorrhages associated with previous stroke and older age, that is, markers of previous cerebrovascular pathology.

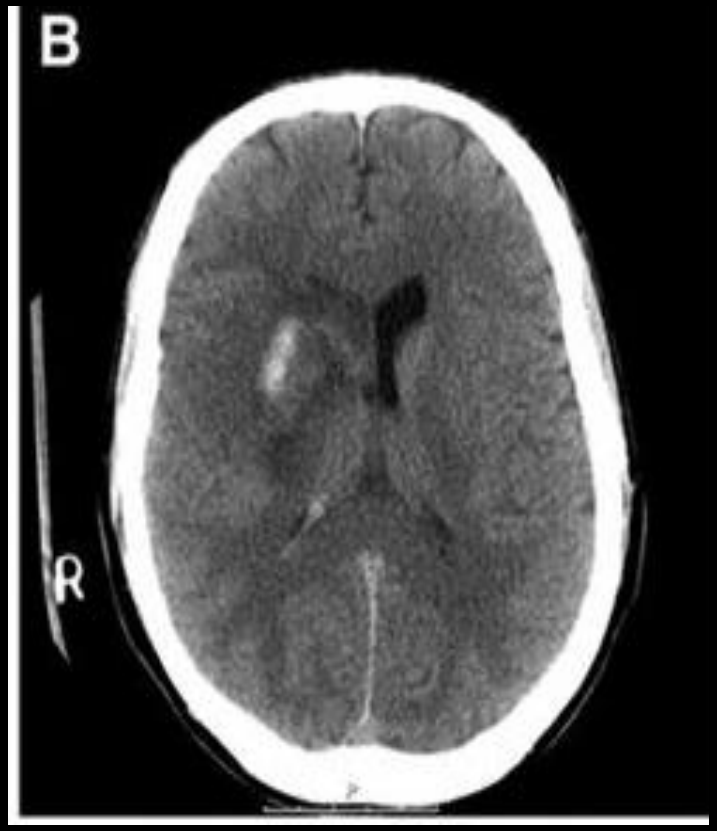
- Randomized clinical trials have shown that r-tPA dosed at 0.9 mg/kg with a maximum dose of 90 mg is not only safe but also effective.
- There are some who propose the use of lower doses of r-tPA in populations at higher risk of ICH, such as East Asian populations, as a way to decrease the risk of bleeding.
- For example in Japan, 0.6 mg/kg of r-tPA is the only approved dose since 2005 for acute stroke presenting within 3 hours of symptom onset.
- The practice of administering lower doses of r-tPA for select high-risk patients is not followed in the United States.

The Heidelberg Bleeding Classification
Anatomic Description of Intracranial Hemorrhages

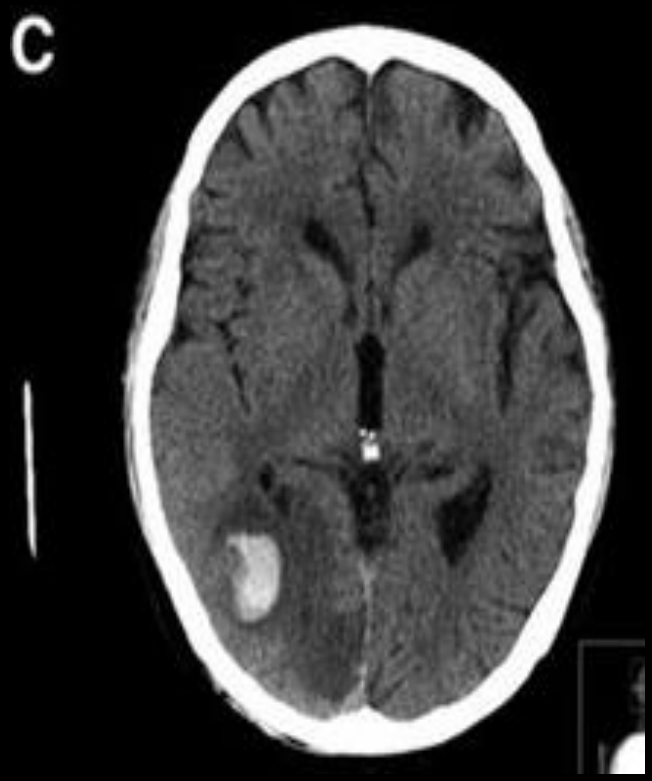
Class	Type	Description
1	Hemorrhagic transformation of infarcted brain tissue	
1a	**HI1**	Scattered small petechiae, no mass effect
1b	**HI2**	Confluent petechiae, no mass effect
1c	**PH1**	Hematoma within infarcted tissue occupying <30%, no substantive mass effect
2	Intracerebral hemorrhage within and beyond infarcted brain tissue	
	PH2	Hematoma occupying ≥30% of the infarcted tissue, with obvious mass effect
3	Intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage	
3a	Parenchymal hematoma remote from infarcted brain tissue	
3b	Intraventricular hemorrhage	
3c	Subarachnoid hemorrhage	
3d	Subdural hemorrhage	



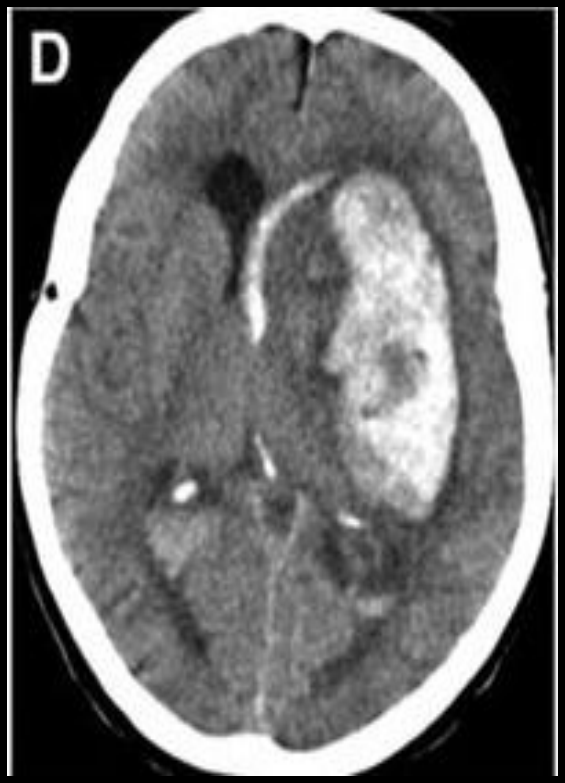
CT with hemorrhagic infarction (HI) type 1 of right temporal lobe and basal ganglia.



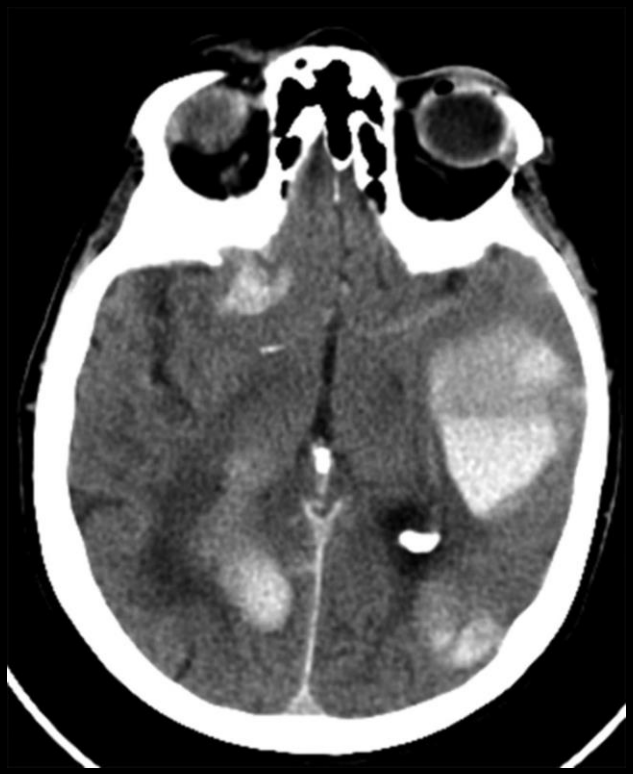
B, CT with HI type 2 of right striatum.



CT with parenchymal hematoma (PH) type 1 in right posterior cerebral artery territory.



CT with extended PH type 2 of left basal ganglia, capsula interna and externa with additional blood in both lateral ventricles and mass effect causing a shift of midline structures to the right.



Bilateral parenchymal hematomas (remote parenchymal hematoma [PH]) with fluid level in the left PH indicating coagulation disorder.

- Most SICH hemorrhages will occur within the first 24 hours after receiving IV r-tPA, with the bulk of fatal hemorrhages occurring within the first 12 hours.
- Because of this, close monitoring of the patient with acute stroke in an intensive care unit or dedicated stroke unit is imperative status post thrombolysis, with special attention paid to signs of:

1. clinical deterioration
2. decreasing mental status
3. new headache
4. acute hypertension
5. nausea or vomiting

- If a clinician suspects the possibility of a post thrombolysis SICH, then any remaining IV r-tPA should be held immediately until an ICH is excluded.
- Once the thrombolysis infusion has been discontinued and it is determined that the patient is stable enough to be transported for imaging, an emergent non contrast CT head should be obtained.
- Concurrently, the clinician should rule out other causes of neurological deterioration such as hemodynamic instability, seizure, and infection.

- Urgently obtain laboratory studies including prothrombin time (PT), partial thromboplastin time (PTT), platelet count, fibrinogen levels, and type and cross.
- If a serious or life-threatening hemorrhage is confirmed, them attempts should be made to mitigate the hemorrhage.
- Urgent treatment includes the transfusion of cryoprecipitate (6-8 units) followed by platelets (6-8 units) in order to rapidly correct the fibrinolytic state produced by r-tPA.
- The on-call neurosurgeon should be alerted to the SICH, and a hematologist should also be consulted in order to weigh-in on the patient's coagulation status. Fibrinogen levels should be rechecked every 4 hours and cryoprecipitate transfused as needed to maintain fibrinogen levels >150 mg/dL.51 There should be periodic complete blood counts as well as PT/PTT measurements with blood transfusions administered if necessary.

Protocol for Management of Postthrombolysis ICH

Suspect ICH (new headache, nausea, vomiting, etc)

- Discontinue r-tPA infusion
- STAT blood draw: PT, PTT, platelet count, fibrinogen, type & cross
- STAT noncontrast CT head

Hemorrhage confirmed?

- Administer 6-8 units of cryoprecipitate, followed by 6-8 units platelets
- Consult neurosurgeon & alert to ICH
- consult hematologist & alert to current coagulation status
- Administer e-aminocaproic acid 4-5 gm IV over 1 hour, followed by 1 gm PO or IV hourly until bleeding is controlled or tranexamic acid 10 to 15 mg/kg IV over 10 to 20 minutes.
- Fibrinogen levels should be rechecked every Q 4 hours & cryoprecipitate transfused PRN to maintain fibrinogen levels > 150 mg/dL
- Blood pressure monitoring Q 15 minutes
- Periodic blood work (CBC, PT/PTT) to re-assess coagulation status & need for blood transfusion
- Consider repeat CT head to assess for ICH growth
- Consensus decision regarding surgical and/or medical therapy

- The patient should continue to be cared for in an ICU or neurointensive care unit with vital signs and neuro checks every 15 minutes during the acute setting.
- The intensivist should implement intracranial pressure monitoring and intubation when appropriate.
- A repeat CT head should be considered to assess for ICH growth and clinical status followed closely.

- Aminocaproic acid inhibits fibrinolysis by preventing the conversion of plasminogen to plasmin and increases fibrinogen levels that are reduced in patients with SICH.
- Tranexamic acid is a newer analog of aminocaproic acid. Much of our current knowledge on the efficacy and safety of both e-aminocaproic acid and tranexamic acid comes from studies involving patients with aneurysmal subarachnoid hemorrhage. In many of these trials, there was a reduction in the rebleeding rate in those patients treated with tranexamic acid or e-aminocaproic acid, but this was offset by an increased risk of thrombotic complications, cerebral ischemia, and hydrocephalus.

- The usefulness of other agents including prothrombin complex concentrate (PCC), fibrinogen, fresh frozen plasma (FFP), and recombinant factor VII in post thrombolysis ICH is unknown.
- Since FFP activates the coagulation cascade, potentially driving fibrin formation, it can theoretically counter the effect of r-tPA, which increases plasmin activity. However, FFP must be administered slowly and in large volumes to prevent transfusion-related reactions and fluid overload. The need for large volumes of FFP increases the time it takes for reversal of the underlying coagulopathy in a patient with ongoing SICH.

- Spontaneous ICH, which suggest a target blood pressure of 160/90 mm Hg and that the acute lowering of SBP to 140 mm Hg in patients presenting with a SBP of 150 to 220 mm Hg is probably safe.
- The decision about whether to surgically remove a ICH remains controversial, and the benefit of surgery uncertain.
- It is crucial to remember that surgical intervention should only ever be considered after adequate reversal of the fibrinolytic effects of r-tPA

- A question that commonly arises in clinical practice is: ‘‘For how long after r-tPA administration is it reasonable to attempt to reverse the lytic effects if SICH occurs?’’
- Although r-tPA is short acting with rapid clearance, its effects on the coagulation profile (prolonged PT/PTT and reduced fibrinogen levels) may last 24 hours or more post infusion.
- We propose a window of 24 hours for lytic reversal in SICH, as most SICH will occur within this time frame, and this window is consistent with time monitored in the ICU, follow-up CT head, duration of coagulation abnormalities, and initiation of antiplatelet therapy.
- However, as most define hemorrhages attributable to thrombolysis as occurring within 36 hours, one could argue that a 36-hour window for lytic reversal is also appropriate, especially when considering the likelihood of poor prognosis and high mortality.

۱۰ واحد(هر ۱۰ کیلو ۱ کیسه) کرایو در عرض ۱۰-۳۰ دقیقه انفوزیون کنید.
این عمل را تکرار کنید تا سطح فیبرینوژن به ۱۵۰-۲۰۰ برسد.

ترانگزامیک اسید (۲ ویال ۵۰۰ واحدی) به میزان ۱۰mg/kg-۱۵در طی ۱۰-۲۰ دقیقه تجویز کنید هر ۸ ساعت تا ۲٤ ساعت

در صورت پلاکت کمتر از ۱۰۰۰۰۰بمیزان ٦-۸ واحد پلاکت تزریق کنید.

در صورتیکه بیمار سابقه مصرف وارفارین دارد PCCیاFFP و ویتامین K تجویز کنید.

در صورتیکه بیمار به هر علتی در ٤ ساعت اخیر هپارین مصرف کرده است mg ۱ پروتامین به ازای هر ۱۰۰ واحد هپارین تجویز کنید.

فشار خون سیستولیک را به زیر 140 برسانید.

مشاوره اورژانس نوروسرجری درخواست کنید.