The Effect of Non Steady State and Steady State Clopidogrel Carboxylic Acid Plasma Concentration on Clopidogrel Responsiveness in Patients Planned For Percutaneous Coronary Intervention

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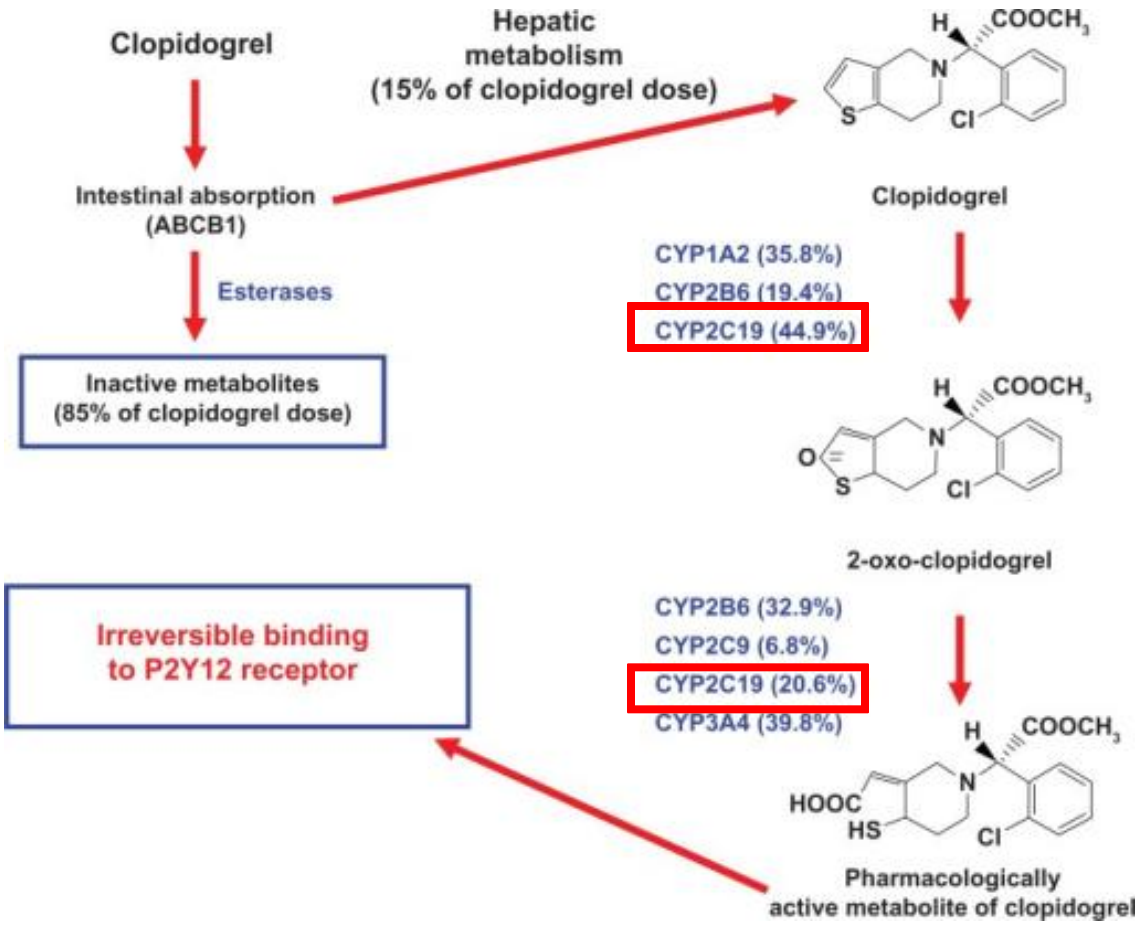
Double Antiplatelet Therapy (DAPT)

- Aspirin and most commonly, Clopidogrel
- DAPT has been shown to improve clinical outcomes following percutaneous coronary intervention (PCI) over single antiplatelet therapy
- Even with DAPT, post-procedural thrombotic and ischemic events still occur
- Increased use of DAPT is associated with increased risk of bleeding
- Careful balance between thrombotic and bleeding risk

CLOPIDOGREL

- An ADP-receptor antagonist.
- It is a prodrug that undergoes a two-step process by hepatic cytochrome (CYP) P450 enzymes to produce an unstable active metabolite.
- It is also rapidly metabolized to an inactive carboxylic acid derivative that accounts for 85% of clopidogrel-related circulating compounds.

CLOPIDOGREL METABOLISM



CLOPIDOGREL RESPONSE

- High variability in response
- Concept of clopidogrel resistance, clopidogrel non-responsiveness or high residual platelet reactivity
- Varies from 4-30% after administration of clopidogrel
- High residual platelet reactivity after clopidogrel doses – predictive of stent thrombosis and long term adverse clinical outcomes

POTENTIAL MECHANISM(S) AFFECTING CLOPIDOGREL RESPONSE

- Extrinsic mechanisms:

1. Patient non-compliance
2. Inappropriate dosing or under-dosing of clopidogrel
3. Drug-drug interactions

- Intrinsic mechanisms:

1. Genetic polymorphism - CYP2C19; *2 and *3 variants highly prevalent in Asian population
2. Increase release of ADP
3. Alternate pathways of platelet activation

PLATELET FUNCTIONT TEST (PFT)

- Directly phenotype platelet aggregation level in response to a specific agonist
- Useful tool to measure clopidogrel responsiveness

POINT OF CARE PFTs

IN MALAYSIA….

- National Cardiovascular Database (NCVD) – PCI Registry: 16 centres, a full report every 2 years

	2007-2009 (%)	2010-2012 (%)
Clopidogrel given prior to PCI	95.4	98.2
Clopidogrel given 6-24 hours prior to PCI	30.3	34.6
Clopidogrel given for > 3 days prior to PCI	34.6	28.9
Starting dose of 75mg	41.6	58.1

- High burden of clopidogrel usage in the country – on the increasing trend
- Important to obtain optimal degree of platelet inhibition with optimal dosage and duration of clopidogrel therapy
- To minimize bleeding risk and to improve prevention of long term thrombotic vascular events

What we were interested in…

1. Trends of inhibition of ADP-induced platelet aggregation in different clopidogrel pre-treated patients prior to PCI

ORIGINAL ARTICLE

Trends of Platelet Inhibition in Different Clopidogrel Pretreatment Patterns in Malaysian Patients Undergoing Elective Percutaneous Coronary Intervention

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INTRODUCTION

Double antiplatelet therapy (DAPT), in particular the combination of aspirin and clopidogrel, has been shown to improve clinical outcomes following percutaneous coronary intervention (PCI) [1,2]. It has been demonstrated that an adequate loading dose of clopidogrel prior to elective PCI reduces major cardiovascular events, including stent thrombosis [3]. The rationale for the use of DAPT over aspirin monotherapy largely centers on the pharmacodynamic properties of aspirin. Aspirin, an inhibitor of the cyclo-oxygenase enzyme has been shown to be ineffective in whether there is an association between soluble P-selectin (sP-selectin) and platelet aggregation level under influence of antiplatelet drugs, particularly when there are differences in the use of antiplatelet therapies.

Significant inter-individual variability in post-treatment platelet inhibition has led to some difficulty in standardizing the optimal dose and duration of established antiplatelet therapy. This has resulted in wide variations in practice patterns, especially in developing countries. Nonetheless, DAPT loading prior to planned or possible ad hoc PCI cases

What we were interested in…

2. Distribution of CYP2C19 genotypes in a multiethnic population and their impact on ADP-induced platelet aggregation in clopidogrel pre-treated patients prior to PCI

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RESEARCH ARTICLE

CYP2C19 genotypes and their impact on clopidogrel responsiveness in percutaneous coronary intervention

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Abstract *Background* Cytochrome P450 2C19 (CYP2C19) loss-of-function polymorphisms are more common in Asian populations and have been associated with diminished antiplatelet response to clopidogrel. In this era of 'personalised medicine', combining genotyping and phenotyping as a strategy to personalise antiplatelet therapy warrants further exploration. *Objective* This study aimed to investigate the prevalence and impact of CYP2C19*2, *3 and *17 genotypes on clopidogrel responsiveness in a multiethnic Malaysian population planned for percutaneous coronary intervention. *Setting* Between October 2010 and March 2011, a total of 118 consecutive patients planned for percutaneous coronary intervention were enrolled in Sara- (rs4986893, 636G > A) and *17 (rs11188072, −3402C > T) alleles were performed by polymerase chain reaction-restriction fragment linked polymorphism method. Whole blood ADP-induced platelet aggregation was assessed with multiple electrode platelet aggregometry (MEA) using the Multiplate Analyzer. *Main outcome measures* The distribution of CYP2C19*2, *3 and *17 among different ethnic groups and the association between genotype, clopidogrel responsiveness and clinical outcome were the main outcome measures. *Results* The highest prevalence of poor metabolisers (carriers of at least one copy of the *2 or *3 allele) was among the Chinese (53.7 %), followed by the Malays (26.9 %), Ibans (16.4 %) and other races (3.0 %). Poor

What we were interested in…

- ♥ Pattern of prescription with platelet inhibition√
- ♥ Genotyping and platelet inhibition √
- ♥ Pharmacokinetic and platelet inhibition ?

3. The effect of non-steady state and steady state plasma concentrations of clopidogrel and clopidogrel carboxylic acid on ADP-induced platelet aggregation in clopidogrel-treated patients prior to PCI

What did we do…..

- A total of 150 patients planned for PCI were enrolled between October 2010 and March 2011 from Sarawak General Hospital.
- All patients received 75 mg aspirin daily for at least two days prior to PCI.
- 32 patients received 75mg clopidogrel daily for equal or less than 3 days(non-steady state) and 118 patients received 75mg clopidogrel for at least 4 days (steady state) prior to PCI.
- All patients were assessed for their post-treatment ADP-induced platelet aggregation with multiple electrode platelet aggregometry (MEA) and plasma concentrations of clopidogrel and clopidogrel carboxylic acid.

Analytical Measure(s)…

- Blood samples collected a single time point within 24 hours after clopidogrel pre-treatment but prior to PCI.
- Plasma concentration of clopidogrel and clopidogrel carboxylic acid with LC-MS/MS
- MEA with Multiplate® - clopidogrel poor responder cutoff set at 468 AU*min (ref: Sibbings 2009)
- All statistical analysis - SPSS version 17; and $p<0.05$ was considered statistically significant.

FINDINGS (1)

Demographics		Clopidogrel ≤ 3 Days	Clopidogrel ≥ 4 Days	P-value
n		32	118	
%		21.3	78.7	
Age		60.94 (6.83)	57.31 (12.104)	0.030
Gender	Female	5 (15.6%)	31 (26.3%)	0.211
	Male	27 (84.4%)	87 (73.7%)	
Race	Chinese	19 (59.4%)	57 (48.3%)	0.340
	Malay	5 (15.6%)	29 (24.6%)	
	Iban	4 (12.5%)	24 (20.3%)	
	Others	4 (12.5%)	8 (6.8%)	
Indication for PCI	STEMI	7 (21.9%)	45 (38.1%)	0.020
	NSTEMI	4 (12.5%)	20 (16.9%)	
	Unstable angina	0 (0%)	12 (10.2%)	
	ACS but not specified	2 (6.25%)	6 (5.1%)	
	Others	19 (59.4%)	35 (29.7%)	
ACS event	≤ 7 Days Prior to PCI	4 (12.5%)	6 (5.1%)	
	≥ 8 Days Prior PCI	9 (28.1%)	70 (59.3%)	

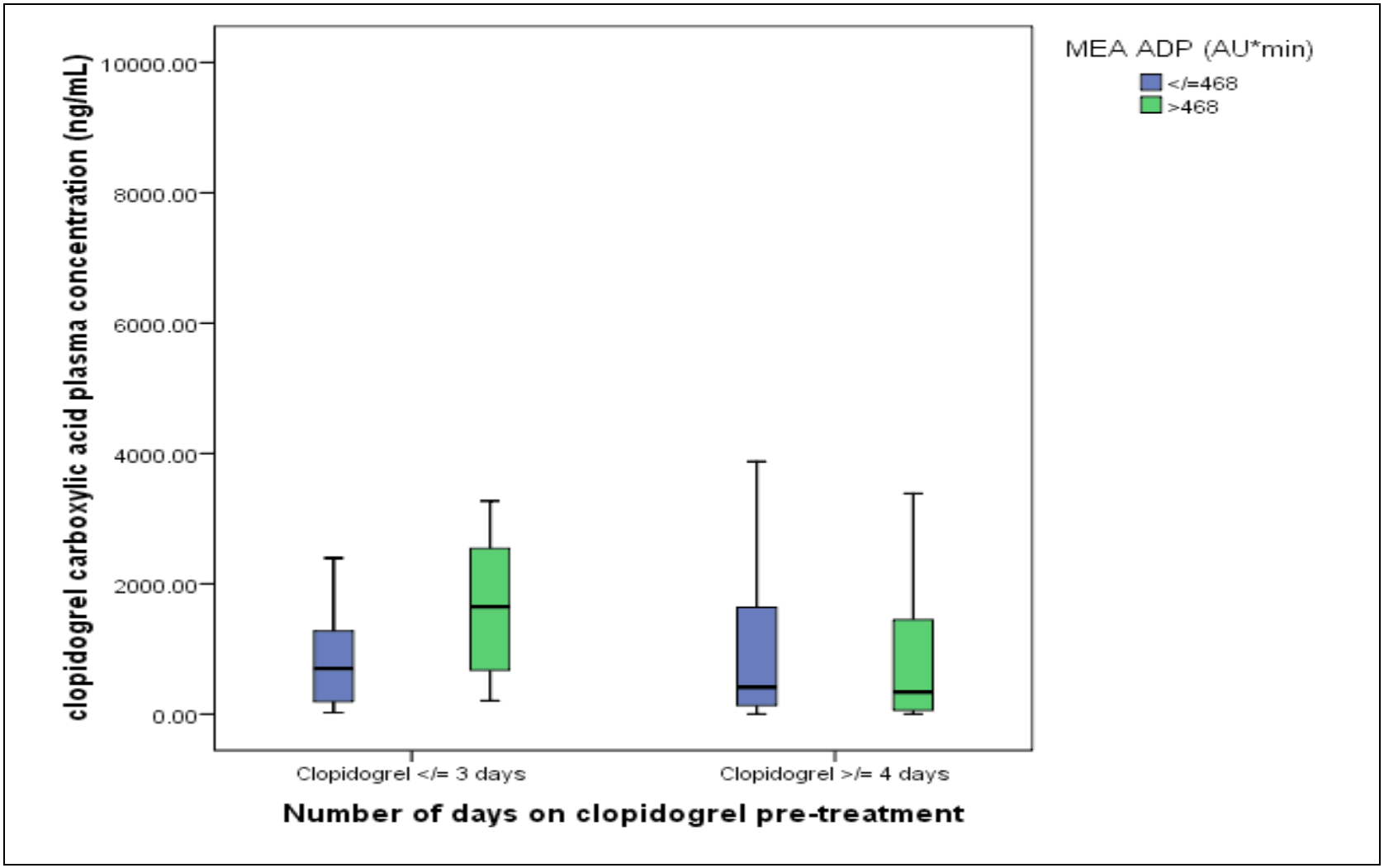
FINDINGS (2)

Cardiovascular Disease (CVD) Risk Factor(s)		Clopidogrel ≤ 3 Days	Clopidogrel ≥ 4 Days	P-value
Hypertension		26 (81.3%)	83 (70.3%)	0.219
Hyperlipidemia		25 (78.1%)	82 (69.5%)	0.338
Diabetes Mellitus		9 (28.1%)	37 (31.4%)	0.725
Smoking Status	Current	4 (12.5%)	13 (11.0%)	0.143
	Former	10 (31.3%)	56 (47.4%)	
	Never	18 (56.3%)	49 (41.5%)	
Family History of CVD		7 (21.9%)	37 (31.4%)	0.269

FINDINGS (3)

Parameters [Mean (SD)]	Clopidogrel ≤ 3 Days	Clopidogrel ≥ 4 Days	P-value
MEA ASPI (AU*min)	130.47 (105.05)	109.97 (85.55)	0.255
MEA ADP (AU*min)	365.41 (168.12)	288.91 (159.40)	0.019
Clopidogrel plasma concentration (ng/mL)	1.40 (2.47)	0.86 (1.59)	0.243
Clopidogrel carboxylic acid plasma concentration (ng/mL)	1204.49 (1692.78)	981.12 (1113.31)	0.347

FINDINGS (4)


clopidogrel carboxylic acid plasma concentration (ng/mL)
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8000.00
6000.00
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2000.00
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MEA ADP (AU*min)
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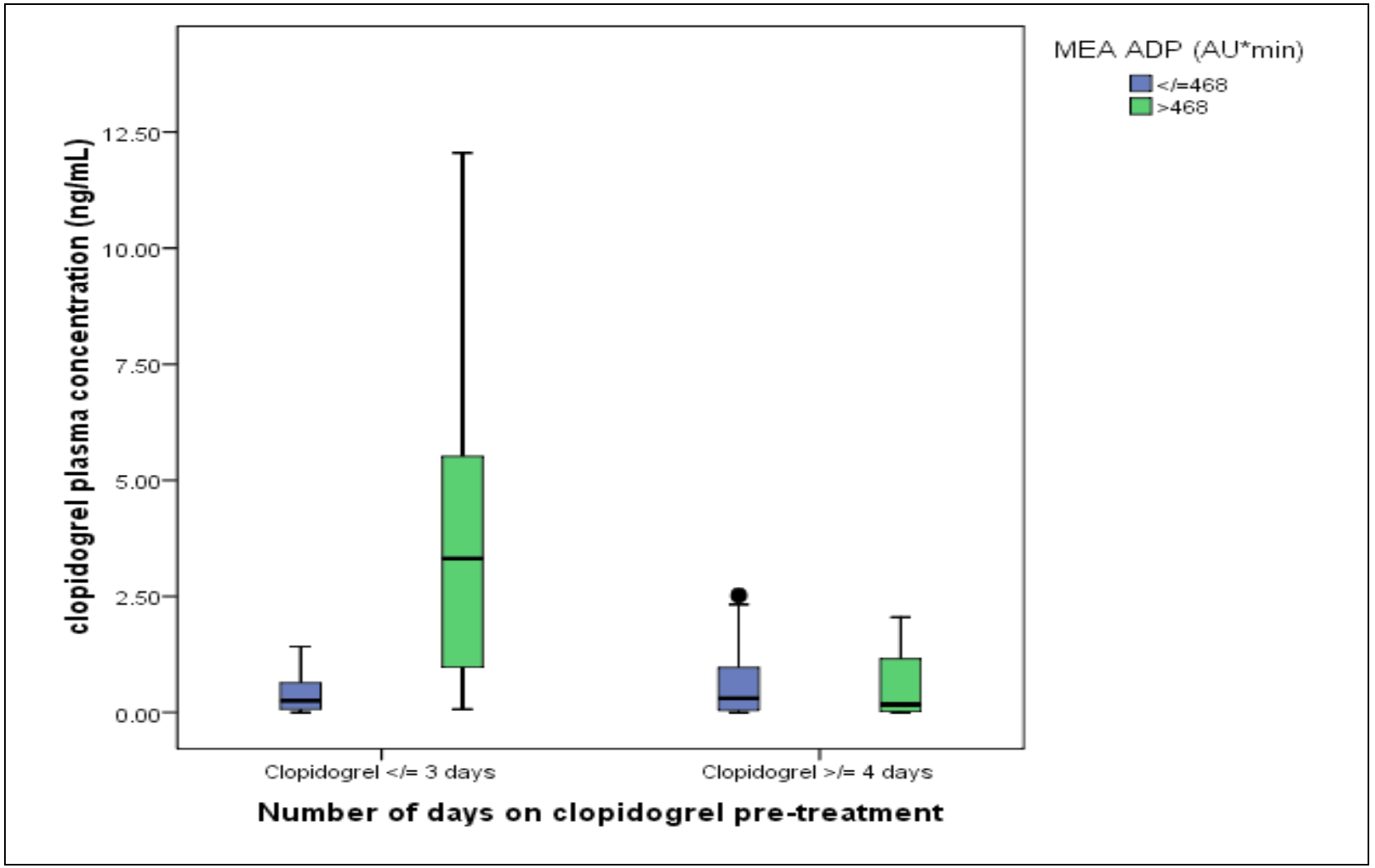
Clopidogrel </= 3 days
Clopidogrel >/= 4 days
Number of days on clopidogrel pre-treatment

FINDINGS (5)


MEA ADP (AU*min)
</=468
>468
clopidogrel plasma concentration (ng/mL)
12.50
10.00
7.50
5.00
2.50
0.00
Clopidogrel </= 3 days
Clopidogrel >/= 4 days
Number of days on clopidogrel pre-treatment

PREVALENCE OF CLOPIDOGREL NON-RESPONDERS

- From our data, the prevalence of clopidogrel non-responsiveness in non-steady state and steady state group was 21.9% and 12.7%, p=0.149; respectively.

LIMITATIONS

- Single centre experience
- Observational study design in a clinical practice setting
- Unable to quantify active metabolite(s) of clopidogrel

CONCLUSION

- Our data indicated that there was no significant difference between non-steady state and steady state plasma concentrations of clopidogrel and clopidogrel carboxylic acid, with respect to ADP-induced platelet aggregation.

- Clopidogrel carboxylic acid might be a more useful tool is identifying poor compliance and variable metabolism in clopidogrel treated patients, rather than to characterize antiplatelet action of clopidogrel.

- Therefore, investigation into the role of the active metabolite of clopidogrel is still warranted.


THANK YOU