Al-Mustaqbal University
College of Pharmacy
5th Stage
Applied therapeutics I
Lecture: 1

STROKE

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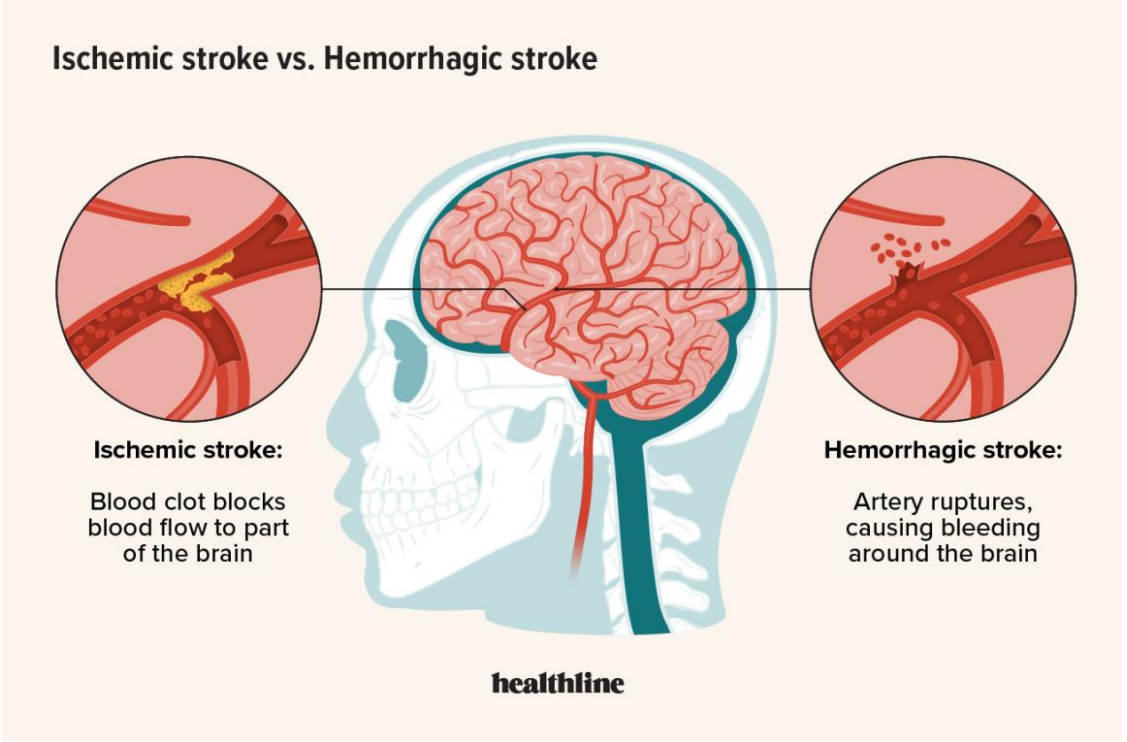
Stroke

- Stroke involves the abrupt onset of **focal neurologic dysfunction** that lasts **at least 24** hours and is caused by cerebral, spinal, or retinal infarction.
- Stroke can be either **ischemic** or **hemorrhagic**.
- Transient ischemic attacks (**TIAs**) are focal ischemic neurologic deficits **lasting <24** hours and usually **<30 minutes**.



Pathophysiology of Ischemic Stroke

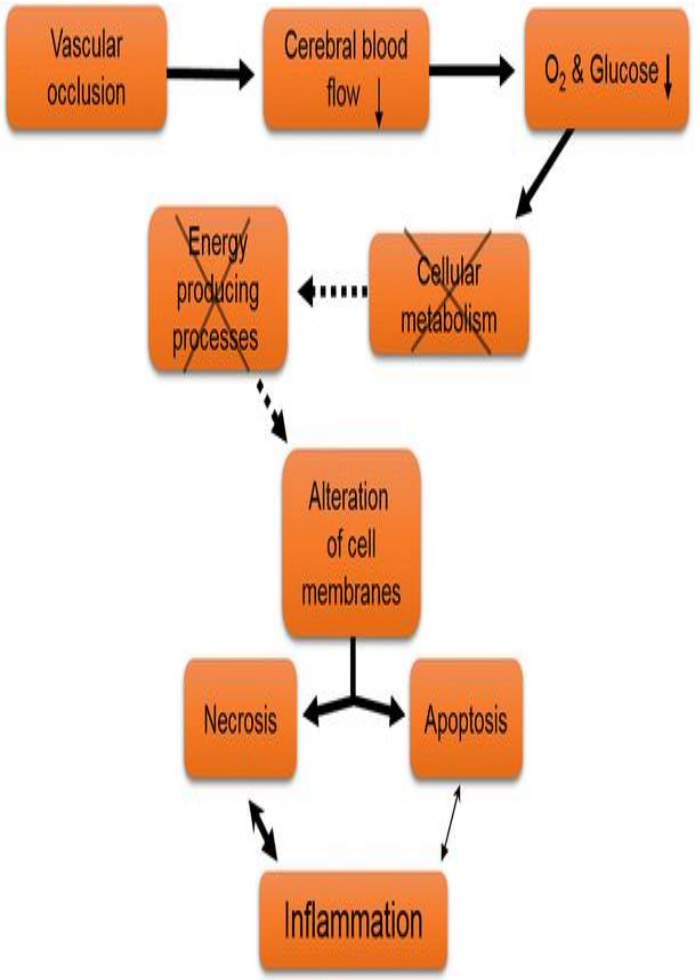
- Ischemic stroke (**87%** of all strokes) results from **occlusion of a cerebral artery** that reduces cerebral blood flow.
- Ischemic strokes are due **either to local thrombus** formation or **emboli from a distant site**.
- **Atherosclerosis** of large intracranial or extracranial arteries or small artery disease can **result in ischemic stroke**.
- **Emboli** can arise from the **heart** in patients with atrial fibrillation, valvular heart disease, or other prothrombotic heart problems and cause about **25%** of ischemic strokes.

Pathophysiology of Ischemic Stroke

- The stroke cause is **undetermined** in some cases.
- **Decreased cerebral blood flow** can lead to **infarction** of cerebral tissue with a surrounding area that is ischemic **but** may maintain membrane integrity (the **ischemic penumbra**).
- This penumbra is an area of brain tissue that is **potentially salvageable** with **urgent** pharmacologic and endovascular treatment interventions.

Pathophysiology of Ischemic Stroke

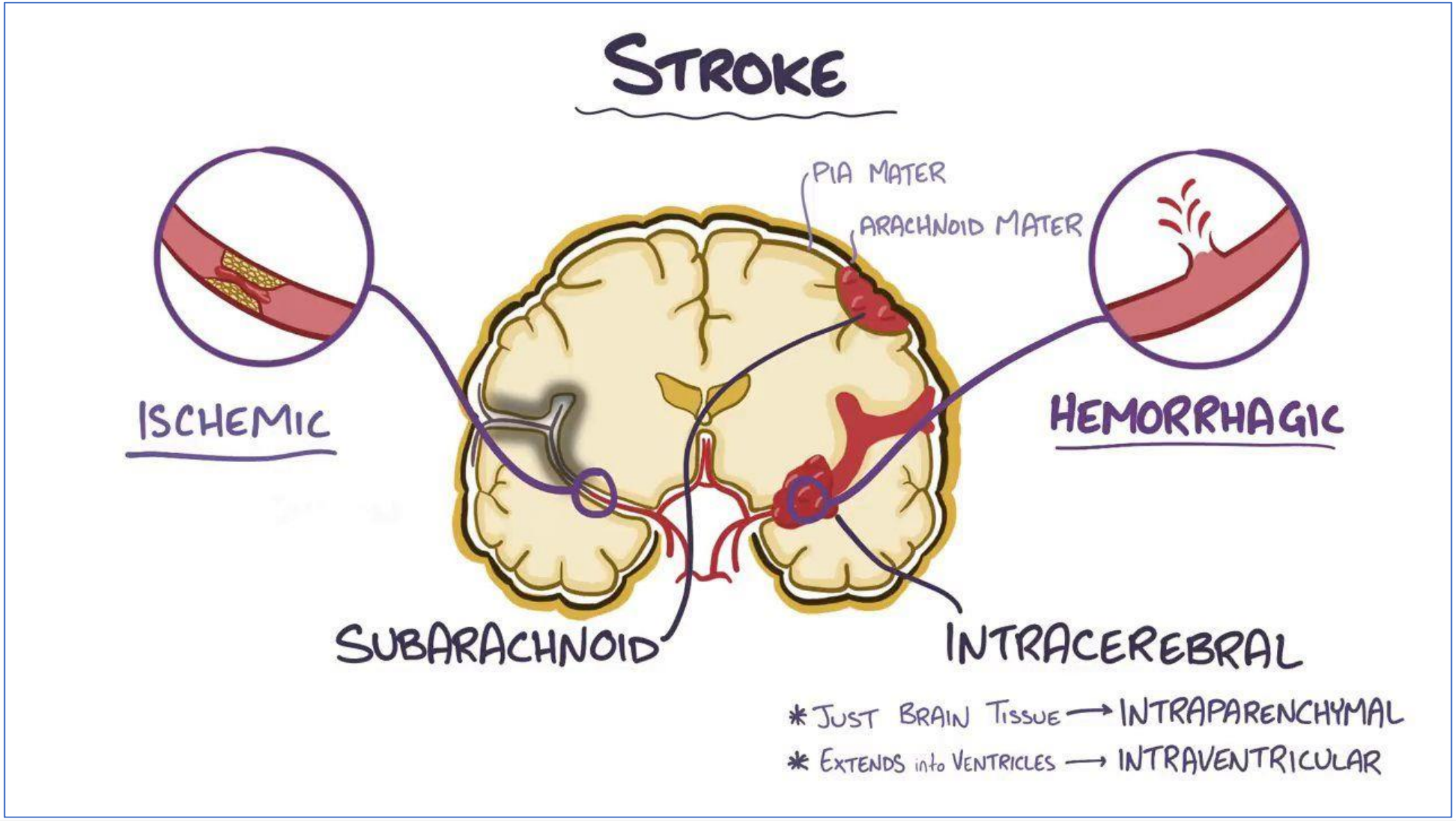
- **Insufficient oxygen supply** in ischemic tissue leads to ATP depletion with lactate buildup due to anaerobic metabolism and accumulation of intracellular sodium and water, leading to cytotoxic edema and eventual cell lysis.
- An **influx of calcium** intracellularly activates lipases and proteases, **resulting** in protein degradation and free fatty acid release from cellular membranes.
- Release of **excitatory amino acids** (eg, glutamate, aspartate) in ischemic tissue propagates neuronal damage and produces damaging prostaglandins, leukotrienes, and reactive oxygen species.
- These processes occur within **2–3 hours** of the onset of ischemia and **ultimately** lead to cellular apoptosis and necrosis.
- The most common **modifiable risk factors** for ischemic stroke include hypertension, cigarette smoking, diabetes, atrial fibrillation, and dyslipidemia.



Pathophysiology of Hemorrhagic Stroke

- Hemorrhagic strokes (**13% of strokes**) include subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH).
- **SAH** may result from trauma or rupture of an intracranial aneurysm or arteriovenous malformation (AVM).
- **ICH** occurs when bleeding in the brain parenchyma results in hematoma formation.
- **Intracranial hematoma** causes mechanical compression of brain parenchyma.
- **Early hematoma expansion** often occurs within **3 hours** of hemorrhage onset, contributing to worsened functional outcome and increased mortality.
- **Secondary mechanisms** of injury are mediated by the subsequent inflammatory response, cerebral edema, and damage from blood product degradation.

Pathophysiology of Hemorrhagic Stroke



Clinical Presentation

- Patients may be **unable** to provide a reliable history because of **cognitive or language deficits**. **Family members** or **other witnesses** may need to provide this information.
- **Symptoms** include unilateral weakness, inability to speak, loss of vision, vertigo, or falling.
- **Ischemic stroke** is not usually painful, but some patients complain of headache.
- Pain and headache are more common and severe in **hemorrhagic stroke**.

Clinical Presentation

- Neurologic deficits on physical examination depend on the brain area involved.

✓ **Hemi- or monoparesis** and **hemisensory deficits** are common.

✓ Patients with posterior circulation involvement may have **vertigo and diplopia**.

✓ Anterior circulation strokes commonly result in **aphasia**.

✓ Patients may experience **dysarthria, visual field defects, and altered levels of consciousness**.

Diagnosis

- Blood glucose, platelet count, and coagulation parameters (eg, prothrombin time, aPTT) are used in **stroke assessment** to **determine treatment eligibility**.
- Tests for **hypercoagulable states** (protein C and S deficiency, antiphospholipid antibody) should be done only when the **etiology cannot be determined** based on the presence of well-known risk factors.
- **CT and MRI** head scans can **reveal areas of hemorrhage and infarction**.
- Vascular imaging with computed tomography angiography (**CTA**) is recommended in patients with **endovascular treatment indications**.
- Carotid Doppler (CD), electrocardiogram (ECG), transthoracic echocardiogram (TTE), and transcranial Doppler (TCD) studies can each provide valuable diagnostic information.

Treatment

- Goals of treatment are to:
- (1) **reduce** ongoing neurologic injury acutely to **reduce** mortality and long-term disability.
- (2) **prevent** complications secondary to immobility and neurologic dysfunction
- (3) **prevent** stroke recurrence

Treatment

- GENERAL APPROACH

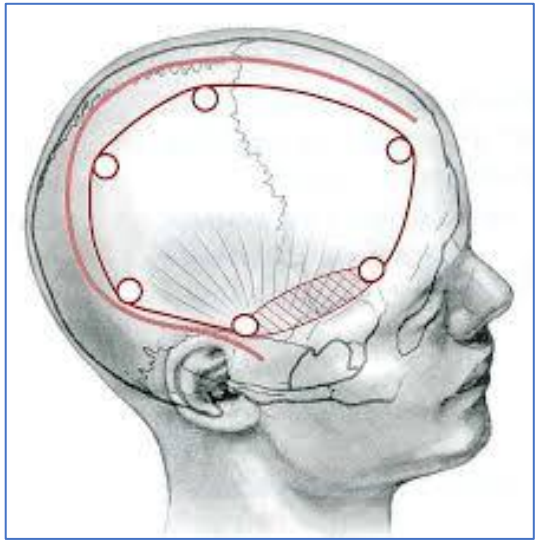
1. **Ensure** adequate respiratory and cardiac support and **determine quickly from CT** scan whether the lesion is ischemic or hemorrhagic.
2. **Evaluate ischemic stroke patients** presenting within hours of symptom onset for pharmacologic and mechanical reperfusion therapy.
3. Patients with **TIA require urgent assessment** and **intervention** to reduce the risk of stroke, which is highest in the first few days after TIA.
4. **Assess patients with hemorrhagic stroke** to determine whether they are candidates for surgical intervention.
5. **After the acute phase**, focus on preventing progressive deficits, minimizing complications, and instituting secondary prevention strategies.

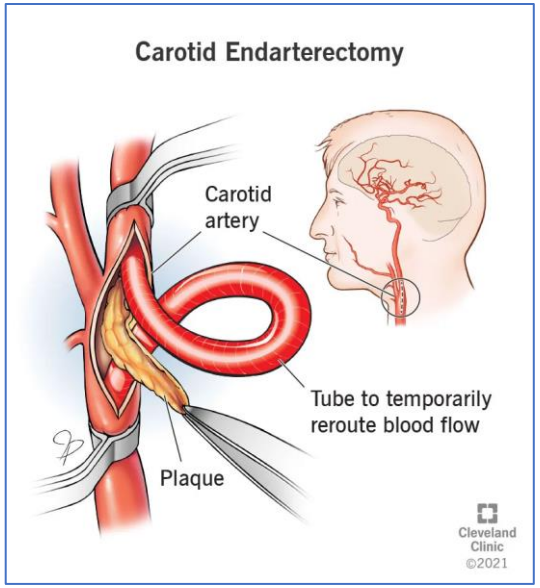
Nonpharmacologic Rx in Ischemic Stroke

- Endovascular intervention and thrombectomy with retrievable stents to **reperfuse ischemic brain** tissue is **recommended** by the American Heart Association (**AHA**) and American Stroke Association (**ASA**).
- **Thrombectomy** is **strongly recommended** for patients with **anterior circulation occlusion** in the internal carotid artery (ICA) or the M1 segment of the middle cerebral artery (MCA) who are within **6 hours of symptom onset** and may be considered in select patients within 6–24 hours of symptom onset.
- The **benefit** of mechanical thrombectomy is **less clear in posterior circulation occlusions** and should be considered on a case-by-case basis.

Nonpharmacologic Rx in Ischemic Stroke

- **Decompressive hemicraniectomy** is a surgical procedure to reduce intracranial pressure (typically due to cerebral edema) and can **reduce mortality** and **improve functional outcome** in select patients.
- For **all ischemic stroke patients**, coordinated care with a multidisciplinary approach to assessment and early rehabilitation reduces overall disability due to stroke.
- In **secondary prevention**, **carotid endarterectomy** of an ulcerated or stenotic carotid artery is effective in reducing stroke incidence and recurrence in appropriate patients and in centers where operative morbidity and mortality are low.
- In **patients younger than age 70**, **carotid stenting** is a less invasive alternative and can reduce recurrent stroke risk when **combined** with aspirin and clopidogrel therapy.





Nonpharmacologic Rx in Hemorrhagic Stroke

- In **SAH** from ruptured intracranial aneurysm or arteriovenous malformation AVM, **early** intervention with either surgical clipping or endovascular coiling of the vascular abnormality **reduces mortality from rebleeding**.
- **Early** surgical intervention and hematoma removal are **recommended** for patients with cerebellar hemorrhage and neurologic deterioration, brainstem compression, or hydrocephalus from ventricular obstruction.
- The **usefulness** of surgical hematoma evacuation is not well-established for patients with **cerebral hemorrhage**.
- **Ventricular drainage** with an extraventricular drain (**EVD**) is reasonable in patients with hydrocephalus causing decreased consciousness.

Temperature Management

- **Fever worsens outcomes** in patients with **both** hemorrhagic and ischemic stroke.
- **Identification** of the source and pharmacologic and/or nonpharmacologic management is **recommended** to maintain the normothermia range.
- Because of limited supporting data, induced hypothermia should be done only in the setting of controlled, clinical trials.

Pharmacologic Therapy of Ischemic Stroke

- **Alteplase** initiated within **4.5 hours** of symptom onset improves functional ability after ischemic stroke.
- Adherence to a **guideline-recommended protocol** is essential to achieving positive outcomes:
- (1) activate the stroke team; (2) obtain CT scan to rule out hemorrhage; (3) treat as early as possible within **4.5 hours** of symptom onset;
- (4) meet all inclusion criteria with no contraindications ;
- (5) administer alteplase **0.9 mg/kg IV** total dose (maximum 90 mg), with **10% infused** as an initial **bolus over 1 minute** and the **remainder** given **over 1 hour**;
- (6) **avoid** anticoagulant and antiplatelet therapy for **24 hours after alteplase**; and (7) **monitor** the patient closely for elevated blood pressure (BP), neurologic status, and hemorrhage.

Pharmacologic Therapy of Ischemic Stroke

TABLE 13-2 Inclusion Criteria and Contraindications to Alteplase Use in Acute Ischemic Stroke

Inclusion criteria

- Age 18 years or older
- Clinical diagnosis of ischemic stroke with neurologic deficit
- Time of symptom onset well established to be <4.5 hours before treatment would begin

Contraindications

- Symptoms/imaging consistent with SAH 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 x 10^9/L], INR>1.7, aPTT >40 sec, PT >15 sec)
- Severe head trauma in prior 3 months
- Gastrointestinal malignancy or bleeding within prior 21 days

Warnings/Use Clinical Judgment

- History of intracranial hemorrhage
- History of ischemic stroke within prior 3 months
- 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 of Ischemic Stroke

- **Aspirin** 160–325 mg/day started within **24–48 hours** of symptom onset (and **24 hours** after alteplase completion) **reduces** long-term death and disability.
- An **alternate antiplatelet agent** may be considered for patients with aspirin allergy or other severe contraindications.
- For patients with **elevated BP who are eligible for alteplase**, treatment to a goal **BP <185/110 mm Hg** is recommended **before** thrombolytic administration.
- While data are limited, it is also reasonable to maintain **BP <185/110 mm Hg** for patients undergoing **mechanical thrombectomy**.
- For patients **not** requiring IV thrombolysis or endovascular intervention, BP is often allowed to rise as high as **220/120 mm Hg for the first 48–72 hours because** early BP reduction does not prevent death or improve the level of dependency.

Pharmacologic Therapy of Ischemic Stroke

- For patients with **comorbid conditions** requiring BP management, a reduction of **15% is probably safe**.
- If BP is treated, **short-acting** and **easily titrated IV agents** are **preferred**:

✓**Labetalol**: 10–20 mg IV over 1–2 minutes; may repeat

✓**Nicardipine**: 5 mg/hr IV; titrate up by 2.5 mg/hr every 5–15 minutes; maximum 15 mg/hr

✓**Clevidipine**: 1–2 mg/hr IV; titrate by doubling the dose every 2–5 minutes; maximum 21 mg/hr

✓Other **potential agents**: hydralazine, enalaprilat, nitroprusside IV infusion, labetalol IV infusion.

Pharmacologic Therapy of Ischemic Stroke

- Use of urgent **anticoagulation** (eg, unfractionated heparin or low-molecular-weight heparin) is **not routinely recommended** in the **early phase** of acute ischemic stroke treatment.
- Use of **immediate anticoagulation** for non-stroke indications (eg, prophylaxis of venous thromboembolism) should be **weighed against the risk** of intracranial hemorrhagic conversion.

Pharmacologic Therapy of Ischemic Stroke

- **Secondary prevention of ischemic stroke:**
- **All patients** who have had an acute ischemic stroke or TIA **should receive** long-term **antithrombotic therapy** for secondary prevention.
- **Antiplatelet** therapy should be used in **non-cardioembolic stroke**; aspirin, extended-release dipyridamole plus aspirin, and clopidogrel are **all first-line agents**.
- Studies of the combination of **clopidogrel plus ASA have shown conflicting results** on reduction of recurrent stroke, and some found an increase in hemorrhagic events.
- For patients with **atrial fibrillation** and a presumed **cardiac source of embolism** for stroke or TIA, oral anticoagulation with a vitamin K antagonist (warfarin), apixaban, dabigatran, edoxaban, or rivaroxaban is **recommended**.

Pharmacologic Therapy of Ischemic Stroke

- **Secondary prevention of ischemic stroke:**

✓Adults with **previously treated hypertension** who experience a stroke or TIA **should be restarted** on antihypertensive treatment after the first few days of the index event to reduce the risk of recurrent stroke and other vascular events.

- **Useful options** include a thiazide diuretic, angiotensin-converting enzyme (ACE) inhibitor, angiotensin receptor blocker, or combination treatment with a thiazide plus ACE inhibitor.
- **Selection** of specific drugs should be **individualized** based on patient comorbidities.
- Adults **not previously treated for hypertension** who experience a stroke or TIA and have a **BP ≥140/90 mm Hg** should be prescribed antihypertensive treatment several days after the index event.
- A reasonable goal BP for patients who experienced a stroke or TIA is **<130/80 mm Hg**.

Pharmacologic Therapy of Ischemic Stroke

- **Secondary prevention of ischemic stroke:**
- **Statin therapy** is recommended to prevent stroke recurrence in **all ischemic stroke patients** regardless of baseline lipid levels.
- Patients **≤75 years** of age experiencing ischemic stroke of presumed atherosclerotic origin should be treated with high-intensity statin therapy with a target of achieving ≥50% LDL- cholesterol.
- For patients **>75 years**, moderate- or high-intensity statin therapy can be initiated as **tolerated**.
- **Ezetimibe** may be **added** for patients taking maximally tolerated statin therapy but with LDL cholesterol **≥70 mg/dL (1.81 mmol/L).**
- A **proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor** may be considered in very high-risk patients who are taking maximally tolerated statins and ezetimibe with LDL cholesterol **≥70 mg/dL (1.81 mmol/L).**

Pharmacologic Therapy of Hemorrhagic Stroke

- The usefulness of **pharmacotherapy** is **limited** in spontaneous **ICH**.
- **Because** hypertension in hemorrhagic stroke increases the risk of hematoma expansion, it is reasonable for **patients with a systolic BP >220 mm Hg** to receive aggressive BP lowering with continuous IV infusion medications.
- Acute lowering of systolic BP to a **goal** of **140 mm Hg** is safe and may improve functional outcome.
- For patients with **SAH due to aneurysm rupture**, BP control to at least a systolic **BP <160 mm Hg** is reasonable in the period from symptom onset to aneurysm obliteration.
- When **intracranial hemorrhage** occurs in a patient on **anticoagulants**, use of **reversal agents** to correct the medication-induced coagulopathy should be considered.

EVALUATION OF THERAPEUTIC OUTCOMES

- **Monitor patients** with acute stroke intensely for the development of neurologic worsening (recurrence or extension of stroke), complications (venous thromboembolism, infection), and adverse treatment effects.
- The most common **reasons** for clinical **deterioration** in stroke patients include:
- (1) **extension** of the original lesion in the brain; (2) **development** of cerebral edema and raised intracranial pressure; (3) **hypertensive** emergency;
- (4) **infection** (eg, urinary and respiratory tract); (5) venous **thromboembolism**; (6) **electrolyte** abnormalities and **rhythm** disturbances; and (7) **recurrent** stroke.

EVALUATION OF THERAPEUTIC OUTCOMES

- For patients receiving **alteplase therapy**, monitor for bleeding with neurologic examination and BP every 15 minutes for **1 hour**, **then** every half-hour for 6 hours, **then** every hour for 17 hours, **then** once every shift thereafter.
- For aspirin, clopidogrel, extended-release dipyridamole plus aspirin, warfarin, and other oral anticoagulants, **monitor for bleeding daily**.
- For patients receiving **warfarin**, check the PT/INR and hemoglobin/hematocrit **daily**.

THANK YOU FOR YOUR ATTENTION