Optimizing Antithrombic Strategies in Acute Ischemic Stroke: Focus on post-thrombolysis care

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Disclosures

- No relevant financial relationships
Objectives

- Explain latest updates and options for ischemic and hemorrhagic stroke management and standards of care.
  - Review antithrombotic medications
  - Discuss window in which to start antithrombic medications
  - Select appropriate antithrombotic medications
  - Review indications for dual antiplatelet therapy
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Definitions

- AIS – acute ischemic stroke
- DAPT – dual antiplatelet therapy
- DOAC – direct oral anticoagulant
- ICH – intracranial hemorrhage
- LMWH – low molecular weight heparin
- NIHSS – National Institutes of Health Stroke Scale
- TNK – tenecteplase
- TPA – tissue plasminogen activator; also known as alteplase
- UFH – Unfractionated heparin
Antithrombotics

- Anticoagulants
  - Vitamin K Antagonist (warfarin)
  - Direct Thrombin Inhibitors (dabigatran)
  - Factor Xa Inhibitors (apixaban, rivaroxaban)
- Antiplatelets
  - COX-1 Inhibitor (aspirin)
  - P2Y12 Inhibitors (clopidogrel, ticagrelor)

Inhibit clotting factors

Inhibit platelets
Anticoagulants

Intrinsic Pathway

XII → XIIa
XI → Xla
IX → IXa
X → Xa

Extrinsic Pathway

Tissue Factor (III) → VIIa → VII

Factor Xa Inhibitors
(Apixaban, Betrixaban, Edoxaban, Rivaroxaban)

Warfarin

Prothrombin (II) → Thrombin (IIa)
Fibrinogen (I) → Fibrin (Ia)

Heparin

Direct Thrombin Inhibitors
(Argatroban, Dabigatran)

Antiplatelets

Thrombolytics

- Break down fibrin clots
- ~6% risk of intracranial hemorrhage (ICH)
Patient Case

• 59 year-old male presents with left sided weakness
  • Last known well 1 hour prior to arrival
• PMH: T2DM, HTN, CKD, tobacco use
• Home medications: metformin, lisinopril
• BP 152/90 mmHg, HR 80, RR 18, 97% on RA, T 36.4 °C
• Labs within normal limits except
  • POC glucose = 194
  • Serum creatinine = 2.18 mg/dL
  • Hgb = 11.2
  • HgbA1c = 9.1
• NIHSS = 5
• Head CT shows no acute intracranial findings
• CTA shows no large vessel occlusion
• Receives alteplase and is admitted to the ICU
When should antithrombic medications be initiated after an acute ischemic stroke in patients who have received thrombolytic therapy?
The timing of initiation of antiplatelet therapy or anticoagulation should be made on an individual level, balancing risk and benefit.

Aspirin
- Administration of aspirin is recommended in patients with AIS within 24 to 48 hours after onset.
- Start antiplatelet therapy even if the underlying cause of the stroke is still undetermined.
- For patients who have received a thrombolytic (alteplase or tenecteplase), aspirin administration is generally delayed until 24 hours later.
- For patients who do not receive thrombolytic therapy, aspirin can be initiated immediately.

**2013 Guidelines:** Initiation of anticoagulant therapy within 24 hours of treatment with intravenous rtPA is not recommended.

**2019 Guidelines:** The risk of antithrombotic therapy within the first 24 hours after treatment with IV alteplase (with or without mechanical thrombectomy) is uncertain.

• Use might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk.

Safety Measures

▪ What two things need to happen before giving aspirin?
  ▪ Rule out bleeding complications
    ▪ Repeat head CT or MRI 24 hours after thrombolytic administration
      ▪ Up for debate
      ▪ FIAT trial showed no benefit
  ▪ Swallow study
    ▪ Must be done before giving any oral medications, not just antithrombotics

Dysphagia screening before the patient begins eating, drinking, or receiving oral medications is effective to identify patients at increased risk for aspiration.

DVT prophylaxis

In immobile stroke patients without contraindications, intermittent pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended over routine care to reduce the risk of deep vein thrombosis (DVT).

The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in patients with AIS is not well established.

- Utilize non-pharmacologic methods when able
- If using pharmacotherapy, wait at least 24 hours after thrombolytic administration.

Pop Quiz

True or False:
All patients who present with an acute ischemic stroke have an indication for anticoagulation.

FALSE
What antithrombic medications should be administered after an acute ischemic stroke?
Antithrombotic medication selection

- Determine underlying mechanism
  - Cardioembolic $\rightarrow$ anticoagulation
  - Noncardioembolic $\rightarrow$ antiplatelet therapy

- Causes of cardioembolic strokes
  - Atrial fibrillation
  - Prosthetic heart valves
  - Patent foramen ovale (PFO)
  - Intracardiac thrombus
  - Infective endocarditis
  - Others

Atrial fibrillation

Timing of anticoagulant administration

- Optimal timing to initiate anticoagulation is an area of uncertainty
- Depends on
  - risk of hemorrhagic transformation
  - infarct size
  - other factors (i.e. uncontrolled hypertension)
- TIMING trial showed that early initiation (within 4 days) was noninferior to delayed start of DOACs (between 5 and 10 days)

For most patients with an AIS in the setting of atrial fibrillation, it is reasonable to initiate oral anticoagulation between 4 and 14 days after the onset of neurological symptoms.

Choice of anticoagulant

- Afib $\rightarrow$ DOACs preferred over warfarin
  - Factor Xa inhibitors
    - Apixaban
    - Edoxaban
    - Rivaroxaban
  - Direct thrombin inhibitor
    - Dabigatran
- Mechanical valve replacement $\rightarrow$ warfarin
- LV thrombus $\rightarrow$ warfarin
- VTE $\rightarrow$ DOACs
Dual Antiplatelet Therapy (DAPT)

- **Indications**
  - High-risk TIA (ABCD² score ≥4)
  - Mild ischemic stroke (NIHSS ≤3)

- **Regimens**
  - Clopidogrel 300-600 mg load followed by 75 mg daily + aspirin 325 mg load followed by 81 mg daily for 21 days
  - Followed by aspirin monotherapy
  - Ticagrelor is an alternative to clopidogrel
    - Clopidogrel has no activity in patients with CYP2C19 loss-of-function allele

### ABCD² Score

<table>
<thead>
<tr>
<th>Age:</th>
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<tbody>
<tr>
<td>≥60 years</td>
<td>1 point</td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>0 points</td>
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**Blood pressure elevation when first assessed after TIA:**

| Systolic ≥140 mmHg or diastolic ≥90 mmHg | 1 point |
| Systolic <140 mmHg and diastolic <90 mmHg | 0 points |

**Clinical features:**

| Unilateral weakness | 2 points |
| Isolated speech disturbance | 1 point |
| Other                | 0 points |

**Duration of TIA symptoms:**

| ≥60 minutes             | 2 points |
| 10 to 59 minutes        | 1 point  |
| <10 minutes             | 0 points |

**Diabetes:**

| Present | 1 point |
| Absent  | 0 points |

DAPT

- Evidence
  - CHANCE and POINT trials
    - Patients with moderate and severe ischemic stroke were not enrolled
    - Larger brain infarcts are more likely to undergo hemorrhagic transformation
  
- Duration
  - 21 days per the CHANCE trial
    - Risk of recurrent stroke highest in the acute setting
    - Longer therapy associated with no additional benefit for stroke prevention but increased risk of bleeding complications
  - Aspirin monotherapy after 21 days

Guideline statement on DAPT

In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset.

<table>
<thead>
<tr>
<th>Acute ischemic stroke patient s/p thrombolytic administration</th>
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<tr>
<td>Hold antithrombotic medications for 24 hours</td>
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- **Start aspirin within 48 hours of symptom onset**

- Stroke work-up to determine underlying cause

- **Cardioembolic**
  - Stop aspirin and start anticoagulation

- **Noncardioembolic**
  - Aspirin monotherapy vs DAPT
Patient Case

- 59 year-old male presents with left sided weakness
  - Last known well 1 hour prior to arrival
- PMH: T2DM, HTN, CKD, tobacco use
- Home medications: metformin, lisinopril
- BP 152/90 mmHg, HR 80, RR 18, 97% on RA, T 36.4 °C
- Labs within normal limits except
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Case Questions

When should aspirin be initiated in this patient?
  • 24 to 48 hours after alteplase administration

What two things need to be done prior to aspirin administration?
  • Rule out major bleeding complications from alteplase
  • Swallow study
Case Questions

On hospital day 4, telemetry reveals atrial fibrillation. What modifications should be made to patient’s antithrombotic regimen?

A. Continue aspirin monotherapy
B. Initiate dual antiplatelet therapy with clopidogrel and aspirin
C. Stop aspirin and start apixaban
D. Start triple therapy with aspirin, clopidogrel, and apixaban
For patients with a history of ischemic stroke, atrial fibrillation, and coronary artery disease, the usefulness of adding antiplatelet therapy to oral anticoagulants is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events.

Unstable angina and coronary artery stenting represent special circumstances in which management may warrant dual antiplatelet/oral anticoagulation.
Bonus Questions

What other pharmacotherapy recommendations would decrease this patient’s risk of stroke?

- Control hypertension
  - Increase lisinopril or add another antihypertensive agent
- Lipid/cholesterol management
  - Add atorvastatin or rosuvastatin
- Tobacco cessation
  - Consider nicotine replacement, varenicline, or bupropion
- Blood glucose control
  - Add SGLT2i
  - Evaluate appropriateness of metformin based on GFR
  - Consider GLP-1 agonist
Patient Case #2

- 61 year-old female presents with left sided weakness
- Last known well 12 hours prior to arrival
- PMH: hypothyroidism
- Home medications: levothyroxine
- BP 112/60 mmHg, HR 64, RR 18, 99% on RA, T 36.7°C
- Labs within normal limits
- NIHSS = 3
- Head CT shows no acute intracranial findings
- CTA shows no large vessel occlusion
Case Questions

• Is this patient in the window for thrombolytic therapy?
  • No

• What antithrombotic medication regimen is most appropriate for this patient?
  • DAPT with aspirin and clopidogrel for 21 days

• When should these medications be initiated?
  • As soon as possible

• How long should each of these medications be continued?
  • DAPT for 21 days, then aspirin monotherapy indefinitely
Immediate antithrombotic treatment of acute ischemic stroke

Patient presenting with acute ischemic stroke not or ON prior to arrival small

Eligible for IVT or MT?

Yes

No

"Heat with IVT and/or MT withheld antplatelets and anticoagulants for at least 24 hours after IVT"

In stroke evaluation completed?

Yes

Start antplatelet therapy as soon as possible. Consider contraindications to using MT. Guide antplatelet selection, while evaluating the ischemic stroke mechanism.

No

Wait and test the patient for a fibrinolytic.

SDS score 4-5

Start DAPT

Start aspirin alone

SDS score >5

Continue evaluation to determine ischemic mechanism.

Choose long-term antithrombotic therapy according to stroke mechanism treatment algorithm.

Antithrombotic therapy according to cause of acute ischemic stroke

Patient with acute ischemic stroke who has completed an evaluation to determine the cause.

Are any of the following present?

- Low-grade acute ischemia
- Continuous hypotension
- Hemodynamic shock
- Shock-like symptoms

Is the patient stable?

Yes

No

Outpatient therapeutic options should be considered.

Are there any of the following indications for aspirin or clopidogrel?

- Prior history of atrial fibrillation
- Prior history of ischemic stroke
- Prior history of transient ischemic attack

Withhold antplatelet therapy and consider anticoagulation.

Refuse patient for cardiac arrest.

Additional information:

- For DAPT, aspirin and clopidogrel should be used.
- For anticoagulation, Warfarin is preferred.
- Consider antiplatelet therapy in selected patients.

Stop antplatelet therapy and consider anticoagulation.

Anticoagulant therapy according to stroke mechanism.

- Direct oral anticoagulant agents are more rapid anticoagulant effect than warfarin, a factor that may influence the choice of agent and timing of OA initiation.
- Some experts prefer DAPT, based upon observational evidence.
- Long-term single-agent anticoagulant therapy for secondary stroke prevention with apixaban, dabigatran, or rivaroxaban extended-release formulations.

Other indications for anticoagulants include atrial fibrillation, ventricular tachycardia, mechanical heart valve, and treatment of venous thromboembolism.

Intracranial hemorrhage, cerebral evaluation, and/or select patient other laboratory tests.

"Larger" effects 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 MR. Though less reliable, large infarct size can also be defined clinically (e.g., mNIPS score > 15).

Long-term anticoagulation therapy is associated (though less effective) if OA contraindicated or refused.

References:

- National Institutes of Health Stroke Scale (NIHSS)
- National Institute of Neurological Disorders and Stroke (NINDS)
- American Heart Association (AHA)
- American Stroke Association (ASA)
- European Stroke Organization (ESO)
- World Stroke Organization (WSO)
- International Stroke Conference (ISC)
- International Stroke Forum (ISF)
- Cerebrovascular Diseases (CVD)
- Neurology and Stroke (N&ST)
- Neurology (NEURO)
- Stroke (STROKE)
Hold antithrombic medications for at least 24 hours after thrombolytic therapy

Start aspirin within 48 hours for patients who received a thrombolytic

For patients who do not receive thrombolytic therapy, antithrombotic medications may be started immediately

Dysphagia screening should be performed prior to administration of oral medications

Choice of antithrombotic medication is based on the underlying cause of stroke
  - Anticoagulation for cardioembolic strokes
  - Antiplatelet therapy for noncardioembolic strokes

DAPT is indicated in mild ischemic strokes and high-risk TIAs
Questions?

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