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Research Article

## Comparative Non-Randomised Observational Study of Prasugrel and Ticagrelor in Patients Undergoing Percutaneous Coronary Intervention

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### ABSTRACT

Percutaneous Coronary Intervention (PCI) is the primary guideline-recommended treatment strategy for patients presenting with CAD, STEMI, NSTEMI, Unstable Angina. It is known that, the use of oral P2Y<sub>12</sub> receptor antagonists (Prasugrel and Ticagrelor) in PCI patients could lead to improved outcomes compared with clopidogrel. This study has been designed for review and analysis of clinical safety and outcomes of these agents in patients undergoing PCI. Out of 100 patients (50 in Prasugrel group & 50 in Ticagrelor group) considered for the study, the incidence of stroke, stent thrombosis was comparable between the groups with  $P = 0.044$ ,  $P = 0.041$  respectively and was not comparable for MI ( $P = 0.245$ ). Single Death was reported. The results differed significantly for Palpitations/Arrhythmia ( $P = 0.018$ ), SOB ( $P = 0.000$ ), Dizziness ( $P = 0.005$ ), Creatinine levels ( $P = 0.000$ ), Fatigue ( $P = 0.003$ ), Headache ( $P = 0.000$ ) and did not differ significantly for Bleeding and Back pain in both the drug groups with  $P = 1.000$ ,  $P = 0.438$  respectively. Also, majority of the patients showed decreased platelet count in both the drug groups. Withdrawal parameters, like withdrawal due to cost ( $P = 0.172$ ) and withdrawal due to fear of side effects ( $P = 1.000$ ) when evaluated for both the drugs showed no significant difference. Outcomes associated with Prasugrel were not superior to outcomes associated with Ticagrelor when 30 days to 6 months follow up was done. The clinical safety, side effects and withdrawal parameters were comparable and the results showed no significant difference between these drug groups.

**Keywords:** Percutaneous Coronary Intervention, Ticagrelor, Prasugrel, Dual Anti-Platelet therapy, Acute Coronary Syndrome, Coronary Artery Disease.

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### INTRODUCTION:

High mortality rate in Indian population (range, 2.1%-6.7%), is due to Acute Coronary Syndrome which has become an overburden.<sup>1</sup> Another reason for the high mortality rate is Coronary Artery Disease. The treatment guidelines for patients with ACS and CAD is the dual antiplatelet therapy (DAPT).<sup>2</sup> The recent guidelines of the American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) recommended the use of the newer P2Y<sub>12</sub> inhibitors (Ticagrelor and Prasugrel) over Clopidogrel for patients with ACS undergoing PCI.<sup>3,4</sup> Compared with placebo, recurrent major adverse cardiovascular events (MACE) have been reduced among patients with stable Coronary Artery Disease or Acute Coronary Syndrome (ACS) with dual antiplatelet therapy.<sup>5</sup> The dual antiplatelet therapy is the combination of Aspirin

along with an Adenosine diphosphate receptor antagonist. Greater and more rapid platelet inhibition is provided by the third generation thienopyridine Prasugrel and the cyclopentyltriazolopyrimidine Ticagrelor than their antecedent clopidogrel.<sup>6</sup> After Percutaneous Coronary Intervention or Acute Coronary Syndrome, there was a considerable reduction in the risk of thrombotic events in patients who received dual antiplatelet therapy, but it has been associated with an increased risk of major bleeding.<sup>7</sup>

To date, there are few randomized clinical trial data directly comparing the safe and efficacy of Prasugrel with Ticagrelor. With the exception that Prasugrel may be better at reducing stent thrombosis, no apparent difference in major bleeding, the indirect comparisons showed no significant efficacy differences between the two drugs.<sup>8</sup> There are also few non-randomized trial data on this study which also showed no

significant difference between these two drugs. Based on the patient clinical presentation, baseline risk profile and management strategy, the choice of IDEAL DAPT regimen and duration for patients with CAD requires a customized approach.<sup>9</sup>

This study was undertaken as a non-randomized, prospective, observational study to compare the efficacy and safety of Prasugrel and Ticagrelor in patients undergoing Percutaneous Coronary Intervention and 30 days to 6 months follow-up was done succeeding the treatment.

#### Objectives:

- To observe the major adverse clinical outcomes during index hospitalization in 1 month after discharge.
- To access the safety and side effects of these drugs by using BARC (Bleeding Academic Research Consortium) Criteria for bleeding.

#### MATERIALS AND METHODS:

**Study Design:** A hospital based Prospective, Non-randomized Observational Study.

#### Study Site and Study Period:

This study was conducted for 6 months (i.e. September 2019 – February 2020) in Asia's first health city, Apollo Hospitals, Jubilee Hills, Hyderabad.

#### Sample Size:

The total numbers of patients included in this study are 100. Out of which, 50 patients were using Ticagrelor and 50 patients were using Prasugrel.

#### Method of Data Collection:

Subjects enrolled in the study were admitted in CICU and CSICU. Informed consent was obtained from all the subjects. The disease condition was evaluated after obtaining consent from each of them. Patient details including demographics, chief complaints, past medical history, family history, other comorbidities, physical examination, laboratory investigations, contact details and other relevant information has been collected from case reports. The patients who revisited the outpatient department of Cardiology, Apollo Hospitals were examined for side effects and clinical outcomes. The obtained clinical data and the results were re-examined and entered in the data collection forms and

further results obtained were tabulated and graphs were plotted.

#### Inclusion Criteria:

- Patients of age >18 years
- Patients who are conscious and co-operative.
- Patients who received Elective (or) Emergent PCI and are on medications-Ticagrelor/Prasugrel.
- Includes patients of both the gender.
- Patients who are willing to give information.

#### Exclusion Criteria:

- Patients who are not conscious, not co-operative and who cannot communicate verbally are excluded.
- Patients in cardiogenic shock.
- Patient with known bleeding diathesis.
- Patient with allergic/hypersensitivity to drug.
- Patient undergoing PABG (Penile Artery By-pass surgery).

#### Statistical Analysis:

Microsoft Office, Word 2010 and excel 2019 were used to produce the results in the form of charts and percentages.

SPSS Statistics Software (Version 1.0.0.86, Trial version) was used for statistical analysis with P value  $\leq 0.05$ . Multivariate analysis was used to compare Primary endpoints, Secondary endpoints and withdrawal parameters whereas Paired t-test was used to compare the platelet count before and after the medication use.

**Ethical Committee Approval No:** AHJ-028/10-19

#### RESULTS:

##### Patients Baseline Characteristics:

A total of 100 patients were enrolled in this study (n=50 in Prasugrel group and n=50 in Ticagrelor group). The entire baseline Demographics i.e. Sex, Age, Body Mass Index, Diagnosis along with the different Clinical laboratory tests i.e. Left Ventricular dysfunction and Angiographic lesion severity in two treatment groups are considered (Table-1).

TABLE 1: BASELINE CHARACTERISTICS OF PATIENTS WHO UNDERWENT PERCUTANEOUS CORONARY INTERVENTION (N=100)

Parameters	Ticagrelor (n=50)	Prasugrel (n=50)
Sex n, (%)		
Male	35(70%)	38(76%)
Female	15(30%)	12(24%)
Age n, (%)		
Early adulthood (19-35)	0(0%)	1(2%)
Adulthood (36-50)	10(20%)	20(40%)
Late adulthood (51-65)	24(48%)	24(48%)
Young old (66-74)	14(28%)	5(10%)
Old (75-84)	2(4%)	0(0%)
Old-old (>85)	0(0%)	0(0%)
BMI n, (%)		
Under weight (<18.5)	0(0%)	1(2%)
Healthy (18.5-24.9)	16(32%)	14(28%)
Overweight (25-29.9)	18(36%)	22(44%)
Obese (>30)	16(32%)	13(26%)
LV dysfunction n, (%)		
Normal	23(46%)	17(34%)
Mild	19(38%)	21(42%)
Moderate	2(4%)	7(14%)
Severe	6(12%)	5(10%)
Angiographic lesion severity n, (%)		
Single vessel disease	24(48%)	29(58%)
Double vessel disease	12(24%)	14(28%)
Triple vessel disease	14(28%)	7(14%)
Diagnosis n, (%)		
Unstable angina	18(36%)	14(28%)
STEMI	18(36%)	16(32%)
NSTEMI	14(28%)	20(40%)

BMI – Body Mass Index, LV – Left Ventricular, STEMI – ST-segment Elevation Myocardial Infarction, NSTEMI – Non-ST-segment Elevation Myocardial Infarction.

### Primary Endpoints:

The primary endpoints did not differ significantly in both the drug groups for Myocardial Infarction (P >0.05), whereas it

differed significantly in case of Stroke, Stent thrombosis and Death (P <0.05). The respective results for all the parameters are illustrated in Table-2 and corresponding graph is plotted (Figure-1).

TABLE 2: INTERGROUP COMPARISON OF PRIMARY ENDPOINTS

Primary endpoints	Ticagrelor n (%)	Prasugrel n (%)	P-value (intergroup)
1.No endpoints	44 (88%)	47(94%)	
2.MI	2 (4%)	1 (2%)	0.245(NS)
3.Stroke	0	1 (2%)	0.044(S)
4.Stent thrombosis	3 (6%)	1(2%)	0.041(S)
5.Death	1 (2%)	0	0.044(S)

NS – Non-Significant, S – Significant. Significance level,  $\alpha = 0.05$

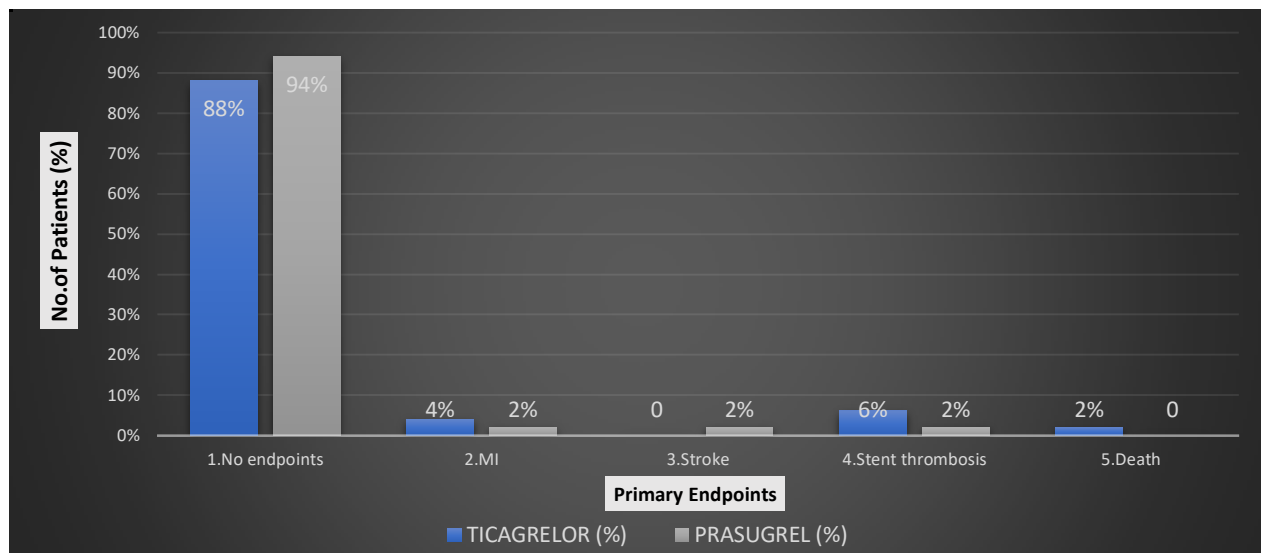


Figure 1: Comparison of primary endpoints (in %)

**Secondary Endpoints:**

The secondary endpoints differ significantly for Palpitations/Arrhythmia, SOB, Dizziness, Creatinine levels,

Fatigue, Headache (P <0.05) and did not differ significantly for Bleeding and Back pain in both the groups (P >0.05) which are demonstrated in detail in Table-3 and the respective graph is plotted (Figure-2).

TABLE 3: INTERGROUP COMPARISON OF SECONDARY ENDPOINTS.

Safety endpoints	Ticagrelor n (%)	Prasugrel n (%)	P-value (intergroup)
1.No endpoints	21(42%)	20(40%)	
2.Palpitations/Arrhythmia	2 (4%)	5(10%)	0.018(S)
3.SOB	10(20%)	3(6%)	0.000(S)
4.Creatinine Raised	5(10%)	0	0.000(S)
5.Dizziness	4(8%)	1(2%)	0.005(S)
6.Back Pain	3(6%)	4(8%)	0.438(NS)
7.Fatigue	2(4%)	6(12%)	0.003(S)
8.Headache	0	8(16%)	0.000(S)
9.Bleeding	3(6%)	3(6%)	1.000(NS)

NS – Non-Significant, S – Significant. Significance level, α=0.05

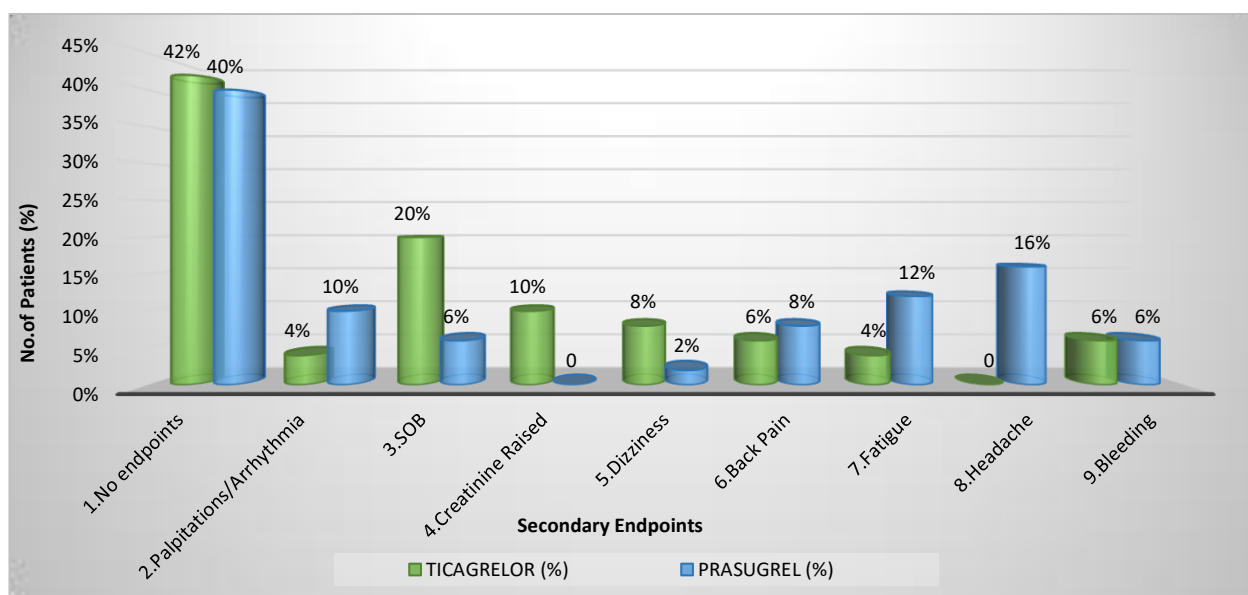


Figure 2: Comparison of Secondary Endpoints (in %).

**Withdrawal Parameters:**

The withdrawal parameters did not differ significantly in both the drug groups ( $P > 0.05$ ) that are illustrated in Table-4 and is also graphically represented (Figure-3).

TABLE 4: COMPARISON OF WITHDRAWAL PARAMETERS.

Parameter	Ticagrelor n = 50	Prasugrel n = 50	P-value (Intergroup)
1.No withdrawal	44 (88%)	47 (94%)	
2.Due to cost	4 (8%)	1 (2%)	0.172 (NS)
3.Due to fear of side effects	2 (4%)	2 (4%)	1.000 (NS)

NS – Non-Significant, Significance level,  $\alpha = 0.05$

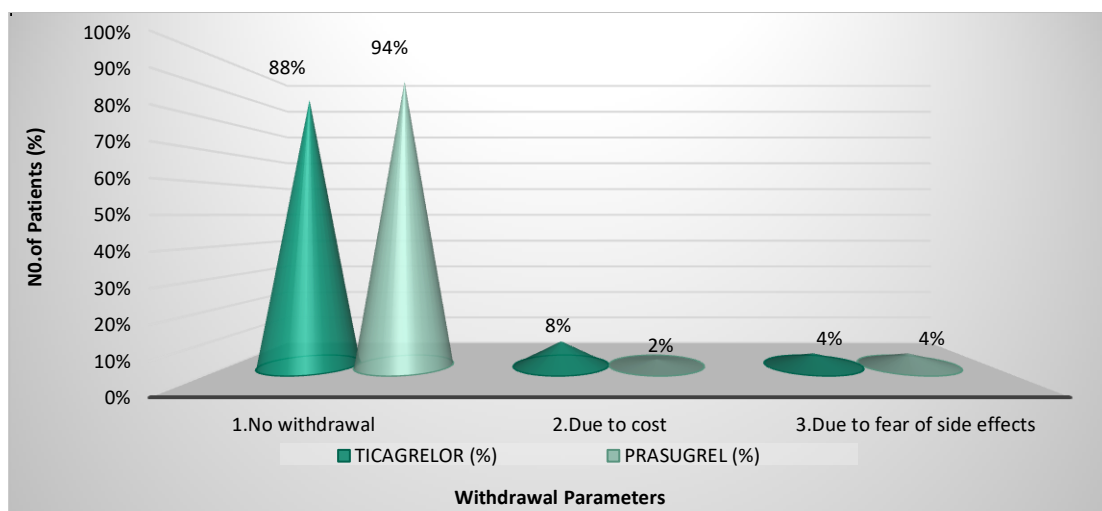


Figure 3: Comparison of Withdrawal Parameters (in %).

**Platelet count before and after the use of Anti-Platelet medications:**

Platelet count is one of the factors that relates directly to the efficacy of Anti-platelet medications. Statistical analysis was

made using Paired t-test at Confidence Interval of 95% (Table 5). The platelet count was decreased from 292.34 (Mean of the platelet count before use of medications) to 239.60 (Mean of the platelet count after the use of medications).

TABLE 5: PLATELET COUNT BEFORE AND AFTER PCI (I.E. USE OF ANTI-PLATELET MEDICATIONS).

**Paired Samples Test**

	Paired Differences						T	df	Sig. (2-tailed)
	Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference					
				Lower	Upper				
Pair 1 Platelets before PCI - Platelets after PCI	52.74000	65.90177	6.59018	39.66366	65.81634	8.003	99	.000	

Significance level,  $\alpha = 0.05$ , Confidence Interval – 95%

**DISCUSSION:**

Percutaneous coronary intervention (PCI) is the primary guideline-recommended treatment strategy for patients presenting with CAD, STEMI, NSTEMI, Unstable Angina.<sup>10</sup> For patients diagnosed with CAD and undergoing Percutaneous Coronary Intervention (PCI), newer oral

P2Y12 receptor antagonists (i.e. Prasugrel and Ticagrelor) are recommended over clopidogrel.<sup>11,12</sup> Following PCI, the adverse events associated were reduced with the addition of oral platelet P2Y12 ADP receptor inhibitors along with Aspirin. Therefore, dual-antiplatelet therapy (DAPT) in PCI patients has been recommended for use before and after the procedure for a minimum period of 6-12 months.<sup>13</sup> As the

superiority of one agent over the other remains unclear in Indian population, research has been ongoing for further evaluation of these drugs.

This prospective, non-randomised observational study has been designed for review and analysis of these agents (Prasugrel and Ticagrelor) in patients undergoing PCI. The findings obtained from this study may recommend that the use of either Prasugrel or Ticagrelor in PCI patients could lead to improved outcomes.

The comparative effectiveness and safety evaluation between prasugrel and ticagrelor were presented in this observational study. Primary end points include Myocardial Infarction (MI), Stroke, Stent Thrombosis and Death whereas the Secondary end points include Palpitation/Arrhythmia, SOB, Dizziness, Creatinine levels, Fatigue, Headache, Back pain and Bleeding.

In this Prospective Non-randomized Observational study, a total of 100 patients were considered in the ratio of 1:1 (Ticagrelor and Prasugrel). Out of 100 patients, males were found to be dominant<sup>14</sup> (70% in Ticagrelor group & 76% in Prasugrel group) compared to females (30% in Ticagrelor group & 24% in Prasugrel group).

The total population was divided into different age groups according to the WHO guidelines i.e., early adulthood (19 – 35years), adulthood (36 – 50years), late adulthood (51 – 65years), young old (66 – 74years), old (75 – 84years), old-old (> 85years). Most of the patients using these two drugs were found to be in late adulthood<sup>15</sup> (48% in Ticagrelor group & 48% in Prasugrel group).

The total population was distributed based on BMI into different groups<sup>16</sup> i.e., Underweight (< 18.5), Healthy (18.5-24.9), Over weight (25.0-29.9), Obese (>30). Distribution of patients that were found to be in Healthy group are (32% in Ticagrelor & 28% in Prasugrel), Over weight (36% in Ticagrelor & 44% in Prasugrel), Obese (32% in Ticagrelor & 26% in Prasugrel).

According to the study conducted, the patients were found to be diagnosed with CAD, STEMI, NSTEMI, Unstable Angina.<sup>8</sup>

Based on the 2D- ECHO results, we considered LV function of the patients<sup>17</sup> and divided into categories of Normal(46% of patients in Ticagrelor & 34% of patients in Prasugrel), Mild(38% of patients in Ticagrelor & 42% of patients in Prasugrel), Moderate(4% of patients in Ticagrelor & 14% of patients in Prasugrel) and Severe (12% of patients in Ticagrelor & 10% of patients in Prasugrel).

The patients are further divided based on the number of vessels involved. Patients with single vessel disease were found to be 48% in Ticagrelor group & 58% in Prasugrel group, double vessel disease were found to be 24% in Ticagrelor group & 28% in Prasugrel group and triple vessel disease were found to be 28% in Ticagrelor group & 14% in Prasugrel group. Thus, most of patients were found to be having Single Vessel Disease.<sup>18</sup>

This study reported that prasugrel and ticagrelor did not differ significantly for their clinical efficacy. Clinical Safety and Tolerance were comparable in both the groups in patients who underwent PCI at the end of 6 months.<sup>1</sup>

In this study Stent Thrombosis was comparable between both the groups<sup>1</sup>, with 3(6%) patients in Ticagrelor group and 1(2%) patient in Prasugrel group. Based on the statistical tests applied for this parameter, the p-value was found to be non-significant. Therefore, there is no significant difference in both these drug groups.

Prasugrel group reported less MI events compared to Ticagrelor group i.e., (2% and 4% respectively). Prasugrel group were found with 2% of stroke cases & no cases were found in Ticagrelor group. Single Death case was reported in Ticagrelor group.

One of the factors that directly relates to the efficacy of ticagrelor and prasugrel is the platelet count. Majority of the patients showed decreased platelet count in both the drug groups.<sup>19</sup> The results showed significant difference in the platelet count when paired 't' test method was used statistically.

In the Intergroup Comparison of ticagrelor and prasugrel, the secondary endpoints showed the following results. Overall, Backpain and Bleeding showed no significant difference between these two drug groups at 6-months follow-up.<sup>6</sup>

Palpitations/Arrhythmia was found in 2 patients of Ticagrelor group and 5 patients in Prasugrel group.<sup>6</sup>

Shortness of breath was not frequently reported in prasugrel group when compared to Ticagrelor group. Higher rate of incidence of SOB was found in Ticagrelor group.<sup>20</sup>

In other secondary endpoints like, Dizziness, Creatinine levels, Fatigue and Headache showed significant difference between these two drug groups when multivariate statistical method was applied.<sup>6</sup>

Both Prasugrel and Ticagrelor have been approved by ICP (International Clinical Practice) Guidelines for the prevention of Secondary thrombotic events in patients with ACS. However, there is a difference in the cost of these drugs. India has been able to lift a significant percentage of its population out of poverty, but many still live in it. So, there is a chance of withdrawal of the drug by the subjects since they may not be able to afford for the treatment. Also, the drug usage may be discontinued by few because of the unusual effects caused by them after using for a particular period of time. Considering this situation of Indian population, withdrawal parameters i.e. withdrawal due to cost and withdrawal due to fear of side effects are included in this study. The results obtained from these two parameters, showed no significant difference between these two drug groups.<sup>21</sup>

## CONCLUSION:

Overall, the Comparison of efficacy and safety of Ticagrelor and Prasugrel in patients undergoing PCI showed minimal differences in both drug groups because of the low sample size considered. Thus, we conclude that both the Anti-platelet drugs are equally efficacious.

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**Conflict of interest:** There are no conflicts of interests.

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