STROKE PREVENTION UPDATE

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DISCLOSURES

none
STROKE PREVENTION UPDATE

Stroke is a leading cause of morbidity and disability in US

Approximately 795,000 strokes occur in the United States each year.

Globally, in 2013 there were 6.5 million stroke deaths, making stroke the second-leading cause of death behind ischemic heart disease.

- Approximately how many neurons are lost per minute during the average stroke?
  - A. 200
  - B. 2 thousand
  - C. 2 million
  - D. 2 billion
Approximately how many neurons are lost per minute during the average stroke?

- A. 200
- B. 2 thousand
- C. 2 million
- D. 2 billion

Time is brain

<table>
<thead>
<tr>
<th>Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurons Lost</strong></td>
</tr>
<tr>
<td>Per Stroke</td>
</tr>
<tr>
<td>Per Hour</td>
</tr>
<tr>
<td>Per Minute</td>
</tr>
<tr>
<td>Per Second</td>
</tr>
</tbody>
</table>

Saver JL. Stroke 2006;37:263-266
Time is brain

Prevention - risk factors

<table>
<thead>
<tr>
<th>Changeable</th>
<th>Not changeable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Age</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Sex</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Race</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Previous TIA or stroke</td>
</tr>
<tr>
<td>Tobacco</td>
<td>Family history/genetics</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>Stubbornness</td>
</tr>
<tr>
<td>High BMI, decondition</td>
<td></td>
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</table>
ANTIPLATELET THERAPY FOR STROKE PREVENTION

Objectives:
1. mechanism of action of antiplatelet agents
2. Review of important antiplatelet studies in stroke
3. Current research

PREVENTING STROKE FROM PLATELET DYSFUNCTION

The sequential steps of platelet activation can be targeted with medications
1. Inhibition of COX1—irreversibly with aspirin, competitive binding with NSAIDs
2. Inhibition of membrane receptor ADP P2Y12—clopidogrel, ticlodipine, prasugrel, ticagrelor
3. Inhibition of phosphodiesterase—maintains elevated cAMP, dipyridamole
4. Inhibition of GPIIb/IIIa receptor—Abciximab, eptifibatide (integrillin)
ASPIRIN

Irreversibly blocks COX activity of prostaglandin H synthase 1 and 2 (COX-1 and COX-2) by acetylation of a serine residue of the COX channel.

It is much more potent on COX-1 and Prevents TXA2 generation.

Aspirin is rapidly absorbed in stomach and intestine, peak plasma level within 30 minutes.

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ASPIRIN

Dose is usually 81mg-325mg. Higher does not inhibit platelet function further.

First dose is 325 mg for acute strokes. Daily dose is 81 mg.

Side effects:
Bleeding, hemolytic anemia in GP6D deficiency, Reye syndrome, tinnitus.
**NSAIDS AND ASPIRIN**

NSAIDs competitively and reversibly bind COX-1

When the NSAID wears off, those platelets that were reversibly bound by the NSAID can become active. *This is concerning as it could impair the antiplatelet activity of aspirin.*

**THIENOPYRIDINE INHIBITORS**

This includes clopidogrel (Plavix), ticlopidine (Ticlid), prasugrel (Effient), ticagrelor (Brillinta)

*Inhibits ADP-mediated platelet activation*

Bleeding time is prolonged. This can be reversed quickly with *desmopressin* or *dexamethasone*
CLOPIDOGREL

Dosed 75mg per day
Develops antiplatelet efficacy within a few hours of loading dose 300-600 mg
Antiplatelet effect lasts up to a week when medication stopped. The effect on platelets is irreversible and the active drug metabolite is slowly cleared.

Side Effects:
TTP, hemorrhage, itching

TICAGRELOR (BRILLINTA)
PRASUGREL (EFFIENT)

P2Y12 receptor antagonists can be used in patients with clopidogrel resistance or allergy

Ticagrelor—Binds a different site, is reversible
Used for Acute Coronary Syndrome
Side effects: shortness of breath, bleeding, ventricular pauses

Prasugrel—binds same site as clopidogrel.
Works faster than clopidogrel—90% of platelets inhibited in 1 hr
Side effects: Hypertension, TTP, bleeding, nausea
Black box Warning about not using with history of TIA or Stroke
DIPYRIDAMOLE

Inhibits activity of adenosine deaminase and phosphodiesterase
Aspirin-dipyridamole (Aggrenox) dosed 25mg-200mg BID

Side Effects:
Headache (39.7%)—usually improves after 7 days
GI upset
In monotherapy, bleeding similar to placebo

EVIDENCE FOR USE

There are many studies about each of these medications
I’ll try to highlight important ones
PRIMARY STROKE PREVENTION

Must balance risk of bleeding with likelihood of stroke

Class IIa; Level of Evidence A: use of aspirin for cardiovascular prophylaxis is reasonable for people whose 10-year risk of cardiovascular event is >10%

It can be useful for high risk women with diabetes
No other antiplatelet agents have been study to recommend for primary prevention.

SECONDARY PREVENTION

Aspirin has been studied many times

International Stroke Trial IST: 19435 patients, aspirin vs placebo.
14 day recurrent stroke rate 2.8 vs 3.9%

Chinese Acute Stroke Trial CAST: 21100 patients, aspirin vs placebo
14% relative risk reduction in mortality at 4 weeks (3.3 vs 3.9%)

CAST and IST pooled analysis: reduction of 9 non-fatal strokes or deaths per 1000 patients

Aspirin is safe and effective given at early times from stroke onset
ASPIRIN

Meta-analysis by Antithrombotic Trialist Collaboration (ATTC)

16 secondary prevention trials including 17000 patients, 43000 person years and 3306 events

Absolute reduction in serious vascular events (6.7% vs 8.2% per year, p<0.0001)

22% reduction in stroke (2.08% vs 2.54% per year; RR, 0.78; 0.61-0.99, P=0.002)

Non-significant increase in hemorrhagic stroke

ASPIRIN VS WARFARIN

For all stroke subtypes:
SPIRIT Trial Aspirin vs high target warfarin (INR 3-4.5)
Stopped early, more bleeds in warfarin group, no difference in ischemic events

For Non-Afib
WARSS Trial Aspirin vs warfarin (INR 1.4-2.8)
No difference in stroke, death, bleeding

-Non-significant trend toward better stroke prevention in warfarin group, but also significantly higher bleeding risk in this group
**WASID**

For symptomatic intracranial atherosclerosis
Aspirin 1300mg vs warfarin INR 2-3
Stopped early due to high adverse events in the warfarin arm, increased death, hemorrhage.

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**FOR AF**

Aspirin is worse than Warfarin in many studies
Aspirin + Clopidogrel is worse than Warfarin in **ACTIVE** trials
**META-ANALYSIS**

- Decrease in intracranial hemorrhage is clear
- There is more GI bleeding in the NOAC pooled group

*Lancet* 2014; 383:955-62

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**CHANCE**

**Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events**

114 centers in China
5170 Patients within 24hrs of minor stroke or high-risk TIA

Randomized to clopidogrel + aspirin for 21 days followed by clopidogrel + placebo for days 22-90
OR
placebo + aspirin for 90 days
CHANCE

Found that combination therapy is superior for reducing stroke and is safe in first 90 days.

The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 21 days (Class IIB, Level of Evidence B). (New recommendation) –AHA/ASA Guideline from 2014

POINT

Ongoing NIH-NINDS sponsored trial
Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial (POINT)
Plan to enroll 5000 patients with minor stroke (NIHSS <3) or high risk TIA (ABCD2 >4)
Patients to be enrolled within 12hrs of symptoms onset
Aspirin 325mg plus 600mg load of clopidogrel followed by 75mg daily for 3 months vs aspirin 325mg plus placebo for 3 months
IN SUMMARY

A  - Aspirin/Apixaban
B  - Blood Pressure and Blood sugar control
C  - Cholesterol control, No Cigarettes, Cholesterol medication
D  - Healthy Diet (fruits, vegetables, nuts etc.), No Drinking
E  - Exercise and weight loss
F  - Follow up (for 1st few years)
G  - Group support (stroke group, family, community)

QUESTIONS
REFERENCES


REFERENCES


