KANSAS INITIATIVE FOR STROKE SURVIVAL

A PROJECT BY AND FOR KANSANS

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Antiplatelet medications in stroke

"First Tuesdays" Lecture Series

Introduction and Goal of “First Tuesdays”

- Sabreena Slavin MD – Vascular Neurologist and Neurohospitalist at KU School of Medicine
- Didactic lecture series as part of the Kansas Initiative for Stroke Survival
- Updates in Practice and FAQ’s on Acute Stroke Care
- 30 minutes of didactic/question and answers

Outline

- Review of commonly used antiplatelet medications in the US market
- Three main questions:
  - Dosage of Aspirin?
  - DAPT vs monotherapy?
  - Which antiplatelet medication is “best”?

Nomenclature

- Antiplatelets have mechanism of action to prevent platelet aggregation and/or function. Ex: Aspirin, Clopidogrel, Dipyridamole
- Anticoagulants inhibit parts of the coagulation cascade. In general, have higher bleeding rates. Ex: Warfarin, Apixaban, Rivaroxaban
- “Blood thinners” = anticoagulants NOT antiplatelets
  - No contraindication to tPA with antiplatelet use

Aspirin

- Mechanism of action: irreversible COX inhibitor → prevents synthesis of prostaglandins (prevents inflammation/pain/fever) and thromboxane (prevents platelet aggregation)
- Side effects: bleeding, GI upset
- Dosage = 81 mg daily vs 325 mg daily

Rothwell et al, *Lancet* 2016

Clopidogrel (Plavix)

- Mechanism of action: irreversibly inhibits binding of ADP to the P2Y12 platelet-receptor → prevents formation of the glycoprotein IIb/IIIa complex → prevents aggregation of platelets
- This is an inactive prodrug that must be metabolized by the liver using CYP2C19 to its active form before it can work
- About 30% of the US population have a loss of function of a CYP2C19 allele, giving them resistance against Clopidogrel
- Also PPI use can decrease Clopidogrel effectivity
- Dose = 75 mg daily

Dipyridamole

- Mechanism of action: inhibits phosphodiesterase E
  → prevents reuptake and breakdown of adenosine
  → prevents platelet function
- Side effects: Vasodilation causing headaches, GI side effects, more bleeding than ASA or Clopidogrel
- Dose = Aggrenox 1 tab bid (contains 25 mg ASA and 200 mg Dipyridamole)

Ticagrelor (Brilinta)

- Mechanism of action: Reversibly inhibits binding of ADP to the P2Y12 platelet-receptor → prevents formation of the glycoprotein IIb/IIIa complex → prevents aggregation of platelets
- Does not come in a prodrug form, so no issues with resistance
- More rapid onset and more pronounced platelet inhibition than Clopidogrel
- Dose = 90 mg bid

Benefit for Aspirin (antiplatelet therapy)

- CAST study[1]: RCT with ASA vs placebo in over 21,000 patients started within 48 hours of onset of symptoms.
  - There was a 14% reduction in mortality with ASA in the first four weeks (3.9% vs 3.3%)
  - There was also significantly fewer recurrent ischemic strokes in ASA group (2.1% vs 1.6%).

- WARSS study[2]: RCT with ASA vs warfarin in patients with a stroke within 30 days, randomized 2206 patients.
  - No difference in primary outcome of recurrent stroke or death from vascular cause in either group (17.8% warfarin vs 16% aspirin)
  - More significant bleeding episodes in warfarin group

- Helped establish evidence of ASA for secondary stroke prevention in general group of patients

1. Chen et al, *Lancet* 1997; 2. Mohr et al, *NEJM* 2001

Dose of Aspirin?

- ADAPTABLE: A large recent trial randomizing open label Aspirin 81 mg daily vs 325 mg daily in over 15,000 patients with cardiovascular risk factors.

Mulder et al, *NEJM* 2021

Results of ADAPTABLE

Table 2. Primary Effectiveness Outcome, Key Secondary Effectiveness Outcomes, and Primary Safety Outcome.*

Outcome	81-mg Group	325-mg Group	Hazard Ratio (95% CI)	P Value
	events (estimated percentage)			
Primary effectiveness outcome: death from any cause, hospitalization for MI, or hospitalization for stroke	590 (7.28)	569 (7.51)	1.02 (0.91–1.14)	0.75
Death from any cause	315 (3.80)	357 (4.43)	0.87 (0.75–1.01)	
Hospitalization for MI	228 (2.99)	213 (2.87)	1.06 (0.88–1.27)	
Hospitalization for stroke	102 (1.23)	92 (1.27)	1.09 (0.82–1.45)	
Occurrence of PCI or CABG	471 (6.05)	446 (5.96)	1.04 (0.92–1.19)	
Hospitalization for transient ischemic attack	20 (0.23)	25 (0.35)	0.79 (0.44–1.42)	
Primary safety outcome: hospitalization for major bleeding with associated blood-product transfusion	53 (0.63)	44 (0.60)	1.18 (0.79–1.77)	0.41

Mulder et al, *NEJM* 2021

DAPT vs Monotherapy

- CHANCE trial: RCT of 5170 patients with mild stroke/TIA randomized to receive ASA alone for 90 days vs Clopidogrel plus ASA for first 21 days then ASA alone for 90 days
  - Stroke occurred in 10.6% patients in the DAPT group, in comparison with 14.0% patients in the aspirin group (HR 0.78, 95% CI 0.65–0.93)
  - Similar rates of bleeding

Wang et al *Circulation* 2015

DAPT vs Monotherapy

- POINT trial: RCT of 4881 patients who received ASA alone vs ASA plus Clopidogrel for 90 days
  - Major ischemic events occurred in 5% of those receiving DAPT vs in 6.5% in those receiving ASA alone (HR 0.75, 95% CI 0.59-0.95) with most occurring during the first week after initial event.
  - Major hemorrhage occurred in 0.9% receiving DAPT vs 0.4% in ASA alone (HR 2.32, 95% CI 1.10—4.87)

Johnston et al, *NEJM* 2018

Conclusions of recent DAPT trials

- Historically, studies also showed that reduced rate of stroke prevention in DAPT long term is balanced out by rate of major bleeding.
- Evidence that most recurrent strokes happen early in POINT trial in conjunction with CHANCE trial show that short-term DAPT is beneficial
- Current practice: ASA plus Clopidogrel for 21 days, then monotherapy alone
- In those with large artery disease, DAPT is used for 90 days or even longer if recurrent events

Evidence for Dipyridamole

- ESPIRT[1]: RCT of 2700 patients allocated to Dipyridamole/ASA vs ASA alone over median follow up of 3.5 years:
  - Primary event (stroke, MI, bleeding, or death from vascular cause) occurred in 13% on ASA/Dipyridamole vs 16% on ASA alone (HR 0.80, 95% CI 0.66-0.98)
  - However, 470 patients in Dipyridamole group discontinued medication vs 180 in ASA group

- RCT[2] of Dipyridamole/ASA vs Clopidogrel: 20,000 patients followed for mean of 2.5 years
  - Recurrent stroke occurred in 9% of patients receiving Dipyridamole/ASA vs 8.8% receiving Clopidogrel
  - There were more major hemorrhage events in Dipyridamole/ASA group (4.1%) than Clopidogrel (3.6%) (HR 1.15, 95% CI 1.00-1.32)

1. The ESPRIT study group, *Lancet* 2008; 2. Sacco et al, *NEJM* 2008

Evidence for Ticagrelor

- PLATO trial[1] in acute coronary syndrome: RCT comparing Ticagrelor vs Clopidogrel in over 18,000 patients admitted with acute coronary syndrome
  - Composite outcome of death from vascular causes, MI, or stroke occurred in 9.8% of patients with Ticagrelor vs 11.7% with Clopidogrel (HR 0.84, 95% CI 0.77-0.92)
- Other recent cardiac studies shows no difference in outcomes but more major bleeding and dyspnea with Ticagrelor[2]

- For stroke, SOCRATES[3]: RCT in over 13,000 patients with nonsevere ischemic stroke/TIA comparing Ticagrelor and Aspirin
  - Death, MI, or stroke happened within 90 days in 6.7% of patients receiving Ticagrelor vs 7.5% with Aspirin (nonsignificant)
- Also, meta-analysis[2] of 5 RCTs looking at DAPT: Clopidogrel/ASA vs Ticagrelor/ASA showed no difference between two groups in preventing recurrent stroke or death. However, Clopidogrel/ASA group had decreased functional disability than Ticagrelor/ASA.

1. Wallentin et al, *NEJM* 2009; 2. Turgeon et al, *JAMA* 2020;
3. Johnston et al, *NEJM* 2016; 4. Lun et al, *JAMA Neurology* 2021

Eptifibatide (Integrilin)

- Mechanism of action: IV peptide that reversibly binds glycoprotein IIb/IIIa complex preventing platelet aggregation
- Being used more frequently during endovascular intervention in acute stroke cases with carotid stent placement

Studies on Eptifibatide

- Positive data on Eptifibatide on patients with acute stroke in conjunction with IV thrombolysis[1] and endovascular thrombectomy[2]
- MOST study: RCT of Eptifibatide or Argatroban (anticoagulant) vs placebo in addition to alteplase within 3 hours, looking at 90 day mRS
- Observational study[3] of 29 cases (including 16 who received IV tPA) on Eptifibatide post emergent extracranial carotid artery stenting in acute stroke shows one patient with symptomatic ICH[4]

1. Derex et al, *J Am Heart Assoc* 2018; 2. Ma et al, *Stroke* 2022;
3. Osteraas et al, *J Stroke Cerebrovasc Dis* 2020

Conclusions

- All patients post stroke should be on at least one antiplatelet medication. Start with Aspirin 81 mg daily. Not much evidence that higher dose is better.
- After mild stroke or TIA, consider DAPT with ASA/Clopidogrel for 21 days then monotherapy long term.
- Can consider escalation to Clopidogrel in those who had stroke on ASA.
  - Check P2Y12 level to address whether patient may be resistant
- Can consider change in certain patients (eg. poor Clopidogrel metabolizers) to Dipyridamole or Ticagrelor in select cases. Cost and side effect profile can be prohibitive.

Questions?

- Call for help anytime!
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