Name(s)

- **Generic:** clopidogrel *(kloh PID oh grel)* | **Brand:** Plavix

Therapeutic Category

- Anti-Platelet Agent | Thienopyridine | P2Y12 Antagonist

Indication(s)

1. **ST-segment elevation myocardial infarction (STEMI):** Decrease rate of **myocardial infarction (MI)** and stroke in patients with acute STEMI. Medically managed. Used with aspirin.
2. **Non-ST-segment elevation myocardial infarction (NSTEMI):** Decrease rate of MI and stroke in patients with NSTEMI, unstable angina, acute coronary syndromes. For both medically managed patients and patients that have undergone coronary revascularization.
3. **MI, ischemic stroke, peripheral atherosclerotic disease:** Decrease rate of MI and stroke in patients that have a recent history of MI, stroke, or atherosclerotic disease.

- OFF LABEL: Carotid artery atherosclerosis (symptomatic); Carotid artery stenting, Coronary artery bypass graft surgery; Percutaneous coronary intervention for stable ischemic heart disease; Stable ischemic heart disease; Transcatheter aortic valve replacement (thromboprophylaxis); Transcatheter mitral valve repair w/ MitraClip device (thromboprophylaxis)

Dosage Form / Strength / Dosing

- **Dosage Form:** Tablet
  - Tablets: 75 mg, 300 mg
- Consideration(s) in Acute coronary syndrome: CYP2C19 polymorphism testing to ensure greatest efficacy for clopidogrel
- **Dosing** for **STEMI:** Adult & Geriatric
  - In combination with aspirin and parenteral anticoagulant
  - IF ***reperfusion fibrinolytic therapy*** is used:
    - **Age ≤75 years old**: 300 mg once as loading dose, then 75 mg once daily as maintenance
    - **Age >75 years old**: 75 mg once daily
  - IF *percutaneous coronary intervention (PCI)* is **required after fibrinolytic therapy:**
    - **WITH fibrinolytic** 300 mg loading dose is administered; then 75 mg once daily
    - **≤24 hours** of fibrinolytic **w/o loading dose of clopidogrel**: Initiate **300 mg** loading dose; then 75 mg once daily
    - **>24 hours** of fibrinolytic **w/o loading dose of clopidogrel**: Initiate **600 mg** prior to PCI; then 75 mg once daily
  - If *percutaneous coronary intervention (PCI)* for reperfusion **NOT** following fibrinolytic therapy:
    - Initiate 600mg loading dose ASAP before PCI; then 75 mg once daily after PCI
    - Some literature prefers ticagrelor or prasugrel over clopidogrel in lower bleed risk patients
  - IF *NO reperfusion strategy* planned:
    - Initiate 300mg loading dose once at dx; then 75 mg once daily
  - Duration of therapy considerations:
    - Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin
    - UNLESS pt is at risk for bleeding; DAPT for ≥12 months
    - AFTER 12 months DAPT continuation can be considered and re-evaluated based on bleed risk or risk of thrombotic events.
    - IF DAPT complete d/c clopidogrel but aspirin is continued indefinitely
- **Dosing** for **NSTEMI:** Adult & Geriatric
  - Administer clopidogrel in combination with parenteral anticoagulant and aspirin regardless of therapy strategy.
  - Remember that some literature prefers ticagrelor or prasugrel over clopidogrel in low bleed risk pts
  - IF *ischemia-guided approach* used
    - Initiate 300 mg (or 600 mg) once at dx; then 75 mg once daily
    - 600 mg considered unless the patient is at a high risk for bleeding

  - IF *invasive approach* (reperfusion using percutaneous coronary intervention)
    - 600 mg once ASAP prior to PCI; then 75 mg once daily
  - Duration of therapy considerations:
    - Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin
    - UNLESS pt is at risk for bleeding; DAPT for ≥12 months
    - AFTER 12 months DAPT continuation can be considered and re-evaluated based on bleed risk or risk of thrombotic events.
    - IF DAPT complete d/c clopidogrel but aspirin is continued indefinitely
- (OFF LABEL) Dosing for *PCI for stable ischemic heart disease*
  - Administer clopidogrel in combination with parenteral anticoagulant and aspirin regardless of therapy strategy.
  - Initiate 600 mg once ≥2 hours prior to PCI (≥24 hours preferred); then 75 once daily
  - Duration of therapy: DAPT as typically recommended in other treatments w/ aspirin indefinitely after
    - IF **bare metal stent implant**: DAPT for 1-12 months (shorter duration if high bleed risk) with re-evaluation after 6-12 months for bleed and ischemic risks for ending therapy.
    - IF **drug eluting stent implantation** (drug-coated stent): DAPT for 3-12 months (duration based on bleed risk). Assess bleed and ischemic risks after 6-12 months if extension of 18 to 24 months needed.
- (OFF LABEL) (Not Covered, Refer to Guidelines) Dosing for carotid artery atherosclerosis (symptomatic); coronary artery bypass graft surgery; stable ischemic heart disease. Dosing is generally similar with 75 mg once daily being the norm with changes in loading dose or duration of therapy.
- **Dosing** for **Stroke/Transient ischemic attack**
  - Intracranial atherosclerosis b/t 50%-99% stenosis of major intracranial artery (secondary prevention)
    - Aspirin for all pts /w clopidogrel considered in combination for short-term use w/in 30 days. Clopidogrel indefinitely can be used in place of aspirin for long-term stroke prevention
    - 75 mg once daily w/ aspirin (duration varies based on stenosis severity)
      - 50%-69% stenosis: clopidogrel w/ aspirin for 21 days; d/c clopidogrel after
      - 70%-99% stenosis: clopidogrel w/ aspirin for 90 days; d/c clopidogrel after
  - *Ischemic/Transient stroke/attack* (secondary prevention)
    - Single-agent antiplatelet therapy generally preferred. Therapy agents are aspirin, clopidogrel, aspirin/ER dipyridamole
    - 75 mg once daily indefinitely
    - IF IV alteplase was received, antiplatelet therapy delayed for ≥24 hours; then ASAP thereafter
  - *Minor ischemia stroke* OR *high-risk transient ischemic attack* (high risk being $ABCD^2$ score ≥4)
    - Short-term combination w/ aspirin considered w/ antiplatelet therapy initiated w/in 24 hours of stroke onset
    - IF IV alteplase was received, antiplatelet therapy delayed for ≥24 hours; then ASAP thereafter
    - Initiate 300 mg to 600 mg w/ aspirin; then 75 mg once daily for 21 days; then single agent use thereafter indefinitely (i.e. – clopidogrel, aspirin, aspirin/ER dipyridamole)
- (OFF LABEL) (Not covered, Refer to Guidelines) Dosing for transcatheter aortic valve replacement (thromboprophylaxis); transcatheter mitral valve repair w/ MitraClip device (thromboprophylaxis)
- **Prasugrel** to clopidogrel transitional dosing
  - IF pt received prasugrel for ≤5 days: Clopidogrel 300mg loading 24 hours after last prasugrel dose; then 75 mg once daily. However some literature suggests no loading dose.
  - IF pt received prasugrel for >5 days: Clopidogrel 75 mg once daily 24 hours after last dose of prasugrel
- **Ticagrelor** to clopidogrel transitional dosing
  - 600 mg loading dose 12 hours after last ticagrelor dose; then 75 mg once daily
- Dosing in Pediatrics (Not covered; Refer to latest literature)
- Adjust dosing in renally impaired

Mechanism of Action & Pharmacology

- Irreversibly blocks P2Y12 component of ADP receptors on platelet surface which prevents activation of the GPIIb/IIIa receptor complex which reduces platelet aggregation. Clopidogrel blocked platelets remain blocked for 7-10 days (platelet's lifespan)
- Biotransformation of clopidogrel is required in vivo to the active thiol metabolite in order to be effective so CYP2C19 polymorphism testing important to determine efficacy
- **Absorption:** Rapidly absorbed | **Metabolism:** Hepatic; CYP450-mediated, primarily CYP2C19 oxidation to active thiol metabolite | **Excretion:** 50% urine; 46% feces | **Onset of Action:** Dose dependent; 300-600 mg w/in 2 hours; 50-100 mg/day w/in second day | **Time to Peak:** 45 minutes (approx. 0.75 hours) | **Duration of Action:** ~5 days | **Half-Life Elimination:** ~11 days overall; various stages of inactive drug and metabolites vary between 30 minutes to 6-8 hours | **Protein Binding:** 94-98% depending on stage of metabolism

Side Effects

- 1-10%: hemorrhage (minor-major), bruising, hematoma, epistaxis (bloody nose)
- <1%: abnormal hepatic function tests, confusion, diarrhea, duodenal ulcer, rash, dermatitis, fever, ulcer

BLACK BOX WARNING: Antiplatelet effect is diminished in patients with two loss-of-function alleles of the CYP2C19 gene.

Clopidogrel is a prodrug and its efficacy is determined by its conversion to the active metabolite by the cytochrome P450 system (primarily CYP2C19). Recommended doses of clopidogrel are reduced in patients that are homozygous for nonfunctional alleles of the CYP2C19 gene (aka CYP2C19 poor metabolizers). Consider using an alternative platelet $P2Y_{12}$ inhibitor in CYP2C19 poor metabolizers.

Drug Interactions

- Anticoagulants will have their effects increased by antiplatelet agents such as clopidogrel (exception enoxaparin, heparin)
- Calcium channel blockers may diminish clopidogrel's effects
- Amiodarone, pantoprazole, decrease serum concentrations of the active metabolite(s) of clopidogrel
- CYP2C19 inducers (Strong) (i.e. – rifampin, dexamethasone, phenytoin, carbamazepine, phenobarbital, St John's wort) increase serum concentrations of active metabolite(s)
- CYP2C19 inhibitors (Strong) (i.e. – ketoconazole, clarithromycin, ritonavir, grapefruit) decrease serum concentrations of active metabolite(s)
- CYP2C8 inhibitors (i.e. – paclitaxel, pioglitazone) and BCRP/ABCG2 inhibitors (i.e. – ozanimod, talazoparib) may get increased serum levels from clopidogrel
- Vitamins/Minerals (ADEK, Folate, Iron) may increase antiplatelet effects
- Warfarin effects are increased by clopidogrel

Monitoring Parameters

- CYP2C19 | Signs of bleeding | Hemoglobin and hematocrit levels

Patient Counseling Information

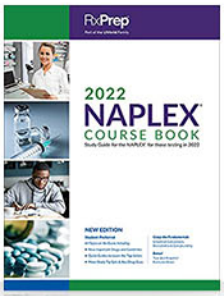
- Used to lower chances of heart attack or stroke | Can be taken w/ or w/o food | Watch for irregular bleeding/bruising | Notify MD feeling wheezing, chest tightness, blue skin, swelling, dizzy, headache, fatigue, feeling weak, shaking, increase in hunger, or irregular sweating | D/c for 5 days prior to surgery

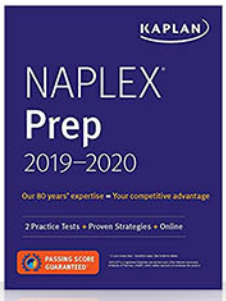
Reference(s)

- https://www.drugs.com/ppa/clopidogrel.html

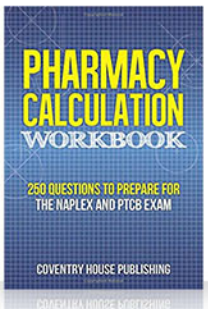
PREPARE FOR SUCCESS!

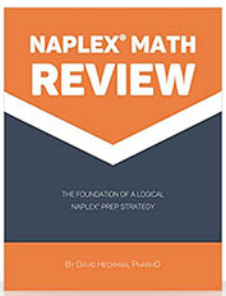
Comprehensive (NAPLEX)

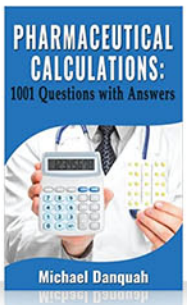


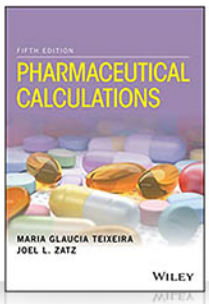


Calculations (NAPLEX)

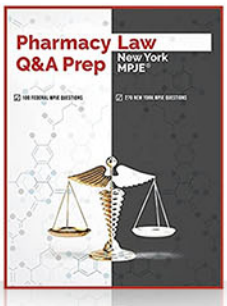


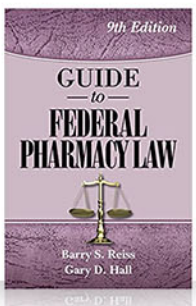




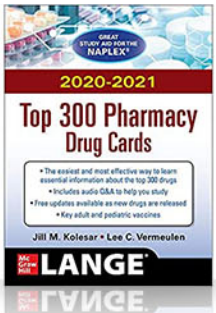


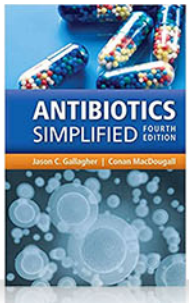
Pharmacy Law (MPJE)

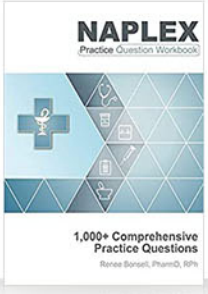


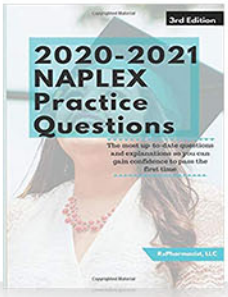


Supplemental









DISCLAIMERS

DRUG CARDS DAILY

Monday at 7 am EST
(6 am CST, 4 am PST)

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