

APPROPRIATE USE OF NON-ASPIRIN ANTI-PLATELET AGENTS

Background

Non-aspirin (non-ASA) anti-platelet agents (clopidogrel, ticlopidine, dipyridamole, and cilostazol) are being used with increasing frequency in medical practice. The reasons most often cited for this increased utilization include ASA allergy, gastrointestinal (GI) intolerance to ASA, or insufficient clinical response with ASA alone. In 2004, Idaho Medicaid spent over \$1.2 million on these agents, representing a cost increase of approximately 45% over the previous year. In 2004, clopidogrel alone was ranked number 32 in terms of cost according to Idaho Medicaid records, with just over \$1 million spent on claims.

Table I: Comparison of Anti-Platelet Agents

Antiplatelet Agents	FDA-Approved Indications					Cost*	
	ACS	Stroke/TIA	PVD	Post-Stent	IC	Generic	Brand
Aspirin	X	X				\$ 0.6-1.7	N/A
Clopidogrel (Plavix®)	X	X	X			N/A	\$ 115
Ticlopidine (Ticlid®)		X		X		\$ 86	\$ 145
Aspirin/ER Dipyridamole (Aggrenox®)		X				N/A	\$ 122
Cilostazol (Pletal®)					X	\$ 27	\$112

*Monthly cost based on prices obtained from www.drugstore.com on August 25, 2005.

Abbreviations: ACS=acute coronary syndrome, TIA=transient ischemic attack, PVD=peripheral vascular disease, IC=intermittent claudication.

It is important to note that all FDA-approved indications regarding the use of non-ASA anti-platelet agents in vascular disease are for secondary prophylaxis only, whereas ASA is approved for both primary and secondary prevention.

The GI tolerability of these agents relative to ASA has recently been questioned. A study by Chan et al. demonstrated that the risk of rebleeding in patients with prior GI ulceration due to ASA was greatly reduced when a proton pump inhibitor (PPI) was added to ASA versus switching patients to clopidogrel.¹

A brief comparison of clopidogrel and ticlopidine:

- ❖ Clopidogrel (Plavix®)
 - Most prescribed non-ASA anti-platelet agent
 - Widely held to be less GI damaging than ASA; however, recent data suggests that ASA + PPI is likely superior¹
 - Although not an FDA-labeled indication, it has become the standard of care for use in combination with ASA after coronary stent placement²
- ❖ Ticlopidine (Ticlid®)
 - Has fallen out of favor with many prescribers due to reports of life-threatening hematological adverse reactions including agranulocytosis, neutropenia, and thrombotic thrombocytopenic purpura
 - According to Beers' criteria, ticlopidine is often misused in the elderly and should be avoided when possible in that population³

Guidelines on use of anti-platelet agents in vascular disease prophylaxis^{2,4,5}

The following recommendations were obtained from CHEST guidelines last updated in 2004. Only indications with the strongest level of evidence (Level A, data derived from randomized controlled trials with consistent results) are included. Grade 1 and 2 describe clarity of benefits over risks (Grade 1 = experts are very certain that benefits outweigh the risks, Grade 2 = experts less certain of magnitude of benefits over risks).

Acute Coronary Syndrome (non-ST-segment elevation MI or unstable angina)

- ASA 160-325 mg upon presentation, continue indefinitely at 75–162 mg daily (1A)
- ASA allergy or GI intolerance*: clopidogrel 300 mg bolus followed by 75 mg/d indefinitely (1A)
- Delayed diagnostic catheterization or CABG > 5 days following coronary angiography: clopidogrel 300 mg bolus followed by 75 mg/d for 9-12 months in addition to ASA (1A)
*Since the publication of these recommendations, the study by Chan et al. demonstrated that the risk of rebleeding in patients with GI ulceration due to ASA was reduced when a PPI was added to ASA compared with switching to clopidogrel

Noncardioembolic stroke or TIA

- Treatment with an anti-platelet agent is recommended (Grade 1A); aspirin (50-325 mg), ASA/ER dipyridamole (Aggrenox[®]) or clopidogrel (75 mg) are all acceptable options
- ASA/ER dipyridamole twice daily preferred over ASA (2A)

Stent placement

- ASA + ticlopidine or ASA + clopidogrel preferred over systemic anticoag. therapy (1A)
- Clopidogrel + ASA preferred over ticlopidine + ASA (1A)
- Patients with low atherosclerotic risk: clopidogrel for at least 2 weeks following placement of bare metal stent (1A)
- Long-term tx post percutaneous coronary intervention (PCI): ASA 75-162 mg/d (1A)
- After PCI: clopidogrel 75 mg/d in addition to ASA for at least 9-12 months (1A)

Intermittent claudication

- Chronic limb ischemia: lifelong aspirin therapy in patients with clinically manifest coronary or cerebrovascular disease (1A); ASA preferred over clopidogrel (2A)
- Disabling intermittent claudication unresponsive to conservative measures and not a surgical candidate: initiate cilostazol (2A)

Summary

- ❖ **ASA has been the gold standard of anti-platelet therapy for many years and it is still considered a cost-effective first-line of therapy for most patients**
- ❖ **Clopidogrel is safer than ticlopidine**
- ❖ **When a combination of clopidogrel and ASA is used, it may be prudent to use ASA at a dose of 75-100 mg/d to minimize the bleeding risk²**
- ❖ **In patients who suffered a GI bleed while on ASA, the addition of a PPI to ASA therapy is likely safer than switching to clopidogrel¹**

References

1. Chan FKL, Ching JYL, Hung LCT et al. Clopidogrel versus aspirin and esomeprazole to prevent recurrent ulcer bleeding. *NEJM* 2005;352:238-44.
2. American College of Chest Physicians. The seventh ACCP conference on antithrombotic and thrombolytic therapy: Evidence-based guidelines. *Chest* 2004;126(3)-supplement.
3. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med.* 1997 Jul 28;157(14):1531-6.
4. Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *NEJM* 2001;345(7):494-502.
5. Steinhubl S, Berger P, Mann J, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA* 2002;288;2411-2420.