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Pharmacogenomic Approach to Guiding Antiplatelet Therapy after Percutaneous Coronary Intervention

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ABSTRACT

Clopidogrel, Prasugrel, Aspirin, Ticagrelor are the antiplatelet drugs which are used by the patients after percutaneous coronary intervention. Activation of these drugs is mainly by the genes and hence pharmacogenomics of these drugs is considered as the major factor for drug response. Clopidogrel alone or mostly along with aspirin as a dual therapy is preferred to reduce adverse cardiovascular events occurring after PCI. Clopidogrel, is a prodrug & its metabolism need CYP2C19 gene, which plays a key role in showing efficacy accordingly to the patients CYP2C19 alleles, and conversion of the drug to its active metabolite. CYP2C19 varies inter individual, and these variants are the reason for inter individual patient therapeutic efficacy difference. prasugrel activation is mediated by CYP450.Ticagrelor is activated by CYP3A4/5. This review presents the importance of pharmacogenomics in anti-platelet therapy, in reducing the adverse outcomes after percutaneous coronary intervention, and also it describes the CYP2C19 gene alleles variability inter-individually, and its therapeutic outcomes. Use of other antiplatelet drugs like prasugrel, ticagrelor, aspirin, in case of clopidogrel CYP2C19 poor metabolizers, their therapeutic recommendations & pharmacogenomics is also described.

Keywords: *CYP2C19, Pharmacogenomics, PCI, Clopidogrel, prasugrel, Ticagrelor, Aspirin.*

INTRODUCTION

PHARMACOGENETICS:

The word pharmacogenomics', is the combination of genomics which is the study of gene and also pharmacology, study of drugs. Pharmacogenetics demonstrates the relation between gene's and drugs, that is how the genes in the individual affect the drug therapy. pharmacogenomic studies are useful to put a check to cancer, HIV/AIDS, CVD. (Orrico, (2019). Pharmacogenomics is a part of precision medicine, from these type of studies we can know how the medicines in our body shows response to our inherited genes, by this pharmacogenomics we can personalize the medications to each individual patient based on their genome makeup, so the adverse effects, treatment effectiveness & safety to patients can be possible (Orrico, (2019).

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Percutaneous coronary intervention is also known as coronary angioplasty. This procedure is used mainly for treating obstructive coronary artery disease. Other conditions like unstable angina and acute myocardial infraction are treated using PCI. Major indications for PCI include, STEMI which can be abbreviated as ST elevation myocardial infraction, non-ST elevation acute coronary syndrome, unstable and stable angina. PCI is contraindicated in patients who are intolerable to long-term antiplatelet therapy or to the patients with presence of any significant comorbid condition that may lead to death of the person.

After PCI, the patient is treated with certain drug therapy like anti-coagulant therapy, anti-platelet therapy and glycoprotein therapy. Anti-platelet therapy is the major treatment for the PCI patient. This therapy should be done by considering certain factors like patient response to the drugs.

Anti-platelet therapy in percutaneous coronary intervention.

Platelet activity:

Glycoprotein receptors are present on the surface of the platelet. When there is a damage to vascular endothelium reactive proteins like collagen are exposed and they react with platelet GPIa and GPIb receptors, this leads to release of mediators like TXt2, ADP and 5HT. GPIIb/IIIa receptors undergo changes for binding to fibrinogen and VonWillebran factor (vWF) and leads to formation of "platelet plug." (Tripathi, 2013).

Antiplatelet drugs:

Anti-platelet drugs obstruct platelet function and useful in prophylaxis for thromboembolic disorders (Tripathi, 2013; Knauer et al., 2015).

- Aspirin.
- Dipyridamole.
- P2Y12 receptor blockers:

1. Ticlopidine.
2. Clopidogrel.
3. prasugrel.

- GPIIb/GPIIIa antagonists:

a. Abciximab.
b. Eptifibatide.
c. Tirofiban.

Dual anti-platelet therapy, is known as therapy with both the drugs example- aspirin and clopidogrel. This can be a standard treatment for individuals with CAD& PCI. PCI individuals with base metal stents aspirin is taken at dose of 325mg once a day for at least 30days and in patients with sirolimus eluting stent aspirin should be used for three months.

Clopidogrel prevents platelet activation and aggregation by inhibiting the P2Y12 ADP receptors on surface of platelets. This inhibition is irreversible.

Abciximab is used 10 to 60 minutes before the PCI procedure at a dose of 0.25mg/kg IV bolus (Tripathi, 2013).

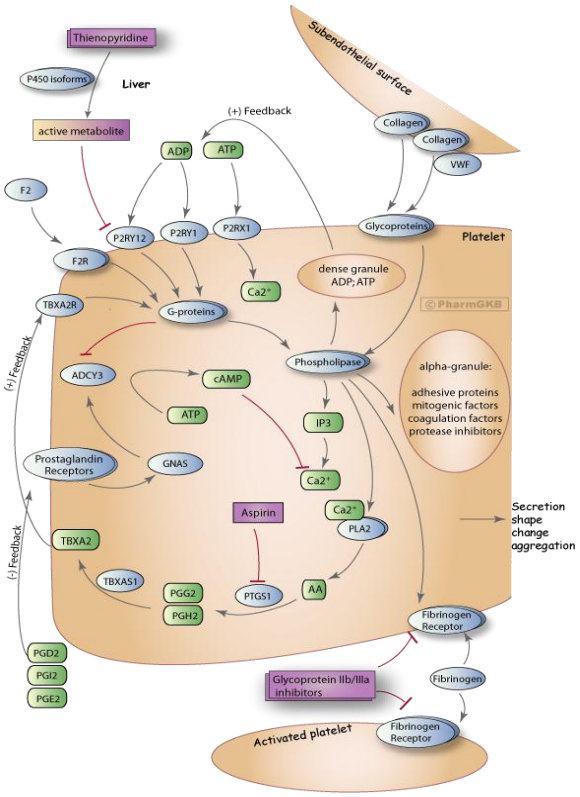

Fig. 1: antiplatelet drugs effect on platelet aggregation pathway (source: modified from Cpicpgx.org)

PHARMACOGENOMICS OF ANTI PLATELET DRUGS:

Clopidogrel Pharmacogenetics:

MECHANISM: clopidogrel belongs to thienopyridine anti platelet group (second generation) it is a P2RY12 inhibitor, which inhibits irreversibly, aggregation of platelets and its activation is done through the blockage of ADP. As it a platelet inhibitor it interrupts with the formation of thrombus, which involves platelet activation.

Resistance to clopidogrel is seen, if the patient has taken the pharmacological treatment, after there is no change or decrease in the activity of platelets. Presence of thrombosis or ischemic event for those who are high on treatment platelet reactivity, which is abbreviated as HTPR, is an indication for the drug treatment failure.

To assess the platelet's response, platelet function assay is done, which measures (PRU). Efficacy of the drug can be between: 95-208PRU, platelet reactivity unit ≥ 208 indicates Clopidogrel resistance, and if the platelet reactivity unit is ≤ 95 it indicates major bleeding (Dean, 2018).

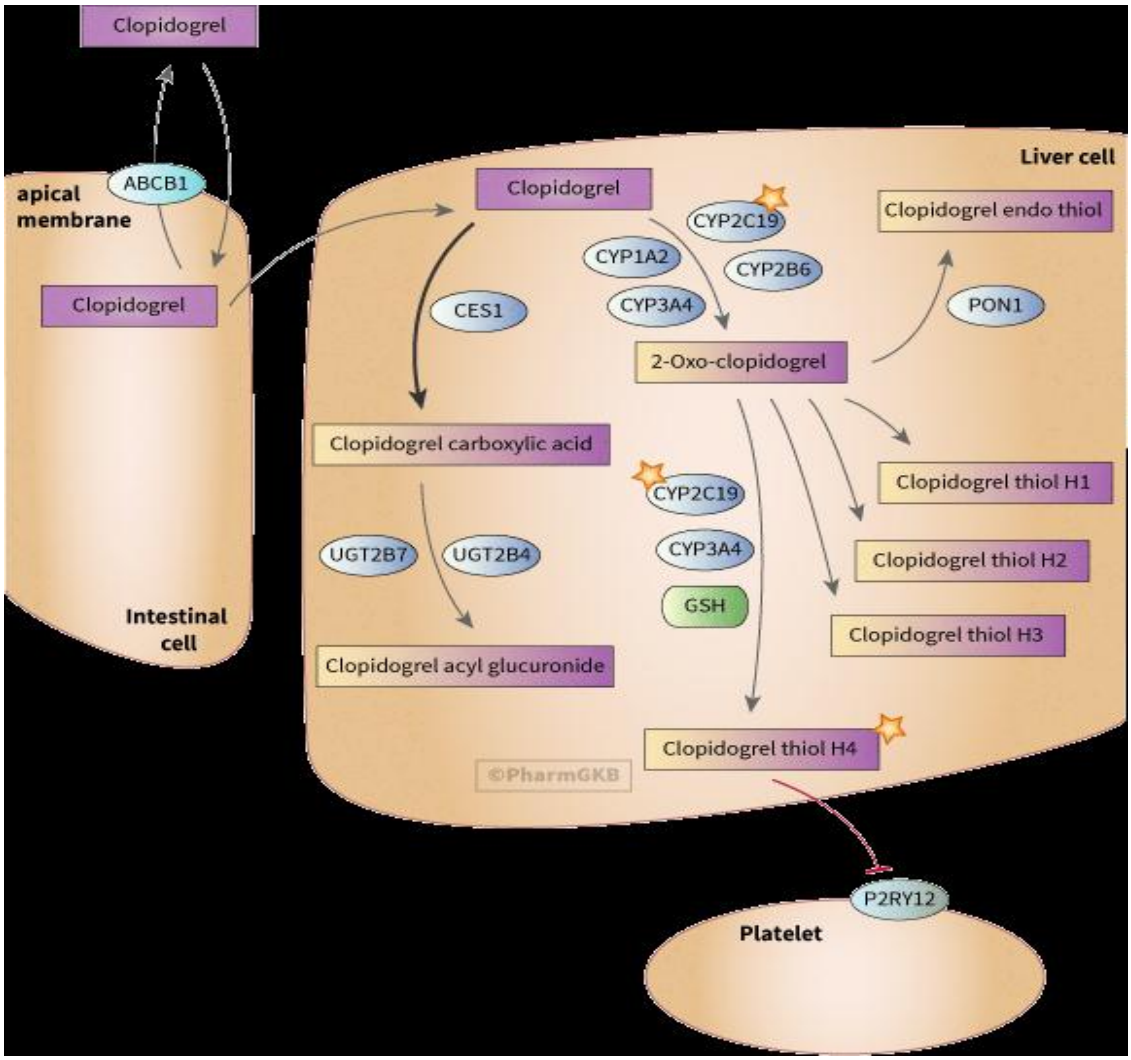

Fig. 2: This figure shows the metabolism of clopidogrel & genes involved. (source: modified from Cpicpgx.org)

GENE: CYP2C19

Gene CYP2C19, and its variant alleles are totally responsible for the effectiveness, variability of clopidogrel metabolism and treatment out comes between different individuals.

The decreased response to the drug's reason is the variability present in the gene CYP2C19, along with this gene there are some more genes which effect the action of the drug clopidogrel, they are P2Y12, GPIIIA, ABCB1. This gene CYP2CI9 belongs to family cytochrome P450, which is involved mainly in metabolizing lipids, hormones, toxins and drugs. Clopidogrel is a prodrug, formation of an intermediate metabolite named 2-oxo-clopidogrel and the active metabolite are done by the main enzyme, which is CYP219.

Almost similarly to 85% of majority of the drug clopidogrel is hydrolyzed to inactive metabolites through esterases including carboxyl esterase leaving only up to 15% of the drug for transformation to an active metabolite. To form the active metabolite two sequential oxidative reactions by CYP450 occur, oxidation step, which is the primary step, *CYP2B6, CYP2C19, CYP1A2*, these three genes are involved in the primary reaction, following the primary oxidation step, a sequential secondary oxidation step follows, in this step *CYP3A4, CYP2B6, CYP2C19, CYP3A5, CYP2C9.*CYP2C19 gene is highly polymorphic it has 35 variant star alleles. CYP2C19*17 allele functions as rapid metabolizers phenotype with one * 17 i.e., CYP2C19 (*1/*17) and exhibits ultra-rapid metabolizers phenotype with 2* 17 alleles i.e., CYP2C19(*17/*17). The enzyme performance is notes as increased in both rapid and ultra-rapid metabolizers. CYP2C19*1 it functions as normal metabolizer, also known as wild type allele, as seen in other rapid and poor metabolizer alleles, here no variants are exhibited, normal enzyme activity is seen. CYP2C19*2 and CYP2C19*3 non-functional alleles, which come under poor metabolizers.[(4)]The less common non-functional ones among alleles of CYP2C19 are CYP2C19*4 to CYP2C19*8, and the responsiveness of these and decreased effectiveness of the enzyme on drug in patients undergoing percutaneous coronary intervention are noted to be similar as with the normal nonfunctional alleles (CYP2C19*2 and CYP2C19*3). However, alleles from *2 to *8 are all loss of function alleles, amongst *3 allele is reporting more effect on efficacy of drug, platelet reactivity.PR for gene CYP2C19 are recommended to be advised with different receptor inhibitor of site P2Y12. And also, if there are no contraindications patients with intermediate and poor metabolizers of CYP2C19 are recommended with other drug therapy, mostly of which drugs ticagrelor, and prasugrel are preferred according to CPIC, 2013 (Yang, et al. 2015).

A research study on 465 cardiovascular disease study patients, in a total of patient count with 465 there were 183 patients who were noted with wild homozygous, DNA sequencing test has been done to total 465 patients for the gene CYP2C19. 198% & 18.8% were loss of function and gain of function alleles respectively. Switching to other anti-platelet drug mostly prasugrel for those who are slow metabolizers, and discontinuing or lowering the drug dose for those whose genotypes are ultra-rapid and rapid metabolizers, to overcome the bleeding disease. There have been no cardiac symptoms, no other cardiac events and bleeding events reported on three years regular follow up. Genotyping the CYP2C19 is important to improve clinical outcomes (Cavallari, 2017).

A pharmacogenomic study with 347 Turkish patients who underwent PCI with stent findings concluded that CYP2C19*17 polymorphism increases the clopidogrel anti platelet activity and CYP2C19*2 polymorphism does not respond to clopidogrel therapy (Saydam, (2017).

Therapeutic Recommendations Based on Genotype:

1. Ultra-Rapid Metabolizers: No action is required.
2. Intermediate Metabolizers:

(a) Percutaneous Coronary Intervention: Double the dose up to 150 mg per each day, starting dose of 600mg (loading dose), choose another different drug if there are no contraindications.

(b) Other conditions: no action is required.

3. Poor Metabolizers:

(a) Percutaneous Coronary Intervention: Choose another different drug, where they are not metabolized through CYP2C19, example: they are TICAGRELOR & prasugrel.

(b) Other conditions: know the inhibition level through the formation of platelet aggregation (Dean, 2018).

Table 1: Anti platelet therapeutic recommendations (Dean, 2018)

Phenotype of CYP2C19	Percentage of patient	Genotype	Example of diplotene's	Clopidogrel implications
Ultra-rapid	Similar to 2 to 5%	Person with two increased functional alleles	CYP2C19(*17/*17)	Platelet aggregation is less and platelet inhibition will be high.
Rapid	Similar to 2-30%	Persons with one increased and one normal functional allele.	CYP2C19(*1/*17)	Persons will be having more platelets level of inhibition and less levels aggregation.
Normal	Similar to 35-50%	Persons having two normal alleles	CYP2C19(*1/*1)	Individual's will be having both normal platelet aggregation and inhibition levels.
Intermediate	Similar to 18-45%	Person will be having single normal functional allele and another non-functional one	CYP2C19(*2/*17) CYP2C19(*1/*3) CYP2C19(*1/*2)	Patients are noted to have more risk towards CAD, platelet inhibition will be comparatively less to others, platelet aggregation is high.
Poor	Similar to 2-15%	The person will be having two non-functional alleles.	CYP2C19(*3/*3) CYP2C19(*2/*3) CYP2C19(*2/*2)	Patients are more prone towards risk of adverse cardio events, as the platelets aggregation is high, and the platelet inhibitions levels are low.

A study conducted to patients undergoing stent & percutaneous coronary infraction, with patients count 719, comparison between prospective genotype guided therapy against retrospective non tailored group, named as interventional and control group respectively. Cardiovascular deaths, stroke, acute coronary syndrome during 12 months after intervention occurred 32(10.1%) and 59(14.1%) patients in the interventional group and control group respectively. There is no difference between thrombolysis in MI bleeding criteria, so a genome guided therapy helps in reducing the cardiovascular events, bleeding events (Mirabbasi, 2017).

Implications of CYP2C19 genotype for response of clopidogrel: pharmacokinetic part and pharmacodynamics, poor metabolizers (PM) and intermediate metabolizers (IM), as compared to others the level of concentration of the drug metabolite named active thiol was low. Plasma concentrations were less in PM and IM following 75mg dose. Platelet aggregation was lesser in PM and IM. There is and 30% reduction of active metabolite concentration noticed in IM and PM patients, following a 300 mg of clopidogrel dose (Yang, 2015).

Study on genome wide PAPI (pharmacogenomics of anti-platelet intervention.) on the chromosome 10q24, thirteen single nucleotide polymorphisms were noted, in the clutters of *CYP2C18- CYP2C19- CYP2C9- CYP2C8* which are variants. they have given the main drug clopidogrel for a total of seven days to 429 healthy people and their responses were noted, Platelet response is hereditary for the drug clopidogrel, as there has been a decreased drug responsiveness with a similarly to 12% of variation to aggregation of platelets and patients with variants allele are likely to get ischemic events, cardiovascular disease, and even death (Fang, 2019).

The effects of gene CYP2C19 clinical outcomes have not been noticed in patients who are lesser risk to coronary artery disease (low frequency of PCI (≤20%)) and patients with arterial fibrillation. Clopidogrel therapy is not much effective as in lower risk indications that is which can be managed with drugs for ACS, compared to patients who are higher at risk like condition PCI (Sibbing, 2010).

The influence of drug Clopidogrel after PCI study reported clinical outcomes like bleeding, and CAD, thrombosis with variant allele of CYP2C19 genotype, In a twenty clinical studies conducted around with an individual patient count about 15056, out of 15056 patients about 1301patients were reported with adverse CVD event, this study demonstrated and showed that the poor metabolizers with , LOF allele carriers that is *2 and *3 people were at more risk to major adverse cardiac events (MACE), Risk of bleeding was inverse to the above. A subgroup analysis with high loading dose group with 600mg and 300mg daily dose remains same with increased risk to MACE. And also, the same subgroup analysis between China, Korea, Japan showed that the risk for MACE is higher in china (Shuldiner, 2009).

A randomized trial, among 5059 individuals who are genotyped to SNP'S, compared between placebo and clopidogrel, individual's with present history of atrial fibrillation and coronary syndrome, clopidogrel has shown less rate of cardiovascular outcome, in patients irrespective with genetically determined metabolizer phenotype., the same has be reported in individual's with two different LOF alleles (heterozygote's) and also in those individual's carrying two similar LOF alleles(homozygotes) effect of gain of function allele was contrast to this. Bleeding function did not change with respect to the genotypic group, among 1156 genotyped patients (Pare & Mehta, 2010).

A systemic review and meta-analysis of 42,016 patients among which 3545 cardio vascular disease. And 579 stent thromboses and 1413 bleeding events, with randomized and treatment only groups, patients with one or more CYP2C19 allele with low enzyme activity proved to have less active metabolite with lower platelet inhibition and also low bleeding risk, and higher risk for MACE. There is no demonstration that CYP2C19 has been linked to the effect of the drug (CLOPIDOGREL) on bleeding and cardiovascular disease, it has only association with the responsiveness of clopidogrel (Holmes & Perel, (2011).

A randomized control trail done in patients undergoing CAD,PCI, between two groups , the first is antiplatelet therapy done conventionally and antiplatelet therapy given personalized to individuals , with a complete patient count 600, 301 and 299 in each group respectively, at 180 days, MI(myocardial infraction), death, and also stroke is reported , with a count of 3 & 18 respectively. And MI and death were lesser compared to control group, significantly three were no bleeding events notes between two groups, therefore personalized antiplatelet therapy with CYP19 genotype after PCI decreases the MACE (Scherbakov & Von Haehling (2013).

A study which is randomized also proved that there is nonadherence to the clopidogrel drug leads and puts a way to High on treatment platelet reactivity. And also demonstrated that there has been a three-fold increased risk to adverse cardio vascular events in those who has LOF alleles. (Sherry-ann brown & Naveen Pereira, 2018).

PHARMACOGENOMICS OF PRASUGREL

Prasugrel is the 3rd generation thienopyridine and is used widely for the treating ACS patients who are undergoing PCI. prasugrel when administered orally and after absorption carboxylesterases hydrolyses it to yield an active metabolite (R138727). This active metabolite is formed by hepatic activation of thiolacetone by CYP3A4, CYP2C9, CYP2C19, and CYP2D6. This hepatic bioactivation of prasugrel is mediated by CYP450. In fact, some studies have proved that there was no significant relation between pharmacokinetic and pharmacodynamic properties of prasugrel with CYP450.

On comparison of carriers and non-carriers of LOF which is CYP2C19*2, individuals who are carriers, reported to have more platelet reactivity, and high risk to HTPR than non-carriers. Along with CYP450 other genes were also tested but no relative response was found with prasugrel (Yang et al., 2015). Prasugrel is more potent in CAD patients and has faster onset of action. P2Y12 receptor mediated platelet aggregation is inhibited better compared to Clopidogrel (Wallentin & Siegbahn, 2008). This antiplatelet therapy also resulted in decrease in MACE after PCI (Wiviott et al., 2007).

PHARMACO GENOMICS OF TICAGRELOR:

This drug, inhibit ADP induced platelet aggregation reversibly with faster onset and offset of action compared with Clopidogrel. Ticagrelor doesn't require hepatic bio activation to create active metabolite, upon the oral admiration of this drug which has a cyclo pentyl triazolo pyrimidine (allosteric ADP antagonist) structure, produces two metabolites, upon which one is active primary named ARC124910XX and another is inactive named ARC133913XX.This process is mediated by CYP3A4/5. Ticagrelor efficacy is may be influenced by CYP3A4 AND CYP3A5 variant alleles, which required further studies to prove this hypothesis. The active metabolite generation by CYP3A4 is responsible for drug interaction with statins (Yang et al., 2015). Ticagrelor inhibits the P2Y (12) receptor by binding to it reversibly. There are three gene loci which are responsible for the drug active and inactive (primary and secondary metabolites respectively), concentration, and no CVD deaths, CYP3A4 (rs62471956 & rs563242128), UGT2B7 (rs61361928), SLCO1BI (rs113681054) (Tatarunas et al., 2017).

The variant alleles & the normal frequent ABCB1C3435 >T gene were found genotyped for a set zof patient in PLATO trail.

ASPIRIN:

Action of Aspirin is by inhibiting Cyclo oxygenase enzyme irreversibly, that is irreversible acetylation of serine 529 place. Effect of the drug is not same with the persons. Resistance to the drug is biochemically defined by using methods such as,

- Light transmission aggregators.
- Bleeding time.
- Platelet formation analyzer. (Goodman et al., 2008)

Pharmacogenomics of aspirin:

Cyclo oxygenase I:

Cyclo oxygenase is the major molecular target of the aspirin. Studies that were conducted initially stated that, comparison of both individuals with minor haplotype that is (c.(-8.42G;50T)) and common haplotype (c.(-842A;50)), the prior ones have shown good inhibition of PG &AA platelet aggregation. Aspirin resistance is associated with c.-842G allele (Yang et al., 2015).

Studies that were conducted previously stated that COX1A-842C50T and GPIIIa PL A1/A2 genetic polymorphism were not found in people of China. In people with genotype P2Y1 CT893/AG1622 after treating with aspirin, there has been no change noted among the therapeutic effect of aspirin, & the decline of component arachidonic acid was less in CC893/GG1622, CC893/AG1622, and CC893/AA1622 genotyping group (Cambria-Kiely & Gandhi, 2002).

Glycoprotein IIIa:

Glycoprotein IIIa regulates the binding to fibrinogen leads to platelet aggregation & formation of thrombosis. Previous studies had

stated that, variant of ITGB3 gene P1A1/A2 (c.176 T>C, p. L59p.rs5918) encode GPIIIa subunit was considered to be a leading pathway with CVD risks. ITGB3 P1A1/A2 may also influence under the DAPT, whereas the variability of drug aspirin remined undetermined (Yang et al., 2015).

Glycoprotein VI:

Glycoprotein VI and GPIa/IIa receptor complex on platelet is the binding site for collagen and stimulates platelet aggregation. This GPVIc.655 C>T variant (p.P2193, rs 1613663) has special role in patients with coronary vascular disease who are undergoing current platelet treatment. Deaths due to CAD, and risks of stroke, myocardial infraction are associated with the c.759C > T variant of gene GpIa (ITGA2; rs 1126643). Higher risk towards the myocardial infraction and & high platelet reactivity are seen in individuals who has altered GPIba mRNA translation and has taken aspirin for the cause CAD (Yang et al., 2015).

CONCLUSION

Many randomized trails, observational studies, and also some small clinical trials have shown improved clinical outcomes in patients genotyped for CYP2C19 after PCI when compared to non-genotyped patients using clopidogrel. Use of alternative drug for patients who are carriers of non-functional alleles, poor metabolizers, rapid & also ultra-rapid metabolisers also suggested improved outcomes, with decreased adverse cardiovascular events in patients after percutaneous coronary intervention.

ABBREVATIONS

PCI	Percutaneous coronary intervention
GP	Glycoprotein
ADP	Adenosine diphosphate
PRU	Platelet reactivity unit
CPIC	Clinical Pharmacogenetics Implementation Consortium
PM	Poor metabolisers
IM	intermediate metabolisers
URM	Ultra-rapid metabolisers
PAPI	pharmacogenomics of anti-platelet intervention
MACE	Major adverse cardiac events
HTPR	high on treatment platelet reactivity
CAD	Coronary artery disease.
AA	Arachidonic acid
PG	Prostaglandins
DAPT	Dual antiplatelet therapy study

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