
بسم الله الرحمن الرحيم

HYPER ACUTE BRAIN ISCHEMIC ATTACKS

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- Cerebrovascular diseases include some of the most common and devastating disorders:
- ischemic stroke(80%)
- hemorrhagic stroke(10%)
- cerebrovascular anomalies such as intracranial aneurysms and arteriovenous malformations (AVMs)

Introduction:

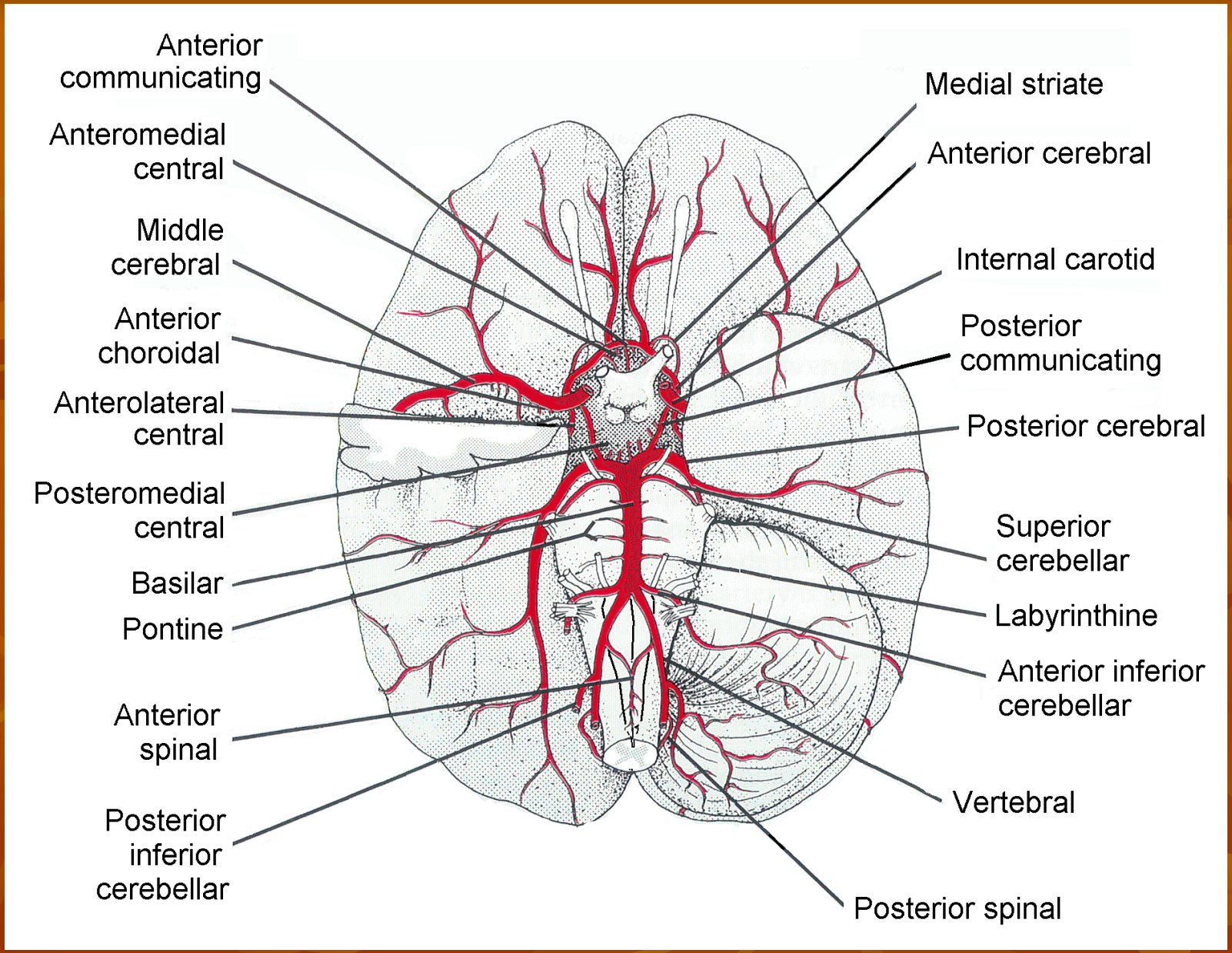
- **Stroke is a leading cause of mortality worldwide.**
- Unfortunately its incidence is more and the age of occurrence is one decade earlier in our country, Iran
- About 80-90 percent of stroke etiology is ischemic.
- The only approved drug treatment for eligible AIS patients is thrombolytic therapy by recombinant tissue plasminogen activator (tPA).
- Related level of evidence is the highest (1a).

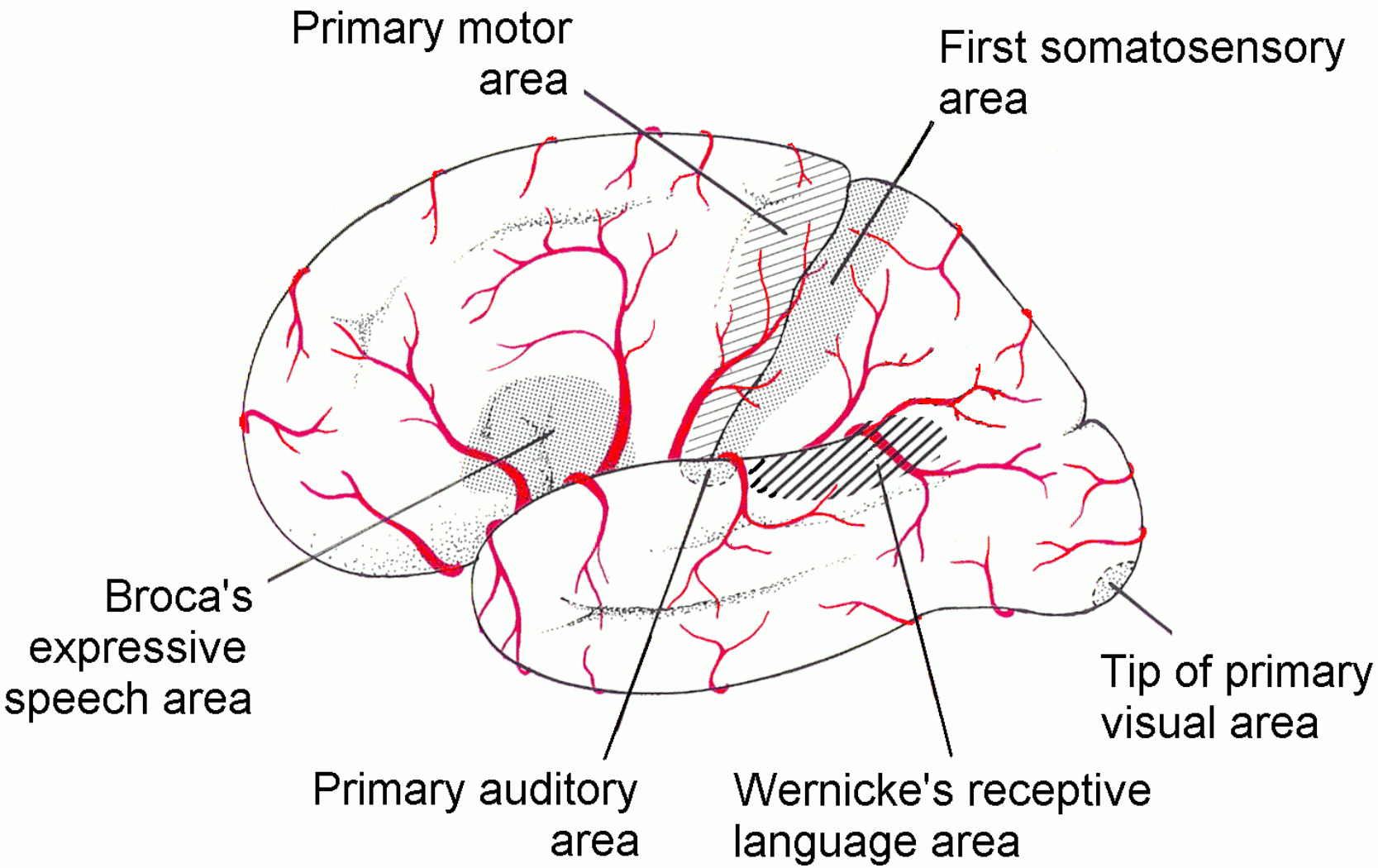
- A stroke, or cerebrovascular accident, is defined by this abrupt onset of a neurologic deficit that is attributable to a focal vascular cause.
- Thus, the definition of stroke is clinical, and laboratory studies including brain imaging are used to support the diagnosis.

ISCHEMIC STROKE

- A fall in cerebral blood flow to zero causes death of brain tissue within 4 to 10 min;
- values <16 to 18 mL/100 g tissue per min cause infarction within an hour;
- and values <20 mL/100 g tissue per min cause ischemia without infarction unless prolonged for several hours or days.

- Tissue surrounding the core region of infarction is ischemic but reversibly dysfunctional and is referred to as the ischemic penumbra.
- The ischemic penumbra will eventually infarct if no change in flow occurs, and hence saving the ischemic penumbra is the goal of thrombolytic therapy and newer therapies under investigation.


Anterior communicating
Anteromedial central
Middle cerebral
Anterior choroidal
Anterolateral central
Posteromedial central
Basilar
Pontine
Anterior spinal
Posterior inferior cerebellar
Medial striate
Anterior cerebral
Internal carotid
Posterior communicating
Posterior cerebral
Superior cerebellar
Labyrinthine
Anterior inferior cerebellar
Vertebral
Posterior spinal


Primary motor area
First somatosensory area
Broca's expressive speech area
Primary auditory area
Wernicke's receptive language area
Tip of primary visual area

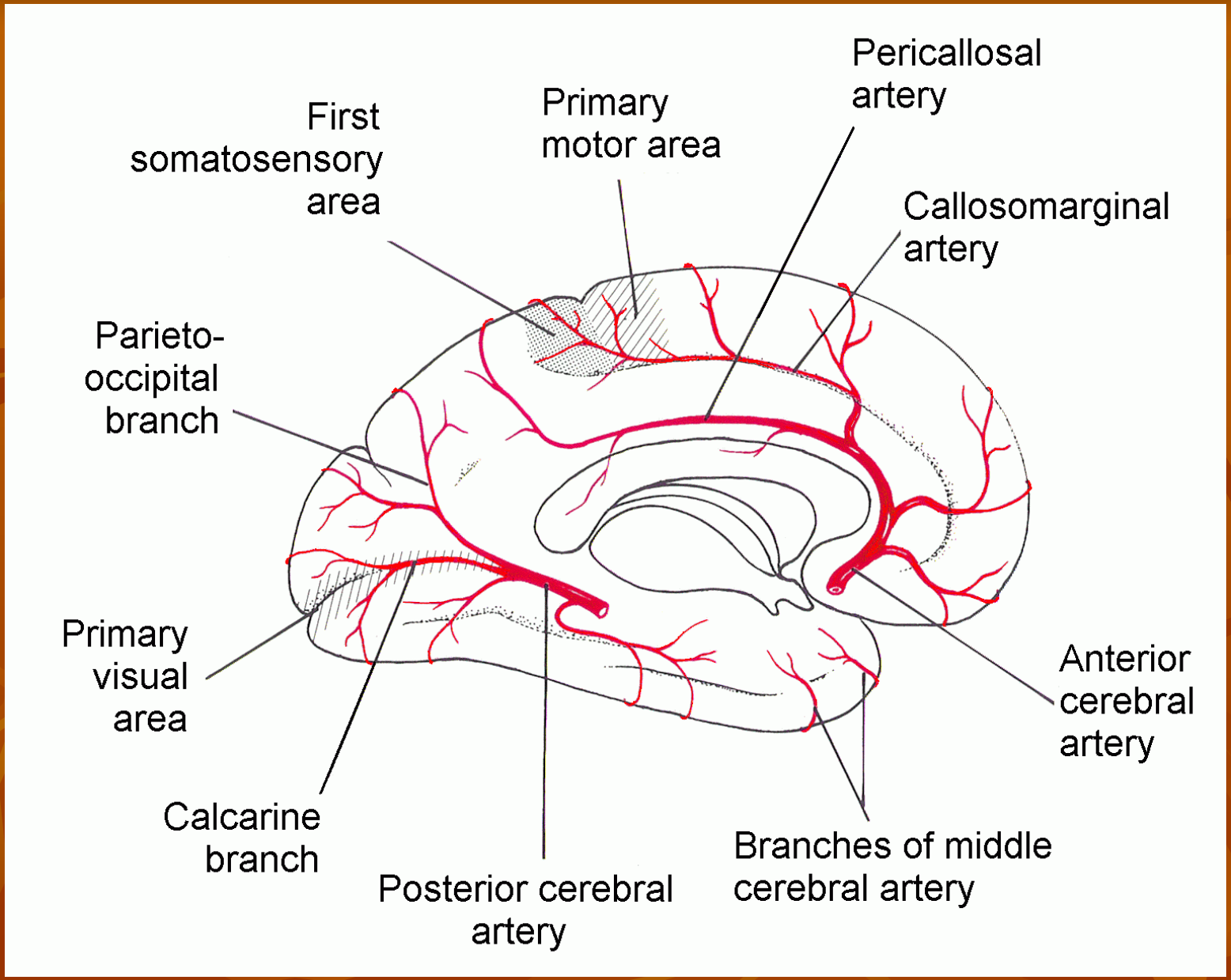

Pericallosal artery
Primary motor area
First somatosensory area
Callosomarginal artery
Parieto-occipital branch
Primary visual area
Anterior cerebral artery
Calcarine branch
Posterior cerebral artery
Branches of middle cerebral artery

TABLE 65.1 Risk Factors for Ischemic Stroke

Nonmodifiable	Modifiable
Age	Arterial hypertension
Gender	Transient ischemic attacks
Race/ethnicity	Prior stroke
Family history	Asymptomatic carotid bruit/stenosis
Genetics	Cardiac disease Aortic arch atheromatosis Diabetes mellitus Dyslipidemia Cigarette smoking Alcohol consumption Increased fibrinogen Elevated homocysteine Lack of physical activity Low serum folate Elevated anticardiolipin antibodies Oral contraceptive use Obesity

- A TIA is a prognostic indicator of stroke, with one-third of untreated TIA patients having a stroke within 5 years. About 1 in 10 patients with TIA experience a stroke in the next 3
- months.
- The 5% to 6% annual mortality rate after TIA is mainly caused by MI.
- .
- .

IV Thrombolytic Therapy

- current data do not support the use of IV streptokinase (1.5 million units) in acute ischemic stroke
- Tenecteplase (TNK) is a thrombolytic agent with a longer half-life, improved fibrin specificity, and increased resistance to plasminogen activator inhibitor 1 (PAI-1) compared to tPA
- Desmoteplase is a genetically engineered version of a clot-dissolving protein from vampire bats. lack of benefit in phase III
- Abciximab is a chimeric mouse/human monoclonal antibody with high binding for the platelet glycoprotein IIb/IIIa receptor. lack of benefit in phase III
- Argatroban is a direct IV thrombin inhibitor that was studied not powered to assess efficacy

Ia Thrombolytic Therapy

- Recombinant prourokinase (r-pro-UK) within 6 hours of symptom onset. The efficacy of treatment seemed to fall off after approximately 5 hours. also encountered a higher risk for intracranial hemorrhage with neurological deterioration within 24 hours of treatment (10%)
- While pro-UK was not approved by the FDA, the off-label use of intra-arterial tPA has become widely used within the interventional stroke realm
- In general, poor outcome factors for acute intra-arterial thrombolysis include older age, coma and quadriplegia at presentation, thrombotic (as opposed to embolic) occlusions, longer occlusions with poor collaterals, bilateral vertebral artery and caudal basilar artery occlusions, and failure to recanalize occluded arteries.
- Furthermore, it is currently unclear which thrombolytic drug and what doses to use; the type, amount, and timing of antithrombotic strategies to use afterward; and the relationship of outcome to time to treatment. There may also be a longer time window for treatment for the vertebrobasilar as opposed to carotid circulation.

Thrombolytic Therapy (rtPA=alteplase)

- recombinant tissue plasminogen activator (rtPA) remains the only proven intervention for emergency management of acute ischemic stroke and the only approved therapy for acute ischemic stroke by the FDA.
- The dose of rtPA is 0.9 mg/kg, with a maximum dose of 90 mg; 10% of the total dose is given as an initial bolus, and the rest is infused over 60 minutes

- fewer than 2% of all ischemic stroke patients received rtPA and Successful centers have treated up to 15% to 20%
- Hemorrhages 6-8% in studies are usually large-volume lobar bleeds, often multiple, with blood/fluid levels; intraventricular and subarachnoid extension is not uncommon mostly within 36 hours of treatment with 50 % mortality

- selected patients in pre-administration requires close adherence to protocol guidelines.
- Then post-administration (Patient management following rtPA) requires close neurological and blood pressure monitoring, as well as capabilities to handle potential hemorrhagic complications associated with thrombolytic therapy, by physicians experienced in the management of cerebrovascular disease

50 %deviations from national treatment guidelines

- onset from 3 to 4.5 hours.
- Possible exceptions include patients older than age 80, patients with a combination of previous stroke and DM, patients on oral anticoagulants regardless of INR values, patients with NIHSS scores above 25, and patients with evidence of major infarct or CT with compromise of more than one-third of the middle cerebral artery (MCA) territory

Approved treatment windows:

- **1996:** Less than 3 hours- IV thrombolysis


The New England
Journal of Medicine

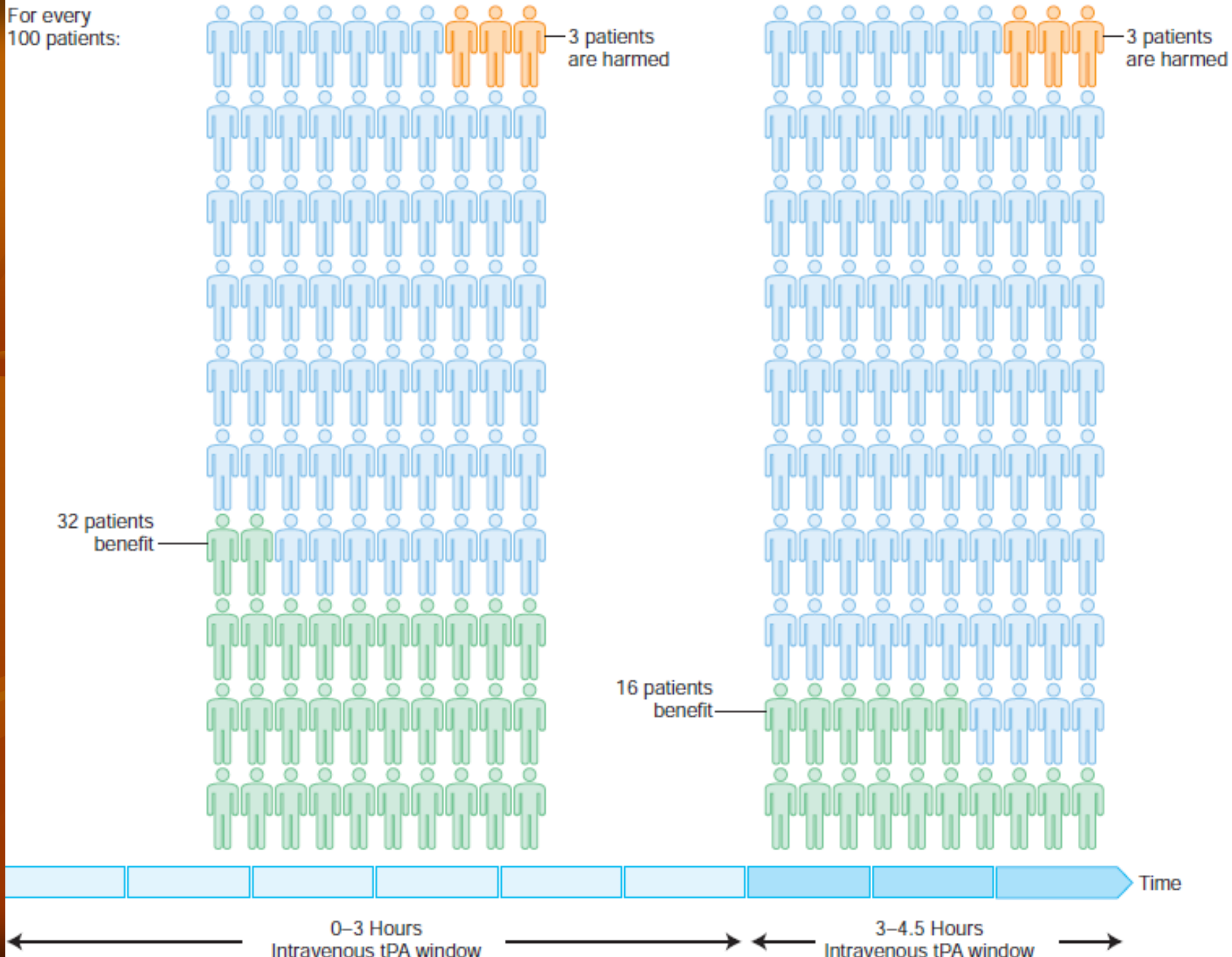
- **2009:** 3-4.5 hours- IV thrombolysis in more selected cases


AHA/ASA Science Advisory

Expansion of the Time Window for Treatment of Acute Ischemic Stroke With Intravenous Tissue Plasminogen Activator

A Science Advisory From the American Heart Association/American Stroke Association

- **2015:** Less than 6 hours- Mechanical thrombectomy in selected cases


For every
100 patients:
3 patients
are harmed
32 patients
benefit
3 patients
are harmed
16 patients
benefit
Time
0–3 Hours
Intravenous tPA window
3–4.5 Hours
Intravenous tPA window

Inclusion Criteria for IV thrombolysis of Patients with Ischemic Stroke 0-3 or 3-4.5 Hours from Symptom Onset to Beginning Treatment:

- Diagnosis of ischemic stroke
  - Non-Contrast Brain CT
- Causing measurable neurological deficit
  - Usually NIHSS scores ≥4, may be even 1-2
- Aged ≥18 years

Inclusion criteria

- time of onset (< 3 hours), Patients who awoke from sleep had symptom onset defined as "when last seen awake and normal."
- neurological deficit measurable on the NIH Stroke Scale,
- and CT scan without evidence of intracranial
- hemorrhage.

Exclusion criteria:

1- Significant head trauma or prior stroke in previous 3 months

2- Symptoms suggest subarachnoid hemorrhage

3- Arterial puncture at non-compressible site in previous 7 days

4- History of previous intracranial hemorrhage

5- Intracranial neoplasm, arteriovenous malformation, or aneurysm

6- Recent intracranial or intraspinal surgery

7- Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)

8- Active internal bleeding

9- Acute bleeding diathesis

Exclusion criteria (cont.):

10- Platelet count <100 000/mm3

11- Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal

12- Current use of anticoagulant with INR >1.7 or PT >15 seconds

13- Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)

14- Blood glucose concentration <50 mg/dL (2.7 mmol/L)

15- CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)

Relative exclusion criteria:

1. Only minor or rapidly improving stroke symptoms (clearing spontaneously)
2. Pregnancy
3. Seizure at onset with postictal residual neurological impairments
4. Major surgery or serious trauma within previous 14 days
5. Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
6. Recent acute myocardial infarction (within previous 3 months)

*Additional **Relative** Exclusion Criteria Within 3 to 4.5 Hours From Symptom Onset:*

- Aged >80 years
- Severe stroke (NIHSS>25)
- Taking an oral anticoagulant regardless of INR
- History of both diabetes and prior ischemic stroke

Most of these were absolute in ASA-2007

AHA/ASA Scientific Statement:
Age Issues: Recommendations

- For otherwise medically eligible patients ≥18 years of ageIV tPA administration **within 3 hours is equally recommended for patients ≤80 and ≥80 years of age**. (*Class I; Level of Evidence A*).
  - Older age is an adverse prognostic factor in stroke but ***does not modify the treatment effect of thrombolysis.***
  - Although older patients have poorer outcomes, higher mortality, and higher rates of sICH than those <80 years of age, compared with control subjects, *IV tPA provides a better chance of being independent at 3 months across all age groups.*

AHA/ASA Scientific Statement: **Pregnancy and Postpartum**

- IV tPA administration for ischemic stroke may be considered in pregnancy when the **anticipated benefits of treating moderate to severe stroke outweigh the anticipated increased risks of uterine bleeding** (*Class IIb; Level of Evidence C*).

- The ***safety and efficacy of IV tPA in the early postpartum period (<14 days after delivery) have not been well established*** (*Class IIb; Level of Evidence C*).

- **Urgent consultation** with an obstetrician-gynecologist and potentially a perinatologist to assist with management of the mother and fetus is recommended (*Class I; Level of Evidence C*).

AHA/ASA Scientific Statement: Menstruation and Menorrhagia-2

- When there is a history of **recent or active vaginal bleeding causing clinically significant anemia**, then **emergent consultation** with a gynecologist is probably indicated before a decision about IV tPA is made (*Class IIa; Level of Evidence C*).
- In patients who are menstruating or have active vaginal bleeding and are treated with alteplase, the **degree of vaginal bleeding should be monitored for 24 hours after alteplase** (*Class I; Level of Evidence C*).

AHA/ASA Scientific Statement: **Anticoagulant Use**

- IV tPA may be reasonable in patients who have a history of warfarin use and an INR ≤1.7 (*Class IIb; Level of Evidence B*).
- IV tPA in patients who have received a dose of **LMWH (prophylactic/treatment dose) within the previous 24** hours is not recommended. (*Class III; Level of Evidence B*). sICH:*8.5 , mortality: *5.4

AHA/ASA Scientific Statement: History of Recent Acute MI

- In concurrent AIS and acute MI, treatment with IV tPA at the dose appropriate for cerebral ischemia, *followed by percutaneous coronary angioplasty and stenting if indicated*, is reasonable (*Class IIa; Level of Evidence C*).
- For AIS and a history of recent MI in the past 3 months, treating IV tPA is reasonable if:
  - the recent MI was non-STEMI (*Class IIa; Level of Evidence C*),
  - the recent MI was STEMI involving the right or inferior myocardium (*Class IIa; Level of Evidence C*),
  - and may be reasonable *if the recent MI was STEMI involving the left anterior myocardium* (*Class IIb; Level of Evidence C*).

AHA/ASA Scientific Statement: **Intracranial Neoplasms**

- IV tPA treatment is **probably recommended** for patients with AIS who harbor an **extra-axial intracranial neoplasm** (*Class IIa; Level of Evidence C*).

- IV tPA treatment for patients with AIS who harbor an **intra-axial intracranial neoplasm** is **potentially harmful** (*Class III; Level of Evidence C*).

AHA/ASA Scientific Statement: **Seizure at Stroke Onset Syndrome**

- IV tPA is reasonable in patients with a seizure at the time of onset of acute stroke if evidence suggests that **residual impairments are secondary to stroke** and not a postictal phenomenon (Class IIa; Level of Evidence C).

AHA/ASA Scientific Statement:
Concurrent Antiplatelet Medication

- The administration of **aspirin (or other antiplatelet agents)** as an adjunctive therapy within 24 hours of IV tPA is not recommended (*Class III; Level of Evidence C*).
- The **concurrent administration of other intravenous antiplatelet agents** that inhibit the glycoprotein IIb/ IIIa receptor is not recommended outside a clinical trial (*Class III; Level of Evidence B*).
- **IV tPA is recommended** for patients **taking (one) antiplatelet drug** monotherapy before stroke on the basis of evidence that the benefit of alteplase outweighs a possible small increased risk of sICH (*Class I; Level of Evidence A*).
- **IV tPA is recommended** for **patients taking antiplatelet drug combination therapy** (eg. aspirin and clopidogrel) before stroke on the basis of evidence that the benefit of alteplase outweighs a probable increased risk of sICH (*Class I; Level of Evidence B*).

AHA/ASA Scientific Statement:

Aortic Arch Dissection and Cervicocephalic Arterial Dissection, Known or Suspected

- IV tPA in AIS **known or suspected to be associated with aortic arch dissection** is not recommended and is **potentially harmful** *(Class III; Level of Evidence C)*.

- IV tPA in AIS known or suspected to be associated with **extracranial cervical arterial dissection** is **reasonably safe within 4.5 hours** and is probably recommended *(Class IIa; Level of Evidence C)*.

- IV tPA usefulness and hemorrhagic risk in AIS known or suspected to be associated with **intracranial arterial dissection** remain **unknown, uncertain**, and not well established *(Class IIb; Level of Evidence C)*.

AHA/ASA Scientific Statement:

Suspicion of SAH on Pretreatment Evaluation

- **IV tPA is contraindicated in patients presenting with symptoms and signs most consistent with an SAH (*Class III; Level of Evidence C*).**

AHA/ASA Scientific Statement:

Diabetic Hemorrhagic Retinopathy or Other Ophthalmological Conditions

- Use of IV tPA in patients presenting with AIS who have a **history of diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions** is **reasonable** to recommend, but the potential increased risk of visual loss **should be weighed** against the anticipated benefits of reduced stroke-related neurological deficits (*Class IIa; Level of Evidence B*).

AHA/ASA Scientific Statement:

Catheterization Laboratory Environment/ Endovascular Complications/Stroke Syndrome

- IV tPA is reasonable for the treatment of AIS complications of cardiac or cerebral angiographic procedures, depending on the ***usual eligibility criteria*** (*Class IIa; Level of Evidence A*).

AHA/ASA Scientific Statement: **Sickle Cell Disease**

- Acute management of ischemic stroke resulting from SCD should include optimal hydration, correction of hypoxemia, correction of systemic hypotension, and blood exchange to reduce the percentage of hemoglobin S levels (*Class I; Level of Evidence B*).
- IV tPA for children and adults presenting with an AIS with known SCD is not well established (*Class IIb; Level of Evidence C*).

2015 AHA/ASA Focused Update of the 2013 Guidelines

- ***Patients eligible for intravenous r-tPA should receive intravenous r-tPA even if endovascular treatments are being considered (Class I; Level of Evidence A). (Unchanged)***
- **Patients should receive endovascular therapy with a stent retriever if they meet *all the following criteria (Class I; Level of Evidence A).* (New recommendation):**
  - (a) Prestroke mRS score 0 to 1,
  - (b) acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies,
  - (c) causative occlusion of the internal carotid artery or proximal MCA (M1),
  - (d) age ≥18 years,
  - (e) NIHSS score of ≥6,
  - (f) ASPECTS of ≥6, and
  - (g) treatment can be initiated (groin puncture) within 6 hours of symptom onset

Poor prognosis (less favorable outcome and/or increased risk)

- mass effect or low attenuation on a third or more of the MCA territory on pretreatment CT scan; advanced age; prior head injury; DM; marked elevation of the blood pressure before, during, and after treatment; hypertension requiring postrandomization antihypertensive treatment; severe pretreatment neurological deficits


THANKS FOR YOUR ATTENTION