CLOPIDOGRIL

Class: Antiplatelet Agent, Thienopyridine

Indications: reduces rate of atherothrombotic events (myocardial infarction, stroke, vascular deaths) in patients with recent MI or stroke, or established peripheral arterial disease; reduces rate of atherothrombotic events in patients with unstable angina (UA) or non-ST-segment elevation MI (NSTEMI) managed medically or with percutaneous coronary intervention (PCI) (with or without stent) or CABG; reduces rate of death and atherothrombotic events in patients with ST-segment elevation MI (STEMI) managed medically

Unlabeled : In patients with allergy or major gastrointestinal intolerance to aspirin, initial treatment of acute coronary syndromes (ACS) or prevention of coronary artery bypass graft closure (saphenous vein); stable coronary artery disease (in combination with aspirin); in patients having undergone peripheral artery percutaneous transluminal angioplasty; symptomatic carotid artery stenosis (including recent carotid endarterectomy

Dosage:

- **Recent MI, recent stroke, or established peripheral arterial disease (PAD):**

Oral: 75 mg once daily. **Note:** The ACCF/AHA guidelines for PAD recommend clopidogrel as an alternative to aspirin (Class Ib recommendation) or in conjunction with aspirin for those who are not at an increased risk of bleeding but are of high cardiovascular risk (Class IIb recommendation). These recommendations also pertain to those with intermittent claudication or critical limb ischemia, prior lower extremity revascularization, or prior amputation for lower extremity ischemia.

-Coronary artery disease (CAD), established: Oral: 75 mg once daily. **Note:** Established CAD defined as patients 1-year post ACS, with prior revascularization, coronary stenosis >50% by angiogram, and/or evidence for cardiac ischemia on diagnostic testing (includes patients after the first year post-ACS and/or with prior CABG surgery) (Guyatt, 2012).

-Secondary prevention of cardioembolic stroke (patient not candidate for oral anticoagulation): Oral: 75 mg once daily (in combination with aspirin).

-Acute coronary syndrome (ACS):

-*Unstable angina, non-ST-segment elevation myocardial infarction (UA/NSTEMI):* Initial: 300 mg loading dose, followed by 75 mg once daily for up to 12 months (in combination with aspirin indefinitely). The American College of Chest Physicians recommends combination aspirin dose of 75-100 mg (Guyatt, 2012).

-*ST-segment elevation myocardial infarction (STEMI):* receiving fibrinolytic therapy (in combination with aspirin and appropriate anticoagulant) (O'Gara, 2013): **Note:** If patient is to undergo primary PCI, see *percutaneous coronary intervention (PCI) for acute coronary syndrome* dosing.

-Age ≤75 years: Loading dose of 300 mg followed by 75 mg once daily for at least 14 days up to 1 year (in the absence of bleeding)
-Age >75 years: 75 mg once daily (no loading dose) for at least 14 days up to 1 year (in the absence of bleeding)

-Percutaneous coronary intervention (PCI) for acute coronary syndrome (eg, UA/NSTEMI or STEMI):

Loading dose: 600 mg given as early as possible before or at the time of PCI, followed by 75 mg once daily (in combination with aspirin 81 mg/day). **Note:** If fibrinolytic administered within the previous 24 hours, administer 300 mg loading dose instead. The use of ticagrelor (instead of clopidogrel) in combination with aspirin has been suggested.

***-PCI after fibrinolytic therapy* (O'Gara, 2013):**

-Fibrinolytic administered **with** a loading dose of clopidogrel: Continue 75 mg once daily and do not administer an additional loading dose.

-Fibrinolytic administered within previous 24 hours **without** a loading dose of clopidogrel: Administer 300 mg loading dose before or at the time of PCI.

-Fibrinolytic administered more than 24 hours ago without a loading dose of clopidogrel: Administer 600 mg loading dose before or at the time of PCI.

-Higher versus standard maintenance dosing:

May consider a maintenance dose of 150 mg once daily for 6 days, then 75 mg once daily thereafter in patients not at high risk for bleeding (Anderson, 2013; CURRENT-OASIS 7 Investigators, 2010); however, in another study, in patients with high on-treatment platelet reactivity, the use of 150 mg once daily for 6 months did not demonstrate a difference in 6-month incidence of death from cardiovascular causes, nonfatal MI, or stent thrombosis compared to standard dose therapy (Price, 2011).

-Duration of clopidogrel (in combination with aspirin) after stent placement for ACS and non-ACS indications: Premature interruption of therapy may result in stent thrombosis with subsequent fatal and nonfatal MI. At least 12 months of clopidogrel is recommended for those with ACS receiving either stent type (bare metal [BMS] or drug eluting stent [DES]) or those receiving a DES for a non-ACS indication (ie, elective PCI). Those receiving a BMS for a non-ACS indication should be given at least 1 month and ideally up to 12 months; if patient is at increased risk of bleeding, give for a minimum of 2 weeks (Levine, 2011). A duration >12 months, regardless of indication, may be considered in patients with DES placement (Anderson, 2013; Levine, 2011; O'Gara, 2013).

-CYP2C19 poor metabolizers (ie, *CYP2C19*2* or **3* carriers): Although routine genetic testing is not recommended in patients treated with clopidogrel undergoing PCI, testing may be considered to identify poor metabolizers who would be at risk for poor outcomes while receiving clopidogrel; if identified, these patients may be considered for an alternative $P2Y_{12}$ inhibitor (Levine, 2011). An appropriate regimen for this patient population has not been established in clinical outcome trials. Although a 600 mg loading dose, followed by 150 mg once daily produced greater active metabolite exposure and antiplatelet response compared to the 300 mg/75 mg regimen, it does not appear that this dosing strategy improves outcomes for this patient population (Price, 2011; Simon, 2011).

-Atrial fibrillation (in patients not candidates for warfarin and at a low risk of bleeding) (Canadian labeling; ACTIVE Investigators, 2009; unlabeled use in U.S.): Oral: 75 mg once daily (in combination with aspirin 75-100 mg once daily). **Note:** Combination may also be used as an alternative for patients with atrial fibrillation and mitral stenosis.

-Carotid artery stenosis, symptomatic (including recent carotid endarterectomy) (unlabeled use): Oral: 75 mg once daily.

-Peripheral artery percutaneous transluminal angioplasty (with or without stenting) or peripheral artery bypass graft surgery, postprocedure (unlabeled use): Oral: 75 mg once daily. **Note:** For below-knee bypass graft surgery with prosthetic grafts, combine with aspirin 75-100 mg/day .

-Prevention of coronary artery bypass graft closure (saphenous vein) and postoperative adverse cardiovascular events (unlabeled use): Oral: Aspirin-allergic patients: 75 mg once daily.

-Secondary prevention of cardioembolic stroke (patient not candidate for oral anticoagulation) (unlabeled use): Oral: 75 mg once daily (in combination with aspirin) (Guyatt, 2012)

Renal Impairment :

No adjustment is necessary. **Note:** GFR stage 5 (ie, ESRD or an eGFR <15 mL/minute) is associated with higher residual platelet reactivity with maintenance dosing (Muller, 2012).

Hepatic Impairment:

Use with caution; experience is limited. **Note:** Inhibition of ADP-induced platelet aggregation and mean bleeding time prolongation were similar in patients with severe hepatic impairment compared to healthy subjects after repeated doses of 75 mg once daily for 10 days.

Available dosage form in the hospital: 75MG TAB

Common side effect: 3% to 10%:

Dermatologic: Rash (4%), pruritus (3%)

Hematologic: Bleeding (major 4%; minor 5%), purpura/bruising (5%), epistaxis (3%

Pregnancy Risk Factor: B