Clopidogrel (Plavix®)

Thrombosis Canada
Thrombose Canada

Objective:

- To describe the clinical pharmacology and therapeutic application of clopidogrel.
- To discuss drug dosing, duration of therapy, genetic polymorphisms affecting drug metabolism, and potential drug interactions with proton pump inhibitors.

Background:

Clopidogrel (Plavix®, generics) is an oral platelet inhibitor that has demonstrated cardiovascular protection as monotherapy or in combination with acetylsalicylic acid (ASA) in patients with acute coronary syndrome (ACS), symptomatic peripheral arterial disease (PAD), and cerebrovascular disease.

Mechanism of Action:

Clopidogrel is categorized as a thienopyridine which irreversibly blocks the $P2Y_{12}$ adenosine diphosphate (ADP) receptor and thereby inhibits ADP-induced platelet aggregation. Clopidogrel is a prodrug which is metabolized into its active agent by the hepatic cytochrome P450 (CYP450) enzyme system (3A4 and 2C19).

Indications:

- Clopidogrel monotherapy is a treatment option for secondary prevention of atherothrombotic events (myocardial infarction, stroke, or limb ischemia) in patients with stable atherosclerosis.
- Clopidogrel may be used as monotherapy in patients not considered candidates for ASA monotherapy (e.g. those with ASA allergies or at high risk of ASA-related gastrointestinal bleeding).
- Clopidogrel in combination with ASA is indicated for the secondary prevention of atherothrombotic events in patients with ACS and who receive PCI. The recommended duration of treatment is typically 12 months. Patients who tolerate 1 year of dual antiplatelet therapy (DAPT) with clopidogrel without a major bleeding event and are not at high risk of bleeding may extend DAPT beyond 1 year. Patients who have clinical or angiographic features that increase the risk of thrombotic cardiovascular (CV) events might benefit from extended DAPT beyond 1 year.
    1. Risk factors for bleeding include: need for oral anticoagulation in addition to DAPT, age >75, frailty, anemia with a hemoglobin <110 g/L, chronic renal failure, weight <60 kg, hospitalization for bleeding within the past year, previous stroke or intracranial bleeding and regular need for NSAIDS or prednisone.
    2. Clinical features that increase the risk of thrombotic cardiovascular (CV) events include: diabetes mellitus, chronic kidney disease, prior stent thrombosis, and current tobacco use.
    3. Angiographic features that increase the risk of CV events include: three or more stents implanted or lesions stented, use of a biodegradable vascular scaffold, long lesion length,

complex lesions, left main or proximal left anterior descending artery stenting and multivessel PCI

- For patients undergoing elective PCI (PCI for a non-ACS indication like stable ischemic heart disease), DAPT is recommended for 6-12 months. In patients who have additional high risk clinical or angiographic features for thrombotic CV events as outlined above and who are at low risk of bleeding, it is reasonable to extend the duration of DAPT for up to 3 years followed by single agent therapy with ASA or clopidogrel. In patients who are at high risk of bleeding, the duration of DAPT may be shortened to a minimum of 1 month (if a bare-metal stent [BMS] is used) or 3 months (if a drug eluting stent [DES] is used).
- For patients with an acute high-risk TIA or minor ischemic stroke of non-cardioembolic origin, who are not at high bleeding risk, DAPT is recommended with the combination of clopidogrel (300 or 600 mg loading dose followed by 75 mg daily) and ASA (160 mg loading dose followed by 80 mg daily) for a duration of 21 days after the event, followed by ASA monotherapy thereafter.
- Clopidogrel is a treatment option for secondary prevention of recurrent cerebral vascular events in patients who develop an ischemic stroke or transient ischemic attack while receiving ASA therapy.
- For patients with stable symptomatic PAD, with high risk for vascular events, low bleeding risk, and contraindications to low dose rivaroxaban, DAPT (aspirin and clopidogrel or aspirin and ticagrelor) may be an option noting limiting evidence for this approach.

Dosing:

- There is a delay of approximately 4 days to peak antiplatelet activity if a loading dose of clopidogrel is not given. Therefore, in patients at very high risk for thrombosis, a loading dose of 300 or 600 mg should be given.
- ACS or acute high-risk TIA or minor ischemic stroke of non-cardioembolic origin: 300-600 mg loading dose followed by 75 mg daily.
- For all other indications, the dose is 75 mg once daily.
- When switching from ticagrelor to clopidogrel, a loading dose of 300-600 mg should be considered in the early post-ACS period; otherwise, switching directly to 75 mg daily is recommended.
- When switching from prasugrel to clopidogrel, clopidogrel should be initiated at 75 mg daily.

Monitoring:

It is advisable to obtain a baseline complete blood count prior to initiating clopidogrel. Ongoing monitoring of platelet function or coagulation parameters in patients taking clopidogrel is not required.

Adverse Effects:

The most common adverse reaction to clopidogrel is an increased rate of bruising and bleeding. The risk of bleeding is increased when clopidogrel is taken with ASA, and in particular, when clopidogrel is taken with an anticoagulant. Gastrointestinal bleeding has been reported. Skin rash is uncommon but statistically more frequent than with ASA. Blood disorders such as agranulocytosis, granulocytopenia, aplastic anemia, neutropenia, and thrombocytopenia have been reported, but are rare events.

Peri-Procedural Management:

Clopidogrel should be discontinued 5 days prior to an invasive procedure (if it is safe to hold it). However, caution should be used in discontinuing clopidogrel in patients at high risk of thrombotic events, including those with recently implanted coronary stents, and consultation with a specialist is advised. There is increased risk of stent thrombosis when antiplatelet therapy is discontinued prior to 1 year following stent implantation. In patients who have undergone PCI and who require elective noncardiac surgery, surgery should be delayed for at least 1 month following BMS placement and 3 months following DES placement. If there is a need for semi urgent noncardiac surgery, we suggest delaying surgery for at least 1 month after PCI. For patients who require surgery earlier, one of three approaches is used (consultation with a specialist is advised):

1. Continue the DAPT without interruption (especially if recent stent placement).
2. Continue ASA and hold clopidogrel 5 days preoperatively.
3. Hold the oral antiplatelet therapy 5 days preoperatively, admit the patient and start intravenous eptifibatide.

Special Considerations:

Genetic polymorphisms: Variations of CYP450 alleles (especially 2C19) may affect the conversion of the pro-drug clopidogrel to its active metabolite. This may lead to reduced benefit of clopidogrel. Specific testing for these variants is not recommended.

Proton pump inhibitors: Some proton pump inhibitors (PPIs) are strong 2C19 inhibitors that can reduce the effect of clopidogrel on platelet aggregation. This can increase the risk of recurrent cardiovascular events. Pantoprazole is not a strong 2C19 inhibitor and should be used whenever a proton pump inhibitor is required. We recommend selective use of PPIs in patients receiving DAPT at high risk of upper gastrointestinal bleeding.

Compared to the other $P2Y_{12}$ platelet inhibitors: Prasugrel and ticagrelor have faster and greater platelet inhibition versus clopidogrel and have demonstrated less inter-individual variability in their effect. In general, they are more effective than clopidogrel but are more costly.

Other Relevant Thrombosis Canada Clinical Guides:

- Acetylsalicylic Acid (ASA)
- Ischemic Stroke or TIA: Secondary Prevention
- Perioperative Management of Antiplatelet Therapy
- Peripheral Arterial Disease
- Prasugrel (Effient®, generic)
- Ticagrelor (Brilinta®)

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