Optimizing Antithrombic Strategies in Acute Ischemic Stroke: Focus on post-thrombolysis care

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Disclosures

- No relevant financial relationships

Objectives

- Explain latest updates and options for ischemic and hemorrhagic stroke management and standards of care.
  - Review antithrombotic medications
  - Discuss window in which to start antithrombic medications
  - Select appropriate antithrombotic medications
  - Review indications for dual antiplatelet therapy

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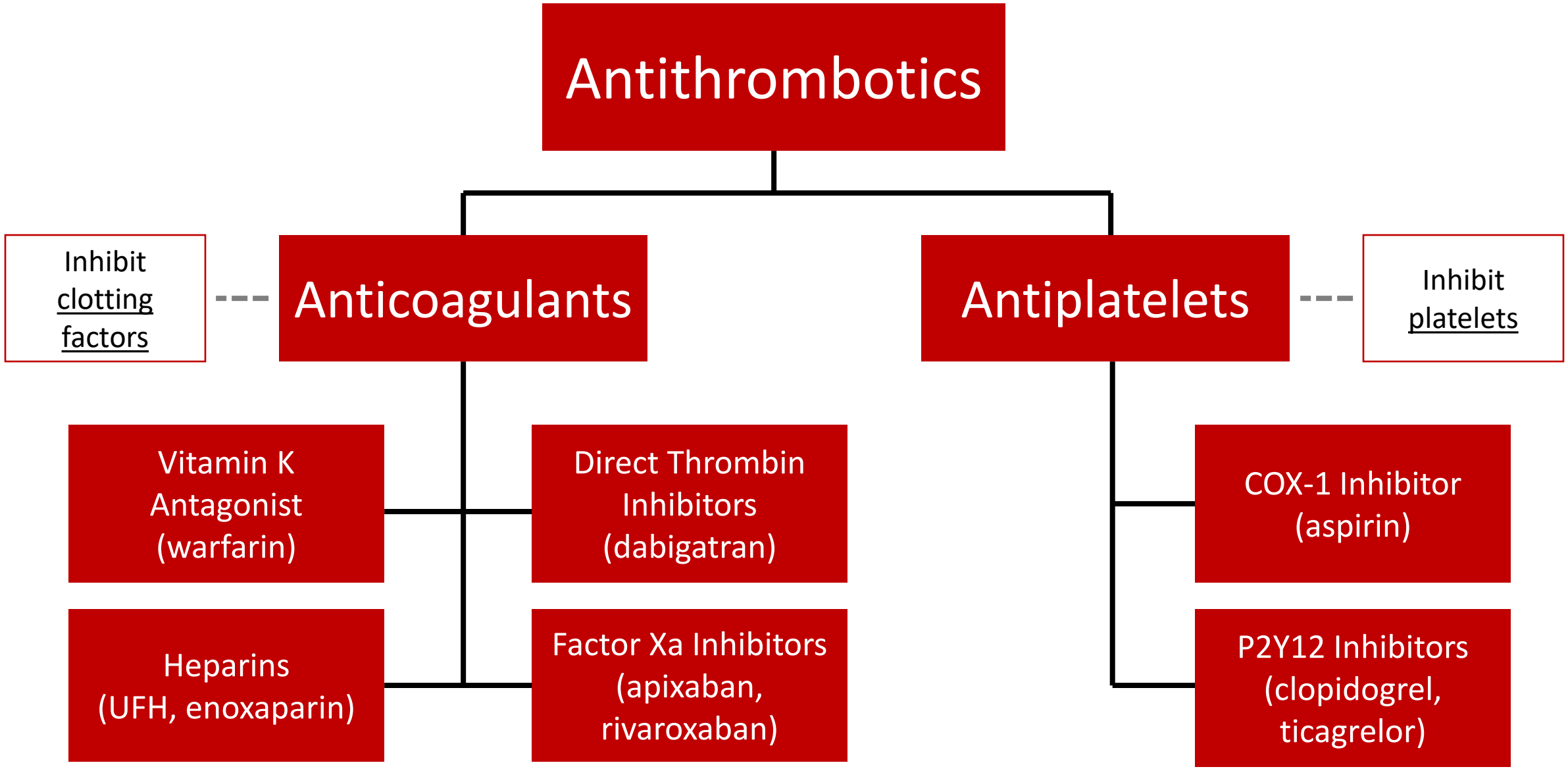
Definitions

- AIS – acute ischemic stroke
- DAPT – dual antiplatelet therapy
- DOAC – direct oral anticoagulant
- ICH – intracranial hemorrhage
- LMWH – low molecular weight heparin
- NIHSS – National Institutes of Health Stroke Scale
- TNK – tenecteplase
- TPA – tissue plasminogen activator; also known as alteplase
- UFH – Unfractionated heparin


Antithrombotics
Anticoagulants
Inhibit clotting factors
Antiplatelets
Inhibit platelets
Vitamin K Antagonist (warfarin)
Direct Thrombin Inhibitors (dabigatran)
Heparins (UFH, enoxaparin)
Factor Xa Inhibitors (apixaban, rivaroxaban)
COX-1 Inhibitor (aspirin)
P2Y12 Inhibitors (clopidogrel, ticagrelor)

Anticoagulants

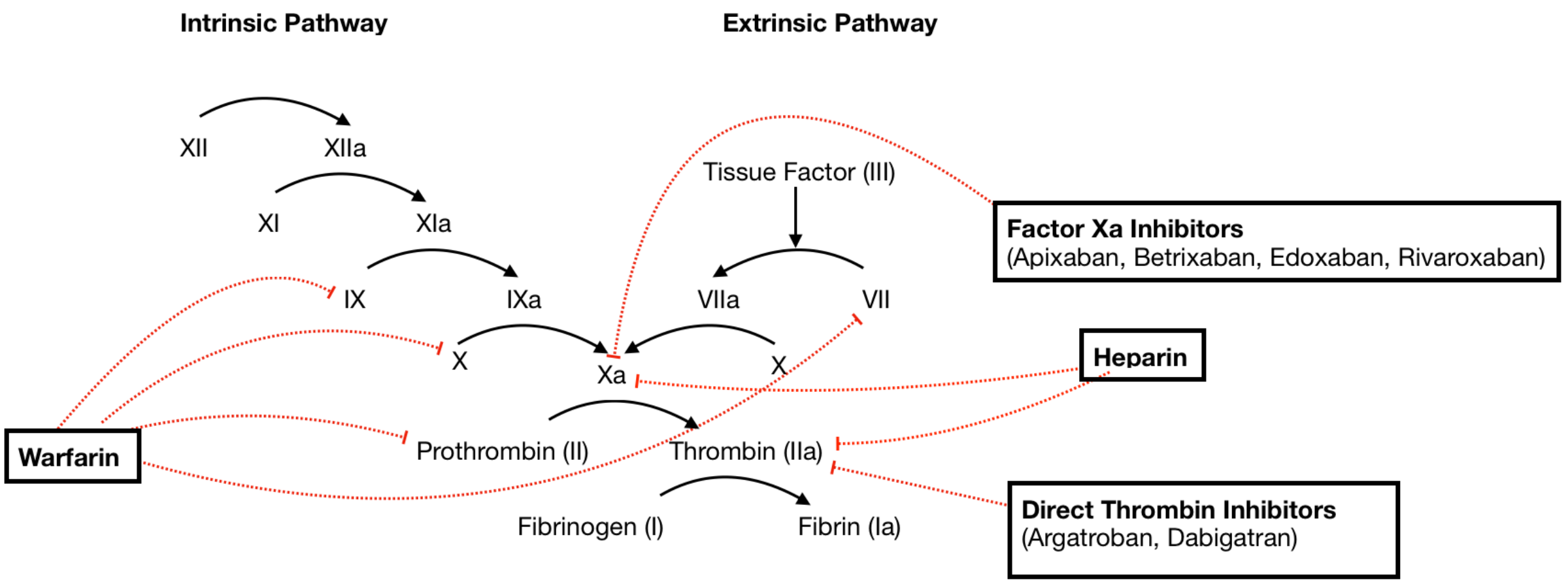
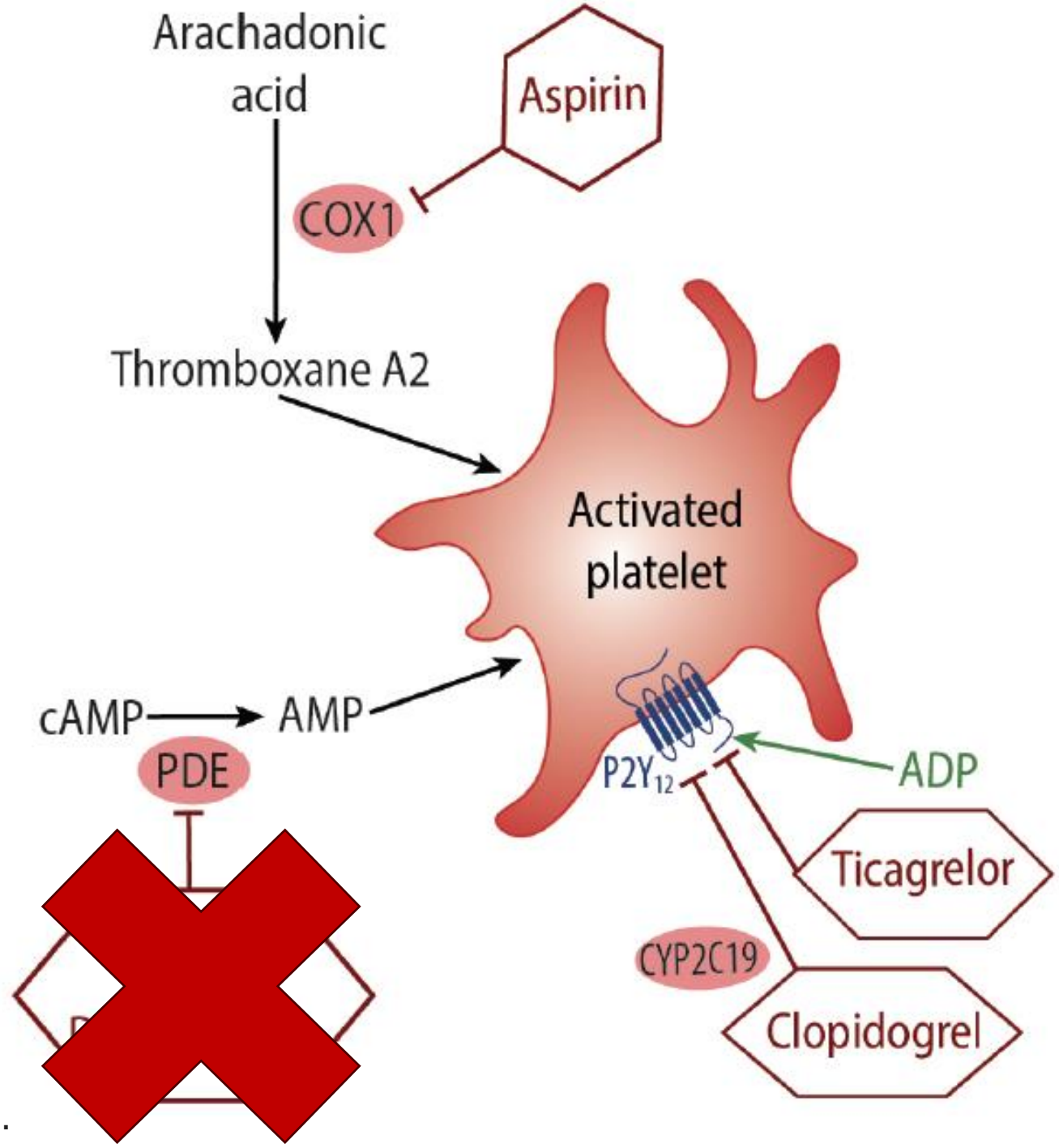


Image source: Wikipedia

Antiplatelets



Indraswari F, et al. Practical Neurology. Jan 2022. 35-39.

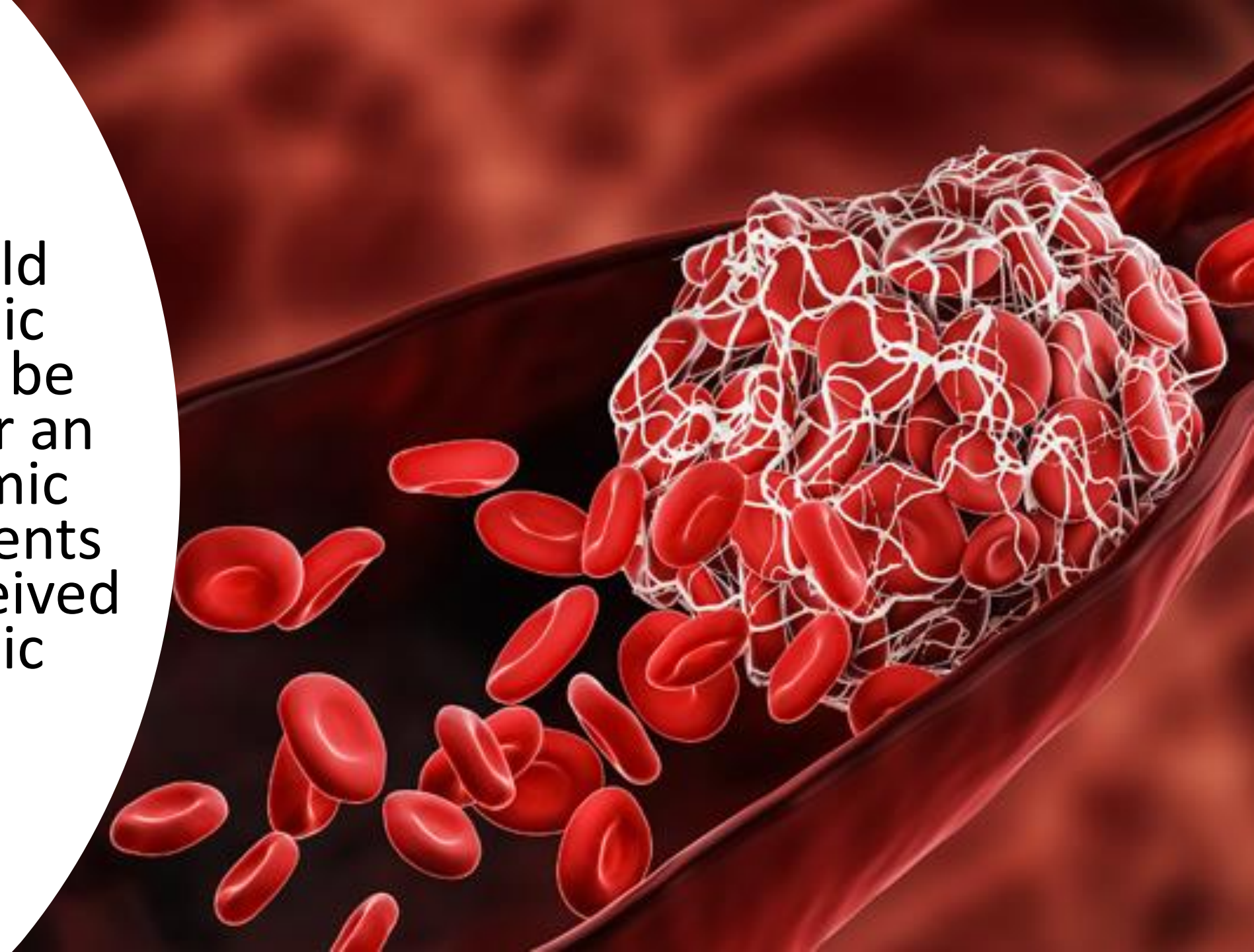
Thrombolytics

- Break down fibrin clots
- ~6% risk of intracranial hemorrhage (ICH)

Patient Case

- 59 year-old male presents with left sided weakness
  - Last known well 1 hour prior to arrival
- PMH: T2DM, HTN, CKD, tobacco use
- Home medications: metformin, lisinopril
- BP 152/90 mmHg, HR 80, RR 18, 97% on RA, T 36.4 ^{O}C
- Labs within normal limits except
  - POC glucose = 194
  - Serum creatinine = 2.18 mg/dL
  - Hgb = 11.2
  - HgbA1c = 9.1
- NIHSS = 5
- Head CT shows no acute intracranial findings
- CTA shows no large vessel occlusion
- Receives alteplase and is admitted to the ICU

When should antithrombic medications be initiated after an acute ischemic stroke in patients who have received thrombolytic therapy?



Timing of antithrombotic administration

- The timing of initiation of antiplatelet therapy or anticoagulation should be made on an individual level, balancing risk and benefit.
- Aspirin
  - Administration of aspirin is recommended in patients with AIS within 24 to 48 hours after onset.
  - Start antiplatelet therapy even if the underlying cause of the stroke is still undetermined.
  - For patients who have received a thrombolytic (alteplase or tenecteplase), aspirin administration is generally delayed until 24 hours later.
  - For patients who do not receive thrombolytic therapy, aspirin can be initiated immediately.

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

Guideline Statements

2013 Guidelines: Initiation of anticoagulant therapy within 24 hours of treatment with intravenous rtPA is not recommended.

2019 Guidelines: The risk of antithrombotic therapy within the first 24 hours after treatment with IV alteplase (with or without mechanical thrombectomy) is uncertain.

- Use might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk.

Jauch EC, et al. *Stroke*. 2013;44(3):870-947.
Powers WJ, et al. *Stroke*. 2019;50(12):e344-e418.

Safety Measures

- What two things need to happen before giving aspirin?
  - Rule out bleeding complications
    - Repeat head CT or MRI 24 hours after thrombolytic administration
      - Up for debate
      - FIAT trial showed no benefit
  - Swallow study
    - Must be done before giving any oral medications, not just antithrombotics

Dysphagia screening before the patient begins eating, drinking, or receiving oral medications is effective to identify patients at increased risk for aspiration.

Powers WJ, et al. *Stroke*. 2019;50(12):e344-e418.
Tabaac B, et al. *J Stroke Cerebrovasc Dis*. 2023;32(6):107092.

DVT prophylaxis

In immobile stroke patients without contraindications, intermittent pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended over routine care to reduce the risk of deep vein thrombosis (DVT).

The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in patients with AIS is not well established.

- Utilize non-pharmacologic methods when able
- If using pharmacotherapy, wait at least 24 hours after thrombolytic administration.

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

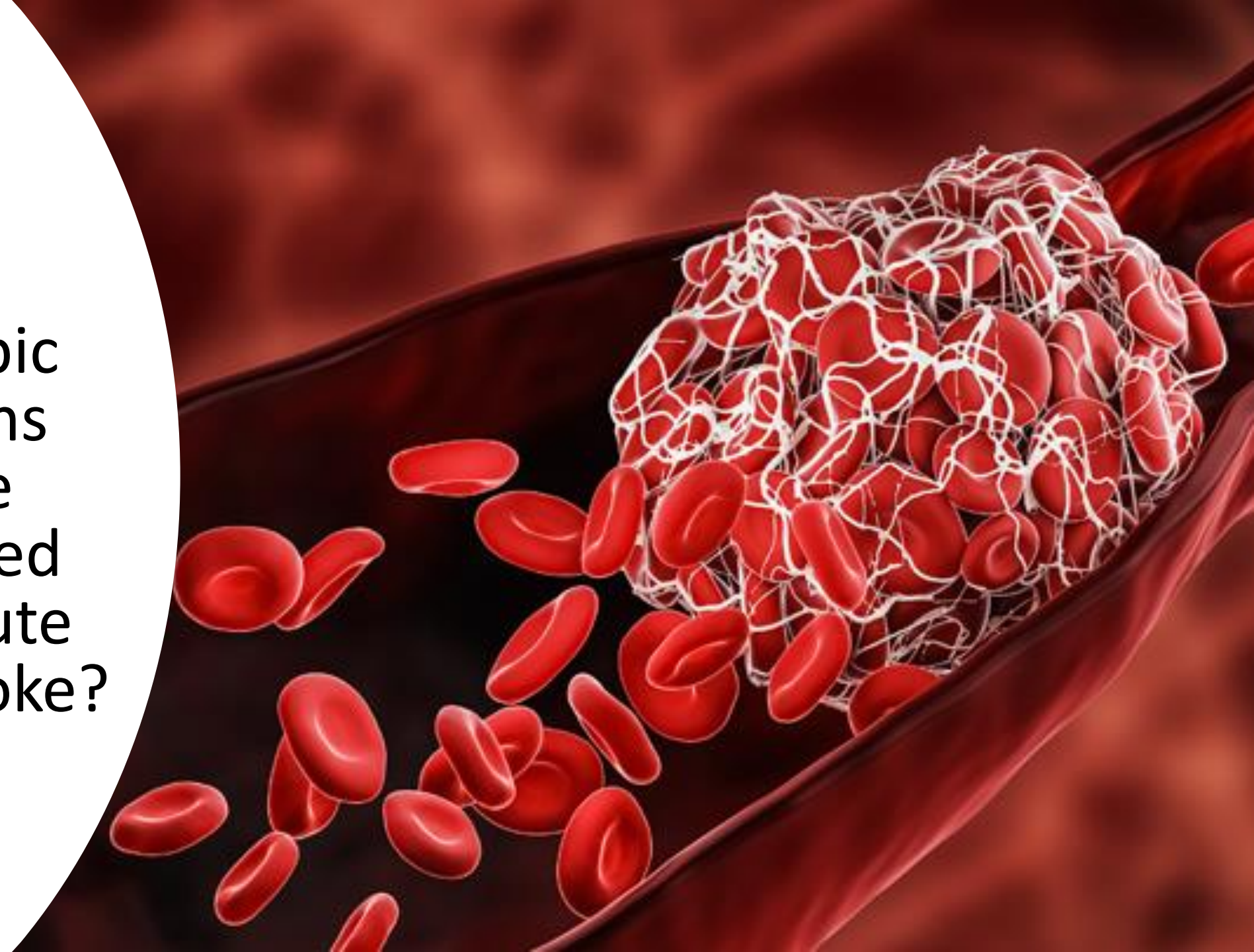
Pop Quiz

True or False:

All patients who present with an acute ischemic stroke have an indication for anticoagulation.

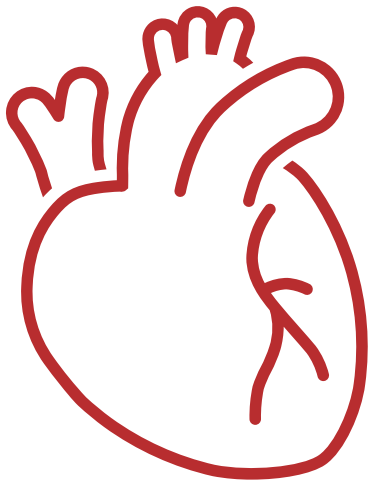
FALSE

What antithrombic medications should be administered after an acute ischemic stroke?



Antithrombotic medication selection

- Determine underlying mechanism
  - Cardioembolic → anticoagulation
  - Noncardioembolic → antiplatelet therapy



- Causes of cardioembolic strokes
  - **Atrial fibrillation**
  - Prosthetic heart valves
  - Patent foramen ovale (PFO)
  - Intracardiac thrombus
  - Infective endocarditis
  - Others

Greco A, et al. *J Am Coll Cardiol*. 2023;82(15):1538-1557.

Atrial fibrillation

Timing of anticoagulant administration

- Optimal timing to initiate anticoagulation is an area of uncertainty
- Depends on
  - risk of hemorrhagic transformation
  - infarct size
  - other factors (i.e. uncontrolled hypertension)
- TIMING trial showed that early initiation (within 4 days) was noninferior to delayed start of DOACs (between 5 and 10 days)

For most patients with an AIS in the setting of atrial fibrillation, it is reasonable to initiate oral anticoagulation between 4 and 14 days after the onset of neurological symptoms.

Oldgren J, et al. *Circulation*. 2022;146(14):1056-1066.
Greco A, et al. *J Am Coll Cardiol*. 2023;82(15):1538-1557.

Choice of anticoagulant

- Afib → DOACs preferred over warfarin
  - Factor Xa inhibitors
    - Apixaban
    - Edoxaban
    - Rivaroxaban
  - Direct thrombin inhibitor
    - Dabigatran
- Mechanical valve replacement → warfarin
- LV thrombus → warfarin
- VTE → DOACs

Dual Antiplatelet Therapy (DAPT)

- Indications
  - High-risk TIA (ABCD^2 score ≥4)
  - Mild ischemic stroke (NIHSS ≤3)
- Regimens
  - Clopidogrel 300-600 mg load followed by 75 mg daily + aspirin 325 mg load followed by 81 mg daily for 21 days
  - Followed by aspirin monotherapy
  - Ticagrelor is an alternative to clopidogrel
    - Clopidogrel has no activity in patients with CYP2C19 loss-of-function allele

ABCD^2 Score	
Age:	
≥60 years	1 point
<60 years	0 points
Blood pressure elevation when first assessed after TIA:	
Systolic ≥140 mmHg **or** diastolic ≥90 mmHg	1 point
Systolic <140 mmHg **and** diastolic <90 mmHg	0 points
Clinical features:	
Unilateral weakness	2 points
Isolated speech disturbance	1 point
Other	0 points
Duration of TIA symptoms:	
≥60 minutes	2 points
10 to 59 minutes	1 point
<10 minutes	0 points
Diabetes:	
Present	1 point
Absent	0 points

Johnston SC, et al. Lancet 2007; 369:283.

DAPT

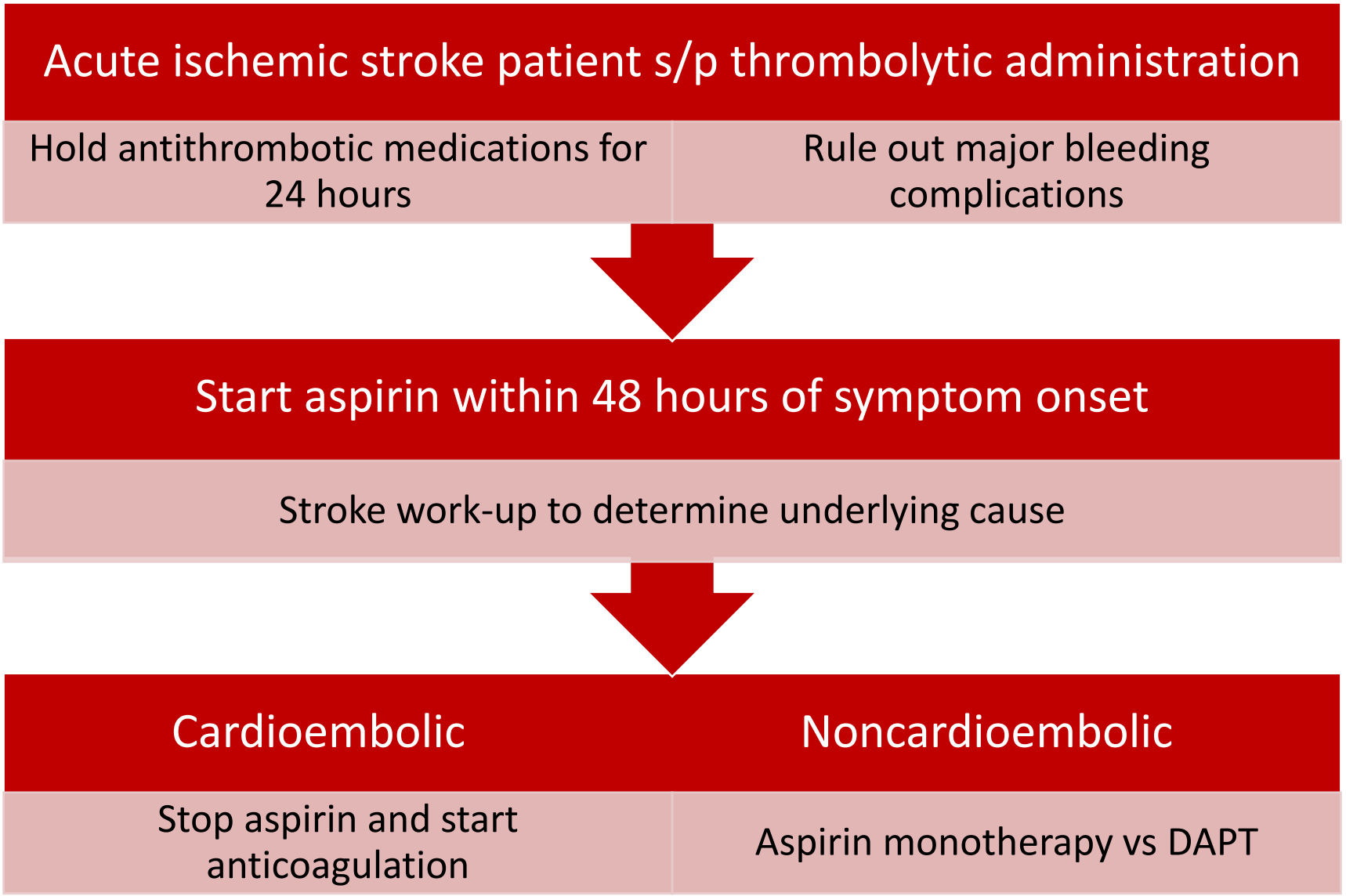
- Evidence
  - CHANCE and POINT trials
    - Patients with moderate and severe ischemic stroke were not enrolled
    - Larger brain infarcts are more likely to undergo hemorrhagic transformation
- Duration
  - 21 days per the CHANCE trial
    - Risk of recurrent stroke highest in the acute setting
    - Longer therapy associated with no additional benefit for stroke prevention but increased risk of bleeding complications
  - Aspirin monotherapy after 21 days

Wang Y, et al. *N Engl J Med*. 2013;369(1):11-19.
Johnston SC, et al. *N Engl J Med*. 2018;379(3):215-225.

Guideline statement on DAPT

In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset.

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


Acute ischemic stroke patient s/p thrombolytic administration
Hold antithrombotic medications for 24 hours
Rule out major bleeding complications
Start aspirin within 48 hours of symptom onset
Stroke work-up to determine underlying cause
Cardioembolic
Noncardioembolic
Stop aspirin and start anticoagulation
Aspirin monotherapy vs DAPT

Patient Case

- 59 year-old male presents with left sided weakness
  - Last known well 1 hour prior to arrival
- PMH: T2DM, HTN, CKD, tobacco use
- Home medications: metformin, lisinopril
- BP 152/90 mmHg, HR 80, RR 18, 97% on RA, T 36.4 ^{O}C
- Labs within normal limits except
  - POC glucose = 194
  - Serum creatinine = 2.18 mg/dL
  - Hgb = 11.2
  - HgbA1c = 9.1
- NIHSS = 5
- Head CT shows no acute intracranial findings
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Case Questions

When should aspirin be initiated in this patient?

- 24 to 48 hours after alteplase administration

What two things need to be done prior to aspirin administration?

- Rule out major bleeding complications from alteplase
- Swallow study

Case Questions

On hospital day 4, telemetry reveals atrial fibrillation.

What modifications should be made to patient's antithrombotic regimen?

A. Continue aspirin monotherapy
B. Initiate dual antiplatelet therapy with clopidogrel and aspirin
C. Stop aspirin and start apixaban
D. Start triple therapy with aspirin, clopidogrel, and apixaban

Triple therapy

For patients with a history of ischemic stroke, atrial fibrillation, and coronary artery disease, the usefulness of adding antiplatelet therapy to oral anticoagulants is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events.

Unstable angina and coronary artery stenting represent special circumstances in which management may warrant dual antiplatelet/oral anticoagulation.

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

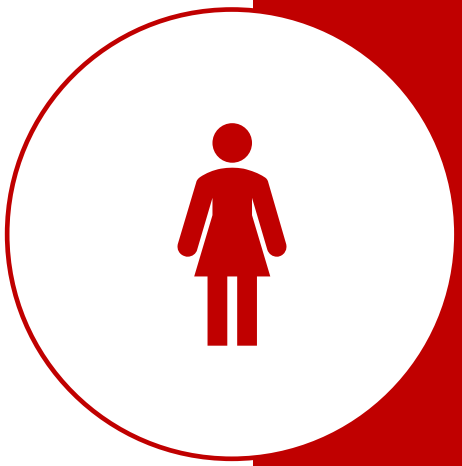
Bonus Questions

What other pharmacotherapy recommendations would decrease this patient's risk of stroke?

- Control hypertension
  - Increase lisinopril or add another antihypertensive agent
- Lipid/cholesterol management
  - Add atorvastatin or rosuvastatin
- Tobacco cessation
  - Consider nicotine replacement, varenicline, or bupropion
- Blood glucose control
  - Add SGLT2i
  - Evaluate appropriateness of metformin based on GFR
  - Consider GLP-1 agonist

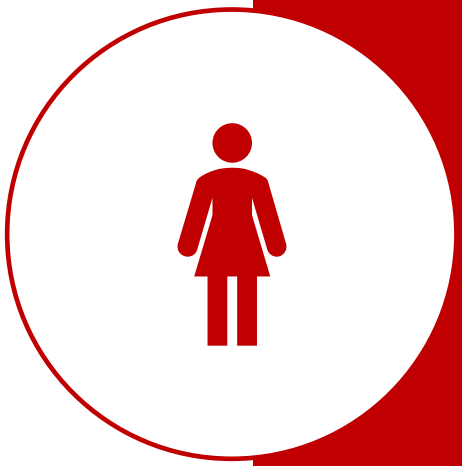
Patient Case #2

- 61 year-old female presents with left sided weakness
- Last known well 12 hours prior to arrival
- PMH: hypothyroidism
- Home medications: levothyroxine
- BP 112/60 mmHg, HR 64, RR 18, 99% on RA, T 36.7 ^{O}C
- Labs within normal limits
- NIHSS = 3
- Head CT shows no acute intracranial findings
- CTA shows no large vessel occlusion

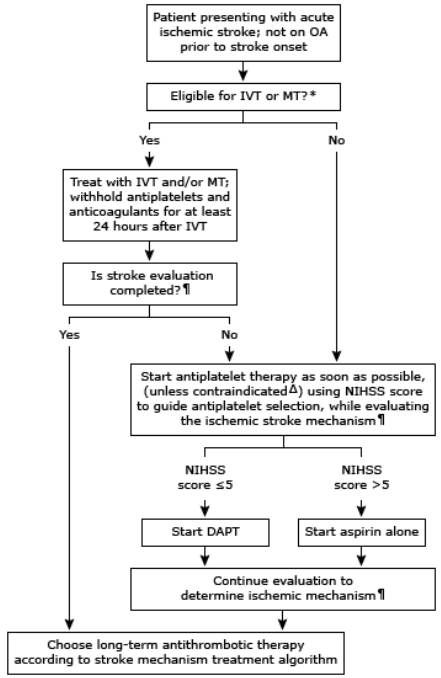


Case Questions

- Is this patient in the window for thrombolytic therapy?
  - No
- What antithrombotic medication regimen is most appropriate for this patient?
  - DAPT with aspirin and clopidogrel for 21 days
- When should these medications be initiated?
  - As soon as possible
- How long should each of these medications be continued?
  - DAPT for 21 days, then aspirin monotherapy indefinitely



Immediate antithrombotic treatment of acute ischemic stroke



This algorithm is intended to provide basic guidance regarding the immediated use of antithrombotic therapy for patients with an acute ischemic stroke. For further details, including scoring of the NIHSS and suggested dosing regimens of antithrombotic agents, refer to the relevant UpToDate topic reviews.

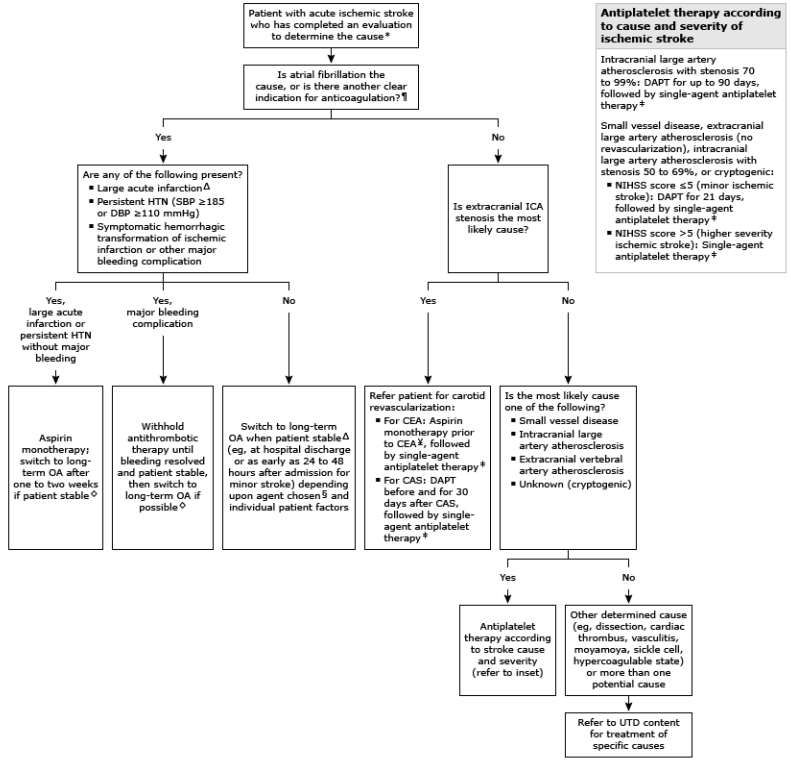
OA: oral anticoagulants; IVT: intravenous thrombolysis; MT: mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale; DAPT: dual antiplatelet therapy (eg, aspirin and clopidogrel, or aspirin and ticagrelor).

* Refer to text and associated algorithm for details.

¶ Brain and large vessel imaging, cardiac evaluation, and (for select patients) other laboratory tests.

Δ For severe systemic or symptomatic intracranial bleeding, withhold all anticoagulant and antiplatelet therapy for one to two weeks or until the patient is stable.

Antithrombotic therapy according to cause of acute ischemic stroke



This algorithm is intended to provide basic guidance regarding the immediate use of antithrombotic therapy for patients with an acute ischemic stroke. For further details, including scoring of the NIHSS and suggested dosing regimens of antithrombotic agents, refer to the relevant UpToDate topic reviews.

HTN: hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure; ICA: internal carotid artery; CEA: carotid endarterectomy; OA: oral anticoagulation; CAS: carotid artery stenting; DAPT: dual antiplatelet therapy (eg, aspirin and clopidogrel, or aspirin and ticagrelor); NIHSS: National Institutes of Health Stroke Scale; CT: computed tomography; MRI: magnetic resonance imaging.

* Brain and neurovascular imaging, cardiac evaluation, and (for select patients) other laboratory tests.

¶ Indications for long-term oral anticoagulation include atrial fibrillation, ventricular thrombus, mechanical heart valve, and treatment of venous thromboembolism.

Δ "Large" infarcts are defined as those that involve more than one-third of the middle cerebral artery territory or more than one-half of the posterior cerebral artery territory based upon neuroimaging with CT or MRI. Though less reliable, large infarct size can also be defined clinically (eg, NIHSS score >15).

◇ Long-term aspirin therapy is alternative (though less effective) if OA contraindicated or refused.

§ Direct oral anticoagulant agents have a more rapid anticoagulant effect than warfarin, a factor that may influence the choice of agent and timing of OA initiation.

¥ Some experts prefer DAPT, based upon observational evidence.

‡ Long-term single-agent antiplatelet therapy for secondary stroke prevention with aspirin, clopidogrel, or aspirin-extended-release dipyridamole.

Summary

- Hold antithrombic medications for at least 24 hours after thrombolytic therapy
- Start aspirin within 48 hours for patients who received a thrombolytic
- For patients who do not receive thrombolytic therapy, antithrombotic medications may be started immediately
- Dysphagia screening should be performed prior to administration of oral medications
- Choice of antithrombotic medication is based on the underlying cause of stroke
  - Anticoagulation for cardioembolic strokes
  - Antiplatelet therapy for noncardioembolic strokes
- DAPT is indicated in mild ischemic strokes and high-risk TIAs

Questions?

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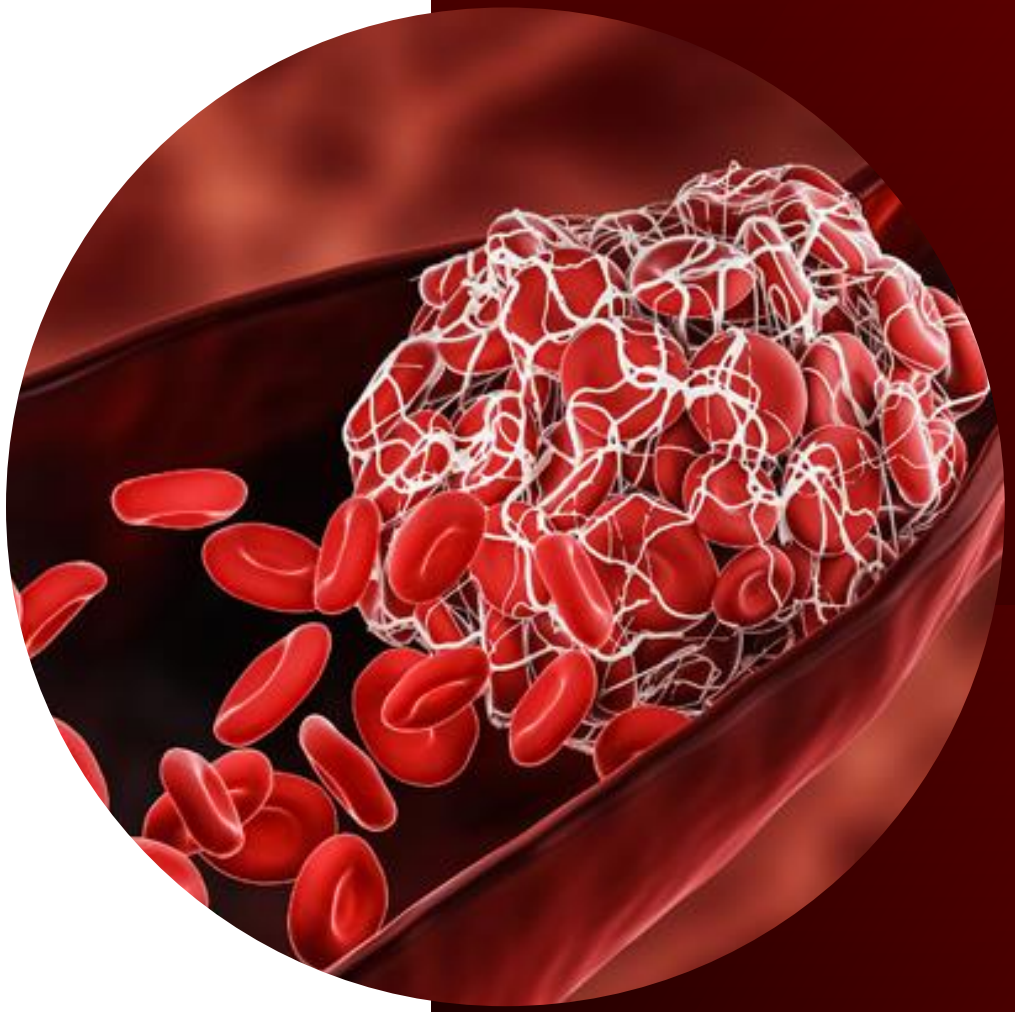

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