For the use only of a Registered Medical Practitioner or a Hospital or Laboratory

This package insert is continually updated: Please read carefully before using a new pack.

PLAVIX®
CLOPIDOGREL TABLETS I.P.

COMPOSITION
Each film coated tablet contains:
Clopidogrel Bisulphate I.P. 97.875 mg (molar equivalent of 75 mg of clopidogrel base)

List of Excipients
Each tablet contains hydrogenated castor oil, hydroxypropyl cellulose, mannitol E421, microcrystalline cellulose and polyethylene glycol 6000 as inactive ingredients. The pink film coating contains ferric oxide E172, hypromellose 2910, lactose monohydrate, titanium dioxide and triacetin. The tablets are polished with Carnauba wax.

Pharmaceutical Form
Film coated tablet.
Plavix® 75 mg film coated tablets are pink, round, biconvex, film coated, debossed with "75" on one side and "1171" on the other side.

INDICATIONS
Clopidogrel is indicated in adults for the prevention of atherothrombotic events in:

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 has 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.

Acute Coronary Syndrome
- For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave myocardial infarction [MI]) including patients who are to be managed medically and those who are to be managed with percutaneous coronary intervention (with or without stent) or CABG, clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke or refractory ischemia.
- For patients with ST-segment elevation acute myocardial infarction, clopidogrel has been shown to reduce the rate of death from any cause and the rate of a combined endpoint of death, re-infarction or stroke.

DOSAGE AND ADMINISTRATION
Recent MI, Recent Stroke, or Established Peripheral Arterial Disease
Clopidogrel should be given as a single daily dose of 75 mg.

Acute Coronary Syndrome
For patients with non-ST-segment elevation acute coronary syndrome (unstable angina/non-Q-wave MI), clopidogrel should be initiated with a single 300-mg loading dose and then continued at 75 mg once daily. Acetylsalisylic acid (ASA) (75 mg up to 325 mg once daily) should be initiated and continued in combination with clopidogrel. In CURE, most patients with Acute Coronary Syndrome also received heparin.

For patients with ST-segment elevation acute myocardial infarction, the recommended dose of clopidogrel is 75 mg once daily, administered in combination with ASA, with or without thrombolytics. Clopidogrel may be initiated with or without a loading dose (300 mg was used in CLARITY).

Pharmacogenetics

CYP2C19 poor metaboliser status is associated with diminished antiplatelet response to clopidogrel. A higher dose regimen (600-mg loading dose followed by 150 mg once daily) in poor metabolisers increases antiplatelet response (see Pharmacokinetics, Pharmacogenetics). Consider the use of higher clopidogrel doses in patients who are poor CYP2C19 metabolisers. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

SPECIAL POPULATIONS

Children: Safety and effectiveness in pediatric populations have not been established see Pharmacodynamics, Clinical Efficacy/Clinical Studies section).

Elderly: No dosage adjustment is necessary in elderly patients.

***Hepatic impairment*:** No dosage adjustment is necessary. See Precautions, Pharmacokinetics, Special populations section

Renal impairment: No dosage adjustment is necessary. See Precautions, Pharmacokinetics, Special populations section

ADMINISTRATION

Clopidogrel can be administered with or without food.

CONTRAINDICATIONS

- Hypersensitivity to the drug substance or any component of the product.
- Active pathological bleeding such as peptic ulcer or intracranial haemorrhage.

WARNINGS

None

PRECAUTIONS

Bleeding and haematological disorders

Due to the risk of bleeding and haematological undesirable effects, blood cell count determination and/or other appropriate testing should be promptly considered whenever such suspected clinical symptoms arise during the course of treatment (See Adverse Reaction). Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel should be undertaken with caution.

As with other anti-platelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions, and in patients receiving treatment with acetylsalicylic acid, heparin, glycoprotein IIb/IIIa inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), or selective serotonin reuptake inhibitors (SSRIs). If a patient is to undergo elective surgery and an antiplatelet effect is not desired, clopidogrel should be discontinued 5 to 7 days prior to surgery.

Clopidogrel prolongs bleeding time and should be used with caution in patients who have lesions with a propensity to bleed (particularly gastrointestinal and intraocular). Drugs that might induce

gastrointestinal lesions (such as acetylsalicylic acid and Non-Steroidal Anti-Inflammatory Drugs) should be used with caution in patients taking clopidogrel.

Patients should be told that it may take longer than usual to stop bleeding when they take clopidogrel alone or in combination with ASA, and that they should report any unusual bleeding (site or duration) to their physician. Patients should inform physicians and dentists that they are taking clopidogrel before any surgery is scheduled and before any new drug is taken.

Recent ischemic stroke
In patients with recent transient ischaemic attack or stroke who are at high risk of recurrent ischaemic events, the combination of ASA and clopidogrel has been shown to increase major bleeding. Therefore, such addition should be undertaken with caution outside of clinical situations where the combination has proven to be beneficial.

Thrombotic Thrombocytopenic Purpura (TTP)
Thrombotic Thrombocytopenic Purpura (TTP) has been reported very rarely following the use of clopidogrel, sometimes after a short exposure. It is characterised by thrombocytopenia and microangiopathic hemolytic anemia associated with either neurological findings, renal dysfunction or fever. TTP is a potentially fatal condition requiring prompt treatment, including plasmapheresis (plasma exchange).

Acquired haemophilia
Acquired haemophilia has been reported following use of clopidogrel. In cases of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered. Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, and clopidogrel should be discontinued.

Cytochrome P450 2C19 (CYP2C19)
Pharmacogenetics: In patients who are CYP2C19 poor metabolisers clopidogrel at recommended doses forms less of the active metabolite of clopidogrel and has a smaller effect on platelet function.
Poor metabolisers with acute coronary syndrome or undergoing percutaneous coronary intervention treated with clopidogrel at recommended doses may exhibit higher cardiovascular event rates than do patients with normal CYP2C19 function (see Pharmacokinetics, Pharmacogenetics). Tests are available to identify a patient's CYP2C19 genotype; these tests can be used as an aid in determining therapeutic strategy. Consider the use of higher clopidogrel doses in patients who are known CYP2C19 poor metabolisers (see Pharmacogenetics, Dosage and Administration, General).

Cross-reactivity among thienopyridines
Patients should be evaluated for history of hypersensitivity to another thienopyridine (such as ticlopidine, prasugrel) since cross-reactivity among thienopyridines has been reported. (see Adverse Reaction section). Thienopyridines may cause mild to severe allergic reactions such as rash, angioedema, or haematological reactions such as thrombocytopaenia and neutropaenia. Patients who had developed a previous allergic reaction and/or haematological reaction to one thienopyridine may have an increased risk of developing the same or another reaction to another thienopyridine. Monitoring for cross-reactivity is advised.

Renal impairment
Experience with clopidogrel is limited in patients with severe renal impairment. Therefore, clopidogrel should be used with caution in this population**.**

Hepatic impairment
Experience is limited in patients with severe hepatic disease who may have bleeding diatheses. Clopidogrel should therefore be used with caution in this population.

Excipients
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucosegalactose malabsorption should not take this medicine.

INTERACTIONS

Drugs associated with bleeding risk: There is an increased risk of bleeding due to the potential additive effect. The concomitant administration of drugs associated with bleeding risk should be undertaken with caution.

Thrombolytics: The safety of the concomitant administration of clopidogrel, thrombolytics and heparin was assessed in patients with acute myocardial infarction. The incidence of clinically significant bleeding was similar to that observed when thrombolytics and heparin are co-administered with acetylsalicylic acid.

Glycoprotein IIb/IIIa inhibitors: As a pharmacodynamic interaction between clopidogrel and glycoprotein IIb/IIIa inhibitors is possible, concomitant use should be undertaken with caution.

Injectable anticoagulants: In a clinical study conducted in healthy subjects, clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on the inhibition of platelet aggregation induced by clopidogrel. As a pharmacodynamic interaction between clopidogrel and heparin is possible, concomitant use should be undertaken with caution.

Oral anticoagulants: Because of the increased risk of bleeding, the concomitant administration of warfarin with clopidogrel should be undertaken with caution**.**

Acetylsalicylic acid: Acetylsalicylic acid did not modify the clopidogrel-mediated inhibition of ADP-induced platelet aggregation, but clopidogrel potentiated the effect of acetylsalicylic acid on collagen-induced platelet aggregation. However, concomitant administration of 500mg of acetylsalicylic acid twice a day for one day did not significantly increase the prolongation of bleeding time induced by clopidogrel intake. As a pharmacodynamic interaction between clopidogrel and acetylsalicylic acid is possible, concomitant use should be undertaken with caution. However clopidogrel and ASA (75-325 mg once daily) have been administered together for up to one year.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs): In a clinical study conducted in healthy volunteers, the concomitant administration of clopidogrel and naproxen increased occult gastrointestinal blood loss. However, due to the lack of interaction studies with other NSAIDs it is presently unclear whether there is an increased risk of gastrointestinal bleeding with all NSAIDs. Consequently, NSAIDs and clopidogrel should be co-administered with caution.

Selective Serotonin Reuptake Inhibitors (SSRIs): Since SSRIs affect platelet activation and increase the risk of bleeding, the concomitant administration of SSRIs with clopidogrel should be undertaken with caution.

Other concomitant therapy:
Since clopidogrel is metabolised to its active metabolite partly by CYP2C19, use of drugs that inhibit the activity of this enzyme would be expected to result in reduced drug levels of the active metabolite of clopidogrel. The clinical relevance of this interaction is uncertain. Concomitant use of strong or moderate CYP2C19 inhibitors (e.g., omeprazole) should be discouraged (see Precautions, and Pharmacokinetics, Pharmacogenetics). If a proton pump inhibitor is to be used concomitantly with clopidogrel, consider using one with less CYP2C19 inhibitory activity, such as pantoprazole.

Proton Pump Inhibitors (PPI): In a crossover clinical study, clopidogrel (300-mg loading dose followed by
75 mg/day) alone and with omeprazole (80 mg at the same time as clopidogrel) were administered for 5 days. The exposure to the active metabolite of clopidogrel was decreased by 45% (Day 1) and 40% (Day 5) when clopidogrel and omeprazole were administered together. Mean inhibition of platelet aggregation (IPA) with 5 μM ADP was diminished by 39% (24 hours) and 21% (Day 5) when clopidogrel and omeprazole were administered together.

In a second interaction study with omeprazole 80 mg administered 12 hours apart from the clopidogrel standard regimen, the results were similar, indicating that administering clopidogrel and omeprazole at different times does not prevent their interaction that is likely to be driven by the inhibitory effect of omeprazole on CYP2C19.

In a third interaction study with omeprazole 80 mg administered with a higher dose regimen of clopidogrel (600-mg loading dose followed by 150 mg/day), a degree of interaction was observed similar to that noted in the other omeprazole interaction studies. However, active metabolite formation and platelet aggregation were at the same level as clopidogrel administered alone at the standard dose regimen.

In a crossover clinical study, healthy subjects were administered clopidogrel (300-mg loading dose followed by 75 mg/day) alone and with pantoprazole (80 mg at the same time as clopidogrel) for 5 days.
The exposure to the active metabolite of clopidogrel was decreased by 20% (Day 1) and 14% (Day 5) when clopidogrel and pantoprazole were administered together. Mean inhibition of platelet aggregation was diminished by 15% (24 hours) and 11% (Day 5) when clopidogrel and pantoprazole were administered together. These results indicate that clopidogrel can be administered with pantoprazole.

The CURRENT trial compared 2 dosing regimens of clopidogrel (600-mg loading dose, then 150 mg/day for 6 days followed by 75 mg/day up to 30 days vs. 300-mg loading dose followed by 75 mg/day up to 30 days). A subanalysis (n=18,432) correlated PPI use (mainly omeprazole and pantoprazole) at randomization and hospital discharge and demonstrated no interaction between clopidogrel and PPI use for the primary endpoint (CV death, MI or stroke) or any secondary endpoints, including stent thrombosis.

A number of other clinical studies have been conducted with clopidogrel and other concomitant medications to investigate the potential for pharmacodynamic and pharmacokinetic interactions. No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both atenolol and nifedipine. Furthermore, the pharmacodynamic activity of clopidogrel was not significantly influenced by the co-administration of phenobarbital or oestrogen.

The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel. Antacids did not modify the extent of clopidogrel absorption.

Although the administration of clopidogrel 75 mg/day did not modify the pharmacokinetics of S-warfarin (a CYP2C9 substrate) or INR in patients receiving long-term warfarin therapy, coadministration of clopidogrel with warfarin increases the risk of bleeding because of independent effects on hemostasis.

However, at high concentrations *in vitro*, clopidogrel inhibits CYP2C9.It is unlikely that clopidogrel may interfere with the metabolism of drugs such as phenytoin and tolbutamide and the NSAIDs, which are metabolised by cytochrome P450 2C9. Data from the CAPRIE study indicate that phenytoin and tolbutamide can be safely co-administered with clopidogrel.

CYP2C8 substrate drugs: Clopidogrel has been shown to increase repaglinide exposure in healthy volunteers. *In vitro* studies have shown the increase in repaglinide exposure is due to inhibition of CYP2C8 by the glucuronide metabolite of clopidogrel. Due to the risk of increased plasma concentrations, concomitant administration of clopidogrel and drugs primarily cleared by CYP2C8 metabolism (e.g., repaglinide, paclitaxel) should be undertaken with caution.

In addition to the above specific interaction studies, patients entered into large clinical studies (CAPRIE and CURE) received a variety of concomitant medications including diuretics, beta-blocking agents, angiotensin converting enzyme inhibitors, calcium antagonists, cholesterol lowering agents, coronary vasodilators, anti-diabetic agents (including insulin), anti-epileptic agents, GPIIb/IIIa antagonists and hormone replacement therapy, without evidence of clinically significant adverse interactions.

PREGNANCY
Reproduction studies have been performed in rats at doses up to 500mg/kg per day and in rabbits at doses up to 300mg/kg per day and have revealed no evidence of impaired fertility or harm to the foetus 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, this drug should not be used during pregnancy, unless, in the opinion of the physician, there is a clear need.

LACTATION
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, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to a nursing woman.

DRIVING A VEHICLE OR PERFORMING OTHER HAZARDOUS TASKS
No impairment of driving or psychometric performance was observed following clopidogrel administration.

ADVERSE REACTIONS

Clinical studies experience:
Clopidogrel has been evaluated for safety in more than 42,000 patients, including over 9,000 patients treated for 1 year or more. Clopidogrel 75 mg/day was well tolerated compared to acetylsalicylic acid (ASA) 325 mg/day in CAPRIE. The overall tolerability of clopidogrel in this study was similar to ASA regardless of age, gender and ethnicity. The clinically relevant adverse effects observed in CAPRIE, CURE, CLARITY and COMMIT are discussed below.

***Haemorrhagic disorders**:*
In CAPRIE, the overall incidence of bleeding on clopidogrel and ASA was the same (9.3%). The incidence of severe cases was 1.4% and 1.6% in the clopidogrel and ASA groups, respectively.

In patients receiving clopidogrel, gastrointestinal bleeding occurred at a rate of 2.0% and required hospitalisation in 0.7%. In patients receiving ASA, the corresponding rates were 2.7% and 1.1%, respectively.

The overall incidence of other bleeding disorders was higher in the clopidogrel group (7.3%) compared to ASA (6.5%). However, the incidence of severe events was similar in both treatment groups (0.6% vs. 0.4%). The most frequent events reported were purpura/bruising and epistaxis. Other less frequently reported events were haematoma, haematuria and eye bleeding (mainly conjunctival).

The incidence of intracranial bleeding was 0.4% for clopidogrel compared to 0.5% for ASA.

In CURE, there was an increase in major and minor bleeding between the Clopidogrel + ASA group compared with the placebo+ASA group (event rates 3.7% vs. 2.7%, for major, respectively, and 5.1% vs. 2.4% for minor). The principal sites for major bleeding included gastrointestinal and at arterial puncture sites.

The increase in life-threatening bleeding in the clopidogrel+ASA group compared to the clopidogrel- placebo + ASA group was not statistically significant (2.2% vs. 1.8%). There was no difference between the two groups in the rate of fatal bleeding (0.2% in both groups). The rate of non-lifethreatening major bleeding was significantly higher in the clopidogrel+ASA group compared with the placebo+ASA group (1.6% vs. 1%), and the incidence of intracranial bleeding was 0.1% in both groups.

The major bleeding event rate for Clopidogrel + ASA was dose-dependent on ASA (<100 mg: 2.6%; 100-200 mg: 3.5%; >200 mg: 4.9%) as was the major bleeding event rate for placebo + ASA (<100 mg: 2.0%; 100-200 mg: 2.3%; >200 mg: 4.0%).

There was no excess in major bleeds within 7 days after coronary bypass graft surgery in patients who stopped therapy more than five days prior to surgery (4.4% clopidogrel + ASA vs. 5.3% placebo + ASA). In patients who remained on therapy within five days of bypass graft surgery, the event rate was 9.6% for clopidogrel + ASA, and 6.3% for placebo + ASA.

The overall incidence of bleeding is described in Table 1 for patients receiving both clopidogrel and ASA in CURE.

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

Table 1 - CURE Incidence of bleeding complications (% patients)

Event	CLOPIDOGREL (+ ASA)[a] (n=6259)	Placebo (+ASA)[a] (n=6303)	P-value
Major bleeding [b]	3.7 [c]	2.7 [d]	0.001
Life-threatening bleeding	2.2	1.8	0.13
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	0.005
Significantly disabling	0.4	0.3	
Intraocular bleeding with significant loss of vision	0.05	0.03	
Requiring 2-3 units of blood	1.3	0.9	
Minor bleeding ¶	5.1	2.4	<0.001

a Other standard therapies were used as appropriate.
b Life threatening and other major bleeding.
c Major bleeding event rate for clopidogrel + ASA was dose-dependent on ASA: <100 mg=2.6%; 100 200 mg= 3.5%; >200 mg=4.9%
Major bleeding event rates for clopidogrel + ASA by age were: <65 years = 2.5%, ≥65 to <75 years = 4.1%, ≥75 years 5.9%
d Major bleeding event rate for placebo + ASA was dose-dependent on ASA: <100 mg=2.0%; 100 200 mg= 2.3%; >200 mg=4.0%
Major bleeding event rates for placebo + ASA by age were: <65 years = 2.1%, ≥65 to <75 years = 3.1%, ≥75 years = 3.6%
Led to interruption of study medication

In CLARITY, the incidence of major bleeding (defined as intracranial bleeding or bleeding associated with a fall in hemoglobin >5 g/dL) was similar between groups (1.3% versus 1.1% in the clopidogrel + ASA and in the placebo + ASA groups, respectively). This was consistent across subgroups of patients defined by baseline characteristics, and type of fibrinolytics or heparin therapy. The incidence of fatal bleeding (0.8% versus 0.6% in the clopidogrel + ASA and in the placebo + ASA groups, respectively) and intracranial hemorrhage (0.5% versus 0.7%, respectively) was low and similar in both groups.

The overall rate of noncerebral major bleeding or cerebral bleeding in COMMIT was low and similar in both groups as shown in Table 2 below.

Table 2 - Number (%) of Patients with Bleeding Events in COMMIT

Type of bleeding	Clopidogrel (+ ASA) (N = 22961)	Placebo (+ ASA) (N = 22891)	P-value
Major[a] noncerebral or cerebral bleeding[b]	134 (0.6%)	125 (0.5%)	0.59
Major noncerebral	82 (0.4%)	73 (0.3%)	0.48
Fatal	36 (0.2%)	37 (0.2%)	0.90
Hemorrhagic stroke	55 (0.2%)	56 (0.2%)	0.91
Fatal	39 (0.2%)	41 (0.2%)	0.81
Other noncerebral bleeding (non major)	831 (3.6%)	721 (3.1%)	0.005
Any noncerebral bleeding	896 (3.9%)	777 (3.4%)	0.004

a Major bleeds are cerebral bleeds or non-cerebral bleeds thought to have caused death or that required transfusion.
b The relative rate of major noncerebral or cerebral bleeding was independent of age. Event rates for clopidogrel + ASA by age were: <60 years=0.3%, ≥60 to <70 years=0.7%, ≥70 years 0.8%. Event rates for placebo + ASA by age were: <60 years=0.4%, ≥60 to <70 years=0.6%, ≥70 years=0.7%.

Haematological disorders:
In CAPRIE, severe neutropaenia (<0.450G/L) was observed in 4 patients (0.04%) on clopidogrel and 2 patients (0.02%) on ASA.

Two of the 9599 patients who received clopidogrel and none of the 9586 patients who received ASA had neutrophils counts of zero. Although the risk of myelotoxicity with clopidogrel appears to be quite low, this possibility should be considered when a patient receiving clopidogrel demonstrates fever or other sign of infection.

One case of aplastic anaemia occurred on clopidogrel treatment.

The incidence of severe thrombocytopaenia (<80 G/L) was 0.2% on clopidogrel and 0.1% on ASA; very rare cases of platelet count <=30 G/L have been reported.

In CURE and CLARITY, the number of patients with thrombocytopenia or neutropenia was similar in both groups.

Other clinically relevant adverse drug reactions pooled from CAPRIE and CURE, CLARITY and COMMIT studies with an incidence < 0.1% as well as all serious and relevant ADR with an incidence < 0.1 % are presented below.

The following CIOMS frequency rating is used, when applicable:
Very common ≥ 10 %; Common ≥ 1 and <10 % ; Uncommon ≥ 0.1 and <1 %;
Rare ≥ 0.01 and <0.1 %; Very rare <0.01 %, Unknown (cannot be estimated from available data).

- **Central and peripheral nervous system disorders**
    - Uncommon: **headache, dizziness, paraesthesia**
    - Rare: **vertigo**
- **Gastrointestinal system disorders**
    - Common: dyspepsia, abdominal pain, diarrhoea
    - Uncommon: nausea, gastritis, flatulence, constipation, vomiting, gastric ulcer, duodenal ulcer
- **Platelet, bleeding and clotting disorders**
    - Uncommon: bleeding time increased, platelets decreased
- **Skin and appendages disorders:**
    - Uncommon: rash, pruritus
- **White cell and RES disorders**
    - Uncommon: leucopenia, neutrophils decreased, eosinophilia

Post-marketing experience
Adverse reactions have been ranked under heading of system-organ class. Frequencies for the following adverse reactions are not known (cannot be estimated from available data).

Blood and the lymphatic system disorders:
- Serious cases of bleeding, mainly skin, musculo-skeletal, eye (conjunctival, ocular, retinal) and respiratory tract bleeding, epistaxis, haematuria and haemorrhage of operative wound; cases of bleeding with fatal outcome (especially intracranial, gastrointestinal and retroperitoneal haemorrhage), agranulocytosis, aplastic anaemia/pancytopenia, thrombotic thrombocytopenic purpura (TTP), acquired haemophilia A.

Cardiac disorders:

- **Kounis syndrome (vasospastic allergic angina** / allergic myocardial infarction**)** in the context of a hypersensitivity reaction due to clopidogrel

Immune system disorders:

- Anaphylactoid reactions, serum sickness
- Cross-reactive drug hypersensitivity among thienopyridines (such as ticlopidine, prasugrel) (see Precautions section)

Psychiatric disorders:

- Confusion, hallucinations

Nervous system disorders:

- Taste disturbances

Vascular disorders:

- Vasculitis, hypotension

Respiratory, thoracic and mediastinal disorders:

- Bronchospasm, interstitial pneumonitis, eosinophilic pneumonia

Gastrointestinal disorders:

- Colitis (including ulcerative or lymphocytic colitis), pancreatitis, stomatitis

Hepato-biliary disorders:

- Hepatitis (non-infectious), acute liver failure

Skin and subcutaneous tissue disorders:

- Maculopapular erythematous or exfoliative rash, urticaria, pruritus, angioedema, bullous dermatitis (erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, **acute generalised exanthematous pustulosis (AGEP)**), drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), eczema, lichen planus.

Musculoskeletal, connective tissue and bone disorders:

- Arthralgia, arthritis, myalgia

Renal and urinary disorders:

- Glomerulopathy

Reproductive systems and breast disorders:

- Gynaecomastia

General disorders and administration site conditions:

- Fever

Investigations:

- Abnormal liver function test, blood creatinine increase

OVERDOSAGE

Overdose following clopidogrel administration may lead to prolonged bleeding time and subsequent bleeding complications. Appropriate therapy should be considered if bleeding is observed. No antidote to the pharmacological activity of clopidogrel has been found. If prompt correction of prolonged bleeding time is required, platelet transfusion may reverse the effects of clopidogrel.

PHARMACODYNAMICS

Mode of Action/ Pharmacodynamic characteristics

Clopidogrel is a prodrug, one of whose metabolites is an inhibitor of platelet aggregation. Clopidogrel must be metabolised 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. Due to the irreversible binding, platelets exposed are affected for the remainder of their lifespan (approximately 7-10 days) and recovery of normal platelet function occurs at a rate consistent with platelet turnover. Platelet aggregation induced by agonists other than ADP is also inhibited by blocking the amplification of platelet activation by released ADP.

Because the active metabolite is formed by CYP450 enzymes, some of which are polymorphic or subject to inhibition by other drugs, not all patients will have adequate platelet inhibition.

Repeated doses of 75 mg/day produced substantial inhibition of ADP-induced platelet aggregation from the first day; this increased progressively and reached steady state between Day 3 and Day 7. At steady state, the average inhibition level observed with a dose of 75 mg/day was between 40% and 60%. Platelet aggregation and bleeding time gradually returned to baseline values, generally within 5 days after treatment was discontinued.

Clinical efficacy / Clinical studies

The clinical evidence for the efficacy of clopidogrel is derived from four double-blind trials involving more than 81,090 patients: the CAPRIE study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events), a comparison of clopidogrel to ASA, and the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events), the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy – Thrombolysis in Myocardial Infarction), and the COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial / Second Chinese Cardiac Study), studies comparing clopidogrel to placebo, both given in combination with ASA and other standard therapy.

Recent Myocardial Infarction (MI), Recent Stroke or Established Peripheral Arterial Disease The CAPRIE trial was a 19,185-patient, 304-center, international, randomized, double-blind, parallel group study comparing clopidogrel (75 mg daily) to ASA (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) objectively 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 (See Table 4 below).
As shown in the table, clopidogrel was associated with a lower incidence of outcome events of every kind. The overall 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 again lower in the clopidogrel group.

The curves showing the overall event rate are shown in Figure 1. The event curves separated early and continued to diverge over the 3-year follow-up period.
Although the statistical significance favoring clopidogrel over ASA was marginal (P=0.045), and represents the result of a single trial that has not been replicated, the comparator drug, ASA, is itself effective (vs. placebo) in reducing cardiovascular events in patients with recent myocardial infarction or stroke. Thus, the difference between clopidogrel and placebo, although not measured directly, is substantial.

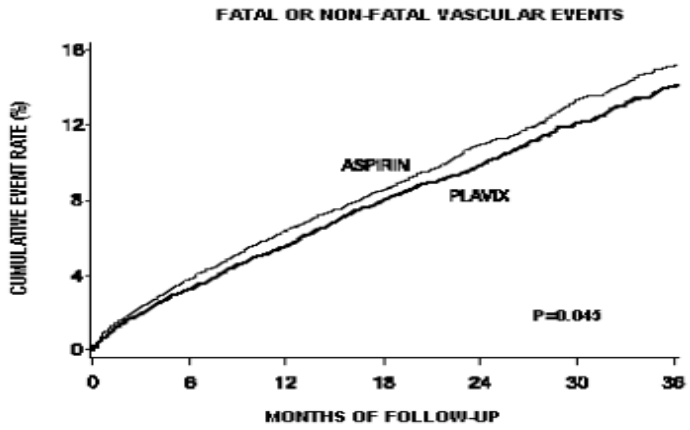
The CAPRIE trial included a population that was randomized on the basis of 3 entry criteria. The efficacy of clopidogrel relative to ASA was heterogeneous across these randomized subgroups (P=0.043). It is not clear whether this difference is real or a chance occurrence. Although the CAPRIE trial was not designed to evaluate the relative benefit of clopidogrel over ASA 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 was not numerically superior to ASA.

In the meta-analyses of studies of ASA vs. placebo in patients similar to those in CAPRIE, ASA was associated with a reduced incidence of thrombotic events. There was a suggestion of heterogeneity in these studies too, with the effect strongest in patients with a history of myocardial infarction, weaker in patients with a history of stroke, and not discernible in patients with a history of peripheral vascular disease. With respect to the inferred comparison of clopidogrel to placebo, there is no indication of heterogeneity.

Table 4 - Outcome Events in the CAPRIE Primary Analysis

	Clopidogrel	ASA
Patients	9599	9586
IS (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%)

Figure 1 - Fatal or Non-Fatal Vascular Events in the CAPRIE Study



Acute Coronary Syndrome

The CURE study included 12,562 patients with acute coronary syndrome without ST segment elevation (unstable angina or non-Q-wave myocardial infarction) 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 segment elevation) or elevated cardiac enzymes clopidogrel- 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 (300 mg loading dose followed by 75 mg/day) or placebo, and were treated for up to one year. Patients also received ASA (75-325 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 (9.30%) in the clopidogrel-treated group and 719 (11.41%) in the placebo-treated group, a 20% relative risk reduction (95% CI of 10% 28%; p=0.00009) for the clopidogrel-treated group (see Table 5 below).

At the end of 12 months, the number of patients experiencing the co-primary outcome (CV death, MI, stroke or refractory ischemia) was 1035 (16.54%) in the clopidogrel-treated group and 1187 (18.83%) in the placebo-treated group, a 14% relative risk reduction (95% CI of 6% 21%, p=0.0005) for the clopidogrel-treated group (see Table 5).

In the clopidogrel-treated group, each component of the two primary endpoints (CV death, MI, stroke, refractory ischemia) occurred less frequently than in the placebo-treated group.

The benefits of clopidogrel hydrogen sulfate were maintained throughout the course of the trial (up to 12 months) (see Figure 2 below).

In CURE, the use of clopidogrel 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 were independent of the use of other acute and long-term cardiovascular therapies, including heparin/LMWH (low molecular weight heparin), IV glycoprotein IIb/IIIa (GPIIb/IIIa) inhibitors, lipidlowering drugs, beta-blockers, and ACE-inhibitors. The efficacy of clopidogrel was observed independently of the dose of ASA (75-325 mg once daily). The use of oral anticoagulants, non-study antiplatelet drugs and chronic NSAIDs was not allowed in CURE.

The use of clopidogrel in CURE was associated with a decrease in the use of thrombolytic therapy (71 patients [1.1%] in the clopidogrel group, 126 patients [2.0%] in the placebo group; relative risk reduction of 43%, P=0.0001), and GPIIb/IIIa inhibitors (369 patients [5.9%] in the clopidogrel group, 454 patients [7.2%] in the placebo group, relative risk reduction of 18%, P=0.003). The use of clopidogrel in CURE did not impact the number of patients treated with CABG or PCI (with or without stenting) (2253 patients [36.0%] in the clopidogrel group, 2324 patients [36.9%] in the placebo group; relative risk reduction of 4.0%, P=0.1658).

Table 5 - Outcome Events in the CURE Primary Analysis

Outcome	Clopidogrel (+ ASA)[a] (n=6259)	Placebo (+ ASA)[a] (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=0.00009
Co-primary outcome (Cardiovascular death, MI, Stroke, Refractory Ischemia)	1035 (16.5%)	1187 (18.8%)	14% (6.2, 20.6) P=0.00052
All Individual Outcome Events:[b]			
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)
Refractory ischemia	544 (8.7%)	587 (9.3%)	7% (-4.0, 18.0)

a Other standard therapies were used as appropriate.

b 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.

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

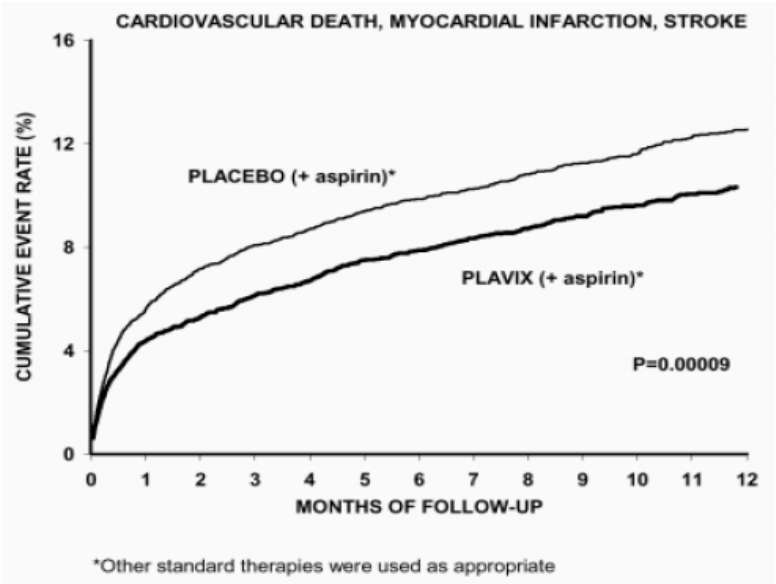
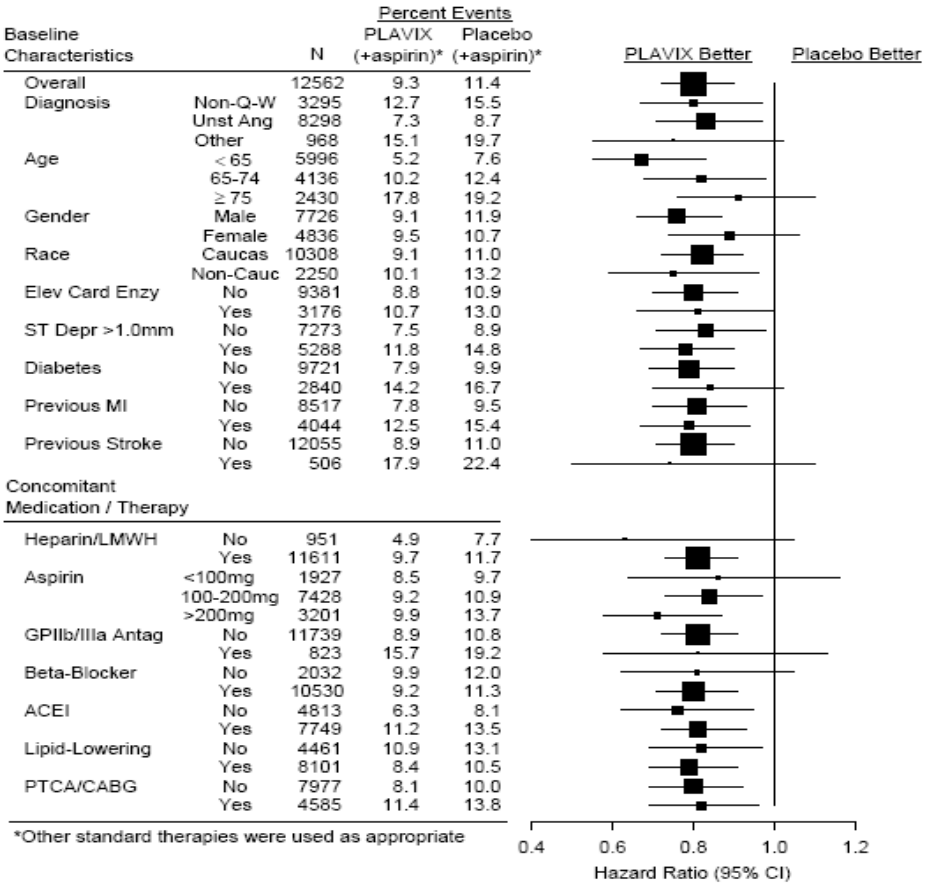


Figure 3 - Hazard Ratio for Patient Baseline Characteristics and On-Study Concomitant Medications/Interventions for the CURE Study



In patients with ST-segment elevation acute myocardial infarction, safety and efficacy of clopidogrel have been evaluated in two randomized, placebo controlled, double-blind studies, COMMIT, a large outcome study, and CLARITY, a supportive study of a surrogate endpoint.
The randomized, double-blind, placebo-controlled CLARITY trial included 3,491 patients presenting within 12 hours of the onset of an ST elevation myocardial infarction and planned for thrombolytic therapy. Patients were randomized to receive clopidogrel (300-mg loading dose, followed by 75 mg/day) or placebo until angiography, discharge, or Day 8. Patients also received ASA (150 to 325 mg as a loading dose, followed by 75 to 162 mg/day), a fibrinolytic agent and, when appropriate, heparin for 48 hours. The patients were followed for 30 days.

The primary endpoint was the occurrence of the composite of an occluded infarct related artery (defined as TIMI Flow Grade 0 or 1) on the predischarge angiogram, or death or recurrent myocardial infarction by the clopidogrel-time of the start of coronary angiography.

The patient population was mostly Caucasian (89.5%) and included 19.7% women and 29.2% patients ≥ 65 years. A total of 99.7% of patients received fibrinolytics (fibrin specific: 68.7%, non fibrin specific: 31.1%), 89.5% heparin, 78.7% beta blockers, 54.7% ACE inhibitors and 63% statins.

The number of patients who reached the primary endpoint was 262 (15.0%) in the clopidogrel-treated group and 377 (21.7%) in the placebo group, but most of the events related to the surrogate endpoint of vessel patency (see Figure 4 and Table 6 below).

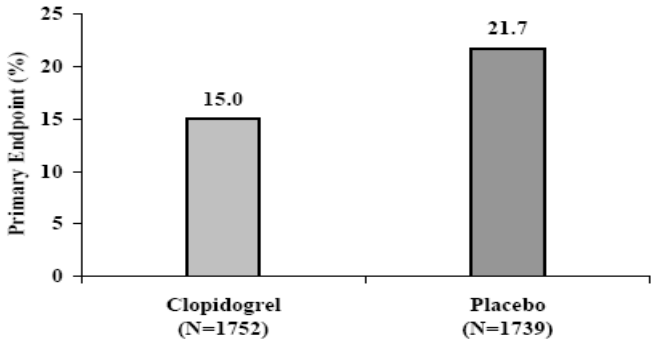
The randomized, double-blind, placebo-controlled, 2x2 factorial design COMMIT trial included 45,852 patients presenting within 24 hours of the onset of the symptoms of suspected myocardial infarction with supporting ECG abnormalities (i.e., ST elevation, ST depression or left bundle-branch block). Patients were randomized to receive clopidogrel (75 mg/day) or placebo, in combination with ASA (162 mg/day), for 28 days or until hospital discharge whichever came first.

The co-primary endpoints were death from any cause and the first occurrence of re infarction, stroke or death. The patient population included 28% women, 58% patients ≥60 years (26% patients ≥70 years) and 55% patients who received thrombolytics, 68% received ACE-inhibitors, and only 3% had percutaneous coronary intervention (PCI).

As shown in Table 7, and Figure 5 and Figure 6 below, clopidogrel 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).

The effect of clopidogrel did not differ significantly in various pre-specified sub-groups as shown in Figure 7. Additionally, the effect was similar in non-prespecified subgroups including those based on infarct location, Killip class or prior MI history (see Figure 8). Such sub-group analyses should be interpreted very cautiously.

Figure 4 - Event Rates for the Primary Composite Endpoint in the CLARITY Study



Based on odds of an occluded infarct-related artery (TFG 0/1), death or MI by angiography for clopidogrel versus placebo (OR: 0.64 [0.53 to 0.76]; p < 0.001)

Table 6 - Event Rates for the Primary Composite Endpoint in the CLARITY Study

	Clopidogrel 1752	Placebo 1739	OR	95% CI
Number (%) of patients reporting the composite endpoint	262 (15.0%)	377 (21.7%)	0.64	0.53, 0.76
Occluded IRA				
N (subjects undergoing angiography)	1640	1634		
n (%) patients reporting endpoint	192 (11.7%)	301 (18.4%)	0.59	0.48, 0.72
Death				
n (%) patients reporting endpoint	45 (2.6%)	38 (2.2%)	1.18	0.76, 1.83
Recurrent MI				
n (%) patients reporting endpoint	44 (2.5%)	62 (3.6%)	0.69	0.47, 1.02

The total number of patients with a component event (occluded IRA, death, or recurrent MI) is greater than the number of patients with a composite event because some patients had more than a single type of component event

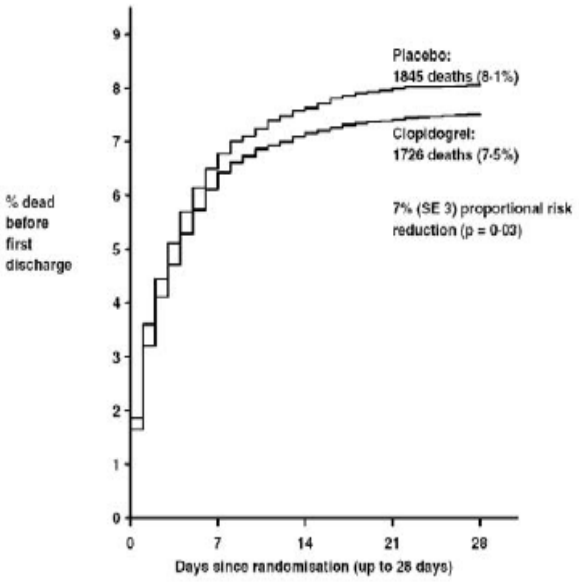
Table 7 - Outcome Events in the COMMIT Analysis

Event	Clopidogrel (+ ASA) (N = 22,961)	Placebo (+ ASA) (N = 22,891)	Odds ratio (95% CI)	p-value
Composite endpoint: Death, MI, or Stroke[a]	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[b]	270 (1.2%)	330 (1.4%)	0.81 (0.69, 0.95)	0.011
Non-fatal Stroke[b]	127 (0.6%)	142 (0.6%)	0.89 (0.70, 1.13)	0.33

a 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.

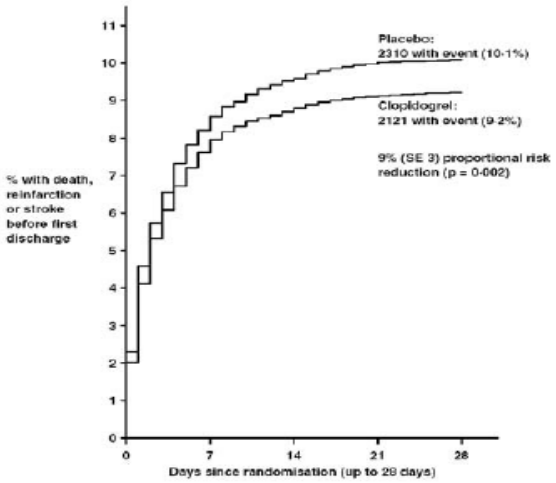
b Non-fatal MI and non-fatal stroke exclude patients who died (of any cause).

Figure 5 - Cumulative Event Rates for Death in the COMMIT Study[a]



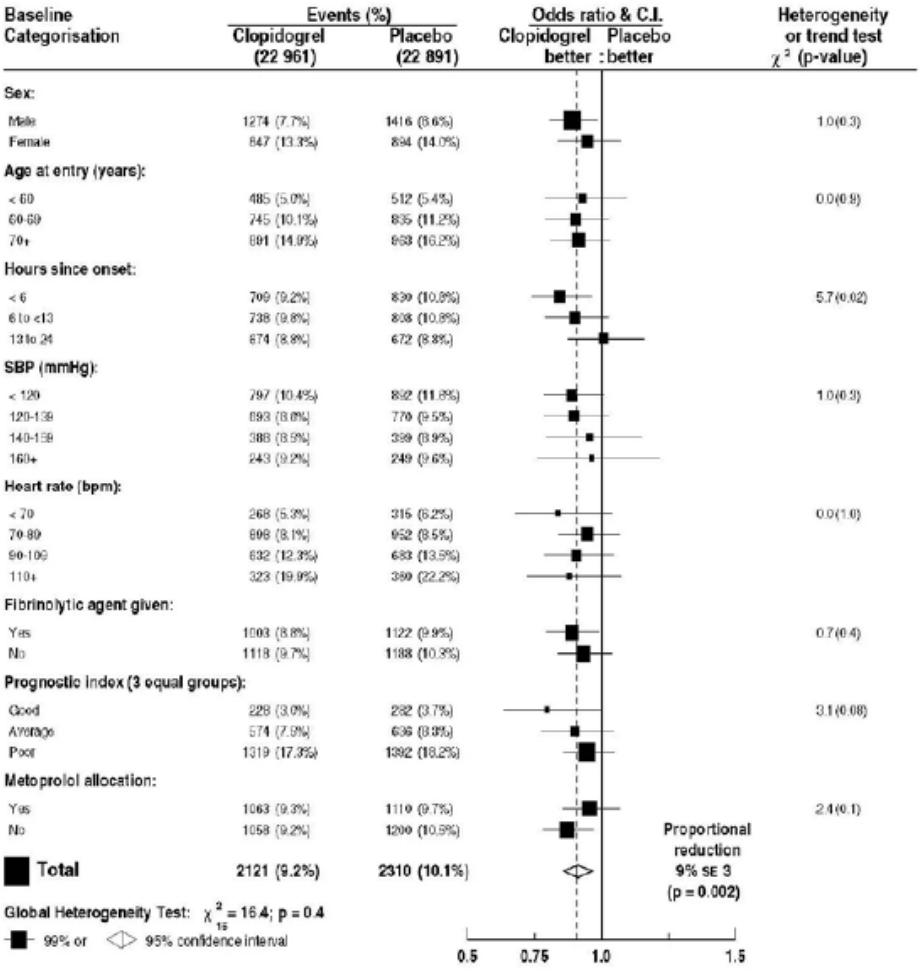
a All treated patients received ASA

Figure 6 - Cumulative Event Rates for the Combined Endpoint Re-Infarction, Stroke or Death in the COMMIT Study [a]



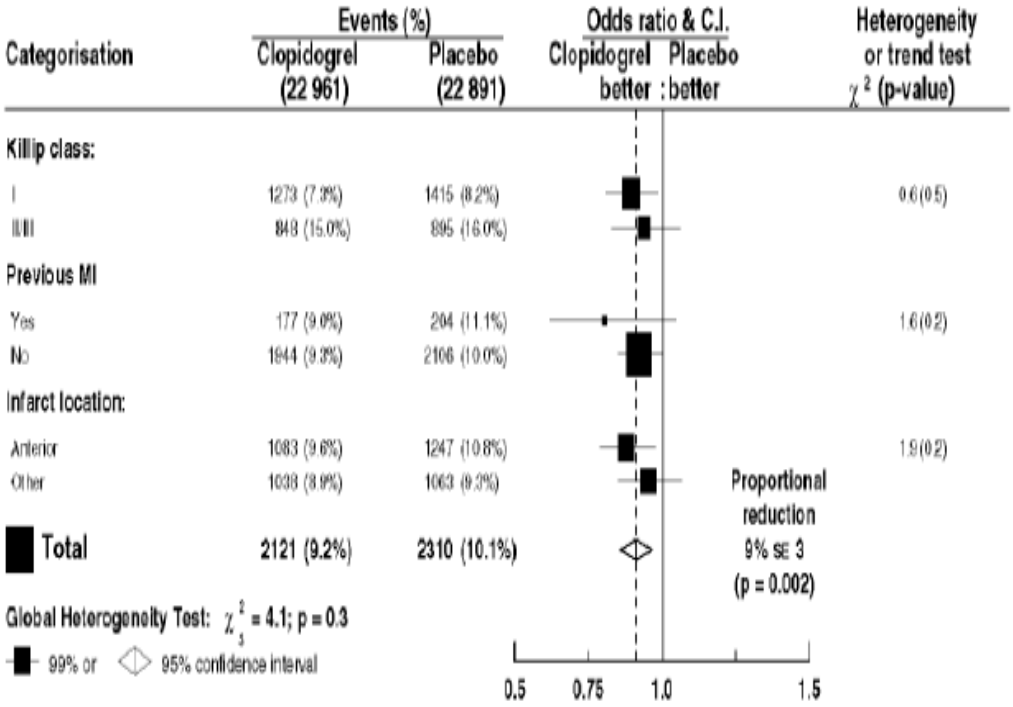
a All treated patients received ASA

Figure 7 - Proportional Effects of Adding Clopidogrel to ASA 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 8 - Effects of Clopidogrel plus ASA in the Non-Prespecified Subgroups in the COMMIT Study



Paediatric Studies
A randomised, 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. In this study, 906 paediatric patients (neonates and infants) with cyanotic congenital heart disease palliated with a systemic-to-pulmonary arterial shunt were randomised to receive Clopidogrel 0.2 mg/kg/day (n=467) or placebo (n=439) along with concomitant background therapy up to the time of second stage surgery. The mean time between shunt palliation and first administration of study medicinal product was 20 days. Approximately 88% of patients received concomitant ASA (range of 1 to 23 mg/kg/day). There was no significant difference between groups in the primary composite endpoint of death, shunt thrombosis or cardiac related intervention prior to 120 days of age following an event considered of thrombotic nature (89 [19.1%] for the clopidogrel group and 90 [20.5%] for the placebo group) (see Dosage and Administration, Special Populations). Bleeding was the most frequently reported adverse reaction in both clopidogrel and placebo groups; however, there was no significant difference in the bleeding rate between groups.

PHARMACOKINETICS

Absorption
After single and repeated oral doses of 75 mg/day, clopidogrel is rapidly absorbed. Mean peak plasma levels of unchanged clopidogrel (approximately 2.2 2.5 ng/mL after a single 75-mg oral dose) occurred approximately 45 minutes after dosing. Absorption is at least 50%, based on urinary excretion of clopidogrel metabolites.

Distribution
Clopidogrel and the main circulating (inactive) metabolite bind reversibly in vitro to human plasma proteins (98% and 94%, respectively). The binding is nonsaturable in vitro up to a concentration of 100 mg/L.

Metabolism
Clopidogrel is extensively metabolised by the liver. In vitro and in vivo, clopidogrel is metabolized according to two main metabolic pathways: one mediated by esterases and leading to hydrolysis into its inactive carboxylic acid derivative (85% of circulating metabolites), and one mediated by multiple cytochromes P450. Clopidogrel is first metabolised 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. The active metabolite is formed mostly by CYP2C19 with contributions from several other CYP enzymes, including , , CYP1A2, CYP2B6 and CYP3A4. The active thiol metabolite which has been isolated in vitro, binds rapidly and irreversibly to platelet receptors, thus inhibiting platelet aggregation.

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. Cmax occurs approximately 30 to 60 minutes after dosing.

Elimination
Following an oral dose of 14C-labelled clopidogrel in man, approximately 50% was excreted in the urine and approximately 46% in the faeces in the 120-hour interval after dosing. After a single, oral dose of 75 mg, clopidogrel has a half life of approximately 6 hours. The elimination half-life of the main circulating (inactive) metabolite was 8 hours after single and repeated administration.

Pharmacogenetics
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.

The CYP2C19*1 allele corresponds to fully functional metabolism while the CYP2C19*2 and CYP2C19*3 alleles are nonfunctional. The CYP2C19*2 and CYP2C19*3 alleles account for the majority of reduced function alleles in white (85%) and Asian (99%) poor metabolisers. 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 metaboliser status will possess two loss-of-function alleles as defined above. Published frequencies for poor CYP2C19 metaboliser 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 metaboliser groups (ultrarapid, extensive, intermediate and poor), evaluated pharmacokinetic and antiplatelet responses using 300 mg followed by 75 mg/day and 600 mg followed by 150 mg/day, each for a total of 5 days (steady state). No substantial differences in active metabolite exposure and mean inhibition of platelet aggregation (IPA) were observed between ultrarapid, extensive and intermediate metabolisers. In poor metabolisers, active metabolite exposure was decreased by 63-71% compared to extensive metabolisers. After the 300 mg/75 mg dose regimen, antiplatelet responses were decreased in the poor metabolisers with mean IPA (5 μM ADP) of 24% (24 hours) and 37% (Day 5) as compared to IPA of 39% (24 hours) and 58% (Day 5) in the extensive metabolisers and 37% (24 hours) and 60% (Day 5) in the intermediate metabolisers. When poor metabolisers received the 600 mg/150 mg regimen, active metabolite exposure was greater than with the 300 mg/75 mg regimen. In addition, IPA was 32% (24 hours) and 61% (Day 5), which were greater than in poor metabolizers receiving the 300 mg/75 mg regimen and were similar to the other CYP2C19 metaboliser groups receiving the 300 mg/75 mg regimen. An appropriate dose regimen for this patient population has not been established in clinical outcome trials.

Active Metabolite Pharmacokinetics and Antiplatelet Responses by CYP2C19 Metaboliser Status

	Dose	Ultrarapid (n=10)	Extensive (n=10)	Intermediate (n=10)	Poor (n=10)
AUC_{last} (ng.h/mL)	300 mg (Day 1)	33 (11)	39 (24)	31 (14)	14 (6)
	600 mg (Day 1)	56 (22)	70 (46)	56 (27)	23 (7)
	75 mg (Day 5)	11 (5)	12 (6)	9.9 (4)	3.2 (1)
	150 mg (Day 5)	18 (8)	19 (8)	16 (7)	7 (2)
IPA (%)[a]	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)

Values are mean (SD)
a Inhibition of platelet aggregation with 5μM ADP; larger value indicates greater platelet inhibition

Consistent with the above results, in a meta-analysis including 6 studies of 335 clopidogrel-treated subjects at steady state, it was shown that active metabolite exposure was decreased by 28% for intermediate metabolisers, and 72% for poor metabolisers while platelet aggregation inhibition (5 μM ADP) was decreased with differences in IPA of 5.9% and 21.4%, respectively, when compared to extensive metabolisers.

The influence of CYP2C19 genotype on clinical outcomes in patients treated with clopidogrel has not been evaluated in prospective, randomized, controlled trials. There have been a number of retrospective analyses; however, to evaluate this effect in patients treated with clopidogrel for whom there are genotyping results: CURE (n=2721), CHARISMA (n=2428), CLARITY-TIMI 28 (n=227) and TRITON-TIMI 38 (n=1477), as well as a number of published cohort studies.

In TRITON-TIMI 38 and 3 of the cohort studies (Collet, Sibbing, Giusti) the combined group of patients with either intermediate or poor metaboliser status had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolisers.

In CHARISMA and one cohort study (Simon), an increased event rate was observed only in poor metabolisers when compared to extensive metabolisers.

In CURE and CLARITY and one of the cohort studies (Trenk), no increased event rate was observed based on metaboliser status.

None of these analyses was adequately sized to detect differences in outcome in poor metabolisers.

Special populations
The pharmacokinetics of the active metabolite of clopidogrel is not known in these special populations.
Gender
In a small study comparing men and women, less inhibition of ADP-induced platelet aggregation was observed in women, but there was no difference in prolongation of bleeding time. In the large, controlled clinical study (Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events; CAPRIE), the incidence of clinical outcome events, other adverse clinical events, and abnormal clinical laboratory parameters was similar in men and women.

Elderly
In elderly (≥75 years) volunteers compared to young healthy volunteers, there were no differences in platelet aggregation and bleeding time. No dosage adjustment is needed for the elderly.

Paediatric patients
No information available

Hepatic impairment
After repeated doses of 75 mg clopidogrel 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. The mean bleeding time prolongation was also similar in the two groups.

Renal impairment
After repeated doses of 75 mg clopidogrel per day in patients with severe renal impairment (creatinine clearance from 5 to 15 mL/min), inhibition of ADP induced platelet aggregation was lower (25%) than that observed in healthy volunteers, however, the prolongation of bleeding time was similar to healthy volunteers receiving 75 mg of clopidogrel per day.

Ethnicity
The prevalence of CYP2C19 alleles that result in intermediate and poor CYP2C19 metabolism differs according to ethnicity (see Pharmacokinetics, Pharmacogenetics, Section 16.5). From literature, limited data in Asian populations are available to assess the clinical implication of genotyping of this CYP on clinical outcome events.

NON-CLINICAL SAFETY DATA

Animal Pharmacology
Safety pharmacology studies did not reveal any relevant effects to the central nervous, cardiovascular, respiratory, gastrointestinal and renal systems.

Acute toxicity
At very high doses (≥ 1500 mg/kg), a poor gastric tolerability (gastric erosions and/or vomiting) of clopidogrel was reported in rat, mice and baboon.

Chronic toxicity
During preclinical studies in rat and baboon, the most frequently observed effects at very high doses (more than 300 times the therapeutic dose of 75 mg/day on a mg/kg basis) were acute gastritis, gastric erosions and/or vomiting. At lower doses, an increase in liver weight was observed in mice, rats and baboons associated with increases in cholesterol plasma levels in rats and baboons, and a slight hypertrophy of the smooth endoplasmic reticulum in centrilobular hepatocytes in rats. No histopathological changes were seen in mice or baboons. The liver findings were a consequence of an effect on hepatic metabolizing enzymes observed at high doses, a phenomenon that is generally recognized as having no relevance to humans receiving lower therapeutic doses. After one year of treatment at doses representing at least 7 times (rats) or between 10 or 23 times (baboon) the exposure seen in humans receiving the clinical dose of 75 mg/day, none of these effects were observed.

Carcinogenicity
There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 100 mg/kg/day, which afforded plasma exposures >25 times that in humans at the recommended daily dose of 75 mg/day.

Genotoxicity
Clopidogrel has been tested in a range of *in vitro* and *in vivo* genotoxicity studies, and showed no genotoxic activity.

Teratogenicity and Impairment of fertility
Clopidogrel was found to have no effect on the fertility of male and female rats and was not teratogenic in either rats or rabbits (at doses up to 52 times the recommended human dose on a mg/m^2 basis).

When given to lactating rats, clopidogrel caused a slight delay in the development of the offspring. Specific pharmacokinetic studies performed with radiolabelled clopidogrel have shown that the parent compound or its metabolites are excreted in the milk. Consequently, a direct effect (slight toxicity), or an indirect effect (low palatability) cannot be excluded.

INCOMPATIBILITIES / COMPATIBILITIES

Not applicable

STORAGE CONDITIONS AND SHELF-LIFE

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