

## COMPARATIVE EVALUATION OF EFFICACY AND SAFETY OF ASPIRIN + CLOPIDOGREL WITH ASPIRIN+TICAGRELOR IN PATIENTS WITH CARDIOVASCULAR DISEASES. AN OBSERVATIONAL STUDY.

Dr. Pinki Saini<sup>1</sup>, Dr. Poonam Patel<sup>2</sup>, Dr. Murtuza Bhora<sup>3</sup>, Dr. S. Tripathi<sup>4</sup> & Dr. P. Nyati<sup>5</sup>

PG Resident<sup>1</sup>, Associate Professor<sup>2</sup>, Assistant Professor<sup>3</sup>, Professor<sup>4</sup>, Professor & Head<sup>5</sup>

Department of Pharmacology, Index Medical College, Indore<sup>1,2,3,4&5</sup>

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**Address for Correspondence:** Dr. Poonam Patel, Associate Professor, Department of Pharmacology, Index Medical College, Indore

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### Abstract

**Background:** Coronary artery disease (CAD) is one of the most common causes of mortality and morbidity in both developed and developing countries. It is a leading cause of death in India, and its contribution to mortality is rising. Platelets play an essential role in the pathogenesis of acute coronary syndromes (ACS). Therefore an important part of the treatment of ACS, and of primary and secondary preventive measures in coronary heart disease, consists of antiplatelet treatment. Dual antiplatelet therapy (DAPT) provides more intense platelet inhibition than single antiplatelet therapy resulting in incremental reductions in the risk of thrombotic events after percutaneous coronary intervention (PCI) or ACS, but it has been associated with an increased risk of major bleeding. It is interesting to consider that there is no Indian data on the efficacy of recently developed antiplatelet drugs other than in combination with aspirin, and that we remain unaware of the extent to which combinations with aspirin improve efficacy but increase risk.

**Methodology:** Study was prospective, observational clinical study carried out in the Department of Medicine, of Index Medical College Hospital & Research Centre. A total of 80 patients with CAD were enrolled for the study and were equally divided in two groups each of 40 for evaluating efficacy and safety of dual antiplatelet therapy. Follow-up was done at 8 weeks, 16 weeks, and 24 weeks, patients were asked to provide information regarding their current medications, any morbidity and their complications [if any]. Demographic parameters were analyzed by descriptive statistics. Comparison between groups was done by Chi-square Test. Survival analysis was done by suitable statistical method.

**Result:** The median age was 55 years in group 1 and 57 years in group 2. Hypertension was most common associated disorders in group 1 [25 (62.55%)] and group 2 [27 (67.5%)], which was followed by diabetes and dyslipidemia. index events for present study enrolment was unstable angina, non-ST-segment elevation MI, ST-segment elevation MI and others amongst the study groups. With 6 months of follow-up, the rate of the primary event like death from any cause was 7.5 percent in the clopidogrel

plus aspirin group and 2.5 percent in the ticagrelor plus aspirin group. The primary safety end point (severe bleeding) was 2.5 % in the clopidogrel plus group 1 and none in group 2.

**Conclusion:** the combination of clopidogrel plus aspirin was found to be non inferior to aspirin plus ticagrelor dual therapy in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes among patients with stable cardiovascular disease or multiple cardiovascular risk factors. The risk of moderate to severe bleeding was increased slightly in both the groups. Our findings do support the use of dual antiplatelet therapy across the broad population tested where single antiplatelet therapy are not giving maximum benefits

**Keywords:** Acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), Coronary artery disease (CAD), Dual antiplatelet therapy (DAPT)

### Introduction:

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels and they include<sup>1</sup> coronary heart disease, cerebrovascular disease, Peripheral arterial disease, Rheumatic heart disease, Congenital heart disease, Deep vein thrombosis and Pulmonary embolism. Cardiovascular diseases remain the most common causes of death, responsible for 35% of all deaths, almost 1 million deaths each year. Approximately one-fourth of these deaths are sudden. In addition, cardiovascular diseases are highly prevalent, diagnosed in 80 million adults, or ~35% of the adult population<sup>2</sup>. Ischemic heart disease (IHD) and stroke constitute the majority of CVD mortality in India (83%), with IHD being predominant<sup>3</sup>. The ratio of IHD to stroke mortality in India is significantly higher than the global average, and is comparable to that of Western industrialized countries. Most cardiovascular diseases can be avoided or delayed by cut shorting the risk factors such as tobacco use, unhealthy diet and obesity, physical inactivity and harmful use of alcohol using population-wide strategies. People with cardiovascular disease or who are at high cardiovascular risk (due to the presence of one or more risk factors such as hypertension, diabetes, hyperlipidaemia or already established disease) need early detection and management using counselling and medicines, as appropriate<sup>4</sup>. Atherosclerosis is a chronic inflammatory process that is known to be the underlying cause of coronary artery disease (CAD)<sup>5</sup>. In addition to being the first step of primary hemostasis, platelets play a pivotal role in the thrombotic

process that follows rupture, fissure, or erosion of an atherosclerotic plaque<sup>6</sup>. Because atherothrombotic events are essentially platelet-driven processes, this underscores the importance of antiplatelet agents, which represent the cornerstone of treatment, particularly in the settings of patients with acute coronary syndromes (ACS) and undergoing percutaneous coronary intervention (PCI). Platelets play an essential role in the pathogenesis of acute coronary syndromes (ACS)<sup>7</sup>. Therefore an important part of the treatment of ACS, and of primary and secondary preventive measures in coronary heart disease, consists of antiplatelet treatment. Over the years antiplatelet treatment has evolved and currently several types of antiplatelet drugs are available, each with their specific pharmacological target and with their specific clinical indications. Dual antiplatelet therapy (DAPT) comprising of aspirin and a P2Y12 inhibitor is one of the most commonly prescribed therapies in cardiovascular medicine. Dual antiplatelet therapy (DAPT) provides more intense platelet inhibition than single antiplatelet therapy resulting in incremental reductions in the risk of thrombotic events after percutaneous coronary intervention (PCI) or ACS, but it has been associated with an increased risk of major bleeding. It is interesting to consider that there is no Indian data on the efficacy of recently developed antiplatelet drugs other than in combination with aspirin, and that we remain unaware of the extent to which combinations with aspirin improve efficacy but increase risk.

Therefore this observational study was planned with aim to evaluate the safety and efficacy of antiplatelet drugs in combination Group 1 [patients under aspirin plus clopidogrel], group 2 [aspirin plus ticagrelor] in patients with cardiovascular disorders in Indian populations.

Our Primary Objectives were: 1. To evaluate the safety and efficacy of antiplatelet drugs in combination Group 1 [aspirin + clopidogrel], and group 2 [aspirin + ticagrelor] in patients with CAD.

2. To evaluate any cardiovascular/ atherothrombotic events on patients with antiplatelet therapy.

3. To study the primary bleeding endpoint, is the time to first occurrence of clinically relevant bleeding, defined as Bleeding Academic Research Consortium (BARC) Types 2, 3 or 5 bleeding.

4. To find out percentage of complications [side effect like gastrointestinal and/or nervous and/or allergic manifestations] in patients on antiplatelet drugs regimen attending Medicine OPD

## Methods

Study was prospective, observational clinical study carried out in the Department of Medicine, of Index Medical College Hospital & Research Centre. Permission from the Institutional Ethics Committee was obtained before starting research work. All decisions relating to management of the patient including drugs and investigations was taken by the treating physician only. Investigator did not interfere in the management of patient and only observed the proceedings. Subjects and their accompanying family members were interviewed by pre-structured questionnaire, and past and present prescriptions and case notes, wherever available, were obtained and reviewed. Data regarding anti-platelet mono-therapy and combination therapy were recorded. Other co-administered drugs was recorded. A total of 80 patients with CAD were enrolled for the study with 40 subjects in each group, Group 1 [aspirin + clopidogrel] and group 2 [aspirin + ticagrelor].

Follow-up was done at 8 weeks, 16 weeks, and 24 weeks, patients were asked to provide information regarding their current medications, any morbidity and their complications [if any].

## Inclusion Criteria:

- 1) Subjects who was suffering from cardiovascular disorders and prescribed antiplatelet drugs at Medicine O.P.D.
- 2) Adult patient's  $\geq 18$  years of age of both the sex was included.
- 3) CAD patients with co-morbidities like diabetes mellitus, ischemic heart diseases, congestive heart failure and chronic renal diseases were also included in the study.
- 4) Those who understood the purpose of the study and were ready to provide information regarding their health status along with a signed informed consent document.

## Exclusion Criteria:

- 1) Under 18 years of age
- 2) Contraindication to antiplatelet agents like aspirin, ticagrelor etc.
- 3) Planned surgery within 90 days
- 4) Planned coronary revascularization (surgical or percutaneous) within 90 days
- 5) Need for chronic oral anticoagulation
- 6) Dialysis-dependent renal failure
- 7) Active bleeding or extreme-risk for major bleeding (e.g. active peptic ulcer disease, gastrointestinal pathology with a raised risk for bleeding, malignancies with a raised risk for bleeding)
- 8) Salvage PCI or STEMI presentation
- 9) Liver cirrhosis
- 10) Unable or unwilling to provide informed consent
- 11) Women of child bearing potential (as determined by hospital standard of care)
- 12) Fibrinolytic therapy within 24 hours of index PCI

13) Patients with thrombocytopenia or any other hematological abnormality. Any conditions resulting in severe learning disability (e.g. brain injury).

14) Those unable to comprehend for other reasons will be excluded from the study.

**Statistical Analysis Plan:**

- 1) Demographic parameters was analyzed by descriptive statistics
- 2) Comparison between groups was done by Chi-square Test
- 3) Survival analysis by suitable statistical method

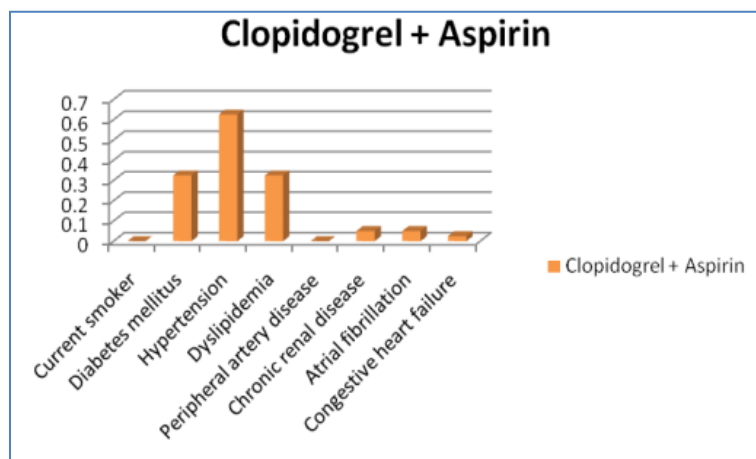
**Results**

A total of 80 patients with CAD were enrolled for the study and equally divided in two groups to see efficacy and safety of dual antiplatelet therapy. The median age was 55 years in group 1

and 57 years in group 2; 22.5 percent and 17.5% of the patients were women in group 1 and group 2 respectively. Majority of the participants were male in both the groups [group 1, 77.5% & group 2, 82.5%] table1. Hypertension was most common associated disorders in group 1 [25 (62.55%)] fig.1 and group 2 [27 (67.5%)] fig.2, which was followed by diabetes and dyslipidemia. Good numbers of study participants were chronic smokers. Percentage of index events for present study enrolment was unstable angina (27.5%/37.5%), non-ST-segment elevation MI (30%/27.5%), ST-segment elevation MI (40%/ 35%) and others (2.5%/0) fig.3 among the study groups. Three quarters took a statin, and more than half took a beta-blocker, proton pump inhibitors. Nearly one thirds took a diuretics, ACE inhibitor or angiotensin II-receptor blocking agents.(fig.4)

**Table 1: Baseline Characteristics of study participants**

Characteristic	Clopidogrel plus Aspirin (N = 40) [Group 1]	Ticagrelor plus Aspirin (N = 40) [Group 2]
Demographic characteristics		
Age — yr	51.01±11.62	52.08±10.98
Median	55	57
Range	39-83	40-79
Age groups		
<40 yrs	6 (15%)	4 (10%)
40-60 yrs	23 (57.5%)	21 (52.5%)
>60 yrs	11(44%)	15 (37.5%)
Sex [M/F]	31[ 77.5%]/9 [22.5%]; 3.44:1	33[82.5%]/7[17.5%]; 4.71:1



**Figure 1: Distribution of cardiovascular risk factors among group1 patients**

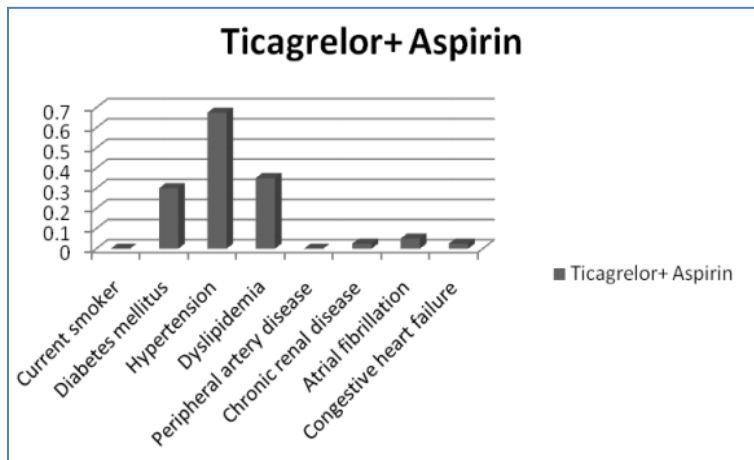


Figure 2: Distribution of cardiovascular risk factors among group 2 patients

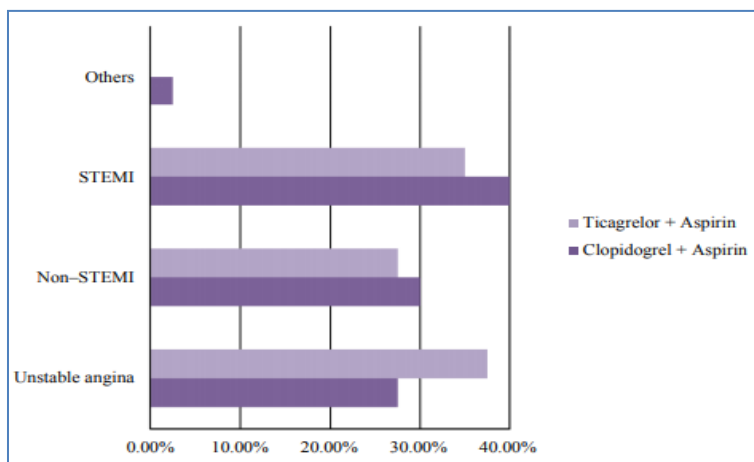


Figure 3: Distribution of present cardiovascular index events among study participants

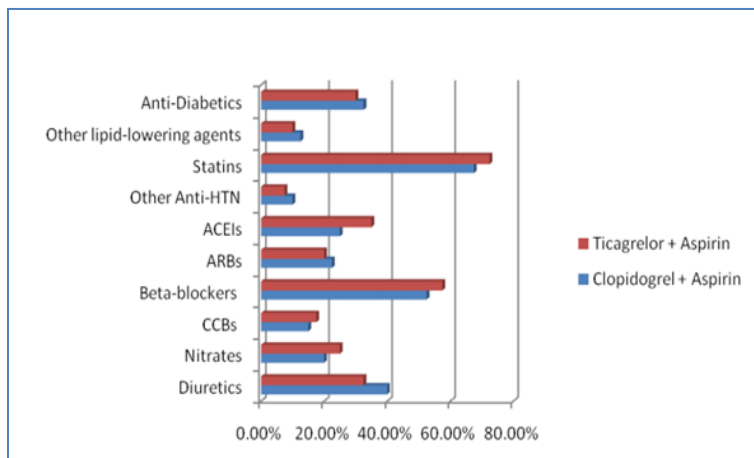


Figure 4: Percentage of concomitant medication intake by study participants

With 6 months of follow-up, the rate of the primary event like death from any cause was 7.5 percent in the clopidogrel plus aspirin group and 2.5 percent in the ticagrelor plus aspirin group

(relative risk, 1.5; 95 percent confidence interval, 0.2647 to 8.5010; P = 0.6469). The rate of the principal secondary efficacy end point (the first occurrence of myocardial infarction, stroke, or

hospitalization for unstable angina, transient ischemic attack, or a revascularization procedure) was 10 percent in the clopidogrel plus group, as compared with 7.5 percent in the ticagrelor plus group 2 (relative risk, 1.33; 95 percent confidence interval, 0.3186 to 5.5793; P = 0.6936). table2

The rate of the primary safety end point (severe bleeding according to the GUSTO definition) was 2.5 percent in the clopidogrel plus group 1 and none in group 2. The rate of moderate bleeding was 5% percent in the ticagrelor group, as compared with zero percent in the clopidogrel

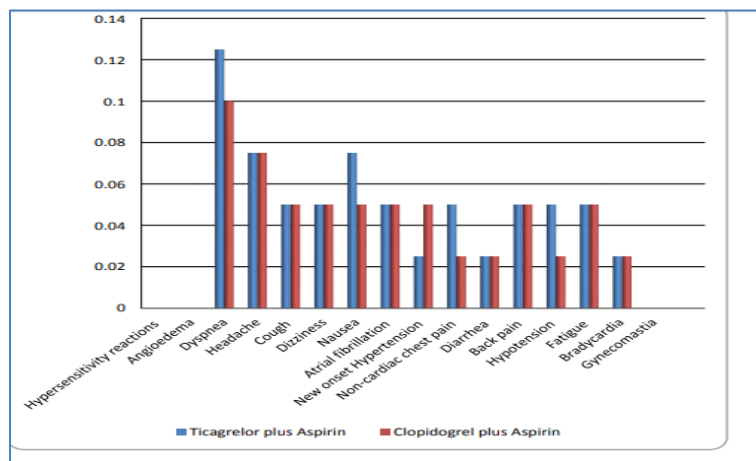
plus aspirin group. The rate of intracranial hemorrhage was 5% and 2.5% in the two treatment groups respectively. About 12.5% and 10% of patients treated ticagrelor plus aspirin and clopidogrel plus aspirin developed dyspnea respectively. Dyspnea was usually mild (majority of the reported cases) to moderate in intensity which led to study drug discontinuation and often resolved during continued treatment. Only few cases serum uric acid levels increased approximately 0.75 mg/dL from baseline on group 1 and approximately 0.38 mg/dL on group 2. (Fig 6)

**Table 2: Safety and efficacy outcomes among participants in two groups**

Outcome	Clopidogrel plus Aspirin (N = 40) [Group 1]	Ticagrelor plus Aspirin (N = 40) No. of patients (%)	(95% CI)	P Value
<b>Primary end point</b>				
-Death from any cause	3 (7.5%)	2 (5%)	95% CI - 10.0104 to 15.3827	P = 0.6462
-Death from cardiovascular causes	2 (5%)	2 (5%)	95% CI - 12.0594 to 12.0594	P = 1.0000
-Myocardial infarction (nonfatal)	3 (7.5%)	3 (7.5%)	95% CI - 13.3058 to 13.3058 –	P = 1.0000
-Stroke (fatal)	1 (2.5%)	0		
-Ischemic stroke (nonfatal)	0	0		
-Stroke (nonfatal)	1 (2.5%)	1 (2.5%)	95% CI - 10.5833 to 10.5833	P = 1.0000
<b>Secondary efficacy end point</b>				
Hospitalization for unstable angina, transient ischemic attack, or revascularization	4 (10%)	3 (7.5%)	95% CI - 11.2616 to 16.4470	P = 0.6942
<b>Safety end points</b>				
Major bleeding	1 (2.5%)	0	-	
-Moderatebleeding	0	2 (5%)	-	
Minor bleeding	5 (12.5%)	3 (7.5%)	95% CI - 9.2282 to 19.4728	P = 0.4589

**Table 3: Types of Bleeding among study participants**

Bleeding Type	Mild	Moderate	Severe
Conjunctival	0	0	0
Epistaxis	1 (2.5%)	0	0
Gastrointestinal	4 (10%)	1 (2.5%)	1 (2.5%)
Gingival	0	0	0
Hemoptysis	0	0	0
Hematuria	0	0	0
Intracranial	2 (5%)	1 (2.5%)	0
Intraocular	0	0	0
Puncture site	1 (2.5%)	0	0
Retroperitoneal	0	0	0
Surgical	0	0	0
Other	0	0	0



**Figure 6: Percentage of patients reporting non-hemorrhagic adverse events in either group**

**Discussion:**

Atherosclerotic vascular disease has a propensity to engender arterial thrombosis, a sequence that has been characterized as an atherothrombotic process<sup>7,8</sup>.

Collectively, atherothrombotic disorders of the coronary, cerebrovascular, and peripheral arterial circulation are the leading cause of death and disability in the world<sup>9</sup>. Their prevalence is increasing, and better means of prevention are needed<sup>10</sup>. Platelets have been shown to play a major role in the pathogenesis of atherothrombosis<sup>7,8</sup>. Low-dose aspirin has been shown to reduce ischemic outcomes in patients above a certain risk threshold<sup>11</sup>. However, aspirin

alone in many instances is not sufficient to prevent ischemic events in patients at high risk. Furthermore, aspirin inhibits only the cyclooxygenase pathway, leaving the adenosine diphosphate P2Y12 receptor unaffected. Dual antiplatelet therapy with clopidogrel, a P2Y12-receptor antagonist, plus aspirin has been shown to reduce ischemic events in patients with unstable angina, myocardial infarction without ST segment elevation, or myocardial infarction with ST-segment elevation, as well as those undergoing angioplasty and stenting<sup>12,13,14,15</sup>.

In our study the median age of the patient was 55 years in group 1 and 57 years in group 2; 22.5 percent and 17.5% of the patients were women

in group 1 and group 2 respectively. Study by Kang HJ et al (2015) showed Asian patients were slightly but significantly younger and had lower body weight and body mass index than non-Asian patients<sup>16</sup>. Hypertension was most common associated disorders in group 1 [25 (62.55%)] and group 2 [27 (67.5%)], which was followed by diabetes and dyslipidemia. Good number of study participants was chronic smokers. There were cases of previous ischemic stroke, previous TIA, previous myocardial infarction, and prior percutaneous coronary intervention/ PCI in both the groups. Median baseline SBP blood pressure was noted 152 and 156 mg Hg in the study groups. Percentage of index events for present study enrolment was unstable angina (27.5%/37.5%), non-ST-segment elevation MI (30%/27.5%), ST-segment elevation MI (40%/ 35%) and others (2.5%/0) among the study groups.(Fig3). PLATO Trial revealed that cardiovascular risk factors like current smoking status and diabetes mellitus were more common in Asian patients; hypertension and dyslipidemia were more common in non-Asian patients. Asian patients less commonly reported a previous MI or coronary revascularization, but a history of nonhemorrhagic stroke was more common in Asian patients. At the time of randomization, the most common type of ACS event in Asian patients was ST-segment elevation MI, whereas non-ST-segment elevation MI was more common in nonAsian patients<sup>16</sup>. Study by Zhao Q et al (2018) identified in their study that the patients had mean age of  $63.6 \pm 8.2$  years, were prevalent men (81.8%), and traditional ischemic risk factors were well represented (diabetes mellitus 43.4%, smoking 49.2%, hypertension 73.8%, hyperlipidaemia 72.2%). Unstable angina was the most common clinical presentation (62.8%)<sup>17</sup>.

Aspirin is an irreversible cyclooxygenase-1 inhibitor indicated to reduce the risk of recurrent vascular events in patients with a history of cardiovascular disease<sup>18</sup>. In the present study almost all the patients (aside from those who died or dropped out) took aspirin and the either clopidogrel/ticagrelor drug in combination. Three

quarters took a statin, and more than half took a beta-blocker, proton pump inhibitors. Nearly one thirds took a diuretics, ACE inhibitor or angiotensin II-receptor blocking agents [Fig 4]. PLATO Trial revealed that concomitant medication was also significantly different between the 2 groups. In Asian patients, a lower proportion was treated with aspirin,  $\beta$ -blocker, statin, and glycoprotein IIb/IIIa inhibitor at baseline. A higher proportion of Asian patients than non-Asian patients had a planned invasive strategy<sup>16</sup>.

The proportion of antiplatelet drug users at 6 months found in the present study was similar to that found in the EuroAspire III survey in the Netherlands<sup>19</sup>. Study had shown that the proportion of MI patients who persistently used antiplatelet drugs was relatively high in the first year, it was not optimal. A discontinuation of antiplatelet drugs early after CHD and PCI might lead to a recurrent ACS event<sup>20,21</sup>. In the present study, the non persistent user proportion at 6 months was driven mostly by early discontinuation due to moderate to severe bleeding. But they restarted dual antiplatelet therapy once their complications were resolved within a gap of few weeks. Decision of restarting antiplatelet therapy purely decided by treating physician based on seriousness of adverse events and how first patients recovered the study by Yasmina A et al (2017) showed that in 30% of the patients who discontinued antiplatelet drugs within 6 months after the first MI, a recurrent ACS occurred within 6 months after the discontinuation date<sup>21</sup>. Early antiplatelet discontinuation might be caused by drug intolerance, major bleeding, invasive procedures, co-medications and patient-related factors<sup>20, 22</sup>. The average adherence to any antiplatelet drug and aspirin was relatively high, while clopidogrel adherence was low<sup>22</sup>. A study by Tuppin et al., in France, showed an approximately similar proportion (81.7%) of adherent users of antiplatelet drugs (aspirin and clopidogrel)<sup>23</sup> to that in our study (78.9%). Another study, in Italy, showed a lower proportion of adherent antiplatelet drug users (58.7%)<sup>24</sup>. The population

of MI patients in our study were, on average, younger than that in the Italian study. Younger patients tend to be more adherent to treatment than older patients<sup>23</sup>, as also observed in the present study. However, even the older patients in the present study showed a high adherence to antiplatelet drugs.

With a median of 6 months of follow-up, the rate of the primary event like death from any cause was 7.5 percent in the clopidogrel plus aspirin group and 2.5 percent in the ticagrelor plus aspirin group (relative risk, 1.5; 95 percent confidence interval, 0.2647 to 8.5010;  $P = 0.6469$ ) [Table 2]. the rate of the principal secondary efficacy end point (the first occurrence of myocardial infarction, stroke, or hospitalization for unstable angina, transient ischemic attack, or a revascularization procedure) was 10 percent in the clopidogrel plus group, as compared with 7.5 percent in the ticagrelor plus group 2 (relative risk, 1.33; 95 percent confidence interval, 0.3186 to 5.5793;  $P = 0.6936$ ).

The rate of the primary safety end point (severe bleeding according to the GUSTO definition) was 2.5 percent in the clopidogrel plus group 1 and none in group 2. The rate of moderate bleeding was 5% percent in the ticagrelor group, as compared with zero percent in the clopidogrel plus aspirin group. The rate of intracranial hemorrhage was 5% and 2.5% in the two treatment groups respectively (table 3).

In this observational study of secondary prevention in patients with cardioembolic ischemic stroke and transient ischemic attack who underwent dual antithrombotic therapy after symptom onset and who did not receive thrombolytic therapy, events included in the primary end point — a composite of stroke, myocardial infarction, or death — were not less common among patients who received ticagrelor plus aspirin than among patients who received clopidogrel plus aspirin during the 180-days follow-up period. There was no evidence of a higher risk of major or intracranial hemorrhage with ticagrelor plus aspirin than clopidogrel with

aspirin, but there were more instances of dyspnea and less minor bleeding in the ticagrelor group. In a large, international trial of secondary prevention by Johnston SC et al (2016)<sup>25</sup> the results were same. In the PLATO study, the primary efficacy end point and net clinical benefits favoured ticagrelor compared with clopidogrel<sup>26, 27</sup>. In the present study, the net clinical benefits of ticagrelor group compared with clopidogrel were not different between patients, although there were differences in baseline characteristics and cardiovascular event rates between groups. Similarly, there was no significant heterogeneity in effects of ticagrelor plus aspirin group compared with clopidogrel plus aspirin on efficacy, bleeding, and other safety end points. The overall net clinical benefit of ticagrelor plus aspirin was primarily the result of reduced cardiovascular events, exceeding the observed increase of major bleeding in patients. In the PLATO (Platelet Inhibition and Patient Outcomes) trial, researchers looked at patients hospitalized for an ACS event who were about to receive medical or invasive management. They found that ticagrelor was associated with a significantly greater reduction in the rate of cardiovascular events and cardiovascular death compared with clopidogrel (9.8% vs 11.7%;  $P=.003$ ). They also found that ticagrelor reduced the rate of all-cause mortality (4.5% vs 5.9%;  $P=0.03$ ). However, the rate of overall major bleeding or fatal/life threatening bleeding was similar with clopidogrel and ticagrelor. These results were consistent regardless of ACS type and management strategy<sup>26</sup>

Although the rate of serious adverse events did not differ significantly between the ticagrelor and clopidogrel groups, discontinuation of study treatment was more common among patients who received ticagrelor. This difference was primarily due to dyspnea, which is a known adverse effect of ticagrelor treatment. Other causes of the higher rate of discontinuation in the ticagrelor group were minor and minimal bleeding events<sup>26,27,28,29</sup>

### Conclusion:

The combination of clopidogrel plus aspirin was not inferior to aspirin plus ticagrelor dual therapy in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes among patients with stable cardiovascular disease or multiple cardiovascular risk factors. Furthermore, the risk of moderate to severe bleeding was increased slightly in both the groups. Our findings do support the use of dual antiplatelet therapy across the broad population tested where single antiplatelet therapy are not giving maximum benefits. There was a potential benefit in symptomatic patients (those with established vascular disease); this finding requires further study involving large number of Indian patients. Data on mortality rates suggest that dual antiplatelet therapy should be used judiciously in patients without a history of established vascular disease.

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### Declarations

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