PHARMACOGENETICS OF ANTIPLATELET THERAPY

Abstract:
Antiplatelet therapy is used in the treatment of patient with acute coronary syndrome stroke and individuals undergoing percutaneous coronary intervention. Platelets are small cells in blood that body is used to form clots and prevent bleeding. Clotting can take place on the exclusive of arteries and mains to heart attack or stroke. Antiplatelet therapy decreases the chances of heart attack. Antiplatelet treatment is a drug treatment that decrease the platelet aggregation. They are used in patients with angina who are going to have an angioplasty or stent procedure. The used in antiplatelet therapy are Aspirin, Clopidogrel, Glycoprotein inhibitors, Prasugrel, Ticagrelor. Antiplatelet therapy is used in various diseases are COVID-19, Ischemic stroke, cardiovascular diseases.

Keywords:
Pharmacogenetics, Antiplatelet therapy, Disorders, Blood clotting, Receptors, Platelet,

INTRODUCTION:

Antiplatelet therapy, mostly contains aspirin (acetylsalicylic acid,) and P2Y12 receptor antagonists, is one of the most given therapies in medicine due to the worldwide high incidence of cardiovascular diseases (CVD). [1] Platelets are key mediators in the pathophysiology of atherothrombosis. Antiplatelet therapy with aspirin and clopidogrel is the cornerstone of treatment in patients with acute coronary syndromes (ACS**)** and percutaneous coronary intervention (PCI), to prevent the risk of thrombotic events and thus improve long-standing clinical outcomes.[2] Anti-platelet medications are a broadly prescribed drug class used in the primary and secondary prevention of thrombotic events associated with cardiovascular disease. The adenosine diphosphate (ADP) receptor inhibitors are a subclass of anti-platelet medications which include clopidogrel, prasugrel, ticagrelor and ticlopidine. Clopidogrel is presently one of the most commonly prescribed medications in the United States and world-wide, specified in patients with acute coronary syndrome (ACS) and in patients suffering percutaneous coronary intervention (PCI). Current findings show that common genetic variation can explain a significant portion of inter-individual variation in clopidogrel response. With the addition of new anti-platelet therapy alternatives for those with a genetic predisposition toward insufficient response, the promise of interpreting these pharmacogenetic perceptions into more effective modified anti-platelet therapy has sparked much excitement and optimism for the future of custom-made medicine.[3] Platelets are the dynamic components of a proper normal homeostasis and significant key members in atherothrombosis.[4]An antiplatelet drug , also known as a platelet agglutination inhibitor or platelet aggregation inhibitor, is a member of a class of pharmaceuticals that depresses platelet accumulation and inhibit thrombus creation.[5]

Basics of Pharmacogenetic Variability and Terminology:

Much of the presented and clinically relevant pharmacogenetic information stems from differences in genes that code for drug metabolizing enzymes or those that alter a drug's skill to act in the body or the body's response to a drug. The most mutual type of genetic difference (or polymorphism) is a single nucleotide polymorphism. The occurrence of specific variations at certain one nucleotide polymorphisms or other polymorphisms can lead to dissimilar forms of a gene, or alleles. As with several other genetic traits, those regularly receive one allele from each parent. [6]

Platelets, Blood Clotting, And Heart Diseases:

Platelets are the minor elements that circulate generally in the bloodstream and help the body protect itself against bleeding and blood loss. A heart attack (myocardial infarction) results when a blood clot interrupts or blocks blood flow to the heart, which have nothing to eat the heart muscle of oxygen and causes heart muscle cells to die; the same process in the brain reasons a stroke. Under usual healthy conditions, the dissimilar parts of flowing blood (such as red and white blood cells and platelets) are not able to twig to the inner lining of blood vessels and cause an obstruction that agitate blood flow. [7]

Antiplatelet Therapy:

Drugs that interfere with platelet role can be classified into three categories: Those that avoid cardiovascular disease (primary prevention), those that treat an severe disease, and those that treat a long-lasting disease (secondary prevention) (Table no 01). There are both oral (taken by mouth) and intravenous (given through a vein) drugs that inhibit platelet purpose and are used to delicacy patients with cardiac and cerebrovascular diseases.

Table no 01: - Roles of Antiplatelet Therapies in Preventing and Treating Heart Diseases:

Antiplatelet Therapy	Primary prevention	Acute Indication	Secondary prevention
Aspirin	Patients at high risk of heart attack or stroke (including those with an older age, history of initial heart disease, diabetes, etc	Heart attack Unstable angina Stroke Coronary angioplasty Coronary bypass surgery	Heart attack Unstable angina Stroke Coronary angioplasty Coronary bypass surgery
Clopidogrel	Studies presently underway	Heart attack Unbalanced angina Coronary	Heart attack Unbalanced angina Coronary stenting

		angioplasty	
Glycoprotein IIb/IIIa Inhibitors	Not appropriate	Heart attack and unstable angina.	Not appropriate

Aspirin*:*
Aspirin is the basis of treatment for patients with any vascular disease, having remained used as a medical product for over 100 years. Although it is not guided for most healthy people to prevent a first heart attack or stroke, it does offer approximately protection for older individuals at high risk, counting smokers or those with diabetes or a family history of atherosclerotic disease at an early age. In studies involving additional than 100 000 patients, aspirin has been shown to diminution the risk of failing from a heart attack or stroke when it is given in the previous hours after symptoms begin.

CLOPIDOGREL:
Clopidogrel is an impartially new drug that reductions the risk of vascular events when it is given with aspirin to patients who have unbalanced chest pain or angina or certain types of heart attacks. When taken repeatedly after a heart attack or stroke, its paybacks are same to those of aspirin.

Glycoprotein IIb/IIIa Inhibitors:
The drugs that do this are the glycoprotein IIb/IIIa inhibitors, and they are a delightful example of drugs that are intended to interfere with a specific biological process. The glycoprotein IIb/IIIa inhibitors are given intravenously to patients who are feeling coronary angioplasty/ stenting or to increase-risk patients with unbalanced angina or a specific type of heart attack.[7]

Current Paradigms of Pharmacogenetics and Platelet-Directed Therapy:
CYP2C19 (-808C>T; rs12248560) is a gain-of-function polymorphism which has been implicated in higher rates of bleeding problems in patients preserved with clopidogrel. CYP2C9 loss-of-function allele posture has also been associated with developed platelet reactivity. Carboxylesterase 1 has been recognized as a usually expressed serine esterase that hydrolysis clopidogrel to inactive metabolites. The G143E polymorphism outcomes in impaired carboxylesterase 1 activity and thus enlarged platelet inhibition by clopidogrel. PON1 and ABCB1 polymorphisms have both been linked to declined platelet inhibition by clopidogrel. Paraoxons 1, a key enzyme in the rate-limiting step of clopidogrel bioactivation, and polymorphisms of its coding gene (Q192R PON1 polymorphism) can disturb plasma concentrations of the active metabolite, clopidogrel-mediated platelet inhibition, and the hazard of stent thrombosis. A 2013 study of clopidogrel pharmacokinetics and pharmacodynamics
established that from top to bottom interpatient inconsistency leftovers even when excluding or regulatory for known ailment, polymorphisms, including CYP2C19, CYP3A5, ABCB1, and PON1 polymorphisms, medications, action compliance, and patient characteristics. This study also controlled for pre-treatment platelet hyperreactivity.[8]

Table no: - 02 Gene polymorphisms linked to antiplatelet response variability of clopidogrel-

Gene	Product	Polymorphism	Platelet reactivity
ABCB1	P-glycoprotein	C3435→T	Deceased
CES1	Carboxylesterase 1	G143→E	Increased
CYP2C9	Cytochrome P450 2C9	CYP2C9; loss of function	Deceased
	Cytochrome P450 2C19		
	Cytochrome P450 2C19	CYP2C19; loss of function	Deceased
	Cytochrome P450 2C19	CYP2C19; loss of function	Deceased
		CYP2C19; loss of function	Increased
PON1	Paraoxonase 1	Q192→R	Deceased

[8]

Antiplatelet Therapy for Atherothrombotic Diseases:
Antiplatelet agents act also by stopping the formation of second messengers, by interrelating with intracellular signalling pathways, by blocking membrane receptors, or by inhibiting platelet combination *per se* (Figure 1). Their main pharmacokinetic/pharmacodynamic characteristics are abridged in Tables 1, 2.
FIGURE-1 Targets of the marketed antiplatelet agents. Arachidonic acid (AA) is produced by sheath phospholipids upon the achievement of phospholipase A_2. The condition is metabolized in cyclic endoperoxides by the cycloxygenase-1 (COX-1) enzyme, before in thromboxane A_2 (TXA_2) by the thromboxane synthase. TXA_2 activates the Thromboxane Proteinoid (TP) receptor in reappearance. ADP, by activating $P2Y_{12}$ receptor, makes an inhibition of adenylate cyclase which downregulates cAMP (a powerful platelet inhibitor) synthesis.

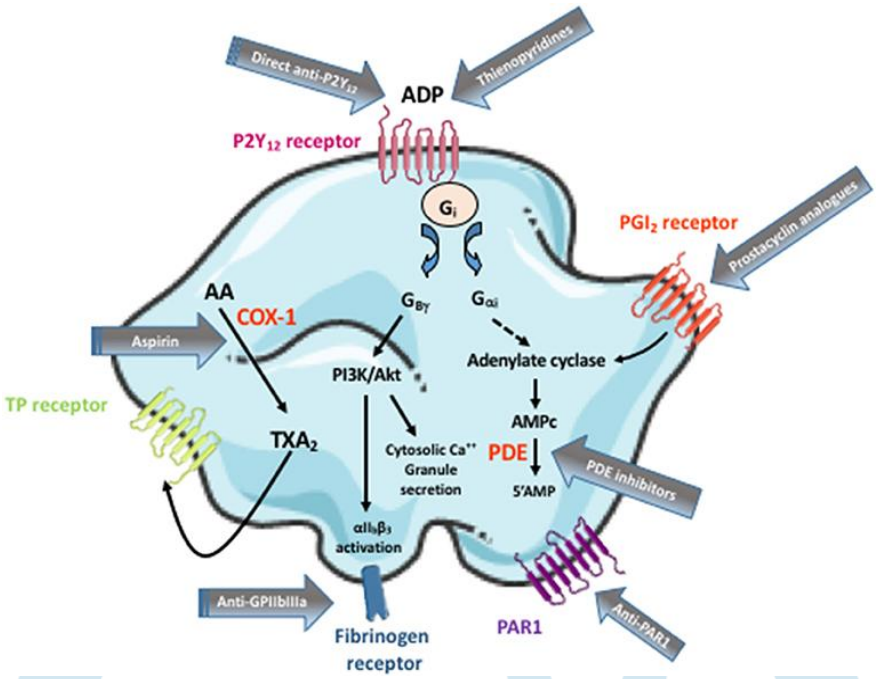

Figure-1- Targets of the marketed antiplatelet agents

Table no 03: - Pharmacological characteristics of oral antiplatelet drugs:

Molecule	Mechanism of action	Drug class	Bioavailability	Elimination half-life	Onset of action after loading dose	Time to steady state platelet inhibition after maintenance dose	Time to platelet function recovery after drug cessation
ASA	Acetylation of COX-1	COX-1 inhibitor	>40%*	15–20 min	~20 min	1 day	5–7 days
Clopidogrel	Irreversible $P2Y_{12}$ antagonist	Thienopyridine	>50%	30 min#	2–6 h	5 days	7 days
Prasugrel	Irreversible $P2Y_{12}$ antagonist	Thienopyridine	>78%	30–60 min#	30 min	3 days	7–10 days
Ticagrelor	Reversible $P2Y_{12}$ antagonist	Cyclopentyl-triazolopyrimidine	36%	7–9 h	30 min	<5 days	3–5 days
Vorapaxar	Reversible PAR1 antagonist	PAR1 inhibitor	98%	5–13 days	–‡	21 days	4–8 weeks
Cilostazol	prevention of cAMP degradation	PDE3A inhibitor	Unknown	11–13 h	–‡	4 days	12–16 h
Dipyridamole&	prevention of cAMP degradation	PDE3 and PDE5 inhibitor	70%	13.6 h	–‡	4–7 days	–

cAMP, cyclic adenosine 3′,5′-monophosphate; COX, cyclooxygenase; PAR,protease-activated receptor; PDE, phosphodiesterase.
**With a lower bioavailability with enteric-coated tablets in comparison to regular or chewable tablets.*
#*Active metabolite.*
&*Extended-release formulation.*
‡*This antiplatelet drug is not administered at a loading dose.*

Table no 04: - Pharmacological characteristics of intravenous antiplatelet drugs:

Molecule	Mechanism of action	Drug class	Elimination half-life	Time to steady state platelet inhibition after maintenance dose	Time to platelet function recovery after drug cessation
ASA	Acetylation of COX-1	COX-1 inhibitor	15–20 min	Few minutes	5–7 days
Cangrelor	Reversible $P2Y_{12}$ antagonist	Adenosine triphosphate analog	3–6 min	≤5 min	30–60 min
Iloprost	Prostacyclin analog	Agonist of prostacyclin receptor	30 min	10–20 min	2 h
Eptifibatide	Reversible GPIIbIIIa inhibitor	Cyclic hexapeptide	2.5 h	≤15 min	4–8 h
Tirofiban	Reversible GPIIbIIIa inhibitor	Peptidomimetic	2 h	20–40 min	4–8 h

GP, glycoprotein; mAb, monoclonal antibody.

Antiplatelet Therapy for Ischemic Stroke:

Stroke is a principal cause of mortality and disability worldwide. Initial appearances of acute cerebral ischemia, such as ischemic stroke and passing ischemic attack (TIA), are often surveyed by recurring vascular events, including repeated stroke. To reduce this burden, antiplatelet therapy is a key component of the organization of no cardioembolic ischemic stroke and TIA. This evaluation will focus on the indication for four antiplatelets: aspirin, aspirin-dipyridamole, clopidogrel, and ticagrelor.[9] The role of single antiplatelet agents after stroke is well well-known, and some large studies support its use. Dual Antiplatelet Therapy with aspirin and clopidogrel was found effective in coronary artery disease but initial studies of chronic DAPT in stroke displayed no added advantage and increased bleeding over single antiplatelet.[10] It is constantly established that antiplatelet therapy decreases the risk of vascular demise by about one sixth and the risk of non-fatal myocardial infarction and stroke by about one third in patients with unbalanced angina, made-up acute myocardial infarction, or a historical past of myocardial infarction, stroke, or a transient ischaemic attack.[11]

Antiplatelet Therapy In COVID-19:

COVID-19 is a communicable disease, first stated in China in December 2019, awarding mostly with fever and cough, which regularly leads to lower respiratory tract illness. It has rapidly supper all over the world, attractive a pandemic in a few months. Giving to current literature, only therapy with dexamethasone then inhibitors of interleukin (IL) 6 (tocilizumab) showed potential advantage in terms of mortality decrease among patients with COVID-19 and simple respiratory failure.[12]

Although platelets are thought to play an essential role in COVID-19–related hypercoagulability, the Randomized Evaluation of COVID-19 Therapy trial showed no obvious profit of aspirin additional to typical thromboprophylaxis or anticoagulant therapy in hospitalized patients with COVID-19. [13]

Essentials:

• Pre-hospital antiplatelet therapy (APT) may be connected with benefits in COVID-19.

We hypothesized that antiplatelet therapy would be connected with a compact risk of in-hospital mortality.[14]

There are expert-based references to continue the use of antiplatelet therapy that were started prior for other indications. However, as of now, the indication regarding the effect of ASA or other antiplatelet therapy on Covid-19's strictness or outcome is lacking. Antiplatelet therapy plays an important role in giving the COVID-19 VIRUS.[15]

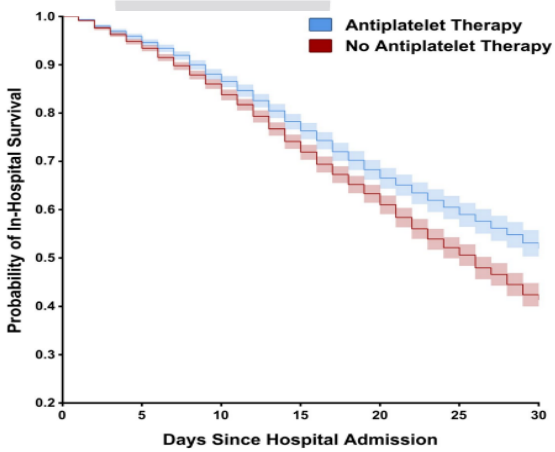

Figure-2 Risk of in hospital mortality

On March 11, 2020, the World Health Organization has formally proclaimed the novel coronavirus disease 2019 (COVID-19) as a global plague. totalling to thrombosis and haemostasis, emergent evidence provisions an assumed role of platelets in host defence against infections, which add a greater layer of complication in evaluating the role of antiplatelet therapy in the situation of viral pneumonia. To offset of increased bleeding risk related with DAPT, evolving findings from large randomized controlled trials deliver evidence supports a net assistance of aspirin-free strategies after PCI for patients at short, middle and high risk for both ischemia and bleeding, which is mostly driven by the decrease in bleeding events.[16]

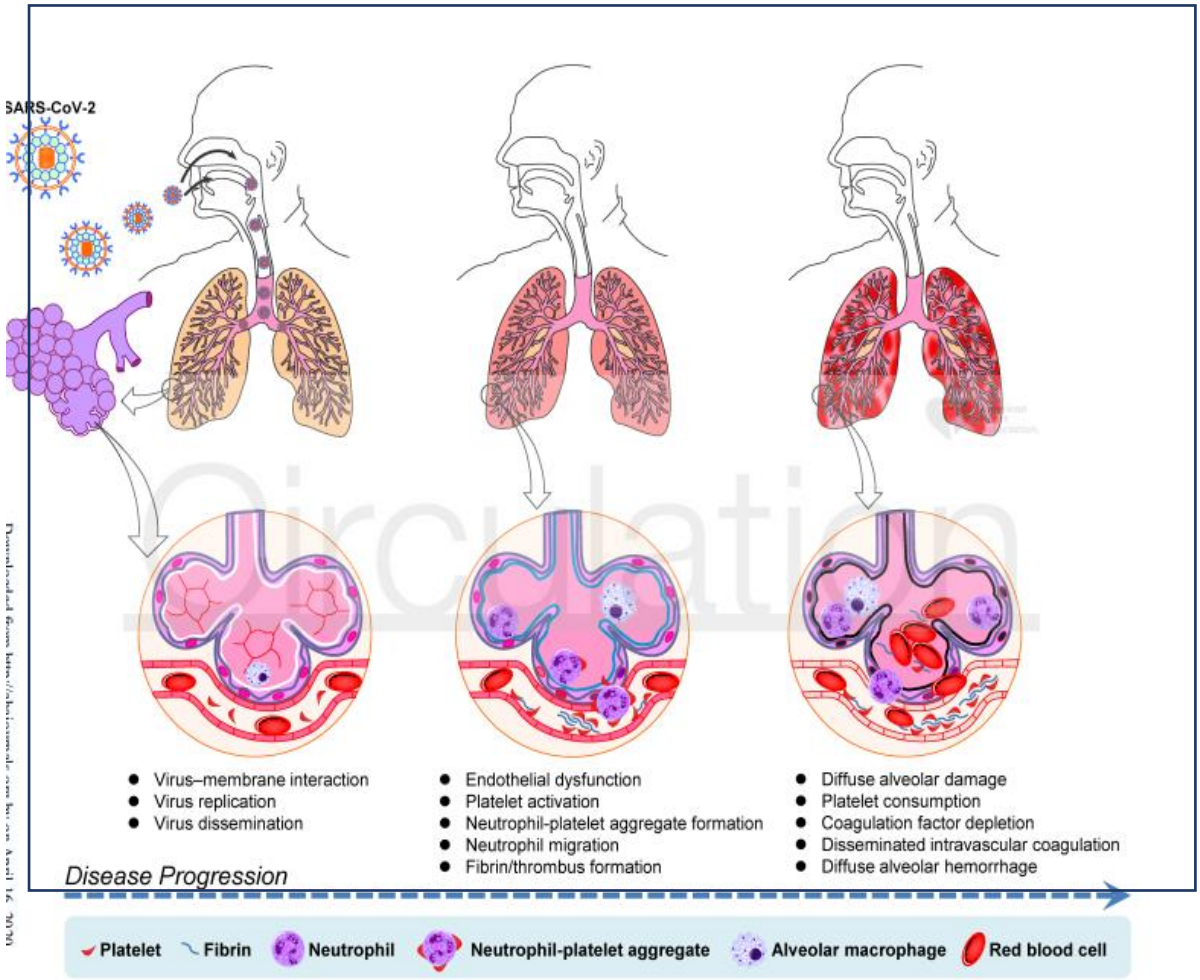

Figure-3 The potential pathophysiological evolution of SARS-CoV-2 infection in lung tissue and inferences for antiplatelet therapy.

Antiplatelet Therapy in Cardiovascular Disease:

Though the need for all-time therapy with one antiplatelet agent i.e., aspirin or clopidogrel, is normally agreed upon in patients who suffered an ischemic cardiovascular event,6,7 the optimum duration of DAPT succeeding an ACS and/or PCI with stent implantation is less well-established. Physically managed ACS patients should obtain DAPT with aspirin and ticagrelor or in case of an enlarged bleeding risk clopidogrel for 12 months acute event.[17] Antiplatelet agents have thus wedged results of cardiovascular disease processes however, because both pathological and physiological purposes of platelets are due to the same mechanism, it is problematic to distinct the therapeutic benefits from harmful effects. The final goal of new antiplatelet policies is to increase efficacy without losing security.[18]

In patients with mutual coronary disease and atrial fibrillation at low bleeding risk, combination antiplatelet and anticoagulant therapy may be measured, in which condition evidence supports the use of clopidogrel and a DOAC, rather than routines that contain a vitamin K antagonist, aspirin, or both, due to fewer bleeding and less hospitalisations lacking significant differences in the frequency of ischaemic events; this contains patients post-ACS or percutaneous coronary intervention. [19]

Clinical Application Antiplatelet Therapy:

In the normal physiological state platelets are minor, anucleate, subcellular fragments that circulate easily in the blood.[20]

A broader application of cell-derived MV in the analysis and prognosis of cardiovascular risk, by means of antiplatelet therapy monitoring has been limited due to the absence of standardized methods for their quantification.[21] More than a few mechanisms can be complex in antiplatelet drug therapy resistance. First, numerous drug-drug interactions have been labelled. pharmacogenetics may be valuable for dose adaptations for exact drugs in patients with abnormal drug metabolism.[22]

The clinical significance of bleeding events has also been further learnt by an analysis of the predictors of bleeding and the relationship among bleeding and mortality within the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition through Prasugrel-Thrombolysis in Myocardial Infarction.[23] Antiplatelet therapy (APT) is an essential part of the treatment of vascular disease. Platelets form the main haemostatic plug at sites of endothelial disturbance. Thrombosis is originated by platelet paracrine factor release, resultant finally in platelet aggregation.[24] Thromboelastogram (TEG) is an index that can comprehensively reproduce dynamic changes of blood coagulation.[25]

Anticoagulants, with indirect (heparins) and direct (bivalirudin) thrombin inhibitors, do not target platelet signalling paths or cell surface inhibitors. Equally heparins and direct thrombin inhibitors block thrombin activation of platelets.[26] One of the key roles of TEG in clinical practice is in hepatobiliary surgery wherever it is used to monitor haemostasis and guide therapy. It has been exposed to be more effective than predictable tests at measuring the risk of bleeding in this complex area. TEG has been used in liver transplantation meanwhile 1980 where it has been shown to diminish transfusion requirements. As well as its use in the organization of haemostasis TEG has more lately been examined as a marker of risk for thrombotic events.[27]

The PFA-100 uses entire blood flow through a capillary device to mimic high shear stress situations that happen in vivo (i.e., is said to simulate primary haemostasis. The PFA-100 gives a single end-point understanding when blood flow through the instrument stops (i.e., the capillary is occluded) as an effect of platelet adhesion and following aggregation after exposure to platelet agonists covered on a membrane in a throwaway cartridge device. This termination is called the closure time (CT).[28]

This study highpoints the position of referring to patients' clinical info when approximating the occurrence of PIMs and PPOs, using STOPP/START criteria. Patients' clinical data often explains why certain choices of medicines are arranged, for example, preceding failure with other treatment, a rare clinical diagnosis that would designate prescribing of sure medicines that would then be potentially unsuitable.[29]

Risk assessment to guide antiplatelet therapy between percutaneous coronary disease patients. Bleeding besides ischaemic risk assessments are based on clinical variables, procedural structures and the use of scores/definitions.[30]

Advances Of Antiplatelet Therapy:

Therapies directing key ways of platelet activation, including thromboxane A2 synthesis, ADP-mediated signalling, and integrin IIb3, have a recognized role in the treatment of cardiovascular arterial disease.[31] Antiplatelet therapy has been recognized as a protective medicine for ischemic cardiovascular ailments both at acute and chronic stages. This therapy is also vital for the prevention of thrombotic events after coronary stent establishment.[32] Pharmacogenomics is a developing field with the potential for the discovery of new drugs based on the knowledge of the human genome, while pharmacogenetics is the study of unpredictability in drug effects in reply to hereditary factors.[33]

New antiplatelet agents whose efficiencies look independent of CYP genotype, such as prasugrel and ticagrelor, deliver a potential advance beyond clopidogrel, and other compounds in clinical development also hold promise for the upcoming treatment of these circumstances.[34] Resonant in nearly every advanced antiplatelet paradigm from the deep drug optimizations that order therapeutic indices to the subtle tunings of G-protein modulation and the multiscale biophysical targets of thrombus growth a novel logic of antithrombotic is developing that looks beyond strength of target inhibition to modulation of higher-order, system effects.[35] The discovery of a 'magic bullet' that selectively targets pathological thrombi has demonstrated subtle, primarily because the molecular events regulating thrombosis are in large part identical to those fundamental haemostasis.[36] Many patients are preserved with antiplatelet drugs currently, as many go to the dental practices for surgical treatment. A typical past method was to suspend the therapy and to convey out a "substitutive" therapy with other anticoagulant drugs. [37] Antiplatelet therapy is important to the treatment of patients who are suffering percutaneous coronary intervention (PCI) or have acute coronary syndromes (ACS). A number of promising antiplatelet therapies presently in progressive clinical testing offer hope for improving cardiovascular outcomes.[38] Many of these drugs are intended to inhibit more professionally the 'classical' targets involved in platelet aggregation (P2Y12, integrin IIb3, TXA2 synthesis) that now do the obtainable antiplatelet agents. Furthermore, new received antiplatelet drugs have other another targets in platelets or in the vasculature site.[39] Dual antiplatelet therapy, targeting more than one path of platelet activation, has been used for patients emerging a thrombotic event, despite an improved risk of bleeding difficulties. [40]

Conclusion:

Antiplatelet therapy contains a several drugs that inhibit blood clot formation. Platelets play a significant role in a physiological haemostasis & thrombus formation. Antiplatelet therapy, generally holds aspirin and P2Y12 receptor antagonists, clopidogrel, ticagrelor, prasugrel. Aspirin works as an antiplatelet agent by irreversibly blocking the enzyme cyclooxygenase -1(COX-1) inside the platelets. P2Y12 inhibitor is a treatment of choice for the prevention of atherothrombotic events in patients with acute coronary syndrome & for those undertaking percutaneous coronary intervention. Antiplatelet therapy used in the various disease like Atherothrombotic diseases, Covid -19, Ischemic stroke, cardiovascular diseases. When we will overcome these the smart clinician be able to use this information in conjunction with the history and other medical tests and information to choose the most effective anti-platelet therapy for each specific patient.

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