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Full Length Research Paper

Evaluation of response to loading doses of clopidogrel therapy in patients undergoing percutaneous coronary intervention (PCI)

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Clopidogrel resistance plays a key role in ischemic recurrence after Percutaneous coronary intervention (PCI). The cytochrome P450 (CYP)–dependent conversion of Clopidogrel to its active metabolite may contribute to the variability in antiplatelet effect of Clopidogrel. To evaluate the response to 600 mg Clopidogrel loading dose versus 300 mg loading dose in patients undergo PCI. A total of 51 patients categorized to two groups: Group I consisted of 11 males (64.7%) and 6 females (35.3%) received 300 mg loading does, while Group II consisted of 28 males (82.4%) and 6 females (17.6%) received 600 mg Clopidogrel loading does. Detection of Clopidogrel response was assessed by measuring of the platelet aggregation percentage and CYP2C19 *2 assay in both groups. Clopidogrel resistance was defined by an arbitrary cut off value of <10% with respect definition as compared to control value. The percentage of Clopidogrel response among the studied patients was 29.2% for 300 mg Clopidogrel and 70.8% for 6oo mg Clopidogrel loading dose. In non or poor response to Clopidogrel group 10 patients (37%), were resistance to 300mg dose and 17 patients (63%) were resistance to 600mg Clopidogrel dose. Clopidogrel resistance groups were more likely have CYP2C19 genotype (CYP2C19*1.CYP2C19*2) (GA). There were highly significant association between good response group, non and poor response groups as regarding to genotype CYP2C19*1, CYP2C19*1 (GG) carriers and CYP2C19*1, CYP2C19*2 (GA) carriers. Platelet aggregation after 600mg Clopidogrel in both CYP2C19*1, CYP2C19*1 (GG) carriers and CYP2C19*1, CYP2C19*2(GA) carriers is statistically non significant with basal aggregation, before PCI and after PCI, while significant with day after PCI and highly significant with inhibition percentage before PCI. Platelet aggregation after 300mg Clopidogrel in both CYP2C19*1, CYP2C19*1 (GG) carriers and CYP2C19*1, CYP2C19*2(GA) carries is a statistically non significant with basal aggregation, before PCI, day after PCI, and after PCI, while significant with inhibition percentage before PCI. There was no variable individual response to the anti platelet effect of the standard dose (300mg) and higher loading dose (600mg) Clopidogrel therapy, but a variable individual response to Clopidogrel between patients carries CYP2C19*1.CYP2C19*2 (GA) genotype and carries CYP2C19*1.CYP2C19*1 (GG) genotype.

Keywords: Clopidogrel, loading dose, cardiology, clinical pharmacy

INTRODUCTION

Coronary artery disease (CAD) is a condition in which the vascular supply to the heart is impeded by atheroma, thrombosis or spasm of coronary arteries. This may impair the supply of oxygenated blood to cardiac tissue sufficiently to cause myocardial ischaemia which, if severe or prolonged, may cause the

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death of cardiac muscle cells, i.e. a myocardial infarction (MI) (Walker and Whittlesea 2007). Clopidogrel is a platelet adenosine diphosphate P2Y12-receptor antagonist that is widely used to prevent vascular events across a wide spectrum of atherothrombotic cardiovascular disease (Eshaghian et al., 2007).

Clopidogrel is rapidly absorbed from the intestine and extensively converted by hepatic cytochrome P450 isoenzymes (CYP3A4, CYP3A5, 2C19) to an active thiol metabolite. This short lived active metabolite binds to the P2Y12 receptor via a disulfide bridge between the reactive thiol group and two cysteine residues (cys17 and cys270) present in the extracellular domains of the P2Y12 receptor. Thus, the binding of ADP to the P2Y12 receptor is permanently inhibited (Ding et al., 2003). Clopidogrel has also been reported to attenuate platelet–leukocyte aggregate formation, and the levels of CRP, p-selectin and CD 40L; and the rate of thrombin formation (Labarthe et al., 2005). Cuisset et al (2006). reported in a recent prospective, randomized, single-center study that increasing the Clopidogrel loading dose from 300 to 600 mg is likely to improve clinical outcome after coronary angioplasty (Cuisset et al., 2006). However, despite the 600-mg loading dose, some patients remained Clopidogrel-resistant and the rate of major adverse cardiac events (MACE), observed at 1 month, although decreased, was still 5%. The superiority of a high dose regimen in reducing ischemic events and the associated risk profile compared to a standard dose has yet to be established in large scale clinical trials (Smith et al., 2006). The loading dose may need to be individually adjusted according to the patient's biological response to Clopidogrel to decrease the rate of (MACE) after stenting (Bonello et al., 2008).

Genetic polymorphisms of CYP2C19 modulate Clopidogrel pharmacokinetics and pharmacodynamics in healthy volunteers, as well as in patients. As compared with subjects with no CYP2C19 variant allele, subjects carrying one or two CYP2C19 loss-of-function alleles have been shown to have lower plasma concentrations of the active metabolite of Clopidogrel and a decrease in the antiplatelet effect of Clopidogrel in ex vivo aggregation tests (Brandt et al., 2007). The study of 2208 patient's withacute myocardial infarction who were treated with Clopidogrel, they evaluated the relationship between genetic determinants of the response to Clopidogrel and subsequent cardiovascular events. Genetic variants in CYP2C19 that result in loss of function were associated with an increase in the risk of death, myocardial infarction, or stroke, especially among patients undergoing PCI (Simon et al., 2009).

Study design

prospective non-randomized study.

Setting

Patients were admitted in national heart institute, Cairo, Egypt in PCI department for coronary angiography, during October 2010 to February 2011.

Patients and Methods

Patients

The studied patients were divided according to loading does to two groups. Group I comprised 17 patients who took 300 mg (4 tablets) loading dose of Clopidogrel the day before undergoing PCI. Group II comprised 34 patients who took 600 mg (8 tablets) loading dose of Clopidogrel the day before undergoing PCI. Patients of Group I consisted of 6 females and 11 males, with mean age of 52.9 ±7.3 years (ranged between 44-65 years). Patients of Group II consisted of 6 females and 28 males with mean age of 52.3±7.8 years (ranged between 37-67 Years).

Inclusion criteria

All Patients with coronary artery stenosis, non-ST segment elevation myocardial infarction, eligible undergoing PCI, age of patients between 35-75 years.

Exclusion criteria

Patients with ST-elevated acute myocardial infarction (ST-EAMI), on chronic oral anticoagulation or thienopyridine treatment within the last 2 weeks before admission, patient with renal hemodialysis, patients had contraindication or hypersensitivity to aspirin or Clopidogrel, patients with malignancy, patients with chronic heart failure class III or IV according New York Heart Association and with platelet count < 100,000/mm^3.

Written consent was obtained from all patient participated in the study.

METHOD

Six and half venous blood samples were collected before admission for PCI as baseline for determination of platelet aggregation percentage and genotyping assay. The patients were given 300 mg (4 tablets) of Clopidogrel loading dose before day of PCI procedure. The day of PCI after loading dose, venous blood samples were collected. Blood samples were collected again after day of PCI procedure for re measuring response to 300 mg of Clopidogrel loading dose by

platelet aggregometry. A dose of 75 mg/day (1 tablet) Clopidogrel was given as maintenance dose for 6 month. The same practical steps were carried out in group II with increase in loading dose of Clopidogrel to 600 mg (8 tablets). A dose of 150 mg/day (2 tablets) Clopidogrel was given as maintenance dose for 6 month. All patients were followed up by phone for one month after taking Clopidogrel maintenance dose for any clinical events or complications.

Samples treatment were proceeded as follows; 4.5 ml of blood were collection into siliconized tubes, contains citrate, thyeophylline adenosine dipyridamole (CTAD) for the measurement of platelet aggregation percentage and 2 ml were collected in vacutainer tube containing potassium ethylene diamine tetra-acetic acid (K2-EDTA) as an anticoagulant in a concentration of 3.6mg/mL with hemogard (lavender) 13x75mm for

Detection of Cytochrome P2C19 681G>A Polymorphism.

Platelet aggregation was assessed by light transmission aggregometry. (Gawaz et al., 1998).

Genotyping assayed by TaqMan polymerase chain reaction (PCR). (Trenk et al., 2008).

Statistical analysis

The collected data was revised, coded, tabulated and introduced to a PC, using Statistical package for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

P- value level of significance, $P>0.05$: Non significant (NS), $P< 0.05$: Significant (S) $P<0.01$: Highly significant (HS).

RESULTS

Total of the 51 patients recruited between October 2010 to February 2011, of whom 17 patients were non randomized to receive 300mg of Clopidogrel as loading dose and 34 patients received 600mg of Clopidogrel as loading dose. There were 39 patients (76.5 %) carried CYP2C19 wild-type homozygote (*1/*1) and 12 (23.7%) carried at least one *2 allele. Detection of Clopidogrel response was assessed by measuring of the platelet aggregation percentage and CYP2C19 *2 investigated in both 300mg and 600mg Clopidogrel users groups. The demographic, baseline, clinical procedure and angiographic data were shown in table (1). There were non significant differences between 300mg and 600mg Clopidogrel loading doses groups as regarding basal aggregation, before PCI and after PCI as table (2)

Clopidogrel resistance was defined by an arbitrary cut off value of <10% with respect definition as compared to control value. The results in table (3), showed that there was non significant difference between 300mg and 600mg Clopidogrel users groups as regarding to good response, poor response and non response *(p*-value 0.619). The percentage of Clopidogrel response among the studied patients was 29.2% for 300mg and 70.8% for 6oomg Clopidogrel loading dose and in poor response to Clopidogrel, 9 patients (40.9%) were resistance to 300mg Clopidogrel loading dose and 13 patients (59.1%), were resistance to 600mg Clopidogrel loading dose and in non response, 1 patient (20%), was resistance to300 mg Clopidogrel loading dose and 4 patients (80%),were resistance to 600 mg Clopidogrel loading dose as shown in table (4). Clopidogrel resistance groups were more likely have CYP2C19 genotype (CYP2C19*1.CYP2C19*2), than Clopidogrel response groups. There were highly significant association between good response group and non or poor response groups with genotype (CYP2C19*1,CYP2C19*1 and CYP2C19*1.CYP2C19*2) (GG,GA) (*P*-value =0.002) (table 4). Platelet aggregation after 600mg Clopidogrel in both CYP2C19*1, CYP2C19*1 carriers (GG) and CYP2C19*1, CYP2C19*2(GA) carriers is a statistically non significant with basal aggregation, before PCI, inhibitor percentage after PCI, while significant with one day after PCI (P =0.043), and highly significant with inhibition percentage before PCI. (P=0.002). Platelet aggregation after 300mg Clopidogrel in both CYP2C19*1, CYP2C19*1 carriers (GG) and CYP2C19*1, CYP2C19*2(GA) carries is a statistically non significant with basal aggregation, before PCI, day after PCI, and inhibit-percentage after PCI, while significant with inhibition percentage before PCI (P=0.023) (table 5). The presence of atherothrombotic risk factors (hypertension, smoker, BMI), age, sex were comparable in both 600mg, 300mg users patients with no statistically difference between them (p>0.05). however, there was a statistically significant of 300mg users and 600mg users Clopidogrel with diabetes (11.8% vs 43.8%) and with ACE I (64.7% vs 34.4%). we could not detect any significant relation between clinical outcome events and any of the platelet function variables between groups (300mg,600mg Clopidogrel users, that we assessed in this study as shown in table (6).

DISCUSSION

The response to different loading dose of Clopidogrel among the studied patients groups were assessed by measuring the platelet aggregation percentage using optical platelet aggregometry after stimulation with 10 µmol/L ADP as an agonist, which has been most extensively evaluated to define Clopidogrel responsiveness. Martin and Talbert (2005), revealed that platelet aggregation might be unsuitable for routine clinical practice due to many reasons; that platelet aggregation was sensitive to changes in temperature and hydrogen ion concentration, it had to be conducted

Table 1. Demographic and clinical characteristics of all studied patients.

			N=51	%
Sex	Male		39	76.5%
	Female		12	23.5%
Age	Mean±SD		52.5±7.5	
	Range		37-67	
Dose	300		17	33.3%
	600		34	66.7%
Genotype	GG		39	76.5%
	GA		12	23.5%
Risk factors:				
Smoker			26	53.1%
Hypertensive			37	75.5%
Diabetic			16	32.7%
BMI	Mean±SD		52.5±7.5	
	Range		37-67	
Prior treatment:				
ASA			43	87.8%
Bblockers			31	63.3%
ACEi			22	44.9%
AT1			5	10.2%
Diuretics			11	22.4%
Nitrates			32	65.3%
Statin			20	40.8%
Cablockers			3	6.1%
Insulin			6	12.2%
Oralantidiabetic			6	12.2%
Coronary lesions:				
Previous PTCA			3	6.1%
Previous CABG			0	.0%
Clinical outcome:				
Re angina			15	50.0%
MI			0	.0%
Stroke			1	3.3%
Bleeding			2	6.7%
Death			0	.0%
Response		No response	5	9.8%
		Poor	22	43.1%
		Good	24	47.1%

BMI=body mass index, ASA=aspirin, ACEI=anticonverted enzyme inhibitor, AT1=angiotensin1, CABG=coronary artery bypass graft, PTCA=percutaneous transluminal coronary angioplasty, MI= myocardial infarction, N= number of patients, GA=CYP2C19*1,*2, GG=CYP2C19*1,*1.

Table 2. Platelet aggregation and inhibition percentage according to loading dose of Clopidogrel

	Dose						*P*-value	Sig
	300(N=17)			600(N=34)				
	Med	IQR		Med	IQR			
Basal aggregation	56.8	19.9	56.8	58.0	43.0	70.0	0.704	NS
Before PCI	27.0	14.2	27.0	24.5	18.0	30.0	0.689	NS
Day after PCI	18.3	11.8	18.3	16.0	10.5	23.5	0.398	NS
Inhibition percentage before PCI	29.8	14.2	29.8	30.5	20.0	39.0	0.704	NS
Inhibition percentage after PCI	36.8	17.8	36.8	35.5	26.0	49.0	0.460	NS

Kruskal-Wallis test, NS= non significant, Med=median, IQR=interquartile range, N=number of patients

Table 3. Patients with Clopidogrel dose (300mg n=17,600mg n= 34). Classified according to the response to Clopidogrel

		Dose				*P**	Sig
		300		600			
		N	%	N	%		
Response	Non response	1	5.9%	4	11.8%	0.619	NS
	Poor response	9	52.9%	13	38.2%		
	Good response	7	41.2%	17	50.0%		

*Fisher's exact test, NS= non significant, n=number

Table 4. Patients groups classified according to the response to Clopidogrel (N=51).

		Good response		Poor response		Non response		*P**	Sig
		N	%	N	%	N	%		
Sex	Male	18	75.0%	18	81.8%	3	60.0%	0.568	NS
	Female	6	25.0%	4	18.2%	2	40.0%		
Age	Mean±SD		52.8±8.1		51.2±7.1		57.0±6.1	0.364**	NS
	Range		37-67		41-65		50-63		
Dose	300	7	29.2%	9	40.9%	1	20.0%	0.561	NS
	600	17	70.8%	13	59.1%	4	80.0%		
Genotype	GG	23	95.8%	14	63.6%	2	40.0%	**0.005**	**HS**
	GA	1	4.2%	8	36.4%	3	60.0%		
			Risk factors:						
	Smoker	13	54.2%	12	57.1%	1	25.0%	0.492	NS
	Hypertensive	19	79.2%	15	71.4%	3	75.0%	0.834	NS
	Diabetic	8	33.3%	8	38.1%	0	.0%	0.328	NS
BMI	Mean±SD		32.2±5.75		29.6±4.1		29.4±3.2	0.183**	NS
	Range		21.6-41		22.3-39.3		26.5-33.6		
			Prior treatment:						
	ASA	19	79.2%	20	95.2%	4	100.0%	0.192	NS
	Bblockers	15	62.5%	13	61.9%	3	75.0%	0.878	NS
	ACEi	10	41.7%	9	42.9%	3	75.0%	0.449	NS
	AT1	3	12.5%	1	4.8%	1	25.0%	0.412	NS
	Diuretics	5	20.8%	4	19.0%	2	50.0%	0.383	NS
	Nitrates	14	58.3%	14	66.7%	4	100.0%	0.256	NS
	Statin	9	37.5%	9	42.9%	2	50.0%	0.867	NS
	Cablockers	1	4.2%	1	4.8%	1	25.0%	0.258	NS

Figure 4 continue

	Good response		Poor response		Non response		*P**	Sig
	N	%	N	%	N	%		
Insulin	3	12.5%	3	14.3%	0	.0%	0.726	NS
Oralantidiabetic	4	16.7%	2	9.5%	0	.0%	0.566	NS
Coronary lesions:								
Previous PTCA	1	4.2%	2	9.5%	0	.0%	0.656	NS
Previous CABG	0	.0%	0	.0%	0	.0%	------	------
Clinical outcome:								
Re angina	7	41.2%	6	60.0%	2	66.7%	0.532	NS
MI	0	.0%	0	.0%	0	.0%	------	------
Stroke	1	5.9%	0	.0%	0	.0%	0.673	NS
Bleeding	0	.0%	2	20.0%	0	.0%	0.117	NS
Death	0	.0%	0	.0%	0	.0%	-----	-----

*fisher exact ,**Student t test, NS=non significant HS= highly significant, BMI=body mass index, ASA=aspirin, ACEI=anticonverted enzyme inhibitor, AT1=angiotensin1, CABG=coronary artery bypass graft, PTCA=percutaneous transluminal coronary angioplasty, MI= myocardial infarction, N= number of patients GA=CYP2C19*1,*2, GG=CYP2C19*1,*1.

Table 5. Platelet aggregation induced by 10µmol/L ADP in the CYP2C19 genotype groups at baseline and 24 and 48 hours after Clopidogrel administration

	Patients receiving loading dose 600mg			Patients receiving loading dose 300mg		
	Time after Clopidogrel administration(h)			Time after Clopidogrel administration(h)		
	0	24	48	0	24	48
CYP2C9 GG genotype	59(43-70)	22(18-29)^{xx}	14(10-17)^{xx}	50(43-89)	18(15-35)^{xx}	21.50(11.50-39)^{x}
CYP2C9 GA genotype	52(38-65)	26(23.50-51)^{x}	29(22-36)	35(26.50-50)	24(19-30.50)	23.50(11-36)

Wilcoxon signed rank test, ^{x} = significant, ^{xx}= highly significant

Table 6. The incidence of clinical outcome in both of 300mg and 600mg Clopidogrel LD (N=51).

		Dose				*P*-value	Sig	Relative risk
		300		600				
		N	%	N	%			
Re angina	Yes	5	50.0%	10	50.0%	1.00	NS	1 (.219-4.56)
	No	5	50.0%	10	50.0%			
MI	Yes	0	.0%	0	.0%	-----	-----	------
	No	10	100.0%	20	100.0%			
Stroke	Yes	0	.0%	1	5.0%	0.472	NS	------
	No	10	100.0%	19	95.0%			
Bleeding	Yes	1	10.0%	1	5.0%	0.605	NS	2.11(.118-37.7)
	No	9	90.0%	19	95.0%			
Death	Yes	0	.0%	0	.0%	----	-----	---
	No	10	100.0%	20	100.0%			

MI= myocardial infarction, NS= non significant, N=number of patients

within 2 hours of sample collection besides technical difficulties and cumbersome nature of the assay require a specialized laboratory setting to perform it. Martin and Talbert (2005).

The result in this work showed that there were no significant differences between loading dose of Clopidogrel 300mg and 600mg as regarding to good response, poor response and non response groups, similarly Angiolillo et al (2004), who reported that inter individual variability in ADP-induced platelet aggregation was not attenuated by a 600mg compared with 300mg LD of Clopidogrel in stable patients undergoing elective PCI. The ADP-induced platelet aggregation at 24 hr was 0.44 in 600mg LD group and 0.38 in 300mg LD group Angiolillo et al (2004). In contrast with Gurbel and Tantry (2007), who found in the largest pharmacodynamic study comparing 300mg and 600mg Clopidogrel LD, the treatment with 600mg LD dose during elective PCI reduced Clopidogrel non responsiveness to 8% compared to 28%-32% after a 300mg LD. Moreover, the study demonstrated a narrow response profile following treatment with 600mg compared to 300mg Clopidogrel (Gurbel and Tantry 2007).

In the current study, there was a highly significant difference between good, poor and non response group, as regarding genotype CYP2C19*1/CYP2C19*1 (GG) and CYP2C19*1/CYP2C19*2 (GA) (*P*-value=0.05). The good response is associated with a higher percentage of wild-type homozygote (GG) than CYP2C19*2allele (GA) (95.8%VS 4.2%), and in poor response is associated with a higher percentage of wild-type homozygote than CYP2C19*2 allele (63.6% vs 36.4%) and in non response is associated with a higher percentage of CYP2C19*2 allele than wild-type homozygote (60% vs 40%). This was in agreement with Trenk et al., (2008). who investigation polymorphisms of the 797 patients included 552(69.3%) were CYP2C19 wild-type homozygote's (*1/*1) and 245(30.7%) carried at least one *2 allele, carries of the CYP2C19*2 allele were significantly more likely than wild-type homozygote's miss the level of RPA>14% after stimulation 5µmol/ADP and found only the loss-of-function CYP2C19 681G>A polymorphisms (*2) was associated with blunted antiplatelet response to Clopidogrel. The allelic variant of CYP2 C19 as compared with wild-type homozygote's, the *2 allelic variant of CYP2C19 is associated with an almost 2-fold risk of highly on Clopidogrel platelet reactivity Trenk et al., (2008). On the other hand, Lev et al (2007) found no association between polymorphisms in the platelet receptors GIIIa, P2Y12 or P2Y1 and response to aspirin or Clopidogrel in cardiac patients. These finding suggest that the variability in response to anti-platelet drugs is multi-factorial and is not caused only by single gene mutations (Lev et al., 2007).

In this work, statistically analysis of the measuring the values of platelet aggregation percentage at 24 hour after 300 mg Clopidogrel administration in Patients group carrying CYP2C19*1,*1genotype (GG) was a highly significance difference from platelet aggregation at baseline (*P*-value= 0.001), and was statistically significance after 48 hr from platelet aggregation at baseline (*P*-value= 0.021), and after administration 600mg Clopidogrel LD is a highly statistically significance after 24 hr and 48 hr of Clopidogrel administration from baseline (*P*-value=0.001) .

In present study we found a non-significant difference between patients groups carrying CYP2C19*1,*2 genotype (GA), after 24 hr and 48 hr of administration 300mg Clopidogrel from percentage platelet aggregation at baseline (*P*> 0.05), and after administration 600mg Clopidogrel LD there was non-statistically significance difference after 48 hr of Clopidogrel administration from baseline (*P*-value =0.109), while after 24 hr of Clopidogrel was significance difference from baseline (*P*-value= 0.012).In accordance with abuzahra et al (2008), randomized patients undergoing PCI to receive different dose Clopidogrel (300mg) (n=42) and 600mg (n=77) platelet aggregation was similar at baseline in the 2 groups, drcease in platelet aggregation at 4 hr was significantly higher in high dose Clopidogrel than low (32 % vs 14% P= 0.04 respectively) (abuzahra et al., 2008; Hochholzer et al (2006), who found of 199 Patients with the lower ADP-induce platelet aggregation before intervention, after administration 600mg Clopidogrel had a significant lower platelet aggregation at baseline. Time from Clopidogrel LD had a strong impact on the change in platelet aggregation where, patient with a time from Clopidogrel loading of <2 hr, the percentage of platelet aggregation from baseline to immediately before PCI was 39±54% and > 2 hr was 62±53% (*P*<0.001) (Hochholzer et al., 2006).

In the present study it was reported that a non significant incidence of clinical events of reangina, re-infarction, stroke, bleeding and death in both groups of 300mg Clopidogrel users and 600mg Clopidogrel users (*P*>0.05) after 30 days follow up, where the values of relative risk is 1.0(0.219-4.56) as regarding the reangina and 2.11(0.118-37.3) as regarding the bleeding , patient with 300mg Clopidogrel LD have 2.11 times higher risk for developing bleeding than 600mg Clopidogrel LD (10% vs 5%)as table (6). In the accordance with Yong et al (2009) Who found that 256 patient with NSTEACS undergoing an early invasive managements strategy there were no significant difference in clinical outcome between two randomized treatment groups (300mg users and 600mg users Clopidogrel) at discharge, 1 month or 6 month, and 600mg Clopidogrel LD was not associated with increased risk of bleeding compared with 300mg LD (Yong et al., 2009). On the other hand, Patti et al (2005); Cuisset et al (2006) they Found that 600mg Clopidogrel LD significantly reduced the incidence of 30-day major adverse cardiac events by about two thirds (from 12% to 4%-5%) (Patti et al., 2005; Cuisset et al., 2006).

CONCLUSION

There was not a variable individual response to the anti platelet effect of the standard dose (300mg) and higher loading dose (600mg) Clopidogrel therapy used in clinical practice for the protection against recurrent thrombotic in patients with coronary heart disease. But a variable individual response to Clopidogrel between patients carries CYP2C19*1.CYP2C19*2 (GA) genotype, Clopidogrel resistance groups were more likely carries CYP2C19*1.CYP2C19*2 (GA) genotype, than Clopidogrel response groups, which is associated with poor clinical outcome after PCI.

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