Management of Acute Ischemic Stroke

The management of acute ischemic stroke involves several phases and considerations:

(1) Ensuring Medical Stability → maintaining airway, breathing, circulation
(2) Reperfusion Therapy → determining eligibility for thrombolytic therapy or mechanical thrombectomy → most effective approaches for salvaging ischemic brain tissue

Update (2022)
Tenecteplase (TNKase)

- not FDA-approved for ischemic stroke; however, high quality evidence indicates that a single IV bolus has similar efficacy and safety outcomes compared to alteplase.
- dose: 0.25 mg/kg (max. 25 mg) IVP over 5 seconds.

- TPA (alteplase) → within 4.5 hours after symptom onset.
  Update (2022): Tenecteplase (TNKase) is not FDA-approved for ischemic stroke; however, there is high-quality evidence that as a single bolus of 0.25 mg/kg (max: 25 mg) over 5 seconds, it has similar efficacy and safety outcomes compared with alteplase.
- Mechanical thrombectomy → indicated for patients with a large artery occlusion who can be treated within 6 hours after symptom onset
  NOTE: eligible patients should receive alteplase without delay even if thrombectomy is being considered.

(3) Additional Antithrombotic Drugs: Antiplatelets and Anticoagulants
(4) Moving to Treat Underlying Pathophysiologic Basis of the Stroke

THROMBOLYTIC THERAPY: ALTEPLASE (ACTIVASE^{R})

- Goal: restore blood flow to the regions of brain that are ischemic but not yet infarcted
- Alteplase → mainstay of treatment for acute ischemic stroke, provided that treatment is initiated within 4.5 hours of clearly defined symptom onset ("time last known well")
- Prior to alteplase, all patients require confirmation of the following:
  - diagnosis is acute ischemic stroke → CT
  - treatment is commencing within the required 4.5 hour time window, defined as the time last seen normal or at baseline
  - there is a persistent, measureable neurologic deficit → NIHSS
  - eligibility criteria (see table)
  - serum glucose must be checked to rule out hypoglycemia as cause of neurologic deficit (diabetics → maintain BG 140-180 mg/dL)
  - CT / MRI is without hemorrhage or other contraindication
  - blood pressure parameters are met → reduce risk of intracerebral hemorrhage
    - requirement for alteplase: SBP $\leq$ 185 / DBP $\leq$ 110
    - antihypertensives of choice: Nicardipine 5-15 mg/hour IV infusion / Labetalol 10-20 mg IVP, may repeat x 1 dose
  - two large bore IV lines are in place
  - accurate body weight has been determined (for alteplase dosing)

ALTEPLASE DOSE

- 0.9 mg/kg of actual body weight (ABW), with a maximum dose of 90 mg
  - 10% of the dose is given as an IV bolus over 1 minute and the remainder is infused over 1 hour

ALTEPLASE (cont.)

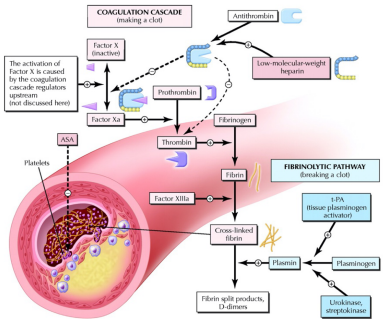
- NOTE: Anticoagulants (i.e., warfarin, DOACs, UFH, LMWH) and antithrombotic agents or antiplatelet agents (i.e., ASA, clopidogrel) should NOT be administered for at least 24 hours after alteplase
    - CT / MRI should be obtained 24 hours after alteplase is initiated before starting treatment with antiplatelet or anticoagulant agents

ALTEPLASE COMPLICATIONS: Intracranial Hemorrhage (ICH) and Angioedema

- Intracerebral Hemorrhage (ICH): risk is 5-7% with alteplase started within 4.5 hours of acute ischemic stroke onset

    Treatment of ICH

    (1) stop alteplase infusion
    (2) obtain a stat CT / MRI
    (3) obtain blood samples for type and crossmatch, PT, aPTT, platelet count, and fibrinogen levels
    (4) if confirmed by CT/MRI, then treat with the following agents:
        a. cryoprecipitate: 10 units to increase levels of fibrinogen and factor VIII
        b. platelets: 6 – 8 units for patients with PLT < 100,000
        c. anti-fibrinolytic agents: (1) aminocaproic acid IV and/or (2) tranexamic acid IV
        d. vitamin K as adjunctive therapy for patients on warfarin prior to alteplase treatment
        e. protamine IV 1 mg for every 100 units of heparin for patients receiving UFH (unfractionated heparin) in the preceding 4 hours

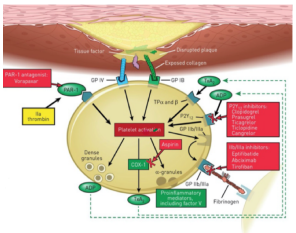


- Angioedema: risk 1-8% of patients treated with alteplase

    Treatment of Angioedema

    (1) stop alteplase infusion
    (2) maintain airway → endotracheal intubation if edema poses high risk in orolingual angioedema
    (3) meds in rapid sequence:
        a. methylprednisolone (Solu-Medrol) 125 mg IVP
        b. diphenhydramine (Benadryl) 50 mg IVP
        c. famotidine (Pepcid) 20 mg IVP
    (4) epinephrine 0.3 ml (0.3 mg) IM if needed (note: may increase BP & bleeding)

ANTIPLATELET AGENTS



- ACC/AHA/NIH: ASA (160-325 mg/day) is the only antiplatelet agent that has been established as effective for the very early treatment (within 48 hours) of acute ischemic stroke
    - ASA → COX-inhibitor → inhibits thromboxane A2 → blocks platelet aggregation → reduces formation of thrombi → reduces risk of stroke

ANTIPLATELET AGENTS (cont.)

- ASA may be given rectally for patients with acute stroke who are NPO or have not had screening for dysphagia
- Clopidogrel (Plavix) is an alternative for patients intolerant or allergic to ASA

- Dual antiplatelet therapy (DAPT) remains largely unproven
  - Dual antiplatelet therapy with ASA plus clopidogrel for 90 days (followed by antiplatelet monotherapy) may be considered for patients with symptomatic atherosclerotic intracranial large artery stenosis

ANTICOAGULATION

- ACC/AHA: guidelines state that urgent anticoagulation is NOT recommended for the treatment of patients with acute ischemic stroke or TIA → increased risk of bleeding
- Atrial Fibrillation and Cardioembolic Stroke
  - For patients with acute cardioembolic stroke or TIA who are at high risk for short-term recurrent stroke due to intracardiac thrombus, some experts favor anticoagulation in patients with a small brain infarct and no evidence of hemorrhage on brain imaging
    - NIHSS > 15 generally have a large infarct → increased risk of bleeding with anticoagulation
  - NOTE: Anticoagulation should not be given for the first 24 hours following treatment with alteplase (TPA)
  - UFH (unfractionated heparin): weight-based nomogram for heparin infusion is initiated without a heparin bolus
  - Enoxaparin (Lovenox) is an alternative to UFH with equal efficacy and advantages in administration and monitoring
    - Enoxaparin (Lovenox) 1 mg/kg SC Q12H

Primary Prevention
of stroke aims to prevent a stroke before it ever happens.

Secondary Prevention
of stroke aims to reduce recurrence of a stroke after it has already occurred.

CASE STUDY
A patient is admitted with atrial fibrillation. Which anticoagulation regimen(s) is (are) indicated for the primary prevention of stroke in this patient?

(A) Enoxaparin 1 mg/kg SC Q12H
(B) Heparin (UFH) 5000 UNIT IV bolus, then 1000 UNITS/HR infusion.
(C) Heparin (UFH) 1000 UNITS/HR
(D) A & B
(E) A & C

Heparin-adjusted nomogram for stroke

Initial dosing for continuous intravenous heparin infusion	
Weight (kg)	**Initial infusion (U/hour)**
<50	500
50 to 59	600
60 to 69	700
70 to 79	800
80 to 89	900
90 to 99	1000
100 to 109	1100
110 to 119	1200
>119	1400

Heparin adjustment based upon aPTT drawn six hours after initiation of therapy			
aPTT (seconds)	**Stop infusion**	**Rate change**	**Repeat aPTT**
<40	No	Increase by 250 U/hour	6 hours
40 to 49	No	Increase by 150 U/hour	6 hours
50 to 59	No	Increase by 100 U/hour	6 hours
60 to 90	No	No change	Next morning
91 to 100	No	Decrease by 100 U/hour	6 hours
101 to 120	No	Decrease by 150 U/hour	6 hours
>120	No	Decrease by 250 U/hour	6 hours

No bolus is administered in patients with acute stroke.

Eligibility criteria for the treatment of acute ischemic stroke with intravenous alteplase (recombinant tissue plasminogen activator or tPA)

Inclusion criteria
Clinical diagnosis of ischemic stroke causing measurable neurologic deficit
Onset of symptoms <4.5 hours before beginning treatment; if the exact time of stroke onset is not known, it is defined as the last time the patient was known to be normal or at neurologic baseline
Age ≥18 years
Exclusion criteria
Patient history
Ischemic stroke or severe head trauma in the previous three months
Previous intracranial hemorrhage
Intra-axial intracranial neoplasm
Gastrointestinal malignancy or hemorrhage in the previous 21 days
Intracranial or intraspinal surgery within the prior three months
Clinical
Symptoms suggestive of subarachnoid hemorrhage
Persistent blood pressure elevation (systolic ≥185 mmHg or diastolic ≥110 mmHg)
Active internal bleeding
Presentation consistent with infective endocarditis
Stroke known or suspected to be associated with aortic arch dissection
Acute bleeding diathesis, including but not limited to conditions defined under 'Hematologic'
Hematologic
Platelet count <100,000/mm^3*
Current anticoagulant use with an INR >1.7 or PT >15 seconds or aPTT >40 seconds or PT >15 seconds*
Therapeutic doses of low molecular weight heparin received within 24 hours (eg, to treat VTE and ACS); this exclusion does not apply to prophylactic doses (eg, to prevent VTE)
Current use of a direct thrombin inhibitor or direct factor Xa inhibitor with evidence of anticoagulant effect by laboratory tests such as aPTT, INR, ECT, TT, or appropriate factor Xa activity assays
Head CT
Evidence of hemorrhage
Extensive regions of obvious hypodensity consistent with irreversible injury
Warnings ¶
Only minor and isolated neurologic signs or rapidly improving symptoms△
Serum glucose <50 mg/dL (<2.8 mmol/L) ◇
Serious trauma in the previous 14 days§
Major surgery in the previous 14 days¥
History of gastrointestinal bleeding (remote) or genitourinary bleeding‡
Seizure at the onset of stroke with postictal neurologic impairments†
Pregnancy**
Arterial puncture at a noncompressible site in the previous seven days¶¶
Large (≥10 mm), untreated, unruptured intracranial aneurysm¶¶
Untreated intracranial vascular malformation¶¶
Additional warnings for treatment from 3 to 4.5 hours from symptom onset△△
Age >80 years
Oral anticoagulant use regardless of INR
Severe stroke (NIHSS score >25)
Combination of both previous ischemic stroke and diabetes mellitus

DOSING CONSIDERATIONS

Enoxaparin (Lovenox) Dosing

Anticoagulant Dosing

Enoxaparin 1 mg/kg SC Q12H → CrCl ≥ 30 ml/min

Enoxaparin 1 mg/kg SC Q24H → CrCl: 15-30 ml/min

- If CrCl < 15 ml/min → use UFH drip (i.e., Heparin Infusion)

DVT Prophylaxis (DVT PPX)

Enoxaparin 40 mg SC Q24H → CrCl ≥ 30 ml/min

Enoxaparin 30 mg SC Q24H → CrCl: 15-30 ml/min

If CrCl < 15 ml/min → use UFH: Heparin 5000 UNITS SC Q12H

Onset of Action

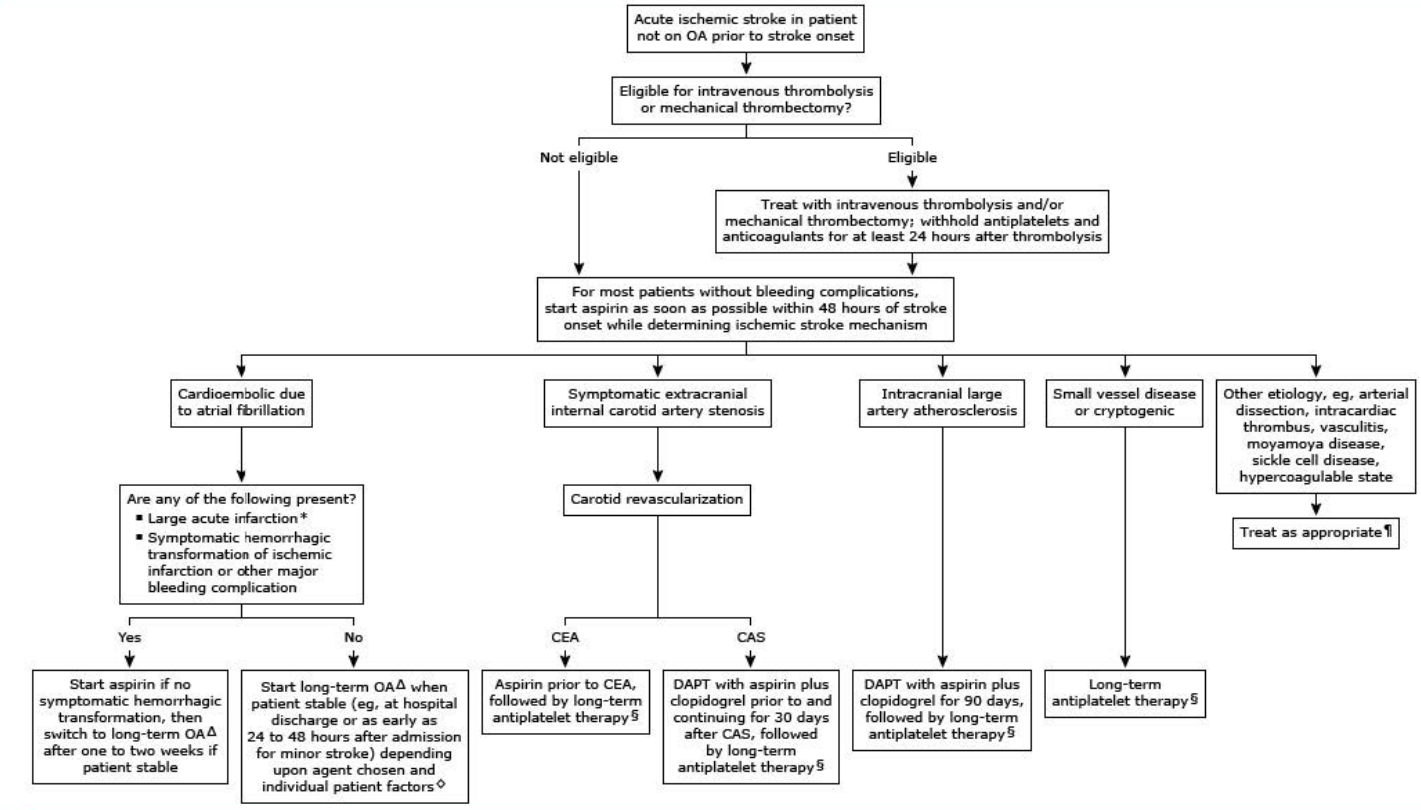
- UFH, Enoxaparin, DOAC's → provide immediate anticoagulant effects.
- Warfarin → Although an INR of 2-3 may be seen in approx. 3 days, this does not represent therapeutic anticoagulation since clotting factors with longer half-lives must also be depleted. So, warfarin requires bridging with UFH (Heparin Infusion) or enoxaparin for approx. 5 days for a complete therapeutic response and thromboembolic protection.

Renal Considerations

- Warfarin and UFH are recommended in patients with renal failure and patients on hemodialysis since warfarin and UFH are hepatically eliminated.
- Note: In patients with severe or ESKD (end-stage kidney disease) with CrCl of 15-29 ml/min not requiring hemodialysis, it's considered appropriate by most experts to use either warfarin or apixaban (Eliquis) 2.5 mg PO BID for non-valvular atrial fibrillation.
    - Apixaban is dosed 5 mg PO BID unless patient has 2 of the following: Cr ≥ 1.5 mg/dL, Age ≥ 80, or body wt. ≤ 60 kg. (Official Labeling / FDA)

GENERAL APPROACH TO ANTITHROMBOTIC THERAPY

General approach to antithrombotic therapy for acute ischemic stroke in patient not on anticoagulation prior to stroke onset



This algorithm is intended to provide basic guidance regarding the use of antithrombotic therapy for patients with acute ischemic stroke. The steps outlined here may not apply to all patients. The selection, timing, and sequencing of specific antithrombotic drugs should be based upon clinical judgment, individual patient characteristics, and the efficacy, safety, and cost profile of the drugs. For further details, including suggested dosing regimens of antiplatelet and anticoagulant agents, refer to the relevant UpToDate topic reviews.

CAS: carotid artery stenting; CEA: carotid endarterectomy; DAPT: dual antiplatelet therapy; OA: oral anticoagulation.

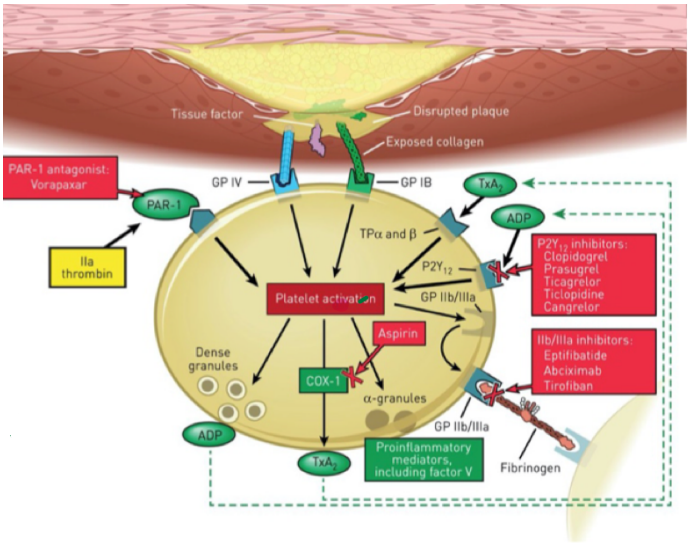
* "Large" infarcts are defined as those that involve more than one-third of the middle cerebral artery territory or more than one-half of the posterior cerebral artery territory based upon neuroimaging with CT or MRI. Though less reliable, large infarct size can also be defined clinically (eg, NIHSS score >15).

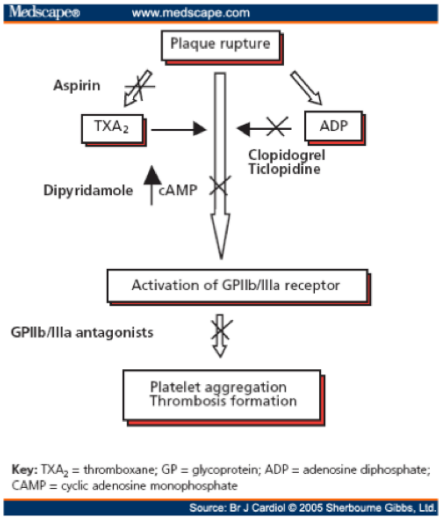
¶ Refer to relevant UpToDate topics for management.

Δ Long-term aspirin therapy is alternative (though less effective) if OA contraindicated or refused.

◇ Non-vitamin K antagonist oral anticoagulant (NOAC) agents have a more rapid anticoagulant effect than warfarin, a factor that may influence the choice of agent and timing of OA initiation.

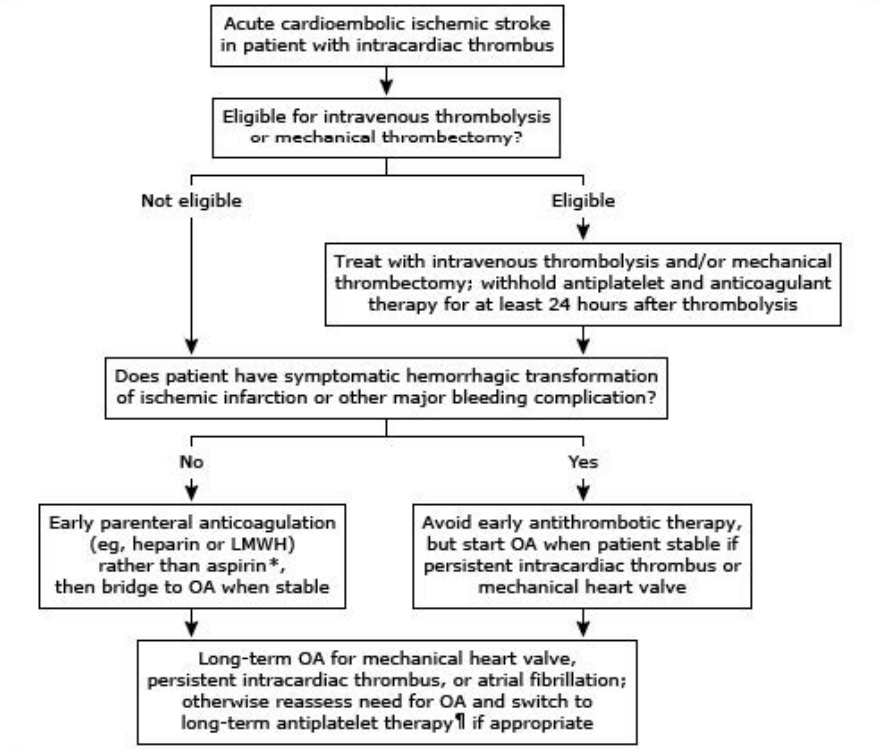
§ Long-term antiplatelet therapy for secondary stroke prevention should be continued with aspirin monotherapy, clopidogrel monotherapy, or the combination of aspirin-extended-release dipyridamole.





ANTITHOMBOTIC THERAPY FOR ACUTE CARDIOEMBOLIC STROKE WITH INTRACARDIAC THROMBUS

General approach to antithrombotic therapy for acute cardioembolic ischemic stroke in patient with intracardiac thrombus



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LMWH: low molecular weight heparin; OA: oral anticoagulation.

* Early aspirin rather than anticoagulation favored by other experts.

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COAGULATION PATHWAYS