

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CLOPIDOGREL TABLETS safely and effectively. See full prescribing information for CLOPIDOGREL TABLETS.

CLOPIDOGREL tablets, for oral use
Initial U.S. Approval: 1997

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of clopidogrel bisulfate depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with clopidogrel bisulfate at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)

-----INDICATIONS AND USAGE-----

Clopidogrel tablets are a P2Y₁₂ platelet inhibitor indicated for:

- Acute coronary syndrome
 - For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], clopidogrel tablets have been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia. (1.1)
 - For patients with ST-elevation myocardial infarction (STEMI), clopidogrel tablets have been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary PCI is unknown. (1.1)
- Recent MI, recent stroke, or established peripheral arterial disease. Clopidogrel tablets have been shown to reduce the combined endpoint of new ischemic stroke, new MI, and other vascular death. (1.2)

-----DOSAGE AND ADMINISTRATION-----

- Acute coronary syndrome (2.1)
 - UA/NSTEMI: 300 mg loading dose followed by 75 mg once daily, in combination with aspirin (75 to 325 mg once daily)

- STEMI: 75 mg once daily, in combination with aspirin (75 to 325 mg once daily), with or without a loading dose.
- Recent MI, recent stroke, or established peripheral arterial disease: 75 mg once daily (2.2)

-----DOSAGE FORMS AND STRENGTHS-----

Tablets: 75 mg, 300 mg (3)

-----CONTRAINDICATIONS-----

- Active pathological bleeding, such as peptic ulcer or intracranial hemorrhage (4.1)
- Hypersensitivity to clopidogrel or any component of the product (4.2)

-----WARNINGS AND PRECAUTIONS-----

- CYP2C19 inhibitors: Avoid concomitant use of omeprazole or esomeprazole. (5.1)
- Bleeding: Clopidogrel bisulfate increases risk of bleeding. Discontinue 5 days prior to elective surgery. (5.2)
- Premature discontinuation increases risk of cardiovascular events. (5.3)
- Recent transient ischemic attack or stroke: Combination use of clopidogrel bisulfate and aspirin is not more effective than clopidogrel bisulfate alone, but increases major bleeding. (5.4)
- Thrombotic thrombocytopenic purpura (TTP) has been reported. (5.5)
- Cross-reactivity among thienopyridines has been reported. (5.6)

-----ADVERSE REACTIONS-----

Bleeding, including life-threatening and fatal bleeding, is the most commonly reported adverse reaction. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Accord Healthcare Inc. at 1-866-941-7875 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

-----DRUG INTERACTIONS-----

- Nonsteroidal anti-inflammatory drugs (NSAIDs): warfarin, selective serotonin and serotonin norepinephrine reuptake inhibitors (SSRIs, SNRIs): Increases risk of bleeding. (7.2,7.3,7.4)

-----USE IN SPECIFIC POPULATIONS-----

Nursing mothers: Discontinue drug or nursing. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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FULL PRESCRIBING INFORMATION

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

The effectiveness of clopidogrel bisulfate is dependent on its activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19 [see *Warnings and Precautions (5.1)*]. Clopidogrel bisulfate at recommended doses forms less of that metabolite and has a smaller effect on platelet function in patients who are CYP2C19 poor metabolizers. Poor metabolizers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel bisulfate at recommended doses exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function. Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy [see *Clinical Pharmacology (12.5)*]. Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers [see *Dosage and Administration (2.3)*].

1 INDICATIONS AND USAGE

1.1 Acute Coronary Syndrome (ACS)

- For patients with non-ST-segment elevation ACS [unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)], including patients who are to be managed medically and those who are to be managed with coronary revascularization, clopidogrel tablets have been shown to decrease the rate of a combined endpoint of cardiovascular death, myocardial infarction (MI), or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia.
- For patients with ST-elevation myocardial infarction (STEMI), clopidogrel tablets have been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction, or stroke. The benefit for patients who undergo primary percutaneous coronary intervention is unknown.

The optimal duration of clopidogrel tablets therapy in ACS is unknown.

1.2 Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

For patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease, clopidogrel tablets have been shown to reduce the rate of a combined endpoint of new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death.

2 DOSAGE AND ADMINISTRATION

2.1 Acute Coronary Syndrome

Clopidogrel tablets can be administered with or without food [see *Clinical Pharmacology (12.3)*].

- For patients with non-ST-elevation ACS (UA/NSTEMI), initiate clopidogrel bisulfate with a single 300 mg oral loading dose and then continue at 75 mg once daily. Initiate aspirin (75 to 325 mg once daily) and continue in combination with clopidogrel bisulfate [*see Clinical Studies (14.1)*].
- For patients with STEMI, the recommended dose of clopidogrel bisulfate is 75 mg once daily orally, administered in combination with aspirin (75 to 325 mg once daily), with or without thrombolytics. Clopidogrel bisulfate may be initiated with or without a loading dose [*see Clinical Studies (14.1)*].

2.2 Recent MI, Recent Stroke, or Established Peripheral Arterial Disease

The recommended daily dose of clopidogrel bisulfate is 75 mg once daily orally, with or without food [*see Clinical Pharmacology (12.3)*].

2.3 CYP2C19 Poor Metabolizers

CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response [*see Clinical Pharmacology (12.5)*], an appropriate dose regimen for this patient population has not been established.

2.4 Use with Proton Pump Inhibitors (PPI)

Avoid using omeprazole or esomeprazole with clopidogrel bisulfate. Omeprazole and esomeprazole significantly reduce the antiplatelet activity of clopidogrel bisulfate. When concomitant administration of a PPI is required, consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite [*see Warnings and Precautions (5.1), Drug Interactions (7.1) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

- 75 mg tablets: Pink colored, round, biconvex, film coated tablets debossed with “CI” on one side and plain on other side.
- 300 mg tablets: Pink colored, oval, biconvex, beveled edged, film coated tablets debossed with “CL” on one side and plain on other side.

4 CONTRAINDICATIONS

4.1 Active Bleeding

Clopidogrel tablets are contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage.

4.2 Hypersensitivity

Clopidogrel tablets are contraindicated in patients with hypersensitivity (e.g.,

anaphylaxis) to clopidogrel or any component of the product [see *Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Diminished Antiplatelet Activity Due to Impaired CYP2C19 Function

Clopidogrel is a prodrug. Inhibition of platelet aggregation by clopidogrel is achieved through an active metabolite. The metabolism of clopidogrel to its active metabolite can be impaired by genetic variations in CYP2C19 [see *Boxed Warning*] and by concomitant medications that interfere with CYP2C19.

Proton Pump Inhibitors

Avoid concomitant use of clopidogrel bisulfate with omeprazole or esomeprazole because both significantly reduce the antiplatelet activity of clopidogrel bisulfate [see *Drug Interactions (7.1)* and *Dosage and Administration (2.4)*].

5.2 General Risk of Bleeding

Thienopyridines, including clopidogrel bisulfate, increase the risk of bleeding. If a patient is to undergo surgery and an antiplatelet effect is not desired, discontinue clopidogrel bisulfate five days prior to surgery. In patients who stopped therapy more than five days prior to CABG the rates of major bleeding were similar (event rate 4.4% clopidogrel bisulfate + aspirin; 5.3% placebo + aspirin). In patients who remained on therapy within five days of CABG, the major bleeding rate was 9.6% for clopidogrel bisulfate + aspirin, and 6.3% for placebo + aspirin.

Thienopyridines inhibit platelet aggregation for the lifetime of the platelet (7 to 10 days), so withholding a dose will not be useful in managing a bleeding event or the risk of bleeding associated with an invasive procedure. Because the half-life of clopidogrel's active metabolite is short, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.

5.3 Discontinuation of clopidogrel bisulfate

Avoid lapses in therapy, and if clopidogrel bisulfate must be temporarily discontinued, restart as soon as possible. Premature discontinuation of clopidogrel bisulfate may increase the risk of cardiovascular events.

5.4 Patients with Recent Transient Ischemic Attack (TIA) or Stroke

In patients with recent TIA or stroke who are at high risk for recurrent ischemic events, the combination of aspirin and clopidogrel bisulfate has not been shown to be more effective than clopidogrel bisulfate alone, but the combination has been shown to increase major bleeding.

5.5 Thrombotic Thrombocytopenic Purpura (TTP)

TTP, sometimes fatal, has been reported following use of clopidogrel bisulfate,

sometimes after a short exposure (<2 weeks). TTP is a serious condition that requires urgent treatment including plasmapheresis (plasma exchange). It is characterized by thrombocytopenia, microangiopathic hemolytic anemia (schistocytes [fragmented RBCs] seen on peripheral smear), neurological findings, renal dysfunction, and fever [*see Adverse Reactions (6.2)*].

5.6 Cross-Reactivity among Thienopyridines

Hypersensitivity including rash, angioedema or hematologic reaction have been reported in patients receiving clopidogrel bisulfate, including patients with a history of hypersensitivity or hematologic reaction to other thienopyridines [*see Contraindications (4.2) and Adverse Reactions (6.2)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed below and elsewhere in the labeling:

- Bleeding [*see Warnings and Precautions (5.2)*]
- Thrombotic thrombocytopenic purpura [*see Warnings and Precautions (5.5)*]

6.1 Clinical Studies Experience

Because clinical trials are conducted under widely varying conditions and durations of follow up, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clopidogrel bisulfate has been evaluated for safety in more than 54,000 patients, including over 21,000 patients treated for 1 year or more. The clinically important adverse reactions observed in trials comparing clopidogrel bisulfate plus aspirin to placebo plus aspirin and trials comparing clopidogrel bisulfate alone to aspirin alone are discussed below.

Bleeding

CURE

In CURE, clopidogrel bisulfate use with aspirin was associated with an increase in major bleeding (primarily gastrointestinal and at puncture sites) compared to placebo with aspirin (see Table 1). The incidence of intracranial hemorrhage (0.1%) and fatal bleeding (0.2%) were the same in both groups. Other bleeding events that were reported more frequently in the clopidogrel group were epistaxis, hematuria, and bruise.

The overall incidence of bleeding is described in Table 1.

Table 1: CURE Incidence of Bleeding Complications (% patients)

| Event | Clopidogrel Bisulfate (+ aspirin) [*] (n=6259) | Placebo (+ aspirin) [*] (n=6303) |
|---|--|--|
| Major bleeding [†] | 3.7 [‡] | 2.7 [§] |
| Life-threatening bleeding | 2.2 | 1.8 |
| Fatal | 0.2 | 0.2 |
| 5 g/dL hemoglobin drop | 0.9 | 0.9 |
| Requiring surgical intervention | 0.7 | 0.7 |
| Hemorrhagic strokes | 0.1 | 0.1 |
| Requiring inotropes | 0.5 | 0.5 |
| Requiring transfusion (≥4 units) | 1.2 | 1.0 |
| Other major bleeding | 1.6 | 1.0 |
| Significantly disabling | 0.4 | 0.3 |
| Intraocular bleeding with significant loss of vision | 0.05 | 0.03 |
| Requiring 2 to 3 units of blood | 1.3 | 0.9 |
| Minor bleeding [¶] | 5.1 | 2.4 |

^{*} Other standard therapies were used as appropriate.

[†] Life-threatening and other major bleeding.

[‡] Major bleeding event rate for clopidogrel bisulfate + aspirin was dose-dependent on aspirin: <100 mg = 2.6%; 100 to 200 mg = 3.5%; >200 mg = 4.9%

Major bleeding event rates for clopidogrel bisulfate + aspirin by age were: <65 years = 2.5%, ≥65 to <75 years = 4.1%, ≥75 years = 5.9%

[§] Major bleeding event rate for placebo + aspirin was dose-dependent on aspirin: <100 mg = 2.0%; 100 to 200 mg = 2.3%; >200 mg = 4.0%

Major bleeding event rates for placebo + aspirin by age were: <65 years = 2.1%, ≥65 to <75 years = 3.1%, ≥75 years = 3.6%

[¶] Led to interruption of study medication.

Ninety-two percent (92%) of the patients in the CURE study received heparin or low molecular weight heparin (LMWH), and the rate of bleeding in these patients was similar to the overall results.

COMMIT

In COMMIT, similar rates of major bleeding were observed in the clopidogrel bisulfate and placebo groups, both of which also received aspirin (see Table 2).

Table 2: Incidence of Bleeding Events in COMMIT (% patients)

| Type of bleeding | Clopidogrel bisulfate (+ aspirin) (n=22961) | Placebo (+ aspirin) (n=22891) | p-value |
|---|---|-------------------------------------|---------|
| Major [*] noncerebral or cerebral bleeding ^{**} | 0.6 | 0.5 | 0.59 |
| Major noncerebral | 0.4 | 0.3 | 0.48 |
| Fatal | 0.2 | 0.2 | 0.90 |
| Hemorrhagic stroke | 0.2 | 0.2 | 0.91 |
| Fatal | 0.2 | 0.2 | 0.81 |
| Other noncerebral bleeding (non-major) | 3.6 | 3.1 | 0.005 |
| Any noncerebral bleeding | 3.9 | 3.4 | 0.004 |

* Major bleeds were cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.

**The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for clopidogrel bisulfate + aspirin by age were: <60 years = 0.3%, ≥60 to <70 years = 0.7%, ≥70 years = 0.8%. Event rates for placebo + aspirin by age were: <60 years = 0.4%, ≥60 to <70 years = 0.6%, ≥70 years = 0.7%.

CAPRIE (clopidogrel bisulfate vs. Aspirin)

In CAPRIE, gastrointestinal hemorrhage occurred at a rate of 2.0% in those taking clopidogrel bisulfate vs. 2.7% in those taking aspirin; bleeding requiring hospitalization occurred in 0.7% and 1.1%, respectively. The incidence of intracranial hemorrhage was 0.4% for clopidogrel bisulfate compared to 0.5% for aspirin.

Other bleeding events that were reported more frequently in the clopidogrel bisulfate group were epistaxis and hematoma.

Other Adverse Events

In CURE and CHARISMA, which compared clopidogrel bisulfate plus aspirin to aspirin alone, there was no difference in the rate of adverse events (other than bleeding) between clopidogrel bisulfate and placebo.

In CAPRIE, which compared clopidogrel bisulfate to aspirin, pruritus was more frequently reported in those taking clopidogrel bisulfate. No other difference in the rate of adverse events (other than bleeding) was reported.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of clopidogrel bisulfate. Because these reactions are reported voluntarily from a population of an unknown size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- *Blood and lymphatic system disorders:* Agranulocytosis, aplastic anemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP), acquired hemophilia A
- *Eye disorders:* Eye (conjunctival, ocular, retinal) bleeding
- *Gastrointestinal disorders:* Gastrointestinal and retroperitoneal hemorrhage with fatal outcome, colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis, gastric/duodenal ulcer, diarrhea
- *General disorders and administration site condition:* Fever, hemorrhage of operative wound
- *Hepato-biliary disorders:* Acute liver failure, hepatitis (non-infectious), abnormal liver function test
- *Immune system disorders:* Hypersensitivity reactions, anaphylactoid reactions, serum sickness

- *Musculoskeletal, connective tissue and bone disorders:* Musculoskeletal bleeding, myalgia, arthralgia, arthritis
- *Nervous system disorders:* Taste disorders, fatal intracranial bleeding, headache
- *Psychiatric disorders:* Confusion, hallucinations
- *Respiratory, thoracic and mediastinal disorders:* Bronchospasm, interstitial pneumonitis, respiratory tract bleeding, eosinophilic pneumonia
- *Renal and urinary disorders:* Increased creatinine levels
- *Skin and subcutaneous tissue disorders:* Maculopapular, erythematous or exfoliative rash, urticaria, bullous dermatitis, eczema, toxic epidermal necrolysis, Stevens-Johnson syndrome, acute generalized exanthematous pustulosis (AGEP), angioedema, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), erythema multiforme, skin bleeding, lichen planus, generalized pruritus
- *Vascular disorders:* Vasculitis, hypotension

7 DRUG INTERACTIONS

7.1 CYP2C19 Inhibitors

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of certain drugs that inhibit the activity of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition [*see Warnings and Precautions (5.1) and Dosage and Administration (2.4)*].

Proton Pump Inhibitors (PPI)

Avoid concomitant use of clopidogrel bisulfate with omeprazole or esomeprazole. In clinical studies, omeprazole was shown to reduce the antiplatelet activity of clopidogrel bisulfate when given concomitantly or 12 hours apart. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established. A similar reduction in antiplatelet activity was observed with esomeprazole when given concomitantly with clopidogrel bisulfate. Consider using another acid-reducing agent with minimal or no CYP2C19 inhibitory effect on the formation of clopidogrel active metabolite. Dexlansoprazole, lansoprazole and pantoprazole had less effect on the antiplatelet activity of clopidogrel bisulfate than did omeprazole or esomeprazole [*see Dosage and Administration (2.4), Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)*].

7.2 Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

Coadministration of clopidogrel bisulfate and NSAIDs increases the risk of gastrointestinal bleeding.

7.3 Warfarin (CYP2C9 Substrates)

Although the administration of clopidogrel 75 mg per day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of clopidogrel bisulfate with warfarin increases

the risk of bleeding because of independent effects on hemostasis.

However, at high concentrations *in vitro*, clopidogrel inhibits CYP2C9.

7.4 SSRIs and SNRIs

Since selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) affect platelet activation, the concomitant administration of SSRIs and SNRIs with clopidogrel may increase the risk of bleeding.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy 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, respectively, 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 bisulfate should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from clopidogrel, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric populations have not been established.

A randomized, placebo-controlled trial (CLARINET) did not demonstrate a clinical benefit of clopidogrel in neonates and infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt. Possible factors contributing to this outcome were the dose of clopidogrel, the concomitant administration of aspirin and the late initiation of therapy following shunt palliation. It cannot be ruled out that a trial with a different design would demonstrate a clinical benefit in this patient population.

8.5 Geriatric Use

Of the total number of subjects in the CAPRIE and CURE controlled clinical studies, approximately 50% of patients treated with clopidogrel bisulfate were 65 years of age and older, and 15% were 75 years and older. In COMMIT, approximately 58% of the patients treated with clopidogrel bisulfate were 60 years and older, 26% of whom were 70 years and older.

The observed risk of bleeding events with clopidogrel bisulfate plus aspirin versus placebo plus aspirin by age category is provided in Table 1 and Table 2 for the CURE and COMMIT trials, respectively [see *Adverse Reactions (6.1)*]. No dosage adjustment is necessary in elderly patients.

8.6 Renal Impairment

Experience is limited in patients with severe and moderate renal impairment [see *Clinical Pharmacology (12.2)*].

8.7 Hepatic Impairment

No dosage adjustment is necessary in patients with hepatic impairment [see *Clinical Pharmacology (12.2)*].

10 OVERDOSAGE

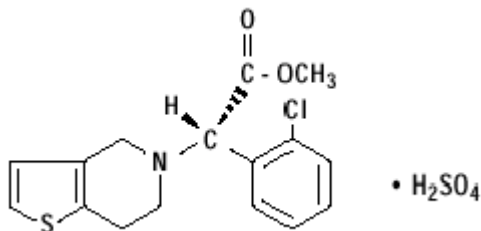
Platelet inhibition by clopidogrel bisulfate is irreversible and will last for the life of the platelet. Overdose following clopidogrel administration may result in bleeding complications. A single oral dose of clopidogrel at 1500 or 2000 mg/kg was lethal to mice and to rats and at 3000 mg/kg to baboons. Symptoms of acute toxicity were vomiting, prostration, difficult breathing, and gastrointestinal hemorrhage in animals.

Based on biological plausibility, platelet transfusion may restore clotting ability.

11 DESCRIPTION

Clopidogrel bisulfate is a thienopyridine class inhibitor of P2Y₁₂ ADP platelet receptors. Chemically it is methyl (+)-(S)- α -(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate (1:1). The empirical formula of clopidogrel bisulfate is C₁₆H₁₆ClNO₂S•H₂SO₄ and its molecular weight is 419.9.

The structural formula is as follows:



Clopidogrel bisulfate is a white to off-white powder. It is practically insoluble in water at neutral pH but freely soluble at pH 1. It also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether. It has a specific optical rotation of about +56°.

Clopidogrel tablets USP for oral administration is provided as either pink colored, round, biconvex, film coated tablets debossed with “CI” on one side and plain on other side containing 97.875 mg of clopidogrel bisulfate which is the molar equivalent of 75 mg of clopidogrel base or pink colored, oval, biconvex, beveled edged, film coated tablets debossed with “CL” on one side and plain on other side containing 391.5 mg of clopidogrel bisulfate which is the molar equivalent of 300 mg of clopidogrel base.

Each tablet contains colloidal anhydrous silica, hydrogenated castor oil, low substituted hydroxypropylcellulose and microcelac 100 as inactive ingredients. The pink film coating contains hydroxy propylmethyl cellulose, iron oxide red, lactose monohydrate, titanium dioxide and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Clopidogrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the P2Y₁₂ class of ADP receptors on platelets.

12.2 Pharmacodynamics

Clopidogrel must be metabolized by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation. The active metabolite of clopidogrel selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet P2Y₁₂ receptor and the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation. This action is irreversible. Consequently, platelets exposed to clopidogrel’s active metabolite are affected for the remainder of their lifespan (about 7 to 10 days). Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Dose-dependent inhibition of platelet aggregation can be seen 2 hours after single oral doses of clopidogrel bisulfate. Repeated doses of 75 mg clopidogrel bisulfate per day inhibit ADP-induced platelet aggregation on the first day, and inhibition reaches steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg clopidogrel bisulfate per day was between 40% and 60%. Platelet aggregation and bleeding time gradually return to baseline values after treatment is discontinued, generally in about 5 days.

Geriatric Patients

Elderly (≥ 75 years) and young healthy subjects had similar effects on platelet aggregation.

Renally-Impaired Patients

After repeated doses of 75 mg clopidogrel bisulfate per day, patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min) and moderate renal impairment (creatinine clearance from 30 to 60 mL/min) showed low (25%) inhibition of ADP-induced platelet aggregation.

Hepatically-Impaired Patients

After repeated doses of 75 mg clopidogrel bisulfate per day for 10 days in patients with severe hepatic impairment, inhibition of ADP-induced platelet aggregation was similar to that observed in healthy subjects.

Gender

In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women.

12.3 Pharmacokinetics

Clopidogrel is a prodrug and is metabolized to a pharmacologically active metabolite and inactive metabolites.

Absorption

After single and repeated oral doses of 75 mg per day, clopidogrel is rapidly absorbed. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Effect of Food

Clopidogrel bisulfate can be administered with or without food. In a study in healthy male subjects when clopidogrel bisulfate 75 mg per day was given with a standard breakfast, mean inhibition of ADP-induced platelet aggregation was reduced by less than 9%. The active metabolite AUC_{0-24} was unchanged in the presence of food, while there was a 57% decrease in active metabolite C_{max} . Similar results were observed when a clopidogrel bisulfate 300 mg loading dose was administered with a high-fat breakfast.

Metabolism

Clopidogrel is extensively metabolized by two main metabolic pathways: one mediated by esterases and leading to hydrolysis into an inactive carboxylic acid derivative (85% of circulating metabolites) and one mediated by multiple cytochrome P450 enzymes. Cytochromes first oxidize clopidogrel to a 2-oxo-clopidogrel intermediate metabolite. Subsequent metabolism of the 2-oxo-clopidogrel intermediate metabolite results in formation of the active metabolite, a thiol derivative of clopidogrel. This metabolic pathway is mediated by CYP2C19, CYP3A, CYP2B6 and CYP1A2. The active thiol metabolite binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation for the lifespan of the platelet.

The C_{max} of the active metabolite is twice as high following a single 300 mg clopidogrel loading dose as it is after four days of 75 mg maintenance dose. C_{max} occurs approximately 30 to 60 minutes after dosing. In the 75 to 300 mg dose range, the pharmacokinetics of the active metabolite deviates from dose proportionality: increasing the dose by a factor of four results in 2.0- and 2.7-fold increases in C_{max} and AUC, respectively.

Elimination

Following an oral dose of ¹⁴C-labeled clopidogrel in humans, approximately 50% of total radioactivity was excreted in urine and approximately 46% in feces over the 5 days post-dosing. After a single, oral dose of 75 mg, clopidogrel has a half-life of approximately 6 hours. The half-life of the active metabolite is about 30 minutes.

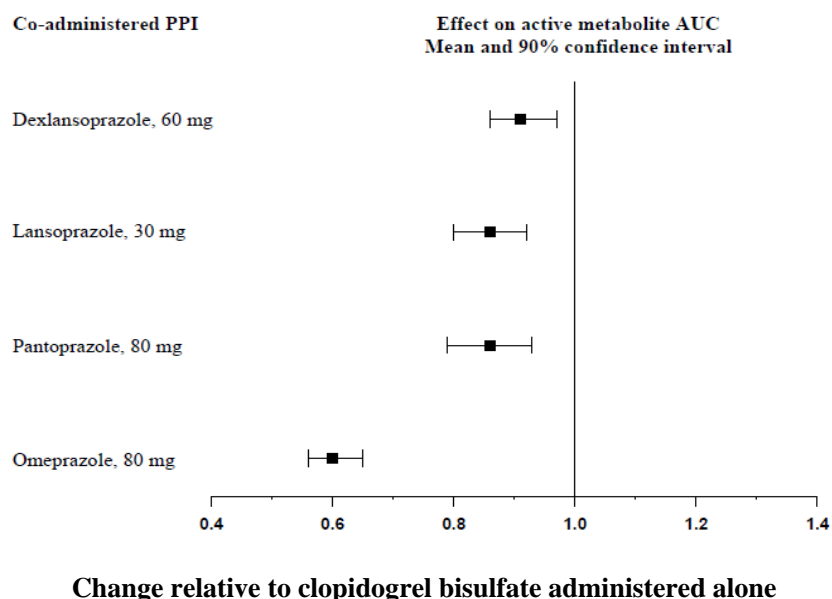
Drug Interactions

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. Concomitant use of certain inhibitors of this enzyme results in reduced plasma concentrations of the active metabolite of clopidogrel and a reduction in platelet inhibition.

Proton Pump Inhibitors (PPI)

The effect of proton pump inhibitors (PPI) on the systemic exposure to the clopidogrel active metabolite following multiple doses of clopidogrel bisulfate 75 mg evaluated in dedicated drug interaction studies is presented in Figure 1.

Figure 1: Exposure to Clopidogrel Active Metabolite Following Multiple Doses of Clopidogrel Bisulfate 75 mg Alone or with Proton Pump Inhibitors (PPIs)



Pharmacodynamic and pharmacokinetic parameters measured in these studies showed that the interaction was highest with omeprazole and least with dexlansoprazole.

12.5 Pharmacogenomics

CYP2C19 is involved in the formation of both the active metabolite and the 2-oxo-clopidogrel intermediate metabolite. Clopidogrel active metabolite pharmacokinetics and antiplatelet effects, as measured by *ex vivo* platelet aggregation assays, differ according to CYP2C19 genotype. Genetic variants of other CYP450 enzymes may also affect the formation of clopidogrel's active metabolite.

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and *3 alleles are nonfunctional. CYP2C19*2 and *3 account for the majority of reduced function alleles in white (85%) and Asian (99%) poor metabolizers. Other alleles associated with absent or reduced metabolism are less frequent, and include, but are not limited to, CYP2C19*4, *5, *6, *7, and *8. A patient with poor metabolizer status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metabolizer genotypes are approximately 2% for whites, 4% for blacks and 14% for Chinese. Tests are available to determine a patient's CYP2C19 genotype.

A crossover study in 40 healthy subjects, 10 each in the four CYP2C19 metabolizer groups, evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg per day and 600 mg followed by 150 mg per day, each for a total of 5 days. Decreased active metabolite exposure and diminished inhibition of platelet aggregation were observed in the poor metabolizers as compared to the other groups. When poor metabolizers received the 600 mg/150 mg regimen, active metabolite exposure and antiplatelet response were greater than with the 300 mg/75 mg regimen (see Table 3). An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Table 3: Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metabolizer Status

| | Dose | Ultrarapid (n=10) | Extensive (n=10) | Intermediate (n=10) | Poor (n=10) |
|---|----------------|----------------------|---------------------|------------------------|----------------|
| C _{max} (ng/mL) | 300 mg (24 h) | 24 (10) | 32 (21) | 23 (11) | 11 (4) |
| | 600 mg (24 h) | 36 (13) | 44 (27) | 39 (23) | 17 (6) |
| | 75 mg (Day 5) | 12 (6) | 13 (7) | 12 (5) | 4 (1) |
| | 150 mg (Day 5) | 16 (9) | 19 (5) | 18 (7) | 7 (2) |
| IPA (%) [*] | 300 mg (24 h) | 40 (21) | 39 (28) | 37 (21) | 24 (26) |
| | 600 mg (24 h) | 51 (28) | 49 (23) | 56 (22) | 32 (25) |
| | 75 mg (Day 5) | 56 (13) | 58 (19) | 60 (18) | 37 (23) |
| | 150 mg (Day 5) | 68 (18) | 73 (9) | 74 (14) | 61 (14) |
| VASP-PRI (%) [†] | 300 mg (24 h) | 73 (12) | 68 (16) | 78 (12) | 91 (12) |
| | 600 mg (24 h) | 51 (20) | 48 (20) | 56 (26) | 85 (14) |
| | 75 mg (Day 5) | 40 (9) | 39 (14) | 50 (16) | 83 (13) |
| | 150 mg (Day 5) | 20 (10) | 24 (10) | 29 (11) | 61 (18) |
| Values are mean (SD) | | | | | |
| [*] Inhibition of platelet aggregation with 5 mcM ADP; larger value indicates greater platelet inhibition | | | | | |
| [†] Vasodilator-stimulated phosphoprotein – platelet reactivity index; smaller value indicates greater platelet inhibition | | | | | |

Some published studies suggest that intermediate metabolizers have decreased active metabolite exposure and diminished antiplatelet effects.

The relationship between CYP2C19 genotype and clopidogrel bisulfate treatment

outcome was evaluated in retrospective analyses of clopidogrel bisulfate-treated subjects in CHARISMA (n=2428) and TRITON-TIMI 38 (n=1477), and in several published cohort studies. In TRITON-TIMI 38 and the majority of the cohort studies, the combined group of patients with either intermediate or poor metabolizer status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers. In CHARISMA and one cohort study, the increased event rate was observed only in poor metabolizers.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg.

Clopidogrel was not genotoxic in four *in vitro* tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one *in vivo* test (micronucleus test by oral route in mice).

Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m² basis).

14 CLINICAL STUDIES

14.1 Acute Coronary Syndrome

CURE

The CURE study included 12,562 patients with ACS without ST-elevation (UA or NSTEMI) and presenting within 24 hours of onset of the most recent episode of chest pain or symptoms consistent with ischemia. Patients were required to have either ECG changes compatible with new ischemia (without ST-elevation) or elevated cardiac enzymes or troponin I or T to at least twice the upper limit of normal. The patient population was largely Caucasian (82%) and included 38% women, and 52% patients ≥65 years of age.

Patients were randomized to receive clopidogrel bisulfate (300-mg loading dose followed by 75 mg once daily) or placebo, and were treated for up to one year. Patients also received aspirin (75 to 325 mg once daily) and other standard therapies such as heparin. The use of GPIIb/IIIa inhibitors was not permitted for three days prior to randomization.

The number of patients experiencing the primary outcome (CV death, MI, or stroke) was 582 (9.3%) in the clopidogrel bisulfate-treated group and 719 (11.4%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10% to 28%; p < 0.001) for the clopidogrel bisulfate-treated group (see Table 4).

Table 4: Outcome Events in the CURE Primary Analysis

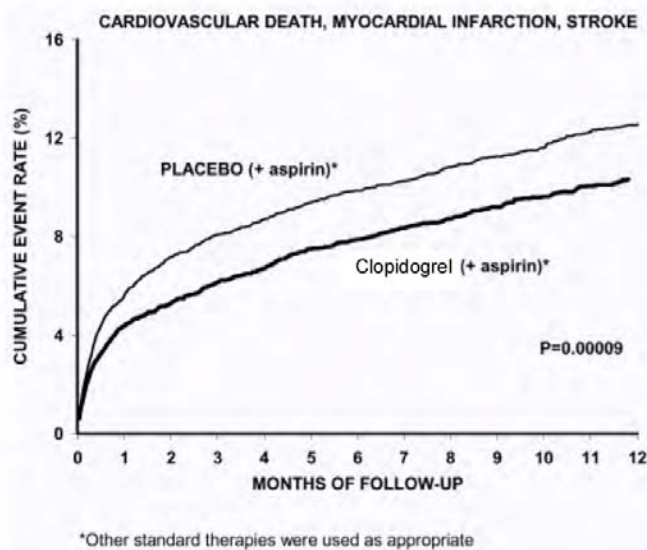
| Outcome | Clopidogrel bisulfate (+ aspirin)* (n=6259) | Placebo (+ aspirin)* (n=6303) | Relative Risk Reduction (%) (95% CI) |
|--|---|-------------------------------|--------------------------------------|
| Primary outcome (Cardiovascular death, MI, stroke) | 582 (9.3%) | 719 (11.4%) | 20% (10.3, 27.9) p < 0.001 |
| All Individual Outcome Events:† | | | |
| CV death | 318 (5.1%) | 345 (5.5%) | 7% (-7.7, 20.6) |
| MI | 324 (5.2%) | 419 (6.6%) | 23% (11.0, 33.4) |
| Stroke | 75 (1.2%) | 87 (1.4%) | 14% (-17.7, 36.6) |

* Other standard therapies were used as appropriate

† The individual components do not represent a breakdown of the primary and co-primary outcomes, but rather the total number of subjects experiencing an event during the course of the study.

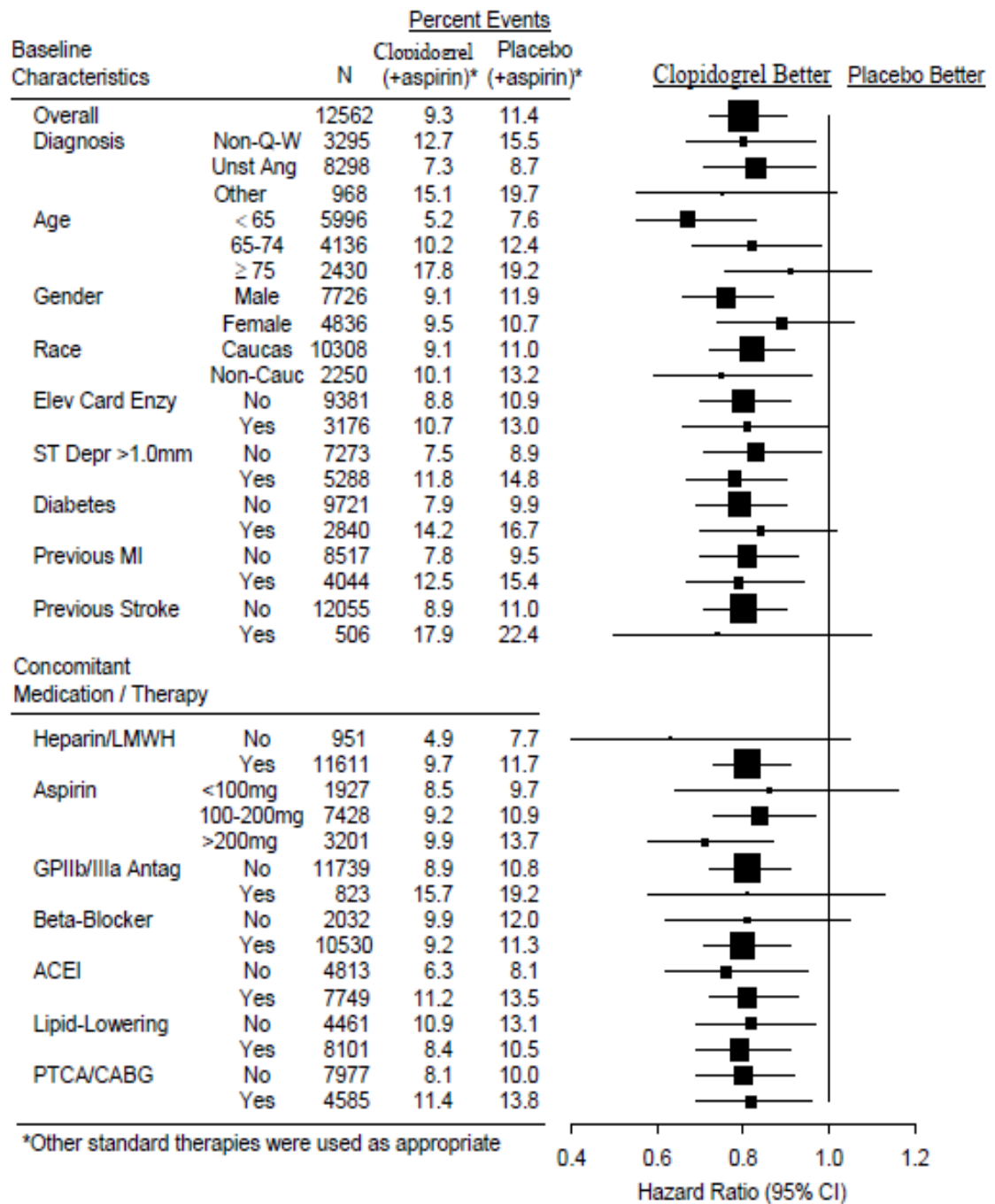
Most of the benefit of clopidogrel bisulfate occurred in the first two months, but the difference from placebo was maintained throughout the course of the trial (up to 12 months) (see Figure 2).

Figure 2: Cardiovascular Death, Myocardial Infarction, and Stroke in the CURE Study



In CURE, the use of clopidogrel bisulfate was associated with a lower incidence of CV death, MI or stroke in patient populations with different characteristics, as shown in Figure 3. The benefits associated with clopidogrel bisulfate were independent of the use of other acute and long-term cardiovascular therapies, including heparin/LMWH, intravenous glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, lipid-lowering drugs, beta-blockers, and ACE-inhibitors. The efficacy of clopidogrel bisulfate was observed independently of the dose of aspirin (75 to 325 mg once daily). The use of oral anticoagulants, non-study antiplatelet drugs, and chronic NSAIDs was not allowed in CURE.

Figure 3: Hazard Ratio for Patient Baseline Characteristics and On-Study Concomitant Medications/Interventions for the CURE Study



The use of clopidogrel bisulfate in CURE was associated with a decrease in the use of thrombolytic therapy (71 patients [1.1%] in the clopidogrel bisulfate group, 126 patients [2.0%] in the placebo group; relative risk reduction of 43%), and GPIIb/IIIa inhibitors (369 patients [5.9%] in the clopidogrel bisulfate group, 454 patients [7.2%] in the placebo

group, relative risk reduction of 18%). The use of clopidogrel bisulfate in CURE did not affect the number of patients treated with CABG or PCI (with or without stenting), (2253 patients [36.0%] in the clopidogrel bisulfate group, 2324 patients [36.9%] in the placebo group; relative risk reduction of 4.0%).

COMMIT

In patients with STEMI, the safety and efficacy of clopidogrel bisulfate were evaluated in the randomized, placebo-controlled, double-blind study, COMMIT. COMMIT included 45,852 patients presenting within 24 hours of the onset of the symptoms of myocardial infarction with supporting ECG abnormalities (*i.e.*, ST-elevation, ST-depression or left bundle-branch block). Patients were randomized to receive clopidogrel bisulfate (75 mg once daily) or placebo, in combination with aspirin (162 mg per day), for 28 days or until hospital discharge, whichever came first.

The primary endpoints were death from any cause and the first occurrence of re-infarction, stroke or death.

The patient population included 28% women, 58% age ≥ 60 years (26% age ≥ 70 years), 55% patients who received thrombolytics, 68% who received ACE-inhibitors, and only 3% who underwent PCI.

As shown in Table 5 and Figure 4 and Figure 5 below, clopidogrel bisulfate significantly reduced the relative risk of death from any cause by 7% (p=0.029), and the relative risk of the combination of re-infarction, stroke or death by 9% (p=0.002).

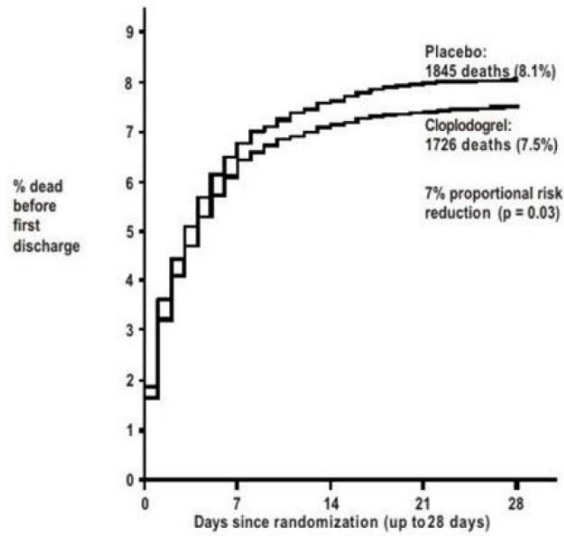
Table 5: Outcome Events in the COMMIT Analysis

| Event | Clopidogrel bisulfate (+ aspirin) (N=22961) | Placebo (+ aspirin) (N=22891) | Odds ratio (95% CI) | p-value |
|---|--|--------------------------------------|----------------------------|----------------|
| Composite endpoint: Death, MI, or Stroke * | 2121(9.2%) | 2310(10.1%) | 0.91(0.86,0.97) | 0.002 |
| Death | 1726(7.5%) | 1845(8.1%) | 0.93(0.87, 0.99) | 0.029 |
| Non-fatal MI** | 270(1.2%) | 330(1.4%) | 0.81(0.69, 0.95) | 0.011 |
| Non-fatal Stroke** | 127(0.6%) | 142(0.6%) | 0.89(0.70, 1.13) | 0.33 |

*The difference between the composite endpoint and the sum of death+non-fatal MI+non-fatal stroke indicates that 9 patients (2 clopidogrel and 7 placebo) suffered both a non-fatal stroke and a non-fatal MI.

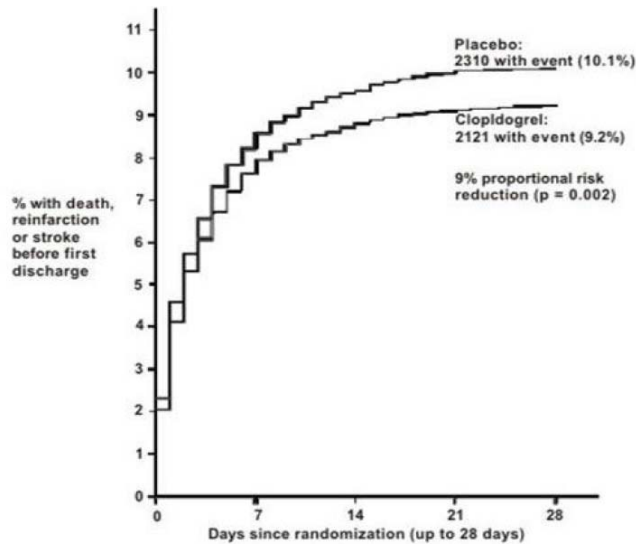
**Non-fatal MI and non-fatal stroke exclude patients who died (of any cause).

Figure 4: Cumulative Event Rates for Death in the COMMIT Study *



* All treated patients received aspirin

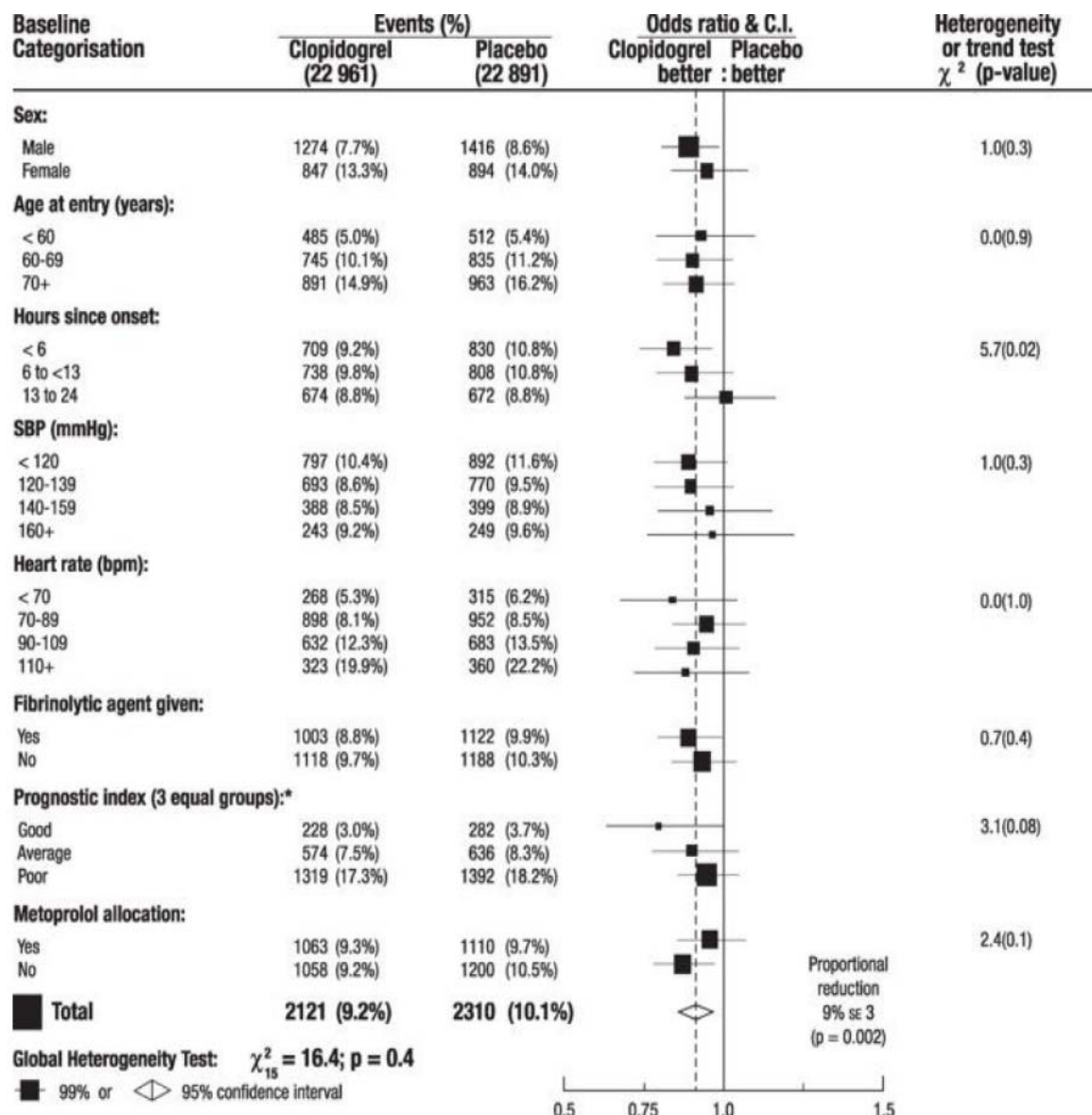
Figure 5: Cumulative Event Rates for the Combined Endpoint Re-Infarction, Stroke or Death in the COMMIT Study *



* All treated patients received aspirin.

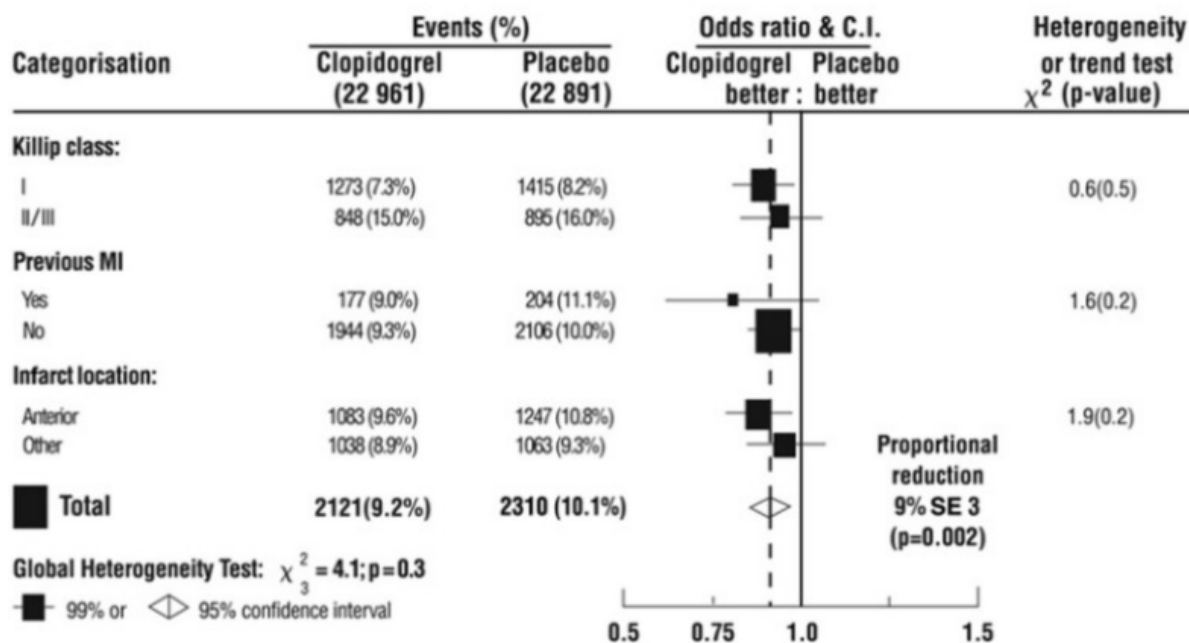
The effect of clopidogrel bisulfate did not differ significantly in various pre-specified subgroups as shown in Figure 6. The effect was also similar in non-prespecified subgroups including those based on infarct location, Killip class or prior MI history (see Figure 7). Such subgroup analyses should be interpreted cautiously.

Figure 6: Effects of Adding Clopidogrel bisulfate to Aspirin on the Combined Primary Endpoint across Baseline and Concomitant Medication Subgroups for the COMMIT Study



*Three similar-sized prognostic index groups were based on absolute risk of primary composite outcome for each patient calculated from baseline prognostic variables (excluding allocated treatments) with a Cox regression model.

Figure 7: Effects of Adding Clopidogrel bisulfate to Aspirin in the Non-Prespecified Subgroups in the COMMIT Study



14.2 Recent Myocardial Infarction, Recent Stroke, or Established Peripheral Arterial Disease

CAPRIE

The CAPRIE trial was a 19,185-patient, 304-center, international, randomized, double-blind, parallel-group study comparing clopidogrel bisulfate (75 mg daily) to aspirin (325 mg daily). The patients randomized had: 1) recent histories of myocardial infarction (within 35 days); 2) recent histories of ischemic stroke (within 6 months) with at least a week of residual neurological signs; or 3) established peripheral arterial disease. Patients received randomized treatment for an average of 1.6 years (maximum of 3 years).

The trial's primary outcome was the time to first occurrence of new ischemic stroke (fatal or not), new myocardial infarction (fatal or not), or other vascular death. Deaths not easily attributable to nonvascular causes were all classified as vascular.

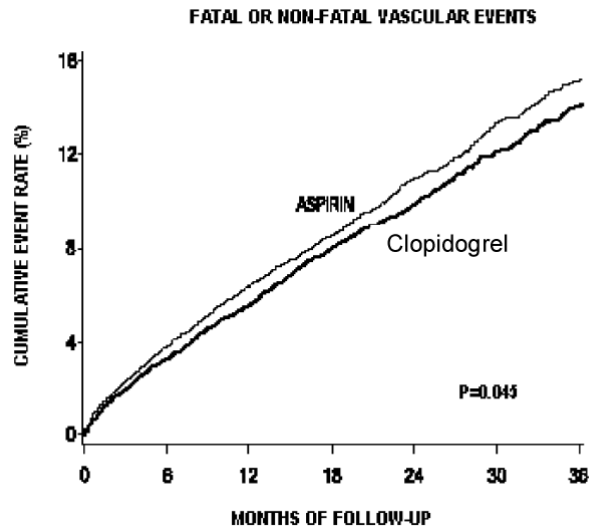
Table 6: Outcome Events in the CAPRIE Primary Analysis

| Patients | <u>clopidogrel bisulfate</u> n=9599 | <u>aspirin</u> n=9586 |
|--------------------------------|--|--------------------------|
| Ischemic stroke (fatal or not) | 438 (4.6%) | 461 (4.8%) |
| MI (fatal or not) | 275 (2.9%) | 333 (3.5%) |
| Other vascular death | 226 (2.4%) | 226 (2.4%) |
| Total | 939 (9.8%) | 1020 (10.6%) |

As shown in Table 6, clopidogrel bisulfate was associated with a lower incidence of outcome events, primarily MI. The overall relative risk reduction (9.8% vs. 10.6%) was 8.7%, $p=0.045$. Similar results were obtained when all-cause mortality and all-cause strokes were counted instead of vascular mortality and ischemic strokes (risk reduction 6.9%). In patients who survived an on-study stroke or myocardial infarction, the incidence of subsequent events was lower in the clopidogrel bisulfate group.

The curves showing the overall event rate are shown in Figure 8. The event curves separated early and continued to diverge over the 3-year follow-up period.

Figure 8: Fatal or Non-Fatal Vascular Events in the CAPRIE Study



The statistical significance favoring clopidogrel bisulfate over aspirin was marginal ($p=0.045$). However, because aspirin is itself effective in reducing cardiovascular events in patients with recent myocardial infarction or stroke, the effect of clopidogrel bisulfate is substantial.

The CAPRIE trial included a population that was randomized on the basis of 3 entry criteria. The efficacy of clopidogrel bisulfate relative to aspirin was heterogeneous across these randomized subgroups ($p=0.043$). It is not clear whether this difference is real or a chance occurrence. Although the CAPRIE trial was not designed to evaluate the relative benefit of clopidogrel bisulfate over aspirin in the individual patient subgroups, the benefit appeared to be strongest in patients who were enrolled because of peripheral vascular disease (especially those who also had a history of myocardial infarction) and weaker in stroke patients. In patients who were enrolled in the trial on the sole basis of a recent myocardial infarction, clopidogrel bisulfate was not numerically superior to aspirin.

14.3 Lack of Established Benefit of Clopidogrel bisulfate plus Aspirin in Patients with Multiple Risk Factors or Established Vascular Disease

CHARISMA

The CHARISMA trial was a 15,603 subject, randomized, double-blind, parallel group study comparing clopidogrel bisulfate (75 mg daily) to placebo for prevention of ischemic events in patients with vascular disease or multiple risk factors for atherosclerosis. All subjects were treated with aspirin 75 to 162 mg daily. The mean duration of treatment was 23 months. The study failed to demonstrate a reduction in the occurrence of the primary endpoint, a composite of CV death, MI, or stroke. A total of 534 (6.9%) patients in the clopidogrel bisulfate group versus 573 (7.4%) patients in the placebo group experienced a primary outcome event (p=0.22). Bleeding of all severities was more common in the subjects randomized to clopidogrel bisulfate.

16 HOW SUPPLIED/STORAGE AND HANDLING

Clopidogrel tablets USP 75 mg are available as pink colored, round, biconvex, film-coated tablets debossed with “CI” on one side and plain on other side. Tablets are provided as follows:

| | |
|------------------|-----------------|
| NDC 16729-218-10 | Bottles of 30 |
| NDC 16729-218-15 | Bottles of 90 |
| NDC 16729-218-16 | Bottles of 500 |
| NDC 16729-218-46 | Blisters of 100 |

Clopidogrel tablets USP 300 mg are available as pink colored, oval, biconvex, beveled edged, film-coated tablets debossed with “CL” on one side and plain on other side. Tablets are provided as follows:

| | |
|------------------|-----------------|
| NDC 16729-219-75 | Blisters of 30 |
| NDC 16729-219-46 | Blisters of 100 |

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

[See Medication Guide]

17.1 Benefits and Risks

- Summarize the effectiveness features and potential side effects of clopidogrel bisulfate.
- Tell patients to take clopidogrel bisulfate exactly as prescribed.
- Remind patients not to discontinue clopidogrel bisulfate without first discussing it with the physician who prescribed clopidogrel bisulfate.

17.2 Bleeding

Inform patients that they:

- will bruise and bleed more easily.
- will take longer than usual to stop bleeding.
- should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that TTP is a rare but serious condition that has been reported with clopidogrel bisulfate and other drugs in this class of drugs.
- Instruct patients to get prompt medical attention if they experience any of the following symptoms that cannot otherwise be explained: fever, weakness, extreme skin paleness, purple skin patches, yellowing of the skin or eyes, or neurological changes.

17.4 Invasive Procedures

Instruct patients to:

- inform physicians and dentists that they are taking clopidogrel bisulfate before any invasive procedure is scheduled.
- tell the doctor performing the invasive procedure to talk to the prescribing health care professional before stopping clopidogrel bisulfate.

17.5 Concomitant Medications

Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take [*see Warnings and Precautions (5) and Drug Interactions (7)*].

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