ANTIPLATELET SELECTION IN SECONDARY STROKE PROPHYLAXIS

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DISCUSSION OBJECTIVES

❖ At the completion of the discussion, participants should be able to:
❖ 1. Discuss the demographics of stroke and its impact in the U.S and worldwide.
❖ 2. Identify the classification / types of stroke based on the initial clinical presentation.
❖ 3. Discuss the various mechanisms of ischemic stroke.
❖ 4. Identify modifiable and non-modifiable risk factors for ischemic stroke.
❖ 5. Be familiar with the available antiplatelet regimens for secondary prevention of ischemic stroke.
PRE TEST QUESTIONS
1. Stroke ranks worldwide as the second leading cause of death.
   A. True
   B. False

PRE TEST QUESTIONS
2. Stroke ranks as the leading cause of long-term disability in the United States.
   A. True
   B. False

PRE TEST QUESTIONS
3. Which of the following are considered strokes?
   a. Ischemic
   b. Hemorrhagic
   c. Subarachnoid hemorrhage
   d. Venous occlusion / thrombosis
   e. all of the above
PRE TEST QUESTIONS

4. Which of the following are acceptable medications for secondary stroke prophylaxis in the U.S.:
   a. Aspirin
   b. Clopidogrel
   c. Aspirin plus sustained release dipyridamole
   d. Ticlopidine
   e. all of the above

EPIDEMIOLOGY OF STROKE

- Stroke ("Brain Attack") is the sudden cessation of blood flow to the brain leading to cerebral infarction.
- The most common neurologic emergency
- Third leading cause of death in the U.S. and 2nd worldwide.
- Leading cause of adult disability in the U.S.

EPIDEMIOLOGY OF STROKE

- Stroke affects people of all ages
- Incidence doubles every 5 years after the age of 55
- Women and men affected equally
- Blacks and Hispanics are at greater risk than non-Hispanic whites.
EPIDEMIOLOGY OF STROKE

- Mortality varies from 10-15% during the initial hospitalization and >30% after 1 year.
- Age is significant predictor for poor outcome.
- Approximately 2/3 of patients have residual symptoms at 1 year.
- 50% return to functional independence and work with approximately 1/3 requiring permanent institutionalization.

STROKE TYPES

- There are two main types of stroke: ischemic and hemorrhagic.
- Ischemic stroke is caused by three main mechanisms: occlusion through thrombosis (arterial or venous), embolism, or systemic hypoperfusion. Account for 85% of all strokes.
- Hemorrhagic stroke is caused by two non-traumatic mechanisms: intracerebral hemorrhage or subarachnoid hemorrhage. Account for 15% of all strokes.

NON-MODIFIABLE RISK FACTORS

- Age- strongest determinant of stroke
- Sex
- Family history
- Race/ethnicity
ISCHEMIC STROKE SUBTYPES

- **Thrombosis**: primary pathology is thrombosis of local arteries with resultant reduced flow or embolization (80%)
- **Embolism**: originate in distal vessels rather than local thrombosis.
- **Global hypoperfusion**: from cardiovascular collapse with either global or regional infarction

MODIFIABLE RISK FACTORS

- Hypertension
- Diabetes
- Hypercholesterolemia
- Heart disease
- Atrial fibrillation
- Smoking
- Carotid occlusive disease
- Sedentary life style

ARTERIAL VASCULAR ANATOMY

1. Extracranial Circulation
   - Aorta
   - Extracranial Carotid System
   - Extracranial Vertebral System

2. Intracranial Circulation
   - Intracranial Carotid System
   - Vertebrobasilar System
CIRCLE OF WILLIS

MECHANISM OF THROMBOTIC STROKES

- Local thrombosis with subsequent reduction in cerebral blood flow.
- Local thrombosis with subsequent embolization of thrombotic debris downstream (intra-arterial embolization).
- Venous thrombosis with backward pressure and edema leading to reduced arterial perfusion.

ATHEROSCLEROTIC THROMBOSIS
THROMBOTIC STROKE SUBTYPES

- Large vessel disease: both extracranial and intracranial carotid and vertebral system and Circle of Willis.
- Small vessel disease: penetrating branches of the intracranial circulation (lacunar disease).

LACUNAR INFARCTS

MCA ISCHEMIC INFARCTION
PCA INFARCT

CEREBELLAR INFARCT

BASILAR ARTERY INFARCT
CARDIOEMBOLIC INFARCTION

VENOUS SINUS THROMBOSIS

VENOUS INFARCTION
CURRENTLY AVAILABLE APPROVED ANTIPLATELET AGENTS

- Aspirin
- Ticlopidine
- Clopidogrel
- Dipyridamole
- ASA/ER dipyridamole

ACUTE POST STROKE THERAPY: ANTIPLATELET VS AntICOAGULATION

Aspirin vs Heparin

A. International Stroke Trial
   1. Randomized open trial comparing Aspirin vs heparin, vs both vs no medication.
   2. Treatment initiated within 48 hours up to 14 days.
   3. Aspirin 300 mg daily group had significant reduction in recurrent stroke during the 14 days and fewer combined non-fatal stroke and death vs heparin or nothing at all.
   4. Aspirin had no increased hemorrhage occurrence.
   5. Heparin had no benefit
   6. Benefits persisted at 6 months

B. Chinese Acute Stroke Trial (CAST)
   1. Randomized placebo controlled trial comparing aspirin 160 mg daily vs placebo.
   2. Treatment onset within 48 hours
   3. Endpoints death any cause or death or dependence at 4 weeks.
   4. 14% reduction in death within 4 weeks vs placebo
   5. Evidence suggests early anticoagulation with heparin or low molecular weight heparin has worse outcomes and higher mortality.
ACUTE POST-STROKE THERAPY

Aspirin Plus Clopidogrel

1. CHANCE Trial
   a. Randomized double blind placebo controlled trial comparing clopidogrel plus aspirin vs placebo plus aspirin in high risk patients with TIA or stroke.
   b. Treatment begun within 24 hours of symptom onset.
   c. Clopidogrel plus aspirin found superior at 90 days in preventing stroke with no increased adverse events.

2. MATCH Trial
   a. Randomized double blind placebo controlled trial comparing aspirin plus clopidogrel vs aspirin alone.
   b. Combination therapy offered no benefit and greatly increased risk of bleeding complications.

3. FASTER Trial
   Aspirin plus clopidogrel demonstrated no benefit vs aspirin alone.

ACUTE POST-STROKE THERAPY

Aspirin plus Dipyridamole

EARLY Trial

1. Randomized controlled trial which was open label.
2. Patients randomized to either aspirin 25 mg and extended release dipyridamole 200 mg BID vs aspirin 100 mg Daily.
3. Enrollment within 24 hours of symptoms and at 7 days all patients received aspirin and extended release dipyridamole combine. No difference in 90 day outcome.

ACUTE POST-STROKE TREATMENT

Heparin in Acute Thrombotic Stroke

TOAST Trial and other studies

1. No benefit of heparin in stuttering TIA or "stroke in evolution".
2. More adverse events vs benefit.
3. DVT prophylaxis with heparin or LMW appear to be safe and not contraindicated.
SECONDARY STROKE PREVENTION

Aspirin
1. Meta-analysis of numerous placebo controlled trials have clearly established the benefit of aspirin in reducing occurrence of ischemic stroke.
2. Relative risk reduction is 15% for all strokes, ischemic or hemorrhagic, 22% for ischemic.
3. Dose varies from 50-1500 mg per day. American College of Chest Physicians recommends 75-100 mg/day
4. Adverse events increase with dose.
5. Inexpensive

SECONDARY STROKE PREVENTION

Clopidogrel
1. Inhibits platelet aggregation by induced adenosine diphosphate.
2. CAPRIE Trial: randomized blinded trial clopidogrel vs aspirin in patients at risk for ischaemic events.
3. Patients randomized to either clopidogrel 75 mg daily or aspirin 325 mg daily and compared compound outcome of ischemic stroke, MI vascular death. Patients had either CVA, MI or symptomatic PAD for enrollment criteria.
4. Clopidogrel group had a annual risk of 5.32% vs aspirin at 5.83%. Relative risk reduction was 8.7%.
5. MATCH, FASTER, CHARISMA

SECONDARY STROKE PREVENTION

Aspirin/ER Dipyridamole
1. Inhibits adenosine deaminase and phosphodiesterase.
2. ESPS-2: randomized placebo controlled double blind trial comparing aspirin alone vs ER dipyridamole alone, ASA plus ER dipyridamole, vs placebo. Primary end points stroke, death or both.
3. Stroke risk reduced 18% in ASA, 16% dipyridamole, 37% in combined group vs placebo. Stroke and death reduced 13% in ASA, 15% dipyridamole and 24% combined group.
4. Relative risk reduction 36% in combined group vs placebo.
SECONDARY STROKE PREVENTION

Ticlopidine

1. Adenosine diphosphate inhibitor
2. Canadian American Ticlopidine Study (CATS)
3. Ticlopidine Aspirin Stroke Study (TASS)
4. African American Stroke Prevention Trial
5. Similar GI affects as aspirin, also rash and diarrhea common. TTP and Neutropenia.

FINAL COMMENTS

POST TEST QUESTIONS

1. Aspirin at any dose is an acceptable choice for the pharmacologic secondary prevention for any ischemic stroke?

A. True
B. False
POST TEST QUESTIONS

2. Combination therapy with Clopidogrel and Aspirin is an approved intervention for secondary ischemic stroke prophylaxis.
   A. True
   B. False

POST TEST QUESTIONS

3. The use of parenteral heparin either fractionated or unfractionated is an appropriate first line intervention in the acute ischemic stroke setting.
   A. True
   B. False

POST TEST QUESTIONS

4. Which of the following risk factors is the strongest determinant for stroke?
   A. Hypertension
   B. Sex
   C. Diabetes
   D. Age
   E. Hyperlipidemia
POST TEST QUESTIONS

5. Which of the following statements is true?
1. Clinical trials suggest that switching antplatelet agents after a patient has suffered a first time or second stroke may be beneficial.
2. Risk of GI hemorrhage is higher in aspirin or aspirin/dipyridamole combination therapy vs clopidogrel.
3. Long term anticoagulation with warfarin or other anticoagulants is an acceptable alternative to antiplatelet therapy in select patients.
4. Subdural hemorrhage is a type of stroke.

BIBLIOGRAPHY


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