



Clinical Guide - Antiplatelet Therapy

Principal Developer: J. Lam

Secondary Developers: J. Cusson, A. Roussin

Background

Antiplatelet agents are drugs which interfere with the ability of platelets to aggregate and form a platelet plug. As antithrombotic agents, they are most useful in clinical states due to arterial vascular disease.

Available Agents

The cheapest and most widely used agent is aspirin. Ticlopidine and clopidogrel are newer, and are recommended for patients with aspirin allergy or intolerance, and when clinical events arise despite ASA therapy. Clopidogrel is recommended over ticlopidine because it is associated with less serious side effects and provides superior benefit to aspirin in patients with vascular disease, such as stroke, myocardial infarction or peripheral arterial disease. This benefit of clopidogrel is enhanced in patients at higher risk, such as those with hyperlipidemia, diabetes, prior coronary bypass surgery and disease in multiple vascular beds. Aspirin and clopidogrel have a synergistic effect and is recommended after an episode of non-ST-segment elevation (NTSE) acute coronary syndromes (ACS) and in patients undergoing coronary stenting, where the combination has been shown to provide better cardiovascular protection. The use of sulfapyrazone as antithrombotic agents either alone or in combination with other antiplatelet agents is not recommended. There is no evidence for dipyridamole alone or in addition to, aspirin and clopidogrel in the management of patients with ACS. Aspirin, clopidogrel or extended-release dipyridamole in combination with aspirin are acceptable options for prevention of ischemic stroke. Results of ongoing clinical studies will clarify the role of the aspirin-dipyridamole combination versus other anti-platelet strategies in stroke prevention.

Indications

An overview of randomized clinical trials have shown that the risk of major vascular events (myocardial infarction, stroke and vascular death) is reduced by approximately 25% and the risk of mortality is reduced by approximately 15% in patients with atherosclerotic vascular disease at high risk.

Cardiac

In patients with ACS with and without ST-segment elevation, regular uncoated aspirin should be given as soon as the diagnosis is made, whether or not thrombolytic therapy and/or heparin is to be administered. Aspirin is also recommended for patients with stable angina, post-angioplasty and CABG where it helps maintain patency as well as reduce the incidence of serious vascular events. Aspirin should be continued indefinitely in all patients unless there are indications for use of warfarin. (See Antithrombotic Therapy Post-MI guidelines). Among high-risk NSTEMI ACS patients, recent evidence suggest added benefit from combination antiplatelet regimen. Clopidogrel (or ticlopidine in case of clopidogrel intolerance) is an effective alternative in cases of aspirin intolerance or allergy. Clopidogrel, 300mg loading, followed by 75mg daily in addition to aspirin is recommended for at least 9 to 12 months in all patients presenting with NSTEMI ACS. This combination may also be useful in stable coronary patients at high risk. In moderate to high risk-patients presenting with NSTEMI ACS, there is additional benefit from the early initiation of GP IIb/IIIa inhibitors such as eptifibatid or tirofiban in addition to aspirin and heparin.

Indications:

1. Antiplatelet therapy is STRONGLY RECOMMENDED for ALL patients with the following unless contraindicated:

A. Cardiac

- ACS patients with and without ST-segment elevation
- Chronic stable angina or documented coronary disease
- following angioplasty or CABG

B. Cerebrovascular

- post TIA, completed strokes
- following carotid endarterectomy

C. Peripheral Vascular Disease

- any peripheral vascular disease

2. Antiplatelet therapy MAY BE BENEFICIAL in the following:

A. Cardiac

- atrial fibrillation if warfarin contraindicated.
- mechanical heart valve in combination with warfarin.
- patients over 50 yrs old with at least 1 additional cardiac risk factor for atherosclerosis.

B. Cerebrovascular

- carotid artery disease

C. Peripheral Vascular Disease

The use of aspirin may modify the natural history of intermittent claudication due to peripheral vascular disease. In the absence of contraindications, aspirin is recommended for patients with peripheral vascular disease for reduction of cardiovascular events (myocardial infarction and stroke). Clopidogrel may be superior to aspirin in reducing ischemic complications in patients with peripheral vascular disease.

Primary Prevention

Although aspirin has been shown to be effective in primary prevention of vascular disease, the overall benefit is small. Therefore, it is prudent to limit its use to individuals 50 years old with one additional risk factor for coronary disease (i.e. diabetes, hypertension, smoking, hyperlipidemia, sedentary lifestyle).

Dosage and Administration

The usual antiplatelet dose of aspirin is 75-325 mg daily. An initial dose of 160 to 325 mg is recommended, and then indefinite therapy with 75 to 162 mg/d. For those with a history of aspirin-induced bleeding or at risk for bleeding, chronic lower dose of aspirin is recommended, <100mg/d. In individuals with cerebrovascular disease, there may be additional benefits to aspirin given in association with slow release dipyridamole, 200 mg BID, although although this combination has not been shown to decrease coronary events. When used in combination with clopidogrel, the dose of aspirin should be <100 mg/d.

The recommended dose for Ticlopidine is 250 mg twice daily. Ticlopidine or clopidogrel is recommended for patients with aspirin intolerance or allergy, and/or patients who have recurrent events despite aspirin therapy. Clopidogrel, 300 mg oral bolus, followed by 75 mg daily, is an effective alternative to ticlopidine, and is preferred over ticlopidine because it is associated with fewer serious side effects and does not require frequent monitoring of blood counts.

Patients may be advised to discontinue clopidogrel or ticlopidine 5 days prior to elective surgery to minimize perioperative bleeding. For patients who have received clopidogrel and have to undergo CABG, it is recommended to discontinue the clopidogrel for 5 days prior to the surgery.

Side Effects

The most common side effect of aspirin is gastrointestinal intolerance which is dose related. Bleeding is a potential.

The most common side effects of Ticlopidine are diarrhea and skin rash. Neutropenia has been reported and is usually reversible. Monitoring of the WBC is recommended every 2 weeks for the first 3 months of therapy.

The most common side effect of Clopidogrel is skin rash. Neutropenia is uncommon, as infrequent as with ASA, and monitoring of the WBC is not necessary.

Contraindications

- familial or acquired bleeding disorder
- thrombocytopenia
- allergy to proposed drug
- caution should be exercised when administering aspirin to patients with asthma and other allergic disorders
- active bleeding

References

1. Hirsh et al. Chest 1998; 114 (Suppl):439-769S.
2. Seventh ACCP Consensus Conference on Antithrombotic Therapy. http://www.chestjournal.org/content/vol126/1_suppl/
3. Antiplatelet Trialists' Collaboration. BMJ 1994; 308:81, 159 and 235.
4. CAPRIE Steering Committee. Lancet 1996; 348:1329.
5. CURE study investigators. N Engl J Med 2001; 345:494-502
6. ACC/AHA/ACP-ASIM Guidelines for the management of patients with chronic stable angina. J Am Coll Cardiol. 1999; 33:2092
7. ACC/AHA Guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction. Circulation 2002; 106:1893.
8. Boersma et al. Lancet 2002; 359:189-198