Frequency of CYP2C19 Gene Polymorphisms (SNP) and its Impact on Clinical Outcome in Ischemic Heart Disease Patients Taking Clopidogrel after percutaneous coronary intervention (PCI)

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Abstract: Clopidogrel an oral thienopyridine derivative capable of inhibiting platelet activation. Clopidogrel is prodrug that is converted into an active drug by hepatic cytochrome CYP2C19, CYP2C19*2 and CYP2C19*3 polymorphic alleles are considered to be important loss- of- function alleles resulting in diminished response to clopidogrel. our study aimed to detect frequency of CYP2C19 gene polymorohisms and its impact on clinical outcome in ischemic heart disease patients taking clopidogrel. Matrial and methods: blood samples were collected from 102 ischemic heart disease patients and the frequency alleles was determined by PCR and all patients were followed by clinical assessment and invasive and non- invasive cardiac investigations .Results:. frequency of CYP2C19*1 was 49%, CYP2C19*2 was 15% and CYP2C19*3 was 1%, CYP2C19*17 was 34%, patients with recurrent ischemic attacks 37patients (35.8%), from those patients, 10 patients were normal metabolizer (27%), and 27 patients were abnormal metabolizers(73%) with p- value 0.047 to myocardial infarction and 0.020 to unstable angina. Conclusion:. Asignificance relation was found between CYP2C19polymorphism and recurrent ischemic attacks in this study and multicenter studies are required to confirm this results.

Key words: some time include other word not used in the title for example, clopidogrel, thienopyridine, cytochrome, metabolizer.

INTRODUCTION:

Cardiovascular diseases (CVD) or heart diseases are a class of diseases that involve the heart or blood vessels. Diseases under the heart disease umbrella include blood vessel diseases, such as coronary artery disease (CAD), heart rhythm problems (arrhythmias), heart infections and heart defects including congenital heart defects [1, 2, 3]. Heart failure is a common clinical syndrome that represents the final stage of a range of different heart diseases [4, 5].

Clopidogrel is a second generation thienopyridine that is transformed in the liver to active form that is specially and irreversibly to platelets P2Y12 receptor, inhibiting ADP- mediated platelets activation and aggregation of note, most of the prodrug (around 85%) is hydrolyzed to inactive metabolites by esterase, leaving only 15% available for transformation to active metabolite two sequential oxidative reactions are necessary to form active metabolite, involving CYP1A2, CYP2B6, and CYP2C19, CYP2C9, CYP3A4, and CYP3A5, respectively [6, 7] dual antiplatelet therapy with clopidogrel and aspirin reduces cardiovascular death and ischemic complications in patients with ACS and those undergoing PCI[8].However, wide interindividual variability in platelet aggregation is commonly observed during dual antiplatelet therapy and some patients still experience thrombotic events [9, 10].

Cytochrome P450 (CYP450) is the generic name given to a large family of enzymes that metabolize most drugs and chemicals of toxicological importance. In humans, there exist 18 mammalian CYP450 families, 44 subfamilies, 57 putative functional enzymes[11, 12]. The family members CYP1, CYP2, and CYP3 of CYP450 represent the top candidate genes in pharmacokinetics [13, 14]. Four CYP2C genes have been identified in humans: CYP2C8, CYP2C9, CYP2C18, and CYP2C19. CYP2C19 enzyme is one of the hepatic cytochrome P450 enzymes that metabolize many important clinical drugs including antiulcer drug omeprazole, antiplatelet drug clopidogrel, anticonvulsant me phenytoinbertilsson, antimalarial drug proguanilthe anxiolytic drug diazepam, and certain antidepressants such as citalopram [15, 16].

There are 35 different variant alleles of *CYP2C19*[17]. The *CYP2C19*1* allele is the normal (wild- type) copy that has full enzymatic activity [18]. The most common variant allele is named as *CYP2C19*2* which result in truncated, nonfunctional protein [19]. Another common allele is named as *CYP2C19*3* which also creates a premature stop codon [20]. Genetic polymorphisms of *CYP2C19* are associated with impaired clopidogrel metabolism in healthy and in patients [21]. Research on CYP2C19 enzyme among egyptional patients is rare. No previous study linked CYP2C19 with the outcome of drug metabolism. The present study is the first to determine cytochrome P450 2C19 polymorphism and to asses Clopidogrel management in patients with CAD in egyptional patients.

Platelet activation and coagulation do not typically occur in intact blood vessels. Rather, these processes are initiated in response to vascular injury or atherosclerotic plaque rupture, which also leads to vasoconstriction at the damaged site to attenuate blood loss. The endothelial cells of the compromised vessels subsequently secrete vonwill brand factor, collagen, and other tissue factors to the blood stream that adhere to and activate circulating platelets [22] activated platelets change shape.

To facilitate further adhesion, initiate the arachidonic acid pathway to produce thromboxane A2(TXA2) and excrete the contents of their granules, releasing ADP, serotonin, and other proteins. Appositive

feedback mechanism promotes further vasoconstriction, addition platelet localization, activated platelet initiate the intrinsic, extrinsic coagulation pathways, which leads to thrombin- mediated conversion of fibrinogen to fibrin.

PATIENTS, MATRIAL, METHODS

Patients

Total 102 patients involved in descriptive cross- sectional study were enrolled from Eldoaa governmental hospital and Cairo health care specialized hospital between April 2017 and April 2018.The ethics committee of the misr university for science and technology approved the study and all patients provided written informed consent. Procedures were carried out in accordance with the approved guidelines.This study was designed to determine the frequency of CYP2C19 polymorphism in CHD patients undergoing PCI and the effect of this polymorphism on 1- year clinical outcomes. Patients were eligible for study enrollment in the cases where (1)ages were higher than 30 and (2) they were diagnosed with CHD using coronary angiography and successfully treated with PCI. Exclusion criteria were as follows (1) aspirin, clopidogrel and contrast agent allergy (2) severe diseases such as tumors and bleeding disorders, (3) hemodynamic instability (systolic blood pressure < 90mmhg and/or diastolic blood pressure <50mmhg) severe ventricular dysfunction (Left ventricular ejection fraction <40 %) and (4) severe liver and kidney dysfunction.

Matrials, Methods

PCI and clopidogrel treatment

PCI was performed in accordance with the standard of care. All patients were administrated 300mg clopidogrel and 40mg atorvastatin prior to operation, operated decided on the choice of anticoagulant and use of glycoprotein IIb/IIIa inhibitor (tirofiban, as well as the type of stent. After PCI patients were treated with 100mg/day aspirin and 75mg/day of clopidogrel for 1 year. We define the success of PCI as follows, (1) achievement of complete revascularization and residual stenosis of < 20% in target vessels of patients, (2) level 3 TIMI blood flow, (3) partial or complete remission of symptoms of myocardial ischemia and (4) no serious complications during hospitalization (such as acute myocardial infarction, urgent target lesion revascularization, death).

Genotype analysis

CYP2C19 genotype was identified using clopidogrel sensitive gene detection kit(DNA- technology Company, Russia).DNA was extracted from whole blood, master mix is prepared, 3pcr tubes is prepared and each tube contain 20mcq from each specific prope, 10 mcq master mix, 20mcq mineral oil, 5mcq DNA all steps were performed in strict accordance to the DNA- technology genetic analyzer manual instructions. According to the CYP2C19*1, *2*3 genotypes, patients carrying *1/*1 were grouped as extensive metabolizers, *1/*2 or *1/*3 as intermediate metabolizers, and *2/*2, *2/*3, *3/*3 as poor metabolizers.

Clinical Endpoints

The clinical endpoints include the following MACE: cardiac death, myocardial infarction, and unstable angina cardiac deaths was defined as any death due to cardiovascular causes or not clearly attributable to non- cardiovascular causes myocardial infarction was defined as recent ischemic symptoms with ST- segmental elevation or depression and abnormally elevated troponin. Unstable angina was defined as resting onset, duration greater than or equal to 20 min or more severe and longer duration of angina than before and higher frequency of onset. Diagnosis was performed during hospitalization according to serum creatine kinase levels, electrocardiogram findings and other indicators.

Statistical analysis

Data was entered in a spreadsheet program. Discrete values were presented in numbers and percentages and inferences were made by chi square test of significance was used in order to compare proportions between two qualitative parameters. Binary logistic regression was used to predict the outcome of categorical variable based on one or more predictor variables the confidence interval was set to 95% and the margin of error accepted was set to 5%. Therefore, the p- value was considered significant was as following:

- P- value < 0.05 was considered significant
- P- value < 0.001 was considered as highly significant
- P- value> 0.05 was considered insignificant

Results:

Study population:

Total of 102 patients provided written informed consent based on inclusion criteria, all of them were enrolled for 1 year follow up with follow –up rate about 100 %, according to CYP2C19 genotype 50, 52

patients were grouped as normal metabolizer and abnormal metabolizers (IM, ULTRAMETABOLIZERS), from abnormal metabolizers, 17 patients were IM, 35 patients were ultra metabolizers

Distribution of the demographic data in the study groups.

From the results in Table (1) and Figures (1, 2 and 3) it could be noticed that the patients <60 years (55.88%) and ≥60 (44.12%) of age (years) were showed in Figure (1), also female (37.25%) and male (62.75%) of sex were showed in Figure (2), meanwhile rural (45.1%) and urban (54.9%) were reported in Figure (3) according to demographic data.

Table (1) Distribution of the demographic data in the study groups.

demographic hic data	Total (n=102)
Age (years)	
<60 years	57 (55.88%)
≥60 years	45 (44.12%)
Range [Mean±SD]	38- 72 [55.78±7.05]
Sex	
Female	38 (37.25%)
Male	64 (62.75%)
Residence	
Rural	46 (45.1%)
Urban	56 (54.9%)

Distribution of risk factors in the study groups.

Table (2)and Figure (4) showed that the DM, HTN and smoking as a risk factors were49 (48.04%), 56 (54.9%) and 40 (39.22%), respectively.

Table (2) Risk factors distribution of the study group.

Risk factors	Total (n=102)
DM	49 (48.04%)
HTN	56 (54.9%)
Smoking	40 (39.22%)

Follow up MACE distribution of the study group

Table (3) and Figure (5) showed that the Non STEMI 1 (0.98%), Ischemic Dilated Cardiomyopathy 1 (0.98%), Myocardial Infarction 8 (7.84%), Unstable Angina 28 (27.45%) and Non 64 (62.75%), respectively, of follow up.

Table (3) Follow up MACE distribution of the study group.

Follow up (MACE)	Total (n=102)
Non STEMI	1 (0.98%)
Ischemic Dilated Cardiomyopathy	1 (0.98%)
Myocardial Infarction	8 (7.84%)
Unstable Angina	28 (27.45%)
Non	64 (62.75%)

Genotyping distribution of the study group.

Table (4) and Figure (6) showed that the *1*1 (0.98%), *1/*1 (48.04%), *1/*17 (34.31%), *1/*2 (14.71%), *1/*3 (0.98%) and *2/*17 (0.98%) of genotyping.

Table (4) Genotyping distribution of the study group.

Genotyping	Total (n=102)
*1*1	1 (0.98%)
*1/*1	49 (48.04%)
*1/*2	15 (14.71%)
*1/*3	1 (0.98%)
*1/*17	35 (34.31%)
*2/*17	1 (0.98%)

Phenotyping distribution of the study group.

The present results in Table (5) and Figure (7) illustrated that the Abnormal metabolizer 52 (50.98%) and Normal metabolizer 50 (49.02%) of phenotyping. Meanwhile, Ultrametablizer andIntermediate metabolizer were 35(34.31%) and 17(16.67%), respectively.

Table (5) Phenotyping distribution of the study group.

phenotyping	Total (n=102)
Abnormal metabolizer	52 (50.98%)
Intermediate metabolizer	17 (16.67%)

Ultrametablizer	35 (34.31%)
Normal metabolizer	50 (49.02%)

Comparison between normal metabolizer and abnormal metabolizer according to demographic data.

From the results in Table (6) could be noticed that the statistically analysis was significantly difference between normal metabolizer and abnormal metabolizer according to age (years) and residenence.

Table (6) Comparison between normal metabolizer and abnormal metabolizer according to demographic data.

Demographic Data	Normal metabolizer (n=50)	Abnormal metabolizer (n=52)	x2	p- value
Age (years)				
<60 years	41 (82.0%)	16 (30.8%)	27.136	<0.001**
≥60 years	9 (18.0%)	36 (69.2%)		
Sex				
Female	18 (36.0%)	20 (38.5%)	0.066	0.797
Male	32 (64.0%)	32 (61.5%)		
Residence				
Rural	32 (64.0%)	14 (26.9%)	14.153	<0.001**
Urban	18 (36.0%)	38 (73.1%)		

x^2: Chi- square test; **p- value <0.001 HS

Comparison between normal metabolizer and abnormal metabolizer according to risk factors.

Table (7) and Figure (11) showed that highly statistically significantly analysis difference between normal metabolizer and abnormal metabolizer according to risk factors.

Table (7) Comparison between normal metabolizer and abnormal metabolizer according to risk factors.

Normal metabolizer (n=50)	Abnormal metabolizer (n=52)	x2	p- value
16 (32.0%)	33 (63.5%)	10.108	<0.001**

18 (36.0%)	38 (73.1%)	14.153	<0.001**
8 (16.0%)	32 (61.5%)	22.176	<0.001**

x^2: Chi- square test; **p- value <0.001 HS

Statistically significant difference between normal and abnormal metabolizer

Table (8) and Figure (12) showed that statistically significantly analysis difference between normal metabolizer and abnormal metabolizer according to Myocardial Infarction, Unstable Angina and non.

Table (8)This table shows highly statistically significant difference between normal metabolizer and abnormal metabolizer according to risk factors.

Follow Up (MACE)	Normal metabolizer (n=50)	Abnormal metabolizer (n=52)	x2	p- value
Non Stemi	1 (2.0%)	0 (0.0%)	0.002	0.984
Ischemic Dilated Cardiomyopathy	1 (2.0%)	0 (0.0%)	0.002	0.984
Myocardial Infarction	1 (2.0%)	7 (13.5%)	4.201	0.047*
Unstable Angina	8 (16.0%)	20 (38.5%)	5.397	0.020*
Non	39 (78.0%)	25 (48.1%)	8.513	0.004*

x^2: Chi- square test; *p- value <0.05 S

Logistic regression of factors affecting normal and abnormal metabolizer.

From the results inTable (9) and Figure (13) it could be found that age (years), residence, HTN and smoking, have a significant effect on the normal metabolizer and abnormal metabolizer.

Table (9) Logistic regression of factors affecting normal metabolizer and abnormal metabolizer.

factors	B	S.E.	Sig.	OR	95% C.I	
					Lower	Upper
Age (years)	0.082	0.041	0.045*	1.086	1.002	1.177
Residence	- 1.722	0.553	0.002*	0.179	0.060	0.529
DM	- 0.736	0.567	0.195	0.479	0.158	1.457
HTN	- 1.249	0.553	0.024*	0.287	0.097	0.848
Smoking	- 2.085	0.605	<0.001**	0.124	0.038	0.407

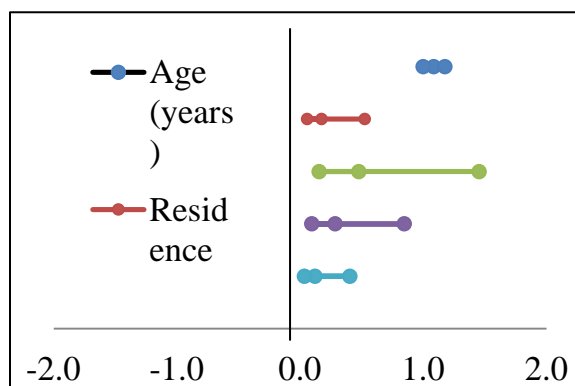OR: Odds Ratio; *p- value <0.05 S; **p- value <0.001 HS

Fig. (1) Odds ratio affecting normal metabolizer and abnormal metabolizer.

Discussion

Cardiovascular diseases are globally the killer number one, representing 31% global deaths in 2014. Of these deaths estimated 7.4 million were due to coronary heart disease[23, 24]. The current standard management for CAD is a dual antiplatelet therapy (aspirin and clopidogrel), in addition to coronary reperfusion or revascularization[25, 26].Knowledge of the individual's genotype can be used to optimize clopidogrel antiplatelet therapy[27]. The pharmacodynamics response to clopidogrel varies widely from subject to subject, and about 25% of patients treated with standard clopidogrel doses display low inhibition of ADP-induced platelet aggregation[28].this poor response to clopidogrel is associated with an increased risk of recurrent ischemic events[29].

Genetic polymorphism in CYP2C19, an enzyme required for clopidogrel bio activation have been shown to be associated with clopidogrel antiplatelet effectiveness, and represents a risk factor for recurrent ischemic cardiac events [30].

To the best of our knowledge, this is the first study in Egyptian population reporting the impact of CYP2C19 loss of function alleles, CYP2C19*2 and CYP2C19*3, in association with recurrent ischemic attacks in patients managed with clopidogrel after PCI, and this second study in Egyptian population reporting frequency of CYP2C19 genetic polymorphism.

The importance of this study related to fact that an understanding of distribution of SNPs is crucial for the future application of pharmacogenomics to different population groups. Such applications have recently been performed in warfare in therapy [31]in our study, the frequency of CYP2C19 *1, *2 and *3, *17 was 48%, 17%, 1%, 34% respectively, allelic frequency of CYP2C19*2 is higher than reported in Iraqi population

(15.2%) [32], Saudi Arabia(15%)[33], Jordanian(16%)[34], Lebanese (13.4%)[35], Tunisian region (11.5%) [36]. German (15.2%) [37], Belgian(9.1%) [38]Ethiopians (14%) [39], and lower than reported in Japanese (27.4%)[40], Chinese (45.5%) [41], Koreans(20.9%)[42]. Malaysians (28%) [43].

In first study in Egyptians population[44]the allelic frequency (12%) is lower than reported in our study. allelic frequency of CYP2C19 *3 is lower than reported in Lebanese (3%) [35], Ethiopians (3%) [38]

Koreans (11.7%)[41]and Japanese (10.8%) [40] and higher than reported in Iraqi population (0.2%)[32], Saudi Arabian population(0.00%)[33], Italians population(0%)[45], Russians (0.3%) [46] and also, the same as Tanzanians population (1%) [47].Allelic frequency of CYP2C19*17 is higher than frequency reported from Saudi Arabian (25.7%), Iraqi population (19.4%), Greece population(19.6%) [48] and African Americans (21.0%)[49].

The current study focused also on determining whether CYP2C19 genetic variants modulate clopidogrel- mediated antiplatelet effects and risk of MACE in patients undergoing PCI after 1 year follow up our main finding were as follow:1- there is difference between abnormal metabolizer(IM, ULRAMETABOLIZER) and normal metabolizer in MACE(p- value 0.047 for MI, and p- value 0.020 for unstable angina), according to logistic regression of factors affecting normal metabolizer and abnormal metabolizer, there is significant effect of age, residence, HTN, smoking on abnormal metabolizer and normal metabolizer.

Several studies have consistently reported that the CYP2C19*2 polymorphism is associated with lower antiplatelet response and increase the rate of recurrent cardiovascular events in Caucasian, Korean, and chines patients [50, 51, 52 53].moreover, the CYP2C19*3 variant is associated with clopidogrel –mediated antiplatelet effects in Asia since the incidence

Conclusion: Asignificant relation between CYP2C19 polymorphism and clinical outcome of ischemic heart disease patients taking clopidogreal after PCI especially smoking, hypertensive patients but meta- analysis study is required to confirm this result.

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تعداد التحور الجيني لجين السيتوكروم ب450 وتأثيره على النتائج السريرية في مرضي نقص تروية القلب الذين يتناولون عقار كلوبيدوجريل بعد التدخل وتركيب دعامات بالقسطرة العلاجية

الملخص: تلعب الصفائح الدموية دورًا رئيسيًا في التطور المرضي لمتلازمة الشريان التاجي الحادة بعد عملية رأب الوعاء التاجي(PCI). يعمل عقار Clopidogrel على تثبيط نشاط الصفائح الدموية. عقار clopidogrel يحتاج إلى انزيم CYP2C19 لتنشيطه في الكبد. ومن بين الأنماط الأليلية اختلاف نيوكلتيدة وحيدة (SNP) للجين CYP2C19. تغير الشكل الجيني للنمط الثاني (CYP2C19*2) والنمط الثالث (CYP2C19*3) أحد أسباب فقدان الدواء لفاعليته.

هدف الدراسة: تحديد معدل تكرار الأنماط الأليلية التالية CYP2C19*1, CYP2C19*2, CYP2C19*3, CYP2C19*17 وتحديد دور SNP في تجدد مشاكل القلب في المرضي المعالجين بعقار clopidogrel بعد عملية PCI

المواد المستخدمة: عينات دم خام تم جمعها من 102من المرضى الذين خضعوا لعملية PCI ويعالجون بعقار Clopidogrel وتم فحص الاختلافات الجينية لهم بواسطة استخدام Real-time PCR

النتائج: أظهرت الدراسة أن نسبة وجود الشكل الجيني 17 ,3 ,2 ,1 للجين CYP2C19 هي على النحو التالي (34%, 1%, 15%, 49%). كما أظهرت النتائج أيضا أن 37 مريض يمثلون حوالي 35.8% من العينة عانوا لاحقا خلال عام كامل من المتابعة من ضيق جديد بالشريان التاجي 10من هؤلاء المرضى لا يعانون من أي اختلاف في الشكل الجيني لجين CYP2C19 وبنسبة (27%) بينما 27 مريضاً يملكون اختلاف في الشكل الجيني لجين CYP2C19علي هيئة متغير النمط الجيني الأول مع الثاني (1*/2*) ومتغير النمط الأول مع الثالث(1*/3*)مع وجود دلالة إحصائية لتكرار الجلطات الشريانية p- value 0.047 والذبحات الصدرية غير المستقرة p- value 0.020

الخلاصة: هناك دلالة إحصائية قوية لارتباط اختلاف الشكل الجيني لجين CYP2C19وتكرار الازمات القلبية في المرضي المعالجين بعقار Clopedogrelبعد عمليات PCIولكن نحتاج مزيد من الدراسات لتأكيد هذه النتائج.

الكلمات المفتاحية: راب الوعاء التاجي, النمط الجيني, أمراض الشريان التاجي, عقار clopedogrel