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# Pharmacotherapy of Stroke

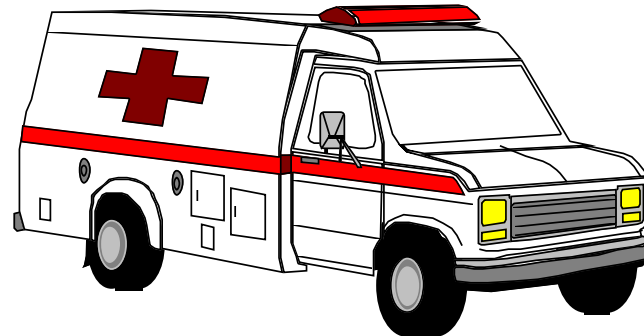
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# Definition

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- Stroke is a term used to describe
  - an abrupt onset of focal neurologic deficit that lasts **at least 24 hours** and is presumed to be of **vascular origin**
- Stroke can be either **ischemic** or **hemorrhagic**
- Transient ischemic attacks (TIAs) are
  - focal ischemic neurologic deficits lasting **less than 24 hours** and usually less than 30 minutes

# Pathophysiology

## Risk Factors For Stroke

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- **Non-modifiable risk factors**

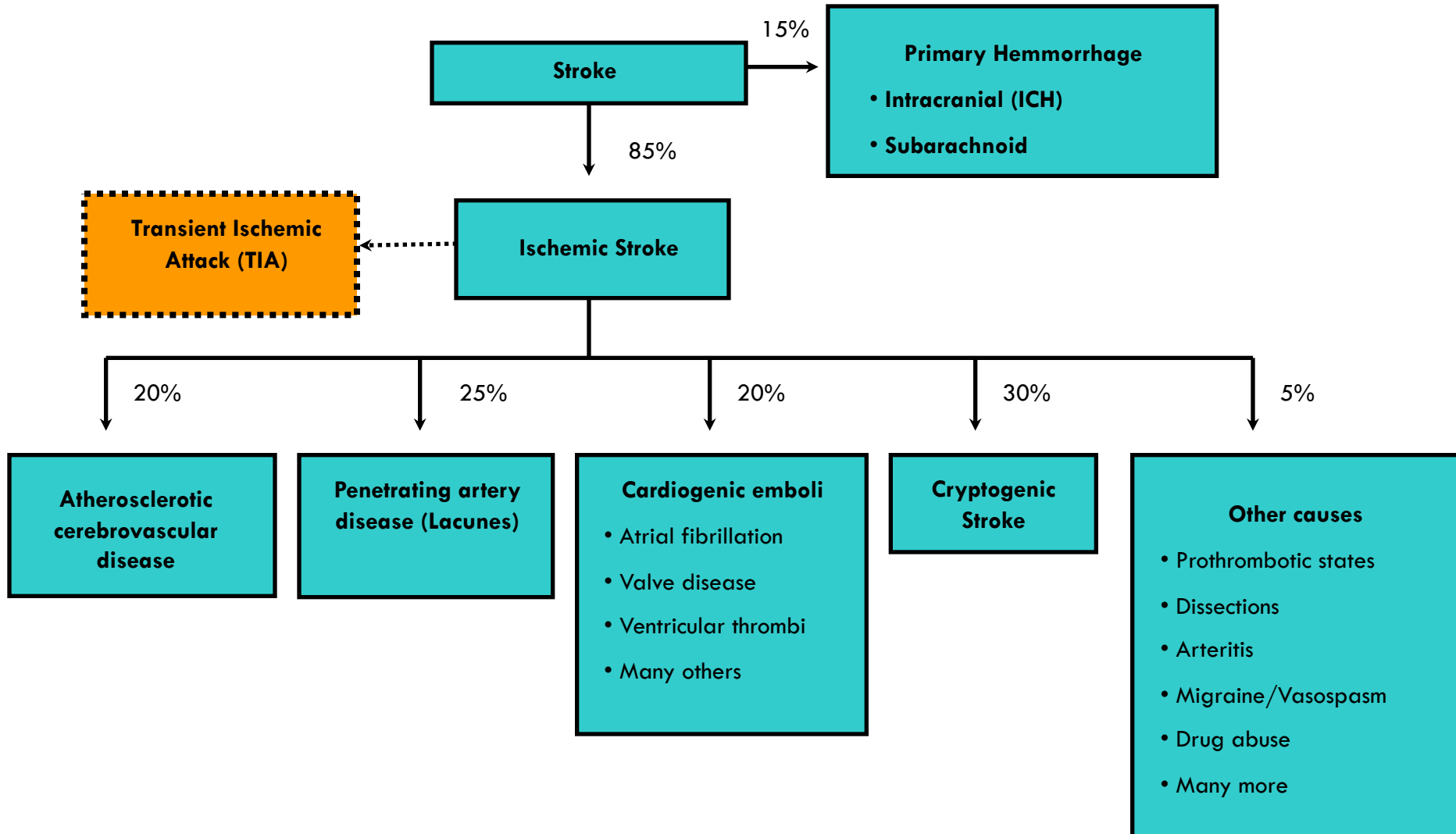
- increased age
- male gender
- race (African American, Asian, Hispanic)
- family history of stroke
- low birth weight

- **Major modifiable risk factors**

- hypertension
- cardiac disease (especially atrial fibrillation)
- diabetes mellitus
- dyslipidemia
- cigarette smoking



# Stroke Classification



# Ischemic Stroke

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- Ischemic strokes account for 88% of all strokes and are due either to
  - local thrombus formation or
  - emboli that occlude a cerebral artery.
- **Cerebral atherosclerosis** is a causative factor in most cases of ischemic stroke, although 30% are of unknown etiology.
- Emboli can arise either from intra- or extracranial arteries.
  - 20% of embolic strokes arise from the heart.

# Hemorrhagic Stroke

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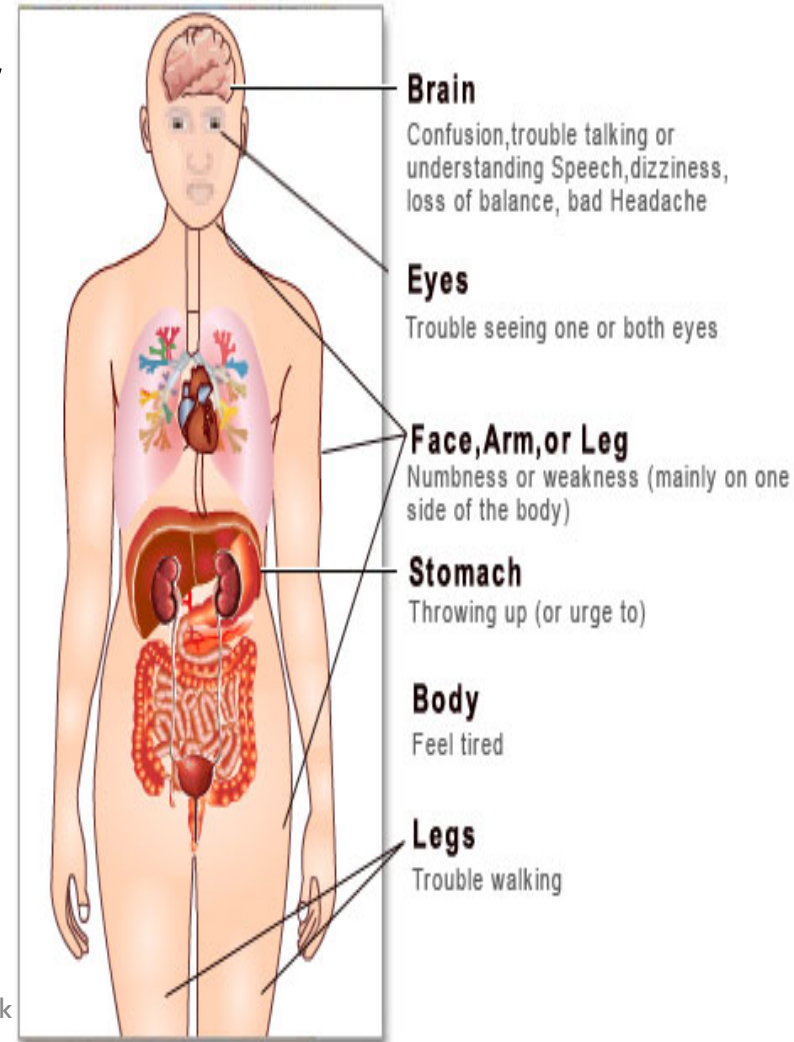
- Hemorrhagic strokes account for 12% of strokes and include
  - **Subarachnoid hemorrhage**
    - may result from trauma or rupture of an intracranial aneurysm or arteriovenous malformation.
  - **Intracerebral hemorrhage**
    - occurs when a ruptured blood vessel within the brain parenchyma causes formation of a hematoma.
  - **Subdural hematomas**
    - most often caused by trauma

# Cont...

- The presence of blood in the brain parenchyma causes damage to surrounding tissue through
  - a **mass effect** and the **neurotoxicity** of blood components and their degradation products.
- Compression of tissue surrounding hematomas may lead to secondary ischemia.
- Much of the early mortality of hemorrhagic stroke is due to an abrupt increase in intracranial pressure that can lead to herniation and death.

# Clinical Presentations

- The patient may not be able to give a reliable history because of cognitive or language deficits
  - Information may need to be obtained from family members or other witnesses
- The patient may experience
  - weakness on one side of the body
  - inability to speak
  - loss of vision
  - Vertigo
  - falling
- Ischemic stroke is not usually painful, but headache may occur and may be severe in hemorrhagic stroke



# Diagnosis

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- **Laboratory tests**

- Laboratory tests for hypercoagulable states should be done only when the cause of the stroke cannot be determined
  - Protein C, protein S, and antithrombin III
  - Antiphospholipid antibodies

# Cont...

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- **Imaging Studies**

- **Computed tomography (CT)** head scan
- **Magnetic resonance imaging (MRI)** of the head will reveal areas of ischemia with higher resolution and earlier than the CT scan.
- **Diffusion-weighted imaging** will reveal an evolving infarct within minutes

# Desired Outcome

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- The goals of treatment for acute stroke are to:
  - reduce the ongoing neurologic injury and decrease mortality and long-term disability
  - Prevent complications secondary to immobility and neurologic dysfunction
  - prevent stroke recurrence



# Treatment

## General Approach

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- The initial approach is
  - to ensure adequate respiratory and cardiac support and
  - to determine quickly whether the lesion is ischemic or hemorrhagic based on a CT scan.
- Ischemic stroke patients presenting within hours of symptom onset should be evaluated for **reperfusion therapy**

# Cont...

## • **Blood Pressure Control**

- Elevated blood pressure should remain untreated in the acute period (first 7 days) after ischemic stroke because of the risk of decreasing cerebral blood flow and worsening symptoms.
- The pressure should be lowered if it exceeds 220/120 mm Hg or there is evidence of aortic dissection, acute myocardial infarction, pulmonary edema, or hypertensive encephalopathy.
- If blood pressure is treated in the acute phase, short-acting parenteral agents (e.g., labetalol, nicardipine, nitroprusside) are preferred.

# Cont...

- Patients with hemorrhagic stroke should be assessed
  - to determine whether they are candidates for surgical intervention via an endovascular or craniotomy approach.
- After the hyperacute phase has passed, attention is focused on
  - preventing progressive deficits
  - minimizing complications and
  - instituting appropriate secondary prevention strategies

# Supportive Therapy

IV fluids	<ul style="list-style-type: none"><li>- Avoid excessive fluid administration</li><li>- NS at 50 ml/h</li></ul>
Blood glucose	<ul style="list-style-type: none"><li>- Treat hypoglycemia with D50</li><li>- Treat hyperglycemia with insulin if Glu &gt; 200mg/dl</li></ul>
Oral intake	<ul style="list-style-type: none"><li>- NPO initially until swallowing assessed</li></ul>
Oxygen	<ul style="list-style-type: none"><li>- Supplement if indicated (<math>\text{SaO}_2 &lt; 90\%</math>)</li></ul>
Temperature	<ul style="list-style-type: none"><li>- Oral or rectal APAP as needed (<math>T &gt; 100.4^\circ\text{F}</math>)</li></ul>

# Treatment

## Pharmacologic Therapy of Ischemic Stroke

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- AHA/ASA Stroke Council guidelines for the management of acute ischemic stroke give grade A recommendations to only two pharmacologic therapies:
  - IV tissue plasminogen activator (alteplase) within 3 hours of onset
  - Aspirin within 48 hours of onset

# IV tissue plasminogen activator

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## Alteplase

- initiated within 3 hours of symptom onset has been shown to reduce the ultimate disability due to ischemic stroke.
- A head CT scan must be obtained to rule out hemorrhage before beginning therapy.
- The patient must also meet specific inclusion criteria and no exclusionary criteria
- The dose is 0.9 mg/kg (maximum 90 mg) infused IV over 1 hour after a bolus of 10% of the total dose given over 1 minute.

## Inclusion and Exclusion Criteria for Alteplase Use in Acute Ischemic Stroke

### Inclusion Criteria (all YES boxes must be checked before treatment)

#### YES

- ☐ Age 18 years or older
- ☐ Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit
- ☐ Time of symptom onset well established to be less than 180 minutes before treatment would begin

### Exclusion Criteria (all NO boxes must be checked before treatment)

#### NO

- ☐ Evidence of intracranial hemorrhage on noncontrast head CT
- ☐ Only minor or rapidly improving stroke symptoms
- ☐ High clinical suspicion of subarachnoid hemorrhage even with normal CT
- ☐ Active internal bleeding (e.g., GI/GU bleeding within 21 days)
- ☐ Known bleeding diathesis, including but not limited to platelet count  $<100,000/\text{mm}^3$
- ☐ Patient has received heparin within 48 hours and had an elevated aPTT
- ☐ Recent use of anticoagulant (e.g., warfarin) and elevated PT ( $>15$  seconds)/INR
- ☐ Intracranial surgery, serious head trauma, or previous stroke within 3 months
- ☐ Major surgery or serious trauma within 14 days
- ☐ Recent arterial puncture at noncompressible site
- ☐ Lumbar puncture within 7 days
- ☐ History of intracranial hemorrhage, arteriovenous malformation, or aneurysm
- ☐ Witnessed seizure at stroke onset
- ☐ Recent acute myocardial infarction
- ☐ SBP  $>185$  mm Hg or DBP  $>110$  mm Hg at time of treatment

# Anti-platelets/Anticoagulants

- Anticoagulant and antiplatelet therapy should be avoided for 24 hours, and the patient should be monitored closely for hemorrhage.
- **Aspirin**
  - 50 to 325 mg/day started between 24 and 48 hours after completion of alteplase
  - has also been shown to reduce long-term death and disability.
- The AHA/ASA guidelines recommend that
  - antiplatelet therapy as the cornerstone of antithrombotic therapy for the **secondary prevention** of ischemic stroke and
  - should be used in noncardioembolic strokes.



# Cont...

- **Aspirin, clopidogrel, and extended-release dipyridamole plus aspirin** are all considered first-line antiplatelet agents
- The combination of aspirin and clopidogrel can only be recommended in patients with
  - ischemic stroke and a recent history of myocardial infarction or coronary stent placement and
  - only with ultra-low-dose aspirin to minimize bleeding risk.
- **Warfarin**
  - the antithrombotic agent of first choice for secondary prevention in patients with **atrial fibrillation** and a **presumed cardiac source of embolism**.

# Cont...

- **Blood Pressure Control**
  - Elevated blood pressure is common after ischemic stroke
  - its treatment is associated with a decreased risk of stroke recurrence.
  - The JNC and AHA/ASA guidelines recommend an **ACEI and a diuretic** for reduction of blood pressure in patients with stroke or TIA after the acute period (first 7 days).
  - **ARBs** can be used in patients unable to tolerate ACEIs

# Cont...

- The National Cholesterol Education Program considers ischemic stroke or TIA to be a **coronary risk equivalent** and recommends
  - the use of **statins** in ischemic stroke patients to achieve an LDL < 100 mg/dL.
- **LMWH or low-dose subcutaneous UH (5,000 units twice daily)** is recommended
  - for prevention of DVT in hospitalized patients with decreased mobility due to stroke and should be used in all but the most minor strokes.

TABLE 1

Recommendations for Pharmacotherapy of Ischemic Stroke

	Recommendation	Recommendation Grades <sup>a</sup>
<b>Acute treatment</b>	Alteplase 0.9 mg/kg IV (maximum 90 mg) over 1 hour in selected patients within 3 hours of onset	Class I, Level A
	Aspirin 160–325 mg daily started within 48 hours of onset	Class I, Level A
<b>Secondary prevention</b>		
Noncardioembolic	Antiplatelet therapy	Class I, Level A
	Aspirin 50–325 mg daily	Class IIa, Level A
	Clopidogrel 75 mg daily	Class IIb, Level B
	Aspirin 25 mg + extended-release dipyridamole 200 mg twice daily	Class IIa, Level A
Cardioembolic (esp. atrial fibrillation)	Warfarin (INR = 2.5)	Class I, Level A
All patients	Antihypertensive treatment	Class I, Level A
Previously hypertensive	ACE inhibitor + diuretic	Class I, Level A
Previously normotensive	ACE inhibitor + diuretic	Class IIa, Level B
Dyslipidemic	Statin	Class I, Level A
Normal lipids	Statin	Class IIa, Level B

ACE, angiotensin-converting enzyme; INR, international normalized ratio.

<sup>a</sup>American Stroke Association Evidence Grading System.

# Cont...

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## Recommendation Class:

I = Conditions for which there is evidence or general agreement that a procedure or treatment is useful and effective.

II = Conditions for which there is conflicting evidence or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.

IIa = Weight of evidence/opinion is in favor of usefulness or efficacy.

IIb = Usefulness/efficacy is less well established by evidence/opinion.

III = Conditions for which there is evidence or general agreement that a procedure or treatment is not useful/effective and in some cases may be harmful.

## Level of Evidence:

A = Data derived from multiple randomized clinical trials.

B = Data derived from a single randomized trial or nonrandomized studies.

C = Expert consensus or case studies.

# Treatment

## Pharmacologic Therapy of Hemorrhagic Stroke

- There are currently **no standard pharmacologic strategies** for treating intracerebral hemorrhage.
- **Medical guidelines** in acutely ill patients in neurointensive care units should be followed for managing
  - blood pressure
  - increased intracranial pressure and
  - other medical complications

# Cont...

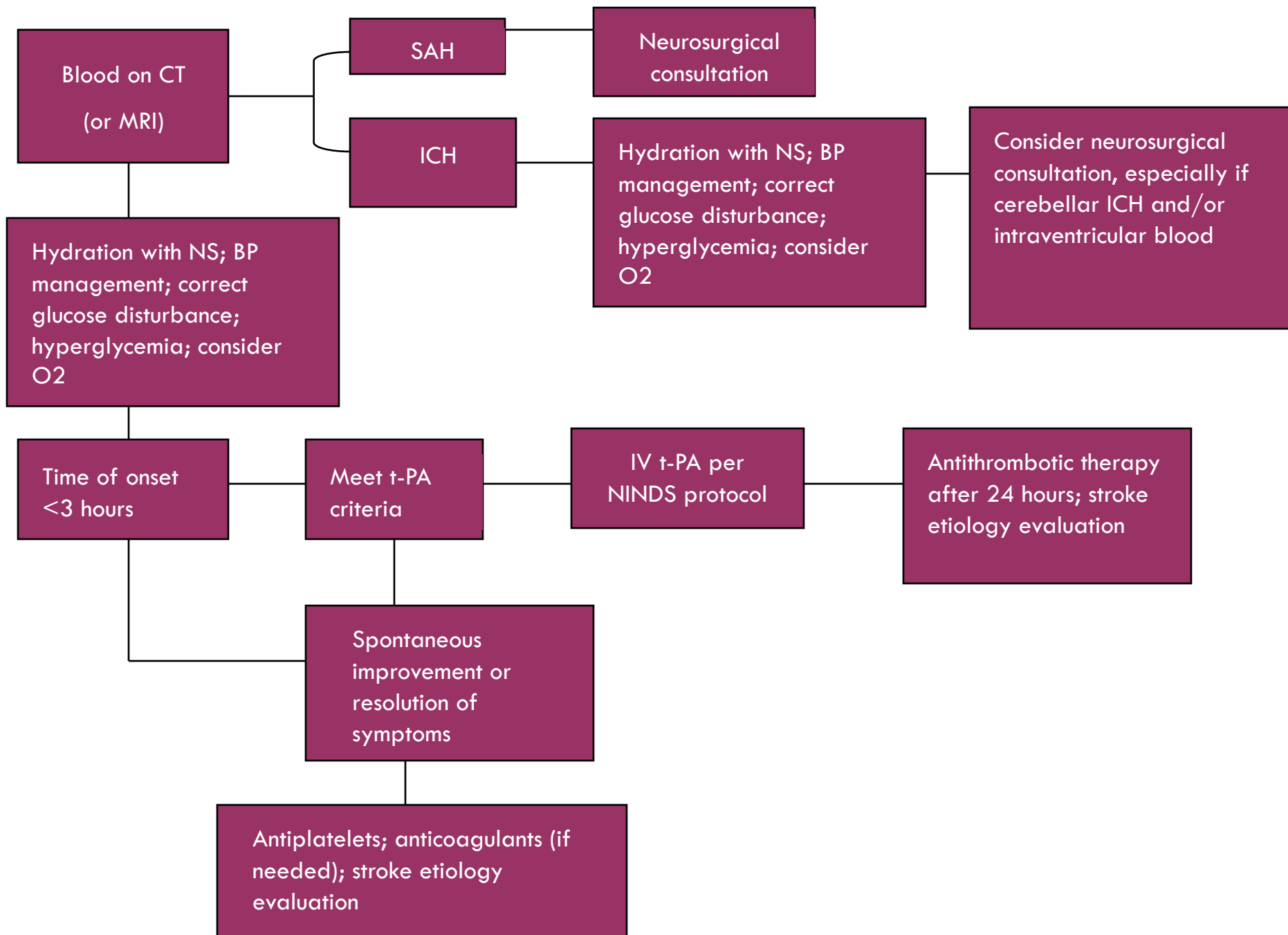
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- Subarachnoid hemorrhage due to **aneurysm rupture** is
  - associated with a high incidence of delayed cerebral ischemia in the **2 weeks** after the bleeding episode.
- **Vasospasm** of the cerebral vasculature is
  - thought to be responsible for the delayed ischemia and occurs **between 4 and 21 days** after the bleed.

# Cont...

- The calcium channel blocker **nimodipine**
  - is recommended to reduce the incidence and severity of neurologic deficits resulting from delayed ischemia.
  - Nimodipine 60 mg every 4 hours should be initiated on diagnosis and continued for 21 days in all subarachnoid hemorrhage patients.
  - If hypotension occurs, it can be managed by
    - reducing the dosing interval to 30 mg every 2 hours (same daily dose)
    - reducing the total daily dose (30 mg every 4 hours) and
    - maintaining intravascular volume and pressor therapy.





# Rehabilitation

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## **American Stroke Association guidelines focus on:**

- Managing co-morbidities
- Training for maximum independence
- Facilitating maximum psychosocial coping and adaptation by patient and family
- Preventing secondary disability
- Enhancing quality of life
- Preventing recurrent stroke

# Evaluation Of Therapeutic Outcomes

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- Patients with acute stroke should be monitored intensely for the development of
  - neurologic worsening
  - Complications and
  - adverse effects from treatments

	Treatment	Parameter(s)	Frequency
Ischemic stroke	Alteplase	BP, neurologic function, bleeding	Every 15 minutes $\times$ 1 hour; every 0.5 hour $\times$ 6 hours; every 1 hour $\times$ 17 hours; every shift after
	Aspirin	Bleeding	Daily
	Clopidogrel	Bleeding	Daily
	ERDP/ASA	Headache, bleeding	Daily
	Warfarin	Bleeding, INR, Hb/Hct	INR daily $\times$ 3 days; weekly until stable; monthly
Hemorrhagic stroke	Nimodipine (for SAH)	BP, neurologic function, ICP	Every 2 hours in ICU
		BP, neurologic function, fluid status	Every 2 hours in ICU
All patients	Heparins for DVT prophylaxis	Temperature, CBC	Temp. every 8 hours; CBC daily
		Pain (calf or chest)	Every 8 hours
		Electrolytes and ECG	Up to daily
		Bleeding, platelets	Bleeding daily, platelets if suspected thrombocytopenia

BP, blood pressure; CBC, complete blood count; DVT, deep vein thrombosis; ECG, electrocardiogram; ERDP/ASA, extended-release dipyridamole plus aspirin; Hb, hemoglobin; Hct, hematocrit; ICP, intracranial pressure; ICU, intensive care unit; INR, international normalized ratio; SAH, subarachnoid hemorrhage.

