Stroke is No Joke! Management of the Treatment Complications of Stroke

A Presentation for HealthTrust Members
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Conflicts of Interest Disclosures

Deena Omar, PharmD, presenter, and Deepali Dixit, PharmD, BCPS, BCCCP, FCCM, preceptor, have no relevant financial relationships with ineligible companies to disclose.

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Learning Objectives for Nurses & Pharmacists

Recall	Recall medications used in the management of acute ischemic stroke (AIS) and hemorrhagic stroke
Recognize	Recognize different treatment options for AIS and hemorrhagic stroke and their adverse effects
Identify	Identify appropriate treatment options for adverse events of stroke medications

Learning Objectives for Pharmacy Techs

Recognize	Recognize different preparations of fibrinolytic medications used to treat acute ischemic stroke (AIS)
Recall	Recall medications used in an AIS patient medication history that may cause orolingual angioedema (OLAE)
Identify	Identify storage considerations for medications used in the management of hemorrhagic stroke

Abbreviations

- **Acute Ischemic Stroke (AIS)**
- **Alteplase (tPA)**
- **Blood Brain Barrier (BBB)**
- **Blood Pressure (BP)**
- **C1-inhibitor (C1-INH)**
- **Cerebrospinal Fluid (CSF)**
- **Computed tomography (CT)**
- **Endotracheal (ET)**
- **Fresh-Frozen Plasma (FFP)**
- **Headache (HA)**
- **High-molecular weight kininogen (HMWK)**
- **Intensive Care Unit (ICU)**
- **Intracranial Hemorrhage (ICH)**
- **Intravenously (IV)**
- **Nausea and Vomiting (N/V)**
- **Orolingual Angioedema (OLAE)**
- **Intracerebral Hemorrhage (ICH)**
- **Intercranial Pressure (ICP)**
- **Subcutaneously (SQ)**
- **Symptomatic intracranial hemorrhage (sICH)**
- **Thromboelastography (TEG)**
- **Tenecteplase (TNK)**
- **Tissue plasminogen activator (tPA)**

STROKE

An interruption of the oxygen supply to the brain typically due to an occlusion or rupture

Source: “About Stroke.” The American Stroke Association. 2019. www.stroke.org/en/about-stroke.

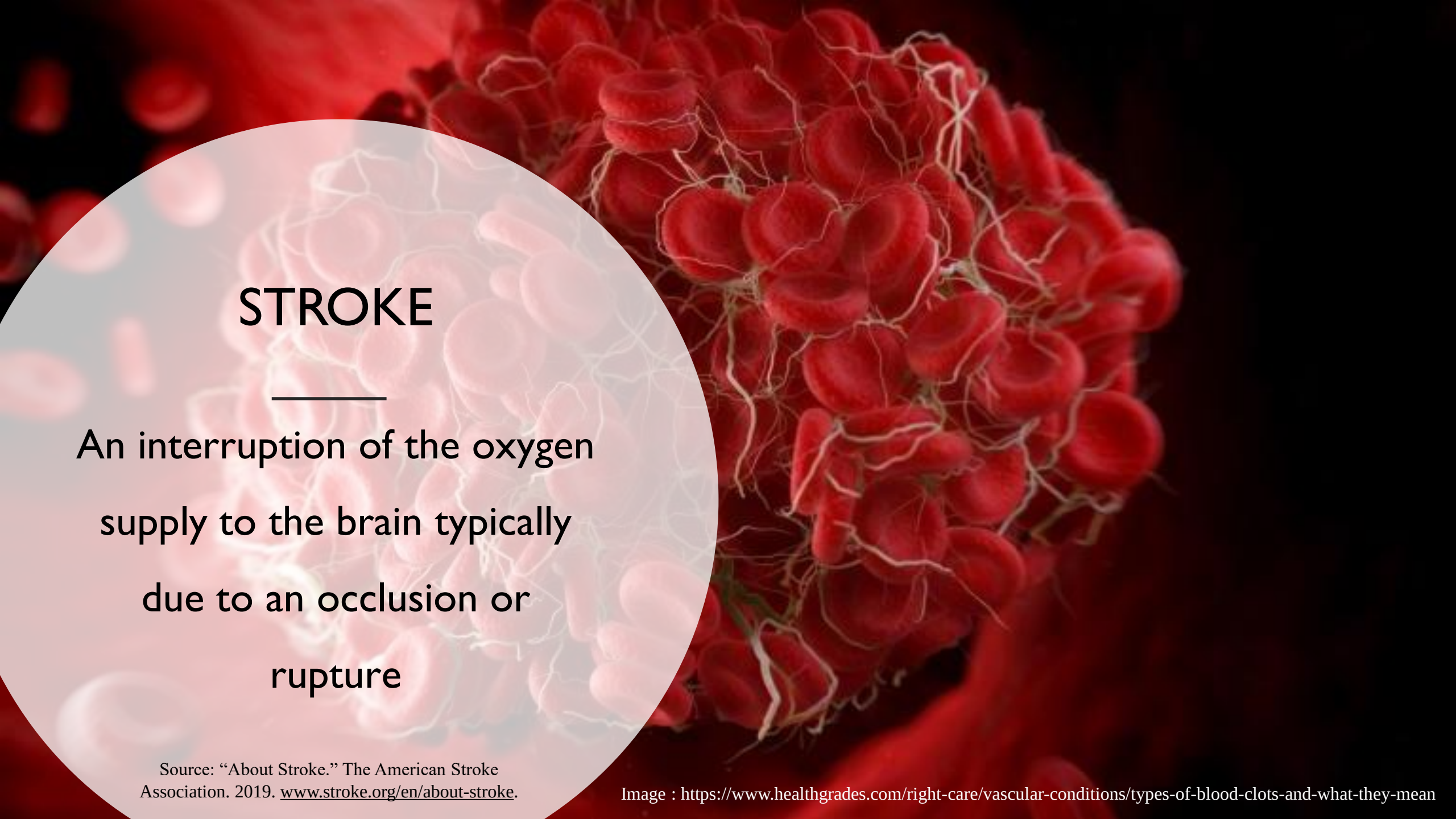


Image : https://www.healthgrades.com/right-care/vascular-conditions/types-of-blood-clots-and-what-they-mean

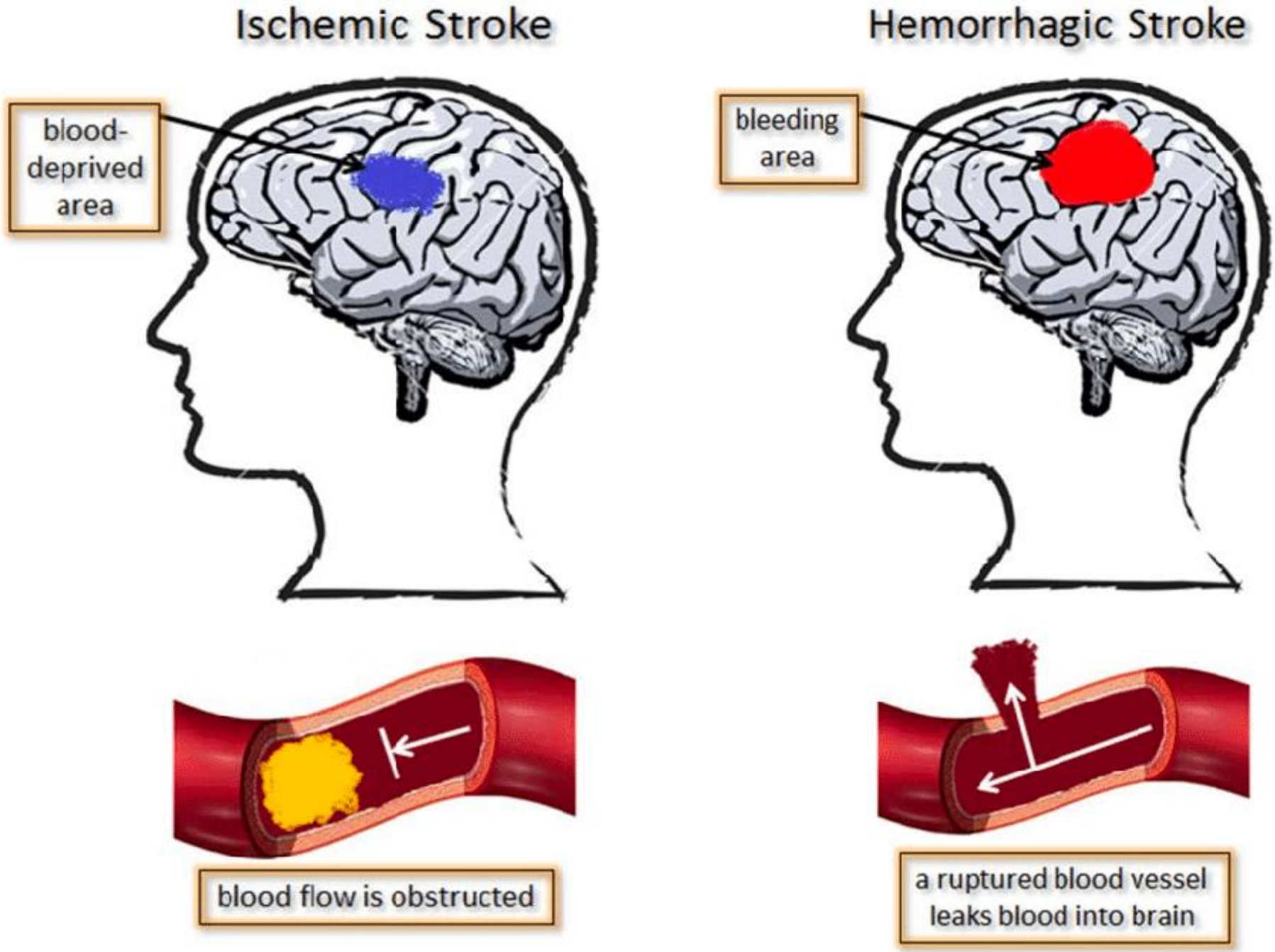
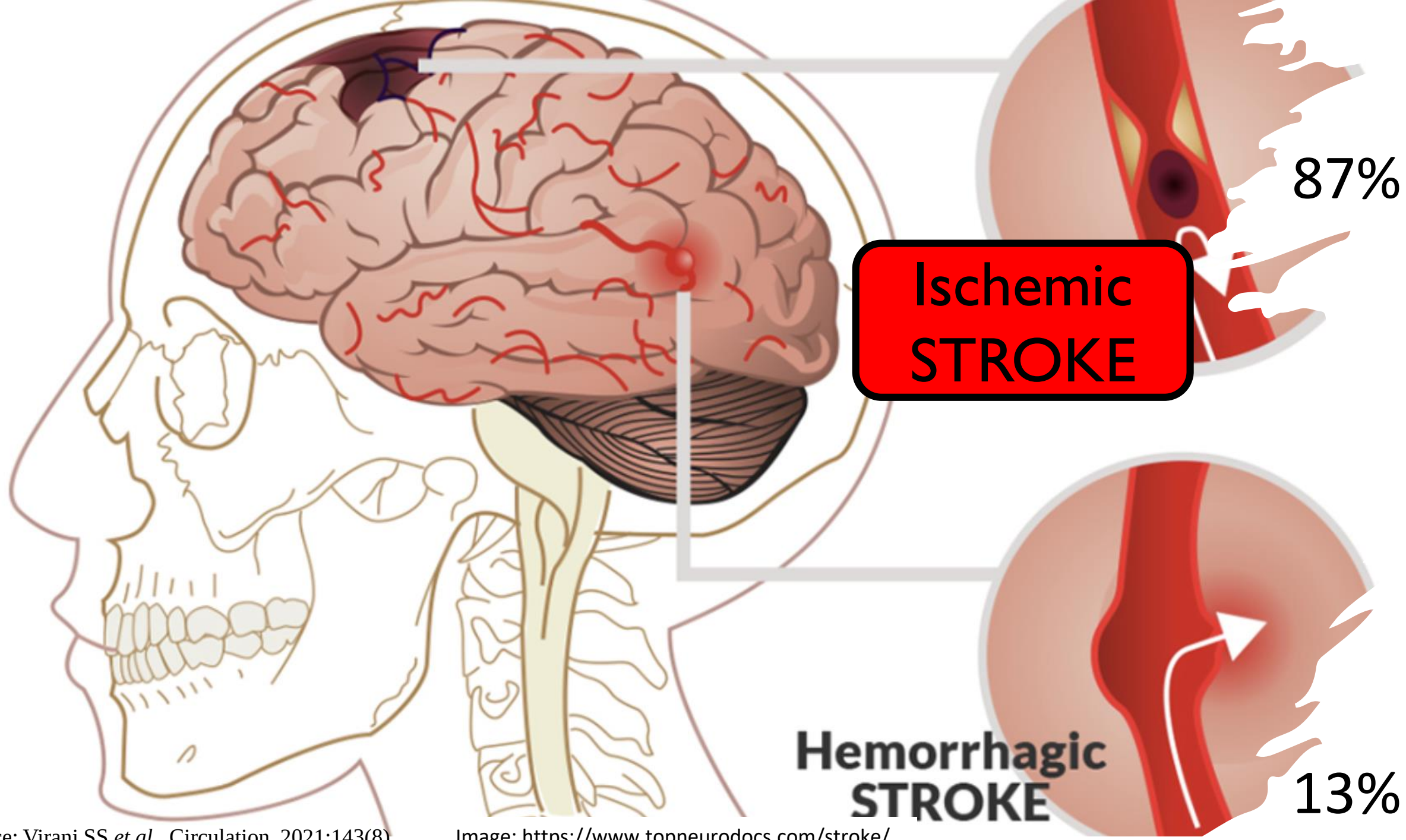
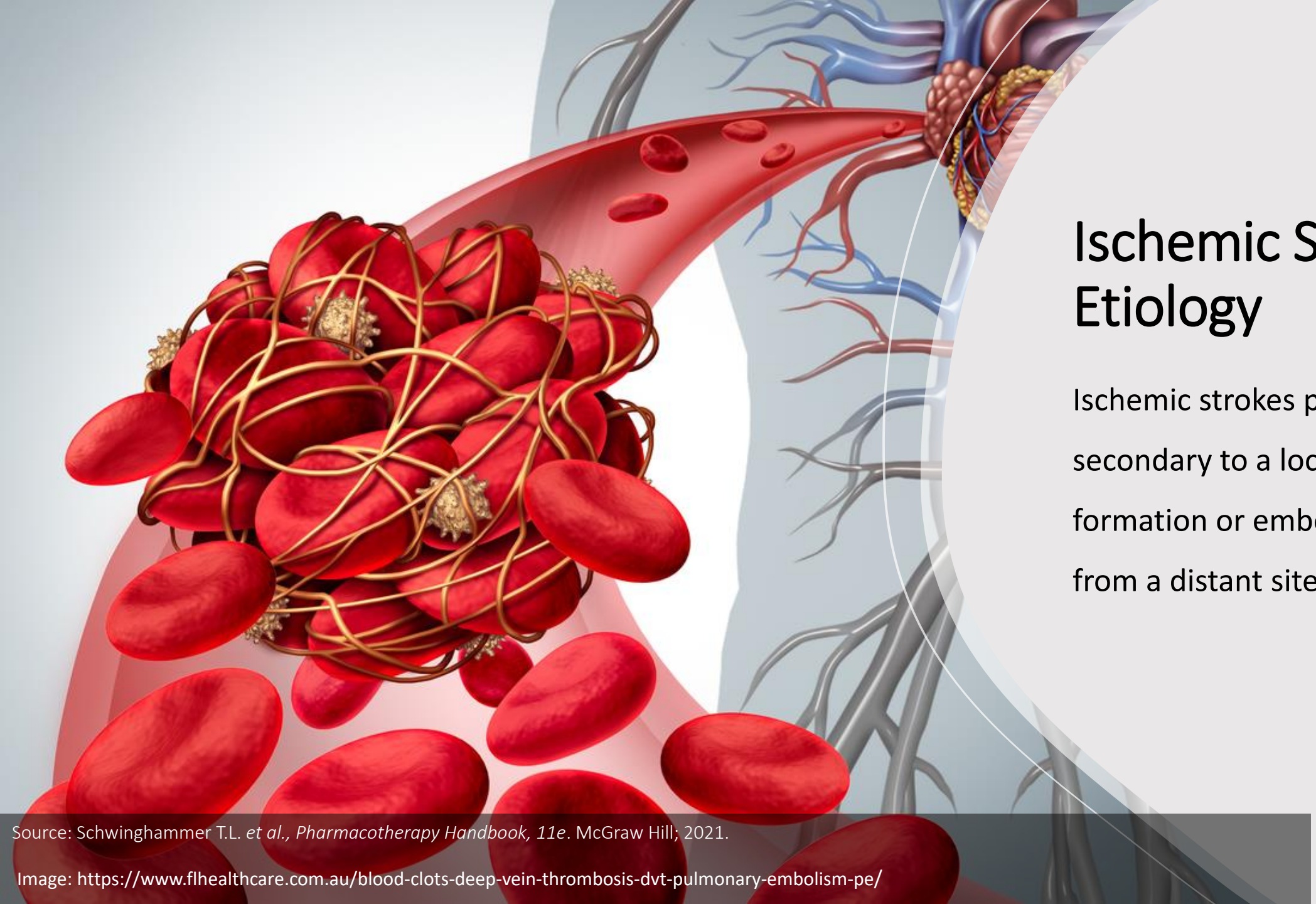


Image: https://www.researchgate.net/figure/Ischemic-versus-hemorrhagic-stroke_fig8_264194897



Source: Virani SS *et al*,. Circulation. 2021;143(8).

Image: https://www.topneurodocs.com/stroke/



Ischemic Stroke: Etiology

Ischemic strokes precipitate secondary to a local thrombus formation or emboli formation from a distant site

Source: Schwinghammer T.L. *et al., Pharmacotherapy Handbook, 11e*. McGraw Hill; 2021.

Image: https://www.flhealthcare.com.au/blood-clots-deep-vein-thrombosis-dvt-pulmonary-embolism-pe/

Goals of Care

Reduce	Reduce ongoing neurologic injury acutely to reduce mortality and long-term disability
Prevent	Prevent complications secondary to immobility and neurologic dysfunction
Prevent	Prevent stroke recurrence

Image: Microsoft PowerPoint Stock Image

Source: Schwinghammer T.L. *et al., Pharmacotherapy Handbook, 11e*. McGraw Hill; 2021.

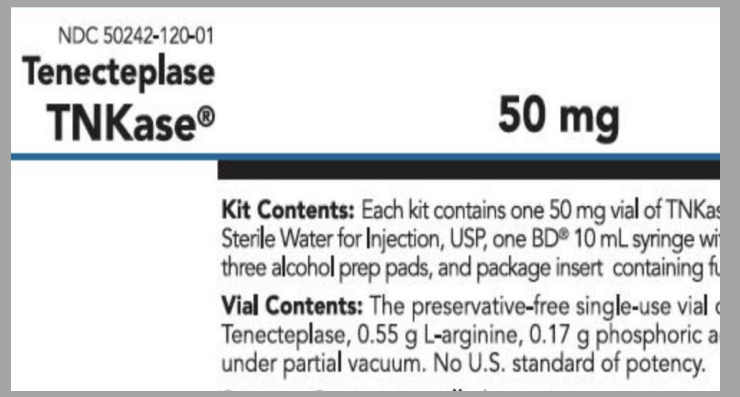
The Ultimate Goal

The goal of treatment and *early intervention* is to salvage as much brain tissue as possible to prevent further ischemia

Image: Microsoft PowerPoint Stock Image

Fibrinolytic Therapy

ALTEPLASE (ACTIVASE®)



TENECTEPLASE (TNKASE ®)

Image: https://rk.md/2019/alteplase/
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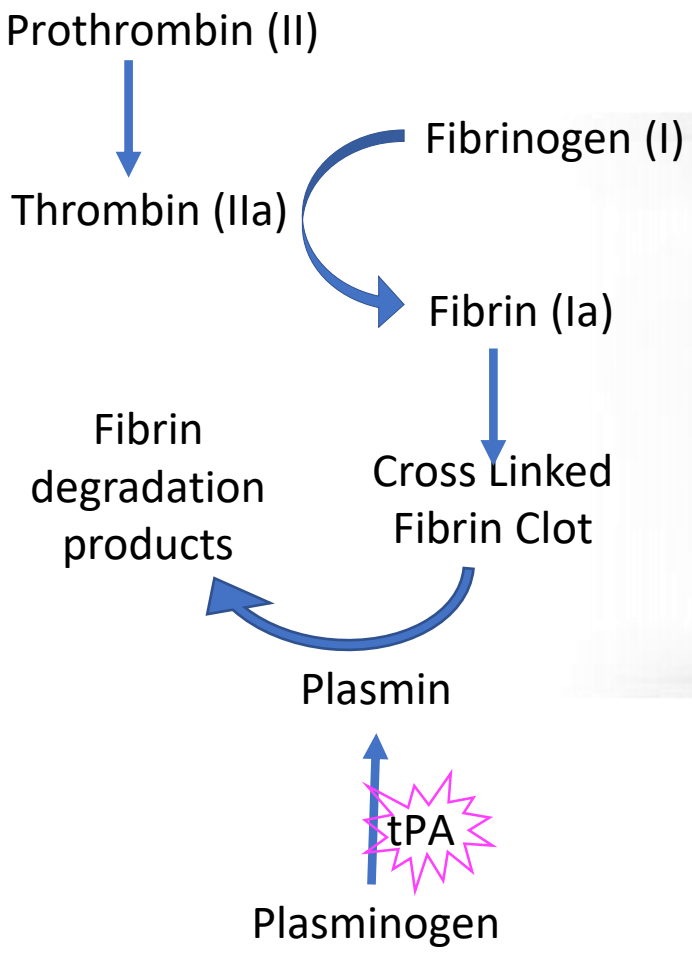

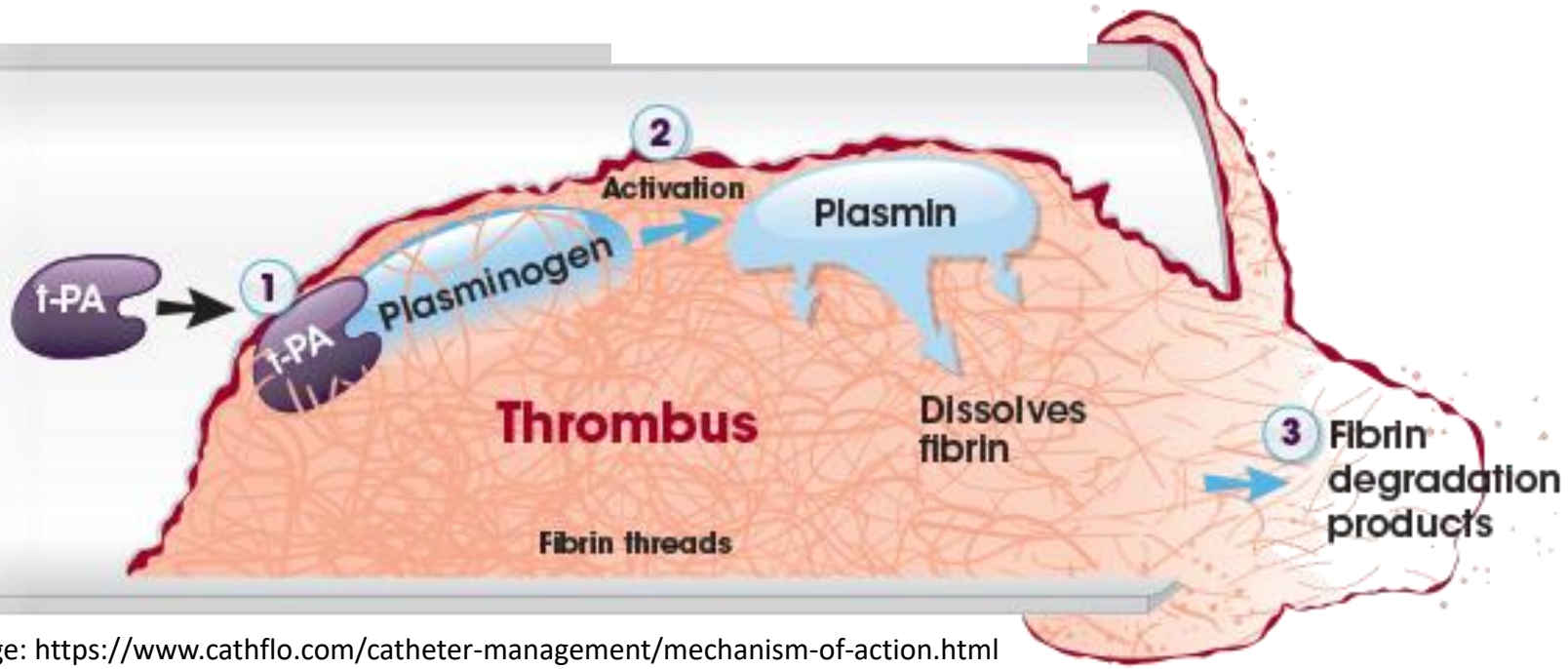

Image: https://www.cathflo.com/catheter-management/mechanism-of-action.html

Mechanism of Action

1. Binds to fibrin
2. Activates fibrin bound plasminogen
3. Converts plasminogen to plasmin
4. Plasmin breaks down fibrin, dissolving the clot

Source: Jilani TN *et al.*, Tissue Plasminogen Activator. 2020.

High Risk Medications

BP >185/110 mmHg

Heparin <48hours AND ↑ aPTT

Thrombocytopenia

INR >1.7
aPTT >40s
PT >15s

Aortic Arch Dissection

Infective Endocarditis

ICH

Prior Stroke

Severe Head Trauma

GI bleed/malignancy

Tx dose LMWH

Glycoprotein IIb/IIIa receptor inhibitors

Source: Powers W *et al.*, Stroke. 2019;50(12):e344-e418.

EXCLUSION CRITERIA

Stroke Assessment

National Institute of Health Stroke Score (NIHSS)

Blood Glucose

Imaging (CT)

Last Known Well

Source: Powers W *et al.*, Stroke. 2019;50(12):e344-e418.

Pharmacist Assessment Question 1

Which of the following is a contraindication to fibrinolytic therapy?

a) History of sickle cell

b) History of intracranial hemorrhage

c) Prophylactic dose of LMWH

d) SBP >160 mmHg

Pharmacist Assessment Question 1: Correct Response

Which of the following is a contraindication to fibrinolytic therapy?

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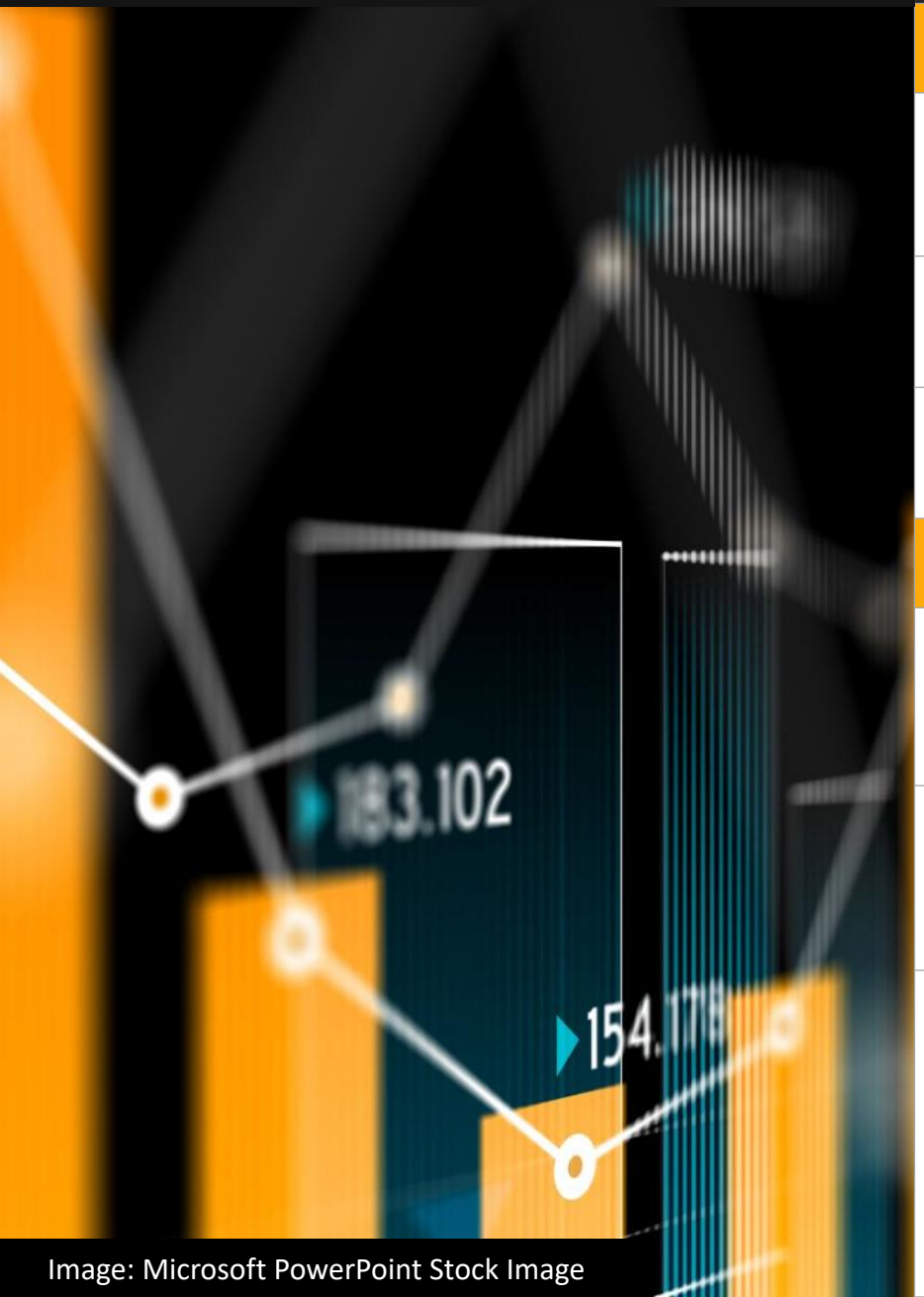
Source: Marler JR. Stroke. 2007;38(12):3302-3307.
SourcHacke W *et al.*, N Engl J Med. 2008;359(13):1317-1329.
Source: Warach SJ *et al.*, Stroke. 2020;51(11):3440-3451.



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Trial	Year	Outcome
Alteplase (tPA)		
NINDS	1995	Improved functional outcomes tPa w/in 3 hours
NINDS-II	1995	Disability benefit
ECASS III	2008	Disability benefit (4.5 hour)
Alteplase (tPA) versus Tenecteplase (TNK)		
ATTEST	2015	No difference in penumbra salvation
EXTEND-IA TNK	2020	TNK was non-inferior to tPA
EXTEND-IA TNK PART II	2020	A higher dose TNK did not improve perfusion. No difference in patient centered outcomes.

ALTEPLASE VERSUS TENECTEPLASE

		ALTEPLASE	TENECTEPLASE
Fibrin Specificity		++	++++
Indications		AIS, STEMI, PE	STEMI (Off-label) PE, AIS
Administration		Continuous infusion	One time push dose
PK	Plasma half life	5 minutes	20-24 min

Source: Chester KW *et al.,* Expert Opin Drug Saf. 2019;18(2):87-96.

Image: https://all-free-download.com/free-photos/hd-picture.html

Alteplase: Pharmacokinetics

- **Clearance**: 2-compartment model
  - First plasma redistribution phase and hepatic clearance
  - Second complex formation with plasminogen activator inhibitor-1 followed by hepatic clearance
- **Half-life** <5 minutes
- Fibrin specificity limits systemic fibrinolysis

Source: Chester KW *et al.,* Expert Opin Drug Saf. 2019;18(2):87-96.

Technician Assessment Question 1

Which of the following fibrinolytic medications used to treat AIS is prepared as a one-time IV push dose?

a) Alteplase

b) Urokinase

c) Tenecteplase

d) Labetalol

Technician Assessment Question 1: Correct Response

Which of the following fibrinolytic medications used to treat AIS is prepared as a one-time IV push dose?

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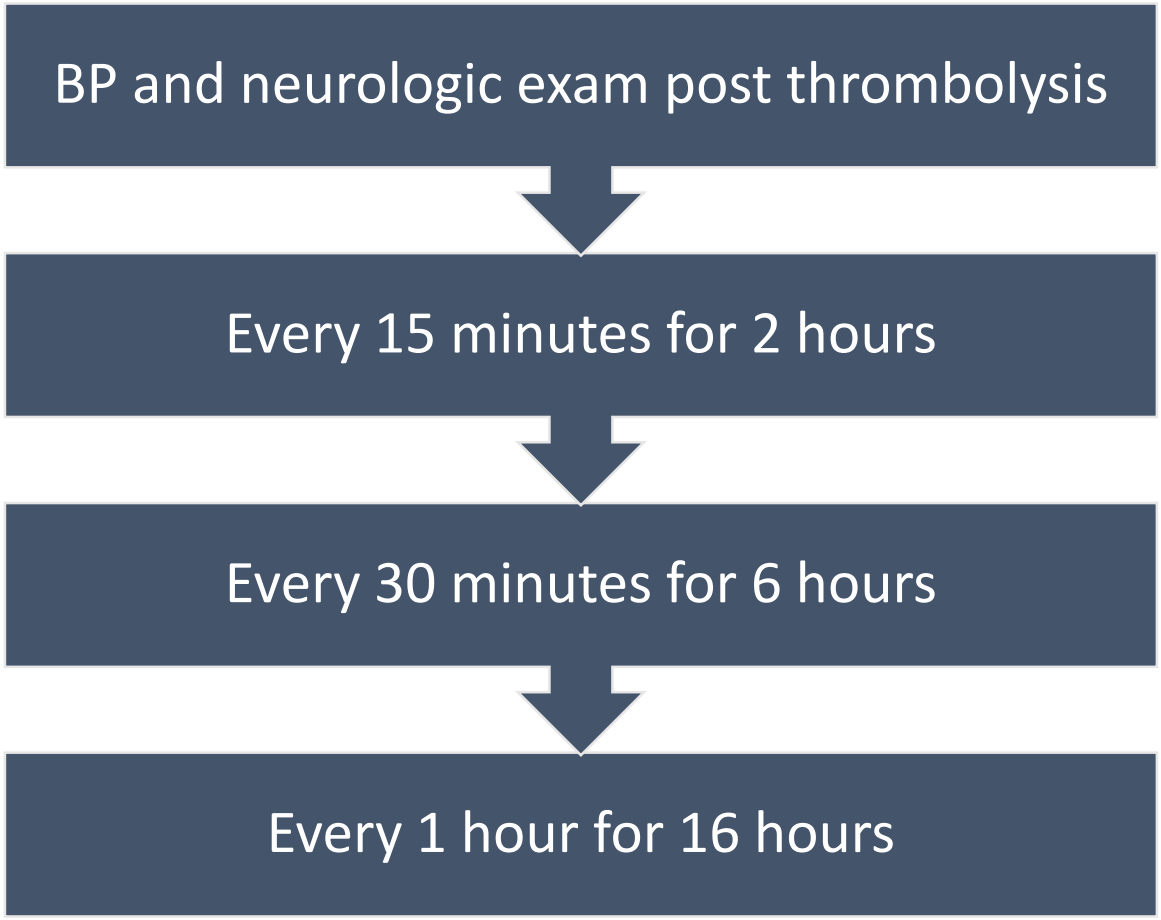
Monitoring: Post Administration



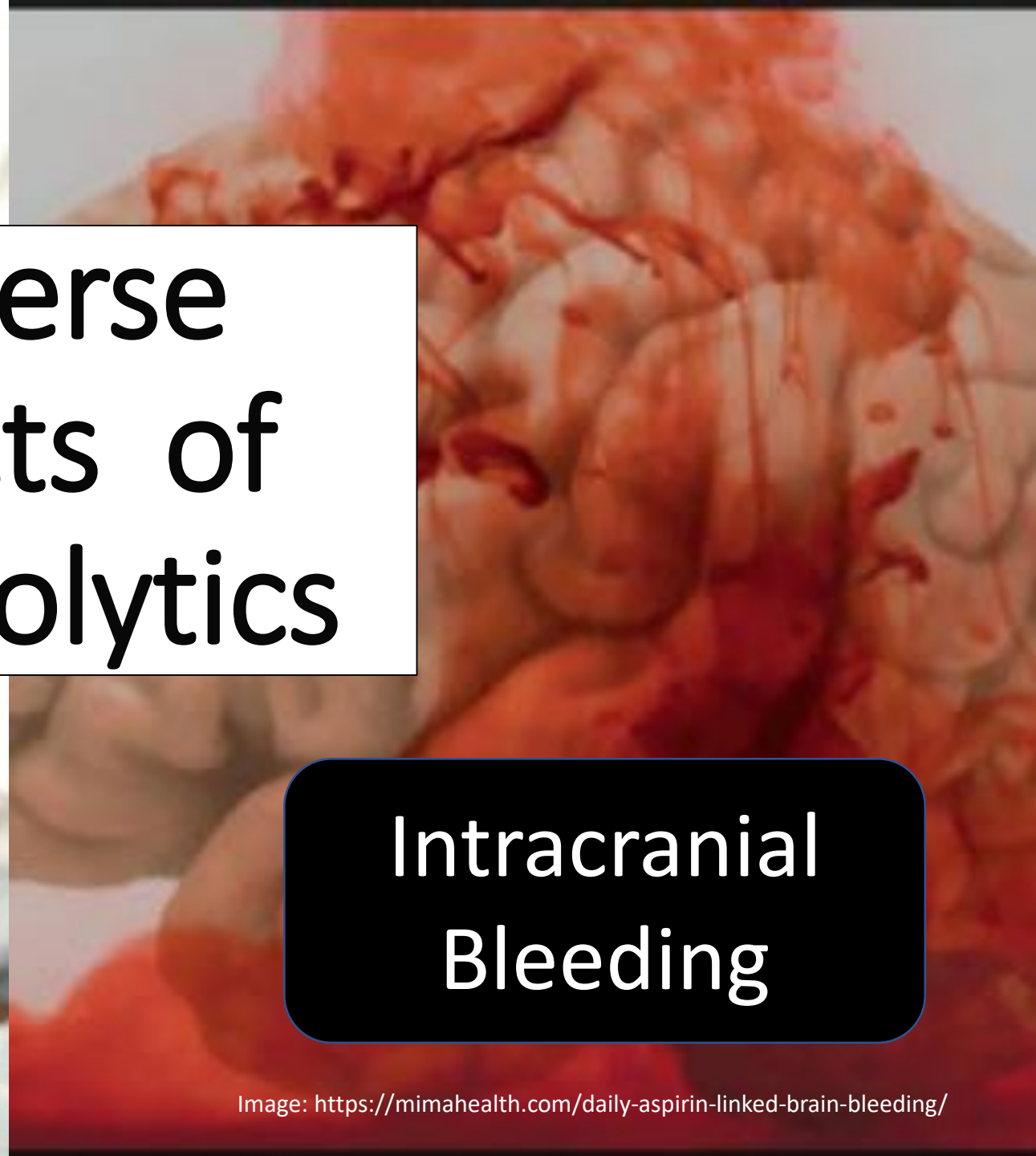
- Close monitoring in an ICU or stroke unit for 24 hours post treatment
- Goal BP post thrombolysis: <180/105 mmHg

Source: Powers WJ *et al.,* Stroke. 2019;50(12).

Adverse Effects of Fibrinolytics

Orolingual Angioedema

Image: Madden B, Chebl R. WestJEM. 2015;16(1):175-177.



Intracranial Bleeding

Image: https://mimahealth.com/daily-aspirin-linked-brain-bleeding/

Orolingual Angioedema (OLAE)

What is it?

Acute swelling of the lips and the tongue

Prevalence

~1.3–5.1% of pts who received fibrinolytic treatment

Classification

- Mild: transient
- Severe: life-threatening upper airway obstruction requiring intubation

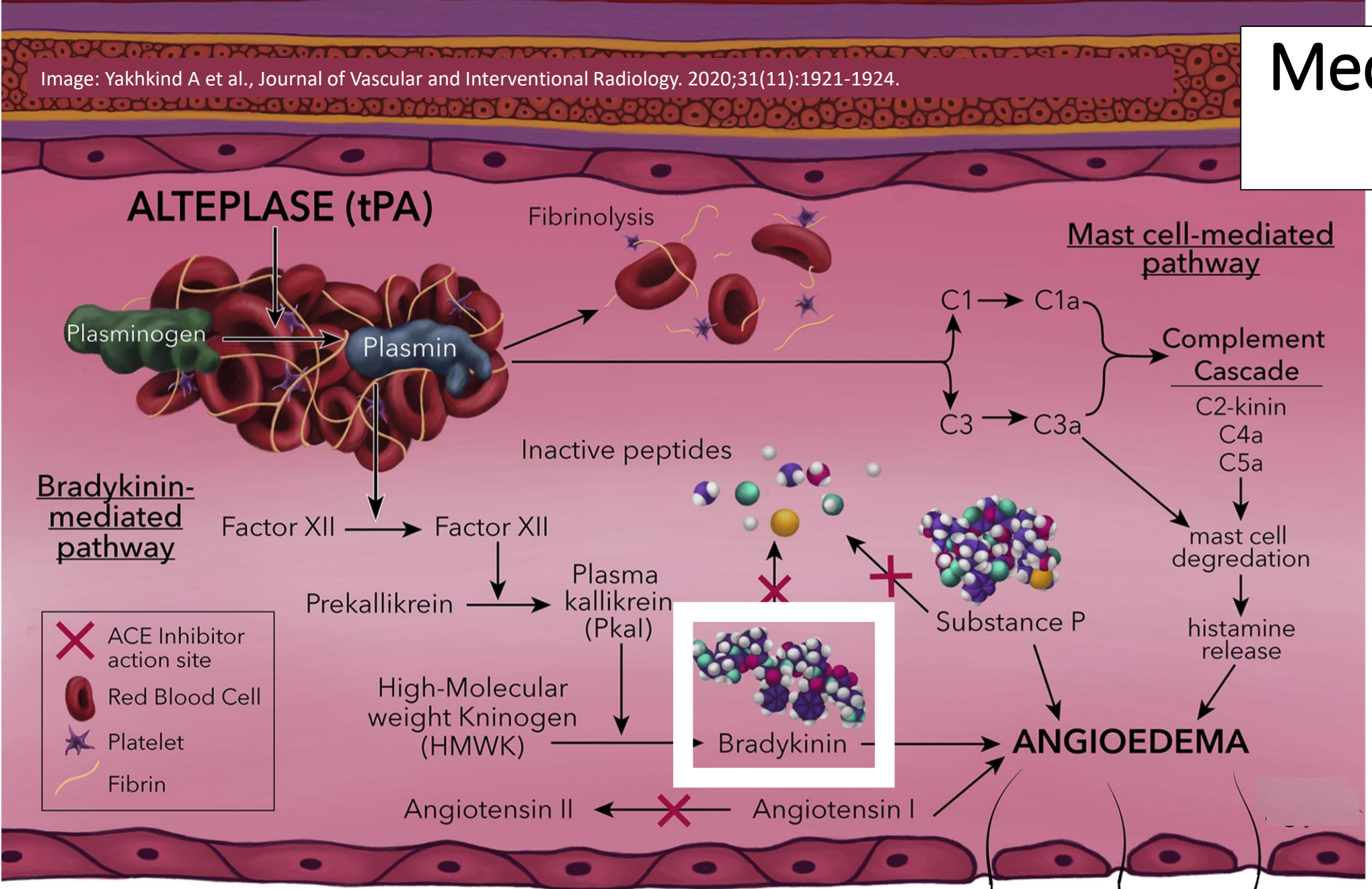
Risk Factors

- Mediation use: ACE-I
- Total insular infarcts

Source: Myslimi F et al., Stroke. 2016;47(7):1825-1830.

Mechanism of OLAE

Image: Yakhkind A et al., Journal of Vascular and Interventional Radiology. 2020;31(11):1921-1924.

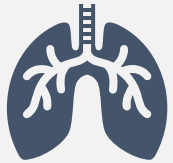


- Vasodilation
- Capillary permeability
- Fluid extravasation
- Edema
- Swelling

Source: Gauberti M et al., Front Med (Lausanne). 2018;5:195.

Source: Rathbun KM. Oxf Med Case Reports. 2019;2019(1):omy112.

OLAE Clinical Manifestation



Presentation

Mild, transient, unilateral swelling of the tongue and lips→ severe, life-threatening upper airway obstruction

Time

May manifest during thrombolysis or soon after the end of infusion

Unilateral swelling typically presents on the side opposite to the lesion

Source: Sczepanski M, Bozyk P. Crit Care Res Pract. 2018;2018:9360918.

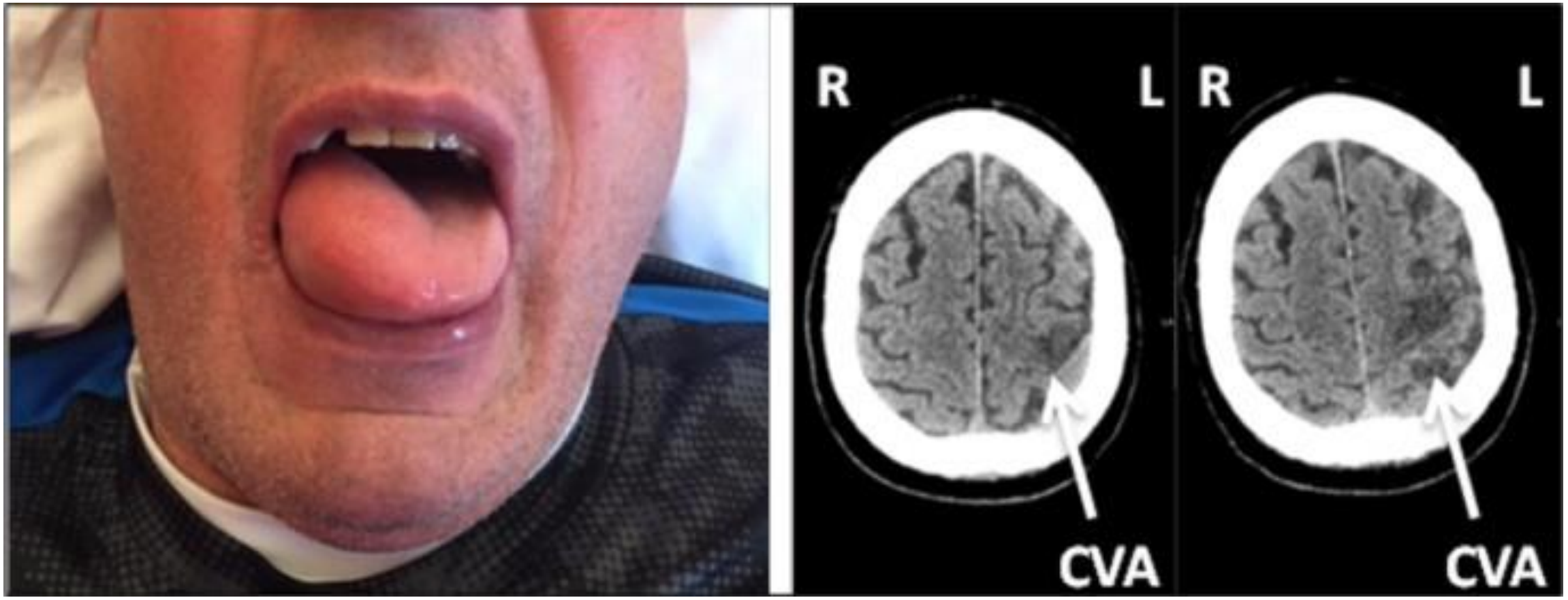


Image: Arts L, van Bloemendaal L, Kooter AJ, Tuinman PR. Intensive Care Med. 2018;44(11):1955-1956.

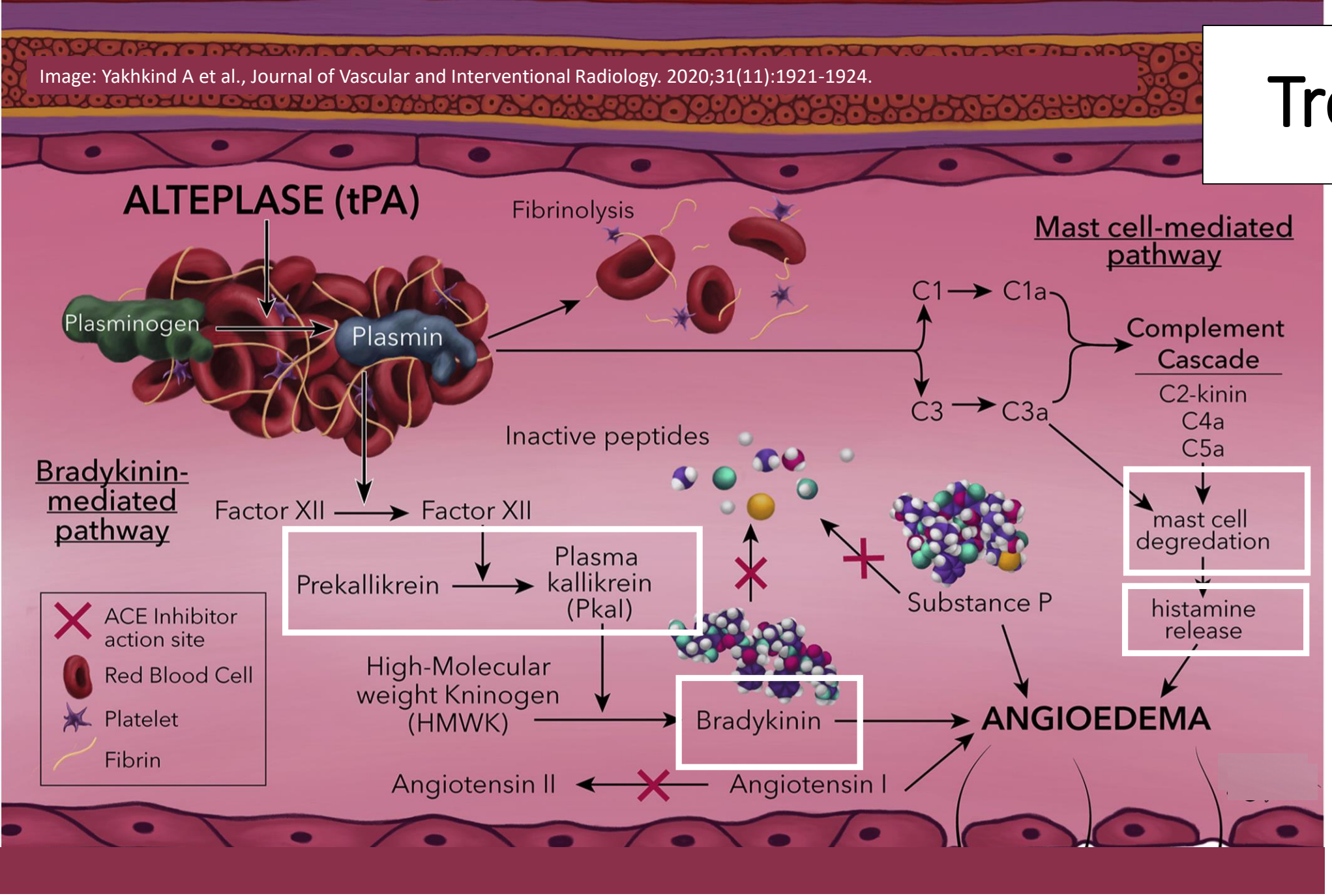
OLAE: Treatment

1. **Maintain Airway**
   - 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 min) poses higher risk of requiring intubation

2. **Discontinue** IV alteplase and hold ACE-I's

Source: Powers WJ *et al.,* Stroke. 2019;50(12).

Treatment



Mast cell down regulation

- Steroids

Histamine Release

- Anti-Histamine

Bradykinin

- Selective bradykinin B_2 receptor antagonist

C1-inhibitor

- ↓ plasma kallikrein activity

Source: Liyanage CK *et al.,* Eur Ann Allergy Clin Immunol. 2017;49(05):196.

OLAE: Treatment

Initial

- Methylprednisolone 125 mg IV
- Diphenhydramine 50 mg IV
- Famotidine 20 mg IV

No relief

- Epinephrine

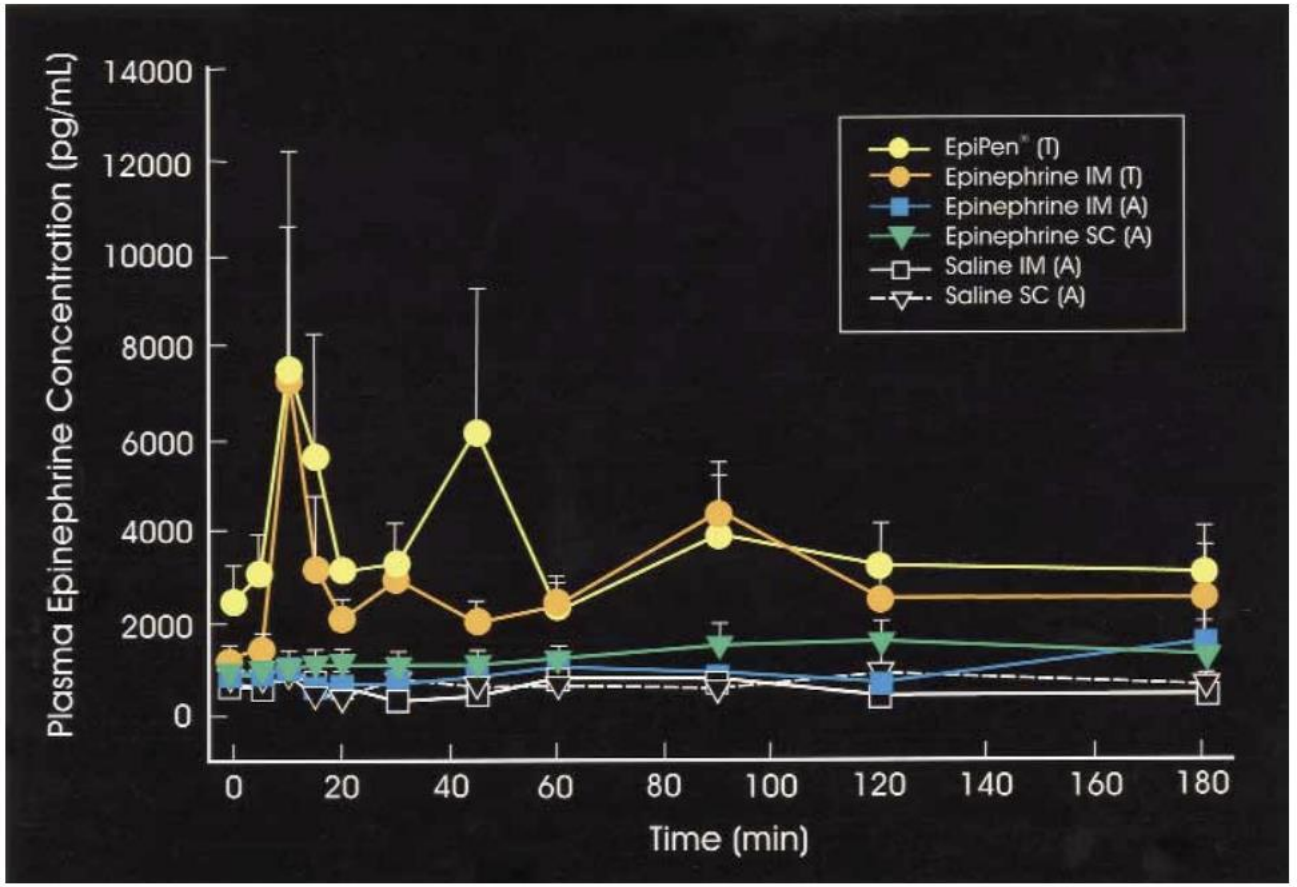
No relief

- Icatibant 30 mg (3 mL) SQ
  - May repeat in 6 hrs
  - Not to exceed 3 injections in 24 hrs
- Cinryze ®
  - 20 IU/kg IV

Source: Myslimi F *et al.,* Stroke. 2016;47(7):1825-1830.
Source: Powers WJ *et al.,* Stroke. 2019;50(12).
Image: Powers WJ *et al.,* Stroke. 2019;50(12).

Epinephrine Administration

If there is further increase in angioedema, administer epinephrine (0.1%) 0.3 mL subcutaneously or by nebulizer 0.5 mL



Source: Powers WJ *et al.,* Stroke. 2019;50(12).
Image: Simons FER *et al.,* Journal of Allergy and Clinical Immunology. 2001;108(5):871-873.

Pharmacist Assessment Question 2

A patient develops OLAE after alteplase administration. Which step should be taken next?

a) No pharmacologic intervention. Monitor the patient.

b) Epinephrine 0.3 mg IM for anaphylaxis

c) Methylprednisolone 125 mg IV, diphenhydramine 50 mg IV, and famotidine 20 mg IV

d) Acetaminophen 500 mg PO x1 dose

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Technician Assessment Question 2

In a patient medication history following AIS, which medications may increase the risk of orolingual angioedema (OLAE)?

a) Angiotensin-converting-enzyme inhibitor (ACE-I)

b) Angiotensin receptor blocker (ARB)

c) Acetaminophen

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Adverse Effects of Fibrinolytics

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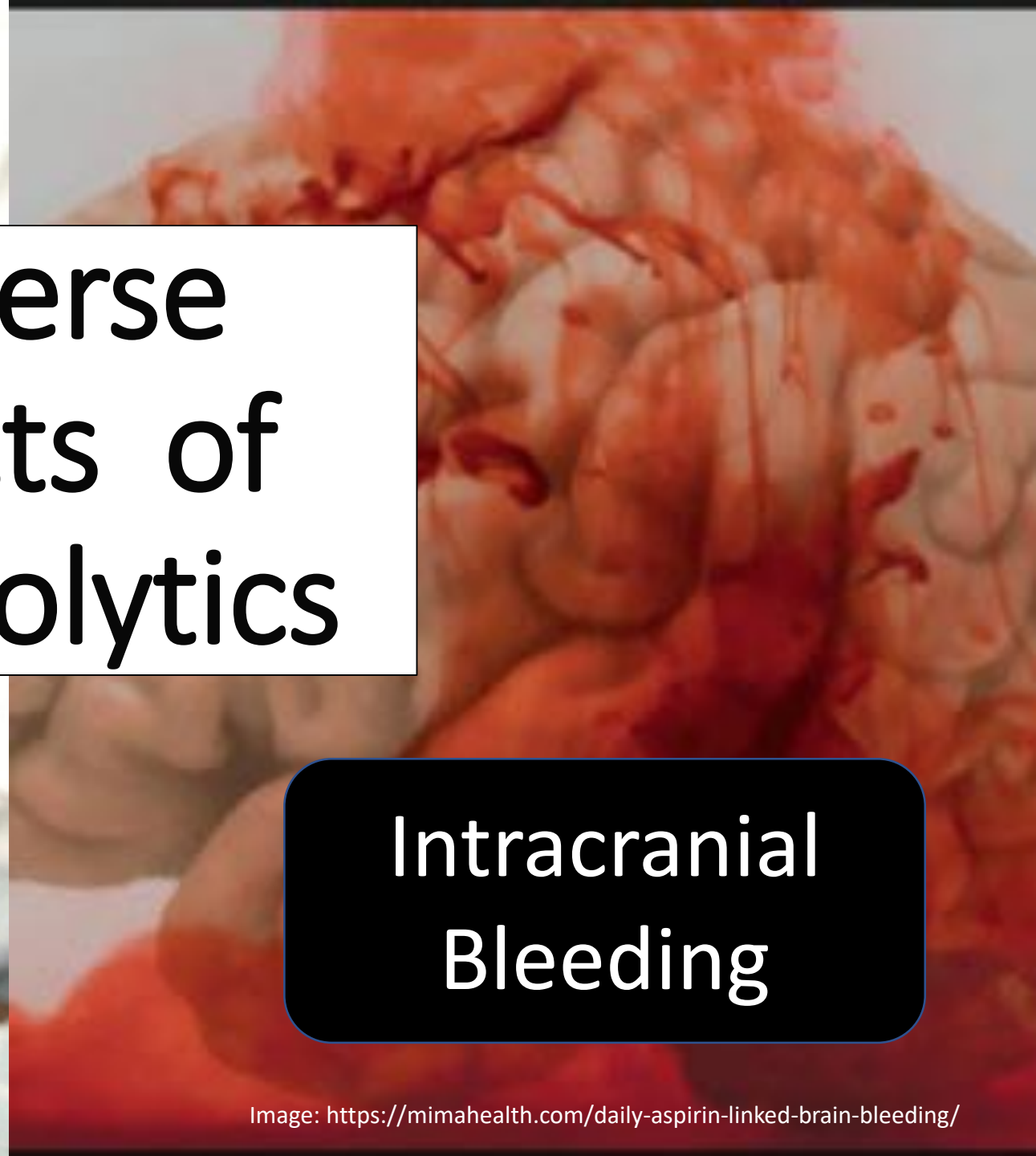


Intracranial Bleeding

Image: https://mimahealth.com/daily-aspirin-linked-brain-bleeding/

Post Thrombolytic intracranial hemorrhage (ICH)

- Hematoma expansion: major predictor of death and disability in pt's with ICH
- Most hemorrhages post fibrinolytic treatment occur in already infarcted brain tissue
- Neurological deterioration may not occur at the onset of the hemorrhage

Source: Yaghi S *et al*., Stroke. 2017;48(12).

Image: Microsoft Word Stock Image

Hemorrhagic Conversion Clinical Manifestations

HA, N/V

Worsening neurologic function

Radiographic appearance of hemorrhage + presence of neurological deterioration (sICH)

12-24 hours

Source: O'Carroll CB, Aguilar MI. Neurohospitalist. 2015;5(3):133-141.

Hemorrhagic Conversion Goals of Treatment

- Cardiovascular and respiratory support
- BP management
- Monitoring for neurological deterioration
- Prevention of hematoma expansion
- Treatment of elevated ICP
- Management of additional complications such as seizures

Source: Yaghi S *et al.*, Stroke. 2017;48(12).

Stroke
Volume 50, Issue 12, December 2019; Pages e344-e418
https://doi.org/10.1161/STR.0000000000000211

American Heart Association.

AHA/ASA GUIDELINE

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

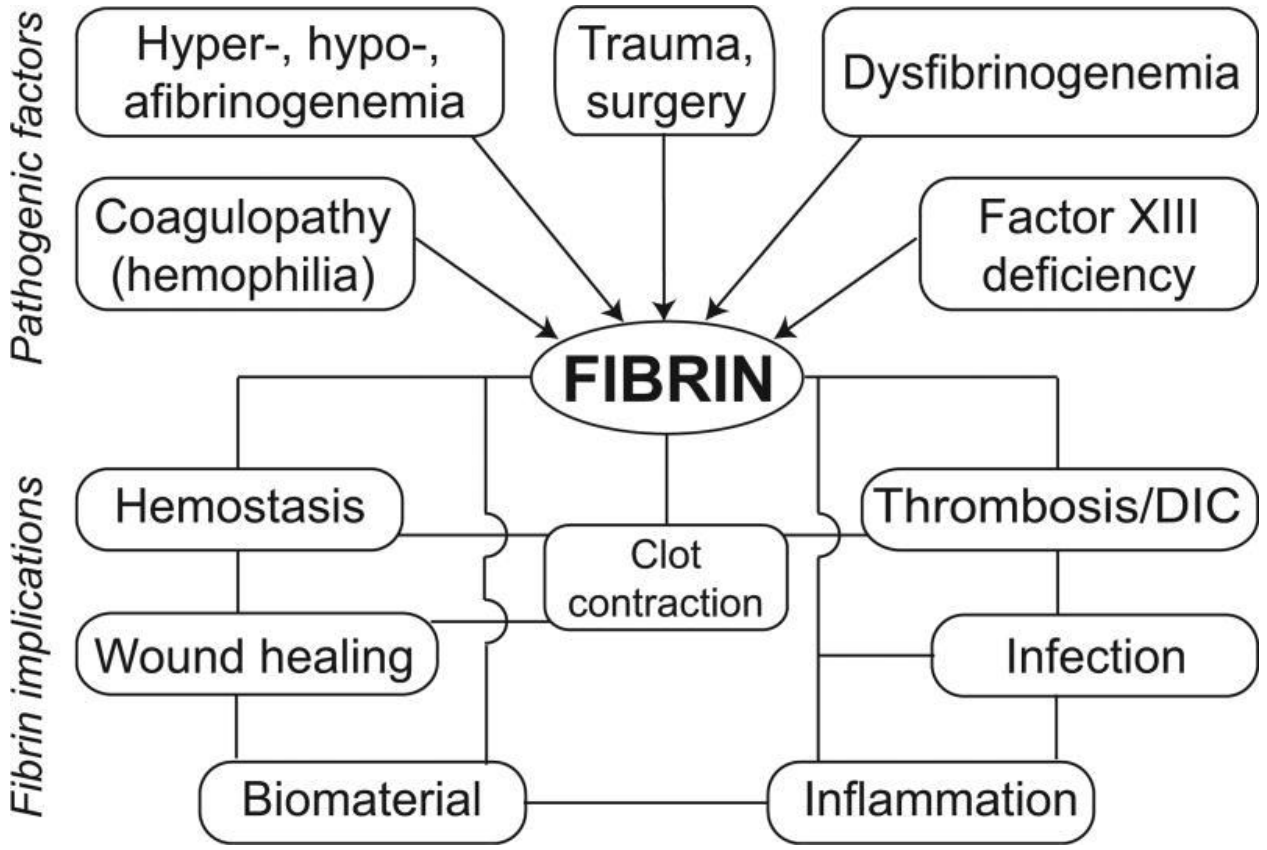
See related article, p 3331

William J. Powers, MD, FAHA, Chair, Alejandro A. Rabinstein, MD, FAHA, Vice Chair, Teri Ackerson, BSN, RN, Opeolu M. Adeoye, MD, MS, FAHA, Nicholas C. Bambakidis, MD, FAHA, Kyra Becker, MD, FAHA, José Biller, MD, FAHA, Michael Brown, MD, MSc, Bart M. Demaerschalk, MD, MSc, FAHA, Brian Hoh, MD, FAHA, Edward C. Jauch, MD, MS, FAHA,

Management of Symptomatic ICH post IV Alteplase

COR IIb	LOE C-EO
Stop alteplase infusion	
CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match	
Emergent nonenhanced head CT	
Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of <150 mg/dL	
Tranexamic acid 1000 mg IV infused over 10 min OR ε-aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h) (Potential for benefit in all patients, but particularly when blood products are contraindicated or declined by patient/family or if cryoprecipitate is not available in a timely manner.)	
Hematology and neurosurgery consultations	
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control	

Image: Powers WJ, et al., Stroke. 2019;50(12).

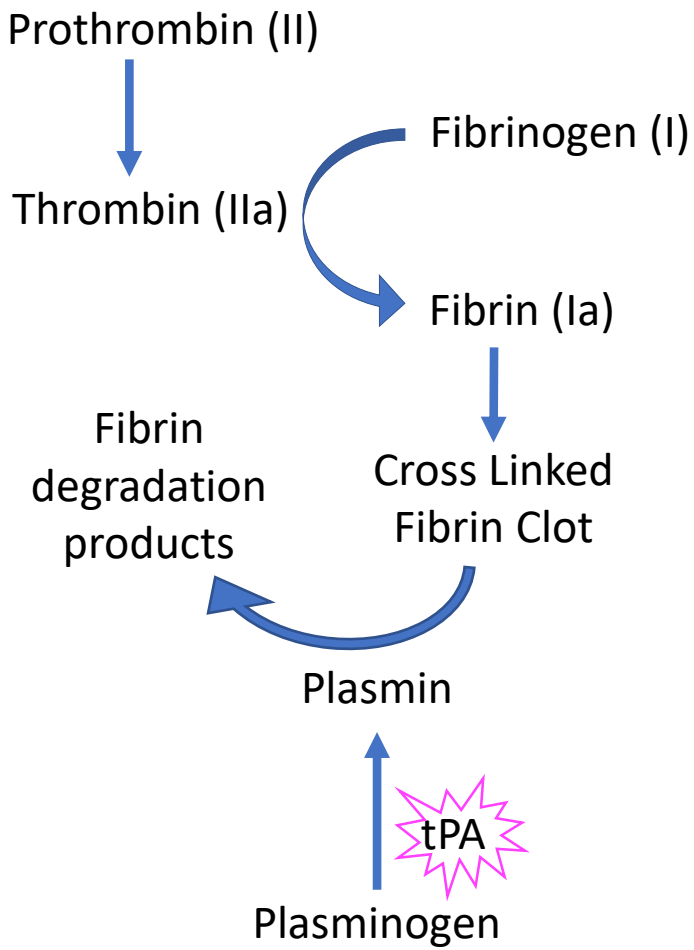


Fibrin

Normal fibrinogen levels: 200 to 400 mg/dL

Image: Litvinov RI, Weisel JW. Semin Thromb Hemost. 2016;42(4):333-343.

Source: Kaur J, Jain A. Stat Pearls Publishing; 2021.

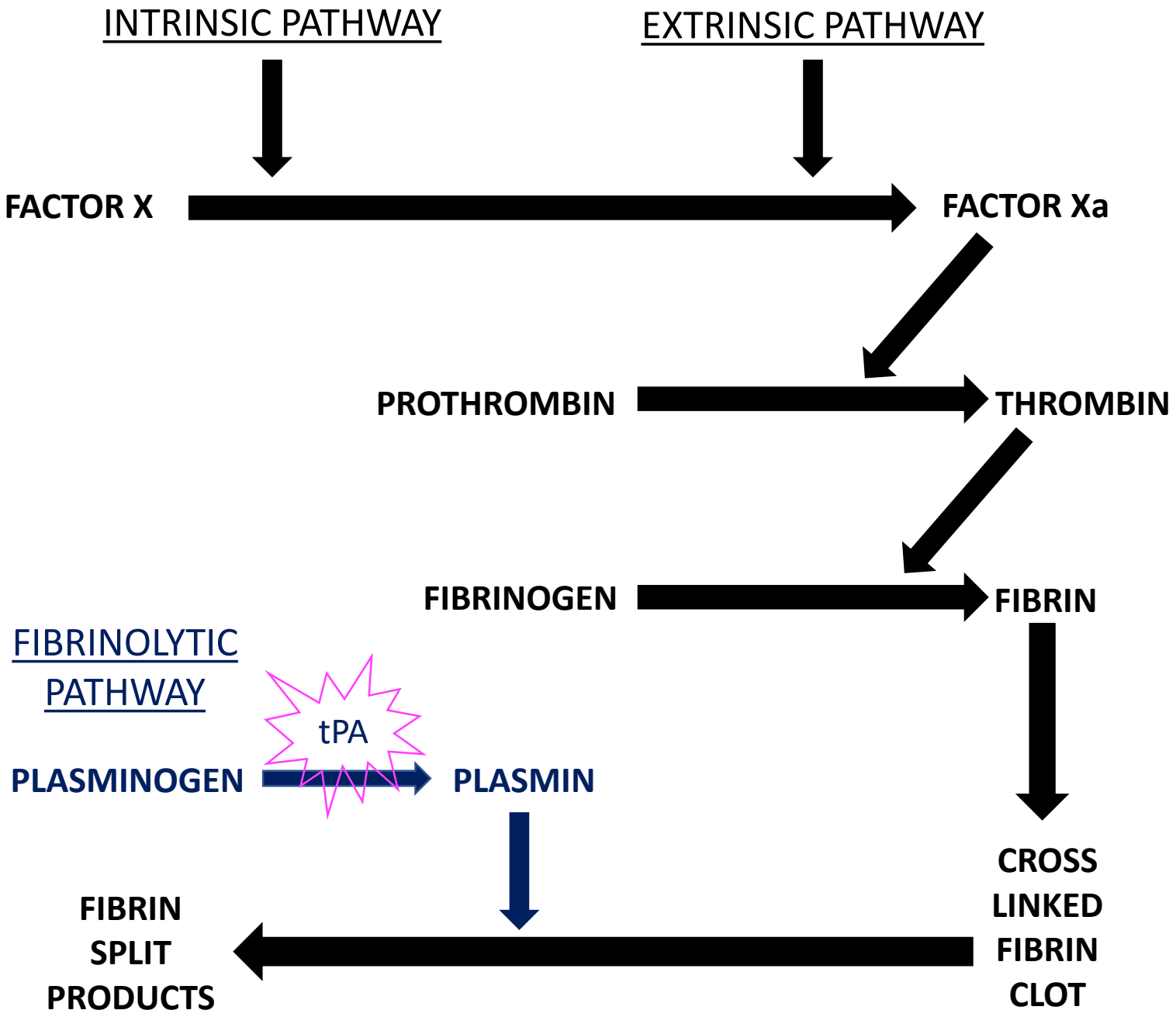


ICH: RISK FACTORS

Risk Factor	Effect on Fibrinogen	Risk
↓ in fibrinogen levels	↓ ≥200 mg/dL from BL w/in 6 hrs of infusion	↑ risk of sICH
Early hypofibrinogenemia	<200 mg/dL 2 hrs post tPA	
Hypofibrinogenemia	<150 mg/dL when diagnosis ICH made	Associated with hematoma expansion
↑ Fibrin degradation products		Associated with ↑ risk of parenchymal hematoma

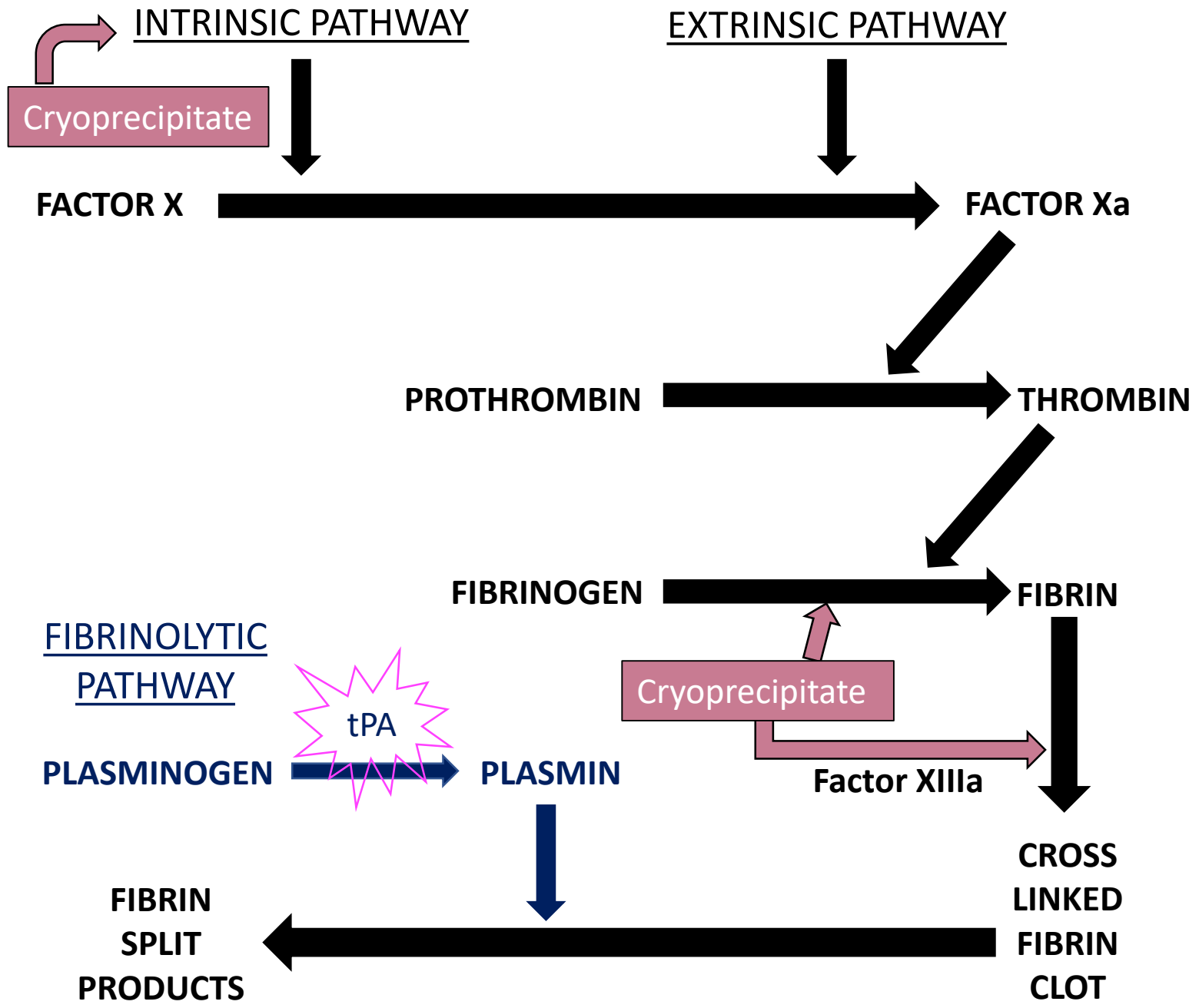
Source: Yaghi S, Willey JZ *et al.,* Stroke. 2017;48(12).

Mechanism of Post Thrombolytic ICH



Source: Trouillas P et al., Stroke. 2004;35:1323–1328.
Source: Yaghi S *et al.,* Stroke. 2017;48(12).

Mechanism of Post Thrombolytic ICH



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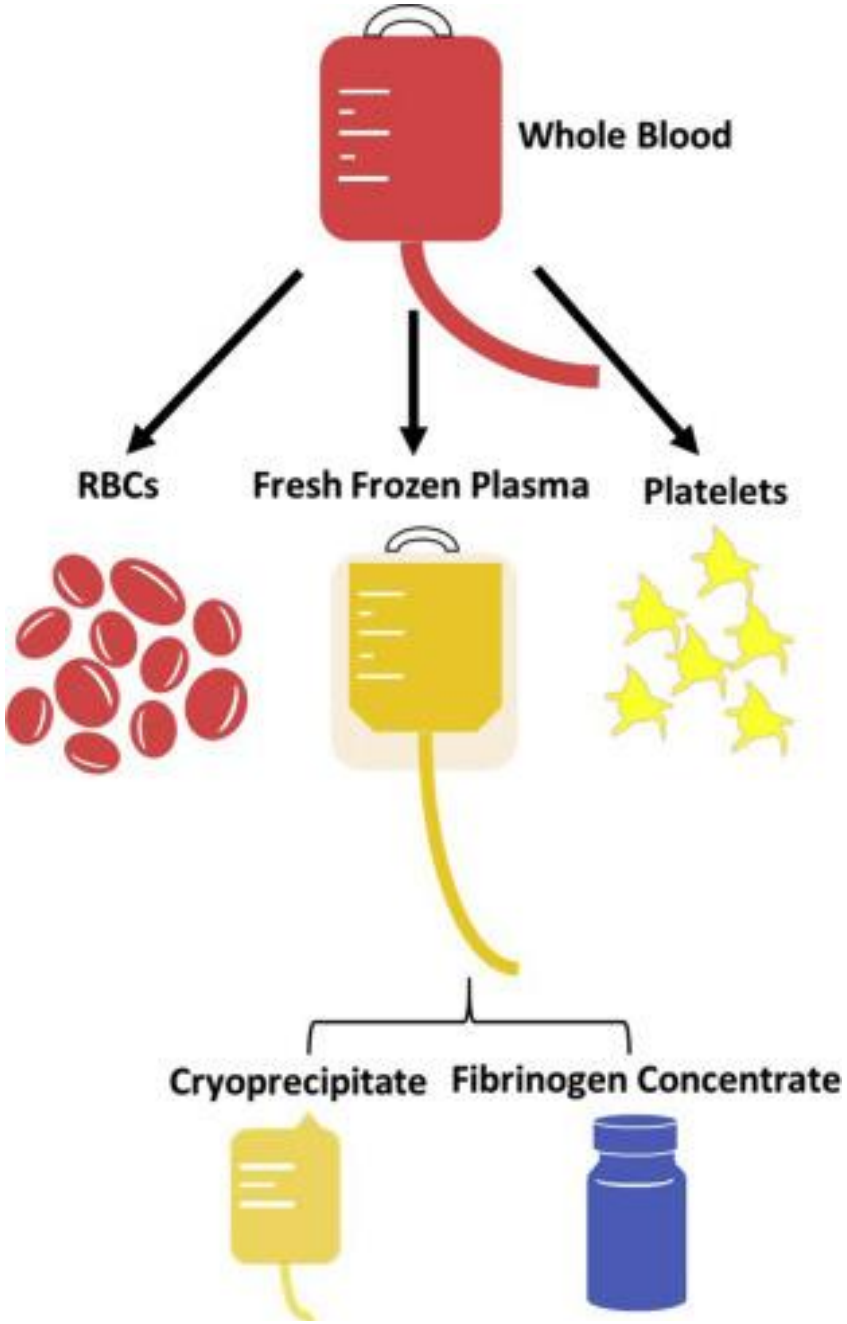


Cryoprecipitate

Cryoprecipitate is derived from fresh-frozen plasma (FFP) and contains

- Fibrinogen (200 mg/unit)
- Factor VIII
- Factor XIII
- Von Willebrand factor

Monitoring

- Goal fibrinogen ≥150 mg/dL
- Fibrinogen <150 mg/dL→ repeat dose (10 units)

Image: https://www.americanjournalofsurgery.com/article/S0002-9610(20)30265-8/fulltext

Source: Yaghi S *et al.,* Stroke. 2017;48(12).

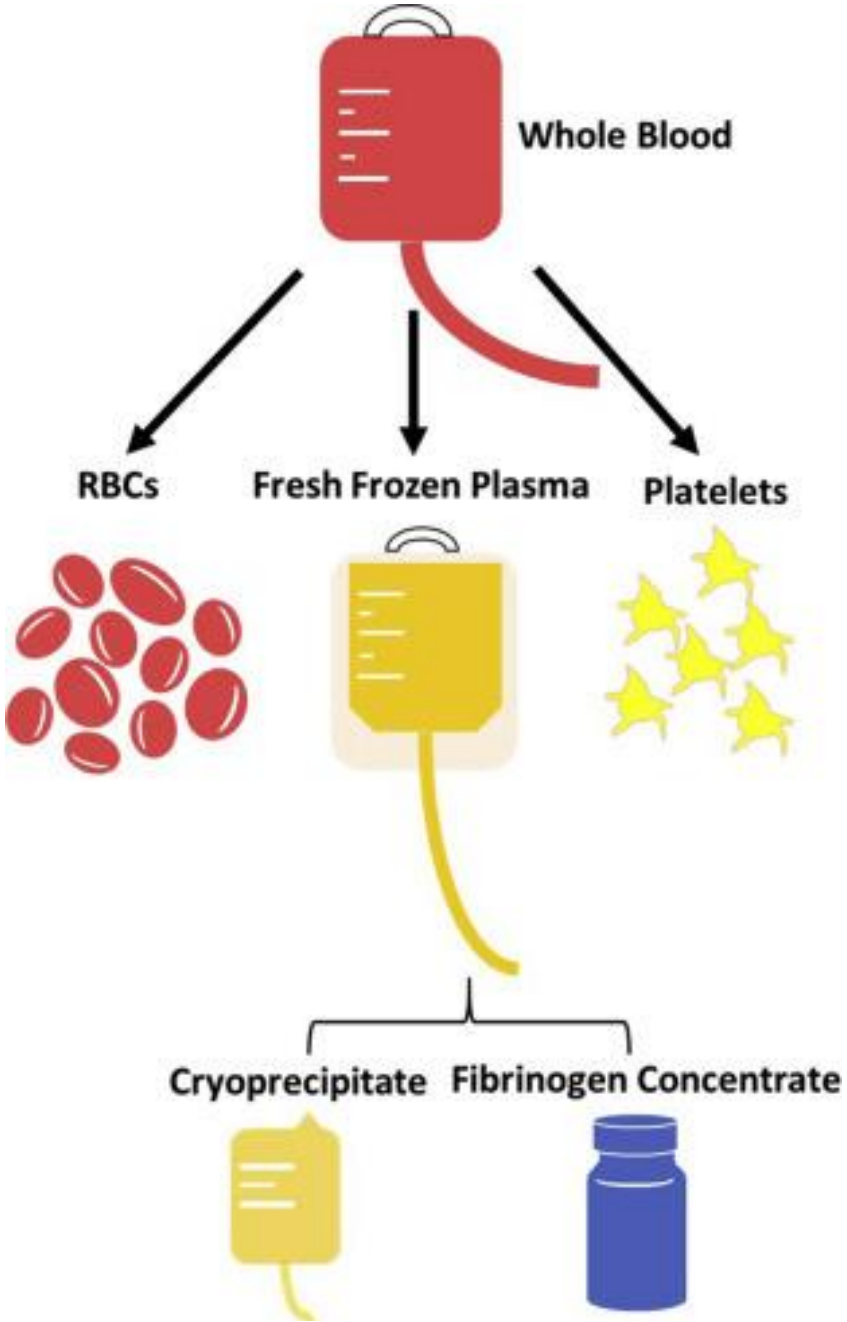


Image: https://www.americanjournalofsurgery.com/article/S0002-9610(20)30265-8/fulltext

Cryoprecipitate

Disadvantages

- Delay in treatment (requires thawing)
- Lack of pathogen inactivation
- Transfusion-related lung injury (TRALI)
- Transfusion-associated circulatory overload (TACO)
- Thrombosis
- Transfusion reactions

Source: Frontera JA *et al*., Neurocrit Care. 2016;24(1):6-46.

Source: Nascimento B et al., Br J Anaesth. 2014;113(6):922-934.

Source: Yaghi S *et al.,* Stroke. 2017;48(12).

Antifibrinolytics

Mechanism

- Inhibits the conversion of plasminogen to plasmin
- Inhibits fibrin cleavage

Tranexamic Acid	ε-Aminocaproic Acid
1 **gram** IV over 10 min	4-5 **grams** IV over 1 h

Source: Powers WJ, et al., Stroke. 2019;50(12).

Source: Mannucci PM. Hemostatic drugs. Wood AJJ, ed. N Engl J Med. 1998;339(4):245-253.

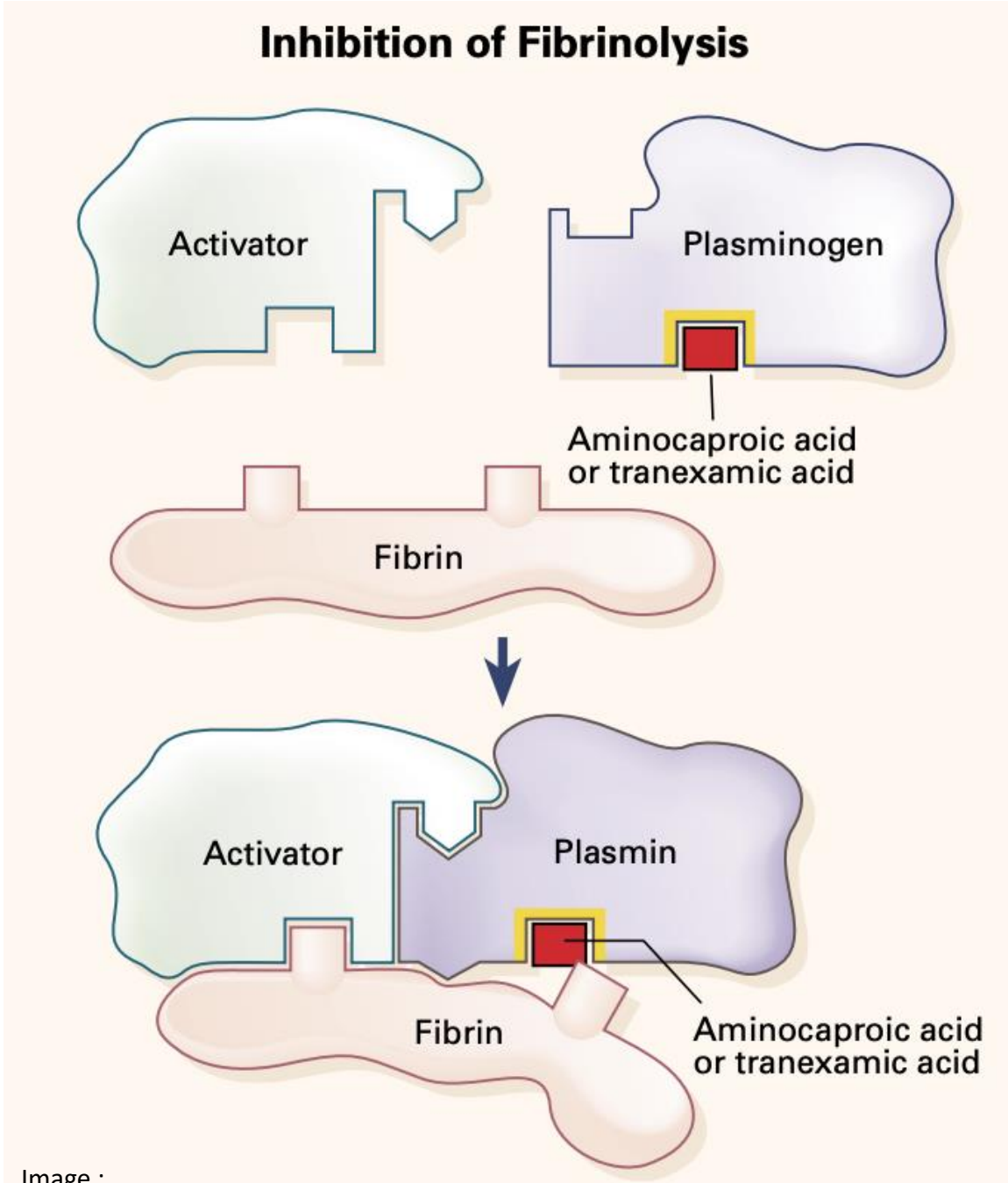


Image :
Mannucci PM. Hemostatic drugs. Wood AJJ, ed. N Engl J Med. 1998;339(4):245-253.

Antifibrinolytics

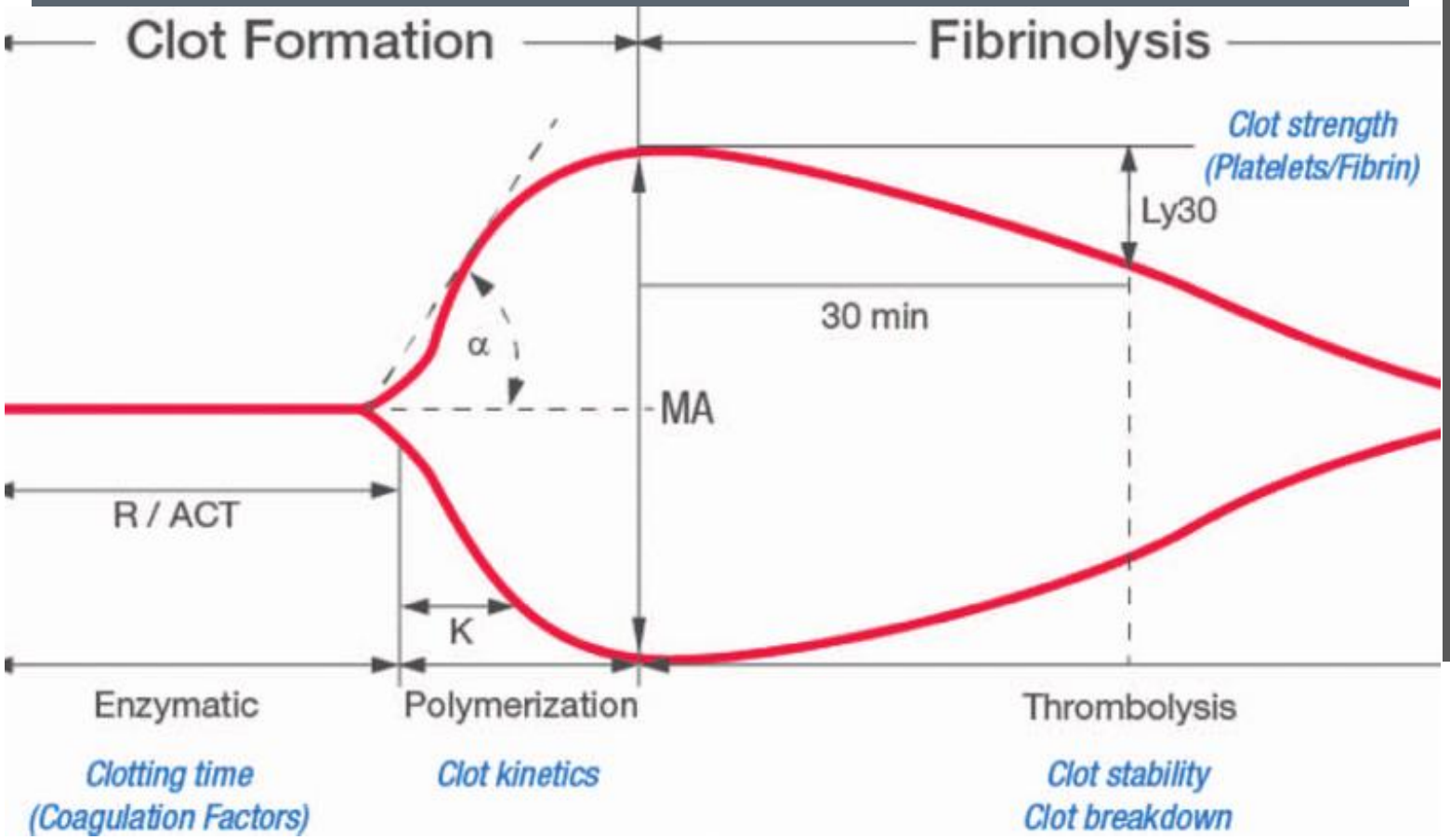


Image: Dias JD *et al*., Archives of Pathology & Laboratory Medicine. 2017;141(4):569-577.

<u>Adverse Effects</u>

- Gastrointestinal disturbances (N/V/D)
- Hypersensitivity reactions
- Seizures (TXA)
- Thrombosis

<u>Monitoring</u>

- CBC, PT, INR, aPTT
- Fibrinogen
- Thromboelastography (TEG)

Source: Lecker I et al., Ann Neurol. 2016;79(1):18-26.
Source: Levy JH *et al.,* Anesthesiology. 2018;128(3):657-670.
Source: Verkerk BS *et al.,* Journal of Pharmacy Practice. 2020;33(6):919-925.
Source: Yaghi S, Willey JZ *et al.,* Stroke. 2017;48(12).

Management of Symptomatic ICH post IV Alteplase

COR IIb	LOE C-EO
Stop alteplase infusion	
CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match	
Emergent nonenhanced head CT	
Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of <150 mg/dL	
Tranexamic acid 1000 mg IV infused over 10 min OR ε-aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h) (Potential for benefit in all patients, but particularly when blood products are contraindicated or declined by patient/family or if cryoprecipitate is not available in a timely manner.)	
Hematology and neurosurgery consultations	
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control	

Image: Powers WJ *et al.,* Stroke. 2019;50(12).

Pharmacist Assessment Question 3

Once confirmed on CT imaging, which of the following should be used to treat hemorrhagic conversion post alteplase treatment?

a) Administer cryoprecipitate 10 units

b) Administer 1 unit of FFP

c) Monitor and supportive care

d) Administer TXA 1 gram

Pharmacist Assessment Question 3: Correct Response

Once confirmed on CT imaging, which of the following should be used to treat hemorrhagic conversion post alteplase treatment?

a) Administer cryoprecipitate 10 units

b) Administer 1 unit of FFP

c) Monitor and supportive care

d) Administer TXA 1 gram

Take Away

- Hematoma expansion is a major predictor of death and disability in patients with ICH
- Goal: Aggressive reversal of coagulopathy + prevent hematoma expansion

Source: Yaghi S *et al.,* Stroke. 2017;48(12).

ALTEPLASE VERSUS TENECTEPLASE

		ALTEPLASE	TENECTEPLASE
Fibrin Specificity		++	++++
Indications		AIS, STEMI, PE	STEMI (Off-label) PE, AIS
Administration		Continuous infusion	One time push dose
PK	Plasma half life	5 minutes	20-24 min

Source: Chester KW et al., Expert Opin Drug Saf. 2019.

Image: https://all-free-download.com/free-photos/hd-picture.html

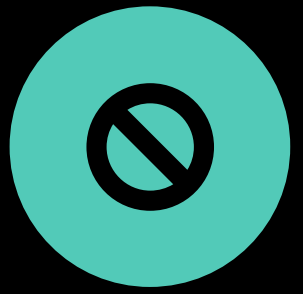
Adverse Effects of Alteplase vs. Tenecteplase

Purpose	Assess the safety of TNK in the real-world setting when compared with standard-dose alteplase
Design	Retrospective analysis of pt's who received IV TNK at 1 comprehensive and 2 regional stroke centers from July 14, 2018, to February 29, 2020.
Groups	TNK: 165 patients tPA: 254 patients
Results (TNK v tPA)	sICH: 3 (1.8%) vs 7 (2.8%) p=0.75 Angioedema: 4 (0.4%) vs 1 (0.4%) p=0.08 90 day functional independence: 100 (61%) vs 140 (57%) p=0.47
Conclusion	The use of TNK for stroke thrombolysis was practical and had comparable efficacy and safety to tPA

Source: Zhong CS *et al.,* Stroke. 2021;52(3):1087-1090.

Recap

Symptoms

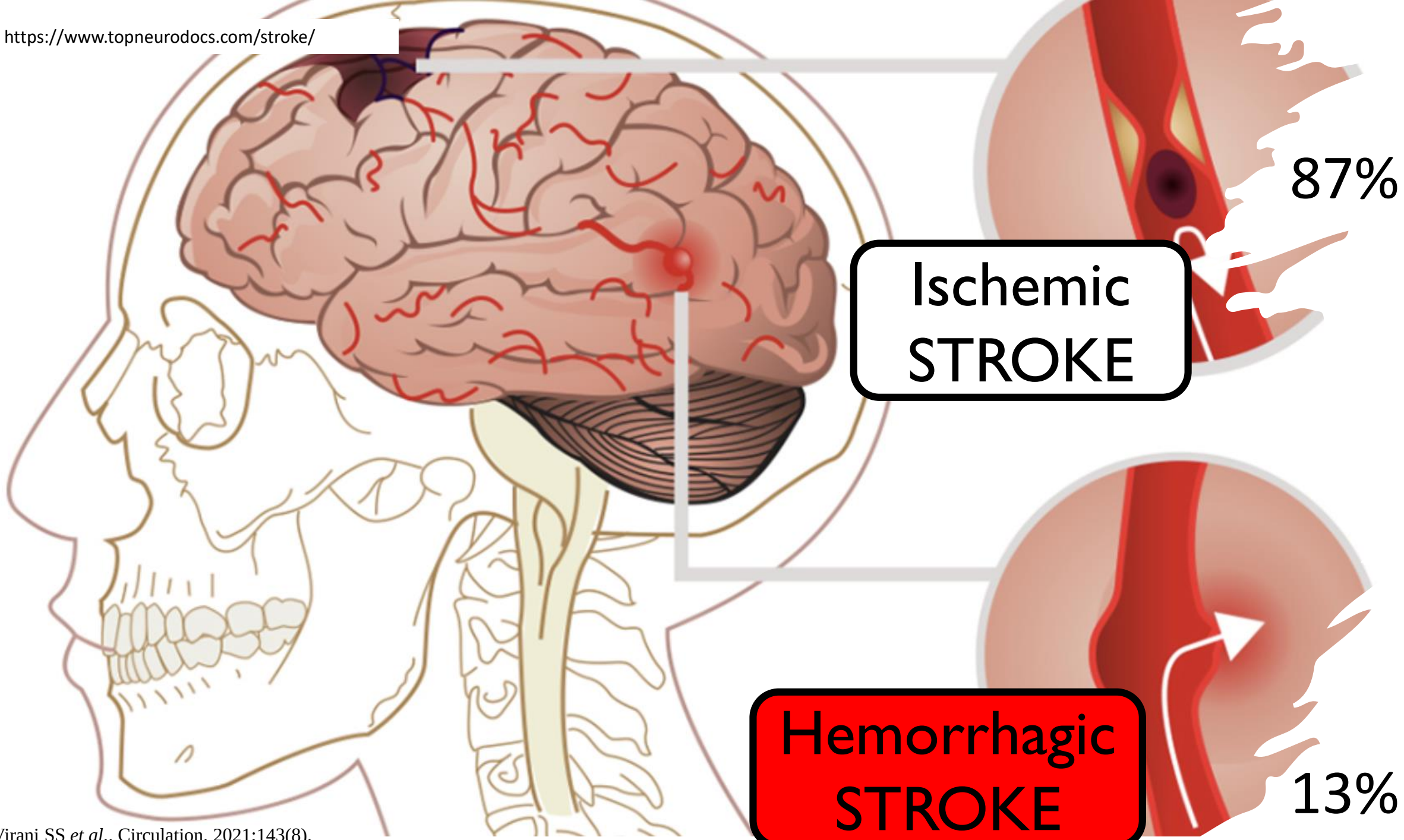


Stop Infusion

Imaging/ Lab work

Treatment

Image: https://www.topneurodocs.com/stroke/



Source: Virani SS *et al*,. Circulation. 2021;143(8).

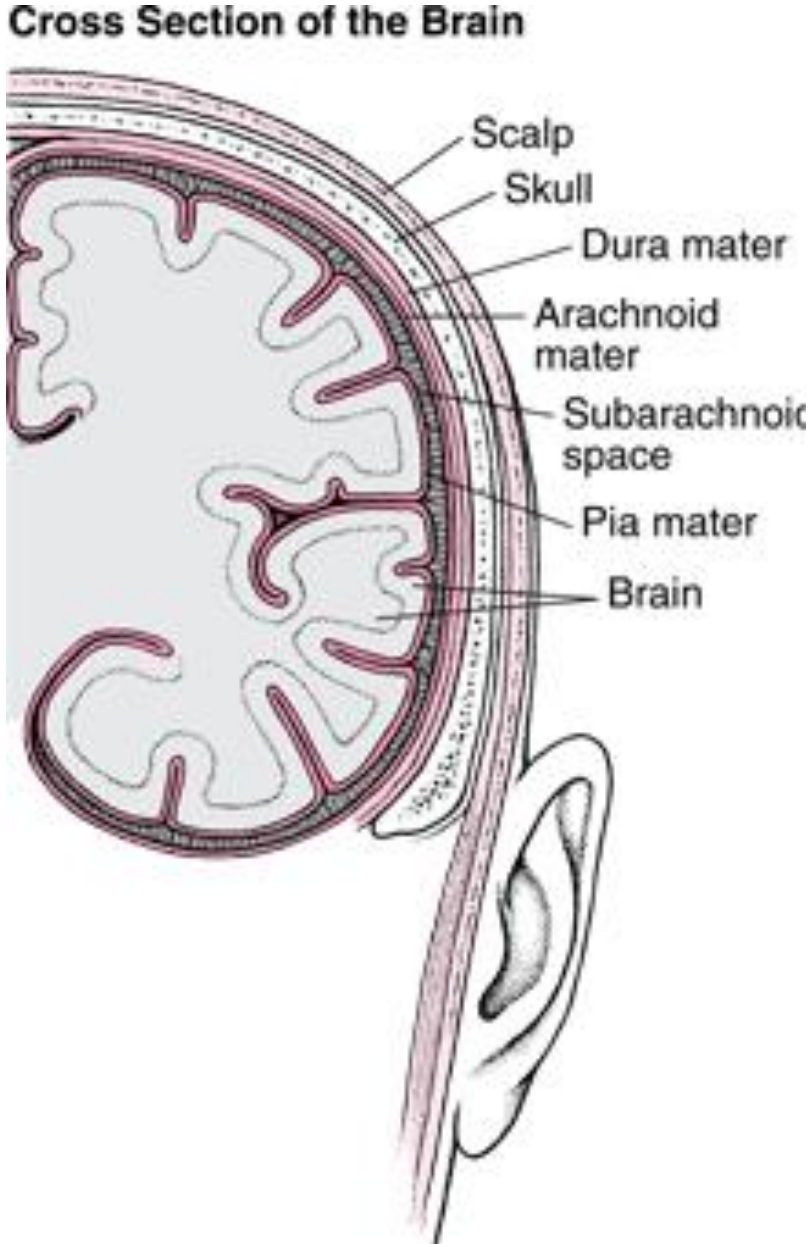
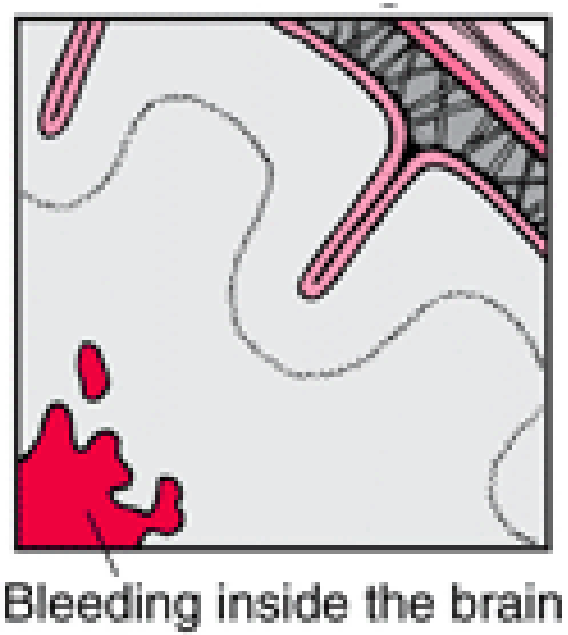
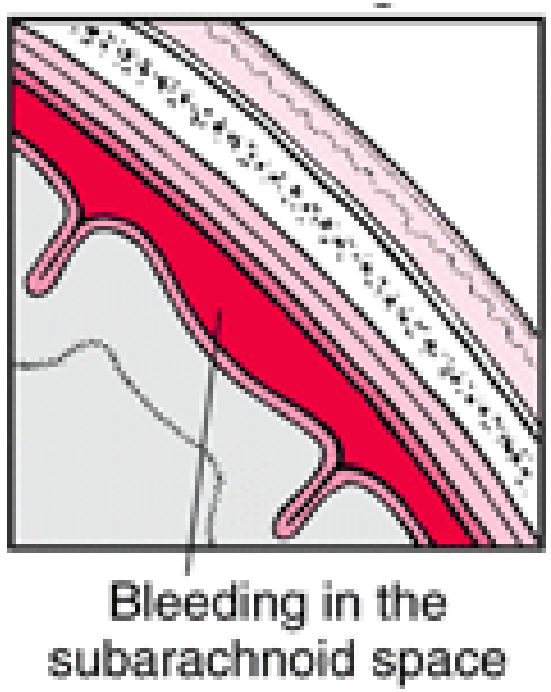


Image: https://www.joeniekrofoundation.com/understanding/what-is-a-hemorrhagic-stroke/



Intracerebral Hemorrhage (ICH)

Results from from bleeding in the brain parenchyma which then leads to hematoma formation



Subarachnoid Hemorrhage (SAH)

Results from trauma or a ruptured aneurysm

Source: Schwinghammer T.L. Pharmacotherapy Handbook. 2021.

Clinical Manifestations of ICH

- Onset sudden (spontaneous vs traumatic)
- Vomiting
- Systolic BP (SBP) >220 mmHg
- Severe headache
- Coma or ↓ level of consciousness
- Symptom progression over minutes or hours
- *Confirmed via imaging

Source: Hemphill JC *et al.,* Stroke. 2015;46(7):2032-2060.

Management of ICH

- Blood Pressure Management
- Anticoagulant Reversal
- ICP management
- Seizure Management/Prevention

Source: Hemphill JC *et al.,* Stroke. 2015;46(7):2032-2060.

Stroke
Volume 46, Issue 7, July 2015; Pages 2032-20
https://doi.org/10.1161/STR.000000000000006

AHA/ASA GUIDELINE

Guidelines for the M
Intracerebral Hemor

BP: Recommendations

Initial SBP	Goal
150-220 mmHg	↓SBP to 140mmHg
>220 mmHg	Reasonable to consider aggressive ↓SBP

1. **For ICH patients presenting with SBP between 150 and 220 mm Hg and without contraindication to acute BP treatment, acute lowering of SBP to 140 mm Hg is safe *(Class I; Level of Evidence A)* and can be effective for improving functional outcome *(Class IIa; Level of Evidence B)*.** (Revised from the previous guideline)
2. **For ICH patients presenting with SBP >220 mm Hg, it may be reasonable to consider aggressive reduction of BP with a continuous intravenous infusion and frequent BP monitoring *(Class IIb; Level of Evidence C)*.** (New recommendation)

Source: Hemphill JC *et al.,* Stroke. 2015;46(7):2032-2060.

Anticoagulant Reversal

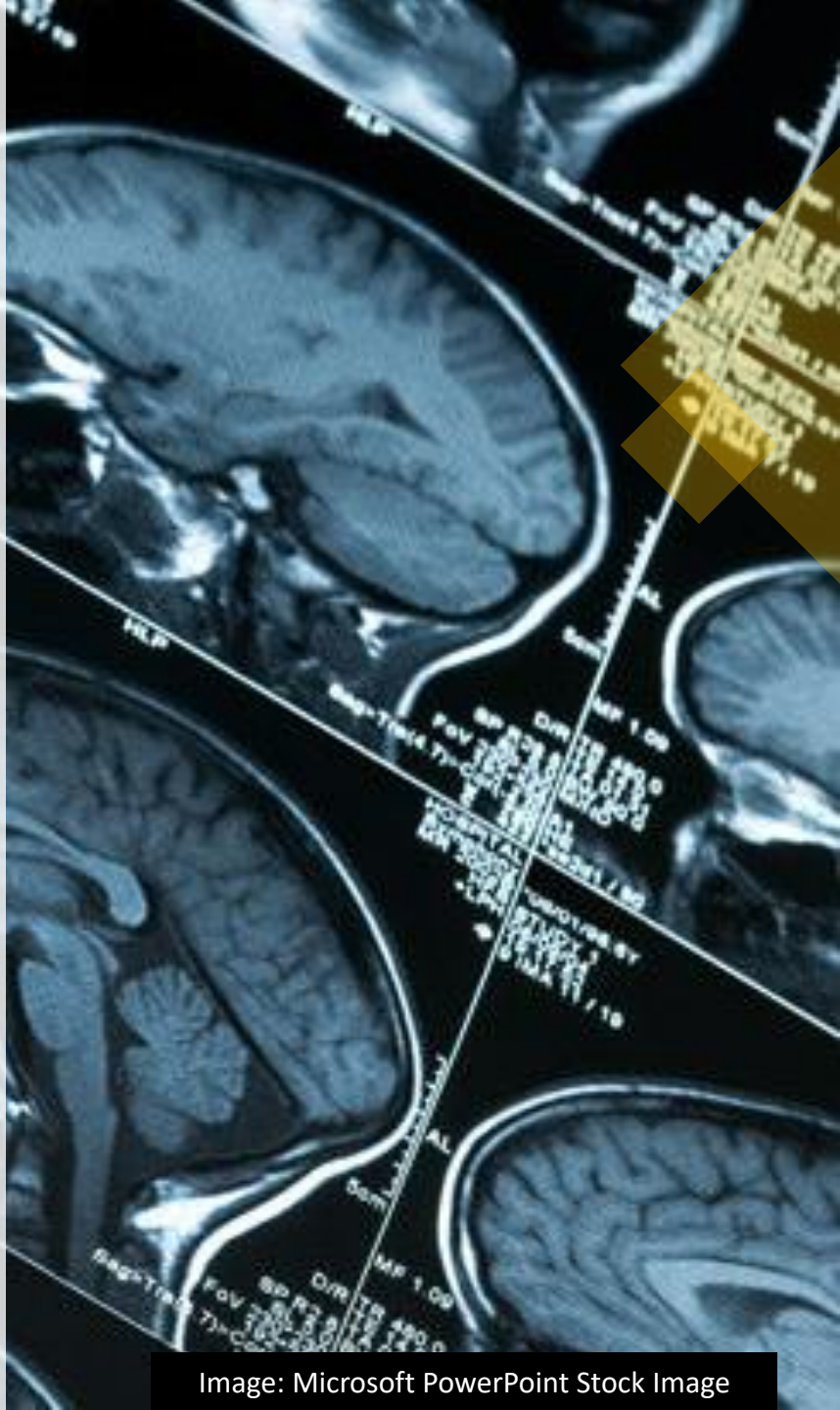
Warfarin	Vitamin K plus one of the following FFP, 3FPCC, 4FPCC, FEIBA
Dabigatran (Pradaxa®)	Idarucizumab (Praxbind®)
Rivaroxaban (Xarelto®) **Apixaban (Eliquis®)**	4F-PCC (Kcentra®) **or** andexanet alfa (Andexxa®)
Unfractionated heparin (UFH) or low molecular weight heparin (LMHW)	Protamine Sulfate

Source: Pollack CV et al., N Engl J Med. 2015. ● Source: Panos NG et al., Circulation. 2020. ● Source: Zareh M et al., West J Emerg Med. 2011.

Cerebral Edema and Elevated ICP

- Significant cause of morbidity and mortality in patients with intracranial tumors, cerebral hematomas, traumatic brain injuries, cerebral infarcts, and ICH's
- ICP and cerebral blood flow are determined by the amount of blood and CSF in the skull and the force exerted by the brain on the inside of the skull
    - Normal ICP: 5 to 15 mmHg

Source: Hemphill JC *et al.,* Stroke. 2015;46(7):2032-2060.



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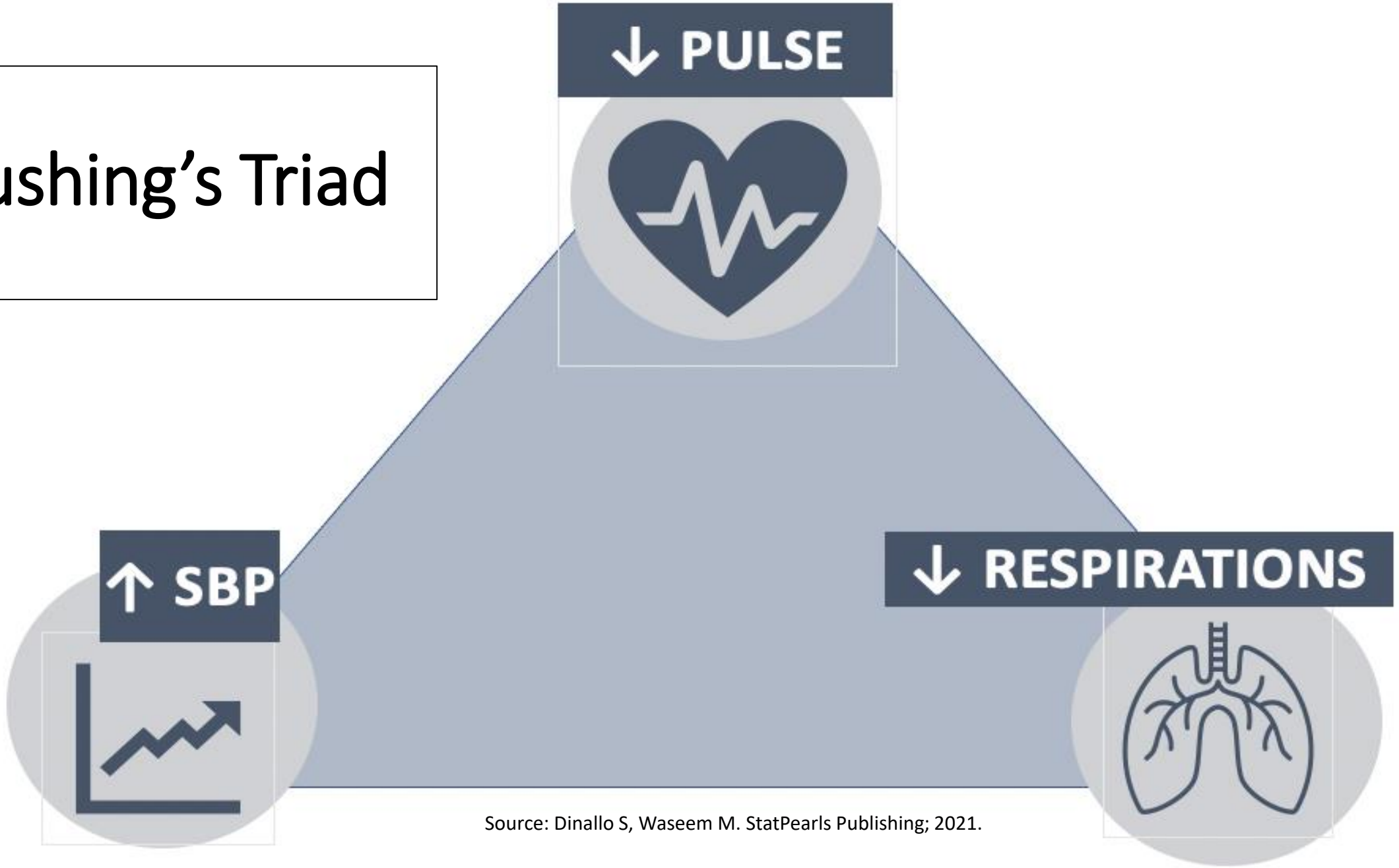
Cushing's Triad



Source: Dinallo S, Waseem M. StatPearls Publishing; 2021.

Hyperosmolar Agents

	Hypertonic Saline	Mannitol
Mechanism	Creates an osmotic gradient and drives fluid from the interstitial space into the intravascular space	A crystalloid composed of a six-carbon simple sugar dissolved in water-osmotic diuretic
Dose	3%: 250 mL bolus	0.25 to 2 g/kg bolus
Administration	Central line preferred, but may use peripheral line emergently	Filter
Monitor	Sodium	Serum Osmolarity

Image: Microsoft PowerPoint Stock Image

Source: Koenig MA. Continuum (Minneap Minn). 2018;24(6):1588-1602.

Neurocrit Care (2020) 32:647–666
https://doi.org/10.1007/s12028-020-00959-7

NEUROCRITICAL CARE SOCIETY

NCS GUIDELINE

Guidelines for the Acute Treatment of Cerebral Edema in Neurocritical Care Patients

Aaron M. Cook[1*], G. Morgan Jones[2], Gregory W. J. Hawryluk[3], Patrick Mailloux[4], Diane McLaughlin[5], Alexander Papangelou[6], Sophie Samuel[7], Sheri Tokumaru[8], Chitra Venkatasubramanian[9], Christopher Zacko[10], Lara L. Zimmermann[11], Karen Hirsch[9] and Lori Shutter[12]

Recommendations for Hyperosmolar Therapy

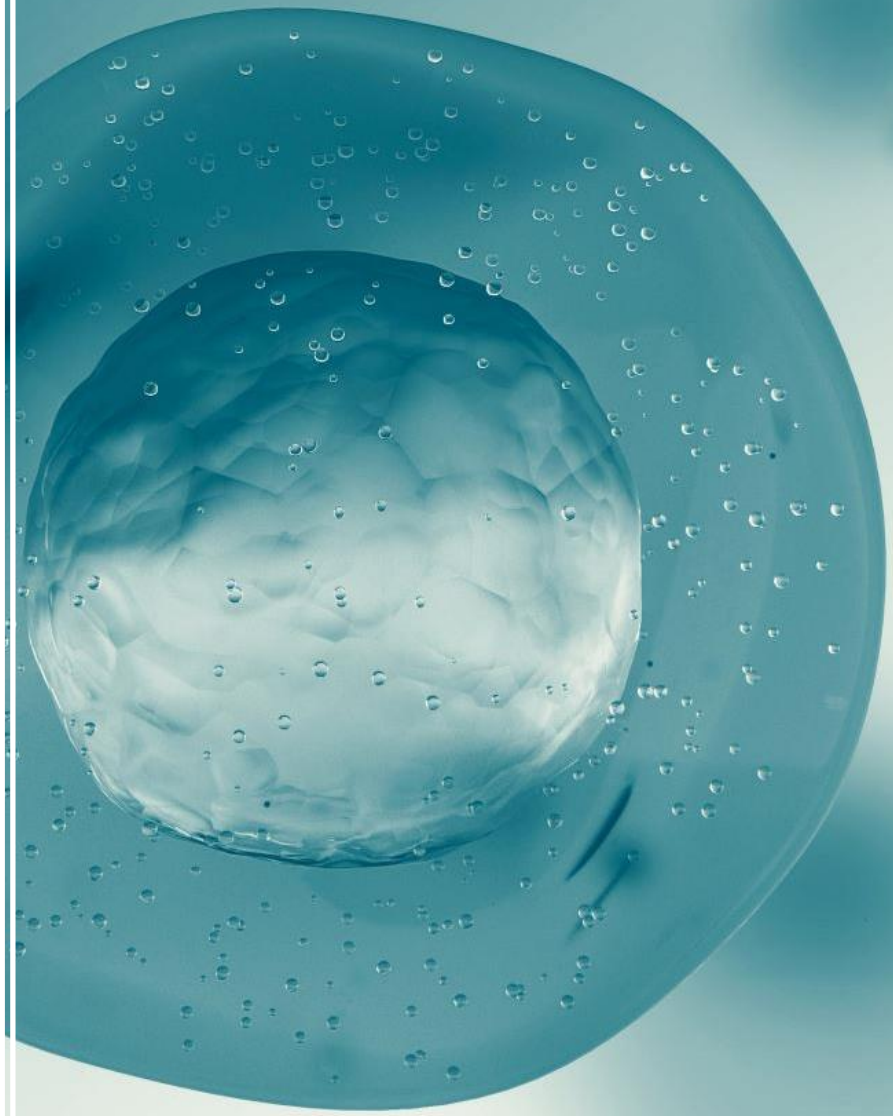
1. We suggest using hypertonic sodium solutions over mannitol for the management of ICP or cerebral edema in patients with intracerebral hemorrhage (conditional recommendation, very low-quality evidence).

Source: Cook AM *et al.,* Neurocrit Care. 2020;32(3):647-666.

Mannitol

- Metabolism: renal
- Half life: ~4 hours
- Adverse effects
  - Hypotension
  - Masking/worsening dehydration
  - Rebound phenomenon with ↑ ICP
  - Renal toxicity secondary to ↑ in serum osmolality

Source: Tenny S *et al.,* In: StatPearls. StatPearls Publishing; 2022.



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Osmolality

OsmolaRity: the concentration of osmotically active particles (molecules or ions) per unit of volume of solution

OsmolaLity: the concentration of dissolved particles per unit of weight of solvent

Normal Serum Osmolality: 275 to 295 mOsm/kg

Goal when administering mannitol

<320 mOsm/kg or an osmolar gap <20 mOsm/kg

Image: Microsoft PowerPoint Stock Image

Source: Torre-Healy A *et al.,* Neurocrit Care. 2012;17(1):117-130.

Recommendations for Assessing the Risk of Renal Injury After Mannitol Administration

1. We suggest using osmolar gap over serum osmolarity thresholds during treatment with mannitol to monitor for the risk of AKI (conditional recommendation, very low-quality evidence).

Case report

Hyperosmolality with hyponatremia, caused by inappropriate administration of mannitol

A. Aviram M.D. [1], A. Pfau M.D. [1], J.W. Czaczkes Ph.D., M.D. [1], T.D. Ullmann M.D. [1]

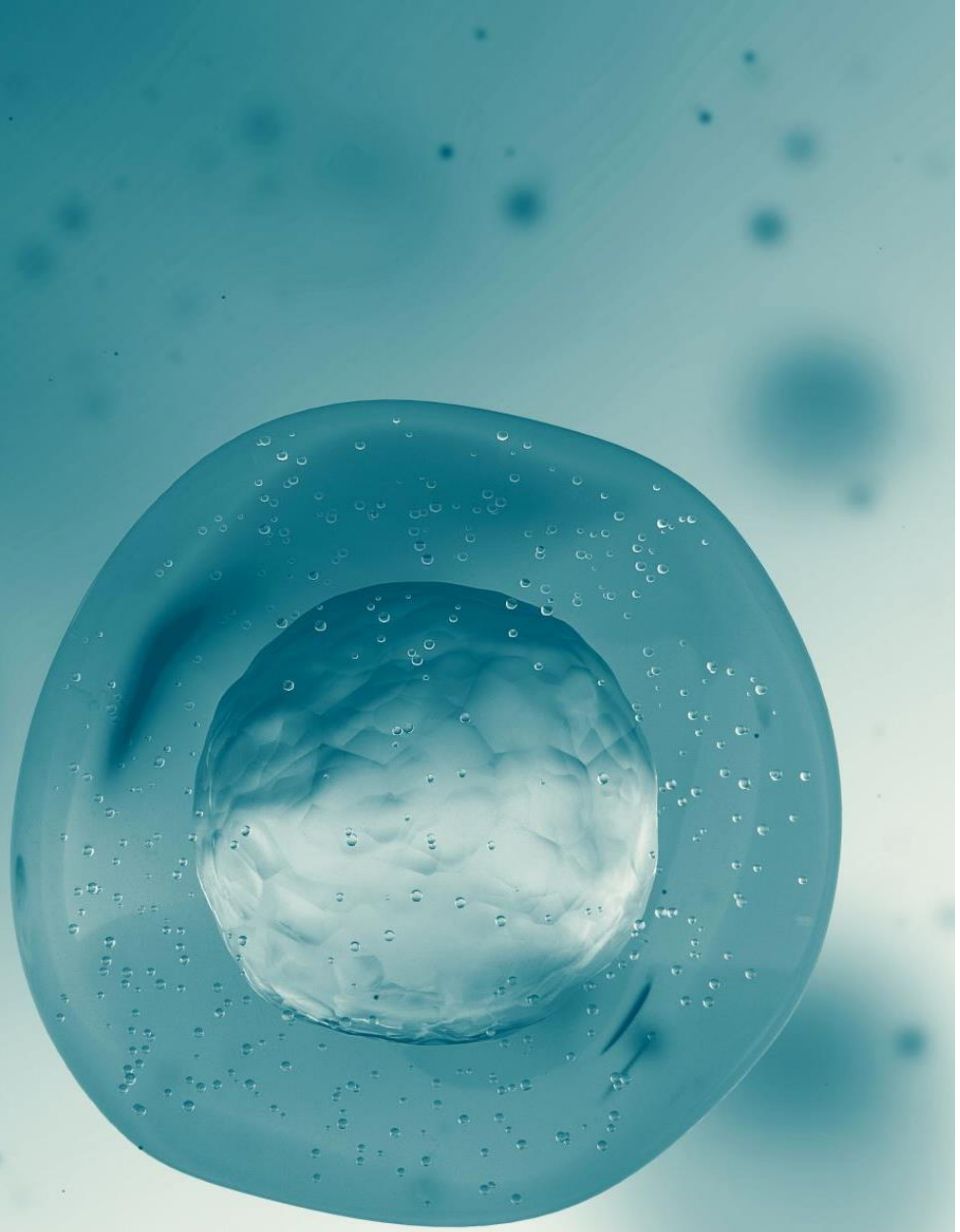
Case Series

Adverse Effects of Inappropriate Mannitol Use

Hyperosmolality and increased instance of AKI

Supportive Care

Source: Aviram A, Pfau A et al., The American Journal of Medicine. 1967;42(4):648-650.



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Hypertonic Saline

Adverse effects

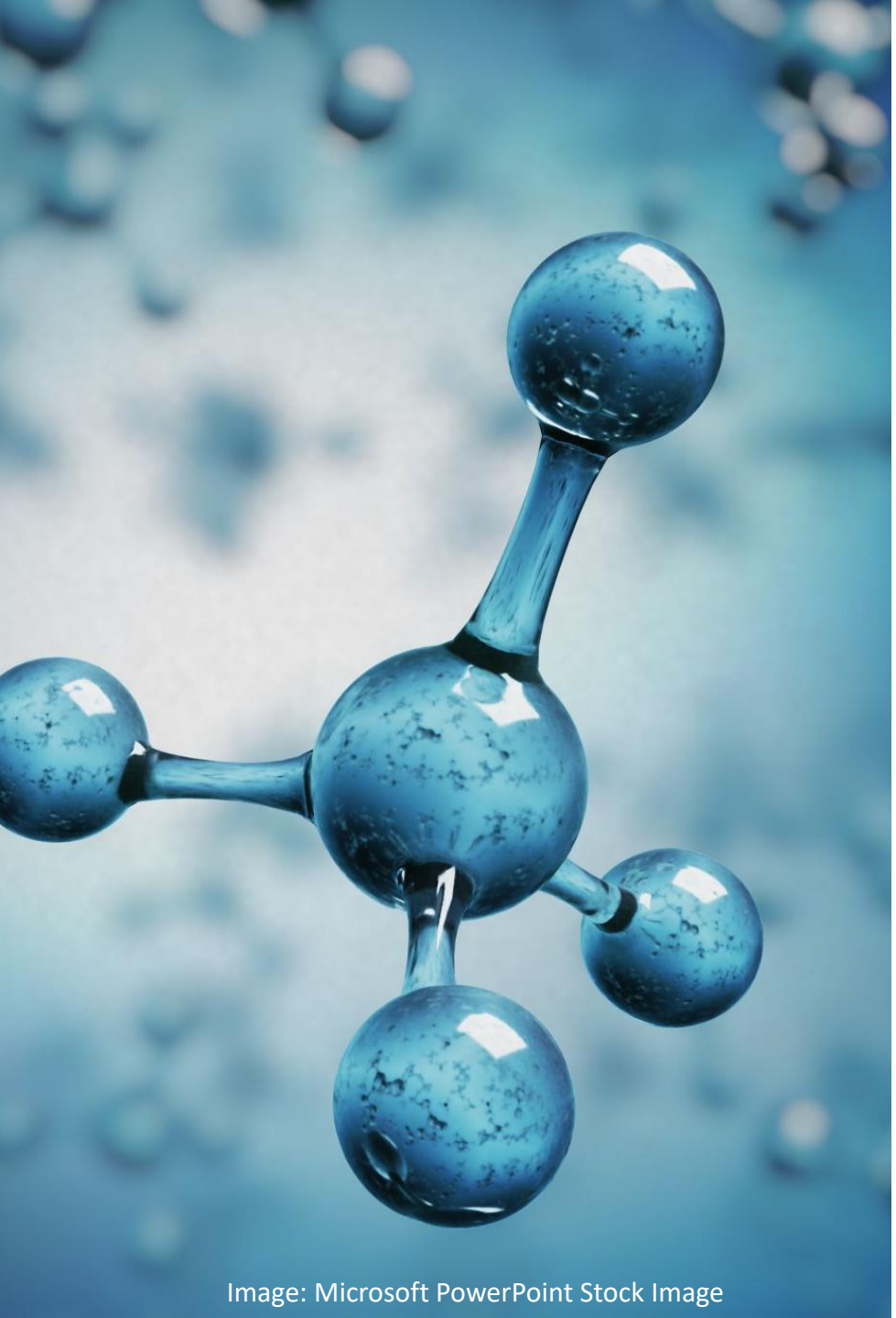
- Hyperchloremic metabolic acidosis
- Hypernatremia
- Osmotic demyelination syndrome, when severe hyponatremia is corrected too rapidly
- Thrombophlebitis
- Extravasation
- Hypervolemia

Source: Mason A, Malik A, Ginglen JG. StatPearls Publishing; 2021.

Hypernatremia

- ↑ free water losses along with ↓ free water intake and inappropriate therapy with isotonic fluids
- Hospitalized patients with hypernatremia have a significantly higher mortality rate compared with patients without
- May results from the therapeutic use of hyperosmolar agents

Source: Aiyagari V et al., Journal of Critical Care. 2006;21(2):163-172.



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Serum Sodium Levels

- An upper serum sodium range of 155–160 mEq/L and a serum chloride range of 110–115 mEq/L may be reasonable to decrease the risk of acute kidney injury
- Hypertonic saline and hypernatremia are not associated with hospital mortality in patients with severe TBI (sodium >145 mEq/L)
- Serum sodium >160 mEq/L was a dependent predictor of mortality

Source: Cook AM *et al.,* Neurocrit Care. 2020;32(3):647-666.
Source: Aiyagari V et al., Journal of Critical Care. 2006;21(2):163-172.
Source: Tan SKR et al., Can J Anaesth. 2016;63(6):664-673.

Image: Microsoft PowerPoint Stock Image

Osmotic demyelination syndrome (ODS)

Brain cells (oligodendrocytes) are at risk of cell shrinkage and hence demyelination

Symptoms:

- Delayed (2-6 days)
- Movement disorders, seizures, quadriparesis, and coma
- May be irreversible

Increased risk if hyponatremia >48h

Source: Luts A *et al,*. Regul Pept. 1990.
Source: Abbott R *et al,*. BMJ. 2005.

Pharmacist Assessment Question 4

What is the desired sodium level for a patient receiving hypertonic saline?

a) >160 mEq/L

b) 155-160 mEq/L

c) 133-143 mEq/L

d) 135-150mEq/L

Pharmacist Assessment Question 4: Correct Response

What is the desired sodium

a) >160 mEq/L

b) 155-160 mEq/L

c) 133-143 mEq/L

d) 135-150mEq/L

Recommendations for Assessing the Risk of Toxicity (Acute Kidney Injury or Unwanted Acidosis) After Hypertonic Sodium Solution Administration

1. We suggest that severe hypernatremia and hyperchloremia during treatment with hypertonic sodium solutions should be avoided due to the association

An upper serum sodium

range of 155–160 mEq/L a

risk of acute kidney injury (conditional recommendation, very low-quality evidence).

Technician Assessment Question 3

Which of the following medications to manage cerebral edema following stroke should not be refrigerated?

a) Hypertonic saline (NaCl 3%)

b) Hypertonic saline (NaCl 23.4%)

c) Mannitol

Technician Assessment Question 3: Correct Response

Which of the following medications to manage cerebral edema following stroke should not be refrigerated?

a) Hypertonic saline (NaCl 3%)

b) Hypertonic saline (NaCl 23.4%)

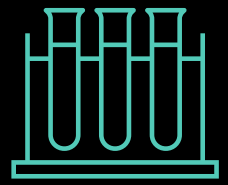
c) Mannitol

Treatment of Hypernatremia

- Stop offending agent
- Calculate the free water deficit
- A correction rate of about 12 mEq/L per day is recommended to avoid rebound cerebral edema

Recap

Hyperosmolar agents and their side effects



Monitoring Parameters

Stop Administration

Treatment/

Supportive Care (patient specific)

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Image: Microsoft PowerPoint Stock Image

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Image: Microsoft PowerPoint Stock Image

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Thank you!

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