

UCLA Clopidogrel in Acute Coronary Syndrome Guideline

Background

The strategy of inhibiting platelet activity at the injured coronary plaque by antiplatelet therapy with the combination of aspirin and clopidogrel represents a new therapeutic approach in patients with acute coronary syndromes.

Clopidogrel (Plavix®) is an inhibitor of ADP induced platelet aggregation acting by direct inhibition of adenosine diphosphate (ADP) binding to its receptor and of the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex. Clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the application of platelet activation by secondarily released ADP. Clopidogrel acts by irreversibly modifying the platelet ADP receptor. Consequently, platelets exposed to clopidogrel are inhibited for the remainder of their life span. The antiplatelet effect is additive to other platelet inhibitors with different mechanisms of action such as aspirin.

Antiplatelet therapy with aspirin has been demonstrated to benefit patients with acute ST segment elevation myocardial infarction and acute coronary syndromes (CV event risk reduction 22-52%) as well have long term benefits in patients with or at risk for atherosclerosis. The CAPRIE trial evaluated clopidogrel directly to aspirin in 19,185 patients with stable atherosclerotic vascular disease and showed a slightly lower risk for major vascular events with clopidogrel relative to aspirin (CV event risk reduction 8%). The combination of aspirin and ADP receptor antagonist in the first 2-4 weeks after coronary stenting has been shown to markedly reduce the risk of stent thrombosis.

CURE Trial

The CURE trial randomized 12,562 ACS patients (no ST elevation) to aspirin alone (75-325 mg per day) or aspirin plus clopidogrel. Clopidogrel was given as a 300-mg loading dose followed by a chronic dose of 75 mg per day. Patients were followed for 3-12 months (average 9 months). In the trial 61% of patients were male, 75% had unstable angina, 93% had abnormal ECGs, and 25% had elevated cardiac enzymes/troponins. Background therapy included unfractionated heparin 46%, LMW heparin 50%, beta blockers 78%, calcium blockers 36%, ACE inhibitors 50%, and lipid lowering drugs 47%. Major cardiovascular events (CV death, nonfatal MI, and stroke) were reduced from 11.5% with aspirin alone to 9.3% with aspirin plus clopidogrel (OR 0.80, $p=0.00005$). The predominate effect was on nonfatal myocardial infarction being reduced from 6.7% to 5.2% (OR 0.77, $p<0.001$). There was an excess of major bleeding, being increased from 2.7% to 3.6% (OR 1.34, $p=0.003$), but life threatening bleeding was not significantly increased (1.8% vs. 2.1%).

Subgroup analysis showed that there was consistent ben-

efit of clopidogrel across all groups, including both high-risk and low-risk patients. Benefits were seen regardless of other medications utilized i.e. beta blockers, statins, ACE inhibitors, and heparin. The study results demonstrate that treating 1000 patients for 9 months with clopidogrel prevents 28 major CV events in 23 patients at a cost of 3 life-threatening bleeds, which are reversible.

Recommended Therapy for ACS

In patients with acute coronary syndromes the initiation of the combination of aspirin and clopidogrel is recommended. Aspirin in an initial dose of 325 mg chewed is recommended in all patients without contraindications, followed by 81-325 mg daily indefinitely. Clopidogrel given as a 300-mg loading dose is recommended in all patients without contraindications, followed by a chronic dose of 75 mg per day (for at least 6 months or indefinitely based on physician discretion). Therapy should be initiated in the Emergency Medical Center and prior to initiation of cardiac catheterization, if possible, in those patients being managed by the invasive strategy. Patients who are allergic to aspirin should receive clopidogrel alone.

Contraindications

Severe Thrombocytopenia (platelet count $< 20K$)
Active pathological bleeding (intracranial hemorrhage or bleeding peptic ulcer)
History of intracranial hemorrhage or hemorrhagic stroke
Severe uncontrolled hypertension
Known hypersensitivity to the drug

Protocol (use in ST elevation AMI, non ST elevation MI, and unstable angina)

1. Administer aspirin 325 mg chewed
2. Administer clopidogrel 300 mg PO (four 75 mg tablets)
3. Administer beta blocker and intravenous heparin per UCLA AMI or CP/UA protocols

Continue aspirin at a dose of 81-325 mg daily indefinitely (lifelong). Continue clopidogrel at a dose of 75 mg daily for at least 6 months or indefinitely based on individual physician discretion. For patients undergoing stenting for an ACS indication, a 6 month or more course is recommended. For patients having stenting in the setting of stable coronary artery disease a 4 week course of clopidogrel may still be considered.

Clinical Pharmacology

Dose dependent platelet inhibition with clopidogrel can be seen within 1 to 2 hours. Maximal platelet effect and achieving steady state can require 3-7 days, in the absence of a loading dose. With the 300 mg loading dose, maximal ef-

fect can be reached in 4 to 6 hours. At steady state, the average level of platelet inhibition is between 40 to 60%. In combination with aspirin 80-90% platelet inhibition levels are achieved. Platelet aggregation and bleeding times gradually return to baseline values after treatment is discontinued, generally after about 5 days.

Clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. No dose adjustment is required in the elderly or patients with renal insufficiency. Experience is limited in patients with severe hepatic disease.

Potential Risks

The major risk with this agent is bleeding. For patients who develop refractory or life-threatening bleeding, the antiplatelet effect of clopidogrel may be reversed by platelet transfusion. There has been concern regarding the risk of excessive perioperative bleeding among patients who require urgent coronary artery bypass surgery after administration of clopidogrel, but this did not increase mortality in the CURE trial. Platelet transfusions are likely to be required to reduce operative bleeding.

Thrombotic thrombocytopenic purpura (TTP) has been reported following the use of clopidogrel, sometimes after short (< 2 week) exposure. TTP is characterized by fever, thrombocytopenia, microangiopathic hemolytic anemia, neurological findings, and renal dysfunction. TTP has not been seen in any of the clopidogrel clinical trials (n > 32,000). In post marketing experience, TTP has been reported at a rate of 4 cases per million patients exposed. TTP can be fatal and requires urgent diagnosis and treatment.

As with other anti-platelet agents, clopidogrel should be used with caution in patients who may be at increased risk of bleeding. The benefits of reducing major CV events must be weighed against the risk of serious or life threatening bleeding. For elective surgeries where an antiplatelet effects is not desired, clopidogrel should be held for 7 days.

Anticoagulation

Antiplatelet therapy with aspirin and clopidogrel can be administered in conjunction with glycoprotein IIb/IIIa receptor antagonists and anticoagulation with heparin, when clinically indicated. In patients with ACS, anticoagulation should be initiated with heparin using the UCLA Heparin Protocol for unstable angina, which is weight adjusted, aiming for a target aPTT of 60 to 85 seconds. In the catheterization laboratory, the activated clotting time (ACT) goal is 200 seconds if a GP IIb/IIIa inhibitor is used or 300 if not.

The aspirin and clopidogrel combination has not been studied in patients who require anticoagulation with warfarin and as such this combination is not recommended for patients requiring anticoagulation.

Monitoring

Routine laboratory monitoring is not required for patients on clopidogrel or the clopidogrel-aspirin combination. Patients should be instructed to report any unusual bleeding to their physician.

For hospitalized patients also treated with a glycoprotein IIb/IIIa receptor antagonist, a CBC with platelets 4 hours after initial bolus dose, and QAM (first day and while on the GP IIb/IIIa drug) is recommended. Patients treated with IV heparin should have monitoring of daily CBC with platelets while heparin is administered.

Other Clinical Implications

The safety and effectiveness of the clopidogrel and aspirin combination in ACS patients in this trial over an average of 9 months follow-up makes it reasonable to consider this combination long term in patients after ACS. It is also reasonable to consider combination treatment in high risk patients with stable coronary artery and other atherosclerotic vascular disease. Individualization of therapy based on consideration of the risks, benefits, and cost is recommended.

Cost

The average retail pharmacy price for clopidogrel is estimated to be \$85 for a 30 day supply. A preliminary cost effectiveness analysis indicates that treatment for 6 months in acute coronary syndrome patients results in a net cost savings (reduction in hospitalization costs greater than increased medication costs).

*UCLA Cardiology Clinical Guidelines Committee
Developed by: Gregg C. Fonarow, M.D.
Implemented: March 23, 2001*