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Pharmacodynamic evaluation of clopidogrel reloading vs. switching to prasugrel or ticagrelor in clopidogrel resistant Indian patients

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HTPR — high on treatment platelet reactivity
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ABSTRACT

Objectives: To compare the pharmacodynamic effects of clopidogrel reloading vs. switching to prasugrel or ticagrelor in high on treatment platelet reactivity (HTPR) patients undergoing percutaneous coronary intervention (PCI).
Methods: Prospective, single-centre study wherein consecutive patients undergoing nonemergent PCI showing HTPR on 600 mg clopidogrel loading were randomized to either clopidogrel reloading (300 mg load, 75 mg OD) or prasugrel (60 mg load, 10 mg OD-in patients > 60 kg) or ticagrelor (180 mg load, 90 mg BD). HTPR is defined as maximum platelet aggregation (MPA) > 46% assessed by 5 μmol/L adenosine diphosphate light transmission aggregometry (ADP-LTA) assay after more than 6 h of clopidogrel loading. Platelet function were assessed at baseline, 6 h or more after clopidogrel loading, 2 h after reloading, day 1 and day 30 post-PCI.
Results: 107 patients enrolled in the study, 32 (29.9%) were found to have HTPR. 10 (9.3%) patients were reloaded with clopidogrel, 10 (9.3%) with prasugrel and 12 (11.2%) with ticagrelor. Mean MPA in clopidogrel, prasugrel and ticagrelor reloaded patients was 42.6 ± 12.5%, 15.8 ± 8.6% and 14.6 ± 7.2% respectively at 2 h after reloading and was 43.7 ± 13.5%, 15.4 ± 5.6% and 12.6 ± 4.6% on day 1 post-PCI. The MPA significantly reduced in prasugrel and ticagrelor cases and not in clopidogrel, also prasugrel and ticagrelor had almost similar MPA after the reload. There was no patient with continued HTPR with ticagrelor or prasugrel while 50% (5/10) of clopidogrel reloaded patients had HTPR. The pharmacodynamic efficacy of maintenance with prasugrel or ticagrelor was better than clopidogrel (MPA at day 30 post-PCI; 15 ± 9.7%, 13.9 ± 5.1% and 50.4 ± 13.1% respectively).
Conclusion: In patients undergoing PCI exhibiting HTPR after clopidogrel loading, ticagrelor or prasugrel reloading produced improved platelet inhibition which was better than clopidogrel reload and this effect was sustained during maintenance phase.

1. Introduction

Current guidelines recommend treating patients undergoing percutaneous coronary intervention (PCI) and drug-eluting stent implantation with a loading dose of P2Y12 receptor antagonist and continuation of same for at least 1 year [1]. Clopidogrel resistance has been defined as high on treatment platelet reactivity (HTPR) [2]. Variable antiplatelet responses to clopidogrel are primarily based on metabolic phenotype of cytochrome 2C19 (CYP2C19) genotype. Patients who are carriers of loss-of-function alleles in the hepatic CYP2C19 system have lower clopidogrel active metabolite levels and are thus clopidogrel resistant [3,4].

High on treatment platelet reactivity (HTPR) while on clopidogrel has been seen to be associated with high adverse event rates in patients undergoing percutaneous coronary intervention (PCI) [5–7]. Newer P2Y12 inhibitors, prasugrel and ticagrelor, are accompanied by a stronger and more consistent antiplatelet action compared with clopidogrel [8–17]. However, there is limited data on the effects of clopidogrel reloading vs. switching to prasugrel or ticagrelor in this group of HTPR patients.

In pharmacodynamic study, in post-PCI patients exhibiting HTPR, prasugrel was more effective than a double maintenance dose of clopidogrel in reducing platelet reactivity (PR) [18]. Ticagrelor therapy was associated with greater platelet inhibition compared with clopidogrel in stable CAD patients with HTPR following a 300-mg clopidogrel loading dose [19]. In the present study, we aimed to compare the pharmacodynamic effects of clopidogrel reloading vs. switching to prasugrel or ticagrelor in clopidogrel resistant Indian patients being taken up for PCI.

2. Methods

Study was a prospective randomized, single-centre, 3-arm, parallel-design study to evaluate the pharmacodynamic response of clopidogrel

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reloading vs. switching to prasugrel or ticagrelor in clopidogrel resistance patients being taken up for PCI.

2.1. Study population

Patients aged 18 to 75 years being taken for elective coronary angiography and possible revascularisation were included in the study.

Patients with acute STEMI and those undergoing urgent coronary angiography and possible revascularisation were excluded from the study. Patients were also excluded if they were already on antiplatelet therapy except aspirin and clopidogrel, had contraindications to antiplatelet therapy, were on chronic oral anticoagulation treatment, or had a history of bleeding diathesis. Patients were also excluded if there was any history of ischemic or hemorrhagic stroke, intracranial neoplasm, arteriovenous malformation or aneurysm, a history of transient ischemic attack, history of active bleeding, or were on dialysis. A written informed consent was obtained prior to the procedure in all patients as per institution protocol. Approval of the institutional ethics committee was taken for study.

2.2. Study Design

Baseline platelet function test was done before clopidogrel loading. All patients clopidogrel naive or otherwise received an initial loading dose of clopidogrel 600 mg in the night prior to the planned PCI. Platelet function was assessed after 6 or more hours of clopidogrel loading. The HTPR patients were randomly assigned in 1:1:1 ratio, using computerized random-number generation to receive 1 of the following 3 regimens: 1) clopidogrel 300 mg loading dose (LD) followed by 75 mg OD maintenance dose (MD); 2) prasugrel 60-mg loading dose (LD) followed by 10-mg OD maintenance dose (MD) in patients ≥60 kg or 3) ticagrelor 180-mg loading dose (LD) followed by 90-mg BD maintenance dose (MD). Patients with no HTPR (clopidogrel sensitive) were continued on Clopidogrel 75 mg OD. All patients received aspirin 325 mg stat followed by 150 mg/day if aspirin naive or aspirin 150 mg/day without preload if already on aspirin. Patients received an intra-arterial dose of 100 to 140 U/kg heparin at time of procedure. Use of periprocedural glycoprotein IIb/IIIa inhibitors was allowed, at the operator's discretion.

2.3. Follow-up

All patients with PCI were followed up in cardiology outpatient department at 30 days.

2.4. Assessment of platelet function

Blood samples were collected for platelet function testing before the clopidogrel LD (baseline), at 6 h or more after clopidogrel loading. Platelet function test was done using Light transmission aggregometry (LTA) assay (Chrono-log corporation, USA, Model 700 Whole Blood/Optical Lumi-Aggregometer), using doses of 5 μmol/L ADP as agonist and reported as a percentage of Maximal Platelet Aggregation (MPA).

Clopidogrel resistant patient (High on Treatment Platelet Reactivity {HTPR}) was defined as MPA >46% for a 5-μmol/L ADP-induced platelet aggregation [2]. Platelet function testing was done again 2 h after reloading with one of the three regimens in Patients with High on treatment platelet reactivity (HTPR). Platelet function testing was done in patients who had PCI on day 1 and day 30 post-PCI. Samples were processed within 1 h by operators who were blinded to treatment.

2.5. Endpoints

The primary endpoint of study was to compare efficacy of clopidogrel reloading vs. switching to prasugrel or ticagrelor in patients with High on treatment platelet reactivity (HTPR) after clopidogrel load by comparing MPA% on each of the three drug regimen at 2 h post-reload and on day 1 post-PCI. Also the efficacy of maintenance dose in the HTPR patients was compared with clopidogrel sensitive patients by comparing MPA% at end of 30 days in different study groups.

The secondary endpoint of study was a composite of major adverse cardiovascular and cerebrovascular events (MACCE) which included cardiac death, myocardial infarction, stent thrombosis; stroke and need for repeat revascularisation at time of hospital discharge and post-PCI at 30 day hospital visit. Stent thrombosis was labelled as acute, subacute, late and very late when event occurred within 24 h, 30 days, <1 year or >1 year respectively after procedure. Definite, probable and possible stent thrombosis was defined according to ARC definition [20].

Safety endpoints included bleeding complications and death from any cause at time of hospital discharge and at post-PCI 30 day

Table 1
Baseline characteristics of all groups.

	All patient	Clopidogrel sensitive	Clopidogrel reload	Prasugrel reload	Ticagrelor reload	p value
Number	107	75 (70.10%)	10 (9.30%)	10 (9.30%)	12 (11.20%)	
Age (years)	57.91 ± 8.15	57.52 ± 8.64	59.90 ± 7.85	59 ± 7.13	57.75 ± 6.32	0.81
Female	24 (22.4%)	15 (20%)	3 (30%)	2 (20%)	4 (33%)	0.697
Weight	69.22 ± 7.43	68.69 ± 8.00	68.70 ± 6.73	73.10 ± 3.54	69.75 ± 6.15	0.364
Diabetic	39 (36.4%)	27 (36%)	6 (60%)	3 (30%)	3 (25%)	0.353
Hypertensive	58 (54.2%)	43 (57.3%)	6 (60%)	5 (50%)	4 (33.3%)	0.456
Smoker	18 (16.8%)	12 (16%)	4 (40%)	1 (10%)	1 (8.3%)	0.185
Tobacco chewer	18 (16.8%)	16 (21.3%)	0 (0%)	1 (10%)	1 (8.3%)	0.255
Family history	5 (4.7%)	3 (4%)	1 (10%)	1 (10%)	0 (0%)	0.585
LDL cholesterol (mg/dl)	7.3.02 ± 25.70	75.4 ± 27.62	59.5 ± 12.55	78.80 ± 20.12	64.67 ± 21.49	0.158
HDL cholesterol (mg/dl)	31.63 ± 7.28	32.0 ± 6.76	26.40 ± 8.5	35.70 ± 7.04	30.33 ± 7.87	0.029
Total cholesterol (mg/dl)	131.42 ± 29.35	133.48 ± 30.18	115.6 ± 18.21	131.42 ± 29.35	125 ± 25.78	0.204
Triglyceride (mg/dl)	127.24 ± 54.34	122.25 ± 41.78	126.2 ± 86.83	130.6 ± 68.31	156.5 ± 74.96	0.247
CSA	54 (50.5%)	35 (46.7%)	6 (60%)	6 (60%)	6 (50%)	0.771
USA	4 (3.7%)	4 (5.3%)	0 (0%)	0 (0%)	0 (0%)	0.621
NSTEMI	10 (9.3%)	8 (10.7%)	0 (0%)	1 (10%)	1 (8.3%)	0.752
MI	36 (33.6%)	24 (32%)	4 (40%)	3 (30%)	5 (41.7%)	0.879
Old MI	21 (19.6%)	17 (22.7%)	3 (30%)	1 (10%)	0 (0%)	0.200
Prior CABG	3 (2.8%)	3 (4%)	0 (0%)	0 (0%)	0 (0%)	0.725
Prior PCI	10 (9.3%)	7 (9.3%)	1 (10%)	2 (20%)	0 (0%)	0.461
LV dysfunction	38 (35.5%)	27 (36%)	5 (50%)	3 (30%)	3 (25%)	0.651

Table 2
Baseline characteristics of clopidogrel sensitive and clopidogrel resistant (HTPR) groups.

	All patients	Clopidogrel sensitive	Clopidogrel resistance (HTPR)	p value
Number	107	75 (70.10%)	32 (29.9%)	
Age (years)	57.91 ± 8.15	57.52 ± 8.64	58.81 ± 6.90	0.455
Female	24 (22.4%)	15 (20%)	9 (28.1%)	0.356
Weight	69.22 ± 7.43	68.69 ± 8.00	70.47 ± 5.80	0.260
Diabetic	39 (36.4%)	27 (36%)	12 (37.5%)	0.883
Hypertensive	58 (54.2%)	43 (57.3%)	15 (46.9%)	0.320
Smoker	18 (16.8%)	12 (16%)	6 (18.8%)	0.728
Tobacco chewer	18 (16.8%)	16 (21.3%)	2 (6.2%)	0.056
Family history	5 (4.7%)	3 (4%)	2 (6.2%)	0.614
LDL cholesterol (mg/dl)	7.3.02 ± 25.70	75.4 ± 27.62	67.47 ± 19.80	0.145
HDL cholesterol (mg/dl)	31.63 ± 7.28	32.0 ± 6.76	30.78 ± 8.44	0.431
Total cholesterol (mg/dl)	131.42 ± 29.35	133.48 ± 30.18	126.59 ± 27.14	0.268
Triglyceride (mg/dl)	127.24 ± 54.34	122.25 ± 41.78	138.93 ± 75.70	0.147
CSA	54 (50.5%)	35 (46.7%)	18 (56.2%)	0.364
USA	4 (3.7%)	4 (5.3%)	0	0.184
NSTEMI	10 (9.3%)	8 (10.7%)	2 (6.2%)	0.472
MI	36 (33.6%)	24 (32%)	12 (37.5%)	0.581
Old MI	21 (19.6%)	17 (22.7%)	4 (12.5%)	0.225
Prior CABG	3 (2.8%)	3 (4%)	0	0.251
Prior PCI	10 (9.3%)	7 (9.3%)	3 (9.4%)	0.995
LV dysfunction	38 (35.5%)	27 (36%)	11 (34.4%)	0.872

hospital visits. Bleeding was classified as minimal, minor, or major according to the TIMI (Thrombolysis in Myocardial Infarction) criteria [16].

2.6. Statistical analysis

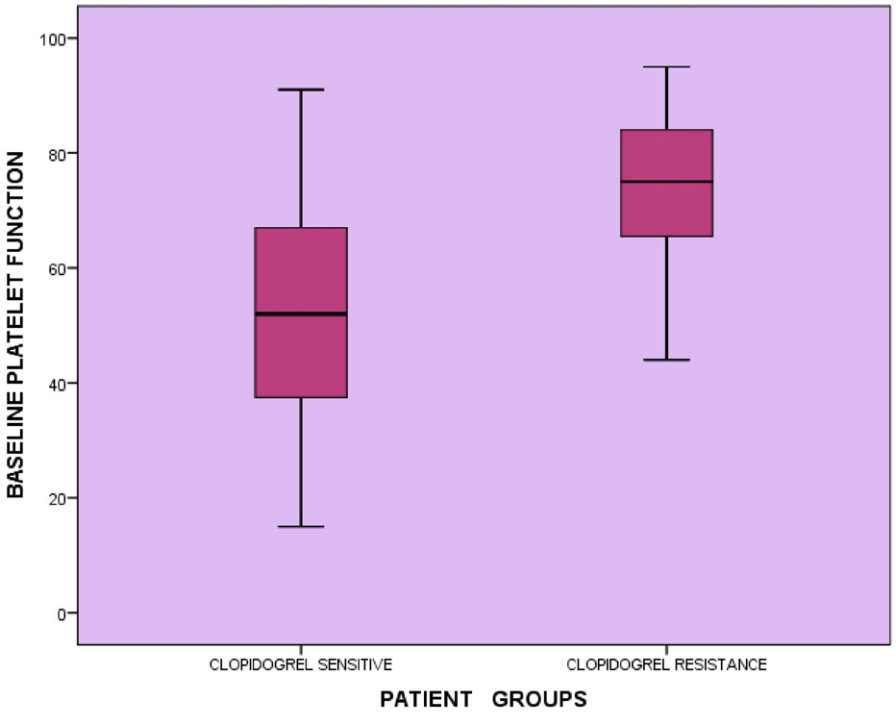
Statistical analysis was done using IBM SPSS Statistical Software (IBM SPSS Statistics version 20.0, IBM SPSS, USA).

Continuous variables were expressed as mean ± standard deviation (SD) and categorical variables were expressed as percentage. For continuous characteristics, means of the treatment groups were compared using analysis of covariance. For continuous characteristics, means of the clopidogrel sensitive and patients with High on treatment platelet reactivity (HTPR) group were compared using independent sample t-test. For categorical characteristics, percents were compared by chi-square tests. Means of MPA (Maximal Platelet Aggregation) of treatment groups were compared using analysis of covariance and comparison between two groups was done using independent sample t- test. Descriptive analysis was used for MACCE and safety end points because the trial was not adequately sized to evaluate clinical endpoints. All tests were 2-tailed, and statistical significance was considered for p values < 0.05.

3. Results

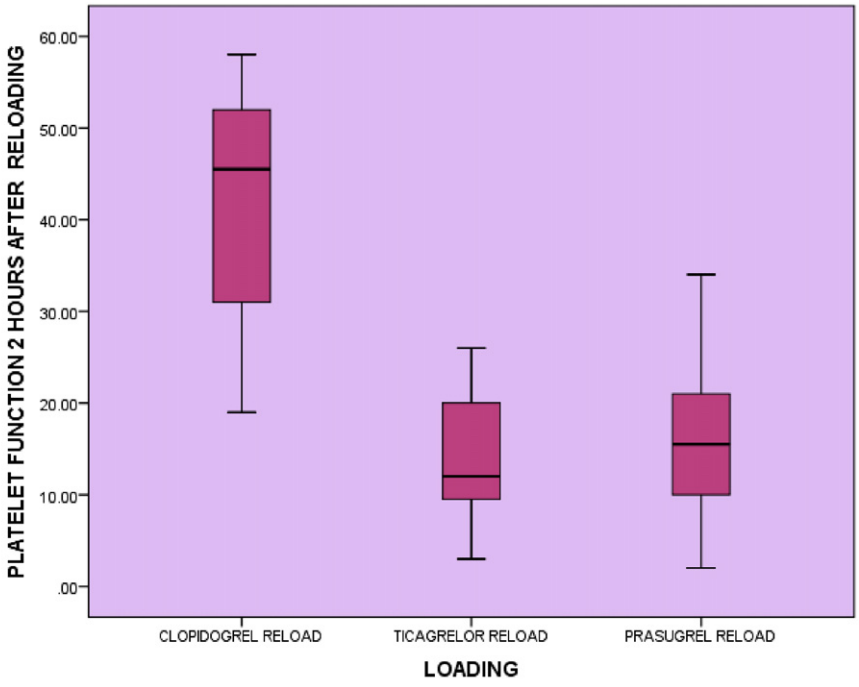
3.1. Patient population

107 patients were enrolled in study from October 2013 to 1st week of November 2014. Of these, 75 (70.1%) patients were clopidogrel sensitive and 32 (29.9%) were found to have HTPR. Of those with HTPR 10 (9.3%) patients were reloaded with extra 300 mg clopidogrel, 10 (9.3%) were reloaded with prasugrel and 12 (11.2%) with ticagrelor. Out of the total of these 107 patients analysed, 73 underwent PCI; all had the maintenance phase study completed; 52 (71.2%) patients were clopidogrel



	Clopidogrel Sensitive(75)	Clopidogrel Resistance{HTPR patients}(32)	P Value
Baseline Platelet Function	51.41±19.90	74.34 ±11.75	<0.001

Fig. 1. Comparison of baseline platelet function between groups.



	Clopidogrel Reload(10)	Ticagrelor Reload(12)	Prasugrel Reload(10)	P Value
2 Hours After Reload Platelet Function	42.60 ±12.48	14.58 ±7.20	15.80 ±8.63	<0.001

Fig. 2. Comparison of platelet function 2 h after reloading between groups.

sensitive, 21 (28.8%) patients had HTPR; 7 (9.6%) were reloaded with clopidogrel, 5 (6.9%) with prasugrel and 9 (12.3%) with ticagrelor.

3.2. Basic demographic profile

Demographics and baseline characteristics for the total population and treatment groups are summarized in Table 1. Mean age of the patients was 57.9 ± 8.15 year. Men comprised 83 (78.6%) and females constituted 24 (22.4%) patients. A total of 39 (36.4%) patients were diabetics. All were on oral antidiabetics and none of these patients was on insulin therapy. HTN was present in 58 (54.2%) and 18 (16.8%) were current smokers.

The most common clinical presentation was stable angina in 54 (50.5%) followed by ST elevation myocardial infarction (STEMI) 36 (33.6%). Non-ST elevation myocardial infarction (NSTEMI) was the admission diagnosis in 10 (9.3%) and 4 (3.7%) presented with unstable angina (USA). 38 (35.5%) patients had LV dysfunction. Prior PCI was done in 10 (9.3%) and 3 (2.8%) patient had prior history of CABG.

Single vessel disease was present in 43 (40.2%) patients whereas double vessel and triple vessel disease was present in 32 (29.9%) and 23 (21.5%) patients respectively. Normal coronaries were found in 9 (8.4%) patients. Procedures were completed through radial route in 98 (91.6%) patients.

All patients received aspirin, beta blockers, statins and heparin. GP IIb/IIIa inhibitors were used in 63 (58.9%) patients.

Demographics and baseline characteristics for the clopidogrel sensitive and HTPR patients are summarized in Table 2, and showed no significant differences among the groups.

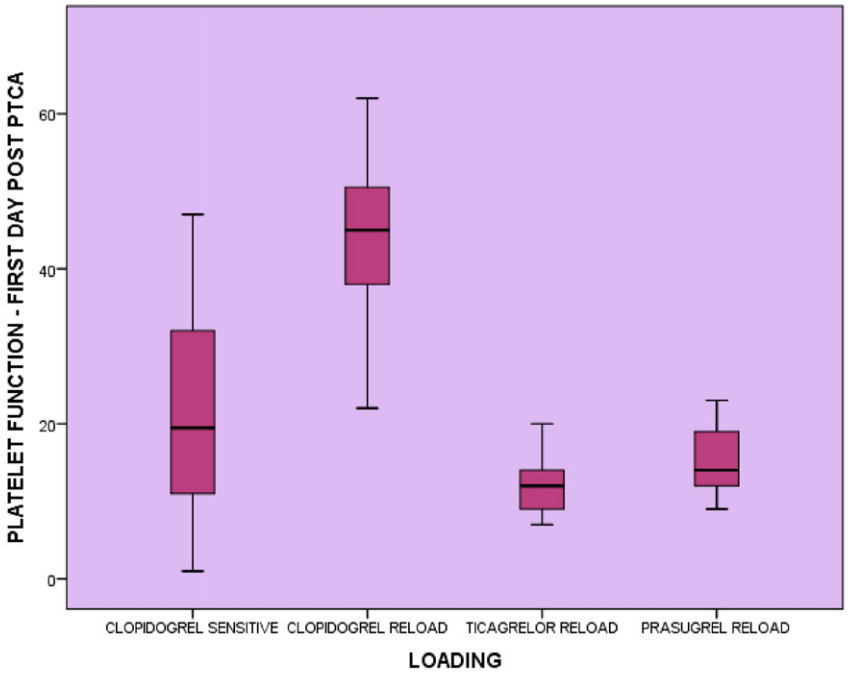
3.3. Pharmacodynamic evaluations

Baseline platelet aggregability in the study cohort was 58.2 ± 20.7%. This baseline MPA was significantly lower in those diagnosed clopidogrel sensitive when compared with those diagnosed clopidogrel resistant (51.4 ± 19.9% vs. 74.3 ± 11.7%, $p < 0.001$) as depicted in Fig. 1.

Fig. 2 shows a comparison of 2 h platelet aggregation study after reloading of HTPR patients. Platelet aggregation showed a decrease at 2 h post-switching to any of three drug regimen. MPA reduced from 59.7 ± 5.2% to 42.6 ± 12.5% with clopidogrel reload patients vs 57.3 ± 3.7% to 15.80 ± 8.6% with prasugrel reload and 59.5 ± 7.8% to 14.6 ± 7.2% with ticagrelor reload. MPA was significantly low with prasugrel and ticagrelor reload as compared to clopidogrel reload

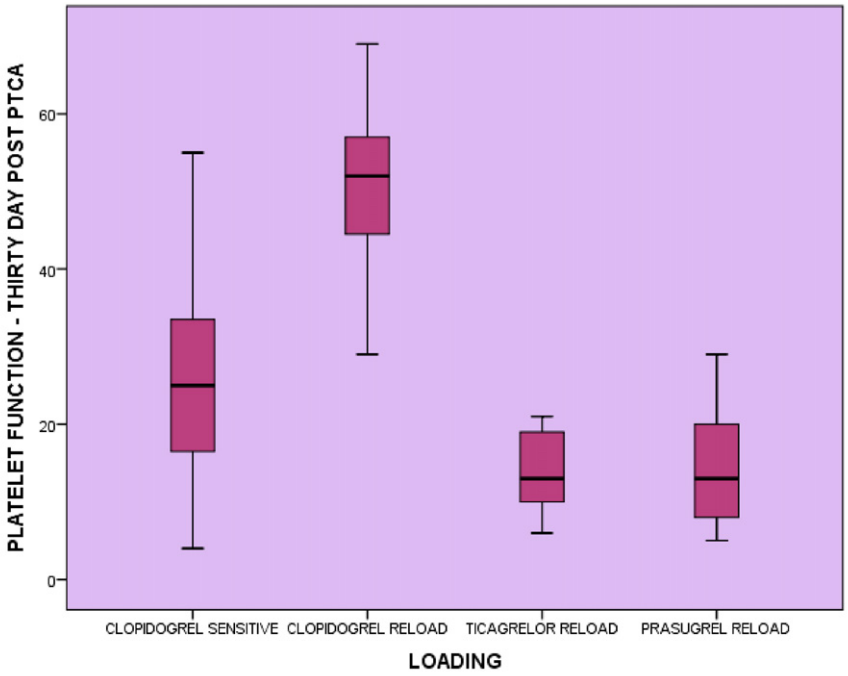
Table 3
Comparison of clopidogrel reload vs prasugrel reload vs ticagrelor reload.

	Clopidogrel reload (Gp. 1)	Ticagrelor reload (Gp. 2)	Prasugrel reload (Gp. 3)	p value (Gp. 1 vs Gp. 2)	p value (Gp. 1 vs Gp. 3)	p value (Gp. 2 vs Gp. 3)
2 h after reload platelet function	42.60 ± 12.48 (n = 10)	14.58 ± 7.20 (n = 12)	15.80 ± 8.64 (n = 10)	<0.001	<0.001	0.722
First day post-Ptca platelet function	43.71 ± 13.46 (n = 7)	12.67 ± 4.58 (n = 9)	15.40 ± 5.60 (n = 5)	<0.001	<0.001	0.341
Thirty Day post-Ptca Platelet function	50.43 ± 13.11 (n = 7)	13.89 ± 5.11 (n = 9)	15 ± 9.67 (n = 5)	<0.001	<0.001	0.780



	Clopidogrel Sensitive (52)	Clopidogrel Reload(7)	Ticagrelor Reload(9)	Prasugrel Reload(5)	P Value
First Day Post PCI Platelet Function	21.56 ±12.86	43.71 ±13.46	12.67 ±4.58	15.40 ± 5.59	<0.001

Fig. 3. Comparison of platelet function first day post-PCI between groups.



	Clopidogrel Sensitive(52)	Clopidogrel Reload(7)	Ticagrelor Reload(9)	Prasugrel Reload(5)	P Value
Thirty Day Post PCI Platelet Function	26.10 ±12.90	50.43 ±13.11	13.89 ±5.11	15 ± 9.67	<0.001

Fig. 4. Comparison of platelet function thirty day post-PCI between groups.

Table 4
Comparison of clopidogrel sensitive vs clopidogrel reload, prasugrel reload and ticagrelor reload.

	Clopidogrel sensitive Gp. 1	Clopidogrel reload Gp. 2	Ticagrelor reload Gp. 3	Prasugrel reload Gp. 4	p value (Gp. 1 vs Gp. 2)	p value (Gp. 1 vs Gp. 3)	p value (Gp. 1 vs Gp. 4)
First day post-Ptca platelet function	21.56 ± 12.87 (n = 52)	43.71 ± 13.46 (n = 7)	12.67 ± 4.58 (n = 9)	15.40 ± 5.60 (n = 5)	<0.001	0.341	0.297
Thirty day post-Ptca platelet function	26.10 ± 12.91 (n = 52)	50.43 ± 13.11 (n = 7)	13.89 ± 5.11 (n = 9)	15 ± 9.67 (n = 5)	<0.001	0.780	0.067

($p < 0.001$), while there was no difference between prasugrel or ticagrelor reload. (15.80 ± 8.6% vs 14.6 ± 7.2%, p = 0.722).

Table 3 and Fig. 3 shows comparison of MPA% of three treatment regimen in HTPR patients on day 1 post-PCI and Fig. 4 at day 30 post-PCI. At first post-PCI day, MPA were 12.6 ± 4.6%, 15.4 ± 5.6% and 43.7 ± 13.4% and at 30 day post-PCI were 13.9 ± 5.1%, 15 ± 9.7% and 50.4 ± 13.1% in ticagrelor, prasugrel and clopidogrel reload groups respectively. Clopidogrel reload group had significantly higher MPA as compared to prasugrel or ticagrelor at day 1 or at day 30 post-PCI ($p < 0.001$). No significant difference was observed between ticagrelor and prasugrel.

A comparison of MPA in clopidogrel sensitive group with all three treatment regimen for HTPR patients are depicted in Table 4. At first post-PCI day, MPA were 12.6 ± 4.6%, 15.4 ± 5.6%, 21.5 ± 12.9%, 43.7 ± 13.4% and at 30 day post-PCI, MPA were 13.9 ± 5.1%, 15 ± 9.7%, 26.1 ± 12.9%, 50.4 ± 13.1% in ticagrelor, prasugrel, clopidogrel sensitive and clopidogrel reload groups respectively. No significant difference was observed between ticagrelor, prasugrel and clopidogrel sensitive group at first day or at day 30 post-PCI. Clopidogrel reload group had significantly higher MPA as compared to clopidogrel sensitive group at day 1 or at day 30 post-PCI ($p < 0.001$).

50% of HTPR patients reloaded with clopidogrel continued to have HTPR after 2 h of reloading and same results were present at end of 30 days post-PCI whereas all patients loaded with prasugrel or ticagrelor had no HTPR at end of 2 h or at end of 30 days post-PCI.

3.4. MACCE

No cardiac death, myocardial infarction, Stent thrombosis, stroke and need for repeat revascularisation occurred during hospital stay or at post-PCI 30 day hospital visit in any of treatment groups.

3.5. Safety end points

Bleeding complications in different treatment groups is shown in Table 5.

At time of discharge, six clopidogrel sensitive patients experienced minor bleeding events; 4 radial haematomas, one femoral haematoma and one gum bleed. Among the HTPR patients, one patient each in clopidogrel reload group and ticagrelor loading group had radial haematoma. One patient had radial haematoma and one patient had nasal bleed in prasugrel group.

At 30 day post-PCI follow-up, in clopidogrel sensitive group one patient had skin petechiae, another patient had skin ecchymoses. One patient in ticagrelor group had skin ecchymoses. No TIMI major or TIMI moderate bleeding or deaths due to any cause occurred in any group at time of discharge or at 30 days post-PCI follow-up.

Table 5
Bleeding complication in different groups.

	Clopidogrel sensitive (n = 75)	Clopidogrel reload (n = 10)	Ticagrelor reload (n = 12)	Prasugrel reload (n = 10)
At time of discharge minor bleed	6 (8.0%)	1 (10%)	1 (8.3%)	2 (20%)
30 day minor bleed	8 (10.66%)	1 (10%)	2 (16.6%)	2 (20%)

4. Discussion

The present study revealed that about 30% patients had High on Treatment Platelet Reactivity (HTPR) after loading with 600 mg clopidogrel as assessed by 5 μM ADP Light transmission aggregometry (LTA) assay. HTPR observed in our population was higher than Kumar et al. study (15.3%) in Indian population; Gaglia et al. study (23.1%) in US population and The RECLOSE 2-ACS (14%) in European population [7,21,22]. There are however other studies which have observed a higher HTPR, like the GRAVITAS trial (40.8%), Breet et al. (42.4%) and Alexopoulos et al. (35.8%) in line with as observed by us [23,24,18].

Our study found no difference between clopidogrel sensitive and HTPR patient group in term of baseline characteristics. This is in contrast to RECLOSE 1 and RECLOSE 2-ACS study which showed HTPR to be associated with older age, previous history of MI, diabetes mellitus, hypercholesterolemia and low ejection fraction which were not correlated in our study [7,23,24]. Our results seem logical as resistance is related to genetic background. Clopidogrel resistance is primarily based on metabolic phenotype of hepatic cytochrome 2C19 (CYP2C19) genotype. Patients who are carriers of loss-of-function alleles in the CYP2C19 system have low clopidogrel active metabolite levels and are thus clopidogrel resistant [3,4]. Clopidogrel resistance is not evidenced by any of demographic features of the patient. Had this been so, it would have been easy to identify patients who could be clopidogrel resistant and we know from clinical knowledge, this is not so.

Our study assessed pharmacodynamic effects of clopidogrel reloading vs. switching to newer agents in this group of HTPR patients. We found that 50% (5/10) of HTPR patients reloaded with clopidogrel continued to have HTPR while the same was resolved completely in all the patients switched to the newer agents' viz. prasugrel or ticagrelor. Bonello et al. showed that even after 2400-mg loading dose of clopidogrel, 8% of patients continued to have HTPR [25]. The GRAVITAS trial showed that in patients with HTPR a higher maintenance dose clopidogrel (150 mg) led to a 22% lower prevalence of HTPR compared with standard-dose clopidogrel at 30 days and 6 months, an effect observed by us in the tune of 50% [23]. RECLOSE 2-ACS study revealed 38% of HTPR patients would still have HTPR after adjusting antiplatelet therapy to very high maintenance dose (300 mg) [7]. Thus with HTPR patients continued on different protocols of clopidogrel dosing only a small proportion could be brought in the clopidogrel sensitive range while large majority continued to have HTPR.

Reloading with newer P2Y12 receptor antagonist (ticagrelor/prasugrel) showed complete disappearance of clopidogrel resistant (HTPR) both at 2 h of reloading and during maintenance phase up to 30 days. These results were similar to those shown in study of Alexopoulos et al. and the SWAP 2 study [26,27]. Further, there was no intergroup difference between the two agents' viz. prasugrel and ticagrelor. HTPR patients receiving prasugrel/ticagrelor had MPA in the same range as clopidogrel sensitive patients or even better.

Thus in HTPR patients, patient should be reloaded with either prasugrel or ticagrelor for better pharmacodynamic effects, but whether it would lead to clinical outcome benefit is still not certain.

4.1. Limitations of study

Sample size of our study was small, so pharmacodynamics could be assessed but evaluation of clinical benefits was not possible.

4.2. Conclusion

In patients undergoing PCI exhibiting HTPR after clopidogrel loading, ticagrelor or prasugrel reloading produced improved platelet inhibition which was better than clopidogrel reload and this effect was sustained through maintenance phase up to 30 days post-PCI at least.

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