جامعة بيرزيت
BIRZEIT UNIVERSITY

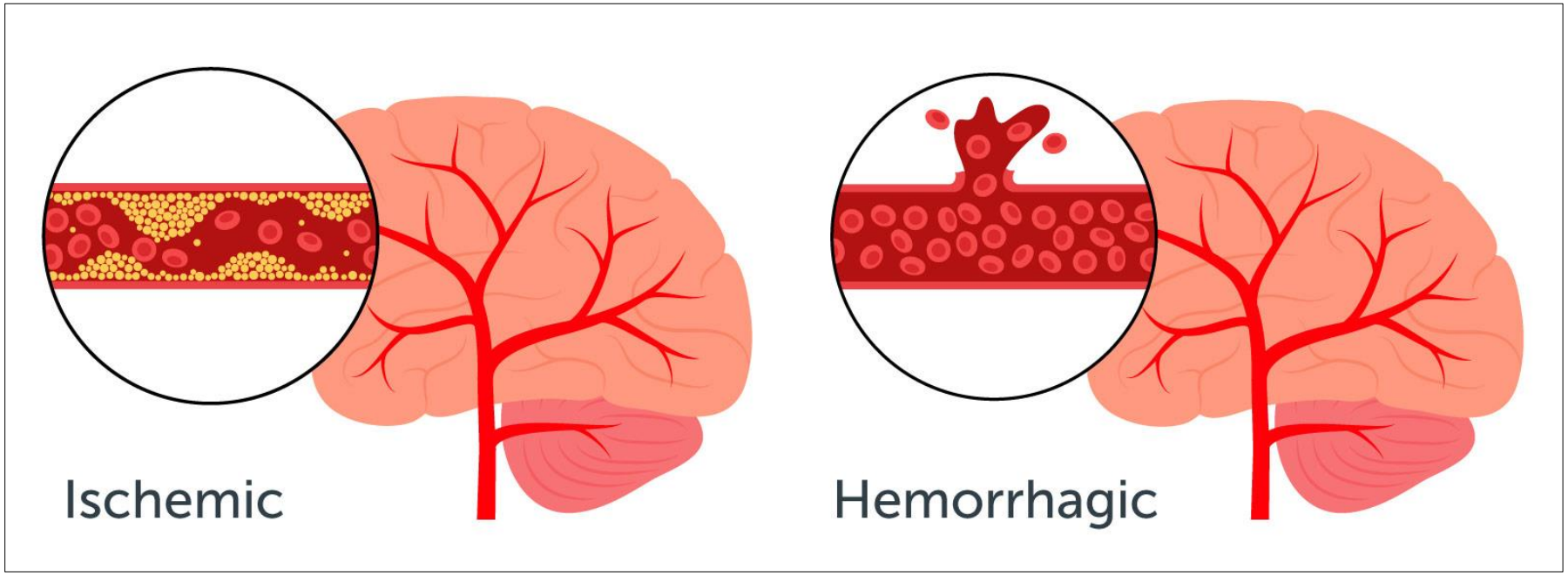
Stroke

11/03/2025

BADER REMAWI

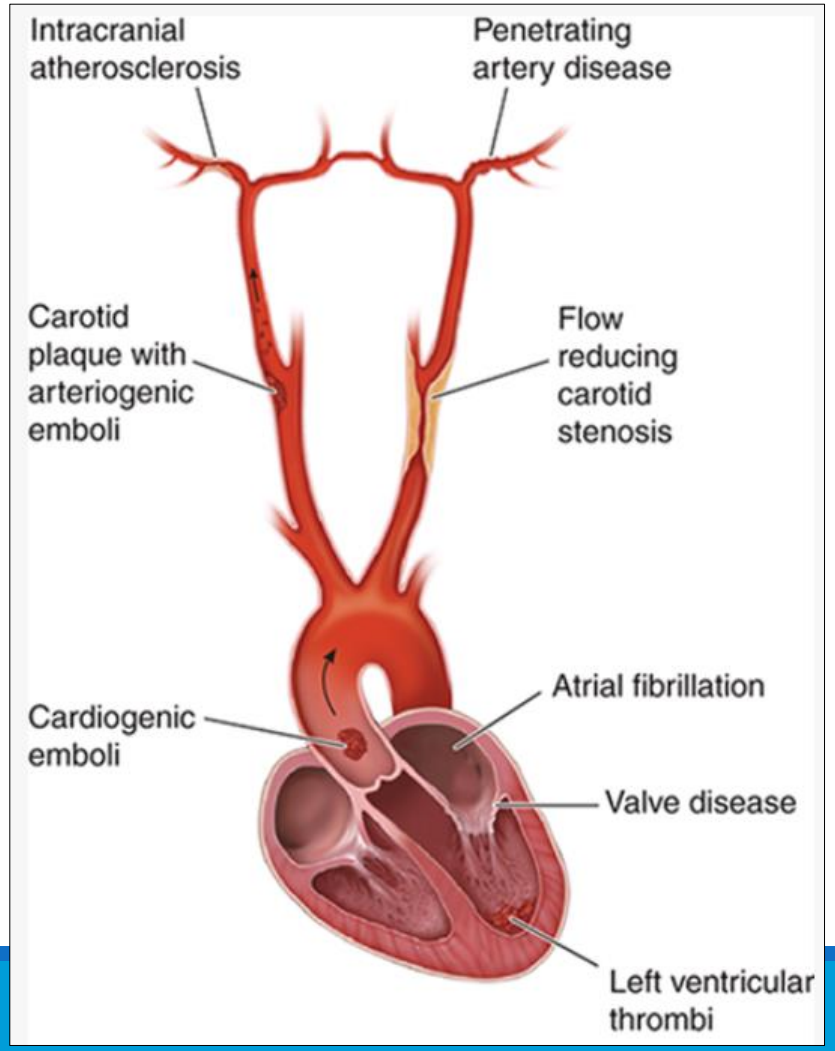
Etiology/Pathophysiology

- Ischemic stroke (87%)
- Hemorrhagic stroke (13%)



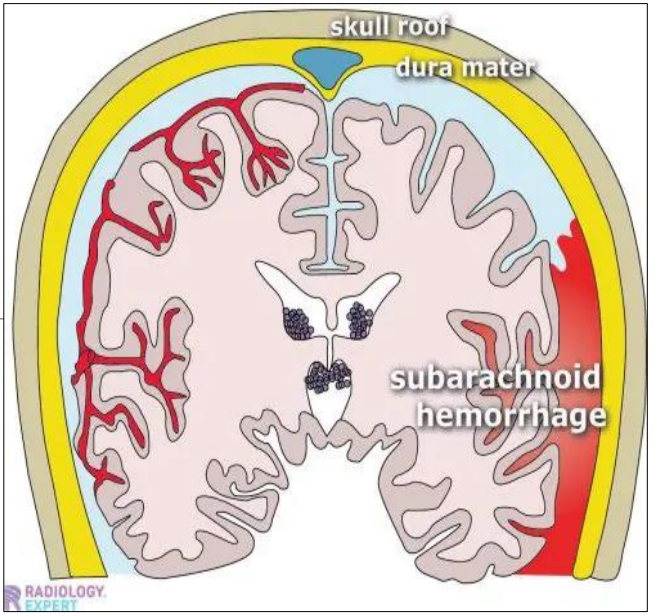
Etiology/Pathophysiology
Ischemic stroke

- In situ thrombosis of an intracranial vessel, typically affecting small penetrating arteries
- Hypoperfusion caused by flow-limiting stenosis of a major extracranial artery
- Occlusion of an intracranial vessel by an embolus arising from a distant site
  - Cardiogenic (atrial fibrillation…): ~ 25% of ischemic stroke cases
  - Non-cardiogenic

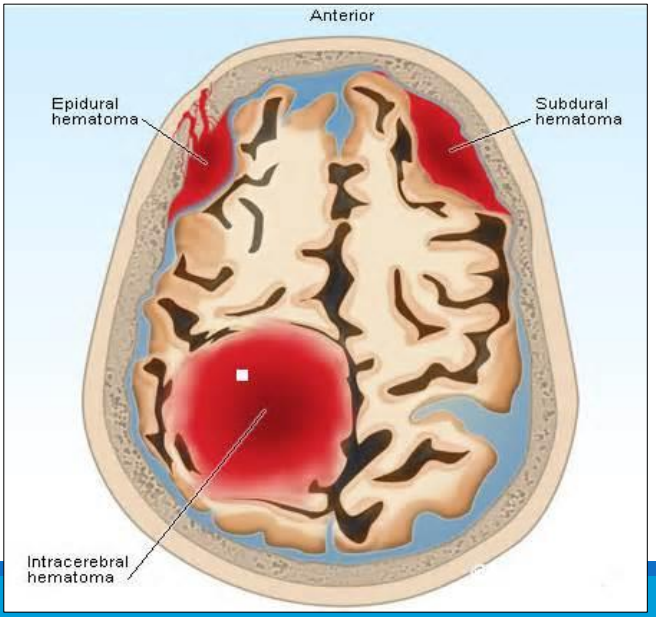


Etiology/Pathophysiology
Hemorrhagic stroke

- **Subarachnoid hemorrhage (SAH)**
  - Blood enters the subarachnoid space
  - Causes: trauma, rupture of intracerebral aneurysm…

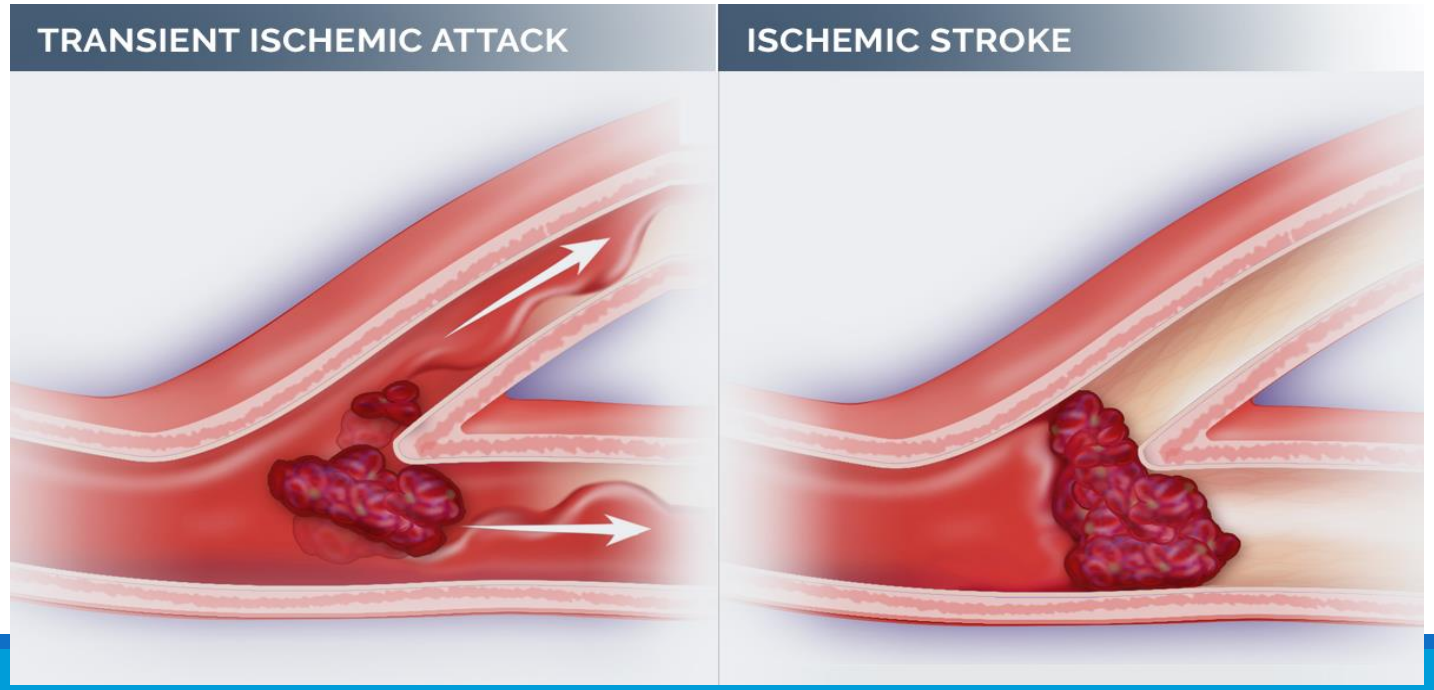


- **Intracerebral hemorrhage (ICH)**
  - Bleeding in the brain parenchyma itself (hematoma formation within the brain)
  - Causes: Uncontrolled HTN (most common), antithrombotic therapy…



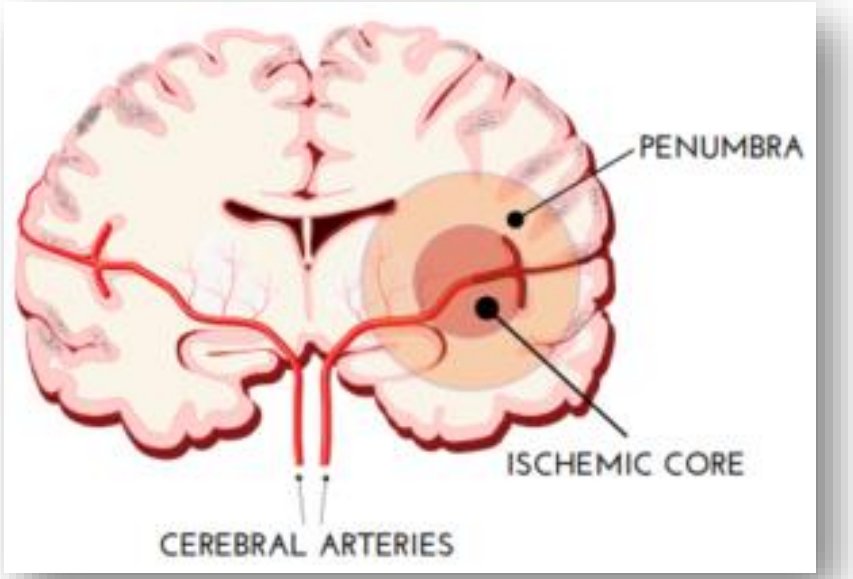
Etiology/Pathophysiology
Stroke vs TIA

- **Stroke**: an episode of neurologic dysfunction caused by focal cerebral infarction
- **Transient ischemic attack (TIA)**: the syndrome of arterial ischemia with transient symptoms (< 24 hours) and without evidence of cerebral infarction

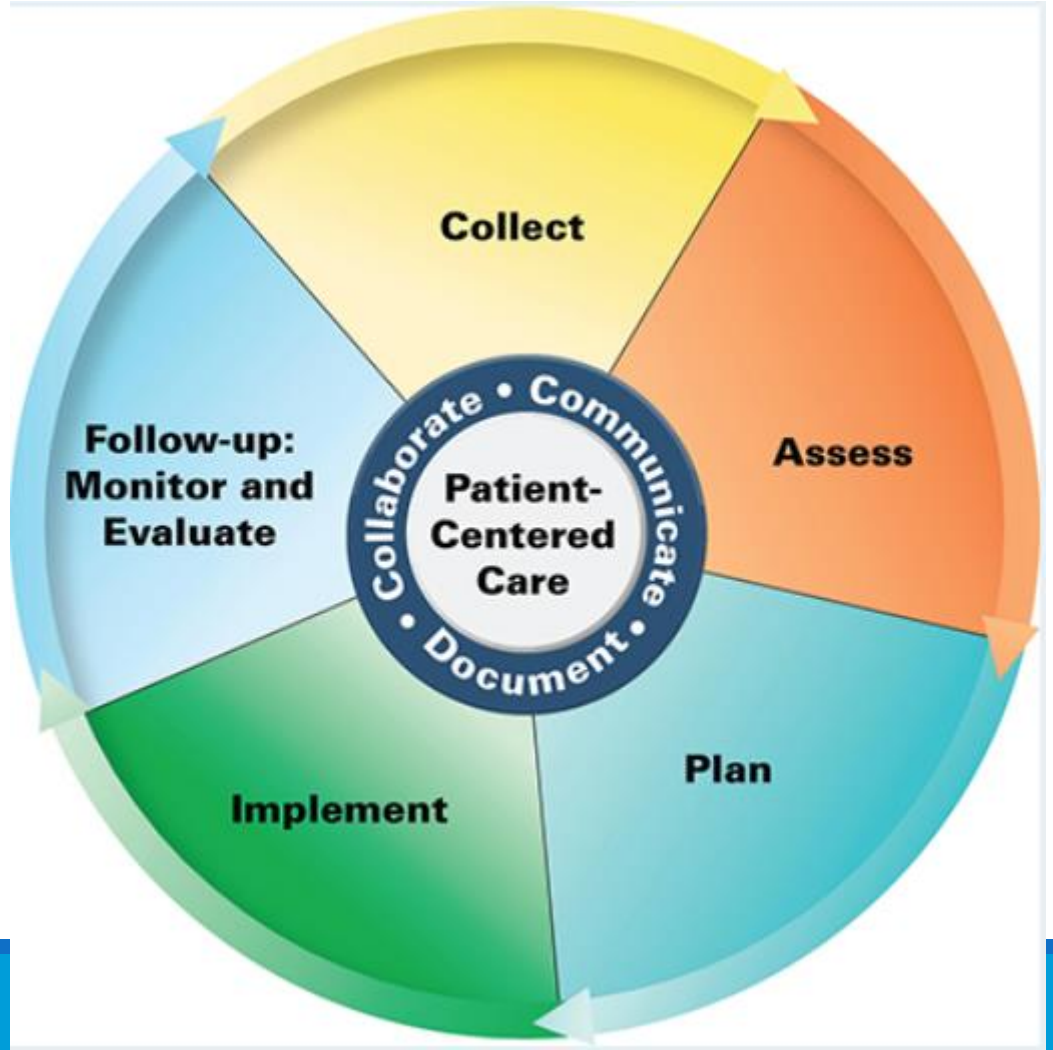


Etiology/Pathophysiology
Penumbra

- An ischemic tissue, surrounding a core area of the infarct, that may maintain membrane integrity
- Reversibly injured brain tissue
- Potentially salvageable with urgent pharmacologic and endovascular interventions



Patient care process



Patient care process

Collect

- Patient characteristics (eg, age, sex, race)
- Patient medical history (personal and family)
- Social history (eg, tobacco/ethanol use)
- Current medications including nonprescription aspirin/nonsteroidal anti-inflammatory drug (NSAID) use, herbal products, dietary supplements, and prior antiplatelet and anticoagulant medication use
- Medication allergies
- Symptoms (time of onset, duration)
- Objective data
  - Blood pressure (BP), heart rate, respiratory rate, height, weight
  - Labs including hemoglobin, platelets, serum creatinine, activated partial thromboplastin time (aPTT), prothrombin time, blood glucose, troponin
  - Noncontrast computed tomography (CT) scan, magnetic resonance imaging (MRI), and/or computed tomography angiography (CTA) may be needed
  - Neurologic examination (eg, National Institutes of Health Stroke Scale [NIHSS] score)
  - Electrocardiogram (ECG) and, in some patients, transthoracic echocardiogram (TTE)

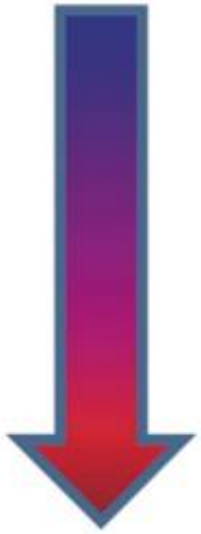
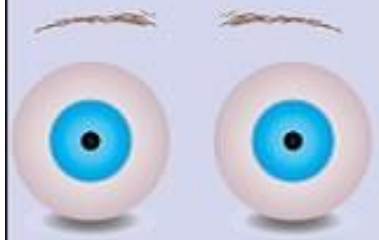
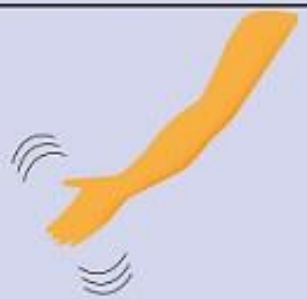
NIHSS SCORE	STROKE SEVERITY	IMPACTED BRAIN DENSITY
0	No Stroke	
0 – 4	Minor Stroke	
5 – 15	Moderate Stroke	
16– 20	Moderate to Severe Stroke	
21 - 42	Severe Stroke	

Figure 1. The National Institutes of Health Stroke Scale or NIH Stroke Scale (NIHSS) is a tool used by healthcare providers to objectively quantify and succinctly communicate the impairment caused by a stroke.

1a—Level of consciousness	0 = Alert; keenly responsive 1 = Not alert, but arousable by minor stimulation 2 = Not alert; requires repeated stimulation 3 = Unresponsive or responds only with reflex
1b—Level of consciousness questions: What is your age? What is the month?	0 = Answers two questions correctly 1 = Answers one question correctly 2 = Answers neither questions correctly
1c—Level of consciousness commands: Open and close your eyes Grip and release your hand	0 = Performs both tasks correctly 1 = Performs one task correctly 2 = Performs neither task correctly
2—Best gaze	0 = Normal 1 = Partial gaze palsy 2 = Forced deviation
3—Visual	0 = No visual lost 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia
4—Facial palsy	0 = Normal symmetric movements 1 = Minor paralysis 2 = Partial paralysis 3 = Complete paralysis of one or both sides
5—Motor arm Left arm Right arm	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
6—Motor leg Left leg Right leg	0 = No drift 1 = Drift 2 = Some effort against gravity 3 = No effort against gravity 4 = No movement
7—Limb ataxia	0 = Absent 1 = Present in one limb 2 = Present in two limbs
8—Sensory	0 = Normal; no sensory loss 1 = Mild-to-moderate sensory loss 2 = Severe-to-total sensory loss
9—Best language	0 = No aphasia; normal 1 = Mild-to-moderate aphasia 2 = Severe aphasia 3 = Mute; global aphasia
10—Dysarthria	0 = Normal 1 = Mild-to-moderate dysarthria 2 = Severe dysarthria
11—Extinction and inattention	0 = No abnormality 1 = Visual, tactile, auditory, spatial, or personal inattention 2 = Profound hemi-inattention or extinction
Score = 0–42	

- **Glasgow Coma Scale**
  - Minor brain injury: 13 – 15 points
  - Moderate brain injury: 9 – 12 points
  - Severe brain injury: 3 – 8 points

Behaviour	Response
 Eye Opening Response	4. Spontaneously 3. To speech 2. To pain 1. No response
 Verbal Response	5. Oriented to time, person and place 4. Confused 3. Inappropriate words 2. Incomprehensible sounds 1. No response
 Motor Response	6. Obeys command 5. Moves to localised pain 4. Flex to withdraw from pain 3. Abnormal flexion 2. Abnormal extension 1. No response

Patient care process

Assess

- Hemodynamic stability (eg, Diastolic blood pressure [DBP] <110 mm Hg, Systolic blood pressure [SBP] <185 mm Hg, if candidate for tissue plasminogen activator candidate; otherwise, BP less than 220/120 mm Hg; O_2-sat >94% [0.94]; temperature <38°C [100.4°F])
- Blood glucose (<60 mg/dL [3.7 mmol/L] or >180 mg/dL [10.0 mmol/L] should be treated)
- Presence of active bleeding and/or bleeding risk factors (Table 39-6)
- Patient's candidacy for tissue plasminogen activator treatment (Table 39-2) or thrombectomy
- Presence of dysphagia (swallowing disorder)

Patient care process

Plan

- Aspirin within 24 to 48 hours unless contraindicated; delay for 24 hours if the patient has been given tissue plasminogen activator
- Antiplatelet drug therapy regimen including specific medication(s), dose, frequency, and duration OR oral anticoagulant, if the patient has atrial fibrillation (see Table 39-2)
- Evaluation for carotid endarterectomy or carotid stenting
- Prophylaxis for venous thromboembolism, if immobile
- Nutritional plan; if the patient has dysphagia, nutrition via nasogastric tube or percutaneous gastrostomy tube
- Treat and manage stroke risk factors (Table 39-2) (eg, BP control, dyslipidemia, diabetes)
- Monitoring parameters including efficacy (eg, stroke symptoms) and safety (eg, signs and symptoms of bleeding [all antiplatelets and oral anticoagulants], headache [dipyridamole]); frequency and timing of follow-up
- Patient education (eg, the purpose of treatment, dietary and lifestyle modification, invasive procedures, drug-specific information, medication administration)
- Self-monitoring for stroke recurrence, the occurrence of bleeding, and when to seek emergency medical attention
- Referrals to other providers when appropriate (eg, physical therapist, occupational therapist, behavioral health, dietician)

Patient care process

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- Improvement of stroke symptoms; neurological examination
- Presence of adverse drug reactions (eg, bleeding [all medications], gastrointestinal upset [aspirin], headache [dipyridamole], cerebral edema, seizures)
- Patient adherence to treatment plan using multiple sources of information
- Adherence to recommended follow-up appointments (eg, neurology, physical therapy)
- Assess for poststroke depression

** Collaborate with patient, caregivers, and other healthcare professionals.*

Desired outcomes of treatment

- Primary prevention of ischemic stroke:
  - Aggressive management of modifiable, well-documented risk factors
  - Falls under *'Primary Prevention of ASCVD'*

- Goals of treatment of acute stroke:
  - Minimize the ongoing neurologic injury to reduce mortality and long-term disability
  - Prevent complications secondary to immobility and neurologic dysfunction
  - Prevent stroke recurrence (secondary prevention)

General approach to treatment

- Presumed acute stroke →
  - Urgent CT scan to identify the stroke type
  - TIA vs. Ischemic stroke vs. Hemorrhagic stroke

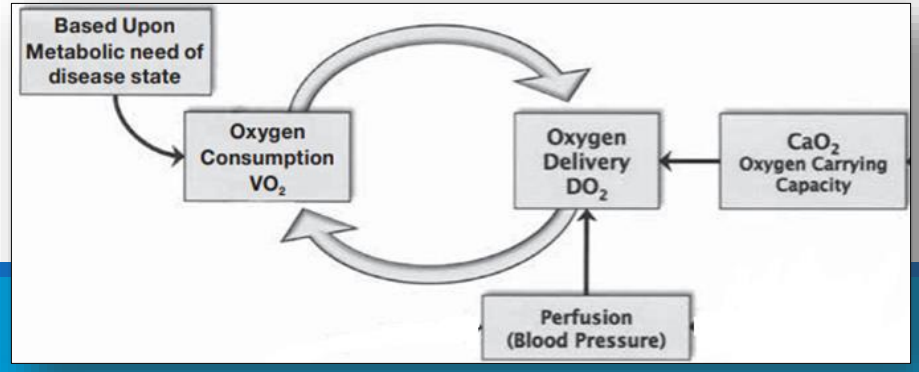
- TIA:
  - Urgent evaluation and intervention to reduce the risk of stroke
  - Risk of stroke is highest in the first few days after TIA

- Acute ischemic stroke:
  - *Hyperacute phase* (first 24 hours after stroke event) vs.
  - *Acute phase* (first week after stroke event)
  - Evaluate patients presenting within hours of symptom onset for pharmacologic and mechanical reperfusion therapy

- Intracerebral hemorrhage:
  - Evaluate patients for pharmacologic and mechanical interventions

Blood pressure target

- Stroke (ischemic or hemorrhagic) → Decreased blood flow to brain → Decreased O_2 delivery → Infarction
- To mitigate this, a compensatory increase in BP occurs to enhance blood flow and O_2 delivery to the brain
- **Permissive hypertension:** Allowing blood pressure to remain high for the first 48 - 72 hours of stroke onset
- Different BP targets:
  - Acute ischemic stroke in patients who are candidates for alteplase
  - Acute ischemic stroke in patients who are not candidates for alteplase (and have no specific comorbidities)
  - Acute ischemic stroke in patients who are not candidates for alteplase (and have specific comorbidities)
  - Acute ischemic stroke in patients who are not candidates for alteplase (and will undergo mechanical thrombectomy)
  - Intracerebral hemorrhage



Blood Pressure Treatment Guidelines in Stroke

Very high BP + (fibrinolytic, or specific comorbidities, or mechanical intervention, or ICH/SAH) → Danger!

Recommendation

Ischemic Stroke with Alteplase Treatment

- Pre-alteplase: lower BP to SBP <185 mm Hg and DBP <110 mm Hg
- Post-alteplase: maintain SBP <180 mm Hg and DBP <105 mm Hg for 24 hours

Ischemic Stroke Without Alteplase Treatment

- Treatment benefit uncertain/not recommended unless BP >220/120 mm Hg
- If comorbid conditions (eg, acute coronary event, acute heart failure, aortic dissection, PE, hypertensive encephalopathy preeclampsia/eclampsia) are present that require acute lowering of BP, lowering BP by 15% is probably safe)

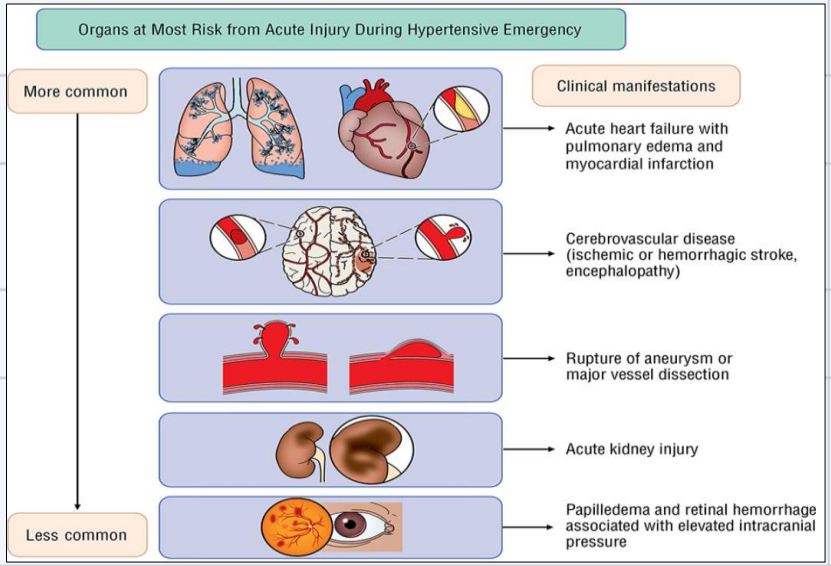
Ischemic Stroke with Mechanical Thrombectomy Without Fibrinolytic Treatment

- It is reasonable to maintain BP ≤185/110 mm Hg before the procedure

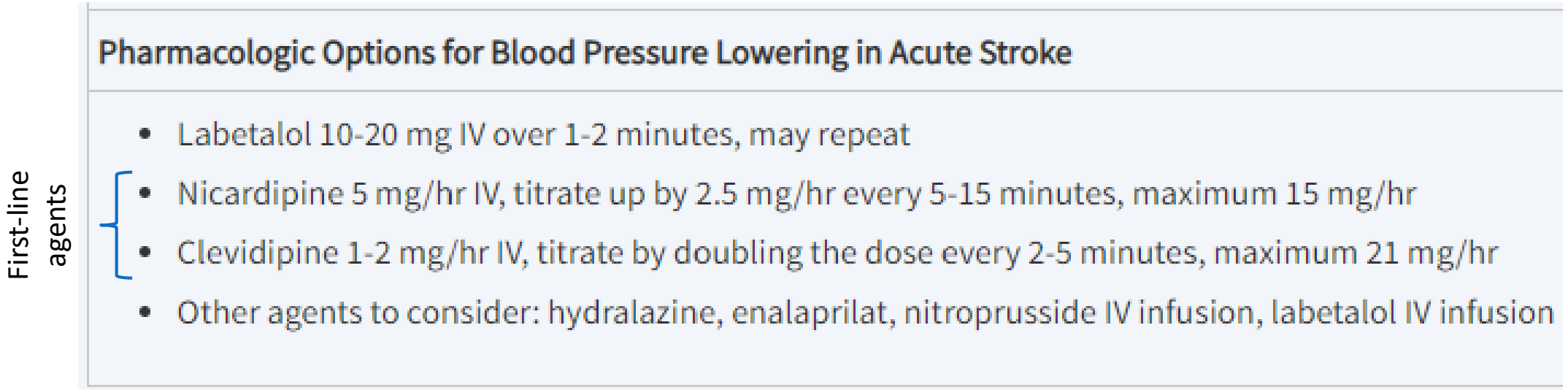
Intracranial Hemorrhage

- Treatment is reasonable for ICH patients with SBP >220 mm Hg
- For ICH patients with SBP 150-220 mm Hg, acute lowering of SBP to 140 mm Hg is safe

SAH due to aneurysm rupture, target SBP < 160 mm Hg



Blood pressure treatment



- Fast- and short-acting antihypertensives are preferred (labetalol, nicardipine, clevidipine…)
- Although patients with acute ischemic stroke commonly present with elevated or normal BP, they may present with hypotension and hypovolemia
  - Correct to maintain systemic perfusion and end organ function

Non-pharmacologic therapy
Ischemic stroke

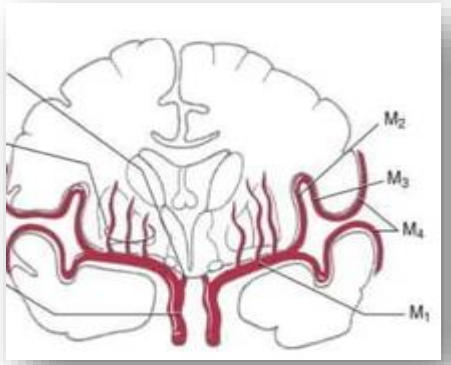
- Lifestyle modification:
  - Recommended for secondary stroke prevention
  - Diet modification (Mediterranean-type diet ‘whole grains, fruits, vegetables, seafood, beans, nuts’; reduce Na intake if HTN)
  - Exercise (consider mobility issues)
  - Smoking cessation/avoidance
  - Moderation of alcohol consumption (≤ 2 drinks/day for men; ≤ 1 drink/day for women)
  - Avoidance of stimulants (e.g. amphetamines, cocaine)

Non-pharmacologic therapy
Ischemic stroke

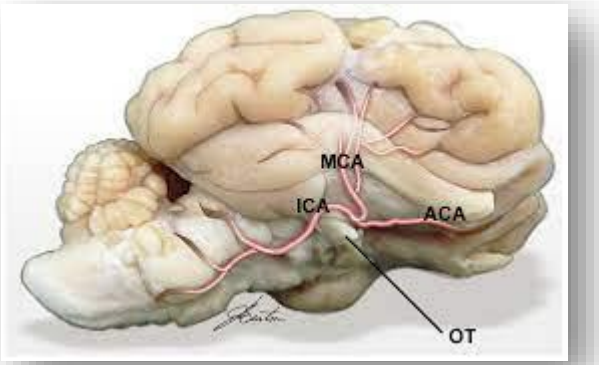
- Early rehabilitation:
  - Recommended for all ischemic stroke patients to reduce disability
- Temperature management:
  - Fever worsens outcomes in ischemic (and hemorrhagic) stroke
  - Identify the source of fever and management
  - Maintain normothermia
  - No evidence for induced hypothermia
- Endovascular and mechanical interventions:
  - Recommended by AHA/ASA to re-perfuse ischemic brain tissue
  - Mechanical thrombectomy
  - Decompressive hemicraniectomy
  - Carotid endarterectomy
  - Carotid stenting

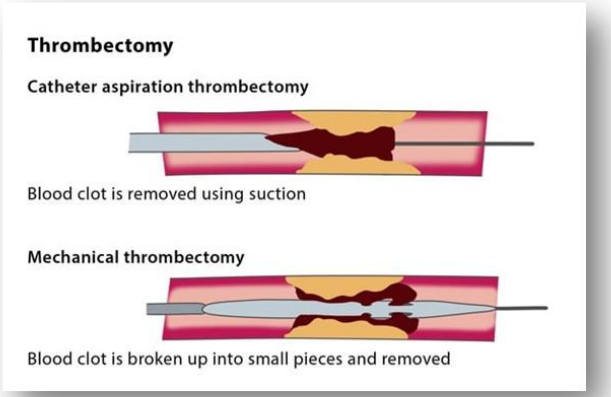
Non-pharmacologic therapy
Ischemic stroke: **Mechanical thrombectomy**

- Indications:
  - ***Anterior circulation arterial occlusion*** in the ICA or the M1 segment of the MCA within 6 hours of symptom onset *(strong recommendation)*
  - ***Anterior circulation arterial occlusion*** in the ICA or the M1 segment of the MCA within 24 hours of symptom onset if a penumbra is present *(may be considered)*
  - ***Posterior circulation arterial occlusion?*** *(case-by-case; less clear benefit)*



ICA: Internal Carotid Artery
MCA: Middle Cerebral Artery



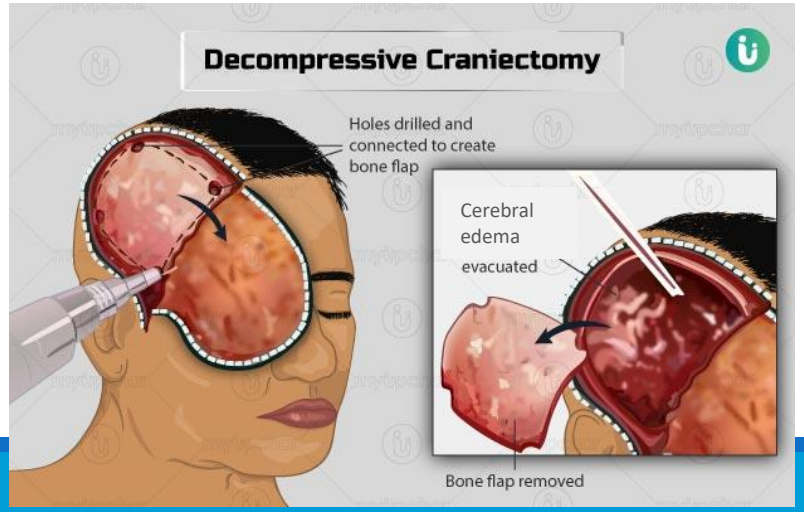


Non-pharmacologic therapy
Ischemic stroke: **Decompressive hemicraniectomy**

- Ischemic stroke → BBB disruption → increased capillary permeability → cerebral edema → increased ICP → neurological complications

- Decompressive hemicraniectomy: Surgical removal of a piece of skull to reduce ICP

- <u>Indications</u>:
  - Patients < 60 years with unilateral MCA infarcts and significant cerebral edema
  - Can be considered in patients > 60 years *(less clear benefit)*
  - Cerebellar infarction and significant swelling

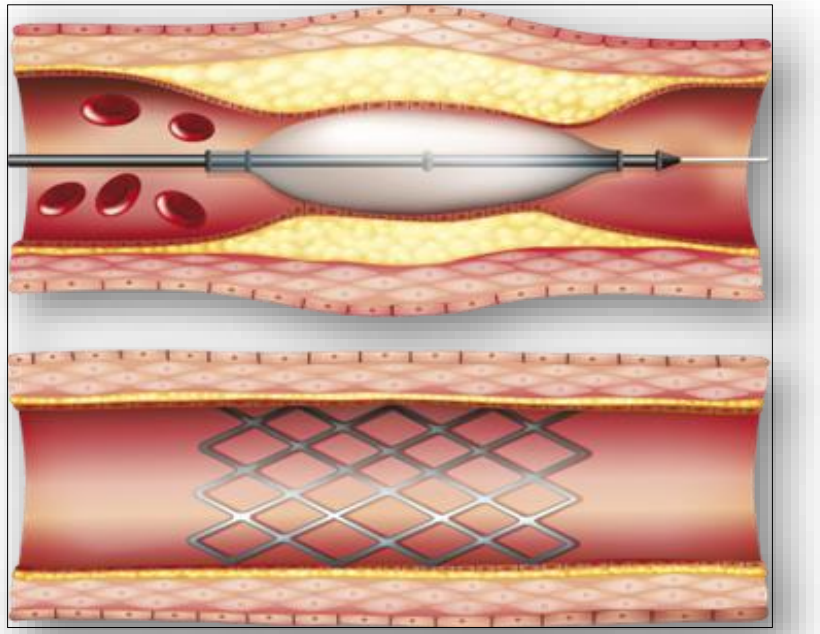


Non-pharmacologic therapy
Ischemic stroke: **Carotid endarterectomy**

- Indications:
  - Secondary prevention of ischemic stroke in patients with 70% - 99% carotid artery stenosis

Non-pharmacologic therapy
Ischemic stroke: **Carotid stenting**

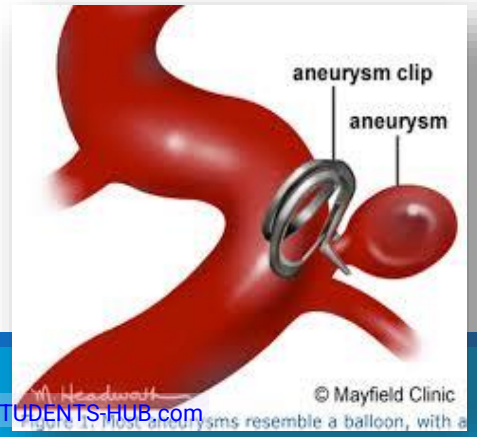
- Indications:
  - Secondary prevention of ischemic stroke when combined with aspirin and clopidogrel (less invasive)

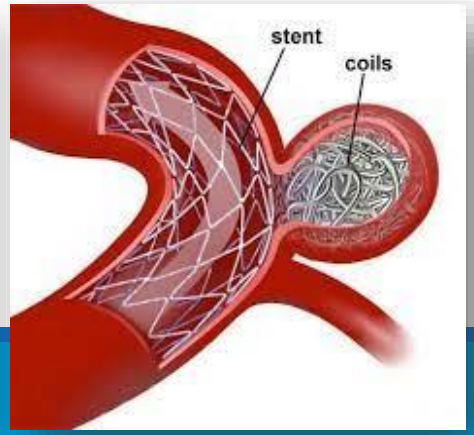


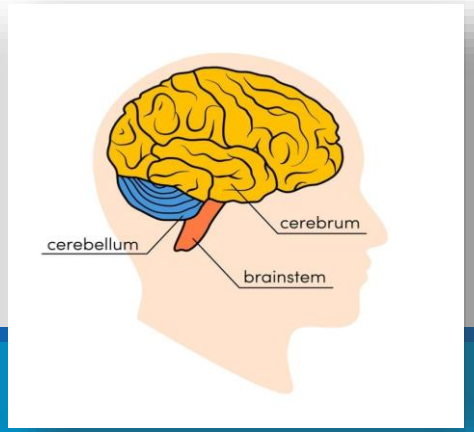
Non-pharmacologic therapy
Hemorrhagic stroke

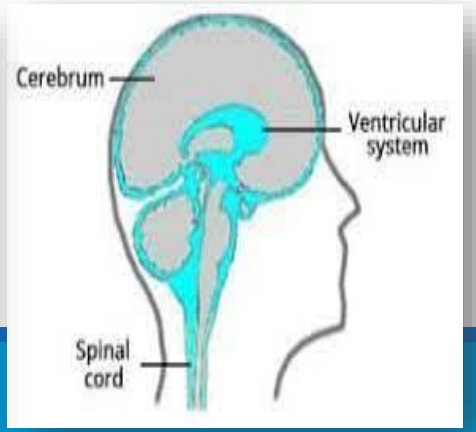
- Temperature management (as in ischemic stroke)
- Surgical clipping or Endovascular coiling indications:
  - To reduce re-bleeding risk in SAH
- Surgical hematoma evacuation (e.g. craniectomy) indications:
  - Cerebellar ICH + (neurologic deterioration, brainstem compression, &/or hydrocephalus from ventricular obstruction)
  - Cerebral ICH *(less clear benefit)*
- Extra-ventricular drainage:
  - Hydrocephalus causing decreased consciousness

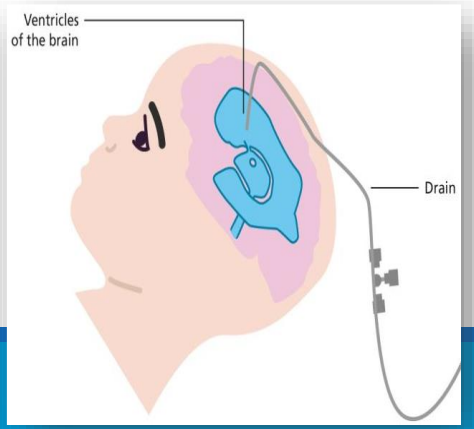
Hydrocephalus: Excess CSF in brain ventricles











Pharmacologic therapy
Ischemic stroke

- Stroke council of the American Stroke Association (ASA) guidelines

- Class (strength) of recommendation:
  - Class I: strong
  - Class IIa: moderate
  - Class IIb: weak
  - Class III: no benefit
  - Class 3: harm

- Level (quality) of evidence:
  - A: high-quality evidence from RCTs, or MA of RCTs
  - B-R (randomized): moderate-quality evidence from RCTs, or MA of RCTs
  - B-NR (non-randomized): moderate-quality evidence from non-randomized trials, observational studies, or MA of such studies
  - C-LD (limited data): randomized or nonrandomized observational studies with limitations of study design, or MA of such studies
  - C-EO (expert opinion): consensus based on clinical experience

Pharmacologic therapy
Ischemic stroke: **Acute treatment**

- The only two pharmacologic agents with ‘Class I’ recommendations:
  - Alteplase initiated within 3 to 4.5 hours of stroke onset
  - Aspirin LD started within 24 to 48 hours of stroke onset

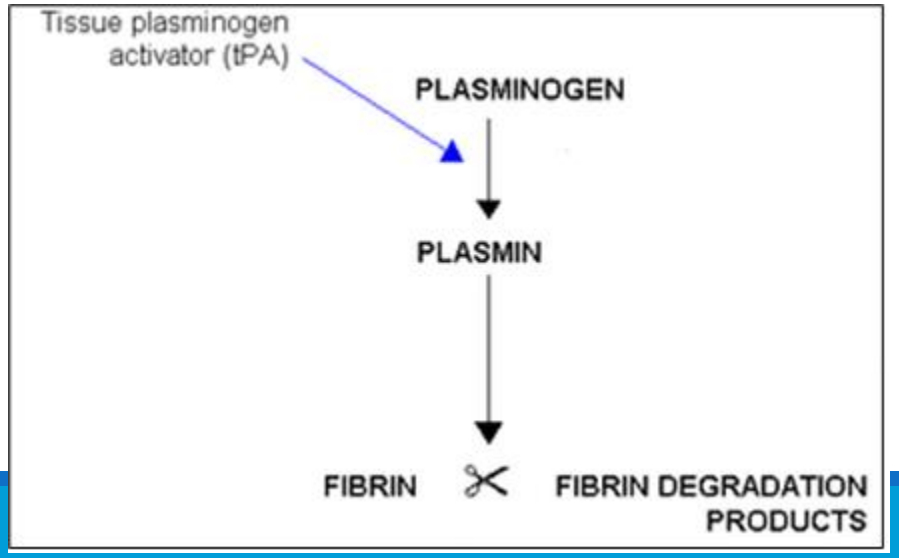
Acute Treatment of Ischemic Stroke[7]		
Recommendation	**Class (Strength) of Recommendation[a]**	**Level (Quality) of Evidence[b]**
Alteplase 0.9 mg/kg IV (maximum 90 mg), 10% as a bolus with the remainder given over 1 hour in selected patients		
• Within 3 hours of onset	I	A
• Between 3 and 4.5 hours of onset	I	B-R
Tenecteplase 0.25 mg/kg IV bolus (maximum 25 mg) may be a reasonable alternative to alteplase for patients who are also eligible to undergo mechanical thrombectomy	IIb	B-R
Tenecteplase 0.4 mg/kg IV bolus (maximum 40 mg) has not been proved to be superior or non-inferior to alteplase but may be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion	IIb	B-R
Aspirin 160-325 mg daily started within 48 hours of onset	I	A
Aspirin 81 mg daily and clopidogrel 75 mg daily for 21 days may be effective in reducing recurrent stroke in patients who do not receive IV alteplase and present with minor, non-cardioembolic stroke (NIHSS ≤ 3)	I	A
Ticagrelor is not recommended over aspirin for treatment of patients with minor acute stroke	III	B-R

Pharmacologic therapy
Ischemic stroke: **Acute treatment (Alteplase)**

- Early pharmacologic reperfusion with IV alteplase:
  - Mainstay of acute pharmacologic treatment
  - Improves the functional ability after ischemic stroke
  - Within 3 - 4.5 hours of symptom onset
  - Prioritize early administration; possibly diminished alteplase benefit in severe stroke

- MOA:
  - Alteplase = recombinant tissue plasminogen activator (rt-PA)
  - Fibrinolytic
  - Binds fibrin + Facilitates conversion of plasminogen to plasmin → Degradation of fibrin clots

- PK/PD:
  - Short half-life (~ 4 minutes)



Pharmacologic therapy
Ischemic stroke: **Acute treatment (Alteplase)**

- Alteplase use is associated with high bleeding risk (including ICH)

- Guideline-recommended protocol (for a positive outcome and minimal risk):
  - Stroke team activation
  - Brain imaging study (e.g. CT scan)
  - Treatment as early as possible (within 4.5 hours of symptom onset)
  - Meeting inclusion and exclusion criteria for alteplase use
  - Administration of alteplase 0.9 mg/kg total dose (maximum 90 mg):
    - 10% as an IV bolus over 1 minute
    - 90% as an IV infusion over 1 hour
  - Avoidance of antithrombotic therapy (anticoagulant or antiplatelet) for 24 hours after alteplase
  - Close patient monitoring for BP, neurologic status, and hemorrhage

- Endovascular intervention (e.g. mechanical thrombectomy) is not a contraindication to alteplase

Inclusion and Exclusion Criteria for Alteplase Use in Acute Ischemic Stroke

Inclusion Criteria
• Age ≥18 years • Clinical diagnosis of ischemic stroke with neurologic deficit • Time of symptom onset well established to be <4.5 hours from treatment initiation
Contraindications
• History of intracranial hemorrhage • History of ischemic stroke within prior 3 months • Symptoms/imaging consistent with subarachnoid hemorrhage or acute intracerebral hemorrhage • Current use of direct thrombin inhibitors or direct factor Xa inhibitors in prior 48 hours • Use of treatment-dose low molecular weight heparin in prior 24 hours • Infective endocarditis • Intra-axial, intracranial neoplasm • Aortic arch dissection • Active internal bleeding or coagulopathy (platelets <100,000/mm^3 [100×10^9/L], INR>1.7, aPTT>40s, PT>15s) • Severe head trauma in prior 3 months • Gastrointestinal malignancy or bleeding within prior 21 days
Warnings/Use Clinical Judgment
• Unruptured/unsecured AVM or aneurysm >10 mm • Major surgery or nonhead trauma • History of bleeding diathesis • Extensive regions of clear hypoattenuation on initial CT scan

Pharmacologic therapy
Ischemic stroke: **Acute treatment (Tenecteplase)**

- A modified form of alteplase

- Tenecteplase vs Alteplase:
  - Higher degree of fibrin specificity
  - Longer half-life
  - Can be administered as a single, rapid IV bolus dose
  - Off-label use for ischemic stroke (though FDA-approved for acute STEMI)

Pharmacologic therapy
Ischemic stroke: **Acute treatment (Aspirin)**

- Early aspirin therapy:
  - Within 24 - 48 hours of symptom onset
  - Should be given in the absence of ASA allergy or contraindications
  - Reduces the long-term risk of death and disability

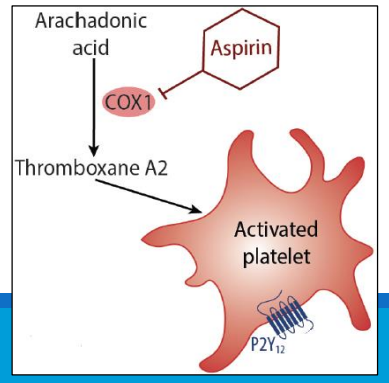
- For patients receiving alteplase:
  - Withhold aspirin (and other antithrombotics) for 24 hours after alteplase administration to reduce hemorrhage risk

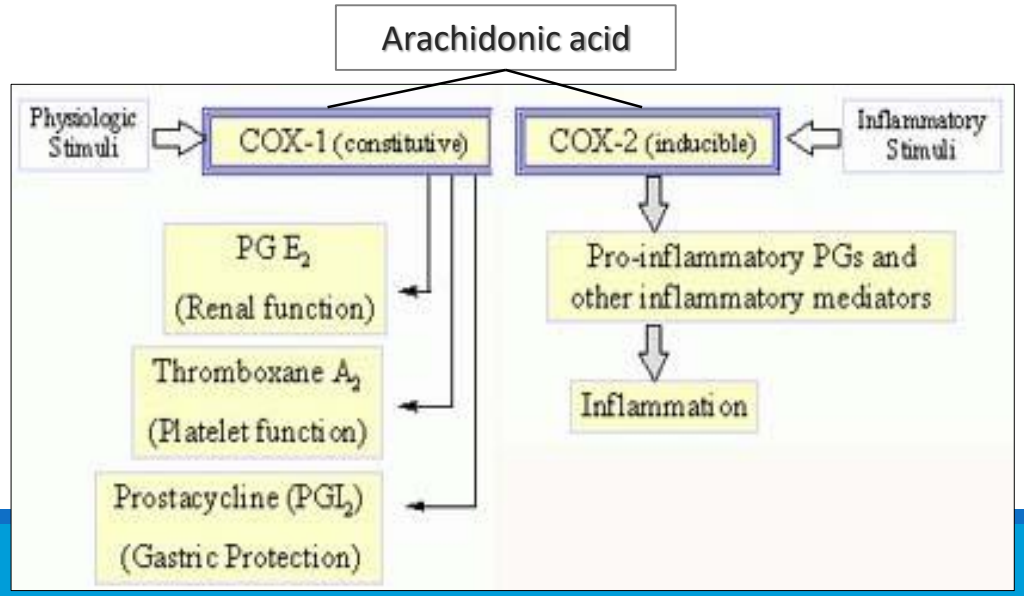
- Non-aspirin antiplatelets:
  - Limited data in the acute phase of ischemic stroke (except some combination therapy regimens)
  - Reasonable in patients having severe ASA allergy or contraindications

Pharmacologic therapy
Ischemic stroke: **Acute treatment (Aspirin)**

- MOA:
  - Antiplatelet
  - Irreversible inhibition of platelet COX-1 →
  - Preventing the conversion of Arachidonic acid to TXA2 (vasoconstrictor, platelet aggregation)

- Dose-dependent pharmacologic effect:
  - Minimum effective dose ~ 50 - 75 mg/day
  - Low doses: ASA selectively inhibits COX-1
  - High doses: ASA may also inhibit COX-2





Pharmacologic therapy
Ischemic stroke: **Acute treatment (Aspirin)**

- PK/PD:
  - Onset of antiplatelet effect < 60 minutes
  - Platelets remain impaired for their life span after ASA exposure '5 - 7 days' (anuclear; cannot synthesize new COX)

- Dose-dependent toxic effects:
  - Upper limit of ASA dose: 300 mg - 325 mg
  - Upper GI discomfort and bleeding (most common adverse effects of ASA)
  - Major bleeding (increases with age)

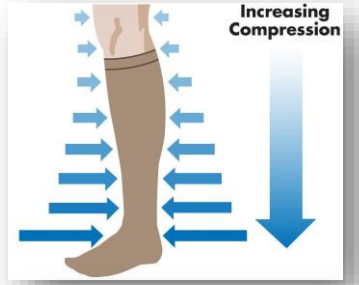
- Aspirin resistance:
  - High on-treatment platelet reactivity
  - Higher doses (or BID dosing) are required to achieve antiplatelet effect
  - Contributing factors: aging, diabetes, hyperlipidemia, smoking, CKD, drug-drug interactions (e.g. NSAIDs), genetic polymorphisms (influencing the activity of COX-1, COX-2, GP IIb/IIIa receptors, ADP receptors)
  - ASA resistance → Worse outcomes in stroke (still, routine testing is not recommended)

Pharmacologic therapy
Ischemic stroke: **Acute treatment (Anticoagulants)**

- Anticoagulants are not routinely recommended in the early phase of acute ischemic stroke
  - e.g. UFH, LMWH
  - Limited clinical benefit

- Anticoagulants may be given for non-stroke indications (e.g. VTE prophylaxis/treatment) in patients with stroke
  - Benefit of anticoagulants vs. Risk of hemorrhagic conversion
  - Acute ischemic stroke → Hemorrhagic stroke

- <u>Immobile patients after stroke should receive</u>:
  - Pharmacologic VTE prophylaxis, or
  - Mechanical VTE prophylaxis
    - e.g. Graduated compression stockings, Intermittent pneumatic compression devices



Pharmacologic therapy
Ischemic stroke: **Secondary prevention**

- Oral antiplatelet therapy:
  - Recommended in non-cardioembolic strokes
  - Aspirin, extended-release dipyridamole plus low-dose aspirin, clopidogrel, ticagrelor

- Oral anticoagulation therapy:
  - Recommended in cardioembolic strokes (atrial fibrillation)
  - Dabigatran, apixaban, edoxaban, rivaroxaban, warfarin

- Other recommended pharmacotherapy:
  - Antilipemic/statin therapy
  - Antihypertensive therapy
  - Antidiabetic therapy

Secondary Prevention of Ischemic Stroke			
Stroke Etiology	**Recommendation**	**Class (Strength) of Recommendation[a]**	**Level (Quality) of Evidence[b]**
Noncardioembolic	Antiplatelet therapy[7]		
	• Aspirin 50-325 mg daily	I	A
	• Aspirin 25 mg + extended-release dipyridamole 200 mg twice daily	I	A
	• Clopidogrel 75 mg daily	I	A
Cardioembolic (especially atrial fibrillation)	Anticoagulant therapy[7]		
	• Vitamin K antagonist (warfarin) (INR = 2-3)	I	A
	• Apixaban 5 mg twice daily	I	A
	• Dabigatran 150 mg twice daily	I	A
	• Edoxaban 60 mg daily	I	A
	• Rivaroxaban 20 mg daily	I	A
Atrial fibrillation without moderate to severe mitral stenosis or a mechanical heart valve	Apixaban, dabigatran, endoxaban, or rivaroxaban is preferred over warfarin	I	B-R

Very high risk: ≥ 2 major ASCVD events; OR 1 major ASCVD event + ≥ 2 high-risk conditions

Major ASCVD events: hx of ischemic stroke; ACS within the past 12 months; hx of MI; symptomatic PAD

High-risk conditions: ≥ 65 years; heterozygous FH; hx of CABG or PCI; diabetes; HTN; CKD; current smoking

Risk Factor	Recommendation[10]	Class (Strength) of Recommendation[a]	Level (Quality) of Evidence[b]
LDL cholesterol > 100 mg/dL (2.59 mmol/L) with no known coronary heart disease, and no major cardiac sources of embolism	Atorvastatin 80 mg daily	I	A
Patients with atherosclerotic disease – high risk/Very high risk	Statins and ezetimibe, if needed; goal LDL cholesterol <70 mg/dL (1.81 mmol/L)	I	A
Very high risk (stroke + another major ASCVD or stroke + multiple high-risk conditions)[c] already taking statins at maximally tolerated dose and ezetimibe, but who still have LDL-cholesterol >70 mg/dL (1.81 mmol/L)	Proprotein convertase subtilisin/kexin type 9 inhibitor therapy	IIa	B-NR
Fasting triglycerides 135-499 mg/dL (1.53 - 5.64 mmol/L) and LDL cholesterol 41-100 mg/dL (1.06-2.59 mmol/L) who are on moderate- or high-intensity statin therapy, with HbA1c <10% (86 mmol/mol), and no history of pancreatitis, atrial fibrillation, or severe heart failure	Icoaspent ethyl 2 g twice daily	IIa	B-R
Fasting triglycerides ≥ 500 mg/dL (5.65 mmol/L)	Identify and address causes of hypertriglyceridemia; implement a very low-fat diet, avoid refined carbohydrates and alcohol; omega-3 fatty acids; fibrate therapy, if needed to prevent acute pancreatitis	IIa	B-NR

Risk Factor	Recommendation[10]	Class (Strength) of Recommendation[a]	Level (Quality) of Evidence[b]
BP >130/80	BP reduction, goal <130/80 mm Hg	I	B-R
Patients who smoke	Smoking cessation with or without drug therapy	I	A
Men who drink > 2 alcoholic drinks per day or women who drink > 1 alcoholic drink per day	Reduce or eliminate alcohol consumption	I	B-NR
Patients who use stimulants and patients with infective endocarditis in the context of intravenous drug use	Cessation of use of substance	I	C-EO
Diabetes - treatment goal	Goal HbA1c ≤7% (53 mmol/mol)	I	A
Diabetes - drug therapy selection	Treatment with glucose-lowering agents with proven cardiovascular benefit (metformin + GLP1 receptor agonist therapy or sodium-glucose cotransporter 2 inhibitor) regardless of baseline HbA1C	I	B-R
Prediabetes, particularly with BMI ≥35 kg/m^2, <60 years, women with a history of gestational diabetes	Metformin 850 mg twice daily	IIb	B-R

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (Antiplatelets)**

- All patients who had acute ischemic stroke or TIA should receive long-term antithrombotic therapy
  - Non-cardioembolic stroke → Antiplatelets

- First-line antiplatelet: Aspirin
  - Has the most data supporting its use
  - Patients already taking ASA at the time of non-cardioemoblic ischemic stroke or TIA → Increasing ASA dose is not more effective at preventing additional strokes

- Alternative first-line antiplatelets:
  - Clopidogrel
  - Extended-release dipyridamole plus low-dose aspirin

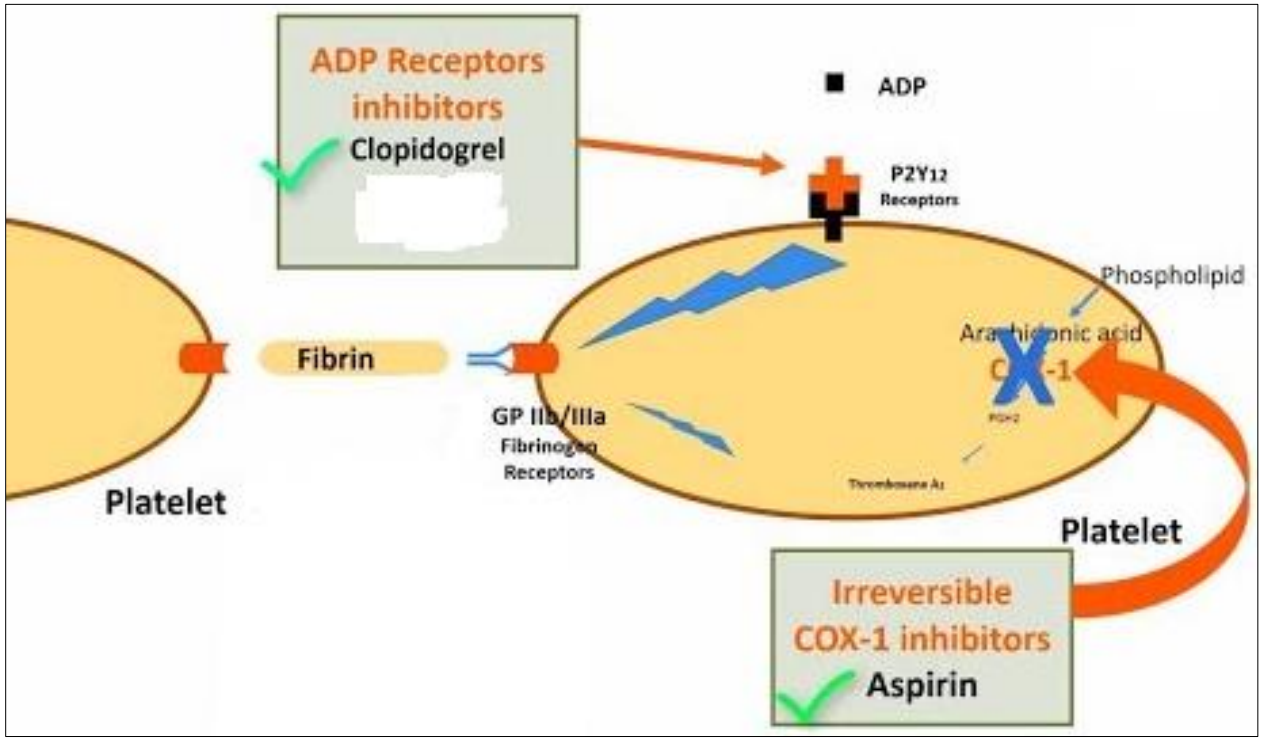
- Off-label antiplatelet: Ticagrelor

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (Clopidogrel)**

- MOA:
  - $P2Y_{12}$ (ADP) receptor antagonist (irreversible blockage) →
  - Prevent activation of GP IIb/IIIa receptors →
  - Inhibiting platelet aggregation

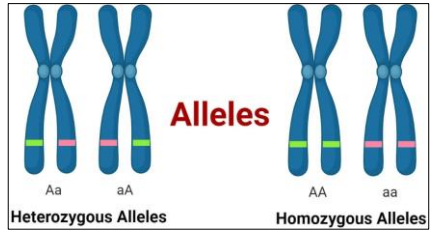
- PK/PD:
  - Maximal antiplatelet effect is delayed for 3 - 7 days
  - Platelets remain impaired for their life span after Clopidogrel exposure (7 - 10 days)

- ADRs:
  - GI bleeding, diarrhea, rash



Pharmacologic therapy
Ischemic stroke: **Secondary prevention (Clopidogrel)**

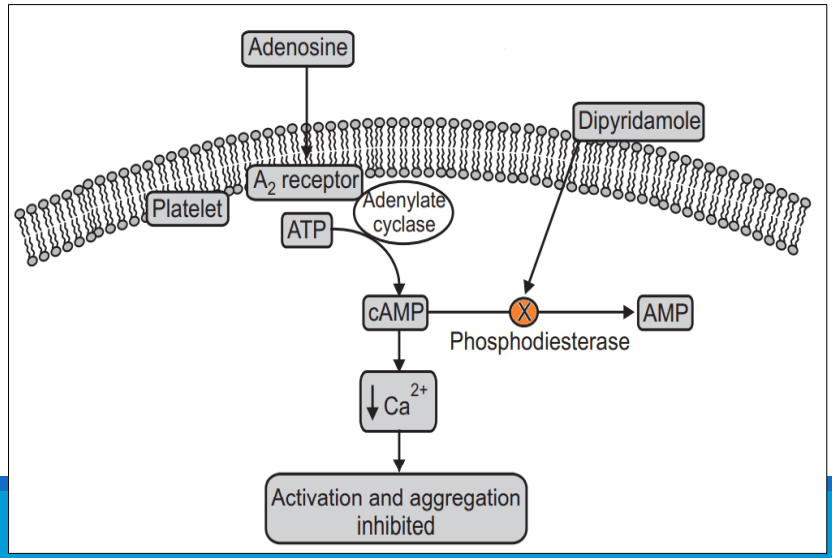
- Clopidogrel is a prodrug:
  - Requires activation by CYP2C19 enzyme
  - Polymorphisms of the alleles encoding for CYP2C19
    - Allele *17 → Increased metabolism
    - Allele *2, Allele *3 → Decreased metabolism
  - Poor metabolizers (two copies of *2 or *3, or one copy of each) → Diminished antiplatelet activity
  - AHA/ASA guidelines do not suggest pharmacogenetic testing prior to using clopidogrel



- Drug-Drug interactions:
  - CYP2C19 inhibitors → Diminished antiplatelet activity
    - e.g. omeprazole, esomeprazole (avoid in patients taking clopidogrel)
  - Opioids slow gastric emptying → Delay & decrease Clopidogrel absorption → Diminished antiplatelet activity

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (ER-DP+ASA)**

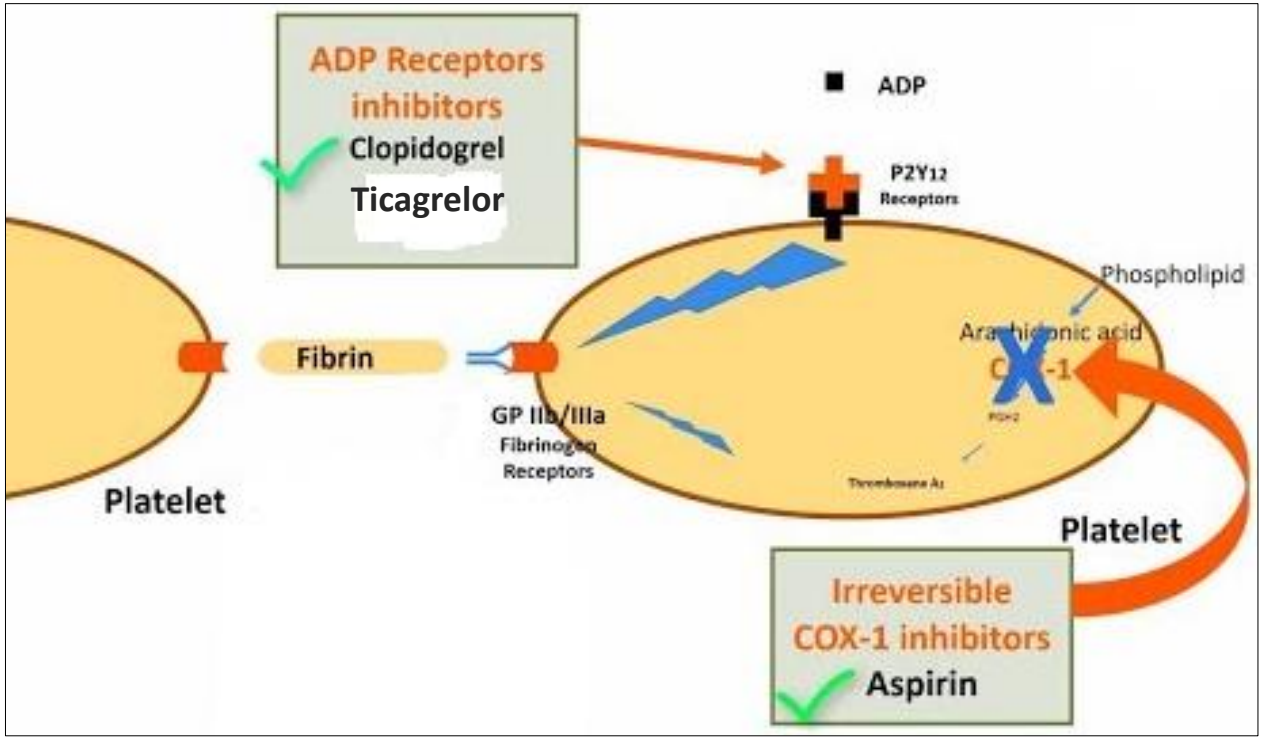
- MOA:
  - PDE inhibitor (at high doses) → Increasing intracellular cAMP and cGMP → Inhibiting platelet activation/aggregation
- Dipyridamole monotherapy failed to show a benefit in stroke prevention over ASA monotherapy
- ER-DP+ASA vs. Clopidogrel:
  - Similar efficacy in preventing recurrent stroke
  - Clopidogrel is better tolerated (less bleeding and headache)
- PK/PD:
  - ER formulation of dipyridamole allows BID administration
  - Using immediate-release dipyridamole with aspirin (cheaper) is unproven
- ADRs:
  - GI bleeding, GI symptoms, headache (main cause for discontinuation)



Pharmacologic therapy
Ischemic stroke: **Secondary prevention (Ticagrelor)**

- MOA:
  - $P2Y_{12}$ (ADP) receptor antagonist (reversible blockage)

- Ticagrelor is not FDA-approved for secondary stroke prevention



Pharmacologic therapy
Ischemic stroke: **Secondary prevention (DAPT)**

- Dual antiplatelet therapy (DAPT) for secondary stroke prevention is an option for select patients
  - Minor stroke or High-risk TIA who did not receive alteplase (or as an alternative to alteplase)

- Short-term DAPT (≤ 90 days):
  - Significantly lower risk of recurrent stroke
  - No accompanying risk of major bleeding

- Long-term DAPT (> 90 days):
  - No additional benefit in reducing recurrent strokes
  - Increased risk of major bleeding

- ASA-Clopidogrel combination:
  - The most studied DAPT
  - Not recommended for > 90 days

- ASA-Ticagrelor combination:
  - Higher incidence of severe bleeding than ASA alone
  - Not recommended for > 30 days

Dual Antiplatelet Recommendations for Patients with Noncardioembolic Ischemic Stroke or TIA

Patient Sub-type	Recommendation	Class (Strength) of Recommendation[a]	Level (Quality) of Evidence[b]
Minor stroke (NIHSS score ≤3)orhigh-risk TIA (ABCD2 score ≥4)[c]	Aspirin and clopidogrel should be initiated within 7 days (ideally within 12-24 hours). Continue for 21-90 days followed by single agent antiplatelet therapy	I	A
Recent (<30 days) minor stroke or TIA attributable to 70-99% stenosis of a major intracranial artery	Aspirin and clopidogrel 75 mg daily for up to 90 days followed by single agent antiplatelet therapy	IIa	B-NR
Recent (within 24 hours) minor stroke or high-risk TIA and concomitant ipsilateral >30% stenosis of a major intracranial artery	Ticagrelor 90 mg twice a day may be added to aspirin for up to 30 days	IIb	B-NR

[c] The ABCD2 score is a clinical prediction rule used to determine the risk for stroke soon after a TIA.

Score 1 point each for age ≥60 years, blood pressure ≥140/90 mm Hg, speech disturbance, unilateral weakness, 10-59 minute duration, diabetes

2 points for duration ≥60 minutes.

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (TAPT)**

- Triple antiplatelet therapy (TAPT) is not recommended for secondary stroke prevention

- <u>TAPT (compared to DAPT and Monotherapy)</u>:
  - Increased risk of major bleeding
  - No additional benefit in reducing the risk of recurrent stroke

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (Anticoagulants)**

- Oral anticoagulation is the treatment of choice for stroke prevention in atrial fibrillation/flutter

- Benefit vs Risk:
  - Patients with AF & recent stroke/TIA history → High risk for stroke recurrence
  - However, anticoagulation carries a significant risk of bleeding

- To assess benefit (stroke prevention): CHA_2DS_2-VASc
  - Stroke risk stratification tool; Assesses the patient's risk of developing stroke
  - CHA_2DS_2-VASc scores > 0 (men) or > 1 (women) → High risk for stroke → Oral anticoagulation needed

- To assess risk (bleeding): HAS-BLED
  - HAS-BLED score > 2 → High risk for bleeding → Intensive patient monitoring needed

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (Anticoagulants)**

CHA_2DS_2-VASc Score		
C	Congestive Heart Failure (Recently decompensated HFrEF or HFpEF or moderate to severe LV dysfunction or HCM)	1
H	Hypertension (includes controlled BP if on antihypertensives)	1
A	Age ≥ 75 years old	2
D	Diabetes	1
S	Stroke, TIA, Thromboembolism	2
V	Vascular (eg, MI, CAD, PAD, or aortic plaque)	1
A	Age 65-74	1
Sc	Sex (Female)	1

HAS-BLED Score for Assessing Bleeding Risk with Oral Anticoagulants

HAS-BLED Symbol	Risk Factor	Score
H	**H**ypertension (SBP >160 mm Hg)	1
A	**A**bnormal renal or liver function	1 (each)
S	Prior **S**troke	1
B	Prior major **B**leeding or **B**leeding predisposition	1
L	**L**abile INRs (in therapeutic range <60% of time)	1
E	**E**lderly (age >65 years)	1
D	**D**rugs of abuse or excessive alcohol use	1 (each)

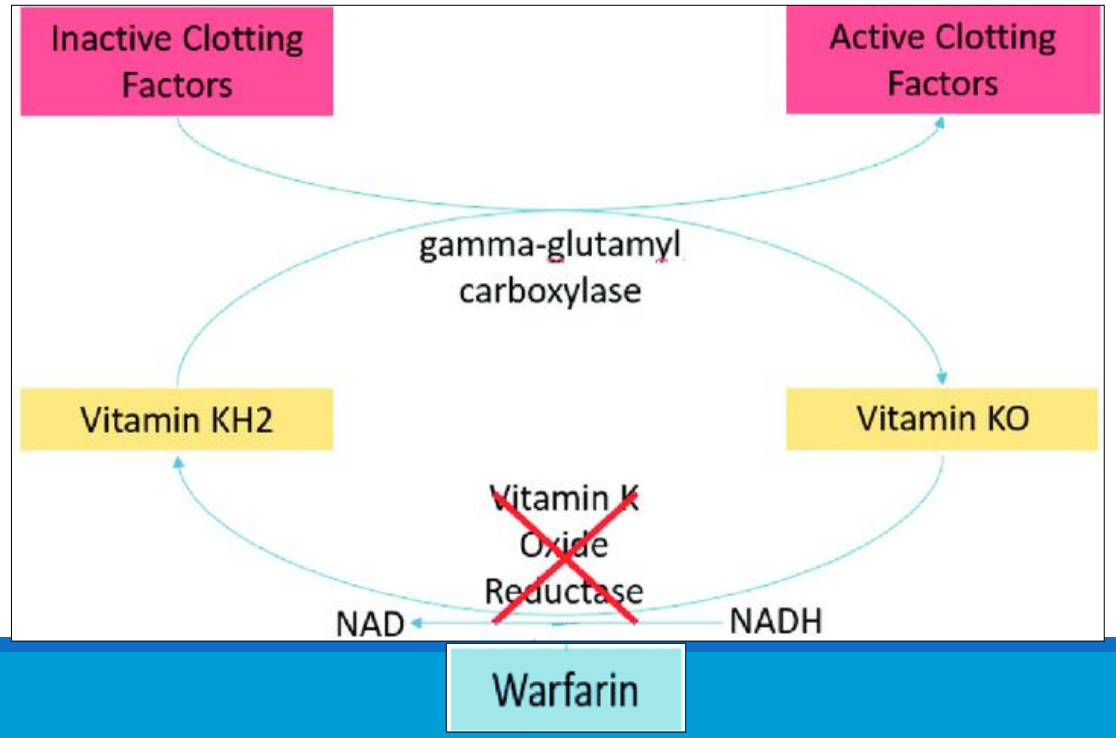
HAS-BLED score >2 associated with clinically relevant and major bleeding.

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (Anticoagulants)**

- Timing of oral anticoagulant initiation:
  - Debated due to risk of hemorrhagic conversion of the infarcted area
  - Low risk of hemorrhagic conversion:
    - Start oral anticoagulation 2 - 14 days after stroke
  - High risk of hemorrhagic conversion:
    - Start oral anticoagulation after 14 days (at least) of stroke

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (Warfarin)**

- MOA:
  - Anticoagulant
  - Inhibition of vitamin K epoxide reductase complex 1 (VKORC1) →
  - Inhibition of activation of clotting factors II, VII, IX, and X (1972)



Pharmacologic therapy
Ischemic stroke: **Secondary prevention (Warfarin)**

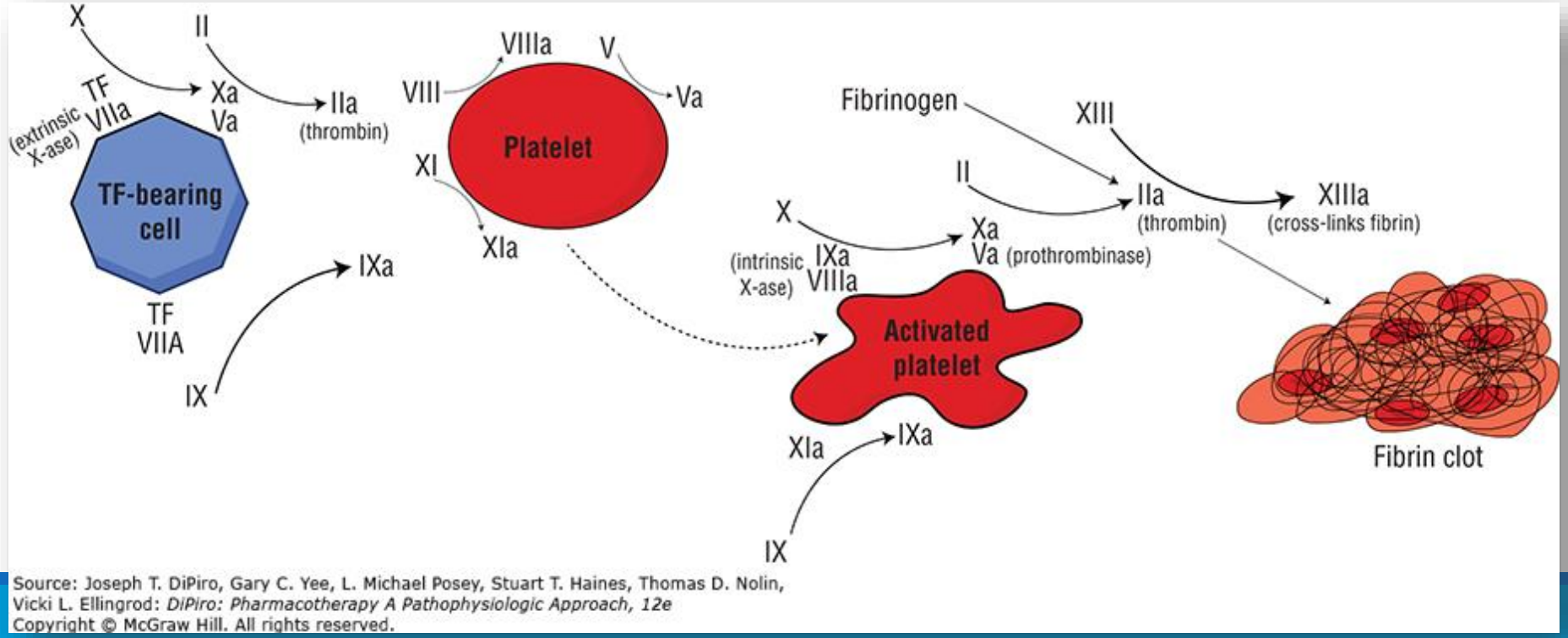
- In AF:
  - Adjusted-dose warfarin reduces stroke risk by 62% compared to placebo
  - Adjusted-dose warfarin reduces stroke risk by 36% compared to aspirin
  - First line in AF with mechanical heart valves or moderate to severe mitral stenosis

- INR target:
  - Recommended INR for secondary stroke prevention is 2 - 3 (prevents stroke with lowest bleeding risk)

- PK/PD:
  - Polymorphisms → Unpredictable PK/PD (requires frequent INR monitoring)
    - CYP2C9 (main metabolizing enzyme for warfarin 'slow metabolizers vs fast metabolizers')
    - VKORC1 (site of action for warfarin)
  - Food and drug interactions

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (DOACs)**

- Direct-acting oral anticoagulants (DOAC):
  - **Direct thrombin (IIa) inhibitors:** Dabigatran
  - **Direct factor Xa inhibitors:** Rivaroxaban, Edoxaban, Apixaban



Source: Joseph T. DiPiro, Gary C. Yee, L. Michael Posey, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod: *DiPiro: Pharmacotherapy A Pathophysiologic Approach, 12e*

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (DOACs)**

- DOAC vs Warfarin:
  - Easier dosing (less/no need for INR monitoring, predictable PK/PD)
  - Less food and drug interactions
  - As effective as (and in some cases superior to) warfarin in reducing stroke risk
  - Fewer rates of serious hemorrhage

- Renal function monitoring:
  - Before using a DOAC: evaluate renal function; adjust dose if significant renal impairment
  - ClCr < 15 mL/min or Hemodialysis: Warfarin or Apixaban are preferred (mainly hepatic metabolism)
  - ClCr > 95 mL/min: Avoid Edoxaban
    - Lower blood levels with better renal function → Increased stroke risk compared to warfarin

- Obese patients:
  - Limited data on using DOAC in BMI > 40 kg/m^2
  - Apixaban and Rivaroxaban may be the best options for BMI > 40 kg/m^2 or body weight > 120 kg

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (DOACs)**

Direct-acting Oral Anticoagulant Dosing Adjustments Required for Renal Impairment.

Direct-acting Oral Anticoagulant	Usual Oral Dosing for Stroke Prevention in Atrial Fibrillation	Dosing Adjustments
Apixaban	5 mg twice daily	2.5 mg twice daily in patients with at least two high-risk characteristics below: Body weight ≤60 kg Serum creatinine ≥1.5 mg/dL (133 µmol/L) Age ≥80 years
Dabigatran	150 mg twice daily	75 mg orally twice daily if creatinine clearance 15-30 mL/min (0.25-0.50 mL/s)
Edoxaban	60 mg daily	30 mg orally daily if creatinine clearance is 15-50 mL/min (0.25-0.83 mL/s)
Rivaroxaban	20 mg daily with food	15 mg orally daily with evening meal if creatinine clearance is ≤50 mL/min (0.83 mL/s)

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (BP control)**

- Elevated BP is very common in ischemic stroke patients
- HTN treatment in ischemic stroke patients → Decreased risk of stroke recurrence

- Guideline recommendations for BP control for secondary stroke prevention:
  - Adults not previously treated for HTN who experience stroke or TIA and have average BP ≥ 130/80 mm Hg:
    - Recommended to prescribe antihypertensive treatment after the first few days of the event
  - Adults with previously treated HTN who experience stroke or TIA:
    - Recommended to restart antihypertensive treatment after the first few days of the event
  - Adults with HTN who experience stroke or TIA:
    - Thiazide diuretic, ACEI, or ARB
    - BP goal < 130/80 mm Hg

Pharmacologic therapy
Ischemic stroke: **Secondary prevention (lipids control)**

- **Statins:** reduce risk of stroke in patients with CAD and elevated plasma lipids
- **Ezetimibe:** add-on therapy
- **PCSK9 inhibitors:** add-on therapy
- **EPA (icosapent ethyl):** add-on therapy in hypertriglyceridemia; for severe hypertriglyceridemia
- **Fibrates:** for severe hyperglyceridemia

Pharmacologic therapy
Hemorrhagic stroke: **Acute treatment**

- Usefulness of pharmacologic interventions is limited in ICH
  - Management of hypertension
  - Reversal of coagulopathy

Acute Treatment of Spontaneous Intracerebral Hemorrhage[6]		
Patients with a severe coagulation factor deficiency or severe thrombocytopenia should receive appropriate factor replacement therapy or platelets	I	C
Prophylactic antiseizure medication is not recommended	III	B

Pharmacologic therapy
Hemorrhagic stroke: **Acute treatment**

- Management of hypertension:
  - HTN in hemorrhagic stroke increases the risk of hematoma expansion
  - Continuous IV infusion antihypertensives

Intracranial Hemorrhage
• Treatment is reasonable for ICH patients with SBP >220 mm Hg • For ICH patients with SBP 150-220 mm Hg, acute lowering of SBP to 140 mm Hg is safe
SAH due to aneurysm rupture, target SBP < 160 mm Hg

- Reversal of coagulopathy:
  - For anticoagulant-associated (drug-induced) ICH
  - Consider reversal agents
    - **Warfarin:** Vitamin K + 4PCC (Clotting factors II, VII, IX, X)
    - **Dabigatran:** Idarucizumab
    - **Rivaroxaban, Apixaban** (but not Edoxaban): Andexanet alfa

Selected Anticoagulant Reversal

Drug	First-Line Reversal Recommendation	Alternate Treatment
Warfarin	Vitamin K 10 mg IV ×1 -and- 4-Factor Prothrombin Complex Concentrate (4PCC) INR 2 to <4: 25 units/kg, max 2,500 units INR 4-6: 35 units/kg, max 3,500 units INR >6: 50 units/kg, max 5,000 units	Vitamin K 10 mg IV ×1 -and- Fresh Frozen Plasma (FFP) 10-15 mL/kg
Dabigatran	Idarucizumab 5 gm IV ×1	Hemodialysis 4PCC 50 units/kg
Rivaroxaban ≤10 mg	Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Rivaroxaban >10 mg or unknown dose	If <8 hours since last dose or unknown time andexanet alfa 800 mg IV bolus at rate of 30 mg/min, followed by 8 mg/min IV infusion up to 120 minutes If ≥8 hours since last dose Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Apixaban ≤5 mg	Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Apixaban >5 mg or unknown dose	If <8 hours since last dose or unknown time Andexanet alfa 800 mg IV bolus at rate of 30 mg/min, followed by 8 mg/min IV infusion up to 120 minutes If ≥8 hours since last dose Andexanet alfa 400 mg IV Bolus at rate of 30 mg/min, followed by 4 mg/min IV infusion up to 120 minutes	4PCC 50 units/kg
Edoxaban	Andexanet alfa not studied	4PCC 50 units/kg

Evaluation of therapeutic outcomes

- Intensive monitoring in acute stroke for:
  - Development of neurologic worsening (stroke recurrence, stroke extension)
  - Complications (VTE, infection)
  - Adverse effects (medications, non-pharmacologic interventions)

- Most common reasons for deterioration in stroke:
  - Extension of the original lesion (ischemic or hemorrhagic) in the brain
  - Development of cerebral edema and elevated ICP
  - Hypertensive emergency
  - Infection (most commonly urinary and respiratory)
  - VTE (DVT, PE)
  - Electrolyte abnormalities (can be associated with brain injury)
  - Cardiac rhythm disturbances (can be associated with brain injury)
  - Recurrent stroke

Evaluation of therapeutic outcomes

- Recurrent stroke occurs in ~ 3 – 4% of patients with non-cardioembolic strokes (per year)
- 1/3 to 1/2 of these recurrent strokes occur while patients are on antiplatelets!
- None of the antiplatelets reduces stroke risk to zero!
- <u>Most important causes of recurrent strokes</u>:
  - Non-adherence (poor understanding of therapy, adverse effects, polypharmacy…)
  - Inappropriate dosing
  - Reduced absorption
  - Increased metabolism
  - Drug-drug interactions
  - Genetic polymorphisms

Impactable

Monitoring Stroke Therapy in Hospitalized Patients

Drug	Adverse Effect	Monitoring Parameters	Comments
Alteplase and tenecteplase	Bleeding	Neurologic examination, blood pressure	Every 15 minutes × 1 hour; every 30 minutes × 6 hours; every 1 hour × 17 hours; every shift after
Aspirin	Bleeding		Daily
Clopidogrel	Bleeding		Daily
Extended-release dipyridamole plus aspirin	Headache, bleeding		Daily
Ticagrelor	Bleeding, bradycardia, dyspnea	Heart rate, respiratory rate	Bleeding daily, heart rate and respiratory rate as clinically indicated
Direct-acting oral anticoagulants	Bleeding		Daily
Warfarin	Bleeding	PT/INR, hemoglobin, hematocrit	Daily