

Ischemic Stroke – Treatment, Prevention

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PREHOSPITAL CARE

- ABC** ± supplemental oxygen.
 - ischemic stroke patient usually maintains airway unless brain stem is affected or significant edema is compressing opposite hemisphere.
- Establish **IV lines**.
- Measure **serum [glucose]** → administer glucose in hypoglycemic patients; otherwise, glucose containing fluids should be avoided.
- Prehospital stroke assessment tools** (e.g. Cincinnati Prehospital Stroke Scale, Los Angeles Prehospital Stroke Scale).
- Transportation to hospital** (unless deficit has existed for several days and is stable) with **prehospital notification** of stroke teams (allows early mobilization of necessary resources).

N.B. patients at risk for stroke must be educated:

If you experience **main warnings of acute ischemic stroke** (sudden weakness or numbness on one body side, sudden loss / change of vision, sudden speech difficulty / language comprehension difficulty, sudden dizziness / gait difficulty) that last for 10 minutes → call 911 immediately!

HOSPITAL CARE

NINDS Recommended Stroke Evaluation Targets for Potential Thrombolysis Candidates:

Time Interval	Time Target
Door to doctor	10 min
Access to neurologic expertise	15 min
Door to CT scan completion	25 min
Door to CT scan interpretation	45 min
Door to treatment	60 min
Admission to monitored bed	3 h

- 25% of patients worsen in first 24-48 hours after admission!
- immediately after initial assessment and stabilization, perform **noncontrast CT**

SUPPORTIVE MANAGEMENT

- Blood GLUCOSE** - determine and treat early (both **hypoglycemia** and **hyperglycemia** can ^{a)}cause symptoms that closely mimic ischemic stroke or can ^{b)}aggravate ongoing neuronal ischemia!):
 - hypoglycemia** → D50
 - hyperglycemia** (> 185* mg/dL) → insulin
 - *threshold for treating according to American Heart Association guidelines (formerly it was > 300 mg/dL)
- Supplemental OXYGEN** – only if indicated (SaO₂ < 90%, hypotensive, etc.)
 - conflicting evidence exists that supernormal oxygenation improves outcome.
- Intravenous FLUIDS** (all stroke victims are dehydrated) - IV isotonic NaCl solution at 50-125 mL/h (unless otherwise indicated) – keep normovolemia (↑ → brain edema; ↓ → reduced perfusion to penumbra)
 - N.B. avoid D5W* and excessive fluid administration! (esp. in large strokes)
 - *animal studies demonstrate that dextrose causes increase in cerebral infarction size
- Temperature** - avoid **hyperthermia** > 100.4°F – increases morbidity (H: oral or rectal **ACETAMINOPHEN** 325-1000 mg q4-6h; not to exceed 4 g/24 h).
- Continuous cardiac monitoring** - for **ischemic changes** or **atrial fibrillation**.
- ICP control** see p. S50 >>
 - risk factors (for dangerous ICP↑) – **large** infarctions, **cerebellar** infarctions.
 - N.B. brain edema peaks on 2nd or 3rd day (causes mass effect for 10 days).
 - prophylactic measures - **head of bed elevated to 30°**, **free water restriction**, **IV mannitol**.
 - **corticosteroids** are not recommended.
 - ICP↑ decreases cerebral blood flow.
- Seizure control**
 - prophylactic anticonvulsants to recent stroke without seizures are not recommended.
 - **benzodiazepines** (**DIAZEPAM***, **LORAZEPAM****) are first-line drugs for ongoing seizures; for recurrent seizures, use prolonged duration parenteral alternatives - **FOSPHENYTOIN**, **PHENOBARBITAL**, **SODIUM VALPROATE**.

*5 mg IV q5-10min; maximum total dose - 20 mg
 **1-4 mg IV over 2-10 min; may repeat q10-15min

8. **Oral intake** - **NPO initially** (aspiration risk is great - avoid oral intake until swallowing assessed! - evaluation by speech-language pathologist ± videofluorographic swallowing study)
 - dysphagia / impaired mastication → **temporary enteral feeding tube**.
 - if patient remains at significant aspiration risk for foreseeable future → **percutaneous endoscopic gastrostomy (PEG)** feeding tube.
 - If oral feedings are restricted for prolonged periods, **IV THIAMINE supplementation** becomes important to prevent Wernicke's disease.
 - **dietitian consultation** - to prevent **poststroke malnutrition**.
9. **FOLEY CATHETERS** increase UTI risk - should be used only when absolutely necessary.
10. **Complex of bedridden patients:**
 - 1) **deep vein thrombosis** (esp. in paretic limbs): sequential compression stockings, SC heparin / low-molecular-weight heparin (**ENOXAPARIN** is generally preferable to **HEPARIN**, except HEPARIN causes less extracranial hemorrhages than ENOXAPARIN).
 - 2) **pulmonary toilet**: chest physical therapy, frequent turning (supine ↔ unaffected side), volumetrics (deep breaths – to prevent atelectasis).
 - 3) **pressure sores**: frequent skin inspection, routine skin cleansing, frequent turning, special mattresses and protective dressings, improve patient's mobility.
 - 4) **limb position** must be **physiologic** and **reverse of Wernicke –Mann position**.
11. **Activity** is tailored to stroke severity.
 - **head of bed elevated to 30°** - aspiration and ICP↑ precaution.
 - **bed rest** for at least 24 hours - to avoid postural hypotension (autoregulation is ineffective in areas of ischemic brain!).
 - **physical therapist** (consultation within first 24 hours of hospitalization) will suggest level of activity.
 - **mobilize patient as early as possible!** (start with passive range-of-motion exercises to affected limbs → out of bed after 24 hours)
 - **at discharge** - encourage to increase activity as tolerated (falls are one of most common causes of injury).
 - patients often benefit from brief, intensive rehabilitation in specialized hospitals before being sent home.
12. Start **occupational, physical, speech** therapy.
13. **Depression** treatment

BLOOD PRESSURE

- should be monitored frequently (or even continuously) for first 48-72 hours.

HYPERTENSION

Caution in lowering BP acutely! (autoregulation is impaired → reduced perfusion to penumbra)
 Generally, **do not treat BP < 220/120 mmHg for 72 hrs** (then do not reduce below 160-170/90-100 for 1 wk)

Non-candidate for thrombolysis:

Blood Pressure	Treatment
DBP < 120 or SBP < 220 or MAP < 130 mmHg	therapy indicated only if other end-organ damage (<i>AMI, aortic dissection, severe CHF, hypertensive encephalopathy, retinal hemorrhages, acute renal failure</i>)
DBP 121-140 or SBP > 220 or MAP > 130 mmHg	a) LABETALOL 10 mg IV → repeat and double q10min up to total dose of 150 mg b) NICARDIPINE 5 mg/h
DBP > 140 mmHg	SODIUM NITROPRUSSIDE IVI 0.5 mcg/kg/min titrate up to 10 mcg/kg/min

Candidate for thrombolysis – hypertension is **treated more aggressively**:

Blood Pressure	Treatment
SBP > 185 or DBP > 110 mmHg	a) LABETALOL 10-20 mg IV 1-2 doses b) ENALAPRIL 1.25 mg IV
<i>POST-THROMBOLYSIS:</i>	
DBP 105-120 or SBP 180-230 mmHg (on 2 readings 5-10 min apart)	LABETALOL 10 mg IV → repeat and double q10min up to total dose of 150 mg
DBP 121-140 or SBP > 230 mmHg (on single reading)	LABETALOL 10-20 mg IV → titrated infusion: a) LABETALOL 1-2 mg/min (up to 8 mg/min) b) NICARDIPINE 5 mg/h (up to 15 mg/h)
DBP > 140 mmHg	SODIUM NITROPRUSSIDE IVI 0.5 mcg/kg/min titrate up to 10 mcg/kg/min

HYPOTENSION

– in small proportion of hypotensive patients, pharmacologically increasing BP may improve flow through critical stenoses.

PATHOGENETIC TREATMENT

Currently, **tPA** and **ASPIRIN** are only generally accepted therapies for acute ischemic stroke

Treatments that have not been proven beneficial:

1. **VASODILATORS** (CO₂, **papaverine**) – cause **paradoxical blood steal** from ischemic tissue.
2. **VISCOSITY REDUCTION** (to improve microcirculation) – may be beneficial only under certain circumstances: **low-molecular-weight dextran**, **mannitol**.
3. **DECREASING METABOLIC DEMANDS** (**hypothermia**, **barbiturates**).
4. **HYPEROXYGENATION**
5. **STEROIDS** (may be effective in fat embolism)
6. **NEUROPROTECTANTS** *see below >>*

Aggressive efforts to **restore cardiovascular circulation** is the only treatment after **WATERSHED INFARCTION** (e.g. after cardiac arrest).

THROMBOLYSIS

Thrombolytic agents → see p. 1597 (1-4) >>

Aim for "**door-to-needle time**" (interval from patient arrival at ED to start of thrombolysis) of **60 min**.

Initial testing:

1. Noncontrast CT
2. Blood work - glucose, prothrombin time, aPTT, platelet count.
3. Pregnancy test.

INCLUSION CRITERIA

1. More than minimal **neurologic deficit** (greater than minimal weakness, isolated ataxia, isolated sensory deficits, or isolated dysarthria)
2. No CT evidence of **intracranial hemorrhage**
3. **Time of onset < 3 hours** (studies show efficacy up to ≤ 4.5 hrs*).
*patients with **MRA-DWI mismatch** benefit most

N.B. reasons for treating (risk/benefit analysis) or not treating patient must be documented clearly!

EXCLUSION CRITERIAI. **History:**

- 1) **seizure** at stroke onset
- 2) **stroke** or serious **head trauma** within 3 months
- 3) **major surgery** or serious **bodily trauma** within 2 weeks
- 4) prior **ICH**
- 5) intracranial **neoplasm**
- 6) symptoms suggestive of **SAH** (even if CT is negative)
- 7) **AVM** or **aneurysm**
- 8) **GI** or **urinary tract hemorrhage** within 21 days
- 9) **arterial puncture** at noncompressible site or **lumbar puncture** within 1 week
- 10) concomitant **oral anticoagulant** (INR > 1.7)
- 11) **heparin** within 48 hrs (aPTT > 40 sec)

N.B. no age limits (also for children?)

II. **Physical examination:**

- 1) **minimal neurological deficit** (NIHSS score < 4) (e.g. minimal weakness, isolated ataxia, isolated sensory deficit, isolated dysarthria).
- 2) **rapidly improving** neurological signs.
- 3) **blood pressure:**
 - a) systolic BP > 185 mmHg
 - b) diastolic BP > 110 mmHg
 - c) aggressive (continuous IV) treatment required to lower BP to this range
- 4) suspected **acute pericarditis**

N.B. patients with **severe neurologic deficit** (NIHSS score > 22) are at increased risk of symptomatic hemorrhagic transformation, but still tend to benefit from thrombolysis!

III. **Laboratory:**

- 1) **platelet** count < $100 \times 10^9/L$
 - 2) **INR** > 1.7 (PT > 15)
 - 3) **aPTT** elevated beyond reference range
 - 4) **glucose** < 50 mg/dL (< 2.78 mmol/L) or > 400 mg/dL (> 22.2 mmol/L)
 - 5) positive **pregnancy test** (in woman of childbearing age)
- blood should be sent for type and screen (in case transfusions are required).
 - ECG is not required before thrombolysis.

IV. **Neuroimaging:**

Immediate noncontrast CT* is imperative - any **intracerebral hemorrhage** is absolute contraindication to thrombolysis!!!

- **early CT signs of major infarction** (edema, mass effect, hypodensity involving > 1/3 of MCA territory) are reason for caution - increased risk of hemorrhage!

***immediate MRI** may be obtained in lieu of CT (MRI should include susceptibility-weighted sequence to detect acute ICH).

N.B. in general, **CT must be \approx normal** for thrombolysis to perform!

TYPES

INTRAVENOUS - only when treatment can be initiated **within 3 hours from stroke onset**.

TIME WINDOW of treatment:

- first 90 minutes \rightarrow odds of favorable outcome increased by 2.8-fold;
- 91-180 minutes \rightarrow 1.6-fold;
- 181-270 minutes \rightarrow 1.4 fold;
- 271-360 minutes \rightarrow did not improve outcome in statistically significant manner.

PREPARATIONS:

- 1) **STREPTOKINASE** – increases morbidity & mortality rates!
- 2) **TISSUE PLASMINOGEN ACTIVATOR (TPA)** (ALTEPLASE) – only drug FDA approved (in 1996) for acute ischemic stroke;
 - 0.9 mg/kg IV (maximum dose, 90 mg).
 - 10% is given by rapid IV injection over 1 minute, remainder by IVI over 60 min.

INTRA-ARTERIAL (s. THROMBOLYSIS IN SITU)

- not approved by FDA, but commonly administered as **off-label therapy at tertiary centers** (esp. after IV tPA failure):

- within 6 hours of onset** - in anterior circulation;
- up to 12-24 hours after onset** - in posterior circulation.

- angiographically directed **recombinant PROUROKINASE**.

PROCEDURE

- ICU
- nothing by mouth.
- patient should be confined to bed rest.
- **close BP regulation is critical in first 24 h** (keep < 185/110 mmHg – use **LABETALOL** or **NITROPRUSSIDE** as necessary):
 - at least q 15 min (for first 2 h after start of therapy);
 - at least q 30 min for next 6 h and at least hourly for next 16 h.
- **antiplatelets** and **anticoagulants** should be avoided for 24 h after thrombolysis.
 - **repeat head CT / MRI** (24 hours after tPA - to rule out asymptomatic hemorrhagic transformation) prior to initiating antithrombotic therapy.

COMPLICATIONS

1. **Intracerebral hemorrhage** (6.4%; vs. 0.6% without thrombolysis) - typically occurs within first 12-36 hours - neurological deterioration, acute hypertension, headache, nausea / vomiting \rightarrow prompt repeat CT; H: cryoprecipitate, platelets, fresh frozen plasma.

N.B. mortality is unchanged and neurologic outcome is significantly improved at 3 months* in patients treated with TPA!

*almost 50% patients achieve essentially full recovery

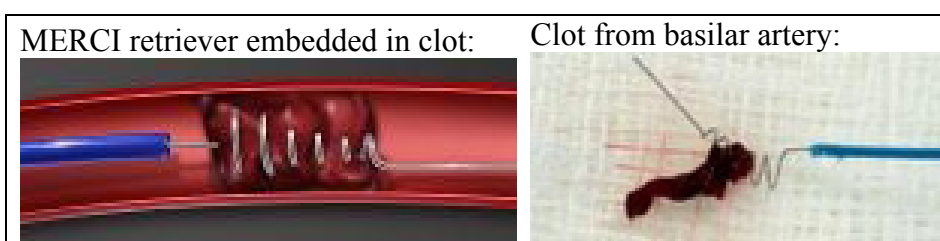
2. **Other bleedings** - GI tract, genitourinary tract (associated with Foley catheters).
3. **Oozing** from vessel puncture sites (30%) - noncompressible arterial punctures, internal jugular or subclavian venous punctures must be avoided.

4. **Angioedema** (rare)
5. **Reperfusion injury** (progressive destruction of reversibly damaged cells) - INFLAMMATORY RESPONSE as leukocytes reenter previously hypoperfused region:
 - 1) leukocyte-endothelial adhesion → direct microcirculation obstruction ("no-reflow" phenomenon)
 - 2) leukocyte infiltration → release of toxic products - free radicals, cytokines (important component of CNS ischemic injury!)
 - main pro-inflammatory cytokines: IL-1, TNF- α (some studies suggest that it may also have protective role), IL-6.
 - inhibition of IL-1 has been shown to produce therapeutic benefit.

MECHANICAL THROMBOLYSIS / THROMBECTOMY

- angiographically-guided.
- used in cerebral vessels 2-5 mm.
- removes clot in matter of minutes (even intra-arterial thrombolysis takes as long as 2 hours to dissolve thrombus) - potentially *extended treatment window!*

Mechanical embolus removal in cerebral ischemia (MERCİ) system - FDA approved **corkscrew-like apparatus** (concentric MERCİ retriever) for persistent vessel occlusion after IV tPA.



- corkscrew itself resides in catheter tip, which shields it from wall of vessel until it is ready to be burrowed into clot.
- once lodged in clot, device and clot are withdrawn from vessel.

AngioJet system (discontinued study) - uses **saline jets** that are directed back into catheter to create low-pressure zone around catheter tip, inducing suction:

- clot is pulled into exhaust lumen and removed from vessel.
- although FDA has approved this device for AV dialysis grafts and fistulae, coronary arteries, saphenous vein grafts, peripheral vessels, *clinical trials for acute stroke are no longer in progress:*
 - 1) in one study (thrombi in ICA), despite angiographic successes, **clinical outcomes were poor** (authors postulated poor collateral flow)
 - 2) in other study (thrombi in MCA), **vessel perforations** occurred → SAH.



AngioJet catheter, shown with its saline jets activated:



Latis laser device (discontinued study) - uses **laser energy** to ablate clots.

- preliminary account of first 5 patients enrolled in trial reported that **device could not be delivered to clot** (although catheter design was changed, efficacy trial was not pursued).

Endovascular photo acoustic recanalization (EPAR) laser (discontinued study) - **laser energy** is delivered by fiberoptics to catheter tip at treatment site.

- laser light absorption by darkly pigmented materials (i.e. clot) occurs inside 1-mm catheter tip → absorption converts photo energy to **acoustic energy**, which then emulsifies clot inside catheter tip.
- acceptable safety, causing no complications during active lasering (1 vessel ruptured during manual injection with 1-mL syringe [instead of recommended 3-mL syringe] → distal catheter balloon → fatal vascular rupture).
- **loss of funding** stopped further clinical testing.

EKOS ultrasound thrombolytic infusion catheter (ongoing studies) - combines distal **ultrasound** transducer with infusion of **thrombolytic** agent through microcatheter.

- ultrasound changes structure of clot to temporarily increase its permeability while providing acoustic pressure gradient to move drug into clot to speed its dissolution.

Devices not evaluated in acute-stroke trials:

1. **Snare-like devices** - simple in design and do not require clot to be amenable to emulsification.
2. **X-Sizer device** - small, moving blades at catheter tip - thrombus excision and aspiration.
3. **Suction thrombectomy** - one of simplest methods of mechanical thrombolysis - suction is applied with syringe to remove thrombus.

Penumbra Aspiration Device – FDA cleared* (Jan 17, 2008) for acute stroke due to large vessel occlusion **within 8 hours** of symptom onset (i.e. for those presenting too late for thrombolysis); 11% develop major intracerebral bleeding after vessel reopening.

*i.e. cleared it to be on shelf but not approved for treatment in stroke patients

ANTIAGGREGANTS

- a) **ASPIRIN** (81-1300 mg/d) - only therapeutic agent (besides thrombolytics) shown to improve outcome in acute stroke (although effect is modest).

N.B. aspirin is not alternative to thrombolysis!

- b) **TICLOPIDINE** (250 mg \times 2/d)
- c) **CLOPIDOGREL** (75 mg/d)

Indications: (start within 24-48 hours of onset, but delay for 24 h after thrombolytic therapy)

- 1) **stable stroke**; if stroke is *unstable (progressing)* – use IV **HEPARIN** see below
- 2) **new-onset TIA**.
- 3) all **lacunar TIAs** / strokes are treated with antiaggregants.

Studies with ABCIXIMAB stopped - dramatically higher rate of intracerebral hemorrhage!!!

ANTICOAGULATION

Indications for immediate* full-dose IV HEPARIN (after stroke or TIA):**

*delay for at least 24 hours after IV fibrinolysis

**vs. low-dose SC heparin

- a) high risk of **cardiogenic re-embolization** (unless source is bacterial endocarditis):
 - 1) AF with proven intracardial thrombus on echocardiography*
 - *AF without thrombus → **ASPIRIN** (160 mg/d) in acute phase → anticoagulation.
 - 2) artificial valves
 - 3) left atrial or ventricular thrombi

- 4) MI during last 4 weeks.
- b) extracranial / intracranial stenosis (large arteries) with **unstable (recent-onset or crescendo) TIAs** or **early unstable (progressive) stroke**; **ASPIRIN** after acute period.
N.B. it is difficult to predict or monitor stroke progression; thus many physicians heparinize all patients with recent mild ischemic stroke in order to prevent worsening that will occur in at least 20% patients.
- c) symptomatic **stenosis of extracranial ICA** prior to short-term operation (otherwise, **ASPIRIN** should be given).
- d) **basilar artery thrombosis** - IV heparin is started before intra-arterial fibrinolysis (alternatively, anticoagulation could be started afterwards if thrombolysis or angioplasty can be performed quickly after admission).
- e) symptomatic **dissection of arteries** supplying brain (after CT exclusion of SAH).
- f) **venous sinus thrombosis** (even if associated with cerebral hemorrhage!); continue as oral anticoagulation for at least 6 months (INR 2-3).
- g) **hypercoagulability** (e.g. protein C and S deficiencies, activated protein C resistance, antithrombin deficiency*, relevant titer of antiphospholipid antibodies).
*may use antithrombin III concentrates

Dosage:

Patient	Loading IV	Maintenance IVI*
Normal	80 U/kg (e.g. 5000 U)	18 U/kg/h (e.g. 1000 U/h)
Elderly	70 U/kg	15 U/kg/h
Pediatric	50 U/kg	25 U/kg/h

*20,000-25,000 U in 250-500 mL D5W

- continue for 3-7 days → make decision about long-term prophylaxis (antiplatelets or anticoagulants).
Bleeding complication rate for 7 days of HEPARIN is ≈ 10%

Monitoring - **aPTT** q6h until reaches therapeutic **1.5-2 times control value** (avoid INR > 2)

- aPTT ≤ 1.2 times control: 80 U/kg bolus + increase of 4 U/kg/h
- aPTT = 1.2-1.5 times control: 40 U/kg bolus + increase of 2 U/kg/h
- aPTT = 1.5-2.3 times control: no change
- aPTT = 2.3-3 times control: decrease by 2 U/kg/h
- aPTT > 3 times control: hold infusion for 1 h → decrease by 3 U/kg/h

for dosage adjustment see also p. 1596 (2a) >>

Contraindications to IV heparin - **risk of cerebral hemorrhage:**

- 1) **large** (> 5 cm) brain infarctions (delay anticoagulation for 5-7 days)
- 2) pronounced **microangiopathic** changes in brain
- 3) uncontrolled **hypertension**
- 4) **bacterial endocarditis** (→ intensive antibiotic therapy)
- 5) **hemorrhagic** infarctions (delay anticoagulation for 2-6 weeks)

N.B. anticoagulation is used ASAP in hemorrhagic venous infarcts!

see p. Vas13 >>

in case of hemorrhagic conversion:

- a) **urgent need of anticoagulation** (e.g. artificial heart valves) → **continue full-dose IV heparin** (only after normalization of INR values by prothrombin complex and/or other warfarin antagonists if received prior oral anticoagulation)
 - b) **other patients** → **switch to SC heparin** in body-weight-adapted dose.
- several randomized controlled trials failed to show significant overall benefit of SC heparin, IV heparinoids, SC low-molecular-weight heparin (LMWH).
N.B. LMWH should not be used routinely in stroke management!; indication for LMWH - indicated early anticoagulation but contraindicated heparin.

NEUROPROTECTIVE AGENTS

At present, **no agent** with putative neuroprotective effects can be recommended for treatment of acute ischemic stroke in humans!!!

- attempt to save ischemic neurons from irreversible injury.
- main target – neurons in **ischemic penumbra**.
- mechanisms of action:
 - b) prevent release of excitatory neurotransmitters - prevent **EARLY ISCHEMIC INJURY**.
 - c) prevent detrimental events associated with return of blood flow - prevent **REPERFUSION INJURY**.

Ischemic cascade appears to be so complex that *targeting single pathway may be ineffective* - optimal therapy may be achieved by “**stroke cocktail**”.

PREVENTION OF EARLY ISCHEMIC INJURY

- ischemia leads to excessive activation of **excitatory amino acid** receptors, accumulation of **intracellular calcium**.

N-methyl-D-aspartate (NMDA) Receptor Antagonists

- most commonly studied neuroprotective agents for acute stroke.

Direct NMDA antagonists - adverse effects (hallucinations and agitation) mimic those seen with **PHENCYCLIDINE**, which binds at similar site.

- DEXTROMETHORPHAN** (noncompetitive NMDA antagonist).
- SELFOTEL** (competitive NMDA antagonist) – increases mortality.
- APTIGANEL** – concerns regarding benefit-to risk-ratios.

Indirect NMDA antagonists - prevent glycine from binding, which in turn prevents glutamate from activating receptor.

AGENT GV150526 - safe and well tolerated, but offers no improvement.

MAGNESIUM - may reduce ischemic injury by increasing regional blood flow, antagonizing voltage-sensitive Ca²⁺ channels, and blocking NMDA receptor.

Modulation of Non-NMDA Receptors

- NALMEFENE** (Cervene) - narcotic receptor antagonist that reduces levels of excitatory neurotransmitters; minimal side effects; no clinical benefit was found in phase III clinical trial.
- LUBELUZOLE** - exact mechanism of action is unclear (may block sodium channels, may reduce release of nitric oxide, neurotransmitter generated by activation of NMDA receptor); trial was unable to confirm efficacy.
- CLOMETHIAZOLE** (GABA agonist) - anticonvulsant and sedative; stroke studies negative.

Calcium channel blockers (**NIMODIPINE**) - did not show efficacy.

Antioxidants (free-radical scavengers)

- TIRILAZAD** did not show benefit.
- ALBUMIN** (antioxidant properties + ability to increase blood flow to penumbra).
- NXY-059** (free-radical trapping agent) - **first neuroprotectant to show efficacy** in acute stroke treatment trial; also shows *vasoprotective* properties (hemorrhagic transformations↓ after tPA).

PREVENTION OF REPERFUSION INJURY

Despite good outcome associated with reopening blood vessel, additional brain injury may result!

Antiadhesion antibodies - block **intercellular adhesion molecule (ICAM)** on endothelium to prevent WBC adhesion to vessel wall.

ENLIMOMAB - murine monoclonal anti-ICAM antibody; increased mortality rates.

HU23F2G - human antileukocytic antibody; no clinical benefit.

Antiplatelet antibodies

ABCIXIMAB – disappointing (increased rate of intracranial hemorrhages).

Membrane stabilization

CITICOLINE (exogenous form of cytidine-5'-diphosphocholine used in membrane biosynthesis) - may reduce ischemic injury by stabilizing membranes and decreasing free radical formation; **modest clinical benefit** in trials.

Neuronal healing

FIBLAST (basic fibroblast growth factor) - poor risk-to-benefit ratios.

SURGICAL CARE

A. Symptomatic **hemorrhagic transformation after thrombolytic therapy** → **hematoma evacuation**.

B. Management of **life-threatening ICP elevations** → **decompressive hemicraniectomy**.

also see p. S50 >>

- **indication** – **malignant MCA stroke** ($\geq 50\%$ MCA territory with stroke volume $\geq 145 \text{ cm}^2$ – mortality $\approx 80\%$ without surgery; vs. zero mortality if $< 145 \text{ cm}^2$).
- achieved ICP reduction:
 - promotes retrograde MCA perfusion via leptomeningeal collaterals.
 - prevents brain herniation.
- 3 studies showed that **early decompressive surgery** (within 48 hours of large MCA infarcts in patients < 60 yrs) **clearly reduces mortality** but impact on functional outcome is still unclear.

N.B. decompressive hemicraniectomy does not treat stroke!

C. Patients with **cerebellar hemorrhages** should have neurosurgical consultation! (→ **decompression and evacuation** of large cerebellar infarctions that compress brain stem).

REHABILITATION

- rehabilitation planning begins *within first day* of acute stroke.
- patients can safely begin **sitting up** once they are fully conscious and neurologic deficits are no longer progressing, usually ≤ 48 h after stroke.
 - AVERT (A Very Early Rehabilitation Trial) results show that **intensive exercise therapy out of bed within 24 hours** of symptom onset is safe method of rehabilitation (even among individuals treated with tPA)
- **resistive exercise** for hemiplegic extremities may increase spasticity!
- comprehensive rehabilitation may improve functional abilities of stroke survivor (despite age and neurologic deficit) → decreased long-term patient care costs.
- 10% patients receive **no benefit** from any treatment.
- **transdisciplinary, holistic approach** that addresses **medical, functional, and psychosocial** issues.
- patients should be seen by **PHYSIATRIST** (rehabilitation specialist) 1 month after discharge and periodically thereafter.
- emphasize using affected limbs!
- most important priority is **AMBULATION**.
 - as long as hemiplegic patients can walk safely and comfortably, gait correction should not be tried (attempts to correct gait often increase spasticity, result in muscle fatigue, and increase already high risk of **falls** → hip fractures).
 - falls are most common in **right-hemisphere lesions** (left-sided neglect, anosognosia, impulsivity).
- second most important priority is **ACTIVITIES OF DAILY LIVING** - more difficult because affected upper limb is less functional than affected lower limb.
- patients should be **TOILETED** after meals to take advantage of *gastrocolic reflex*.
- **mood changes** (due to infarct and patient's frustration at his condition) should be expected.

Techniques of Stroke Rehabilitation:

Author (Type)	Theory
Conventional	Range of motion/strengthening
	Compensatory strategies
	Mobility/activity of daily living training
Bobath (neurodevelopmental therapy)	Suppress synergistic movement
	Facilitate normal movement
Knott, Voss (proprioceptive neuromuscular facilitation)	Suppress normal movement
	Facilitate defined mass movement
Brunnstrom	Facilitate synergistic movement
Rood	Modify movement with cutaneous sensory stimulation
Biofeedback	Modifies function using volitional control and auditory, visual, sensory cues
Forced-use paradigm	Immobilization of unaffected extremity forcing use of affected extremity
Electrical stimulation	Random or coordinated contraction of muscles

- functional imaging (fMRI, SPECT, PET) demonstrates that neurons not usually utilized during normal movement (i.e. areas surrounding infarcts, in ipsilateral homologous sites, and in supplementary motor areas) are activated when rehabilitation strategies are applied.
- **DEXTROAMPHETAMINE, METHYLPHENIDATE, BROMOCRIPTINE** modify *noradrenergic* or *dopaminergic* systems, thus facilitating recovery.

PROPHYLAXIS

Risk factor reduction:

- 1) control **hypertension** - most beneficial preventive measure!
 - all BP \uparrow should be treated.
 - avoid overtreatment in **older patients** (may have focal vascular stenoses and impaired vasomotor reactivity) - achieve normotension gradually!

- 2) treat **cardiac** arrhythmias or diseases
- 3) blood **cholesterol** reduction
- 4) manage **diabetes** mellitus
- 5) **smoking** cessation, limited **alcohol** intake
- 6) avoid **estrogen preparations** (e.g. postmenopausal hormone therapy)

Ischemia prevention strategies in PREGNANCY → see p. Vas1 >>

PROPHYLACTIC SURGERY

EXTERNAL CAROTID ARTERY-MCA ANASTOMOSIS – *no benefit* in multi-institutional, randomized trial!!! → procedure has been largely abandoned. see p. Vas7 >>

CAROTID ENDARTERECTOMY see p. Vas7 >>

ANGIOPLASTY see p. Vas7 >>

ANTIPLATELET AGENTS

- SECONDARY prophylaxis after TIA / stroke (unless contraindicated) - well known to decrease risk of stroke and MI:

- a) **traditional & cheapest first-choice - ASPIRIN** (30-1300 mg/d) - start within 24-48 h of stroke onset.
- b) **modern first-choice - CLOPIDOGREL** (Plavix®) 75 mg/d – modestly more effective than ASPIRIN.
- c) **modern first-choice - ASPIRIN** 25 mg + **extended-release DIPYRIDAMOLE** 200 mg (Persantine®, Aggrenox®) × 2/d – modestly more effective than ASPIRIN.
- d) **TICLOPIDINE** 250 mg × 2/d – effective, but risk of neutropenia.
- e) **CILOSTAZOL** – may be more effective than ASPIRIN (studies in China).

Antiplatelet agents *cannot be* recommended for PRIMARY stroke prophylaxis in healthy individuals! (their risk of stroke is so low that "benefit" is meaningless).

LONG-TERM ANTICOAGULATION

- optimal **duration** of anticoagulation - as long as condition persists and no contraindications emerge.
- **ASPIRIN** is occasionally used simultaneously with **WARFARIN** in certain high-risk patients.
- until **WARFARIN** starts to work, use **HEPARIN** or **LMWH** (“bridging”) – but this may increase risk of bleeding (hemorrhagic stroke transformation).

[keep INR 2-3 unless other indicated]

INDICATIONS (for PRIMARY & SECONDARY stroke prophylaxis) - **risk of cardioembolic stroke**:

- 1) **atrial fibrillation**: [anticoagulation decreases stroke risk ≈ 70%]
 - a) **asymptomatic patient < 65 yrs** → *do not treat* or **ASPIRIN**.
 - b) **asymptomatic patient 65-74 yrs** → **WARFARIN** or **ASPIRIN**.
 - c) **additional risk factors** (age > 75 yrs, recent stroke or TIA, systemic embolism, hypertension, diabetes, congestive heart failure with left ventricular ejection fraction < 25%) → **WARFARIN**.
 - N.B. **elderly** has **increased risk of hemorrhage**; some (but not all) experts advise:
 - if only age > 75 yrs (and no other risk factors), decrease INR to 1.6-2.5
 - if only age > 80 yrs (and no other risk factors), use **ASPIRIN**.
- 2) **acute MI** – anticoagulation (for at least 2-3 months) is indicated only if following exists:
 - a) persistent AF
 - b) left ventricular thrombus / aneurysm
 - c) extensive wall motion abnormalities (left ventricular ejection fraction < 25%).
- 3) **mechanical prosthetic valves** (target INR 3-4.5, depending on valve type).
- 4) **mitral stenosis** with any prior embolic event.
- 5) **dilated cardiomyopathy**
- 6) **other conditions** - left atrial myxoma, intraventricular thrombus, ventricular aneurysm with thrombus, mobile thrombus in ascending aorta.

INDICATIONS for SECONDARY stroke prophylaxis:

A) after stroke confirmed as **cardiogenic**:

- 1) large* **patent foramen ovale** with spontaneous right-to-left shunting
*if small → **ASPIRIN** is sufficient.
- 2) **mitral valve prolapse** with myxomatous leaflets
- 3) **mitral ring calcifications**
- 4) **rupture of chordae tendineae**
- 5) **dyskinetic ventricular wall segment**

B) **thrombophilias**:

- 1) **antithrombin III deficiency**
 - 2) **protein C deficiency** (INR 3-3.5)
 - 3) **protein S deficiency**
 - 4) high titers of **anticardiolipin antibodies** (INR 2.5-3.5).
 - 5) **APC resistance**
 - 6) **plasminogen deficiency/inhibition**
 - 7) **dysfibrinogenemia**
- **alternative** (except for antithrombin III deficiency, anticardiolipin antibodies) - fixed, low-dose SC **HEPARIN** or **LMWH**.
 - after single event of thrombosis → anticoagulation for *at least 6 months*.
 - after recurrent or life-threatening thrombosis or in case of combination of different thrombophilias → *lifelong* anticoagulation.

No randomized studies support oral anticoagulation after ischemic stroke of **arterial** origin (i.e. stenoses of extracranial / intracranial arteries)

- risk of bleeding.
- **ASPIRIN** is preferred (or ICA endarterectomy).
- **WARFARIN** can be stopped after clot organizes and adheres to vessel wall - usually after 3-4 weeks.

Contraindications - **increased risk of bleeding**:

- 1) poor compliance
- 2) uncontrollable hypertension
- 3) aortic dissection
- 4) bacterial endocarditis
- 5) liver disease, alcohol dependency

- 6) bleeding lesions, malignant tumor
- 7) retinopathy with bleeding risk
- 8) advanced microvascular changes in brain
- 9) aneurysm of cerebral artery
- 10) previous spontaneous cerebral hemorrhage
- 11) coagulopathies, thrombocytopenia.

In these cases, use **ASPIRIN** as long-term treatment.

BIBLIOGRAPHY for ch. “Neurovascular Disorders” → follow this [LINK >>](#)