

Brand Name: Brilinta

Generic Name: ticagrelor

Manufacturer¹: AstraZeneca

Drug Class^{1, 3}: Hematological Agent; Platelet Aggregation Inhibitor

Uses:

Labeled Uses^{1, 2, 3, 4}: Arterial thromboembolism prophylaxis in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction), including thrombosis prophylaxis in patients undergoing percutaneous coronary intervention (PCI)

Unlabeled Uses: None at this time

Mechanism of Action^{1, 2, 3, 4}: Ticagrelor and its major metabolite reversibly and noncompetitively bind to the platelet P2Y₁₂ ADP receptor, preventing ADP-mediated activation of the GPIIb/IIIa receptor complex and thereby preventing platelet activation and aggregation.

Pharmacokinetics^{1, 2, 3, 4}:

Absorption:

T _{max}	Parent compound 1.5 hours (range, 1 to 4 hours) Active Metabolite 2.5 hours (range, 1.5 to 5 hours)
V _d	88L
t _{1/2}	Parent compound 7 hours Active Metabolite 9 hours
Clearance	Not Reported
Protein binding	> 99%
Bioavailability	~ 36% (range, 30% to 42%)

Metabolism: Ticagrelor is primarily metabolized in the liver via CYP3A4/5 to its active metabolite (AR-C124910xx). Ticagrelor and its metabolite are weak P-glycoprotein substrates and inhibitors.

Elimination: The primary route of elimination of the parent compound ticagrelor is by hepatic metabolism and the primary route of elimination of its active metabolite is mostly biliary secretion. Ticagrelor is excreted through both the kidneys into urine (26%) and through the feces (58%). Less than 1% of the dose is recovered in the urine as ticagrelor and its active metabolite.

Efficacy^{5, 6, 7}:

Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *The New England Journal of Medicine*. 2009;361(11):1045-1057. Available from: <http://www.nejm.org/doi/full/10.1056/NEJMoa0904327>. Accessed on September 30, 2011.

Study Design: PLATO was a multicenter, randomized, double-blind trial

Description of Study:

Methods: This study included 18,624 patients there were recruited from 862 centers in 43 countries. Inclusion criteria were patients who were hospitalized for an acute coronary syndrome, with or without ST-segment elevation, who had an onset of symptoms during the previous 24 hours. Patients were randomized to receive ticagrelor 90 mg twice daily or clopidogrel 75 mg once daily for 12 months. Patients from both groups also received aspirin daily. The primary efficacy endpoint was the composite of death from vascular causes, myocardial infarction, or stroke. The primary safety endpoint was the first occurrence of any major bleeding event.

Outcome Results: The primary endpoint occurred less often in the ticagrelor group (9.8% of patients) than in the clopidogrel group (11.7% of patients) at 12 months (hazard ratio, 0.84; 95% confidence interval [CI] 0.77 to 0.92; $P < 0.001$). The rate of death from any cause was reduced in the ticagrelor group when compared to the clopidogrel group (4.5% vs. 5.9%, respectively; $P < 0.001$). There was no difference in the rates of major bleeding between the ticagrelor group and the clopidogrel group (11.6% vs. 11.2%, respectively; $P = 0.43$). However, ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting when compared to clopidogrel (4.5% vs. 3.8%, respectively; $P = 0.03$). Ticagrelor was also associated with an increase in fatal intracranial bleeding, but a decrease in other types of fatal bleeding.

Limitations: This study was supported by AstraZeneca, the manufacturer of ticagrelor. Many of the authors had received grant support, lecture fees, and consulting fees from AstraZeneca and other pharmaceutical companies; thus, creating a potential conflict of interest and bias. Results differed between patients enrolled in North America and patients enrolled elsewhere. This raises the questions of whether geographical differences between different patient populations or different practice patterns could have influenced the effects of the randomized treatments. The findings of superiority of ticagrelor over clopidogrel regarding the primary end point and the similarity of both drugs' major bleeding rates may have been due to chance because of the large number of tests performed.

Conclusion: The PLATO study showed that the rate of death from vascular causes, myocardial infarction, or stroke was significantly reduced in patients treated with ticagrelor when compared to patients treated with clopidogrel.

Wallentin L, James S, Storey RF, Armstrong M, Barratt BJ, Horrow J, et al. Effect of *CYP2C19* and *ABCB1* single nucleotide polymorphisms on outcomes of treatment with ticagrelor versus clopidogrel for acute coronary syndromes: a genetic substudy of the PLATO trial. 2010;376:1320-1328. Available from: <http://www.sciencedirect.com/science/article/pii/S0140673610612743>. Accessed on September 30

Study Design: Prospective, randomized, double-blind, double-dummy, parallel-group, international, multicenter phase 3 study

Description of Study:

Methods: The PLATO study was a 12 month study that included 18,624 patients with acute coronary syndrome with and without ST-elevation. It evaluated the safety and efficacy of ticagrelor (180mg loading dose with 90mg twice daily maintenance dose) in comparison to clopidogrel (300mg-600mg loading dose with 75mg maintenance dose) for preventing cardiovascular death, myocardial infarction, and stroke. Patients had the option of volunteering to participate in the genetics sub study of the PLATO trial. The PLATO trial genotyped patient's DNA samples for *CYP2C19* loss-of-function alleles, *CYP2C19* gain-of-function alleles, and the *ABCB1* single nucleotide polymorphism 3435C→T. This sub study was not powered prospectively.

Outcome Results: For the PLATO genetic sub study, 10,285 patients voluntarily consented to give a blood sample for genotyping. The primary outcome of death from vascular causes, myocardial infarction, or stroke occurred less in the ticagrelor group compared to the clopidogrel group, regardless of the *CYP2C19* genotype. The clopidogrel group was associated with an increase event rate at day 30 for patients with any of the loss-of-function *CYP2C19* alleles compared to patients who were without any loss-of-function *CYP2C19* alleles (5.7% vs. 3.8%, respectively; p=0.028). There was no significant association between genotype and treatment drug for major bleeding.

Limitations: Funding for this sub study was provided by AstraZeneca, which creates a potential for bias. Many of the authors received grants, consultancy fees, travel support, lecture fees, honoraria, and royalties from AstraZeneca and other pharmaceutical companies.

Conclusion: The PLATO study in addition to the PLATO study genetic sub study showed that ticagrelor significantly reduces the event rate of death from vascular causes, myocardial infarction, or stroke in comparison to clopidogrel, regardless of *CYP2C19* and *ABCB1* polymorphism. Clinically, ticagrelor and aspirin can be prescribed in patients with acute coronary syndrome without the need for genetic testing in advance.

Held C, Asenblad N, Bassand JP, Becker RC, Cannon CP, Claeys MJ, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes undergoing coronary artery bypass surgery: Results from the PLATO (Platelet inhibition and patient outcomes) trial. Journal of the American College of Cardiology. 2011;57(6):672-684. Available from: <http://www.sciencedirect.com/science/article/pii/S0735109710048321>. Accessed on September 30, 2011.

Study Design: Retrospective analysis of a nonrandomized subgroup of a large prospective randomized trial

Description of Study:

Methods: Out of the 18,624 patients randomized in the PLATO study to either the ticagrelor treatment group or the clopidogrel treatment group, 1,899 of those patients underwent coronary artery bypass graft surgery (CABG). According to the study protocol, ticagrelor was to be discontinued for 24 to 72 hours before surgery and clopidogrel was to be discontinued for 5 days before surgery. The study drug was restarted as soon as possible after completion of the surgery. The primary efficacy endpoint was the composite of death from vascular causes, myocardial infarction, or stroke, and the primary safety endpoint was PLATO study defined total major bleeding.

Outcome Results: Of the study population that underwent CABG, 1,261 patients received their study drug within 7 days before the surgery. The occurrence of the primary endpoint with ticagrelor in comparison to clopidogrel from CABG and onward was 10.6% and 13.1%, respectively (hazard ratio 0.84, 95% CI 0.60 to 1.16; $p=0.29$). Total mortality in association with or after CABG was 4.7% with ticagrelor and 9.7% with clopidogrel (HR: 0.49; 95% CI: 0.32 to 0.77; $p<0.01$). When stopping the study drugs 1 to 4 days before CABG, total mortality was 3.4% in the ticagrelor group compared to 15.5% in the clopidogrel group (HR: 0.21; 95% CI: 0.10 to 0.42; $p<0.01$), and corresponding CV mortality was 3.1% in the ticagrelor group compared to 11.8% in the clopidogrel group (HR: 0.25; 95% CI: 0.12 to 0.53; $p<0.05$). When stopping the study drugs >4 days before CABG, there was no difference in mortality between the ticagrelor group and the clopidogrel group. Also, there was no significant difference in occurrence of major bleeding among patients that underwent CABG with ticagrelor or clopidogrel.

Limitations: Due to the study design being retrospective, the exact causes of the outcomes cannot be definitively proven since observations were simply being made. Multiple authors received grants, consultant fees, honorarium, and lecture fees from AstraZeneca and other pharmaceutical companies. In addition, a few of the authors were employees and had equity ownership in AstraZeneca, which creates a conflict of interest. Ticagrelor was withheld for 24 to 72 hours preoperatively, which is against the recommendations from the manufacturer in the package insert that states ticagrelor should be discontinued 5 days prior to surgery.

Conclusion: Based on the analysis of the PLATO study sub group, for patients with acute coronary syndrome that need to undergo CABG while on antiplatelet therapy,

ticagrelor has a decreased risk for total mortality in association with or after CABG surgery in comparison to clopidogrel. There was no significant difference in the occurrence of the primary endpoint between ticagrelor and clopidogrel. There was no difference in mortality when ticagrelor and clopidogrel were stopped > 4 days before CABG surgery. Ticagrelor was associated with less total mortality than clopidogrel when it was stopped 1 to 4 days before CABG surgery. However, stopping ticagrelor 1 to 4 days prior to surgery does not follow the recommendations set forth by the manufacturer of ticagrelor. There was no significant difference between ticagrelor and clopidogrel in the rate of CABG-associated major bleeding.

Contraindications^{1,2,3,4}:

Bleeding (black box warning): Active bleeding, such as from a peptic ulcer can result in fatal bleeding.

Intracranial bleeding (black box warning): Increased risk of bleeding recurrence in patients with history of bleeding. Can result in fatal bleeding.

Hepatic impairment: Ticagrelor is metabolized in the liver, thus hepatic impairment may increase risk of adverse effects, such as bleeding. There is an additional increased risk for bleeding due to possible reduction in synthesis of coagulation proteins that occur in the liver.

Precautions^{1,2,3,4}:

Abrupt discontinuation: Stopping ticagrelor abruptly can cause an increased risk for myocardial infarction, stent thrombosis, and death

Breast-feeding: Ticagrelor was found to be excreted in the breast milk of lactating rats, but the excretion of ticagrelor in human breast milk is unknown. Use is not recommended.

Children, infants, and neonates: Safety and efficacy have not been established.

Coronary artery bypass graft surgery (CABG) (black box warning): Do not start patients on ticagrelor if they are planned to undergo urgent CABG surgery. When possible, discontinue ticagrelor at least 5 days before surgery.

GI Bleeding: Active pathological bleeding can become fatal with concomitant use of ticagrelor.

Hepatic Disease: Use of ticagrelor has not been studied in moderate or severe hepatic disease. Possible increased risk of bleeding due to reduced synthesis of coagulation proteins in the liver.

Pregnancy: Pregnancy risk factor C. In animal studies, ticagrelor caused abnormalities to the fetus. No adequate studies have been established in humans, only use if benefits outweigh the risks.

Surgery (black box warning): Due to increased risk of bleeding, ticagrelor needs to be withheld at least 5 days prior to surgery.

Adverse Effects:

>10%:

Respiratory: Dyspnea ($\leq 14\%$)

1% to 10%:

Cardiovascular: Ventricular pauses (6%; 2% after 1 month therapy)
Atrial fibrillation (4%)
Hypertension (4%)
Hypotension (3%)
Angina (3%)
Bradycardia (1% to 3%)
Cardiac failure (2%)
Peripheral edema (2%)
Ventricular tachycardia (2%)
Palpitation (1%)
Syncope (1%)
Ventricular extrasystoles (1%)
Ventricular fibrillation (1%)

Central Nervous System: Headache (7%)
Dizziness (5%)
Fatigue (3%)
Fever (3%)
Anxiety (2%)
Insomnia (2%)
Vertigo (2%)

Dermatologic: Bruising (2% to 4%)
Rash (2%)
Pruritus (1%)
Subcutaneous or dermal bleeding

Endocrine & Metabolic: Hypokalemia (2%)
Diabetes Mellitus (1%)
Dyslipidemia (1%)
Hypercholesterolemia (1%)

Gastrointestinal: Diarrhea (4%)
Nausea (4%)

Vomiting (3%)
Abdominal pain (2%)
Constipation (2%)
Dyspepsia (2%)
GI hemorrhage

Genitourinary: Urinary tract infection (2%)
Urinary tract bleeding

Hematologic: Major bleeding (12%; composite of major/life threatening and other major bleeding events)
Minor bleeding (~5%)
Anemia (2%)
Hematoma (2%)
Postprocedural hemorrhage (2%)

Local: Puncture site hematoma (2%)

Neuromuscular & skeletal: Back pain (4%)
Noncardiac chest pain (4%)
Extremity pain (2%)
Arthralgia (2%)
Musculoskeletal pain (2%)
Weakness (2%)
Myalgia (1%)

Renal: Creatinine increased (7%; mechanism undetermined)
Hematuria (2%)
Renal failure (1%)

Respiratory: Epistaxis (6%)
Cough (5%)
Nasopharyngitis (2%)
Bronchitis (1%)
Pneumonia (1%)

< 1%, postmarketing, and/or case reports:

Confusion, conjunctival hemorrhage, gastritis, gout, gynecomastia, hemarthrosis, hemoptysis, intracranial hemorrhage (including fatalities), intraocular hemorrhage, paresthesia, retinal hemorrhage, retroperitoneal hemorrhage

Drug Interactions^{1,2,3,4}:

Anticoagulant Agents (and herbs with anticoagulant properties):

May enhance the anticoagulant effects of anticoagulants causing an increased risk of bleeding

Antiplatelet Agents (and herbs with antiplatelet properties):

May enhance the anticoagulant effect of other antiplatelet agents

Aspirin:

Aspirin may decrease effectiveness of ticagrelor; avoid doses of aspirin > 100mg

Carvedilol:

May increase serum concentration of Carvedilol

Collagenase (systemic):

May enhance the adverse/toxic effect of Collagenase, increasing the risk of injection site bruising and/or bleeding

CYP2C9 Substrates (HIGH risk):

May decrease the metabolism of CYP2C9 substrates

CYP3A4 Inducers (Strong) – Aminoglutethimide, Bosentan, Carbamazepine, Dexamethasone, Efavirenz, Etravirine, Fosphenytoin, Nafcillin, Nevirapine, Oxcarbazepine, Pentobarbital, Phenobarbital, Phenytoin, Primidone, Rifabutin, Rifampin, Rifapentine, herbs with CYP3A4 Inducer properties:

Avoid combination

CYP3A4 Inducers may decrease the serum concentration of ticagrelor and its active metabolite

CYP3A4 Inhibitors (Strong) – Atazanavir, Boceprevir, Clarithromycin, Conivaptan, Darunavir, Delavirdine, Fosamprenavir, Imatinib, Indinavir, Itraconazole, Ketoconazole, Lopinavir, Nefazodone, Nelfinavir, Nicardipine, Posaconazole, Ritonavir, Saquinavir, Telaprevir, Telithromycin, Voriconazole:

Avoid combination

CYP3A4 Inhibitors may increase the serum concentration of ticagrelor and decrease serum concentrations of its active metabolite

Dasatinib:

Dasatinib may enhance the anticoagulant effect of antiplatelet agents

Deferasirox:

Deferasirox may decrease the serum concentration of CYP3A4 substrates

Digoxin:

May increase the serum concentration of digoxin

Drotecogin Alfa:

Antiplatelet agents may enhance the adverse effects of drotecogin Alfa increasing risk of bleeding

Glucosamine:

Glucosamine may enhance the antiplatelet effect of antiplatelet agents

Ibritumomab:

Antiplatelet agents may enhance the adverse effects of ibritumomab impairing platelet function and increasing risk of bleeding

Lovastatin:

May increase serum concentration of lovastatin; avoid doses of lovastatin over 40mg/day

Nonsteroidal Anti-Inflammatory Agents:

NSAIDs may enhance the adverse effects of antiplatelet agents causing an increased risk of bleeding

Omega-3-Acid Ethyl Ester:

Omega-3-Acid Ethyl Esters may enhance antiplatelet effect of antiplatelet agents

PentosanPolysulfate Sodium:

PentosanPolysulfate Sodium may enhance adverse effect of antiplatelet agents causing an increased risk of bleeding

Pentoxifylline:

Pentoxifylline may enhance the antiplatelet effect of antiplatelet agents

Prostacyclin Analogues:

Prostacyclin Analogues may enhance the antiplatelet effect of antiplatelet agents

Rivaroxaban:

May enhance the anticoagulant effect of Rivaroxaban causing an increased risk of bleeding

Salicylates:

Antiplatelet agents may enhance the adverse effects of salicylates causing an increased risk of bleeding

Simvastatin:

May increase the serum concentration of simvastatin; avoid doses of simvastatin over 40mg/day

Thrombolytic Agents:

Antiplatelet agents may enhance the anticoagulant effect of thrombolytic agents

Tocilizumab:

Tocilizumab may decrease the serum concentration of CYP3A4 substrates

Tositumomab and Iodine I 131 Tositumomab:

Antiplatelet agents may enhance the adverse effects of Tositumomab and Iodine I 131 Tositumomab causing an increased risk of bleeding

Vitamin E:

Vitamin E may enhance the antiplatelet effect of antiplatelet agents

Dosing/Administration^{1,2,3,4:}

Adult Dosing

Initial:

Loading dose of ticagrelor 180 mg PO in combination with 325mg of aspirin

Maintenance:

90 mg ticagrelor PO twice daily; starting 12 hours after initial loading dose, in combination with aspirin 75 to 100mg per day (Do not exceed greater than 100mg of aspirin daily)

Pediatrics (≥4 years of age)

Safety and efficacy has not been established

Elderly

Same as adult dosing

<i>Renal impairment</i>	No known dosage adjustment needed
<i>Hepatic impairment</i>	
Mild Hepatic Impairment:	No dosage adjustment needed
Moderate Hepatic Impairment:	Use with caution; not specifically studied
Severe Hepatic Impairment:	Use is contraindicated
<i>Conversion from clopidogrel to ticagrelor:</i>	Initiate ticagrelor 90mg PO twice daily 24 hours after the last clopidogrel dose
<i>Missed Dose</i>	Skip missed dose and remain on regular dosing schedule. Do not double doses.

Use in special circumstances:

Perioperative Period: Due to ticagrelor causing an increased risk of bleeding, the manufacturer recommends stopping the medication at least 5 days prior to surgery

Monitoring Parameters: Signs of bleeding
Signs and symptoms of dyspnea
CBC – hemoglobin and hematocrit
Renal function
Uric acid levels – for patients with gout or risk of hyperuricemia

Conclusion^{4, 7, 8}:

Ticagrelor is an effective antiplatelet therapy for patients with acute coronary syndrome with or without ST-segment elevation. The increased risk of bleeding needs to be greatly considered before starting a patient on this therapy. Based on results from the PLATO study, ticagrelor can significantly reduce the rate of death from vascular causes, myocardial infarction, and stroke in comparison to the leading antiplatelet therapy, clopidogrel. Ticagrelor is dosed twice daily, creating the risk for decreased patient adherence to the medication due to multiple daily doses. A 30-day supply of ticagrelor is more costly than its two other comparable antiplatelet agents, clopidogrel and prasugrel. However, the increase cost of ticagrelor may be outweighed by the increased value it will have for patients with acute coronary syndrome. Given its proven safety and efficacy, ticagrelor appears to have a clinically significant use as an antiplatelet therapy in its approved patient population.

Recommended References:

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Prepared by: Ashley N. Wilhelm, Doctor of Pharmacy Candidate