

**REVIEWED***By Chris Tighe at 1:06 pm, Aug 07, 2018*[print](#)[Close window](#)

CLASSES

ADP (adenosine Diphosphate) Receptor Antagonist Platelet Aggregation Inhibitors

BOXED WARNING

Poor metabolizers

Clopidogrel has a reduced effect on platelet function in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene (i.e., poor metabolizers). Consider another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers. Data have shown that poor metabolizers have a higher risk of mortality, myocardial infarction, and stroke compared to normal metabolizers. Clopidogrel metabolism and, subsequently, platelet inhibition can also be reduced by drugs that significantly inhibit CYP2C19, such as omeprazole and esomeprazole; concomitant use should be avoided. Dexlansoprazole, lansoprazole, and pantoprazole have less effect on antiplatelet activity. Some data indicate patients may have a higher risk of reinfarction and revascularization after acute coronary syndrome when taking clopidogrel in combination with a proton pump inhibitor.

DEA CLASS

Rx

DESCRIPTION

Oral antiplatelet agent; structure and mechanism of action similar to ticlopidine; does not require routine hematologic monitoring; used to reduce atherosclerotic events in patients with a history of recent stroke, recent MI, acute coronary syndromes, or established peripheral arterial disease.

COMMON BRAND NAMES

Plavix

HOW SUPPLIED

Clopidogrel/Clopidogrel Bisulfate/Plavix Oral Tab: 75mg, 300mg

DOSAGE & INDICATIONS

For arterial thromboembolism prophylaxis (i.e., myocardial infarction prophylaxis, stroke prophylaxis, thrombosis prophylaxis).

NOTE: Patients identified as CYP2C19 poor metabolizers have a diminished antiplatelet response to clopidogrel. A higher dosage regimen (600 mg PO loading dose followed by 150 mg PO daily) increases antiplatelet response, however an appropriate dosage regimen for this patient population has not been established in clinical outcome trials.

For patients with recent ischemic stroke, transient ischemic attack (TIA), or myocardial infarction, or established coronary artery disease or peripheral arterial disease.

Oral dosage

Adults

75 mg PO daily. Clinical practice guidelines recommend single antiplatelet therapy such as clopidogrel for patients with established coronary artery disease (1-year post acute coronary syndrome, with prior revascularization, coronary stenoses > 50% by coronary angiogram, and/or evidence for cardiac ischemia on diagnostic testing). In patients with a history of noncardioembolic ischemic stroke or TIA, clinical practice guidelines recommend clopidogrel as a preferred therapy for long-term thrombosis prophylaxis.

For patients with unstable angina or acute myocardial infarction, NSTEMI (non-ST-elevation myocardial infarction).

Oral dosage

Adults

300 mg PO once, then 75 mg PO daily in combination with aspirin (75–325 mg/day PO). Clinical practice guidelines for the management of patients with unstable angina/NSTEMI, recommend clopidogrel be given for ≥ 1 month and ideally up to 12 months to patients in whom a noninvasive treatment strategy is selected; aspirin should be continued indefinitely. In patients with an aspirin allergy, clopidogrel monotherapy can be used.

For patients with acute myocardial infarction, STEMI (ST-segment elevation MI).

Oral dosage

Adults

75 mg PO daily in combination with aspirin (75—325 mg/day PO), with or without a 300 mg PO loading dose or thrombolytics. Clinical practice guidelines recommend patients with STEMI who are managed with thrombolytics receive adjunctive antiplatelet therapy that includes aspirin (162—325 mg PO loading dose) and clopidogrel 300 mg PO loading dose for patients ≤ 75 years of age. For patients > 75 years, no loading dose should be given. Aspirin (81 mg/day PO) should be continued indefinitely and clopidogrel should be continued for ≥ 14 days to ≤ 1 year.

For pediatric arterial thromboembolism prophylaxis† (i.e., thrombosis prophylaxis†, secondary stroke prophylaxis† following arterial ischemic stroke† or transient ischemic attack (TIA)†), including following cardiac surgery† and in other cardiac conditions with a risk for arterial thrombosis (e.g., Kawasaki disease†):.

NOTE: In children with recurrent arterial ischemic stroke or TIAs who fail or are intolerant of aspirin, clopidogrel is recommended as an alternative antiplatelet agent.

NOTE: In children with Kawasaki disease who have severe coronary involvement, clopidogrel is recommended to be used with aspirin.

Oral dosage

Adolescents and Children > 2 years

Dosing not well established. An initial dose of 1 mg/kg/day PO titrated to response has been used most commonly (Max: 75 mg/day) ; in a cohort of 90 pediatric patients (age range: 11 days to 17.9 years, median 6.7 years), the median dose administered was 1.3 mg/kg/day PO. Some studies have reported lower doses of 0.2—0.3 mg/kg/day in children. In a prospective study in 14 children (0.7—84 months; 3 children > 2 years), a dose of 0.2 mg/kg/day resulted in effective platelet inhibition (40—50% inhibition of platelet aggregation) in 2 of the 3 children who were older than 2 years of age.[54148] In another study, dosing was initiated with 0.5—1 mg/kg/day with subsequent doses titrated down to 0.2—0.3 mg/kg/day. Higher doses (> 2—6 mg/kg/day) have been reported and were tolerated in a few reported cases in children ; however, the risk of bleeding may be higher with increasing doses.

Children ≤ 2 years, Infants, and Neonates

0.2 mg/kg/day PO provides platelet inhibition levels similar to those achieved by the standard adult dose based on limited data. In the PICOLO study, which included 34 neonates (≥ 35 weeks gestational age and ≥ 2 kg) and 39 infants/children 30 days—24 months, a dose of 0.2 mg/kg/day achieved the target ADP-induced platelet aggregation inhibition (30—50% inhibition of platelet aggregation) for both the maximum extent and the rate of platelet aggregation. Of the patients randomized, 73.3% had undergone placement of a systemic-to-pulmonary artery shunt, 24.4% had an intracardiac or intravascular stent placed, 1.2% had Kawasaki disease, and the remainder had an arterial graft in place. The majority of patients were also taking ≤ 81 mg/day of aspirin. In another prospective study in 14 children (range, 0.7—84 months; 11 children ≤ 2 years), 93% of patients (13 out of 14) achieved effective platelet inhibition (30—50% inhibition of platelet aggregation) with a dose of 0.2 mg/kg/day.

For patients undergoing percutaneous coronary intervention (PCI).

NOTE: Premature discontinuation of dual antiplatelet therapy after stent placement increases the risk of stent thrombosis. The mortality rate of stent thrombosis is 20—45%.

Oral dosage

Adults

300 mg PO once within 24 hours of fibrinolytic and 600 mg PO once > 24 hours since fibrinolytic as loading dose followed by 75 mg PO daily. In addition to aspirin, clinical practice guidelines recommend clopidogrel for acute coronary syndrome (ACS) and non-ACS patients undergoing PCI with stenting. For ACS patients receiving either drug-eluting stent (DES) or bare metal stent (BMS) or non-ACS patients receiving a DES, continue clopidogrel for ≥ 12 months unless bleeding risk outweighs benefit. For non-ACS patients receiving a BMS, continue clopidogrel for ≥ 1 month and preferably up to 12 months unless the patient is at risk of bleeding; then continue for ≥ 2 weeks. If the risk of morbidity from bleeding outweighs the benefit of clopidogrel therapy after stent implantation, earlier discontinuation (e.g., < 12 months) is reasonable. Continuing clopidogrel for > 12 months may be considered in patients receiving a DES. Results from the DAPT trial demonstrate that continuing dual antiplatelet therapy > 12 months (up to 30 months) in patients receiving a DES significantly reduces the rates of stent thrombosis and risk of ischemic events compared with aspirin alone but is associated with increased bleeding. Premature discontinuation of dual antiplatelet therapy is discouraged, even in the setting of elective surgery. Delay elective surgery for 12 months following DES and for ≥ 1 month following BMS placement. If the surgery can not be delayed, consider continuing aspirin in high-risk patients.

For patients undergoing coronary artery bypass graft surgery (cardiac surgery†).

Oral dosage

Adults

75 mg PO daily. Clinical practice guidelines recommend clopidogrel post operatively in patients who are allergic or intolerant to aspirin.

MAXIMUM DOSAGE

Adults

75 mg/day PO chronic treatment (up to 600 mg PO for single loading dose).

Geriatric

75 mg/day PO chronic treatment (up to 600 mg PO for single loading dose).

Adolescents

Safety and efficacy have not been established; doses up to 6 mg/kg/day (Max: 75 mg/day) PO have been used off-label.

Children

> 2 years: Safety and efficacy have not been established; doses up to 6 mg/kg/day (Max: 75 mg/day) PO have been used off-label.

≤ 2 years: Safety and efficacy have not been established; however, doses of 0.2 mg/kg/day PO have been used off-label.

Infants

Safety and efficacy have not been established; however, doses of 0.2 mg/kg/day PO have been used off-label.

Neonates

Safety and efficacy have not been established; however, doses of 0.2 mg/kg/day PO have been used off-label.

DOSING CONSIDERATIONS

Hepatic Impairment

Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.

Renal Impairment

Experience is limited in patients with severe and moderate renal impairment; specific guidelines for dosage adjustments in renal impairment are not available.

ADMINISTRATION

Oral Administration

May be administered with or without food.

STORAGE

Generic:

- Store at 77 degrees F; excursions permitted to 59-86 degrees F

Plavix:

- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

CONTRAINDICATIONS / PRECAUTIONS

General Information

Clopidogrel is contraindicated in patients with a known hypersensitivity to clopidogrel or any component of the product.

Bleeding, GI bleeding, intracranial bleeding, peptic ulcer disease, surgery, trauma

Clopidogrel increases the risk of bleeding and is contraindicated in patients with active pathological bleeding including GI bleeding and intracranial bleeding. As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions including peptic ulcer disease. When possible, interrupt clopidogrel therapy for 5 days prior to surgery; resume as soon as hemostasis is achieved. Clopidogrel inhibits platelet aggregation for the lifetime of the platelet (7 to 10 days). It may be possible to restore hemostasis by transfusing platelets because the half-life of clopidogrel's active metabolite is short; however, platelets transfused within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective. Use clopidogrel and other drugs that may promote bleeding (e.g., NSAIDs) together with caution.

Hepatic disease

The manufacturer states no dosage adjustment is necessary in patients with hepatic disease. However, a bleeding diathesis may exist in these patients, especially in those with severe liver disease, which may increase the risk of bleeding associated with clopidogrel. In addition, severe hepatic disease may impair the conversion of clopidogrel, the prodrug, to its active form.

Renal disease, renal failure, renal impairment

Experience is limited in patients with severe renal disease or renal failure. Use clopidogrel cautiously in patients with renal impairment.

Poor metabolizers

Clopidogrel has a reduced effect on platelet function in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene (i.e., poor metabolizers). Consider another platelet P2Y12 inhibitor in patients identified as CYP2C19 poor metabolizers. Data have shown that poor metabolizers have a higher risk of mortality, myocardial infarction, and stroke compared to normal metabolizers. Clopidogrel metabolism and, subsequently, platelet inhibition can also be reduced by drugs that significantly inhibit CYP2C19, such as omeprazole and esomeprazole; concomitant use should be avoided. Dexlansoprazole, lansoprazole, and pantoprazole have less effect on antiplatelet activity. Some data indicate patients may have a higher risk of reinfarction and revascularization after acute coronary syndrome when taking clopidogrel in combination with a proton pump inhibitor.

Pregnancy

Clopidogrel is classified as FDA pregnancy risk category B. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m² basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, clopidogrel should be used during pregnancy only if clearly needed.

Breast-feeding

According to the manufacturer, it is unknown if clopidogrel is excreted into human breast milk. Clopidogrel and/or its metabolites are excreted into the milk of lactating rats. Because of the potential for serious adverse reactions in breast-feeding infants from clopidogrel, a decision should be made to discontinue nursing or discontinue clopidogrel, taking into account the importance of the drug to the mother. If a breast-feeding infant experiences an adverse effect related to a maternally administered drug, healthcare providers are encouraged to report the adverse effect to the FDA.

Geriatric

Of the total number of subjects in controlled clinical studies, approximately 50% of patients treated with clopidogrel were geriatric (i.e., 65 years of age and older). Approximately 16% of patients treated with clopidogrel were 75 years of age and over. During clinical trials, the incidence of major bleeding increased with increasing age; the incidence of bleeding was higher in patients treated with combination clopidogrel and aspirin. If bleeding is a potential concern and combination therapy is desired, geriatric patients and their prescribers should be encouraged to use a low dose of aspirin with clopidogrel. The federal Omnibus Budget Reconciliation Act (OBRA) regulates medication use in residents of long-term care facilities.

According to the OBRA guidelines, platelet inhibitors may cause thrombocytopenia and increase the risk of bleeding. Common side effects of platelet inhibitors include headache, dizziness, and vomiting. Concurrent use with aspirin, warfarin, or NSAIDs may increase the risk of bleeding.

Children, infants, neonates

Safe and effective use of clopidogrel has not been established in children, infants and neonates.

Abrupt discontinuation

In an effort to minimize the risk of cardiovascular events, avoid premature discontinuation or lapses in therapy (i.e., abrupt discontinuation) with clopidogrel. Premature discontinuation may increase the risk for cardiovascular events. If clopidogrel must be temporarily discontinued, restart therapy as soon as possible.

Thrombotic thrombocytopenic purpura (TTP)

Thrombotic thrombocytopenic purpura (TTP), sometimes fatal, has been reported rarely in patients receiving clopidogrel, sometimes after short exposure (< 2 weeks). TTP is a serious condition that can be fatal and requires urgent treatment including plasmapheresis (plasma exchange). Thrombocytopenia, microangiopathic hemolytic anemia (schistocytes seen on peripheral smear), neurological findings, renal dysfunction, and fever characterize TTP.

Thienopyridine hypersensitivity

Clopidogrel is contraindicated in patients with a known hypersensitivity to clopidogrel or any component of the product. Evaluate patients receiving clopidogrel for a history of thienopyridine hypersensitivity. Hypersensitivity reactions including rash, angioedema, or hematologic reactions have been reported in patients receiving clopidogrel, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines (e.g., ticlopidine, prasugrel).

ADVERSE REACTIONS

Severe

GI bleeding / Delayed / 2.0-2.0
 peptic ulcer / Delayed / 0.7-0.7
 intracranial bleeding / Delayed / 0.1-0.4
 thrombotic thrombocytopenic purpura (TTP) / Delayed / 0-0.1
 ocular hemorrhage / Delayed / Incidence not known
 pancytopenia / Delayed / Incidence not known
 aplastic anemia / Delayed / Incidence not known
 agranulocytosis / Delayed / Incidence not known
 pancreatitis / Delayed / Incidence not known
 hepatic failure / Delayed / Incidence not known
 exfoliative dermatitis / Delayed / Incidence not known
 anaphylactoid reactions / Rapid / Incidence not known
 angioedema / Rapid / Incidence not known
 toxic epidermal necrolysis / Delayed / Incidence not known
 acute generalized exanthematous pustulosis (AGEP) / Delayed / Incidence not known
 erythema multiforme / Delayed / Incidence not known
 Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) / Delayed / Incidence not known
 Stevens-Johnson syndrome / Delayed / Incidence not known
 serum sickness / Delayed / Incidence not known
 eosinophilic pneumonia / Delayed / Incidence not known
 bronchospasm / Rapid / Incidence not known
 glomerulonephritis / Delayed / Incidence not known
 vasculitis / Delayed / Incidence not known

Moderate

hematoma / Early / 3.7-5.1
 bleeding / Early / 3.7-5.1
 hypertension / Early / 4.3-4.3
 constipation / Delayed / 2.4-2.4
 peripheral edema / Delayed / 1.2-1.2
 gastritis / Delayed / 0.8-0.8
 platelet dysfunction / Delayed / Incidence not known
 melena / Delayed / Incidence not known
 hematuria / Delayed / Incidence not known
 hepatitis / Delayed / Incidence not known
 elevated hepatic enzymes / Delayed / Incidence not known
 colitis / Delayed / Incidence not known
 stomatitis / Delayed / Incidence not known
 hallucinations / Early / Incidence not known
 confusion / Early / Incidence not known
 pneumonitis / Delayed / Incidence not known
 hypotension / Rapid / Incidence not known

Mild

headache / Early / 7.6-7.6
 dizziness / Early / 6.2-6.2
 rash / Early / 6.0-6.0
 abdominal pain / Early / 5.6-5.6
 purpura / Delayed / 5.3-5.3
 dyspepsia / Early / 5.2-5.2
 epistaxis / Delayed / 3.7-5.1
 diarrhea / Early / 4.5-4.5
 pruritus / Rapid / 3.3-3.3
 vertigo / Early / 2.2-2.2
 vomiting / Early / Incidence not known

nausea / Early / Incidence not known
 maculopapular rash / Early / Incidence not known
 urticaria / Rapid / Incidence not known
 fever / Early / Incidence not known
 dysgeusia / Early / Incidence not known
 myalgia / Early / Incidence not known
 arthralgia / Delayed / Incidence not known

DRUG INTERACTIONS

Abciximab: (Moderate) Concomitant use of platelet glycoprotein IIb/IIIa inhibitors (i.e., abciximab, eptifibatide, or tirofiban) with an ADP receptor antagonist (i.e., clopidogrel, prasugrel, ticagrelor, or ticlopidine) may be associated with an increased risk of bleeding.

Acetaminophen; Aspirin, ASA; Caffeine: (Moderate) Although aspirin may be used in combination with clopidogrel, both drugs are associated with bleeding. In clinical trials, bleeding rates with concomitant use of aspirin and clopidogrel vs. placebo vary from similar to increased bleeding with coadministration. Monitor for bleeding during concomitant therapy.

Acetaminophen; Butalbital; Caffeine; Codeine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Acetaminophen; Codeine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Acetaminophen; Diphenhydramine: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as diphenhydramine. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when diphenhydramine is coadministered with clopidogrel.

Acetaminophen; Hydrocodone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Acetaminophen; Oxycodone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Acetaminophen; Propoxyphene: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Acetaminophen; Tramadol: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Ado-Trastuzumab emtansine: (Major) Use caution if coadministration of platelet inhibitors such as clopidogrel with ado-trastuzumab emtansine is necessary due to reports of severe and sometimes fatal hemorrhage, including intracranial bleeding with ado-trastuzumab emtansine therapy. According to the manufacturer of ado-trastuzumab emtansine, if anti-platelet therapy cannot be avoided, additional monitoring of platelets and bleeding risk may be necessary. In a randomized, multicenter, open-label clinical trial of patients with HER2-positive metastatic breast cancer, hemorrhage occurred in 32.2% (\geq grade 3, 1.8%) of patients treated with ado-trastuzumab emtansine (n = 490) compared with 16.4% (\geq grade 3, 0.8%) of those who received lapatinib plus capecitabine (n = 488); some patients who experienced bleeding were also receiving anticoagulation therapy, antiplatelet therapy, or had thrombocytopenia, while others had no known additional risk factors.

Alfentanil: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Aliskiren; Amlodipine: (Moderate) Administer clopidogrel and amlodipine together with caution and monitor for reduced therapeutic response to clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Amlodipine is a weak inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a study of 200 patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), coadministration with a calcium-channel blocker (CCB) was associated with a reduced response to clopidogrel. Concomitant use of a CCB was also associated with a worse clinical outcome with the primary end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, stent thrombosis, and revascularization (PCI or CABG surgery), occurring more frequently in patients receiving a concomitant CCB. Amlodipine represented the largest subgroup of CCBs in the study, therefore it is unknown if these results can be applied to all CCBs. Another study compared concomitant use of amlodipine, a non-P-glycoprotein (P-gp) inhibiting CCB, with concomitant use of a P-gp inhibiting CCB (e.g., verapamil, nifedipine, diltiazem) on the effect of clopidogrel. Only amlodipine was associated with a poor response to clopidogrel suggesting the interaction between amlodipine and clopidogrel may be more clinically relevant compared to P-gp inhibiting CCBs. The authors theorized that by inhibiting P-gp, the intestinal efflux of clopidogrel may be decreased, thereby increasing clopidogrel plasma concentrations and counteracting the effect of CCB-induced CYP3A4 inhibition.

Aliskiren; Amlodipine; Hydrochlorothiazide, HCTZ: (Moderate) Administer clopidogrel and amlodipine together with caution and monitor for reduced therapeutic response to clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Amlodipine is a weak inhibitor of CYP3A4 and may decrease the hepatic metabolism

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Atisikren; Valsartan: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as valsartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when valsartan is coadministered with clopidogrel.

Alogliptin; Pioglitazone: (Major) Do not exceed 15 mg/day of pioglitazone if coadministered with clopidogrel. Coadministration may result in increased concentrations of pioglitazone. Pioglitazone is a CYP2C8 substrate and clopidogrel is a strong inhibitor of CYP2C8. When coadministered with gemfibrozil, another strong CYP2C8 inhibitor, the exposure to pioglitazone was increased by 226%.

Altretamine: (Moderate) An additive risk of bleeding may occur when platelet inhibitors is used with agents that cause clinically significant thrombocytopenia including antineoplastic agents, such as altretamine.

Amlodipine: (Moderate) Administer clopidogrel and amlodipine together with caution and monitor for reduced therapeutic response to clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Amlodipine is a weak inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a study of 200 patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), coadministration with a calcium-channel blocker (CCB) was associated with a reduced response to clopidogrel. Concomitant use of a CCB was also associated with a worse clinical outcome with the primary end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, stent thrombosis, and revascularization (PCI or CABG surgery), occurring more frequently in patients receiving a concomitant CCB. Amlodipine represented the largest subgroup of CCBs in the study, therefore it is unknown if these results can be applied to all CCBs. Another study compared concomitant use of amlodipine, a non-P-glycoprotein (P-gp) inhibiting CCB, with concomitant use of a P-gp inhibiting CCB (e.g., verapamil, nifedipine, diltiazem) on the effect of clopidogrel. Only amlodipine was associated with a poor response to clopidogrel suggesting the interaction between amlodipine and clopidogrel may be more clinically relevant compared to P-gp inhibiting CCBs. The authors theorized that by inhibiting P-gp, the intestinal efflux of clopidogrel may be decreased, thereby increasing clopidogrel plasma concentrations and counteracting the effect of CCB-induced CYP3A4 inhibition.

Amlodipine; Atorvastatin: (Moderate) Administer clopidogrel and amlodipine together with caution and monitor for reduced therapeutic response to clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Amlodipine is a weak inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a study of 200 patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), coadministration with a calcium-channel blocker (CCB) was associated with a reduced response to clopidogrel. Concomitant use of a CCB was also associated with a worse clinical outcome with the primary end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, stent thrombosis, and revascularization (PCI or CABG surgery), occurring more frequently in patients receiving a concomitant CCB. Amlodipine represented the largest subgroup of CCBs in the study, therefore it is unknown if these results can be applied to all CCBs. Another study compared concomitant use of amlodipine, a non-P-glycoprotein (P-gp) inhibiting CCB, with concomitant use of a P-gp inhibiting CCB (e.g., verapamil, nifedipine, diltiazem) on the effect of clopidogrel. Only amlodipine was associated with a poor response to clopidogrel suggesting the interaction between amlodipine and clopidogrel may be more clinically relevant compared to P-gp inhibiting CCBs. The authors theorized that by inhibiting P-gp, the intestinal efflux of clopidogrel may be decreased, thereby increasing clopidogrel plasma concentrations and counteracting the effect of CCB-induced CYP3A4 inhibition. (Minor) Atorvastatin has been reported to attenuate the antiplatelet activity of clopidogrel potentially by inhibiting CYP3A4 metabolism to its active metabolite; however, conflicting data exists. Patients should be monitored for therapeutic effectiveness when clopidogrel is administered with atorvastatin.

Amlodipine; Benazepril: (Moderate) Administer clopidogrel and amlodipine together with caution and monitor for reduced therapeutic response to clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Amlodipine is a weak inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a study of 200 patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), coadministration with a calcium-channel blocker (CCB) was associated with a reduced response to clopidogrel. Concomitant use of a CCB was also associated with a worse clinical outcome with the primary end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, stent thrombosis, and revascularization (PCI or CABG surgery), occurring more frequently in patients receiving a concomitant CCB. Amlodipine represented the largest subgroup of CCBs in the study, therefore it is unknown if these results can be applied to all CCBs. Another study compared concomitant use of amlodipine, a non-P-glycoprotein (P-gp) inhibiting CCB, with concomitant use of a P-gp inhibiting CCB (e.g., verapamil, nifedipine, diltiazem) on the effect of clopidogrel. Only amlodipine was associated with a poor response to clopidogrel suggesting the interaction between amlodipine and clopidogrel may be more clinically relevant compared to P-gp inhibiting CCBs. The authors theorized that by inhibiting P-gp, the intestinal efflux of clopidogrel may be decreased, thereby increasing clopidogrel plasma concentrations and counteracting the effect of CCB-induced CYP3A4 inhibition.

Amlodipine; Hydrochlorothiazide, HCTZ; Olmesartan: (Moderate) Administer clopidogrel and amlodipine together with caution and monitor for reduced therapeutic response to clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Amlodipine is a weak inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a study of 200 patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), coadministration with a calcium-channel blocker (CCB) was associated with a reduced response to clopidogrel. Concomitant use of a CCB was also associated with a worse clinical outcome with the primary end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, stent thrombosis, and revascularization (PCI or CABG surgery), occurring more frequently in patients receiving a concomitant CCB. Amlodipine represented the largest subgroup of CCBs in the study, therefore it is unknown if these results can be applied to all CCBs. Another study compared concomitant use of amlodipine, a non-P-glycoprotein (P-gp) inhibiting CCB, with concomitant use of a P-gp inhibiting CCB (e.g., verapamil, nifedipine, diltiazem) on the effect of clopidogrel. Only amlodipine was associated with a poor response to clopidogrel suggesting the interaction between amlodipine and clopidogrel may be more clinically relevant compared to P-gp inhibiting CCBs. The authors theorized that by inhibiting P-gp, the intestinal efflux of clopidogrel may be decreased, thereby increasing clopidogrel plasma concentrations and counteracting the effect of CCB-induced CYP3A4 inhibition.

Amlodipine; Hydrochlorothiazide, HCTZ; Valsartan: (Moderate) Administer clopidogrel and amlodipine together with caution and monitor for reduced therapeutic response to clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Amlodipine is a weak inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a study of 200 patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), coadministration with a calcium-channel blocker (CCB) was associated with a reduced response to clopidogrel. Concomitant use of a CCB was also associated with a worse clinical outcome with the primary end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, stent thrombosis, and revascularization (PCI or CABG surgery), occurring more frequently in patients receiving a concomitant CCB. Amlodipine represented the largest subgroup of CCBs in the study, therefore it is unknown if these results can be applied to all CCBs. Another study compared concomitant use of amlodipine, a non-P-glycoprotein (P-gp) inhibiting CCB, with concomitant use of a P-gp inhibiting CCB (e.g., verapamil, nifedipine, diltiazem) on the effect of clopidogrel. Only amlodipine was associated with a poor response to clopidogrel suggesting the interaction between amlodipine and clopidogrel may be more clinically relevant compared to P-gp inhibiting CCBs. The authors theorized that by inhibiting P-gp, the intestinal efflux of clopidogrel may be decreased, thereby increasing clopidogrel plasma concentrations and counteracting the effect of CCB-induced CYP3A4 inhibition. (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel

could increase plasma concentrations of drugs metabolized by this isoenzyme, such as valsartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when valsartan is coadministered with clopidogrel.

Amlodipine; Olmesartan: (Moderate) Administer clopidogrel and amlodipine together with caution and monitor for reduced therapeutic response to clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Amlodipine is a weak inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a study of 200 patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), coadministration with a calcium-channel blocker (CCB) was associated with a reduced response to clopidogrel. Concomitant use of a CCB was also associated with a worse clinical outcome with the primary end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, stent thrombosis, and revascularization (PCI or CABG surgery), occurring more frequently in patients receiving a concomitant CCB. Amlodipine represented the largest subgroup of CCBs in the study, therefore it is unknown if these results can be applied to all CCBs. Another study compared concomitant use of amlodipine, a non-P-glycoprotein (P-gp) inhibiting CCB, with concomitant use of a P-gp inhibiting CCB (e.g., verapamil, nifedipine, diltiazem) on the effect of clopidogrel. Only amlodipine was associated with a poor response to clopidogrel suggesting the interaction between amlodipine and clopidogrel may be more clinically relevant compared to P-gp inhibiting CCBs. The authors theorized that by inhibiting P-gp, the intestinal efflux of clopidogrel may be decreased, thereby increasing clopidogrel plasma concentrations and counteracting the effect of CCB-induced CYP3A4 inhibition.

Amlodipine; Telmisartan: (Major) Telmisartan may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and telmisartan together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. Telmisartan is an inhibitor of CYP2C19. (Moderate) Administer clopidogrel and amlodipine together with caution and monitor for reduced therapeutic response to clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Amlodipine is a weak inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a study of 200 patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), coadministration with a calcium-channel blocker (CCB) was associated with a reduced response to clopidogrel. Concomitant use of a CCB was also associated with a worse clinical outcome with the primary end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, stent thrombosis, and revascularization (PCI or CABG surgery), occurring more frequently in patients receiving a concomitant CCB. Amlodipine represented the largest subgroup of CCBs in the study, therefore it is unknown if these results can be applied to all CCBs. Another study compared concomitant use of amlodipine, a non-P-glycoprotein (P-gp) inhibiting CCB, with concomitant use of a P-gp inhibiting CCB (e.g., verapamil, nifedipine, diltiazem) on the effect of clopidogrel. Only amlodipine was associated with a poor response to clopidogrel suggesting the interaction between amlodipine and clopidogrel may be more clinically relevant compared to P-gp inhibiting CCBs. The authors theorized that by inhibiting P-gp, the intestinal efflux of clopidogrel may be decreased, thereby increasing clopidogrel plasma concentrations and counteracting the effect of CCB-induced CYP3A4 inhibition.

Amlodipine; Valsartan: (Moderate) Administer clopidogrel and amlodipine together with caution and monitor for reduced therapeutic response to clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Amlodipine is a weak inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a study of 200 patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), coadministration with a calcium-channel blocker (CCB) was associated with a reduced response to clopidogrel. Concomitant use of a CCB was also associated with a worse clinical outcome with the primary end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, stent thrombosis, and revascularization (PCI or CABG surgery), occurring more frequently in patients receiving a concomitant CCB. Amlodipine represented the largest subgroup of CCBs in the study, therefore it is unknown if these results can be applied to all CCBs. Another study compared concomitant use of amlodipine, a non-P-glycoprotein (P-gp) inhibiting CCB, with concomitant use of a P-gp inhibiting CCB (e.g., verapamil, nifedipine, diltiazem) on the effect of clopidogrel. Only amlodipine was associated with a poor response to clopidogrel suggesting the interaction between amlodipine and clopidogrel may be more clinically relevant compared to P-gp inhibiting CCBs. The authors theorized that by inhibiting P-gp, the intestinal efflux of clopidogrel may be decreased, thereby increasing clopidogrel plasma concentrations and counteracting the effect of CCB-induced CYP3A4 inhibition. (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as valsartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when valsartan is coadministered with clopidogrel.

Amoxicillin; Clarithromycin; Omeprazole: (Major) Avoid concomitant use of clopidogrel and omeprazole as it significantly reduces the antiplatelet activity of clopidogrel when given concomitantly or 12 hours apart. The American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG) and American Heart Association (AHA) state that routine use of proton pump inhibitor (PPI) therapy is not recommended for patients at lower risk of gastrointestinal bleed but should be considered in those at high risk, such as those with a history of gastrointestinal bleed. Clinicians should carefully assess the risks and benefits of PPI use in patients on clopidogrel therapy and administration should be based on clinical need. If necessary, consider using a PPI medication with less pronounced effects on antiplatelet activity, such as rabeprazole, pantoprazole, lansoprazole, or dexlansoprazole. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. All PPIs are CYP219 substrates, and, to varying extents, are also inhibitors; thus, it is possible that any PPI may decrease the conversion of clopidogrel to its active metabolite, thereby reducing its effectiveness.

Anagrelide: (Moderate) Although anagrelide inhibits platelet aggregation at high doses, there is a potential additive risk for bleeding if anagrelide is given in combination with other agents that effect hemostasis such as ADP receptor antagonists including clopidogrel, prasugrel, ticagrelor, or ticlopidine.

Anthracyclines: (Moderate) Avoid coadministration if possible. An additive risk of bleeding may occur when platelet inhibitors is used with agents that cause clinically significant thrombocytopenia including antineoplastic agents, such as anthracyclines. In addition, ticagrelor is a mild CYP3A4 and P-glycoprotein (P-gp) inhibitor; doxorubicin is a major substrate of both CYP3A4 and P-gp. Clinically significant interactions have been reported when doxorubicin was coadministered with inhibitors of CYP3A4 and/or P-gp, resulting in increased concentration and clinical effect of doxorubicin. If not possible, closely monitor for increased side effects of doxorubicin including myelosuppression and cardiotoxicity.

Antimetabolites: (Moderate) An additive risk of bleeding may occur when platelet inhibitors are used with agents that cause clinically significant thrombocytopenia including antimetabolites.

Antithrombin III: (Moderate) Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other agents that affect hemostasis such as anticoagulants.

Antithymocyte Globulin: (Moderate) An increased risk of bleeding may occur when platelet inhibitors are used with agents that cause clinically significant thrombocytopenia, such as antithymocyte globulin. Platelet inhibitors should be used cautiously in patients with thrombocytopenia following the administration of antithymocyte globulin or other drugs that cause significant thrombocytopenia due to the increased risk of bleeding.

Apalutamide: (Moderate) Monitor for an increase in apalutamide-related adverse reactions if coadministration with clopidogrel is necessary. Consider reducing the dose of apalutamide if necessary based on tolerability in patients experiencing grade 3 or higher adverse reactions or intolerable toxicities. Apalutamide is a CYP2C8 substrate and clopidogrel is a strong CYP2C8 inhibitor. Coadministration with another strong CYP2C8 inhibitor decreased the C_{max} of single-dose apalutamide by 21% but increased the AUC by 68%; strong CYP2C8 inhibition is expected to increase the steady-state apalutamide C_{max} by 32% and AUC by 44%. The predicted steady-state exposure of the active moieties (unbound apalutamide plus potency-adjusted unbound N-desmethyl apalutamide) is predicted to increase by 23%.

Apixaban: (Major) The concomitant use of apixaban and platelet inhibitors (e.g., aspirin) may increase the risk of bleeding. In the ARISTOTLE trial (comparative trial of apixaban and warfarin in patients with nonvalvular atrial fibrillation), concomitant use of aspirin increased the bleeding risk of apixaban from 1.8%/year to 3.4%/year. If given concomitantly, patients should be educated about the signs and symptoms of bleeding and be instructed to report them immediately or go to an emergency room.

Aprepitant; Fosaprepitant: (Moderate) Use caution if clopidogrel and aprepitant, fosaprepitant are used concurrently and monitor for an increase in clopidogrel-related adverse effects, including bleeding and bruising, for several days after administration of a multi-day aprepitant regimen. Clopidogrel is a CYP3A4 substrate. Aprepitant, when administered as a 3-day oral regimen (125 mg/80 mg/80 mg), is a moderate CYP3A4 inhibitor and inducer and may increase plasma concentrations of clopidogrel. For example, a 5-day oral aprepitant regimen increased the AUC of another CYP3A4 substrate, midazolam (single dose), by 2.3-fold on day 1 and by 3.3-fold on day 5. After a 3-day oral aprepitant regimen, the AUC of

midazolam (given on days 1, 4, 8, and 15) increased by 25% on day 4, and then decreased by 19% and 4% on days 8 and 15, respectively. As a single 125 mg or 40 mg oral dose, the inhibitory effect of aprepitant on CYP3A4 is weak, with the AUC of midazolam increased by 1.5-fold and 1.2-fold, respectively. After administration, fosaprepitant is rapidly converted to aprepitant and shares many of the same drug interactions. However, as a single 150 mg intravenous dose, fosaprepitant only weakly inhibits CYP3A4 for a duration of 2 days; there is no evidence of CYP3A4 induction. Fosaprepitant 150 mg IV as a single dose increased the AUC of midazolam (given on days 1 and 4) by approximately 1.8-fold on day 1; there was no effect on day 4. Less than a 2-fold increase in the midazolam AUC is not considered clinically important.

Argatroban: (Moderate) An additive risk of bleeding may be seen in patients receiving platelet inhibitors (e.g., clopidogrel, platelet glycoprotein IIb/IIIa inhibitors, ticlopidine, etc.) in combination with argatroban.

Armodafinil: (Major) Armodafinil may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite.

Use clopidogrel and armodafinil together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. Armodafinil is an inhibitor of CYP2C19.

Arsenic Trioxide: (Moderate) Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other drugs that affect hemostasis. Clopidogrel should be used cautiously in patients with thrombocytopenia following the administration of myelosuppressive antineoplastic agents or other drugs that cause significant thrombocytopenia due to the increased risk of bleeding.

Aspirin, ASA: (Moderate) Although aspirin may be used in combination with clopidogrel, both drugs are associated with bleeding. In clinical trials, bleeding rates with concomitant use of aspirin and clopidogrel vs. placebo vary from similar to increased bleeding with coadministration. Monitor for bleeding during concomitant therapy.

Aspirin, ASA; Butalbital; Caffeine: (Moderate) Although aspirin may be used in combination with clopidogrel, both drugs are associated with bleeding. In clinical trials, bleeding rates with concomitant use of aspirin and clopidogrel vs. placebo vary from similar to increased bleeding with coadministration. Monitor for bleeding during concomitant therapy.

Aspirin, ASA; Butalbital; Caffeine; Codeine: (Moderate) Although aspirin may be used in combination with clopidogrel, both drugs are associated with bleeding. In clinical trials, bleeding rates with concomitant use of aspirin and clopidogrel vs. placebo vary from similar to increased bleeding with coadministration. Monitor for bleeding during concomitant therapy. (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Aspirin, ASA; Caffeine; Dihydrocodeine: (Moderate) Although aspirin may be used in combination with clopidogrel, both drugs are associated with bleeding. In clinical trials, bleeding rates with concomitant use of aspirin and clopidogrel vs. placebo vary from similar to increased bleeding with coadministration. Monitor for bleeding during concomitant therapy.

Aspirin, ASA; Carisoprodol: (Moderate) Although aspirin may be used in combination with clopidogrel, both drugs are associated with bleeding. In clinical trials, bleeding rates with concomitant use of aspirin and clopidogrel vs. placebo vary from similar to increased bleeding with coadministration. Monitor for bleeding during concomitant therapy.

Aspirin, ASA; Carisoprodol; Codeine: (Moderate) Although aspirin may be used in combination with clopidogrel, both drugs are associated with bleeding. In clinical trials, bleeding rates with concomitant use of aspirin and clopidogrel vs. placebo vary from similar to increased bleeding with coadministration. Monitor for bleeding during concomitant therapy. (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Aspirin, ASA; Dipyridamole: (Moderate) Although aspirin may be used in combination with clopidogrel, both drugs are associated with bleeding. In clinical trials, bleeding rates with concomitant use of aspirin and clopidogrel vs. placebo vary from similar to increased bleeding with coadministration. Monitor for bleeding during concomitant therapy. (Moderate) Because dipyridamole is a platelet inhibitor, there is a potential additive risk for bleeding if dipyridamole is given in combination with other agents that affect hemostasis such as ADP receptor antagonists including clopidogrel, prasugrel, ticagrelor, or ticlopidine.

Aspirin, ASA; Omeprazole: (Major) Avoid concomitant use of clopidogrel and omeprazole as it significantly reduces the antiplatelet activity of clopidogrel when given concomitantly or 12 hours apart. The American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG) and American Heart Association (AHA) state that routine use of proton pump inhibitor (PPI) therapy is not recommended for patients at lower risk of gastrointestinal bleed but should be considered in those at high risk, such as those with a history of gastrointestinal bleed. Clinicians should carefully assess the risks and benefits of PPI use in patients on clopidogrel therapy and administration should be based on clinical need. If necessary, consider using a PPI medication with less pronounced effects on antiplatelet activity, such as rabeprazole, pantoprazole, lansoprazole, or dexlansoprazole. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. All PPIs are CYP219 substrates, and, to varying extents, are also inhibitors; thus, it is possible that any PPI may decrease the conversion of clopidogrel to its active metabolite, thereby reducing its effectiveness. (Moderate) Although aspirin may be used in combination with clopidogrel, both drugs are associated with bleeding. In clinical trials, bleeding rates with concomitant use of aspirin and clopidogrel vs. placebo vary from similar to increased bleeding with coadministration. Monitor for bleeding during concomitant therapy.

Aspirin, ASA; Oxycodone: (Moderate) Although aspirin may be used in combination with clopidogrel, both drugs are associated with bleeding. In clinical trials, bleeding rates with concomitant use of aspirin and clopidogrel vs. placebo vary from similar to increased bleeding with coadministration. Monitor for bleeding during concomitant therapy. (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Aspirin, ASA; Pravastatin: (Moderate) Although aspirin may be used in combination with clopidogrel, both drugs are associated with bleeding. In clinical trials, bleeding rates with concomitant use of aspirin and clopidogrel vs. placebo vary from similar to increased bleeding with coadministration. Monitor for bleeding during concomitant therapy.

Atazanavir; Cobicistat: (Minor) Clopidogrel requires hepatic biotransformation to an active metabolite; the activation is thought to be mediated by the CYP3A4 isoenzyme. Cobicistat is an inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. Therefore, the therapeutic effectiveness of clopidogrel should be monitored.

Atorvastatin: (Minor) Atorvastatin has been reported to attenuate the antiplatelet activity of clopidogrel potentially by inhibiting CYP3A4 metabolism to its active metabolite; however, conflicting data exists. Patients should be monitored for therapeutic effectiveness when clopidogrel is administered with atorvastatin.

Atorvastatin; Ezetimibe: (Minor) Atorvastatin has been reported to attenuate the antiplatelet activity of clopidogrel potentially by inhibiting CYP3A4 metabolism to its active metabolite; however, conflicting data exists. Patients should be monitored for therapeutic effectiveness when clopidogrel is administered with atorvastatin.

Azilsartan: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as azilsartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when azilsartan is coadministered with clopidogrel.

Azilsartan; Chlorthalidone: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as azilsartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when azilsartan is coadministered with clopidogrel.

Azole antifungals: (Major) Administer clopidogrel and systemic azole antifungals together with caution. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Systemic azole antifungals are inhibitors of CYP3A4 and some also inhibit CYP2C19 (e.g., fluconazole, ketoconazole, miconazole, voriconazole) and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a randomized crossover study, healthy subjects received a clopidogrel loading dose of 300 mg followed by 5 daily doses of 75 mg with or without the ketoconazole (400 mg/day). Ketoconazole decreased the active metabolite of clopidogrel by 48% after the 300 mg dose and 61% after the last maintenance dose was given. Ketoconazole also decreased the area under the concentration-time curve of clopidogrel's active metabolite by 22% after the loading dose and 29% after the last maintenance dose. If coadministration is unavoidable, the therapeutic effectiveness of clopidogrel should be closely monitored.

Barbiturates: (Minor) Barbiturates may induce the CYP3A4 metabolism of clopidogrel to its active metabolite. Patients should be monitored for potential increased antiplatelet effects when clopidogrel is used in combination with CYP3A4 inducers.

Belladonna Alkaloids; Ergotamine; Phenobarbital: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Belladonna; Opium: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Betrixaban: (Major) Monitor patients closely and promptly evaluate any signs or symptoms of bleeding if betrixaban and platelet inhibitors are used concomitantly. Coadministration of betrixaban and platelet inhibitors may increase the risk of bleeding.

Bevacizumab: (Moderate) Due to the thrombocytopenic effects of antineoplastics an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors.

Bexarotene: (Moderate) An additive risk of bleeding may occur when platelet inhibitors are used with agents that cause clinically significant thrombocytopenia including bexarotene.

Bivalirudin: (Moderate) When used as an anticoagulant in patients undergoing percutaneous coronary intervention (PCI), bivalirudin is intended for use with aspirin (300 to 325 mg/day PO) and has been studied only in patients receiving concomitant aspirin. Generally, an additive risk of bleeding may be seen in patients receiving other platelet inhibitors (other than aspirin). In clinical trials in patients undergoing PTCA, patients receiving bivalirudin with heparin, warfarin, or thrombolytics had increased risks of major bleeding events compared to those receiving bivalirudin alone. According to the manufacturer, the safety and effectiveness of bivalirudin have not been established when used in conjunction with platelet inhibitors other than aspirin. However, bivalirudin has been safely used as an alternative to heparin in combination with provisional use of platelet glycoprotein IIb/IIIa inhibitors during angioplasty (REPLACE-2). In addition, two major clinical trials have evaluated the use of bivalirudin in patients receiving streptokinase following acute myocardial infarction (HERO-1, HERO-2). Based on the these trials, bivalirudin may be considered an alternative to heparin therapy for use in combination with streptokinase for ST-elevation MI. Bivalirudin has not been sufficiently studied in combination with other more specific thrombolytics.

Boceprevir: (Moderate) Close clinical monitoring is advised when administering clopidogrel with boceprevir due to an increased potential for clopidogrel-related adverse events. If clopidogrel dose adjustments are made, re-adjust the dose upon completion of boceprevir treatment. Although this interaction has not been studied, predictions about the interaction can be made based on the metabolic pathway of clopidogrel. Clopidogrel is partially metabolized by the hepatic isoenzyme CYP3A4; boceprevir inhibits this isoenzyme. Coadministration may result in elevated clopidogrel plasma concentrations.

Bosentan: (Minor) Bosentan may induce the CYP3A4 metabolism of clopidogrel to its active metabolite. Patients should be monitored for potential increased antiplatelet effects when clopidogrel is used in combination with CYP3A4 inducers.

Brompheniramine; Guaifenesin; Hydrocodone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Brompheniramine; Hydrocodone; Pseudoephedrine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Bupropion: (Moderate) Concomitant treatment with clopidogrel and bupropion can increase bupropion exposure but decrease hydroxybupropion exposure; based on clinical response, bupropion dosage adjustment may be necessary. Adverse reactions to bupropion, such as tremor, nausea, dry mouth, insomnia, headache, or seizures, may be more likely to occur. At high concentrations in vitro, clopidogrel is a potent inhibitor of CYP2B6, and bupropion is a CYP2B6 substrate. In a study in healthy male volunteers, clopidogrel 75 mg once daily increased the C_{max} and AUC of bupropion by 40% and 60%, respectively.

Bupropion; Naltrexone: (Moderate) Concomitant treatment with clopidogrel and bupropion can increase bupropion exposure but decrease hydroxybupropion exposure; based on clinical response, bupropion dosage adjustment may be necessary. Adverse reactions to bupropion, such as tremor, nausea, dry mouth, insomnia, headache, or seizures, may be more likely to occur. At high concentrations in vitro, clopidogrel is a potent inhibitor of CYP2B6, and bupropion is a CYP2B6 substrate. In a study in healthy male volunteers, clopidogrel 75 mg once daily increased the C_{max} and AUC of bupropion by 40% and 60%, respectively.

Candesartan: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as candesartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when candesartan is coadministered with clopidogrel.

Candesartan; Hydrochlorothiazide, HCTZ: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as candesartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when candesartan is coadministered with clopidogrel.

Cangrelor: (Major) Do not administer clopidogrel until the cangrelor infusion is discontinued. The expected antiplatelet effect of a 600 mg loading dose of clopidogrel will be blocked if administered during the cangrelor infusion. Clopidogrel therapy should be initiated immediately after cangrelor discontinuation.

Carbetapentane; Diphenhydramine; Phenylephrine: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as diphenhydramine. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when diphenhydramine is coadministered with clopidogrel.

Carbinoxamine; Hydrocodone; Phenylephrine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of

clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Carbinoxamine; Hydrocodone; Pseudoephedrine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Chlorambucil: (Moderate) An additive risk of bleeding may occur when platelet inhibitors are used with agents that cause clinically significant thrombocytopenia including antineoplastic agents, such as chlorambucil.

Chloramphenicol: (Major) Chloramphenicol may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and chloramphenicol together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Chloramphenicol is an inhibitor of CYP2C19 and CYP3A4.

Chlorpheniramine; Codeine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Chlorpheniramine; Guaifenesin; Hydrocodone; Pseudoephedrine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Chlorpheniramine; Hydrocodone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Chlorpheniramine; Hydrocodone; Phenylephrine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Chlorpheniramine; Hydrocodone; Pseudoephedrine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Chlorpropamide: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as chlorpropamide. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when chlorpropamide is coadministered with clopidogrel.

Chondroitin; Glucosamine: (Moderate) Increased effects from concomitant anticoagulant drugs including increased bruising or blood in the stool have been reported in patients taking methylsulfonylmethane, MSM. Although these effects have not been confirmed in published medical literature or during clinical studies, clinicians should consider using methylsulfonylmethane, MSM with caution in patients who are taking anticoagulants or antiplatelets including clopidogrel until data confirming the safety of these drug combinations are available. During one of the available, published clinical trials in patients with osteoarthritis, those patients with bleeding disorders or using anticoagulants or antiplatelets were excluded from enrollment. Patients who choose to consume methylsulfonylmethane, MSM while receiving clopidogrel should be observed for increased bleeding.

Cilostazol: (Moderate) Because cilostazol is a platelet aggregation inhibitor, a potential additive risk for bleeding exists if cilostazol is given with other agent that affect hemostasis such as ADP receptor antagonists including clopidogrel, prasugrel, ticagrelor, or ticlopidine. Ticlopidine, in addition to its pharmacodynamic effects, is an inhibitor of the hepatic isoenzyme cytochrome P450 2C19 and thus could decrease the metabolism of cilostazol; a reduction in cilostazol dosage should be considered if the two agents are administered concurrently. Multiple doses of clopidogrel do not significantly increase the steady state plasma concentrations of cilostazol.

Cimetidine: (Major) Cimetidine may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and cimetidine together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Cimetidine inhibits CYP3A4 and is a potent CYP2C19 inhibitor.

Ciprofloxacin: (Minor) The therapeutic effectiveness of clopidogrel should be monitored during coadministration with ciprofloxacin. Clopidogrel requires hepatic biotransformation to an active metabolite; the activation is thought to be mediated by the CYP3A4 isoenzyme. Ciprofloxacin is an inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite.

Citalopram: (Major) Citalopram causes dose-dependent QT interval prolongation. Because citalopram is a substrate for CYP2C19, the maximum daily dose of citalopram should not exceed 20 mg/day in patients receiving CYP2C19 inhibitors such as clopidogrel. During concurrent use of citalopram and clopidogrel, clinicians should monitor patients for a potential increase in side effects or toxicity. In addition, platelet aggregation may be impaired by selective serotonin reuptake inhibitors (SSRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving platelet inhibitors (e.g., cilostazol, clopidogrel, dipyridamole, ticlopidine, platelet glycoprotein IIb/IIIa inhibitors). Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SSRI concurrently with an antiplatelet medication and to promptly report any bleeding events to the practitioner.

Cladribine: (Moderate) Due to the thrombocytopenic effects of purine analogs, an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors.

Clobazam: (Moderate) A dosage reduction of clobazam may be necessary during co-administration of clopidogrel. Metabolism of N-desmethyloclobazam, the active metabolite of clobazam, occurs primarily through CYP2C19 and clopidogrel is an inhibitor of CYP2C19. Extrapolation from pharmacogenomic data indicates that concurrent use of clobazam with moderate or potent inhibitors of CYP2C19 may result in up to a 5-fold increase in exposure to N-desmethyloclobazam. Adverse effects, such as sedation, lethargy, ataxia, or insomnia may be potentiated.

Clofarabine: (Moderate) Due to the thrombocytopenic effects of antineoplastics an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors.

Cobicistat: (Minor) Clopidogrel requires hepatic biotransformation to an active metabolite; the activation is thought to be mediated by the CYP3A4 isoenzyme. Cobicistat is an inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. Therefore, the therapeutic effectiveness of clopidogrel should be monitored.

Cobicistat; Elvitegravir; Emtricitabine; Tenofovir Alafenamide: (Minor) Clopidogrel requires hepatic biotransformation to an active metabolite; the activation is thought to be mediated by the CYP3A4 isoenzyme. Cobicistat is an inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. Therefore, the therapeutic effectiveness of clopidogrel should be monitored.

Cobicistat; Elvitegravir; Emtricitabine; Tenofovir Disoproxil Fumarate: (Minor) Clopidogrel requires hepatic biotransformation to an active metabolite; the activation is thought to be mediated by the CYP3A4 isoenzyme. Cobicistat is an inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. Therefore, the therapeutic effectiveness of clopidogrel should be monitored.

Cod Liver Oil: (Moderate) Because fish oil, omega-3 fatty acids inhibit platelet aggregation, caution is advised when fish oils are used concurrently with other platelet inhibitors. Theoretically, the risk of bleeding may be increased. (Moderate) Cod liver oil contains vitamin A and may increase the risk of bleeding if coadministered with platelet inhibitors.

Codeine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Codeine; Guaifenesin: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Codeine; Phenylephrine; Promethazine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Codeine; Promethazine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Collagenase: (Moderate) Cautious use of injectable collagenase by patients taking platelet inhibitors is advised. The efficacy and safety of administering injectable collagenase to a patient taking a platelet inhibitor within 7 days before the injection are unknown. Receipt of injectable collagenase may cause an ecchymosis or bleeding at the injection site.

Cyclophosphamide: (Moderate) Use caution if cyclophosphamide is used concomitantly with clopidogrel, and monitor for possible changes in the efficacy or toxicity profile of cyclophosphamide. The clinical significance of this interaction is unknown. Cyclophosphamide is a prodrug that is hydroxylated and activated primarily by CYP2B6; the contribution of CYP3A4 to the activation of cyclophosphamide is variable. Additional isoenzymes involved in the activation of cyclophosphamide include CYP2A6, 2C9, 2C18, and 2C19. N-dechloroethylation to therapeutically inactive but neurotoxic metabolites occurs primarily via CYP3A4. The active metabolites, 4-hydroxycyclophosphamide and aldophosphamide, are then inactivated by aldehyde dehydrogenase-mediated oxidation. Clopidogrel is a strong CYP2B6 inhibitor, as well as a moderate inhibitor of CYP2C19 and a weak 2C9 inhibitor; conversion of cyclophosphamide to its active metabolites may be affected.

Dabigatran: (Moderate) Coadministration of dabigatran and clopidogrel (300 mg or 600 mg loading dose) resulted in an increase in dabigatran AUC and C_{max} of 30% and 40%, respectively; however capillary bleeding times were not further prolonged compared to clopidogrel monotherapy. In addition, coagulation measures for dabigatran's effect (aPTT, ECT, and TT) were unchanged, and inhibition of platelet aggregation (IPA), a measure of clopidogrel's effect, was unchanged. However, the manufacturer notes that the concomitant use of dabigatran and platelet inhibiting agents may increase the risk of bleeding. Monitor patients closely for signs of bleeding if dabigatran is given concomitantly with any platelet inhibiting agents.

Dabrafenib: (Major) Avoid the concomitant use of dabrafenib and clopidogrel; dabrafenib concentrations may increase resulting in increased toxicity. Use of an alternate agent is recommended. If concomitant use is necessary, monitor patients for dabrafenib toxicity (e.g., skin toxicity, ocular toxicity, and cardiotoxicity). The clopidogrel manufacturer states that a dose adjustment of the CYP2C8 substrate may be necessary. Dabrafenib is a CYP2C8 substrate; the glucuronide metabolite of clopidogrel is a strong CYP2C8 inhibitor. The dabrafenib AUC value increased by 47% when dabrafenib was administered with another strong CYP2C8 inhibitor in a drug interaction study.

Dalteparin: (Moderate) Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other agents that affect hemostasis such as anticoagulants.

Danaparoid: (Moderate) Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other agents that affect hemostasis such as anticoagulants.

Danazol: (Moderate) Administer clopidogrel and danazol together with caution. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Danazol is an inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. Therefore, the therapeutic effectiveness of clopidogrel should be monitored when used concomitantly with danazol.

Darunavir; Cobicistat: (Minor) Clopidogrel requires hepatic biotransformation to an active metabolite; the activation is thought to be mediated by the CYP3A4 isoenzyme. Cobicistat is an inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. Therefore, the therapeutic effectiveness of clopidogrel should be monitored.

Darunavir; Cobicistat; Emtricitabine; Tenofovir alafenamide: (Minor) Clopidogrel requires hepatic biotransformation to an active metabolite; the activation is thought to be mediated by the CYP3A4 isoenzyme. Cobicistat is an inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. Therefore, the therapeutic effectiveness of clopidogrel should be monitored.

Dasabuvir; Ombitasvir; Paritaprevir; Ritonavir: (Severe) According to the manufacturer, concomitant use of dasabuvir; ombitasvir; paritaprevir; ritonavir with strong CYP2C8 inhibitors is contraindicated due to the potential for dasabuvir-induced QT prolongation. Clopidogrel is a potent inhibitor of the hepatic isoenzyme CYP2C8; dasabuvir is primarily metabolized by CYP2C8. In addition, use of these drugs may alter plasma concentrations and/or biotransformation of clopidogrel. Clopidogrel requires hepatic biotransformation to an active metabolite; the activation is thought to be mediated, in part, by the CYP3A4 isoenzyme. Ritonavir is an inhibitor of this enzyme. It is not clear whether clopidogrel's effectiveness would be altered during coadministration.

Dasatinib: (Moderate) Monitor for evidence of bleeding if coadministration of dasatinib and clopidogrel is necessary. Dasatinib can cause serious and fatal bleeding. Concomitant platelet inhibitors may increase the risk of hemorrhage.

Defibrotide: (Severe) Coadministration of defibrotide with antithrombotic agents like platelet inhibitors is contraindicated. The pharmacodynamic activity and risk of hemorrhage with antithrombotic agents are increased if coadministered with defibrotide. If therapy with defibrotide is necessary, discontinue antithrombotic agents prior to initiation of defibrotide therapy. Consider delaying the onset of defibrotide treatment until the effects of the antithrombotic agent have abated.

Denileukin Diffitox: (Moderate) An additive risk of bleeding may occur when platelet inhibitors are used with agents that cause clinically significant thrombocytopenia including antineoplastic agents, such as denileukin diffitox.

Desirudin: (Moderate) Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other agents that affect hemostasis such as anticoagulants.

Desvenlafaxine: (Moderate) Platelet aggregation may be impaired by serotonin norepinephrine reuptake inhibitors (SNRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae,

hemorrhage) in patients receiving platelet inhibitors. Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SNRI with a platelet inhibitor and to promptly report any bleeding events to the practitioner.

Dextromethorphan; Diphenhydramine; Phenylephrine: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as diphenhydramine. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when diphenhydramine is coadministered with clopidogrel.

Diphenhydramine: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as diphenhydramine. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when diphenhydramine is coadministered with clopidogrel.

Diphenhydramine; Hydrocodone; Phenylephrine: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as diphenhydramine. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when diphenhydramine is coadministered with clopidogrel. (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Diphenhydramine; Ibuprofen: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as diphenhydramine. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when diphenhydramine is coadministered with clopidogrel.

Diphenhydramine; Naproxen: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as diphenhydramine. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when diphenhydramine is coadministered with clopidogrel.

Diphenhydramine; Phenylephrine: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as diphenhydramine. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when diphenhydramine is coadministered with clopidogrel.

Dipyridamole: (Moderate) Because dipyridamole is a platelet inhibitor, there is a potential additive risk for bleeding if dipyridamole is given in combination with other agents that affect hemostasis such as ADP receptor antagonists including clopidogrel, prasugrel, ticagrelor, or ticlopidine.

Doxepin: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as doxepin. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when doxepin is coadministered with clopidogrel.

Doxercalciferol: (Moderate) Doxercalciferol is converted in the liver to 1,25-dihydroxyergocalciferol, the major active metabolite, and 1- α , 24-dihydroxyvitamin D₂, a minor metabolite. Although not specifically studied, cytochrome P450 enzyme inhibitors including clopidogrel may inhibit the 25-hydroxylation of doxercalciferol, thereby decreasing the formation of the active metabolite and thus, decreasing efficacy. Patients should be monitored for a decrease in efficacy if clopidogrel is coadministered with doxercalciferol.

Dronabinol, THC: (Moderate) Use caution if coadministration of dronabinol with clopidogrel is necessary, and monitor for an increase in dronabinol-related adverse reactions (e.g., feeling high, dizziness, confusion, somnolence). Dronabinol is a CYP2C9 and 3A4 substrate; clopidogrel is a weak inhibitor of CYP2C9. Concomitant use may result in elevated plasma concentrations of dronabinol.

Dronedarone: (Moderate) Dronedarone is metabolized by and is an inhibitor of CYP3A. Clopidogrel is a substrate for CYP3A4. The concomitant administration of dronedarone and CYP3A substrates may result in increased exposure of the substrate and should, therefore, be undertaken with caution.

Drotrecogin Alfa: (Major) Treatment with drotrecogin alfa should be carefully considered in patients who are receiving or have received any platelet inhibitors within 7 days. These patients are at increased risk of bleeding during drotrecogin alfa therapy.

Duloxetine: (Moderate) Platelet aggregation may be impaired by serotonin norepinephrine reuptake inhibitors (SNRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving platelet inhibitors. Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SNRI with a platelet inhibitor and to promptly report any bleeding events to the practitioner.

Edoxaban: (Major) Coadministration of edoxaban and platelet inhibitors should be avoided due to an increased risk of bleeding during concurrent use. Occasionally, short-term coadministration may be necessary in patients transitioning to and from edoxaban. Long-term coadministration is not recommended. Promptly evaluate any signs or symptoms of blood loss in patients on concomitant therapy.

Elbasvir; Grazoprevir: (Moderate) Administering clopidogrel with elbasvir; grazoprevir may result in elevated clopidogrel plasma concentrations. Clopidogrel is a substrate of CYP3A; grazoprevir is a weak CYP3A inhibitor. If these drugs are used together, closely monitor for signs of adverse events.

Enoxaparin: (Moderate) Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other agents that affect hemostasis such as anticoagulants.

Enzalutamide: (Major) Avoid coadministration of clopidogrel with enzalutamide if possible due to increased enzalutamide exposure. If concomitant use is unavoidable, reduce the dose of enzalutamide to 80 mg once daily; the original dose of enzalutamide may be resumed when clopidogrel is discontinued. Enzalutamide is a CYP2C8 substrate and the acyl-beta-glucuronide metabolite of clopidogrel is a strong CYP2C8 inhibitor.

Coadministration with another strong CYP2C8 inhibitor increased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold.

Eptifibatide: (Moderate) Concomitant use of platelet glycoprotein IIb/IIIa inhibitors (i.e., abciximab, eptifibatide, or tirofiban) with an ADP receptor antagonist (i.e., clopidogrel, prasugrel, ticagrelor, or ticlopidine) may be associated with an increased risk of bleeding.

Escitalopram: (Moderate) The plasma concentration of escitalopram, a CYP2C19 substrate, may be increased when administered concurrently with clopidogrel, a CYP2C19 inhibitor. In addition, platelet aggregation may be impaired by selective serotonin reuptake inhibitors (SSRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication in patients receiving clopidogrel. Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SSRI concurrently with an antiplatelet medication and to promptly report any bleeding events to the practitioner.

Eslicarbazepine: (Major) Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP3A4 isoenzyme is involved in 1 of the steps, and the CYP2C19 isoenzyme is involved in both steps. Eslicarbazepine is an inhibitor of CYP2C19 and inducer of CYP3A4. CYP2C19 inhibitors may reduce plasma concentrations of the active metabolite of clopidogrel and reduce platelet inhibition activity. Administering clopidogrel with a CYP3A4 inducer may result in increased antiplatelet effects. Because eslicarbazepine inhibits CYP2C19 but also induces CYP3A4, the net effect of coadministration of clopidogrel and eslicarbazepine is unknown. Administer clopidogrel and eslicarbazepine together with caution. Monitor for altered efficacy of clopidogrel if coadministered with eslicarbazepine.

Esomeprazole: (Major) Avoid concomitant use of clopidogrel and esomeprazole as it significantly reduces the antiplatelet activity of clopidogrel when given concomitantly or 12 hours apart. The American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG) and American Heart Association (AHA) state that routine use of proton pump inhibitor (PPI) therapy is not recommended for patients at lower risk of gastrointestinal bleed but should be considered in those at high risk, such as those with a history of gastrointestinal bleed. Clinicians should carefully assess the risks and benefits of PPI use in patients on clopidogrel therapy and administration should be based on clinical need. If necessary, consider using a PPI medication with less pronounced effects on antiplatelet activity, such as rabeprazole, pantoprazole, lansoprazole, or dexlansoprazole. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. All PPIs are CYP2C19 substrates, and, to varying extents, are also inhibitors; thus, it is possible that any PPI may decrease the conversion of clopidogrel to its active metabolite, thereby reducing its effectiveness.

Esomeprazole; Naproxen: (Major) Avoid concomitant use of clopidogrel and esomeprazole as it significantly reduces the antiplatelet activity of clopidogrel when given concomitantly or 12 hours apart. The American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG) and American Heart Association (AHA) state that routine use of proton pump inhibitor (PPI) therapy is not recommended for patients at lower risk of gastrointestinal bleed but should be considered in those at high risk, such as those with a history of gastrointestinal bleed. Clinicians should carefully assess the risks and benefits of PPI use in patients on clopidogrel therapy and administration should be based on clinical need. If necessary, consider using a PPI medication with less pronounced effects on antiplatelet activity, such as rabeprazole, pantoprazole, lansoprazole, or dexlansoprazole. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. All PPIs are CYP219 substrates, and, to varying extents, are also inhibitors; thus, it is possible that any PPI may decrease the conversion of clopidogrel to its active metabolite, thereby reducing its effectiveness.

Estramustine: (Moderate) An additive risk of bleeding may occur when platelet inhibitors are used with agents that cause clinically significant thrombocytopenia including antineoplastic agents, such as estramustine.

Etravirine: (Major) Etravirine may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and etravirine together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. Etravirine is an inhibitor of CYP2C19.

Ezetimibe; Simvastatin: (Minor) Theoretically, clopidogrel may interact with simvastatin. CYP3A4 is involved in the hepatic biotransformation of clopidogrel to its active metabolite. Atorvastatin, a CYP3A4 substrate, has been reported to attenuate the antiplatelet activity of clopidogrel possibly by the competitive inhibition of CYP3A4 metabolism of clopidogrel to its active metabolite; however, conflicting data exists. The clinical significance of this theoretical interaction is not known. Simvastatin also is a CYP3A4 substrate and may theoretically be involved in the competitive inhibition of the CYP3A4 metabolism of clopidogrel. Patients should be monitored for a possible decrease in efficacy when clopidogrel is administered with simvastatin.

Felbamate: (Major) Felbamate may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and felbamate together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. Felbamate is a potent inhibitor of CYP2C19.

Fenofibric Acid: (Minor) At therapeutic concentrations, fenofibric acid is a weak inhibitor of CYP2C19. Concomitant use of fenofibric acid with CYP2C19 substrates, such as clopidogrel, has not been formally studied. Fenofibric acid may theoretically increase plasma concentrations of CYP2C19 substrates and could lead to toxicity for drugs that have a narrow therapeutic range. Monitor the therapeutic effect of clopidogrel during coadministration with fenofibric acid.

Fentanyl: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Fish Oil, Omega-3 Fatty Acids (Dietary Supplements): (Moderate) Because fish oil, omega-3 fatty acids inhibit platelet aggregation, caution is advised when fish oils are used concurrently with other platelet inhibitors. Theoretically, the risk of bleeding may be increased.

Fluconazole: (Major) Administer clopidogrel and systemic azole antifungals together with caution. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Systemic azole antifungals are inhibitors of CYP3A4 and some also inhibit CYP2C19 (e.g., fluconazole, ketoconazole, miconazole, voriconazole) and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a randomized crossover study, healthy subjects received a clopidogrel loading dose of 300 mg followed by 5 daily doses of 75 mg with or without the ketoconazole (400 mg/day). Ketoconazole decreased the active metabolite of clopidogrel by 48% after the 300 mg dose and 61% after the last maintenance dose was given. Ketoconazole also decreased the area under the concentration-time curve of clopidogrel's active metabolite by 22% after the loading dose and 29% after the last maintenance dose. If coadministration is unavoidable, the therapeutic effectiveness of clopidogrel should be closely monitored.

Fludarabine: (Moderate) Due to the thrombocytopenic effects of purine analogs, an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors.

Fluoxetine: (Major) Use clopidogrel and fluoxetine together with caution and monitor for reduced clopidogrel effectiveness. Consider alternative therapy to fluoxetine, if possible. Fluoxetine may reduce the antiplatelet activity of clopidogrel through potent inhibition of the CYP2C19 metabolism of clopidogrel to its active metabolite. In a large cohort study of clopidogrel and concomitant CYP2C19-inhibiting selective serotonin reuptake inhibitors (SSRIs) (n = 9,281) vs. non-inhibiting SSRIs (n = 44,278), patients receiving concurrent CYP2C19-inhibiting SSRIs, such as fluoxetine, had an increased risk of composite ischemic events. This risk was more pronounced in patients 65 years and older. Additionally, because SSRIs affect platelet activation, concomitant use with clopidogrel may increase the risk of bleeding. In this study, bleeding events did occur in both groups; however, there were no meaningful differences in bleeding events between groups. Monitor for signs and symptoms of bleeding.

Fluoxetine; Olanzapine: (Major) Use clopidogrel and fluoxetine together with caution and monitor for reduced clopidogrel effectiveness. Consider alternative therapy to fluoxetine, if possible. Fluoxetine may reduce the antiplatelet activity of clopidogrel through potent inhibition of the CYP2C19 metabolism of clopidogrel to its active metabolite. In a large cohort study of clopidogrel and concomitant CYP2C19-inhibiting selective serotonin reuptake inhibitors (SSRIs) (n = 9,281) vs. non-inhibiting SSRIs (n = 44,278), patients receiving concurrent CYP2C19-inhibiting SSRIs, such as fluoxetine, had an increased risk of composite ischemic events. This risk was more pronounced in patients 65 years and older. Additionally, because SSRIs affect platelet activation, concomitant use with clopidogrel may increase the risk of bleeding. In this study, bleeding events did occur in both groups; however, there were no meaningful differences in bleeding events between groups. Monitor for signs and symptoms of bleeding.

Fluvastatin: (Minor) The plasma concentration of fluvastatin may be increased with coadministration of clopidogrel. Fluvastatin is a substrate for CYP2C9. At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9.

Fluvoxamine: (Major) Use clopidogrel and fluvoxamine together with caution and monitor for reduced clopidogrel effectiveness. Consider alternative therapy to fluvoxamine, if possible. Fluvoxamine may reduce the antiplatelet activity of clopidogrel through potent inhibition of the CYP2C19 metabolism of clopidogrel to its active metabolite. In a large cohort study of clopidogrel and concomitant CYP2C19-inhibiting selective serotonin reuptake inhibitors (SSRIs) (n = 9,281) vs. non-inhibiting SSRIs (n = 44,278), patients receiving concurrent CYP2C19-inhibiting SSRIs, such as fluvoxamine, had an increased risk of composite ischemic events. This risk was more pronounced in patients 65 years and older. Additionally, because SSRIs affect platelet activation, concomitant use with clopidogrel may increase the risk of bleeding. In this study, bleeding events did occur in both groups; however, there were no meaningful differences in bleeding events between groups. Monitor for signs and symptoms of bleeding.

Folate analogs: (Moderate) Due to the thrombocytopenic effects of folate analogs, when used as antineoplastic agents, an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors.

Fondaparinux: (Moderate) Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other agents that affect hemostasis such as anticoagulants.

Garlic, Allium sativum: (Moderate) Use together with caution. Garlic produces clinically significant antiplatelet effects, and a risk for bleeding may occur if platelet inhibitors are given in combination with garlic.

Gefitinib: (Major) Gefitinib may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and gefitinib together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. Gefitinib is an inhibitor of CYP2C19. In addition, because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other drugs that affect hemostasis. Clopidogrel should be used cautiously in patients with thrombocytopenia following the administration of myelosuppressive antineoplastic agents or other drugs that cause significant thrombocytopenia due to the increased risk of bleeding. Monitor for reduced efficacy of clopidogrel and for increased bleeding.

Ginger, Zingiber officinale: (Moderate) Ginger inhibits thromboxane synthetase, a platelet aggregation inducer, and is a prostacyclin agonist so additive bleeding may occur if platelet inhibitors are given in combination with ginger, zingiber officinale.

Ginkgo, Ginkgo biloba: (Major) Use Ginkgo biloba with caution in patients taking platelet inhibitors, as it can produce clinically-significant

antiplatelet effects. A compound found in Ginkgo biloba, ginkgolide-B, may act as a selective antagonist of platelet activating factor (PAF). Although a review of Ginkgo biloba in 1992 stated that no known drug interactions exist, spontaneous hyphema has been reported in an elderly male who began taking Ginkgo while stabilized on daily aspirin. After ginkgo was stopped, no further bleeding was noted despite continuing the aspirin therapy. Other clinical data exist that describe spontaneous subdural hematomas associated with chronic Ginkgo biloba ingestion.

Glimepiride: (Moderate) Monitor serum glucose concentrations if glimepiride is coadministered with clopidogrel. Dosage adjustments may be necessary. Glimepiride is metabolized by CYP2C9; clopidogrel inhibits CYP2C9. Serum concentrations of glimepiride may be increased with coadministration of clopidogrel.

Glimepiride; Pioglitazone: (Major) Do not exceed 15 mg/day of pioglitazone if coadministered with clopidogrel. Coadministration may result in increased concentrations of pioglitazone. Pioglitazone is a CYP2C8 substrate and clopidogrel is a strong inhibitor of CYP2C8. When coadministered with gemfibrozil, another strong CYP2C8 inhibitor, the exposure to pioglitazone was increased by 226%. (Moderate) Monitor serum glucose concentrations if glimepiride is coadministered with clopidogrel. Dosage adjustments may be necessary. Glimepiride is metabolized by CYP2C9; clopidogrel inhibits CYP2C9. Serum concentrations of glimepiride may be increased with coadministration of clopidogrel.

Glimepiride; Rosiglitazone: (Moderate) Coadministration of clopidogrel and rosiglitazone may result in increased serum concentrations of rosiglitazone and therefore increased risk for hypoglycemia. The dose of rosiglitazone may require adjustment during concurrent use based on clinical response. Rosiglitazone is metabolized by CYP2C8 and clopidogrel is a strong CYP2C8 inhibitor. (Moderate) Monitor serum glucose concentrations if glimepiride is coadministered with clopidogrel. Dosage adjustments may be necessary. Glimepiride is metabolized by CYP2C9; clopidogrel inhibits CYP2C9. Serum concentrations of glimepiride may be increased with coadministration of clopidogrel.

Glipizide: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as glipizide. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when glipizide is coadministered with clopidogrel.

Glipizide; Metformin: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as glipizide. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when glipizide is coadministered with clopidogrel.

Glyburide: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as glyburide. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when glyburide is coadministered with clopidogrel.

Glyburide; Metformin: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as glyburide. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when glyburide is coadministered with clopidogrel.

Green Tea: (Moderate) Green tea has demonstrated antiplatelet and fibrinolytic actions in animals. It is possible that the use of green tea may increase the risk of bleeding if co administered with aspirin. Caution and careful monitoring of clinical and/or laboratory parameters are warranted with this combination.

Guaifenesin; Hydrocodone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Guaifenesin; Hydrocodone; Pseudoephedrine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Guarana: (Moderate) Guarana has been shown to possess minor antiplatelet activity and, therefore, concurrent use of guarana and anticoagulants or platelet inhibitors should be avoided.

Heparin: (Moderate) Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other agents that affect hemostasis such as anticoagulants. In healthy volunteers receiving heparin, clopidogrel does not alter the effect of heparin on coagulation parameters or require adjustment of the heparin dose. In addition, heparin has no effect on inhibition of platelet aggregation induced by clopidogrel. Nevertheless, the safety of this combination has not been established and concomitant administration of clopidogrel with heparin should be undertaken with caution.

Homatropine; Hydrocodone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Hydrochlorothiazide, HCTZ; Losartan: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as losartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when losartan is coadministered with clopidogrel.

Hydrochlorothiazide, HCTZ; Telmisartan: (Major) Telmisartan may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and telmisartan together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. Telmisartan is an inhibitor of CYP2C19.

Hydrochlorothiazide, HCTZ; Valsartan: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as valsartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when valsartan is coadministered with clopidogrel.

Hydrocodone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Hydrocodone; Ibuprofen: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Hydrocodone; Phenylephrine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Hydrocodone; Potassium Guaiacolsulfonate: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Hydrocodone; Potassium Guaiacolsulfonate; Pseudoephedrine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Hydrocodone; Pseudoephedrine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Hydromorphone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Ibritumomab Tiuxetan: (Moderate) Due to the thrombocytopenic effects of antineoplastics an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors.

Ibrutinib: (Moderate) The concomitant use of ibrutinib and antiplatelet agents such as clopidogrel may increase the risk of bleeding; monitor patients for signs of bleeding. Severe bleeding events have occurred with ibrutinib therapy including intracranial hemorrhage, GI bleeding, hematuria, and post procedural hemorrhage; some events were fatal. The mechanism for bleeding with ibrutinib therapy is not well understood.

Ibuprofen; Oxycodone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Icosapent ethyl: (Moderate) Icosapent ethyl is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA). Because omega-3 fatty acids inhibit platelet aggregation, caution is advised when icosapent ethyl is used concurrently with anticoagulants, platelet inhibitors, or thrombolytic agents. Theoretically, the risk of bleeding may be increased, but some studies that combined these agents did not produce clinically significant bleeding events. In one placebo-controlled, randomized, double-blinded, parallel study, patients receiving stable, chronic warfarin therapy were administered various doses of fish oil supplements to determine the effect on INR determinations. Patients were randomized to receive a 4-week treatment period of either placebo or 3 or 6 grams of fish oil daily. Patients were followed on a twice-weekly basis for INR determinations and adverse reactions. There was no statistically significant difference in INRs between the placebo or treatment period within each group. There was also no difference in INRs found between groups. One episode of ecchymosis was reported, but no major bleeding episodes occurred. The authors concluded that fish oil supplementation in doses of 36 grams per day does not have a statistically significant effect on the INR of patients receiving chronic warfarin therapy. However, an increase in INR from 2.8 to 4.3 in a patient stable on warfarin therapy has been reported when increasing the dose of fish oil, omega-3 fatty acids from 1 gram/day to 2 grams/day. The INR decreased once the patient decreased her dose of fish oil to 1 gram/day. This implies that a dose-related effect of fish oil on warfarin may be possible. Patients receiving warfarin that initiate concomitant icosapent ethyl therapy should have their INR monitored more closely and the dose of warfarin adjusted accordingly.

Idelalisib: (Moderate) Administer clopidogrel and idelalisib with caution. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in 1 of these steps. Idelalisib is a strong inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. Therefore, the therapeutic effectiveness of clopidogrel should be monitored when used concomitantly with idelalisib.

Ifosfamide: (Moderate) An additive risk of bleeding may occur when platelet inhibitors are used with agents that cause clinically significant thrombocytopenia including antineoplastic agents, such as ifosfamide.

Iloprost: (Moderate) When used concurrently with platelet inhibitors, inhaled iloprost may increase the risk of bleeding.

Imatinib: (Moderate) The therapeutic effectiveness of clopidogrel should be monitored when used concomitantly with imatinib. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Imatinib is an inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite.

Intravenous Lipid Emulsions: (Moderate) Because fish oil, omega-3 fatty acids inhibit platelet aggregation, caution is advised when fish oils are used concurrently with other platelet inhibitors. Theoretically, the risk of bleeding may be increased.

Isavuconazonium: (Moderate) Concomitant use of isavuconazonium with clopidogrel may result in increased serum concentrations of clopidogrel. Clopidogrel is a substrate of the hepatic isoenzyme CYP3A4; isavuconazole, the active moiety of isavuconazonium, is a moderate inhibitor of this enzyme. Caution and close monitoring are advised if these drugs are used together.

Isoniazid, INH: (Major) Isoniazid may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and isoniazid together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Isoniazid is an inhibitor of CYP2C19 and CYP3A4.

Isoniazid, INH; Pyrazinamide, PZA; Rifampin: (Major) Isoniazid may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and isoniazid together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Isoniazid is an inhibitor of CYP2C19 and CYP3A4.

Isoniazid, INH; Rifampin: (Major) Isoniazid may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and isoniazid together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Isoniazid is an inhibitor of CYP2C19 and CYP3A4.

Itraconazole: (Major) Administer clopidogrel and systemic azole antifungals together with caution. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Systemic azole antifungals are inhibitors of CYP3A4 and some also inhibit CYP2C19 (e.g., fluconazole, ketoconazole, miconazole, voriconazole) and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a randomized crossover study, healthy subjects received a clopidogrel loading dose of 300 mg followed by 5 daily doses of 75 mg with or without the ketoconazole (400 mg/day). Ketoconazole decreased the active metabolite of clopidogrel by 48% after the 300 mg dose and 61% after the last maintenance dose was given. Ketoconazole also decreased the area under the concentration-time curve of clopidogrel's active metabolite by 22% after the loading dose and 29% after the last maintenance dose. If coadministration is unavoidable, the therapeutic effectiveness of clopidogrel should be closely monitored.

Ivacaftor: (Minor) Use caution when administering ivacaftor and clopidogrel concurrently. Ivacaftor is an inhibitor of CYP3A and clopidogrel is partially metabolized by CYP3A. Co-administration may theoretically increase clopidogrel exposure leading to increased or prolonged therapeutic

effects and adverse events; however, the clinical impact of this has not yet been determined.

Ketoconazole: (Major) Administer clopidogrel and systemic azole antifungals together with caution. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Systemic azole antifungals are inhibitors of CYP3A4 and some also inhibit CYP2C19 (e.g., fluconazole, ketoconazole, miconazole, voriconazole) and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a randomized crossover study, healthy subjects received a clopidogrel loading dose of 300 mg followed by 5 daily doses of 75 mg with or without the ketoconazole (400 mg/day). Ketoconazole decreased the active metabolite of clopidogrel by 48% after the 300 mg dose and 61% after the last maintenance dose was given. Ketoconazole also decreased the area under the concentration-time curve of clopidogrel's active metabolite by 22% after the loading dose and 29% after the last maintenance dose. If coadministration is unavoidable, the therapeutic effectiveness of clopidogrel should be closely monitored.

Lepirudin: (Moderate) An additive risk of bleeding may be seen in patients receiving platelet inhibitors (e.g., clopidogrel, platelet glycoprotein IIb/IIIa inhibitors, ticlopidine, etc.) in combination with lepirudin.

Lesinurad: (Moderate) Use lesinurad and clopidogrel together with caution; clopidogrel may increase the systemic exposure of lesinurad.

Clopidogrel is a mild inhibitor of CYP2C9 at high concentrations, and lesinurad is a CYP2C9 substrate.

Lesinurad; Allopurinol: (Moderate) Use lesinurad and clopidogrel together with caution; clopidogrel may increase the systemic exposure of lesinurad. Clopidogrel is a mild inhibitor of CYP2C9 at high concentrations, and lesinurad is a CYP2C9 substrate.

Levomethadyl: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Levomilnacipran: (Moderate) Platelet aggregation may be impaired by serotonin norepinephrine reuptake inhibitors (SNRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving platelet inhibitors. Patients should be closely monitored for signs and symptoms of bleeding when a platelet inhibitor is administered with an SNRI.

Levorphanol: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Lomustine, CCNU: (Moderate) An additive risk of bleeding may occur when platelet inhibitors are used with agents that cause clinically significant thrombocytopenia including antineoplastic agents, such as lomustine.

Loperamide: (Moderate) The plasma concentration of loperamide, a CYP2C8 and CYP2B6 substrate, may be increased when administered concurrently with clopidogrel, a strong inhibitor of CYP2C8 and CYP2B6. If these drugs are used together, monitor for loperamide-associated adverse reactions, such as CNS effects and cardiac toxicities (i.e., syncope, ventricular tachycardia, QT prolongation, torsade de pointes, cardiac arrest).

Loperamide; Simethicone: (Moderate) The plasma concentration of loperamide, a CYP2C8 and CYP2B6 substrate, may be increased when administered concurrently with clopidogrel, a strong inhibitor of CYP2C8 and CYP2B6. If these drugs are used together, monitor for loperamide-associated adverse reactions, such as CNS effects and cardiac toxicities (i.e., syncope, ventricular tachycardia, QT prolongation, torsade de pointes, cardiac arrest).

Losartan: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as losartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when losartan is coadministered with clopidogrel.

Lovastatin: (Minor) Theoretically, clopidogrel may interact with lovastatin. CYP3A4 is involved in the hepatic biotransformation of clopidogrel to its active metabolite. Atorvastatin, a CYP3A4 substrate, has been reported to attenuate the antiplatelet activity of clopidogrel possibly by the competitive inhibition of CYP3A4 metabolism of clopidogrel to its active metabolite; however, conflicting data exists. The clinical significance of this theoretical interaction is not known. Lovastatin also is a CYP3A4 substrate and may theoretically be involved in the competitive inhibition of the CYP3A4 metabolism of clopidogrel. Patients should be monitored for a possible decrease in efficacy when clopidogrel is administered with lovastatin.

Lovastatin; Niacin: (Minor) Theoretically, clopidogrel may interact with lovastatin. CYP3A4 is involved in the hepatic biotransformation of clopidogrel to its active metabolite. Atorvastatin, a CYP3A4 substrate, has been reported to attenuate the antiplatelet activity of clopidogrel possibly by the competitive inhibition of CYP3A4 metabolism of clopidogrel to its active metabolite; however, conflicting data exists. The clinical significance of this theoretical interaction is not known. Lovastatin also is a CYP3A4 substrate and may theoretically be involved in the competitive inhibition of the CYP3A4 metabolism of clopidogrel. Patients should be monitored for a possible decrease in efficacy when clopidogrel is administered with lovastatin.

Luliconazole: (Minor) Theoretically, luliconazole may decrease the effects of clopidogrel, which is a CYP2C19 and CYP3A4 substrate and requires hepatic biotransformation to an active metabolite. Monitor patients for therapeutic effectiveness. In vitro, therapeutic doses of luliconazole inhibit the activity of CYP2C19 and CYP3A4 and small systemic concentrations may be noted with topical application, particularly when applied to patients with moderate to severe tinea cruris. No in vivo drug interaction trials were conducted prior to the approval of luliconazole.

Lumacaftor; Ivacaftor: (Moderate) Use clopidogrel and lumacaftor; ivacaftor together with caution. If used together, monitor patients closely for potential bleeding complications. Clopidogrel is a prodrug; inhibition of platelet aggregation is achieved through its active metabolite. Clopidogrel biotransformation is primarily mediated by CYP2C19, and in part, by CYP3A4 and CYP2B6. Lumacaftor is a strong CYP3A inducer. In vitro data also suggest that lumacaftor may induce CYP2B6 and CYP2C19. Induction of the isoenzymes responsible for clopidogrel metabolism may increase the exposure of its active metabolites, and increase antiplatelet effects. (Minor) Use caution when administering ivacaftor and clopidogrel concurrently. Ivacaftor is an inhibitor of CYP3A and clopidogrel is partially metabolized by CYP3A. Co-administration may theoretically increase clopidogrel exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.

Lumacaftor; Ivacaftor: (Moderate) Use clopidogrel and lumacaftor; ivacaftor together with caution. If used together, monitor patients closely for potential bleeding complications. Clopidogrel is a prodrug; inhibition of platelet aggregation is achieved through its active metabolite. Clopidogrel biotransformation is primarily mediated by CYP2C19, and in part, by CYP3A4 and CYP2B6. Lumacaftor is a strong CYP3A inducer. In vitro data also suggest that lumacaftor may induce CYP2B6 and CYP2C19. Induction of the isoenzymes responsible for clopidogrel metabolism may increase the exposure of its active metabolites, and increase antiplatelet effects.

Meperidine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Meperidine; Promethazine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Mercaptopurine, 6-MP: (Moderate) Due to the thrombocytopenic effects of purine analogs, an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors.

Metformin; Pioglitazone: (Major) Do not exceed 15 mg/day of pioglitazone if coadministered with clopidogrel. Coadministration may result in increased concentrations of pioglitazone. Pioglitazone is a CYP2C8 substrate and clopidogrel is a strong inhibitor of CYP2C8. When coadministered with gemfibrozil, another strong CYP2C8 inhibitor, the exposure to pioglitazone was increased by 226%.

Metformin; Repaglinide: (Major) Avoid concomitant use of clopidogrel and repaglinide. If coadministration cannot be avoided, initiate repaglinide at 0.5 mg PO before each meal, and do not exceed a total daily dose of 4 mg. Increased glucose monitoring may be required. Concomitant administration of clopidogrel and repaglinide increased the systemic exposure of repaglinide 5.1-fold after a clopidogrel 300 mg loading dose and 3.9-fold on day 3 of clopidogrel 75 mg/day. The acyl-beta-gluconuride metabolite of clopidogrel is a strong CYP2C8 inhibitor, and repaglinide is primarily metabolized by CYP2C8.

Metformin; Rosiglitazone: (Moderate) Coadministration of clopidogrel and rosiglitazone may result in increased serum concentrations of rosiglitazone and therefore increased risk for hypoglycemia. The dose of rosiglitazone may require adjustment during concurrent use based on clinical response. Rosiglitazone is metabolized by CYP2C8 and clopidogrel is a strong CYP2C8 inhibitor.

Methadone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration. Additionally, clopidogrel may theoretically increase methadone plasma concentrations; clopidogrel inhibits CYP2C9 at high concentrations in vitro.

Methoxsalen: (Minor) Agents that affect platelet function, such as platelet inhibitors, could decrease the efficacy of methoxsalen when used during photodynamic therapy.

Methylsulfonylmethane, MSM: (Moderate) Increased effects from concomitant anticoagulant drugs including increased bruising or blood in the stool have been reported in patients taking methylsulfonylmethane, MSM. Although these effects have not been confirmed in published medical literature or during clinical studies, clinicians should consider using methylsulfonylmethane, MSM with caution in patients who are taking anticoagulants or antiplatelets including clopidogrel until data confirming the safety of these drug combinations are available. During one of the available, published clinical trials in patients with osteoarthritis, those patients with bleeding disorders or using anticoagulants or antiplatelets were excluded from enrollment. Patients who choose to consume methylsulfonylmethane, MSM while receiving clopidogrel should be observed for increased bleeding.

Milnacipran: (Moderate) Platelet aggregation may be impaired by serotonin norepinephrine reuptake inhibitors (SNRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving platelet inhibitors (e.g., clobazam, clopidogrel, dipyridamole, ticlopidine, platelet glycoprotein IIb/IIIa inhibitors). Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SNRI with a platelet inhibitor and to promptly report any bleeding events to the practitioner.

Mitotane: (Moderate) Use caution if mitotane and clopidogrel are used concomitantly. Mitotane is a strong CYP3A4 inducer; clopidogrel is partially metabolized by CYP3A4 to an active metabolite, although CYP2C19 plays the major role. Coadministration may increase biotransformation to the active compound, resulting in increased risk for bleeding.

Modafinil: (Major) Modafinil may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and modafinil together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. Modafinil is an inhibitor of CYP2C19.

Montelukast: (Moderate) Concentrations of montelukast may be increased with concomitant use of clopidogrel. Monitor for increased side effects of montelukast if coadministered with clopidogrel. Clopidogrel is a strong 2C8 inhibitor. At clinically relevant concentrations, the cytochrome P450 enzyme CYP2C8 appears to play a major role in the metabolism of montelukast. At high concentrations in vitro, clopidogrel also inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as montelukast. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when montelukast is coadministered with clopidogrel.

Morphine: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Morphine; Naltrexone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Mycophenolate: (Moderate) Platelet Inhibitors inhibit platelet aggregation and should be used cautiously in patients with thrombocytopenia, as mycophenolate can also cause thrombocytopenia.

Nateglinide: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as nateglinide. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when nateglinide is coadministered with clopidogrel.

Nebivolol; Valsartan: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as valsartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when valsartan is coadministered with clopidogrel.

Nelarabine: (Moderate) Due to the thrombocytopenic effects of nelarabine, an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors.

Niacin; Simvastatin: (Minor) Theoretically, clopidogrel may interact with simvastatin. CYP3A4 is involved in the hepatic biotransformation of clopidogrel to its active metabolite. Atorvastatin, a CYP3A4 substrate, has been reported to attenuate the antiplatelet activity of clopidogrel possibly by the competitive inhibition of CYP3A4 metabolism of clopidogrel to its active metabolite; however, conflicting data exists. The clinical significance of this theoretical interaction is not known. Simvastatin also is a CYP3A4 substrate and may theoretically be involved in the competitive inhibition of the CYP3A4 metabolism of clopidogrel. Patients should be monitored for a possible decrease in efficacy when clopidogrel is administered with simvastatin.

Nicardipine: (Major) Nicardipine may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and nicardipine together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Nicardipine is an inhibitor of CYP2C19 and CYP3A4.

Nilotinib: (Major) Concomitant use of nilotinib, a moderate CYP3A4 inhibitor and a CYP2B6 inducer, and clopidogrel, a CYP3A4 and CYP2B6 substrate, may result altered clopidogrel levels. Monitor patients closely for clopidogrel toxicity and efficacy if these drugs are used together; a clopidogrel dose reduction may be necessary.

Nonsteroidal antiinflammatory drugs: (Moderate) NSAIDs can cause GI bleeding, inhibit platelet aggregation, and prolong bleeding time. If NSAIDs are administered with platelet inhibitors, these pharmacodynamic effects may be increased. The manufacturer of clopidogrel advises that caution be used when used in combination with NSAIDs as an increase in occult GI blood loss occurred when clopidogrel was used concomitantly with naproxen.

Obinutuzumab: (Moderate) Fatal hemorrhagic events have been reported in patients treated with obinutuzumab; all events occurred during cycle 1. Monitor all patients for thrombocytopenia and bleeding, and consider withholding concomitant medications which may increase bleeding risk (i.e., anticoagulants, platelet inhibitors), especially during the first cycle.

Omeprazole: (Major) Avoid concomitant use of clopidogrel and omeprazole as it significantly reduces the antiplatelet activity of clopidogrel when given concomitantly or 12 hours apart. The American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG) and American Heart Association (AHA) state that routine use of proton pump inhibitor (PPI) therapy is not recommended for patients at lower risk of gastrointestinal bleed but should be considered in those at high risk, such as those with a history of gastrointestinal bleed. Clinicians should carefully assess the risks and benefits of PPI use in patients on clopidogrel therapy and administration should be based on clinical need. If necessary, consider using a PPI medication with less pronounced effects on antiplatelet activity, such as rabeprazole, pantoprazole, lansoprazole, or dexlansoprazole. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. All PPIs are CYP219 substrates, and, to varying extents, are also inhibitors; thus, it is possible that any PPI may decrease the conversion of clopidogrel to its active metabolite, thereby reducing its effectiveness.

Omeprazole; Sodium Bicarbonate: (Major) Avoid concomitant use of clopidogrel and omeprazole as it significantly reduces the antiplatelet activity of clopidogrel when given concomitantly or 12 hours apart. The American College of Cardiology Foundation (ACCF), American College of Gastroenterology (ACG) and American Heart Association (AHA) state that routine use of proton pump inhibitor (PPI) therapy is not recommended for patients at lower risk of gastrointestinal bleed but should be considered in those at high risk, such as those with a history of gastrointestinal bleed. Clinicians should carefully assess the risks and benefits of PPI use in patients on clopidogrel therapy and administration should be based on clinical need. If necessary, consider using a PPI medication with less pronounced effects on antiplatelet activity, such as rabeprazole, pantoprazole, lansoprazole, or dexlansoprazole. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. All PPIs are CYP219 substrates, and, to varying extents, are also inhibitors; thus, it is possible that any PPI may decrease the conversion of clopidogrel to its active metabolite, thereby reducing its effectiveness.

Oritavancin: (Minor) Coadministration of oritavancin and clopidogrel may result in increases or decreases in clopidogrel exposure and may increase side effects or decrease efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation to an active metabolite; this activation is mediated primarily by CYP2C19 and, in part, by CYP3A and other isoenzymes. Oritavancin weakly induces CYP3A4, while weakly inhibiting CYP2C19. If these drugs are administered concurrently, monitor the patient for signs of toxicity or lack of efficacy.

Oxcarbazepine: (Major) Oxcarbazepine may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use oxcarbazepine and clopidogrel together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. Oxcarbazepine is an inhibitor of CYP2C19.

Oxycodone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Oxymorphone: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Paroxetine: (Moderate) Platelet aggregation may be impaired by selective serotonin reuptake inhibitors (SSRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication in patients receiving clopidogrel. Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SSRI concurrently with an antiplatelet medication and to promptly report any bleeding events to the practitioner.

Pazopanib: (Moderate) Pazopanib is a weak inhibitor of CYP3A4. Coadministration of pazopanib and clopidogrel, a CYP3A4 substrate, may cause an increase in systemic concentrations of clopidogrel. Use caution when administering these drugs concomitantly.

Pegaspargase: (Moderate) Due to the risk of bleeding and coagulopathy during pegaspargase therapy, patients should receive other agents that may increase the risk of bleeding (e.g., anticoagulants, NSAIDs, platelet inhibitors, or thrombolytic agents) with caution.

Pentosan: (Moderate) Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other agents that affect hemostasis such as anticoagulants.

Pentostatin: (Moderate) Due to the thrombocytopenic effects of purine analogs, an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors.

Pentoxifylline: (Moderate) A potential additive risk for bleeding exists if platelet inhibitors are given in combination with other agents that affect hemostasis such as pentoxifylline.

Perindopril; Amlodipine: (Moderate) Administer clopidogrel and amlodipine together with caution and monitor for reduced therapeutic response to clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps. Amlodipine is a weak inhibitor of CYP3A4 and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a study of 200 patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI), coadministration with a calcium-channel blocker (CCB) was associated with a reduced response to clopidogrel. Concomitant use of a CCB was also associated with a worse clinical outcome with the primary end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, stent thrombosis, and revascularization (PCI or CABG surgery), occurring more frequently in patients receiving a concomitant CCB. Amlodipine represented the largest subgroup of CCBs in the study, therefore it is unknown if these results can be applied to all CCBs. Another study compared concomitant use of amlodipine, a non-P-glycoprotein (P-gp) inhibiting CCB, with concomitant use of a P-gp inhibiting CCB (e.g., verapamil, nifedipine, diltiazem) on the effect of clopidogrel. Only amlodipine was associated with a poor response to clopidogrel suggesting the interaction between amlodipine and clopidogrel may be more clinically relevant compared to P-gp inhibiting CCBs. The authors theorized that by inhibiting P-gp, the intestinal efflux of clopidogrel may be decreased, thereby increasing clopidogrel plasma concentrations and counteracting the effect of CCB-induced CYP3A4 inhibition.

Phentermine; Topiramate: (Major) Topiramate may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and topiramate together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. Topiramate is an inhibitor of CYP2C19.

Phenytoin: (Moderate) Monitor phenytoin concentrations more closely when initiating clopidogrel therapy. Phenytoin is metabolized by cytochrome CYP2C9; clopidogrel at high concentrations inhibits CYP2C9. Coadministration could increase plasma concentrations of phenytoin and cause symptoms of toxicity.

Photosensitizing agents: (Minor) Agents, such as platelet inhibitors, that decrease clotting could decrease the efficacy of photosensitizing agents used in photodynamic therapy.

Pioglitazone: (Major) Do not exceed 15 mg/day of pioglitazone if coadministered with clopidogrel. Coadministration may result in increased concentrations of pioglitazone. Pioglitazone is a CYP2C8 substrate and clopidogrel is a strong inhibitor of CYP2C8. When coadministered with gemfibrozil, another strong CYP2C8 inhibitor, the exposure to pioglitazone was increased by 226%.

Pitavastatin: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as pitavastatin. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when pitavastatin is coadministered with clopidogrel.

Platelet Glycoprotein IIb/IIIa Inhibitors: (Moderate) Concomitant use of platelet glycoprotein IIb/IIIa inhibitors (i.e., abciximab, eptifibatide, or tirofiban) with an ADP receptor antagonist (i.e., clopidogrel, prasugrel, ticagrelor, or ticlopidine) may be associated with an increased risk of

bleeding.

Porfimer: (Minor) Agents, such as platelet inhibitors, that decrease clotting could decrease the efficacy of photosensitizing agents used in photodynamic therapy.

Posaconazole: (Major) Administer clopidogrel and systemic azole antifungals together with caution. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Systemic azole antifungals are inhibitors of CYP3A4 and some also inhibit CYP2C19 (e.g., fluconazole, ketoconazole, micronazole, voriconazole) and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a randomized crossover study, healthy subjects received a clopidogrel loading dose of 300 mg followed by 5 daily doses of 75 mg with or without the ketoconazole (400 mg/day). Ketoconazole decreased the active metabolite of clopidogrel by 48% after the 300 mg dose and 61% after the last maintenance dose was given. Ketoconazole also decreased the area under the concentration-time curve of clopidogrel's active metabolite by 22% after the loading dose and 29% after the last maintenance dose. If coadministration is unavoidable, the therapeutic effectiveness of clopidogrel should be closely monitored.

Prasterone, Dehydroepiandrosterone, DHEA (Dietary Supplements): (Moderate) Prasterone is contraindicated for use in patients with active deep vein thrombosis, pulmonary embolism or history of these conditions. Prasterone is also contraindicated in patients with active arterial thromboembolic disease (for example, stroke and myocardial infarction), or a history of these conditions. Thus, patients receiving anticoagulation due to a history of these conditions are not candidates for prasterone treatment. DHEA is converted to androgens and estrogens within the human body and thus may affect hemostasis via androgenic or estrogenic effects. Estrogens increase the production of clotting factors VII, VIII, IX, and X. Androgens, such as testosterone, increase the synthesis of several anticoagulant and fibrinolytic proteins. Because of the potential effects on coagulation, patients receiving prasterone or DHEA concurrently with preventative anticoagulants (e.g., warfarin or heparin) or other platelet inhibitors, including aspirin, ASA should be monitored for side effects or the need for dosage adjustments.

Prasterone, Dehydroepiandrosterone, DHEA (FDA-approved): (Moderate) Prasterone is contraindicated for use in patients with active deep vein thrombosis, pulmonary embolism or history of these conditions. Prasterone is also contraindicated in patients with active arterial thromboembolic disease (for example, stroke and myocardial infarction), or a history of these conditions. Thus, patients receiving anticoagulation due to a history of these conditions are not candidates for prasterone treatment. DHEA is converted to androgens and estrogens within the human body and thus may affect hemostasis via androgenic or estrogenic effects. Estrogens increase the production of clotting factors VII, VIII, IX, and X. Androgens, such as testosterone, increase the synthesis of several anticoagulant and fibrinolytic proteins. Because of the potential effects on coagulation, patients receiving prasterone or DHEA concurrently with preventative anticoagulants (e.g., warfarin or heparin) or other platelet inhibitors, including aspirin, ASA should be monitored for side effects or the need for dosage adjustments.

Prasugrel: (Moderate) Because clopidogrel and prasugrel inhibit platelet aggregation, a potential additive risk for bleeding exists if the drugs are given in combination. Patients should be instructed to monitor for signs and symptoms of bleeding and to promptly report any bleeding events.

Propoxyphene: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Purine analogs: (Moderate) Due to the thrombocytopenic effects of purine analogs, an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors.

Quinine: (Major) Quinine may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and quinine together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Quinine is an inhibitor of CYP3A4 and in vitro studies suggest it is an inhibitor of CYP2C19. Furthermore, at high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as quinine. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when quinine is coadministered with clopidogrel.

Ramelteon: (Moderate) Coadministration of ramelteon with inhibitors of CYP2C9, such as clopidogrel, may lead to increases in the serum concentrations of ramelteon.

Regorafenib: (Major) Regorafenib may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and regorafenib together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. In vitro studies indicate regorafenib is an inhibitor of CYP2C19 and CYP3A4.

Remifentanyl: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Repaglinide: (Major) Avoid concomitant use of clopidogrel and repaglinide. If coadministration cannot be avoided, initiate repaglinide at 0.5 mg PO before each meal, and do not exceed a total daily dose of 4 mg. Increased glucose monitoring may be required. Concomitant administration of clopidogrel and repaglinide increased the systemic exposure of repaglinide 5.1-fold after a clopidogrel 300 mg loading dose and 3.9-fold on day 3 of clopidogrel 75 mg/day. The acyl-beta-gluconuride metabolite of clopidogrel is a strong CYP2C8 inhibitor, and repaglinide is primarily metabolized by CYP2C8.

Rivaroxaban: (Major) Avoid concurrent administration of platelet inhibitors such as clopidogrel with rivaroxaban unless the benefit outweighs the risk of increased bleeding. An increase in bleeding time to 45 minutes was observed in 2 drug interaction studies where clopidogrel (300 mg loading dose followed by 75 mg daily maintenance dose) and rivaroxaban (15 mg single dose) were coadministered in healthy subjects. In the first study, the increase in bleeding time to 45 minutes was observed in approximately 45% of patients. Approximately 30% of patients in the second study had the event. The change in bleeding time was approximately twice the maximum increase seen with either drug alone. No change in the pharmacokinetic parameters of either drug were noted.

Rosiglitazone: (Moderate) Coadministration of clopidogrel and rosiglitazone may result in increased serum concentrations of rosiglitazone and therefore increased risk for hypoglycemia. The dose of rosiglitazone may require adjustment during concurrent use based on clinical response. Rosiglitazone is metabolized by CYP2C8 and clopidogrel is a strong CYP2C8 inhibitor.

Rosuvastatin: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as rosuvastatin. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when rosuvastatin is coadministered with clopidogrel.

Rucaparib: (Moderate) Monitor for decreased efficacy of clopidogrel if coadministration with rucaparib is necessary. Clopidogrel is a prodrug that is metabolized to its active metabolite by CYP2C19. Rucaparib is a weak CYP2C19 inhibitor. Concomitant use may reduce concentrations of the active metabolite, therefore decreasing the antiplatelet activity of clopidogrel.

Sacubitril; Valsartan: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as valsartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when valsartan is coadministered with clopidogrel.

Selegiline: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as selegiline. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when selegiline is coadministered with clopidogrel.

Selexipag: (Severe) Coadministration of selexipag and clopidogrel is contraindicated due to significantly increased exposure to selexipag and its active metabolite, which may cause side effects. Selexipag is a CYP2C8 substrate, and clopidogrel is a strong CYP2C8 inhibitor.

Sertraline: (Moderate) Platelet aggregation may be impaired by selective serotonin reuptake inhibitors (SSRIs) due to platelet serotonin depletion,

possibly increasing the risk of a bleeding complication in patients receiving clopidogrel. Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SSRI concurrently with an antiplatelet medication and to promptly report any bleeding events to the practitioner.

Sildenafil: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as sildenafil. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when sildenafil is coadministered with clopidogrel.

Simeprevir: (Minor) Simeprevir, a mild CYP1A2 inhibitor and a mild intestinal CYP3A4 inhibitor, may decrease the effects of clopidogrel, which is a partially metabolized by CYP3A4 and CYP1A2 to its active metabolite. Monitor patients for therapeutic effectiveness.

Simvastatin: (Minor) Theoretically, clopidogrel may interact with simvastatin. CYP3A4 is involved in the hepatic biotransformation of clopidogrel to its active metabolite. Atorvastatin, a CYP3A4 substrate, has been reported to attenuate the antiplatelet activity of clopidogrel possibly by the competitive inhibition of CYP3A4 metabolism of clopidogrel to its active metabolite; however, conflicting data exists. The clinical significance of this theoretical interaction is not known. Simvastatin also is a CYP3A4 substrate and may theoretically be involved in the competitive inhibition of the CYP3A4 metabolism of clopidogrel. Patients should be monitored for a possible decrease in efficacy when clopidogrel is administered with simvastatin.

Simvastatin; Sitagliptin: (Minor) Theoretically, clopidogrel may interact with simvastatin. CYP3A4 is involved in the hepatic biotransformation of clopidogrel to its active metabolite. Atorvastatin, a CYP3A4 substrate, has been reported to attenuate the antiplatelet activity of clopidogrel possibly by the competitive inhibition of CYP3A4 metabolism of clopidogrel to its active metabolite; however, conflicting data exists. The clinical significance of this theoretical interaction is not known. Simvastatin also is a CYP3A4 substrate and may theoretically be involved in the competitive inhibition of the CYP3A4 metabolism of clopidogrel. Patients should be monitored for a possible decrease in efficacy when clopidogrel is administered with simvastatin.

Sodium Hyaluronate, Hyaluronic Acid: (Moderate) Increased bruising or bleeding at the injection site may occur when using hyaluronate sodium with platelet inhibitors especially if used within the 3 weeks prior to the procedure.

Sufentanil: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Sulfamethoxazole; Trimethoprim, SMX-TMP, Cotrimoxazole: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as sulfamethoxazole. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when sulfamethoxazole is coadministered with clopidogrel.

Sulfinpyrazone: (Major) Sulfinpyrazone, when used as a uricosuric agent should be avoided when possible with concurrent platelet inhibitors due to potential for additive antiplatelet effects and increased bleeding risk.

Tamoxifen: (Moderate) Clopidogrel may decrease the concentrations of the active metabolites of tamoxifen, which can compromise efficacy. At high concentrations, clopidogrel is a CYP2C9 inhibitor. Tamoxifen is metabolized by CYP3A4 and CYP2D6, and to a lesser extent by CYP2C9, to other potent, active metabolites including endoxifen, which have up to 33 times more affinity for the estrogen receptor than tamoxifen. These metabolites are then inactivated by sulfotransferase 1A1 (SULT1A1).

Telithromycin: (Minor) Concentrations of clopidogrel may be increased with concomitant use of telithromycin. Clopidogrel is a CYP3A4 substrate and telithromycin is a strong CYP3A4 inhibitor. Patients should be monitored for increased side effects.

Telmisartan: (Major) Telmisartan may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and telmisartan together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. Telmisartan is an inhibitor of CYP2C19.

Telotristat Ethyl: (Moderate) Use caution if coadministration of telotristat ethyl and clopidogrel is necessary, as the systemic exposure of clopidogrel may be decreased resulting in reduced efficacy. If these drugs are used together, monitor patients for suboptimal efficacy of clopidogrel; consider increasing the dose of clopidogrel if necessary. The active metabolite of clopidogrel is formed mostly by CYP2C19, with contributions from several other CYP enzymes including CYP3A. The mean Cmax and AUC of another sensitive CYP3A4 substrate was decreased by 25% and 48%, respectively, when coadministered with telotristat ethyl; the mechanism of this interaction appears to be that telotristat ethyl increases the glucuronidation of the CYP3A4 substrate.

Terbinafine: (Moderate) Due to the risk for terbinafine related adverse effects, caution is advised when coadministering clopidogrel. Although this interaction has not been studied by the manufacturer, and published literature suggests the potential for interactions to be low, taking these drugs together may increase the systemic exposure of terbinafine. Predictions about the interaction can be made based on the metabolic pathways of both drugs. Terbinafine is metabolized by at least 7 CYP isoenzymes, with major contributions coming from CYP2C8, CYP2C19, and CYP2C9; clopidogrel is a strong inhibitor of CYP2C8, an inhibitor of CYP2C19, and at high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Monitor patients for adverse reactions if these drugs are coadministered.

Tezacaftor; Ivacaftor: (Minor) Use caution when administering ivacaftor and clopidogrel concurrently. Ivacaftor is an inhibitor of CYP3A and clopidogrel is partially metabolized by CYP3A. Co-administration may theoretically increase clopidogrel exposure leading to increased or prolonged therapeutic effects and adverse events; however, the clinical impact of this has not yet been determined.

Thioguanine, 6-TG: (Moderate) Due to the thrombocytopenic effects of purine analogs, an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors.

Thrombolytic Agents: (Major) Concomitant administration of platelet inhibitors and thrombolytic agents could theoretically result in an increased risk of bleeding due to additive pharmacodynamic effects, and combinations of these agents should be approached with caution.

Ticagrelor: (Moderate) Because clopidogrel and ticagrelor inhibit platelet aggregation, a potential additive risk for bleeding exists if the drugs are given in combination. Patients should be instructed to monitor for signs and symptoms of bleeding and to promptly report any bleeding events.

Ticlopidine: (Moderate) Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other drugs that affect hemostasis such as platelet inhibitors. Also, coadministration of clopidogrel and ticlopidine should be avoided. Ticlopidine and clopidogrel inhibit platelets via the same mechanism; combination therapy would therefore be duplicative and not recommended. Furthermore, ticlopidine is a CYP2C19 inhibitor, and clopidogrel requires hepatic biotransformation via CYP2C19 to its active metabolite. When clopidogrel is coadministered with other potent CYP2C19 inhibitors, the plasma concentration and platelet inhibition activity of clopidogrel are reduced. Coadministration of clopidogrel and ticlopidine would be expected to have a similar effect and should be avoided.

Tioconazole: (Major) Administer clopidogrel and systemic azole antifungals together with caution. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Systemic azole antifungals are inhibitors of CYP3A4 and some also inhibit CYP2C19 (e.g., fluconazole, ketoconazole, miconazole, voriconazole) and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a randomized crossover study, healthy subjects received a clopidogrel loading dose of 300 mg followed by 5 daily doses of 75 mg with or without the ketoconazole (400 mg/day). Ketoconazole decreased the active metabolite of clopidogrel by 48% after the 300 mg dose and 61% after the last maintenance dose was given. Ketoconazole also decreased the area under the concentration-time curve of clopidogrel's active metabolite by 22% after the loading dose and 29% after the last maintenance dose. If coadministration is unavoidable, the therapeutic effectiveness of clopidogrel should be closely monitored.

Tirofiban: (Moderate) Concomitant use of platelet glycoprotein IIb/IIIa inhibitors (i.e., abciximab, eptifibatide, or tirofiban) with an ADP receptor antagonist (i.e., clopidogrel, prasugrel, ticagrelor, or ticlopidine) may be associated with an increased risk of bleeding.

Tolbutamide: (Minor) At high concentrations, clopidogrel is an inhibitor of CYP2C9. Because tolbutamide is metabolized by CYP2C9, clopidogrel may interfere with its metabolism. However, this interaction has not been reported clinically.

Topiramate: (Major) Topiramate may reduce the antiplatelet activity of clopidogrel by inhibiting clopidogrel's metabolism to its active metabolite. Use clopidogrel and topiramate together with caution and monitor for reduced efficacy of clopidogrel. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps; the CYP2C19 isoenzyme is involved in both steps. Topiramate is an inhibitor of CYP2C19.

Torsemide: (Minor) At high concentrations in vitro, clopidogrel inhibits the activity of cytochrome P450 2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as torsemide.

Tramadol: (Moderate) Coadministration of opioid agonists delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the C_{max} and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration.

Trazodone: (Moderate) Platelet aggregation may be impaired by trazodone due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving platelet inhibitors (e.g., cilostazol, clopidogrel, dipyridamole, ticlopidine, platelet glycoprotein IIb/IIIa inhibitors). Patients should be instructed to monitor for signs and symptoms of bleeding while taking trazodone concurrently with an antiplatelet medication and to promptly report any bleeding events to the practitioner.

Treprostinil: (Moderate) Reduce the starting dose of oral treprostinil to 0.125 mg twice daily when coadministered with clopidogrel; dose adjustments should be made in 0.125 mg twice daily increments every 3 to 4 days. Human pharmacokinetic studies of oral treprostinil indicate that coadministration of another potent CYP2C8 enzyme inhibitor results in a 2-fold increase in exposure to treprostinil, a CYP2C8 substrate. The clinical significance of this interaction with orally inhaled or parenteral treprostinil or with other CYP2C8 inhibitors is unknown; treprostinil dose adjustments may be necessary. Additionally, monitor patients for signs and symptoms of bleeding if treprostinil is administered with clopidogrel. Treprostinil inhibits platelet aggregation; clopidogrel is a platelet inhibitor. Coadministration increases the risk of bleeding.

Tretinoin, ATRA: (Moderate) An additive risk of bleeding may occur when platelet inhibitors are used with agents that cause clinically significant thrombocytopenia including antineoplastic agents, such as tretinoin.

Valsartan: (Moderate) At high concentrations in vitro, clopidogrel inhibits the activity of CYP2C9. Thus, clopidogrel could increase plasma concentrations of drugs metabolized by this isoenzyme, such as valsartan. Although there are no in vivo data with which to predict the magnitude or clinical significance of this potential interaction, caution should be used when valsartan is coadministered with clopidogrel.

Venlafaxine: (Moderate) Platelet aggregation may be impaired by serotonin norepinephrine reuptake inhibitors (SNRIs) due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving platelet inhibitors (e.g., cilostazol, clopidogrel, dipyridamole, ticlopidine, platelet glycoprotein IIb/IIIa inhibitors). Patients should be instructed to monitor for signs and symptoms of bleeding while taking an SNRI with a platelet inhibitor and to promptly report any bleeding events to the practitioner.

Verteporfin: (Minor) Agents, such as platelet inhibitors, that decrease clotting could decrease the efficacy of photosensitizing agents used in photodynamic therapy.

Vilazodone: (Moderate) Patients should be instructed to monitor for signs and symptoms of bleeding while taking vilazodone concurrently with salicylates or other platelet inhibitors and to promptly report any bleeding events to the practitioner. Platelet aggregation may be impaired by vilazodone due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving platelet inhibitors (e.g., aspirin, cilostazol, clopidogrel, dipyridamole, ticlopidine, platelet glycoprotein IIb/IIIa inhibitors).

Vorapaxar: (Moderate) Because vorapaxar inhibits platelet aggregation, a potential additive risk for bleeding exists if vorapaxar is given in combination with other agents that affect hemostasis such as ADP receptor antagonists including clopidogrel, prasugrel, ticagrelor, or ticlopidine.

Voriconazole: (Major) Administer clopidogrel and systemic azole antifungals together with caution. Clopidogrel requires hepatic biotransformation via 2 cytochrome dependent oxidative steps. The CYP3A4 isoenzyme is involved in one of the metabolic steps, and the CYP2C19 isoenzyme is involved in both steps. Systemic azole antifungals are inhibitors of CYP3A4 and some also inhibit CYP2C19 (e.g., fluconazole, ketoconazole, miconazole, voriconazole) and may decrease the hepatic metabolism of clopidogrel to its active metabolite. In a randomized crossover study, healthy subjects received a clopidogrel loading dose of 300 mg followed by 5 daily doses of 75 mg with or without the ketoconazole (400 mg/day). Ketoconazole decreased the active metabolite of clopidogrel by 48% after the 300 mg dose and 61% after the last maintenance dose was given. Ketoconazole also decreased the area under the concentration-time curve of clopidogrel's active metabolite by 22% after the loading dose and 29% after the last maintenance dose. If coadministration is unavoidable, the therapeutic effectiveness of clopidogrel should be closely monitored.

Vorinostat: (Major) Due to the thrombocytopenic effects of vorinostat, an additive risk of bleeding may be seen in patients receiving concomitant platelet inhibitors. Also, torsades de pointes (TdP) and ventricular tachycardia have been reported with anagrelide. In addition, dose-related increases in mean QTc and heart rate were observed in healthy subjects. A cardiovascular examination, including an ECG, should be obtained in all patients prior to initiating anagrelide therapy. Monitor patients during anagrelide therapy for cardiovascular effects and evaluate as necessary. Drugs with a possible risk for QT prolongation and TdP that should be used cautiously with anagrelide include vorinostat.

Vortioxetine: (Moderate) Platelet aggregation may be impaired by vortioxetine due to platelet serotonin depletion, possibly increasing the risk of a bleeding complication (e.g., gastrointestinal bleeding, ecchymoses, epistaxis, hematomas, petechiae, hemorrhage) in patients receiving platelet inhibitors (e.g., cilostazol, clopidogrel, dipyridamole, ticlopidine, platelet glycoprotein IIb/IIIa inhibitors). Bleeding events related to drugs that inhibit serotonin reuptake have ranged from ecchymosis to life-threatening hemorrhages. Patients should be instructed to monitor for signs and symptoms of bleeding while taking vortioxetine concurrently with an antiplatelet medication and to promptly report any bleeding events to the practitioner.

Warfarin: (Moderate) Because clopidogrel inhibits platelet aggregation, a potential additive risk for bleeding exists if clopidogrel is given in combination with other agents that affect hemostasis such as anticoagulants. At high concentrations in vitro, clopidogrel inhibits CYP2C9, and warfarin is a CYP2C9 substrate. Thus, clopidogrel could increase warfarin plasma concentrations. Although the administration of clopidogrel 75 mg per day did not alter the pharmacokinetics of S-warfarin or the INR in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis. Although there are no in vivo data with which to predict the magnitude or clinical significance of these potential interactions, caution should be used when warfarin is coadministered with clopidogrel.

Zafirlukast: (Minor) Clopidogrel is metabolized by CYP3A4 isozymes to an active metabolite. As a result, drugs that inhibit CYP3A4, such as zafirlukast, theoretically may decrease the hepatic metabolism of clopidogrel to its active metabolite.

PREGNANCY AND LACTATION

Pregnancy

Clopidogrel is classified as FDA pregnancy risk category B. Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m² basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, clopidogrel should be used during pregnancy only if clearly needed.

According to the manufacturer, it is unknown if clopidogrel is excreted into human breast milk. Clopidogrel and/or its metabolites are excreted into the milk of lactating rats. Because of the potential for serious adverse reactions in breast-feeding infants from clopidogrel, a decision should be made to discontinue nursing or discontinue clopidogrel, taking into account the importance of the drug to the mother. If a breast-feeding infant experiences an adverse effect related to a maternally administered drug, healthcare providers are encouraged to report the adverse effect to the FDA.

MECHANISM OF ACTION

Clopidogrel is a thienopyridine compound which acts to antagonize adenosine diphosphate (ADP). Clopidogrel is inactive in vitro and requires hepatic activation to exert its antiplatelet effect. The active metabolite selectively and irreversibly inhibits ADP-induced platelet aggregation. It prevents binding of adenosine diphosphate (ADP) to its platelet P2Y₁₂ receptor. Thus, ADP-mediated activation of the glycoprotein GPIIb/IIIa complex is impaired. Because the glycoprotein GPIIb/IIIa complex is the major receptor for fibrinogen, impaired activation of the GPIIb/IIIa complex prevents fibrinogen binding to platelets which ultimately inhibits platelet aggregation. Because the active metabolite of clopidogrel irreversibly modifies the platelet ADP receptor; platelets exposed to the drug are affected for the remainder of their lifespan (7–10 days). In platelet aggregation studies, clopidogrel 75 mg once daily produced inhibition of ADP-induced platelet aggregation equivalent to that of ticlopidine 250 mg twice daily. The active metabolite of clopidogrel also inhibits platelet aggregation induced by agonists other than ADP by blocking the amplification of platelet activation by released ADP; the active metabolite does not inhibit phosphodiesterase.

PHARMACOKINETICS

Clopidogrel is administered orally; it is inactive in vitro and requires hepatic biotransformation to an active metabolite. Clopidogrel undergoes extensive metabolism by 2 main metabolic pathways. One pathway is mediated by esterases and results in an inactive carboxylic acid derivative, accounting for 85% of circulating metabolites. The other pathway is mediated by multiple cytochrome (CYP) P450 isoenzymes. The cytochromes first oxidize clopidogrel to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the intermediate metabolite results in the formation of the active metabolite, a thiol derivative of clopidogrel. The active metabolite is formed primarily by CYP2C19; CYP3A, CYP2B6, and CYP1A2 contribute to a lesser extent. The active metabolite rapidly and irreversibly binds to platelet receptors, inhibiting platelet aggregation for the lifespan of the platelet. Clopidogrel and the main circulating metabolite bind reversibly in vitro to human plasma proteins (98% and 94%, respectively). Approximately 50% of radiolabeled clopidogrel is eliminated in the urine and about 46% via the feces over a period of 5 days. The half-life of clopidogrel is approximately 6 hours in adults; the half-life of the active metabolite is approximately 30 minutes.

Dose dependent inhibition of platelet aggregation can be seen 2 hours after a single oral dose. With repeated doses of 75 mg/day in adults, maximum inhibition of platelet aggregation is achieved within 3 to 7 days. At steady state, platelet aggregation is inhibited by 40% to 60%. Platelet aggregation and bleeding time gradually return to baseline about 5 days after discontinuation of clopidogrel.

Affected cytochrome P450 isoenzymes: CYP2C9, CYP2C19, CYP2C8, CYP3A, CYP2B6, CYP1A2

Clopidogrel is a substrate and inhibitor of CYP2C19 and a strong inhibitor of CYP2C8. Clopidogrel requires hepatic biotransformation to an active metabolite; this activation is mediated primarily by CYP2C19 and to a lesser extent by CYP3A, CYP2B6, and CYP1A2. At high concentrations in vitro, clopidogrel is a potent inhibitor of CYP2B6 and a mild inhibitor of CYP2C9.

Oral Route

Clopidogrel is rapidly absorbed with a bioavailability of at least 50%. Food does not significantly affect absorption. In adults, peak concentrations occur 30 to 60 minutes after administration.