Pearls and Perils of Anti-platelet therapy

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Role of Platelets in vascular ischemia

A. Injury

B. Initiation

C. Extension

D. Stabilization
Mechanism of action

Abciximab (Reopro)
Eptifibatide (Integrilin)
Tirofiban (Aggrastat)
Clopidogrel
Ticlopidine
Prasugrel
Ticagrelor
Cangrelor
# Efficacy of anti-platelets in stroke

<table>
<thead>
<tr>
<th></th>
<th>Acute treatment of stroke</th>
<th>Secondary prevention non-cardioembolic stroke</th>
<th>Prevention of cardio-embolic stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>12% RRR vs placebo</td>
<td>22% RRR vs placebo</td>
<td>21% RRR vs placebo Inferior to warfarin</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Not studied</td>
<td>Non-inferior to ASA</td>
<td>Maybe better than asa Inferior to warfarin</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>Not studied</td>
<td>21% RRR vs asa</td>
<td>Not studied</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Not studied</td>
<td>Non-inferior to ASA</td>
<td>Not studied</td>
</tr>
<tr>
<td>ASA+ Dipyridamole</td>
<td>Not studied</td>
<td>Non-inferior to ASA</td>
<td>Not studied</td>
</tr>
<tr>
<td>ASA+Clopidogrel</td>
<td>32% RRR vs ASA</td>
<td>Non-inferior to ASA</td>
<td>28% RRR vs ASA Inferior to warfarin</td>
</tr>
</tbody>
</table>

CAST Trial Lancet 1997, IST-3 Lancet 1997; ATT Collaboration Lancet 2009; CAPRIE; Profess; ACTIVE A; ACTIVE W; SPAF; SAMPRIS; CHANCE; MATCH; CHARISMA
Dual Antiplatelet

**Pearl:**

- Aspirin for 3 weeks + clopidogrel for 90 days following a TIA or minor stroke reduces risk for stroke by 32%

- Aspirin + clopidogrel x 90 days in patients with 70-99% stenosis of major intracranial artery may be reasonable

- Dual Antiplatelet (aspirin and clopidogrel) for long term secondary prevention increases risk of bleeding without reduction of stroke and is generally not recommended

CHARISMA Trial, N Engl J Med 2006;354:1706-17
MATCH trial. Lancet 2004;364:331-337
76 y/o male PMH of DM, HTN, HLD, s/p MI (1 month ago) with DES now presents with right sided weakness. Angiogram shows 80% stenosis of L MCA.

Meds: metformin, lisinopril 20mg daily, simvastatin 40mg, aspirin 81mg and clopidogrel 75mg.

Peril:
Do we continue with dual anti-platelets? What role does platelet function testing have? What about newer anti-platelets?
Stroke while on dual anti-platelets

- No clear evidence to suggest increasing dosing of current anti-platelets or that switching to alternative anti-platelets will be effective
- Assess compliance
- Consider aspirin resistance
- Consider platelet function testing to identify clopidogrel non-responder
- Comment on the novel P2Y12 inhibitors used in ACS
Aspirin Resistance in Stroke

- Estimated 12.9% clinical occurrence of stroke despite aspirin therapy
- Estimated 5.2-60% prevalence of aspirin resistance depending on the population studied and platelet function assay used
- 33% of stroke patients who are on ASA have laboratory evidence of ASA resistance
- Aspirin resistance in ischemic stroke patients is associated with short and long term mortality
- Drug-Drug interaction with ibuprofen
- Enteric coated aspirin delays absorption
- Laboratory aggregometry assays; Verify Now POC; Urine TXA metabolite assay

J Neurol 2011;258(11):1979-86
Pharmacotherapy 2005;24(7):942-953
Clopidogrel Resistance

- Clopidogrel requires liver metabolism via CYP 2C19 for active metabolite
- 5-30% of population do not have adequate response
- High on treatment platelet reactivity associated with increased risk for stent thrombosis and stroke after PCI
- Clopidogrel resistance may be associated with thrombotic complications following neurovascular interventions

Clopidogrel Resistance

- Mechanism of poor response
  - Drug-drug interactions (ie. Omeprazole)
  - Genetic polymorphism
  - Non-compliance
  - Diabetes

- How do we measure platelet reactivity on P2Y12 inhibitors?

Angiolillo DJ et al J Am Coll Cardiol. 2014;64(10):1005-1014
Traditional Model of Platelet Aggregation

A

Key

Inactive/active $\alpha_{\text{IIb}}\beta_3$
Inside-out signalling

Key

GPCR
Fibrinogen
Thrombin
ADP/TxA2

B

Light source
Agonist
Platelet Reactivity

PRU = P2Y 12 reaction units

A Therapeutic Window for Platelet Reactivity for Patients Undergoing Elective Percutaneous Coronary Intervention: Results of the ARMYDA-PROVE (Antiplatelet therapy for Reduction of MYocardial Damage during Angioplasty–Platelet Reactivity for Outcome Validation Effort) Study

JACC: Cardiovascular Interventions, Volume 5, Issue 3, 2012, 281 - 289
Limitations of VerifyNow P2Y12 assay

- Not studied in patients with platelet function disorders

- Not studied in patients with platelet count <100K; HCT <33%; Fibrinogen <150K

- Interfering substance
  - Reopro within last 14 days; Integrilin/Aggrastat in last 48 hrs
  - Cilostazol in last 12 hours
  - ASA/NSAIDs do not interfere with P2Y12 assay
Newer Antiplatelets

Ticagrelor (Brilinta®)

PLATO n=18,624

- MI/Stroke/CV Death: Ticagrelor 9.80%, Clopidogrel 12.10%
- non-CABG bleeding: Ticagrelor 4.50%, Clopidogrel 9.90%

HR 0.84 (0.77-0.92)
HR 1.19 (1.02-1.38)

Prasugrel (Effient®)

TRITON-TIMI n=13,608

- MI/Stroke/CV Death: Prasugrel 2.40%, Clopidogrel 3.80%
- non-CABG bleeding: Prasugrel 2.40%, Clopidogrel 1.80%

HR 0.81 (0.73-0.90)
HR 1.32 (1.03-1.68)

Contraindicated in patients with Stroke or TIA

Antiplatelet and Anticoagulant

Stroke prevention in patients with atrial fibrillation and coronary artery disease – do we use warfarin alone? Warfarin + single antiplatelet? Warfarin + dual antiplatelet?
LESS IS MORE

Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation

Morten L. Hansen, MD, PhD; Rikke Sørensen, MD; Mette T. Clausen, MSc Pharm; Marie Louise Fog-Petersen, MSc Pharm; Jakob Raunsø, MD; Niels Gadsbøll, MD, DMSc; Gunnar H. Gislason, MD, PhD; Fredrik Folke, MD; Søren S. Andersen, MD; Tina K. Schramm, MD; Steen Z. Abildstrøm, MD, PhD; Henrik E. Poulsen, MD, DMSc; Lars Køber, MD, DMSc; Christian Torp-Pedersen, MD, DMSc

Arch Intern Med. 2010;170(16):1433-1441
Figure 3. Hazard ratios (HRs) for the risk of nonfatal (n=12,191) and fatal (n=1381) bleeding associated with the use of warfarin, aspirin, clopidogrel, and combinations of these drugs. CI indicates confidence interval.

Figure 4. Hazard ratios (HRs) for the risk of nonfatal (n=9785) and fatal (n=3537) ischemic stroke associated with the use of warfarin, aspirin, clopidogrel, and combinations of these drugs. CI indicates confidence interval.
WOEST trial

Oral Anticoagulation and Antiplatelets in Atrial Fibrillation Patients After Myocardial Infarction and Coronary Intervention

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Hellerup, Copenhagen, and Aalborg, Denmark; and Birmingham, United Kingdom

Figure 3  Benefit and Safety With Triple Therapy Versus Dual Therapies

Triple therapy (oral anticoagulant [OAC] plus aspirin plus clopidogrel [dotted line]) is used as reference (hazard ratio = 1.00). Orange circles indicate OAC plus clopidogrel; yellow circles indicate OAC plus aspirin; green circles indicate aspirin plus clopidogrel. MI = myocardial infarction.
Anti-platelets to the rescue

2-15% risk of thromboembolic complications during neurovascular embolization of ruptured aneurysms

Goal of rescue therapy: recanalize occluded artery and prevent permanent neurologic deficits
IIB or not IIB?

No statistically significant difference in Stroke/hemorrhage

Post-op stroke

Post-op hemorrhage

Glycoprotein IIb/IIIa associated with significantly less short-term and long-term morbidity than fibrinolytics. Trend toward better recanalization.

Relative efficacy of abciximab vs tirofiban/eptifibatide

No statistically significant difference in Stroke/hemorrhage

Relative efficacy of abciximab vs tirofiban/eptifibatide

No statistically significant difference in morbidity
Tirofiban/eptifibatide resulted in significantly higher recanalization rates


