

# CURRENT CONTROVERSIES IN STROKE PREVENTION

IS THERE AN OPTIMAL  
ANTIPLATELET THERAPY



# ANTIPLATELET THERAPY

- Evidence for aspirin effectiveness since the 1950's
- Four agents approved by the FDA for secondary stroke prevention:
  - Aspirin
  - Ticlopidine
  - Clopidogrel
  - Dipyridamole



# ANTIPLATELET THERAPY

- Multiple trails have been done investigating single agents and comparing agents
- Canadian Cooperative, CAPRIE, ESPS 2, MATCH, CHARISMA, ESPRIT, CATS, TASS, DUTCH TIA, SALT, UK-TIA, and others
- Thousands of patients in studies, variable designs, inclusion and exclusion criteria, measured primary and secondary outcome measures, variable dosing, clumping of different stroke mechanisms



# ANTIPLATELET THERAPY

- Bottom line- antiplatelet therapy reduces risk of second event- overall relative risk reduction of 25% and absolute risk reduction of 3.6% for 2 years following initial event (The Antithrombotic Trialists Collaboration)
- Slight risk of bleeding complications- 0.7-1.7 % increased risk over placebo



# ANTIPLATELET THERAPY

Different agents have different mechanisms of action on platelets and endothelium

Vascular pathology is variable in large, medium and small vessel clot or injury

Different anatomy, physiology in small penetrating vessels of brain



# ANTIPLATELET THERAPY

- Aspirin inhibits platelet aggregation by inhibiting cyclooxygenase, also inhibits prostacyclin production in endothelium
- Ticlopidine and Clopidogrel inhibit ADP pathway of platelet aggregation
- Dipyridamole inhibits phosphodiesterase and has direct effects on platelets and endothelium with dilation, anti-inflammatory and antithrombotic effects



# ANTIPLATELET THERAPY

- Aspirin has effect at wide range of dosing, from 30mg to 1900 mg daily
- Minor bleeding effects similar at all doses, major bleeding, particularly GI, increases with dose
- Most studies show no significant difference in benefit with higher dosing, current trend is 50-325 mg daily



# ANTIPLATELET THERAPY

- Ticlopidine is dosed at 250 mg bid, used rarely now because of risk of TTP and neutropenia
- Clopidogrel is dosed at 75mg daily- loading dose is 300 mg- rare TTP.
- Dipyridamole is dosed at 200 mg twice daily, usually given in in extended release form with aspirin. Often causes headache



# ANTIPLATELET THERAPY

- Current recommendations are to start with aspirin or clopidogrel monotherapy or aspirin-dipyridamole ER therapy
- While combination therapy has been tried, multiple studies demonstrate no added benefit and increased risk of bleeding in TIA/stroke patients- this is particularly true for aspirin with clopidogrel



# ANTIPLATELET THERAPY

- There is evidence to support use of ASA-DP ER over aspirin alone with better risk reduction. This likely is attributable to effects of dipyridamole on endothelium. Given anatomy of small penetrating vessels this may be preferred agent for small vessel stroke



# ANTIPLATELET THERAPY

- Cilostazol, similar to dipyridamole, in use for peripheral vascular disease, recently shown in Japanese study of secondary stroke prevention to have 39% relative risk reduction compared to placebo. North American trials are underway



# ANTIPLATELET THERAPY

- Glycoprotein IIb/IIIa antagonists
- Thromboxane receptor antagonist
- Thrombin receptor antagonist
- EPA in fish and omega 3 oils
- Profess trial



# RECURRENT TIA/STROKE ON TREATMENT

- Insure patient compliance with antiplatelet therapy- even in studies there is a 20% non-compliance. Are there side effects interfering with medication ?
- If patient is on aspirin, can increase dose if on low dose (questionable data to support this), continue present dose, switch to clopidogrel or ASA-DP ER



# RECURRENT TIA/STROKE ON TREATMENT

- Combining aspirin and clopidogrel offers no extra protection and increases risk of bleeding complications
- Look at all treatable risk factors and treat aggressively using current guidelines
- Look at specific causes of stroke that require different treatments- cardiembolic event, high grade symptomatic carotid stenosis, hypercoaguable states



# RECURRENT TIA/STROKE ON TREATMENT

- Consider TIA/stroke mimickers :
- Migraine
- Partial seizures
- Metabolic, toxic
- Intracerebral hemorrhage
- Somatic, conversion disorder



# STATINS IN STROKE PREVENTION

- Multiple studies of patients with cardiovascular and cerebrovascular disease show approximate 25% relative risk reduction in ischemic stroke
- This effect is seen most clearly when stroke patients have associated cardiovascular events and/ or PAD



# STATINS IN STROKE PREVENTION

- When the entry event in the study is an ischemic stroke, less benefit is seen with use of statins
- In some studies there was a slight increase in hemorrhagic strokes in patients on statin therapy with low LDL- this was also associated with male gender and older age



# STATINS IN STROKE PREVENTION

- SPARCL trial with 4700 patients showed 16 % relative risk reduction for fatal and non-fatal stroke but a 43% relative risk reduction for fatal stroke.
- Small increase in hemorrhagic strokes seen



# STATINS IN STROKE PREVENTION

- In TIA/stroke patient LDL goal is  $< 70$  mg/dl if there are other risk factors- recurrent events, other vascular disease, tobacco use and diabetes; otherwise goal is  $< 100$  mg/dl
- Meta-analysis of 26 trials showed relationship of LDL reduction and stroke reduction; each 10% LDL reduction was associated with 16% risk reduction



# STATINS IN STROKE PREVENTION

- Several studies show patients admitted with ischemic stroke already on statins have better outcomes by multiple neurological measures
- Beneficial effects of statins are multifactorial including lowering LDL, endothelial anti-inflammatory and increased NO availability



# TIA RISK ASSESSMENT

- Patients with a TIA are at 4-20 % risk of stroke within the following 90 days
- 50% of these strokes will occur within the first 48 hours
- A clinical and diagnostic evaluation is important quickly



# TIA RISK ASSESSMENT

- Lancet article January 27,2007 : volume 369, page 283
- Combines two different validated rating scales into ABCD2
- This needs to be combined with labs, appropriate cardiac evaluation, brain imaging and carotid artery imaging



# TIA RISK ASSESSMENT

- A- age 60 or over – 1 point
- B- blood pressure-  $>140$  systolic or  $>90$  diastolic- 1 point
- C- clinical signs; unilateral weakness 2 points, speech impairment without weakness 1 point
- D- duration-  $>60$  minutes 2 points, 10-59 minutes 1 point
- D- diabetes, 1 point



# TIA RISK ASSESSMENT

- Two day stroke risk was
- 0 % for score of 0-1
- 1-2% for score of 2
- 0-3% for score of 3
- 2-5% for score of 4
- 3-7% for score of 5
- 4-14% for score of 6
- 0-50% fore score of 7

# TIA RISK ASSESSMENT

- Combined data from all data sites was consistent, predicted stroke risk at 2, 7 and 90 days
- In 4799 patients 2 day risk of stroke was
- 1% with score of 1-3, low risk
- 4.1% with score of 4-5, moderate risk
- 8.1% with score of 6-7, high risk



# TIA RISK ASSESSMENT

- Use of a validated clinical scale along with appropriate diagnostic labs, carotid artery imaging, brain imaging, EKG may help in deciding risk of stroke and which patients should be admitted for evaluation and treatment and which can follow up as out patients
- Treatment with antiplatelet agents, antihypertensive agents and statins

