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(REVIEW ARTICLE)

Market review on Clopidogrel Tablet

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Abstract

Antiplatelet drugs are drugs which interfere with platelet function and are useful in the prophylaxis of thromboembolic disorders. Clopidogrel is the most commonly used Antiplatelet drug(1). Clopidogrel was first reported in 1987 to be an inhibitor of ADP induced platelet activation. It was first approved by US-FDA in1997 and was developed and manufactured by bristol-myers squibb (BMS) in collaboration with Sanofi-Aventis. Plavix is a patented brand of Clopidogrel and plavix's patent expired in May, 2012. Plavix (clopidogrel) has been the most prescribed antiplatelet brand-name drug for the prevention of heart attack or stroke, and was the second best-selling drug in the world, with $9.4 billion in global sales in 2010(3). After listening to a lot of people's opinion about clopidogrel, it has been noticed that this drug works very well in about 70to 80% of the people. Some people also experience side effect mainly bleeding, headache, stomach and abdominal pain.re

The growing global population of people suffering from cardiovascular illnesses and other disorders is the fundamental reason for the increased demand for clopidogrel. Furthermore, in the next six years, rising economies in the Asia Pacific area are predicted to be the largest consumers of clopidogrel due to changing lifestyles and an increase in the number of patients with cardiovascular illnesses (3). Furthermore, the patentexpiration of the clopidogrel medicine is expected to open the floodgates for various pharmaceutical businesses to enter the clopidogrel drug production business.Recent studies have raised concern that a significantclinical interaction may exist between Clopidogrel and proton pump inhibitors. Studies suggest PPI may diminish Clopidogrels effect (1).

Since the patent expired in 2012 the drug is now available in over 100 different brands and has many generic formulations. According to many pharma experts the demand for this drug is expected to increase in the future due to the increasing incidence of cardiovascular diseases.

After all the drug cropidogrel has become a necessity for many people today considering the deadly disease of stroke and heart attack (2).

Keywords: Clopidogrel; Patent expiration; Side effects; Necessity

1. Introduction

Nowadays, millions of people around the world are losing their lives due to heart attack and stroke. This may be because of your lifestyle, obesity, diabetes, smoking etc. No one is ready to think of his well-being in the mood of enjoying life and maybe that's why so many people today are dependent on medicines. Unfortunately, in the yr. 2020, when the whole world was under the umbrella of Covid-19, even more drugs for heart attack & stroke were Sold than coved. with the increasing incidence of such diseases, their importance is increasing day by day, and today I am going topresent to you a market review of a drug that treat such diseases. Antiplateret drugs are drugs which interfere with platelet function and areuseful in the prophylaxis of thromboembolic disorders(1).

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Platelets express several glycoprotein integrin receptors on their surface. reactive proteins like collagen and Von will brand factor are exposed when there is damage to vascular endothelium, and they react respectively with platelet GPIa and GPIb receptors. this results in platelet activation and release of proaggregatory and vasoconstrictor in a mediator like TXA2, ADP and 5-ht the platelet GPIIb/IIIa receptors undergoes a conformational change favoring binding of fibrinogen and vow that cross-linked platelets including aggregation and Anchorage to vessels wall or other surfaces. thus a platelet plug is formed in veins due to sluggish blood flow, a fibrinous tale is formed which traps RBC is the red tail. In arteries platelet mass is the main constituent of the thrombus antiplatelet drugs are therefore more useful in arterial thrombosis while anticoagulant are more effective in venous thrombosis (1).

Clopidogrel (prodrug)-the active metabolite of clopidogrel selectively inhibit the binding of adenosine diphosphate to its platelet B2y12 receptor and the subsequent ADP mediated activation of the glycoprotein gpIIb/IIIa complex, thereby inhibiting platelet aggregation. This action is irreversible. Use of Clopidogrel increasing day by day because of its advantages over other antiplatelet drugs like Aspirin, ticlopidine etc. (1).

Plavix (clopidogrel) has been the most prescribed antiplatelet brand-name drug for the prevention of heart attack or stroke, and was the second best-selling drug in the world, with $9.4 billion in global sales in 2010. This drug has been marketed jointly by Sanofi-Aventis and Bristol-Myers Squibb, and the cost of therapy averages about $162 per month. In 2010, Bristol recorded $6.7 billion in Plavix sales, or 34% of its total revenues of $19.5 billion. Sanofi recorded sales of nearly $3 billion, or 7% of its 2010 revenues. In 2006, generic drug-maker Aponte briefly marketed generic Plavix, but was ordered to stop until November 2011. The order was extended by the FDA, and Plavix's patent expired in May, 2012(4).

2. Literature review

Antiplatelet therapy with aspirin and clopidogrel in PCI patients, though effective, is still associated with thrombotic complications. These are multifactorial in origin, but partially attributable to "clopidogrel resistance." However, how best to identify and manage "clopidogrel resistance" remains unclear. Targeting therapeutic changes specifically at those individuals with poor response to clopidogrel is likely to be a solution. A "one size fits all" approach to clopidogrel dosing is probably flawed. This review will explore (1) the definition and mechanisms of clopidogrel resistance, (2) assessment of clopidogrel resistance by (i) platelet function testing and (ii) genetic testing, (3) the management of "clopidogrel resistance," and (4) newer antiplatelet agents, and evolving stent technology (10).

Clopidogrel is a commonly prescribed antiplatelet agent that carries a rare risk of hepatotoxicity. We describe a case of severe clopidogrel-induced hepatitis with liver biopsy assessment. Prompt recognition and withdrawal of the offending agent are imperative to prevent progression and potentially fatal liver injury.

Management of ischemic heart disease in pregnant women is still difficult, as there is little experience with many of the newer treatments such as clopidogrel. The safety of clopidogrel in pregnancy is unknown, especially in combination with aspirin. Its use during gestation has been described in a few case reports. We describe the case of a 36-year-old woman in her 9th week of pregnancy with a history of chronic hypertension, dyslipidemia and CAD, who required antiplatelet treatment. Clopidogrel and aspirin were administrated until one week before delivery and a healthy child was born at 36 weeks of pregnancy by caesarean section, without any complication (3).

Dual antiplatelet therapy with aspirin and a P2Y12 inhibitor is standard therapy following acute coronary syndrome and percutaneous coronary intervention. Despite the use of potent antiplatelet agents, vascular events continue to occur. Lack of response to clopidogrel therapy has been widely investigated using various methods of platelet function testing.

These studies have consistently found an association between poor clopidogrel response and an increased risk of vascular events. Strategies to overcome this problem include higher clopidogrel doses or the use of an alternative P2Y12 agent. To date, the majority of studies investigating tailored antiplatelet therapy have failed to show any reduction in clinical events likely due to the low-risk population studied. Despite this lack of benefit from altering therapy, platelet function testing may be done in certain patient populations. Patients at high risk of deleterious outcomes from stent thrombosis may be an appropriate patient population for platelet function testing to ensure adequate response to therapy. In addition, emerging data suggests a potential role for platelet function testing to assess for bleeding risk (7). The purpose of this article is to review the key studies demonstrating response variability to clopidogrel therapy, strategies to overcome variability, and practical considerations for the clinician.

3. History and patent of clopidogrel

Clopidogrel was first reported in 1987 to be an inhibitor of ADP induced platelet activation. notably the molecular target for clopidogrel was unknown at the time and could be inferred only from its pharmacologicalactivity. Plavix (clopidogrel bisulfate) is a thienopyridine class inhibitor indicated for the treatment of acute coronary syndrome(24). It was first approved by US-FDA in 1997 and was developed and manufactured by bristol-myers squibb in collaboration with Sanofi-Aventis .it is on the World health organization list of essential medicines. in 2018 it was the 39th most commonly prescribed medication in the United States with more than 20 million prescription. it is world's second biggest selling medicine with worldwide sale of more than 9 billion a year in 2006 generic drug maker apotex briefly marketed generic Plavix but was order to stop until November 2011 the order was extended by FDA and Plavix patent expired in May 2012(12).

Figure 1 Palvix Tablets

4. Various brands of clopidogrel available in the market(6)

Table 1 Brands of clopidigrel tablets

Brand name	Manufacturer	Price
Plavix	Sanofi Aventispharma	75.18
Aclotil	Bal pharma limited	37.95
Antiban	Blue crosslaboratory	38
Anticog	Marc. Laboratorypvt.Ltd.	59.00
Aplatin -75	Saga laboratory	39
Aptogril	Aurobindo pharmalimited	49.5
Caplor	Ind. Swift ltd.	24.8
Cidogril	Karnataka antibiotic &pharamaceuticals Ltd.	32.52
Clavix	Intas pharamaceuticalltd.	80
Clowder	Unichem laboratoryltd.	46.7
Clopicard fc	Cipla ltd	100.19
Clopivik	Cardia labs	39.50
Clopod	Biochem pharmaceuticals	30.90
Clotsafe fc	Safemed	38.25

Grelet	Intra laps India pvtltd	80
Klov	Zee laboratory ltd.	48.5
Livigrel	Lividus pharmaceuticalpvt.Ltd.	73
Platloc	Unichem laboratory	39.1
Preva	Intas pharmaceuticalltd.	47.5
Plagril	Dr. Reddys laboratoryltd.	41.70
Platfrin	Medley pharmaceuticalltd.	60.00
Stromix	Ahpl	89.65
Torplatt	Torrent pharamaceuticalltd.	38.00
Zeter	Kopran pharma ltd.	55.00
Zoclop	Lifeline remediespvt.Ltd.	60.00
Torpido	Mesmer pharmaceutical	43.00
Thinrin	Biocon indialtd.	69.00

5. Combination of clopidogrel with other drugs;(5)

Table 2 Combination of clopidogrel tablet with other drugs

Brand name	**API**	**Price**
Deplatt a-75	Aspirin 75mg + Clopidogrel 75mg.	80.85
Clopilet a-75	Aspirin 75mg + Clopidogrel 75mg.	53.50
Rozalet	Rosuvastatin-10mg +Clopidogrel 75mg.	153
Astin cv	Atorvastastins 10mg +Clopidogrel 75mg.	111.00
Ecosprin gold	Aspirin 75mg + atorvastatin 10mg + Clopidogrel 75mg.	108.50

Of all these Brands, PLAVIX is the mostly used in all over Worlds.

6. Benefits of the combination

In Some Patient Combination antiplatelet therapy with Clopidogrel & aspirin may reduce the rate of recurrent stroke during the first 3 months after a minor ischaemic stroke or transient ischemic attack (TIA), A trial of combination antiplatelet therapy in a population has shown a reduction in the risk of recurrent stroke (21).

Some patient's combination of clopidogrel and atorvastatin is used atorvastatin and clopidogrel which prevents heart attack and stroke. Atorvastatin is a lipid lowering medication that blocks an enzyme required in the body to make cholesterol. It lowers the bad cholesterol (LDL), triglycerides and raises the good cholesterol (HDL). clopidogrel is an antiplatelet medication which prevents the platelet from sticking together and decreases the formation of harmful blood clot (20).

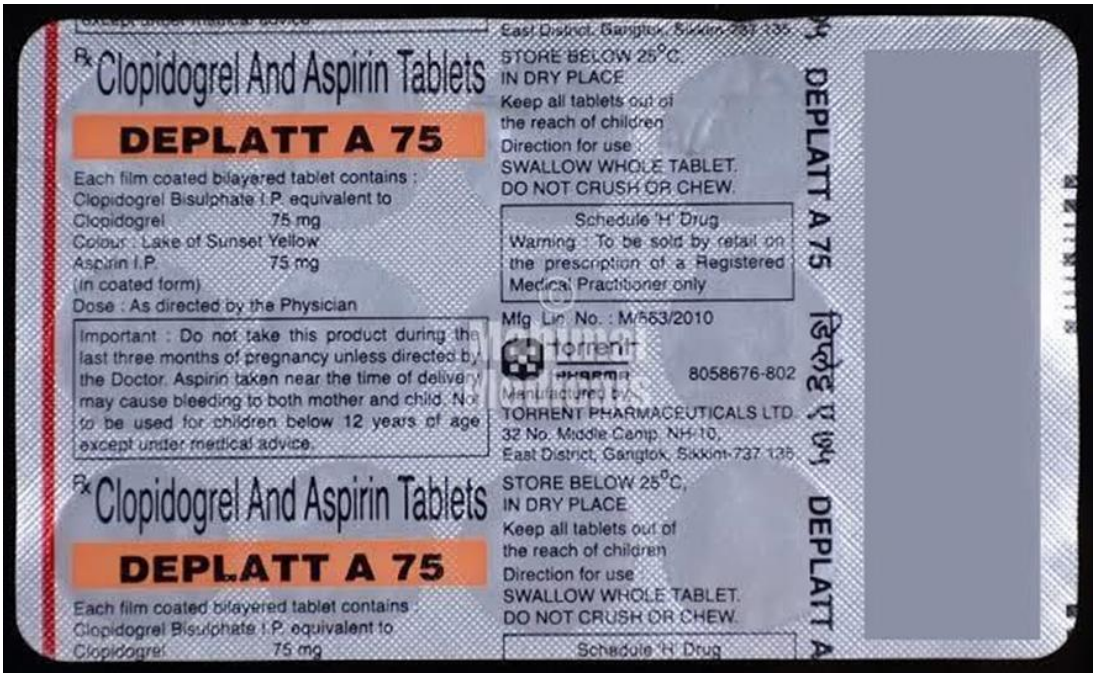

Figure 1 Image of strip of clopidogrel tablet available in market

7. Review and ratings of different patients about clopidogrel (8)

*Plavix (clopidogrel): "I have been taking PLAVIX from the day it came on the market because of my unique clotting problem. My heart doctor has me on both PLAVIX and 325 Mg of aspirin once daily. When I developed atrial fibrillation, they put me on warfarin also. Then I started having bleeding problems. They took me off the warfarin and I was fine on the PLAVIX and aspirin, no clot problems encountered."

10/10

*Plavix (clopidogrel): "Suffered heart attack 12 years ago, then 2 weeks ago suffered severe angina, got scared went to the ER, they ran tests and told me my arteries were severely clogged, need stents put in me, had the stents put in, they put me on Plavix told me I would be on it for life. Well it's been 3 weeks now on the Plavix, love it, so far no side effects."

10/10

*Plavix (clopidogrel): "Had a heart attack on July 3rd, stent put in, put on Plavix for one month. Stent partially collapsed after stopping Plavix and was having some chest pains. Doctor put me back on Plavix and no more problems since. It sure works good for me and no side effects."

10/10

*Plavix (clopidogrel): "I've been using Plavix for a couple years now since I had 2 angioplasties. It works just fine. However, some of the drawbacks are:

- easy bruising, and long recover time - easy bleeding from injuries, so don't take chances - My Doctor told me I'd have to take Plavix for the rest of my life - cost is no concern since my insurance pays all but $9.00 per month"

8/10

This medication has been nothing but a problem for me. I have nose bleeds 5 plus times a day and spend hours a day making them stop. I feel as though I am starting to have arthritis in my hands from applying pressure. I am 33 years old and was a marathon runner then a blocked artery but an end to that and introduced me to this nightmare medication called "PLAVIX" I think the best gift I have ever received was my doctor telling me to take half a dose a day. However, when they found out I was happy and nose bleed free they said maybe I should be on a full dose. This medication makes

me feel like I am a 400 pound 85-year-old man. My blood even turned pink and one point. Overall still on this medication because of doctor's order but do not like it."2/10

"I suffer from constipation, perhaps it's a side effect of the drug, been taking it since April 2008."

8/10

*Since taking this drug my doctor advised that I was anemic and put mean B12. Severe stomach cramps and severe diarrhea. Loss of appetite, fatigue, insomnia, bruising and severe bleeding when having blood tests

7/10

8. My opinion about this review of people

After listening to a lot of people's opinions about clopidogrel, it has been noticed that this drug works very well in about 70 to 80% of the people. Some people also experience side effects mainly bleeding, headache, stomach and abdominal pain. Due to its excellent results, low- cost and rejuvenation of many people this drug is currently in great demand in market.

9. Clopidogrel market latest trends andfuture growth (9): -

Clopidogrel has been the antiplatelet drug of choice among physicians for the treatment of patients with diseases such as acute coronary syndrome or percutaneous coronary intervention since its initial approval in 1997.

The medicine was the first thienopyridine to reach the market, giving it a significant advantage over a number of other treatments for these disorders that are currently available or in clinical development. As a result, the medicine faced little competition and quickly dominated the global market, with its range of applications extending all the time.

The substantial and high-level evidence gathered over the years support the use of Clopidogrel for reduction of mortality and morbidity patients with acute coronary syndrome, myocardial infarction, and a number of other indications. As a result, the drug has developed a formidable presence in the global market over the years. Moreover, the drug's relative ease of use, low rate of incidence of adverse reactions, and good tolerability have made it the de- facto antiplatelet agent for the reduction of atherosclerotic events in patients. These factors have helped the global Clopidogrel market to tread along an excellent growth path in the past few years and the market is expected to embark upon a healthy growth path in the next few years as well. However, the overall profitability of the market has reduced to a certain extent owing to entry of a number of generic products post the patent expiry of Clopidogrel manufacture in 2013. Nevertheless, the vast pool of patients prescribed Clopidogrel on an annual basis across the globe will allow market players excellent growth prospects in the next few years.

10. Global clopidogrel market: overview

Clopidogrel is an antiplatelet agent of thienopyridine, which is primarily used to prevent the blood clots and help against cardiovascular problems associated with the blood clotting. The medications for inhibiting blood clots after a recent heart stroke also use clopidogrel (14), which is a white colored powder that is insoluble in water at neutral pH but freely soluble at pH1. Clopidogrel was the second most successful drug trailing behind Pfizer's Lipitor in 2010. Sold under the brand name Plavix, and marketed by Sanofi and Bristol-Myers Squibb, the demand for clopidogrel is escalating due to the increasing number of heart attack cases across the globe (14).

The patent of clopidogrel manufacturing got expires on Market 31, 2012and is expected to prompt pharmaceutical companies to venture into clopidogrel drug manufacturing.

Moreover, companies such as Dr. Reddy's have acquired the approval to manufacture clopidogrel 300mg. Furthermore, several other organizations such as Roxane Laboratories, Aurobindo Pharma, Sun Pharma, Torrent Pharmaceuticals, and Apotex Crop have gained approval for marketing clopidogrel 75mg. Clopidogrel is also used with aspirin to treat worsening chest pain and to keep blood vessels open and present blood clots after certain heart related operations (12).

11. Global clopidogrel market trends and prospect (14)

The primary factor for the increased demand for clopidogrel is the mounting population across the world who are suffering from cardiovascular diseases and related problems. Additionally, the changing lifestyle and increase in number of patients related with cardiovascular diseases among the emerging economies in the Asia Pacific region are also expected to be the major consumers for clopidogrel in the next six years.

Moreover, the patent expiry of clopidogrel drug is anticipated to open floodgates for various pharmaceutical companies to venture into production of clopidogrel drug.

According to the World Heart Federation, nearly 15 million people suffer from heart attack or related problems globally. Out of these, roughly six million of these patients die while another five million are disabled permanently. This vast patient base is the primary factor that will sustain the demand during the forecast period.

12. Contraindications of clopidogrel

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

-Bleeding, GI bleeding, intracranial bleeding, peptic ulcer disease, surgery, trauma, Clopidogrel increases the risk of bleeding and is contraindicated in patients with active pathological bleeding including GI bleeding and intracranial bleeding. As with other antiplatelet agents, clopidogrel should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions including peptic ulcer disease.

-Poor metabolizers-Clopidogrel has a reduced effect on platelet function in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene (i.e., poor metabolizers).

Consider another platelet P2Y12 inhibitor inpatients identified as CYP2C19 poor metabolizers. Data have shown that poor metabolizers have a higher risk of mortality, myocardial infarction, and stroke compared to normal metabolizers. Clopidogrel metabolism and, subsequently, platelet inhibition can also be reduced by drugs that significantly inhibit CYP2C19, such as omeprazole and esomeprazole; concomitant use should be avoided (6).

13. Drug interactions of clopidogrel

-Alogliptin; Pioglitazone: (Major) Do not exceed 15 mg/day of pioglitazone when administered with clopidogrel. Coad ministration may increase the exposure of pioglitazone, increasing the risk for hypoglycemia.

Pioglitazone is a CYP2C8 substrate and clopidogrel is a strong CYP2C8inhibitor. Coad ministration with another strong CYP2C8 inhibitor increased the exposure of pioglitazone by approximately 3.2-fold (7).

Amoxicillin; Clarithromycin; Omeprazole: (Major) Avoid concomitant use of clopidogrel and omeprazole as it significantly reduces the antiplatelet activity of clopidogrel. If necessary, consider using a PPI medication with less pronounced effects on antiplateletactivity, such as rabeprazole, pantoprazole, lansoprazole, or dexlansoprazole. Clopidogrel requires hepatic biotransformation via 2 cytochromes dependent oxidative steps; the CYP2C19 isozyme is involved in both steps. Omeprazole is an inhibitor of CYP2C19. In clinical studies, use of omeprazole significantly reduced the antiplatelet activity of clopidogrel when administered concomitantly or 12 hours apart.

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

Isoniazid, INH; Pyrazinamide, PZA; Rifampin: (Major) Avoid concomitant use of clopidogrel and rifampin due to the risk of bleeding. Concomitant use results in increased plasma concentrations of clopidogrel's active metabolite and an increase in platelet inhibition.

Clopidogrel is primarily metabolized to its active metabolite by CYP2C19; rifampin is a strong CYP2C19 inducer. (Moderate) Monitor for reduced clopidogrel efficacy during concomitant use of isoniazid. Clopidogrel is primarily metabolized to its active metabolite by CYP2C19; isoniazid is a CYP2C19 inhibitor (7).

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

Tucatinib: (Major) Avoid administration of tucatinib and clopidogrel due to the risk of increased tucatinib exposure which may increase the risk of adverse reactions. If concomitant use is unavoidable, reduce the dose of tucatinib to 100 mg PO twice daily. If clopidogrel is discontinued, résumé the original tucatinib dose after 3 elimination half-lives of lives ofclopidogrel. Tucatinib is a CYP2C8 substrate and clopidogrel is a strong

Aliskiren; Amlodipine: (Moderate) Monitor for reduced therapeutic response to clopidogrel when it is administered with amlodipine. Although clopidogrel is primarily converted to its active metabolite via CYP2C19, it has been suggested that calcium channel blocker (CCB)- induced inhibition of CYP3A4 reduces its conversion to the active metabolite, thereby reducing its antiplatelet effect. Because amlodipine has represented the largest subgroup of CCB studied, it is unknown whether this is a class effect. It has been theorized that CCBs that inhibit P-glycoprotein (P-gp) decrease the intestinal efflux of clopidogrel, thereby increasing its plasma concentrations and counteracting the effect of CCB-induced CYP3A4 inhibition. Amlodipine is not a P-gp inhibitor (7).

Chlorpheniramine; Hydrocodone: (Moderate) Coadministration of opioid agonists, such as hydrocodone, delay and reduce the absorption of clopidogrel resulting in reduced exposure to active metabolites and diminished inhibition of platelet aggregation. Consider the use of a parenteral antiplatelet agent in acute coronary syndrome patients requiring an opioid agonist. Coadministration of intravenous morphine decreased the Cmax and AUC of clopidogrel's active metabolites by 34%. Time required for maximal inhibition of platelet aggregation (median 3 hours vs. 1.25 hours) was significantly delayed; times up to 5 hours were reported. Inhibition of platelet plug formation was delayed and residual platelet aggregation was significantly greater 1 to 4 hours after morphine administration (7).

14. Clopidogrel resistance (10)

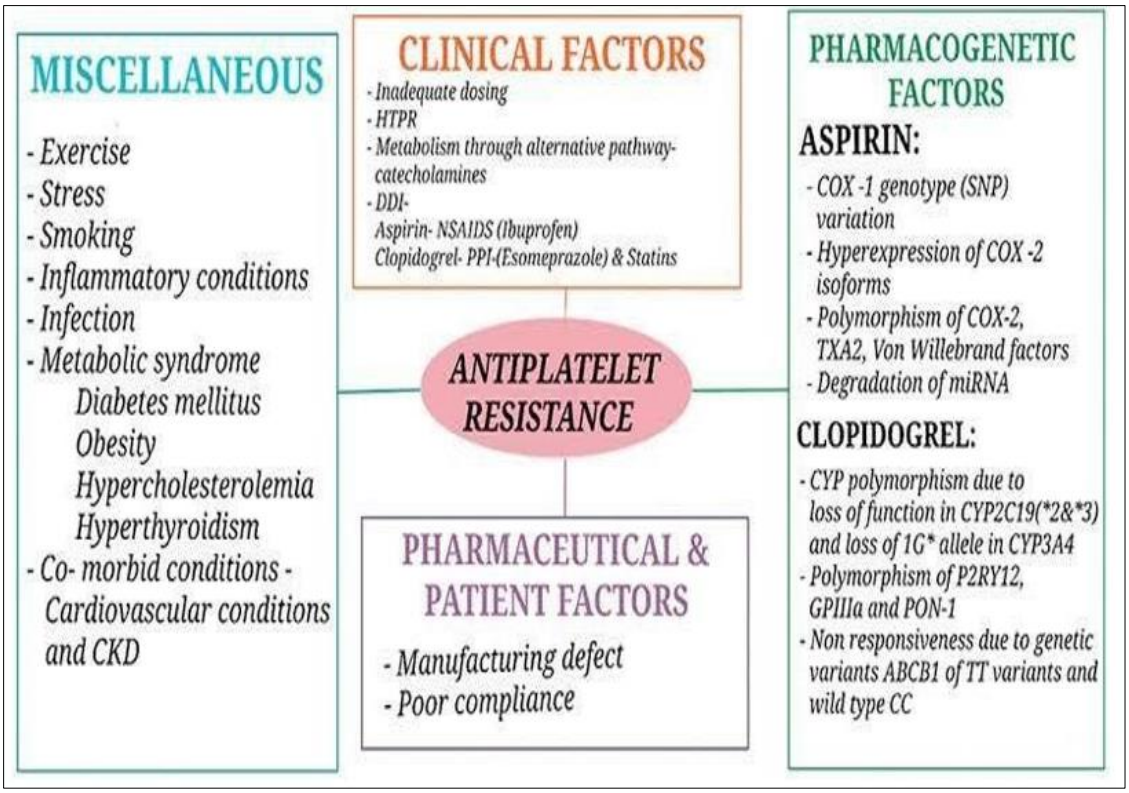

Figure 3 Antiplatelet Resistance

15. Result and discussion

Clopidogrel was significantly more effective than Aspirin and rosuvastatinin the prevention of vascular events. Plavix is the most widely used brand of Clopidogrel. Looking at the opinion of many patients, it has been noticed that many patients have a positive response about this drug, but to some extent its side effects have also been seen. It also has some limitations such as it requires hepatic conversion to active form, irreversible receptor binding and wide variability in response etc. It also has some consequences such as bleeding complication in patient requiring emergency surgical intervention, up to 44% of patients exhibit minimal platelet inhibition etc. Due to its excellent result (17), low cost and rejuvenation of many people this drug is currently in great demand in market. The primary factor for the increased demand for clopidogrel is the mounting population across the world who are suffering from cardiovascular diseases and related problems. Additionally, the changing lifestyle and increase in number of patients related with cardiovascular diseases among the emerging economies in the Asia Pacific region are also expected to be the major consumers for clopidogrel in the next six years (15).

16. Conclusion

Of all the Clopidogrel brands, Plavix is the most used. Clopidogrel was significantly more effective than Aspirin in the prevention of vascular events (ischaemic stroke, myocardial infarction or vascular death) in patients with atherothrombotic disease manifested by recent myocardial infarction, recent ischaemic stroke for symptomatic peripheral arterial occlusive disease. since the patent expired in 2012 the drug is now available in over 100 different brands and has many generic formulations. considering the importance of this drug, the need of the people and the production of these drug from various Pharma companies this drug is currently available in market at very reasonable price. According to many experts the demand for this drug is expected to increase in the future due to the increasing incidence of cardiovascular diseases

Outcomes: -

- Clopidogrel is an essential medicine according to US- FDA.
- Clopidogrel was significantly more effective than Aspirin in the prevention of vascular events.
- Dual antiplatelet therapy with clopidogrel and aspirin is effective for secondary prevention after minor ischemic stroke or transient ischemic attack (TIA)
- The primary efficacy outcome was a major ischemic event (ischemic stroke, myocardial infarction, or death from ischemic vascular causes). The primary safety outcome was major hemorrhage.
- Plavix is the most widely used brand of Clopidogrel.
- Our study indicated no statistically significant increase in the risk of prehospitalization for ACS due to concurrent use of clopidogrel and PPIs overall. Among individual
- PPIs, only omeprazole was found to be statistically significantly associated with increased risk of prehospitalization for ACS.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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