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REVIEW ARTICLE

CLOPIDOGREL AND TICAGRELOR: A NOVEL FUSED RING OF FIVE MEMBER WITH SIX MEMBER HETEROCYCLIC CLASS AS ORALLY ACTIVE ANTICOAGULANT

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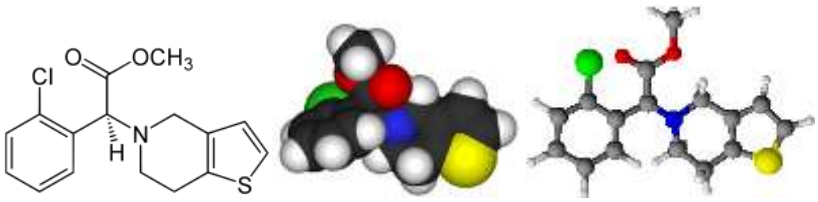
ABSTRACT

Clopidogrel and ticagrelor both drugs have fused ring heterocyclic moiety of five+six member entity having chiral centres. Clopidogrel have thieno-piperidine nucleus having one chiral carbon and ticlagrelor has triazolo-pyrimidine ring having four chiral centres. Both of the drugs act as anticoagulant by inhibiting the receptor $P2Y_{12}$. This protein is found mainly but not exclusively on the surface of blood platelets, and is an important regulator in blood clotting. $P2Y_{12}$ belongs to the Gi class of a group of G protein coupled (GPCR) purinergic receptors and is a chemoreceptor for adenosine diphosphate (ADP). The P2Y family has several receptor subtypes with different pharmacological selectivity, which overlaps in some cases, for various adenosine and uridine nucleotides. This receptor is involved in platelet aggregation, and is a potential target for the treatment of thromboembolisms and other clotting disorders. Two transcript variants encoding the same isoform have been identified for this gene.

KEYWORDS: $P2Y_{12}$, ADP, GPCR, Clopidogrel, Ticagrelor, Hemorrhage, Neutropenia, Thrombotic thrombocytopenic purpura, Coagulation

INTRODUCTION:

Clopidogrel



IUPAC Nomenclature: (+)-(S)-methyl 2-(2-chlorophenyl)-2-(6,7-dihydrothieno[3,2-c]pyridin-5(4*H*)-yl)acetate

Molecular Formula: $C_{16}H_{16}ClNO_2S$, Molecular Mass: 321.82 g/mol, logP: 4.23

Pharmacokinetic data:

Bioavailability	**>50%**
Protein binding	94–98%
Metabolism	Hepatic
Half-life	7–8 hours (inactive metabolite)
Excretion	50% renal, 46% biliary

Table 1: Pharmacokinetics of Clopidogrel

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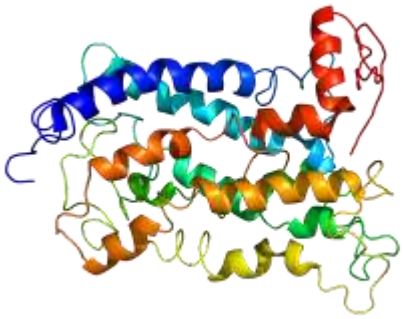
Clopidogrel is an oral, thienopyridine class antiplatelet agent used to inhibit blood clots in coronary artery disease, peripheral vascular disease, and cerebrovascular disease. It is marketed by Bristol-Myers Squibb and Sanofi under the trade name **Plavix**. The drug works by irreversibly inhibiting a receptor called $P2Y_{12}$, an adenosine diphosphate (ADP) chemoreceptor on platelet cell membranes. Adverse effects include hemorrhage, severe neutropenia, and thrombotic thrombocytopenic purpura (TTP).[1-4]



(a)

(b)

Figure 1: (a) $P2Y_{12}$ Receptor (b) Circulatory System

PHARMACOLOGY:

Clopidogrel is a prodrug, the action of which may be related to an ADP receptor on platelet cell membranes. The drug specifically and irreversibly inhibits the $P2Y_{12}$ subtype of ADP receptor, which is important in activation of platelets and eventual cross-linking by the protein fibrin. Platelet inhibition can be demonstrated two hours after a single dose of oral clopidogrel, but the onset of action is slow, so that a loading-dose of 300 mg is usually administered.[5]

The following are coagulation factors and their common names:

Factor I - fibrinogen	Factor IV - ionized calcium (Ca^{++})	Factor VII - stable factor or pro-convertin	Factor X - Stuart-Power factor
Factor II - prothrombin	Factor V - labile factor or pro-accelerin	Factor VIII - antihemophilic factor	Factor XI - Plasma thromboplastin antecedent
Factor III - tissue thromboplastin (tissue factor)	Factor VI - unassigned	Factor IX - plasma thromboplastin component, Christmas factor	Factor XII - Hageman factor
Factor XIII - fibrin-stabilizing factor			

Table 2: Blood Coagulation Factors

Clinical use

Indications

Clopidogrel is indicated for:

- Prevention of vascular ischemic events in patients with symptomatic atherosclerosis
- Acute coronary syndrome without ST-segment elevation (NSTEMI),
- ST elevation MI (STEMI)

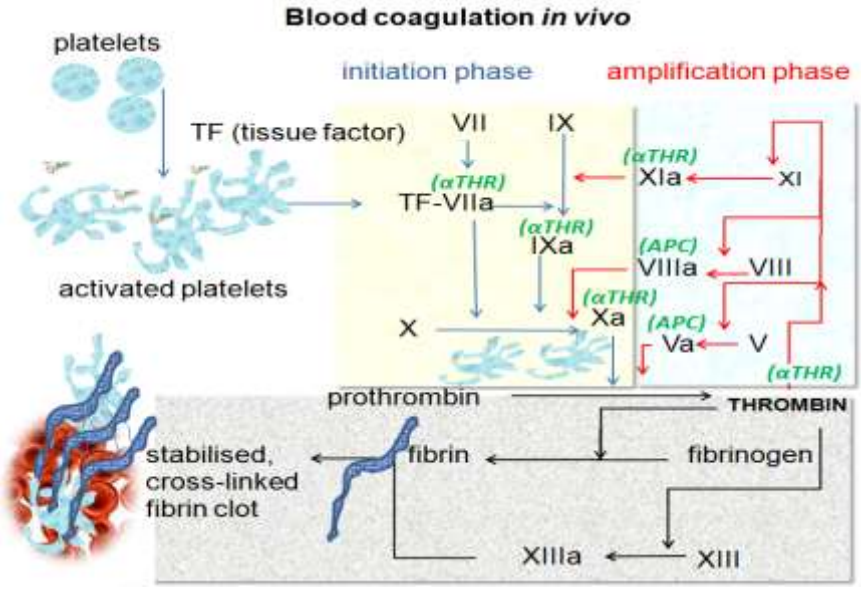


Figure 2: Blood Coagulation Cycle

It is also used, along with acetylsalicylic acid (ASA, brand name Aspirin), for the prevention of thrombosis after placement of intracoronary stent or as an alternative antiplatelet drug for patients who are intolerant to ASA. International guidelines granted the highest grade of recommendation for NSTE-ACS, PCI and stent, for clopidogrel in addition to ASA. Consensus-based therapeutic guidelines also recommend the use of clopidogrel rather than ASA for antiplatelet therapy in patients with a history of gastric ulceration, as inhibition of the synthesis of prostaglandins by ASA can exacerbate this condition. A study has shown that in patients with healed ASA-induced ulcers, however, patients receiving ASA plus the proton pump inhibitor esomeprazole had a lower incidence of recurrent ulcer bleeding than patients receiving clopidogrel.[6] However, a more recent study suggested that prophylaxis with proton pump inhibitors along with clopidogrel following acute coronary syndrome may increase adverse cardiac outcomes, possibly due to inhibition of $CYP2C_{19}$, which is required for the conversion of clopidogrel to its active form. The European Medicines Agency has issued a public statement on a possible interaction between clopidogrel and proton pump inhibitors.[7] However, several cardiologists have voiced concern that the studies on which these warnings are based have many limitations and that it is not certain whether there really is an interaction between clopidogrel and proton pump inhibitors.[8-10]

DOSAGE FORMS:

Clopidogrel is marketed as **clopidogrel bisulfate** (**clopidogrel hydrogen sulfate**), most commonly under the trade names **Plavix**, as 75 mg and 300 mg oral tablets.

PHARMACOKINETICS AND METABOLISM:

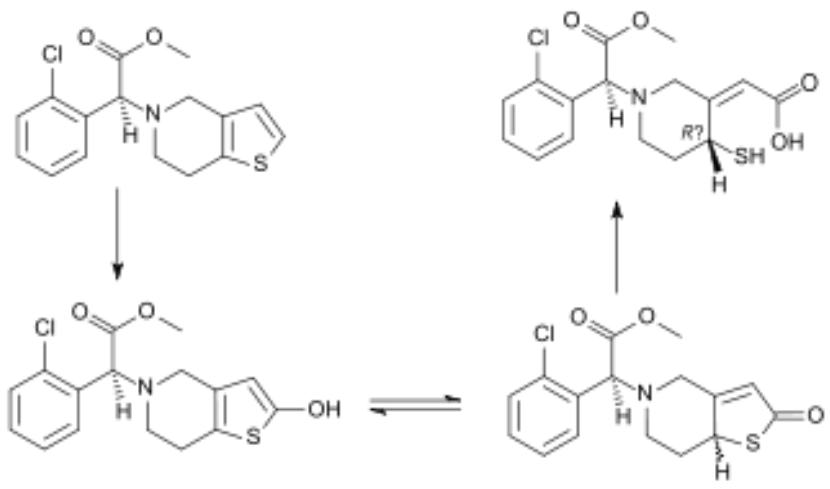


Figure 3: Flowchart of Clopidogrel Metabolism *in-vivo*

Clopidogrel (top left) is being activated. The first step is an oxidation mediated (mainly) by $CYP2C_{19}$, unlike the activation of the related drug prasugrel. The two structures at the bottom are tautomers of each other; and the final step is a hydrolysis. The active metabolite (top right) has *Z* configuration at the double bond C3–C16 and possibly *R* configuration at the newly asymmetric C4. After repeated 75 mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.258 µg/L) beyond two hours after dosing. Clopidogrel is a pro-drug activated in the liver by cytochrome P450 enzymes, including $CYP2C_{19}$. Due to opening of the thiophene ring, the chemical structure of the active has three sites that are stereo chemically relevant, making a total of eight possible isomers. These are: a stereocenter at C4 (attached to the —SH thiol group), a double bond at C3—C16, and the original stereocenter at C7. Only one of the eight structures is an active antiplatelet drug. This has the following configuration: *Z* configuration at the C3—C16 double bond, the original *S* configuration at C7 and although the stereocenter at C4 can't be directly determined, as the thiol group is too reactive, work with the active metabolite of the related drug prasugrel suggests that *R*-configuration of the C4 group is critical for $P2Y_{12}$ and platelet-inhibitory activity. The active metabolite has an elimination half-life of about eight hours and acts by forming a disulfide bridge with the platelet ADP receptor. Patients with a variant allele of CYP2C19 are 1.5 to 3.5 times more likely to die or have complications than patients with the high-functioning allele.[11]

Following an oral dose of ^{14}C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the five days after dosing.

Effect of food: Administration of clopidogrel bisulfate with meals did not significantly modify the bioavailability of clopidogrel as assessed by the pharmacokinetics of the main circulating metabolite.

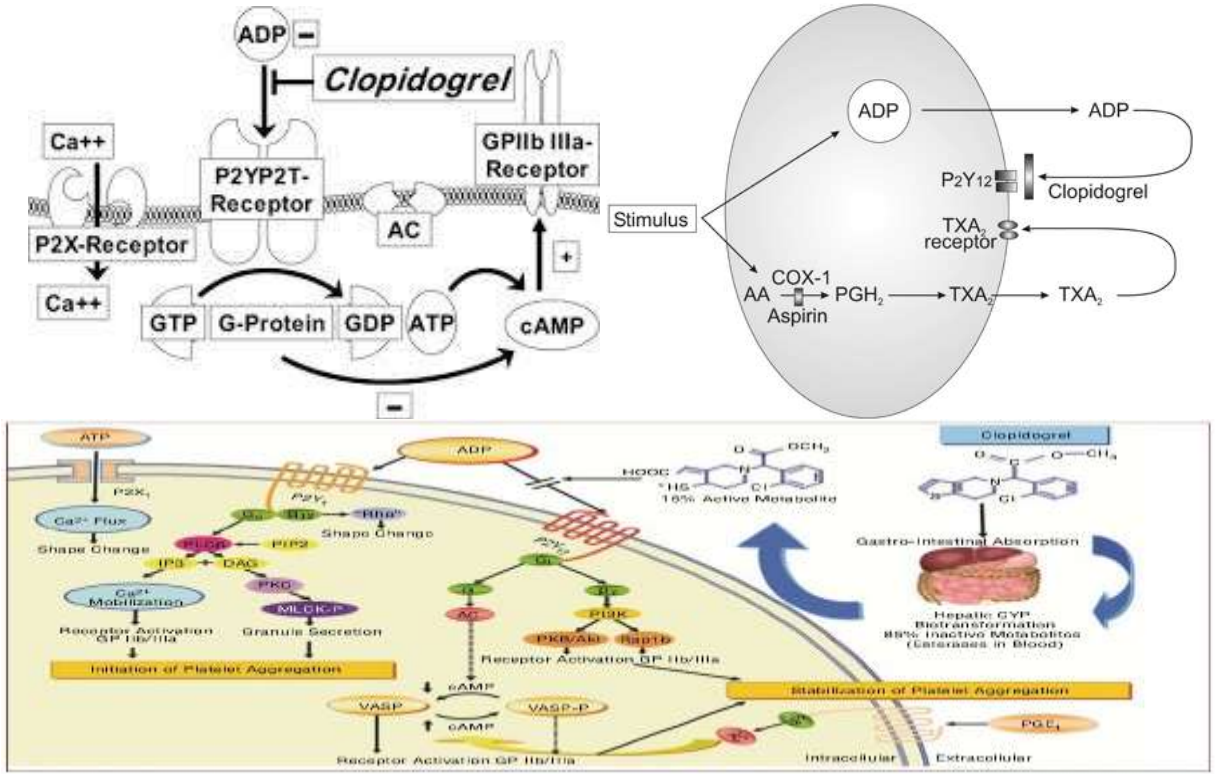


Figure 4: Mode of Action of Clopidogrel

Absorption and distribution: Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), with peak plasma levels (approx. 3 mg/L) of the main circulating metabolite occurring approximately one hour after dosing. The pharmacokinetics of the main circulating metabolite are linear (plasma concentrations increased in proportion to dose) in the dose range of 50 to 150 mg of clopidogrel. Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites. Clopidogrel and the main circulating metabolite bind reversibly *in-vitro* to human plasma proteins (98% and 94%, respectively). The binding is nonsaturable *in-vitro* up to a concentration of 110 µg/mL.[12,13]

Metabolism and elimination: In-vitro and *in-vivo*, clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed. In March 2010,

the U.S. Food and Drug Administration (FDA) added a boxed warning to Plavix alerting that the drug can be less effective in people who cannot metabolize the drug to convert it to its active form.[14]

PHARMACOGENETICS:

$CYP2C_{19}$ is an important drug-metabolizing enzyme that catalyzes the biotransformation of many clinically useful drugs including antidepressants, barbiturates, proton pump inhibitors, antimalarial and antitumor drugs. Clopidogrel is one of the drugs metabolized by this enzyme. Several recent landmark studies have proven the importance of $CP2C_{19}$ genotyping in treatment using clopidogrel or Plavix. In March 2010, the FDA put a black box warning on Plavix to make patients and healthcare providers aware that $CYP2C_{19}$ poor metabolizes, representing up to 14% of patients, are at high risk of treatment failure and that testing is available. Researchers have found that patients with variants in cytochrome P-450 2C19 ($CYP2C_{19}$) have lower levels of the active metabolite of clopidogrel, less inhibition of platelets, and a 3.58 times greater risk for major adverse cardiovascular events such as death, heart attack, and stroke; the risk was greatest in $CYP2C_{19}$ poor metabolizers.[15]

ADVERSE EFFECTS:

Serious adverse drug reactions associated with clopidogrel therapy include:

- Severe neutropenia (low white blood cells) (Incidence: 1/2,000)
- Thrombotic thrombocytopenic purpura (TTP) (Incidence: 4/1,000,000 patients treated)
- Hemorrhage - The annual incidence of hemorrhage may be increased by the co-administration of aspirin.
  - Gastrointestinal hemorrhage (Incidence: 2.0% annually)
  - Cerebral Hemorrhage (Incidence: 0.1 to 0.4% annually)
  - Use of non-steroidal anti-inflammatory drugs is discouraged in those taking clopidogrel due to increased risk of digestive tract hemorrhage
  - Bleeding in the postoperative period. This is especially a problem for patients after heart surgery where Clopidogrel is associated with a more than double the take back for bleeding rate, as well as other complications. The take back for bleeding occurs when there is chest tube clogging in the setting of ongoing bleeding in early postoperative period. Often, if chest tube clogging can be avoided, and the chest tubes drain, the patient can be given platelets until the platelet defect is corrected and the bleeding ceases. But if the bleeding continues, and the chest tubes occlude, then the patient will become hemodynamically unstable and may require an emergency take back to the operating room. This impacts outcomes and costs of care.[16]
- Most studies researching clopidogrel do not compare patients on clopidogrel to patients taking placebo; rather clopidogrel use is compared to aspirin use. Thus attributing side effects directly to clopidogrel is difficult. Other side effects may include:
  - Other gastrointestinal side effects
    - Upper GI discomfort (27% vs 29% in patients taking aspirin alone)
    - Gastric or duodenal ulcer, gastritis
    - Diarrhoea (4.5% of patients in the CAPRIE trial)
  - Rash (6% overall, 0.33% severe)
  - Respiratory (infrequent)
    - Upper respiratory infections, rhinitis, shortness of breath, cough
  - Cardiovascular
    - chest pain
    - edema (generalized swelling)
  - Thrombocytopenia (reduction of platelets, 0.2% severe cases as compared to 0.1% under aspirin)

INTERACTIONS:

Clopidogrel interacts with the following drugs: proton pump inhibitors, phenytoin (Dilantin); tamoxifen (Nolvadex); tolbutamide (Orinase); torsemide (Demadex); fluvastatin (Lescol); a blood thinner such as warfarin (Coumadin), heparin, ardeparin (Normiflo), dalteparin (Fragmin), danaparoid (Orgaran), enoxaparin (Lovenox), or tinzaparin (Innohep); (Activase), anistreplase (Eminase), dipyridamole (Persantine), streptokinase (Kabikinase, Streptase), ticlopidine (Ticlid), and urokinase (Abbokinase).
In November 2009, the FDA announced that clopidogrel should be used with caution in patients on proton pump inhibitors.[17]

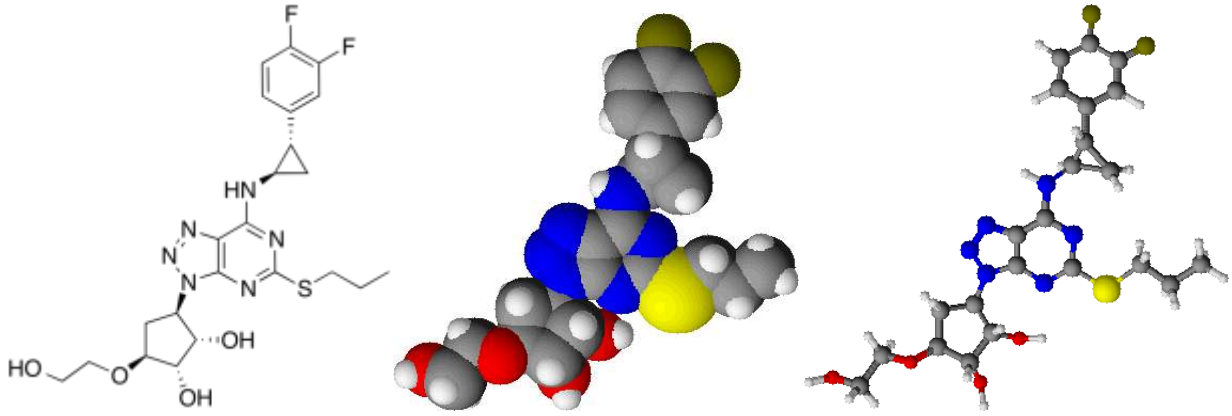
MARKETING AND LITIGATION:

Generic clopidogrel is produced by several pharmaceutical companies in India and elsewhere, and often sold under its INN *clopidogrel*. Clopidogrel is marketed by Cipla under the trade name **Clopivas**, by Sun Pharmaceuticals as **Clopilet**, by Ranbaxy Laboratories as **Ceruvin**, under the name "Clavix" by Intas Pharmaceuticals and under the name "Deplatt" by Torrent Pharmaceuticals. In India, it is sold as **Clopivas AP**, by Cipla, Clopigrel A, by USV, Clopitab A, by Lupin by Lupin(mixed with aspirin). Generic clopidogrel is produced in Slovenia (European Union) under the trade names **Zyllt**, **Kardogrel** and **Clopidogrel Krka** by Krka d.d., Novo Mesto.
Another Generic clopidogrel is produced for Julphar brand (Gulf Pharmaceutical industries) UAE (GCC) under name of

Lavigard by EGIS Pharmaceuticals PLC, Budabest, Hungary ingredient listed as Clopidogrel.[18]

INTRODUCTION:

Ticagrelor (trade name **Brilinta** in the US, **Brilique** and **Possia** in the EU) is a platelet aggregation inhibitor produced by AstraZeneca. The drug was approved for use in the European Union by the European Commission on December 3, 2010. The drug was approved by the US Food and Drug Administration on July 20, 2011.



IUPAC Nomenclature: (1*S*,2*S*,3*R*,5*S*)-3-[7-[(1*R*,2*S*)-2-(3,4-Difluorophenyl)cyclopropylamino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

Molecular Formula: $C_{23}H_{28}F_2N_6O_4S$, Molecular Mass: 522.567 g/mol, logP: 1.90

Pharmacokinetic data:

Bioavailability	**36%**
Protein binding	>99.7%
Metabolism	Hepatic (CYP3A4)
Half-life	7 hrs (ticagrelor), 8.5 hrs (active metabolite AR-C124910XX)
Excretion	Biliary

Table 3: Pharmacokinetics of Ticagrelor

INDICATIONS:

Ticagrelor is indicated for the prevention of thrombotic events (for example stroke or heart attack) in patients with acute coronary syndrome or myocardial infarction with ST elevation. The drug is combined with acetylsalicylic acid unless the latter is contraindicated. Treatment of acute coronary syndrome with ticagrelor as compared with clopidogrel significantly reduces the rate of death.[19]

CONTRAINDICATIONS:

Contraindications for ticagrelor are: active pathological bleeding and a history of intracranial bleeding, as well as reduced liver function and combination with drugs that strongly influence activity of the liver enzyme CYP3A4, because the drug is metabolized via CYP3A4 and excreted via the liver.[20]

ADVERSE EFFECTS:

The most common side effects are shortness of breath (dyspnea, 14%) and various types of bleeding, such as hematoma, nosebleed, gastrointestinal, subcutaneous or dermal bleeding. Allergic skin reactions such as rash and itching have been observed in less than 1% of patients.[21]

PHYSICAL AND CHEMICAL PROPERTIES:

Ticagrelor is a nucleoside analogue: the cyclopentane ring is similar to the sugar ribose, and the nitrogen rich aromatic ring system resembles the nucleobase purine, giving the molecule an overall similarity to adenosine. The substance has low solubility and low permeability under the Biopharmaceutics: Classification System.[22]

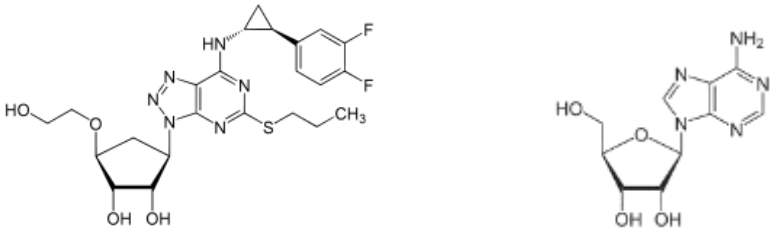


Figure 5: Ticagrelor as a nucleoside analogue and the nucleoside adenosine for comparison

PHARMACOKINETICS:

Ticagrelor is absorbed quickly from the gut, the bioavailability being 36%, and reaches its peak concentration after about 1.5 hours. The main metabolite, AR-C124910XX, is formed quickly via CYP3A4 by de-hydroxyethylation at position 5 3eocrpeuicfe cyclopentane ring.[23] It peaks after about 2.5 hours. Both ticagrelor and AR-C124910XX are bound to plasma proteins (>99.7%), and both are pharmacologically active. Blood plasma concentrations are linearly dependent on the dose up to 1260 mg (the sevenfold daily dose). The metabolite reaches 30–40% of ticagrelor's plasma concentrations. Drug and metabolite are mainly excreted via bile and feces. Plasma concentrations of ticagrelor are slightly increased (12–23%) in elderly patients, women, patients of Asian ethnicity, and patients with mild hepatic impairment. They are decreased in patients that described themselves as 'coloured' and such with severe renal impairment. These differences are considered clinically irrelevant. In Japanese people, concentrations are 40% higher than in Caucasians, or 20% after body weight correction. The drug has not been tested in patients with severe hepatic impairment.[23]

MECHANISM OF ACTION:

Like the thienopyridines prasugrel, clopidogrel and ticlopidine, ticagrelor blocks adenosine diphosphate (ADP) receptors of subtype $P2Y_{12}$. In contrast to the other antiplatelet drugs, ticagrelor has a binding site different from ADP, making it an allosteric antagonist, and the blockage is reversible. Moreover, the drug does not need hepatic activation, which might work better for patients with genetic variants regarding the enzyme $CYP2C_{19}$ (although it is not certain whether clopidogrel is significantly influenced by such variants).[24]

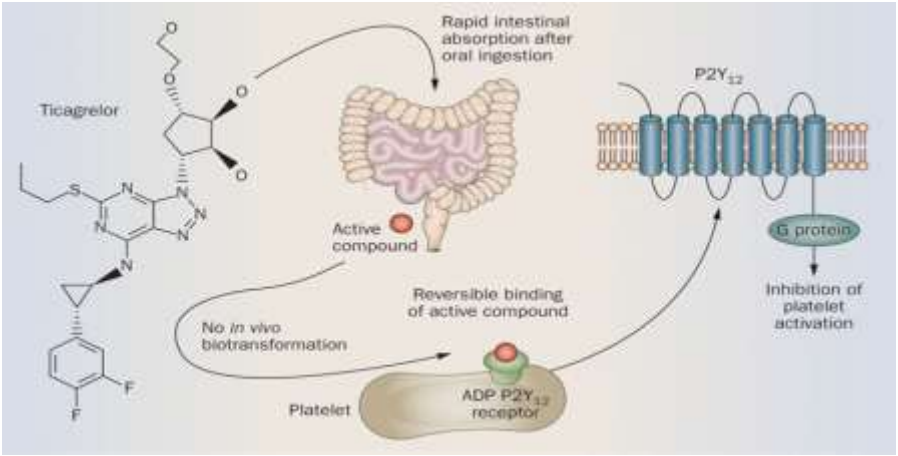


Figure 6: Mode of Action of Ticagrelor

COMPARISON WITH CLOPIDOGREL:

The **PLATO** trial, funded by AstraZeneca, in mid-2009 found that ticagrelor had better mortality rates than clopidogrel (9.8% vs. 11.7%, p<0.001) in treating patients with acute coronary syndrome. Patients given ticagrelor were less likely to die from vascular causes, heart attack, or stroke but had greater chances of non-lethal bleeding (16.1% vs. 14.6%, p=0.0084), higher rate of major bleeding not related to coronary-artery bypass grafting (4.5% vs. 3.8%, P=0.03), including more instances of fatal intracranial bleeding. Rates of major bleeding were not different. Discontinuation of the study drug due to adverse events occurred more frequently with ticagrelor than with clopidogrel (in 7.4% of patients vs. 6.0%, P<0.001). The PLATO trial showed a statistically insignificant trend toward worse outcomes with ticagrelor versus clopidogrel among US patients in the study – who comprised 1800 of the total 18,624 patients. The HR actually reversed for the

composite end point cardiovascular (death, MI, or stroke): 12.6% for patients given ticagrelor and 10.1% for patients given clopidogrel (HR = 1.27). Some believe the results could be due to differences in aspirin maintenance doses, which are higher in the United States. Others state that the central adjudicating committees found an extra 45 MIs in the clopidogrel (comparator) arm but none in the ticagrelor arm, which improved the MI outcomes with ticagrelor. Without this adjudication the trials' primary efficacy outcomes should not be significant.

Consistently with its reversible mode of action, ticagrelor is known to act faster and shorter than clopidogrel. This means it has to be taken twice instead of once a day which is a disadvantage in respect of compliance, but its effects are more quickly reversible which can be useful before surgery or if side effects occur.

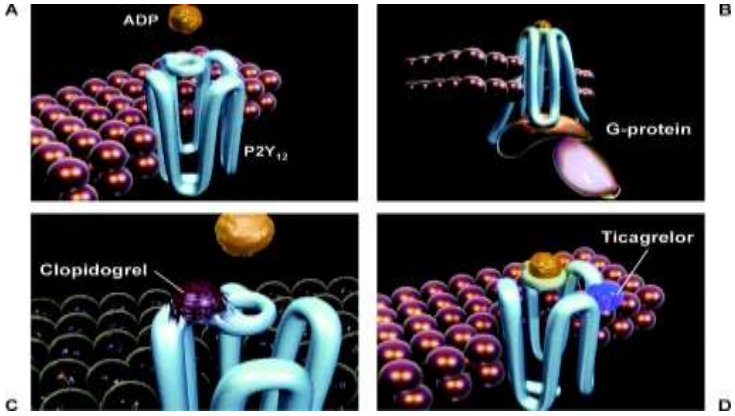


Figure 7: Receptor Binding Sites of Clopidogrel and Ticagrelor

INTERACTIONS:

Inhibitors of the liver enzyme CYP3A4, such as ketoconazole and possibly grapefruit juice, increase blood plasma levels and consequently can lead to bleeding and other adverse effects. Conversely, drugs that are metabolized by CYP3A4, for example simvastatin, show increased plasma levels and more side effects if combined with ticagrelor. CYP3A4 inductors, for example rifampicin and possibly St. John's wort, can reduce the effectiveness of ticagrelor. There is no evidence for interactions via CYP2C9. The drug also inhibits P-glycoprotein (P-gp), leading to increased plasma levels of digoxin, ciclosporin and other P-gp substrates. Ticagrelor and AR-C124910XX levels are not significantly influenced by P-gp inhibitors. In the US a boxed warning states that use of ticagrelor with aspirin doses exceeding 100 mg/day decreases the effectiveness of the medication.[25]

CONCLUSION:

In patients who have an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor as compared with clopidogrel significantly reduce the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non–procedure-related bleeding.

Figure 8: Clopidogrel and Ticagrelor Formulations

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