**Document heading doi: 10.21276/apjhs.2020.7.1.18** **Original Research Article**

# Evaluation of efficacy and safety of antiplatelet combinations [Clopidogrel plus Aspirin versus Ticagrelor plus Aspirin] in patient with the thromobotic cardiovascular diseases – An observational study

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**Received: 29-11-2019 / Revised: 12-01-2020 / Accepted: 11-02-2020**

## ABSTRACT

**Background:** Patients surviving an acute coronary syndrome (ACS) remain at increased risk of ischemic events long term. To test the hypothesis that ticagrelor plus aspirin is safe and superior to clopidogrel plus aspirin for reducing thromobotic cardiovascular diseases and stroke recurrence in Indian patients study was done. **Methodology**: A prospective, observational clinical study was carried out in the Department of General Medicine, of a tertiary care teaching hospital, Haldia, West Bengal. Permission from the Institutional Ethics Committee was obtained before starting research work. Subjects and their accompanying family members was interviewed by pre-structured questionnaire, and past and present prescriptions and case notes, where available, was captured and reviewed. **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 53.08 years in group 1 and 51.67 years in group 2; 17.5 percent and 22.5% of the patients were women in group 1 and group 2 respectively. Majority of the participants were male in both the groups [group 1 (82.5%) & group 2 (77.5%)]. The rate of the primary safety end point (severe bleeding according to the GUSTO definition) was 2.5% in the clopidogrel plus group 1 and 5% in group 2. The rate of moderate bleeding was 2.5% percent in the ticagrelor group and clopidogrel plus aspirin group. The total rate of intracranial hemorrhage was mild 7.5%, moderate 2.5% and severe 2.5% in the two treatment groups respectively. **Conclusion**: The availability of new antiplatelet agents and extended or combination therapy has increased the options for secondary prevention among ACS patients.

**Key words:** Antiplatelet therapy, cardiovascular diseases, coronary artery disease, mortality, morbidity



## INTRODUCTION

Cardiovascular diseases (CVDs) have now become the leading cause of mortality in India. A quarter of all mortality is attributable to CVD. Ischemic heart disease and stroke are the predominant causes and are responsible for >80% of CVD deaths.[1] According to the Global Burden of Disease study age-standardized estimates (2010), nearly a quarter (24.8%) of all deaths in India are attributable to CVD.[2] Patients with a history of acute coronary syndrome (ACS) remain at increased risk of ischemic events long term.[3]

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Data from the Global Registry of Acute Coronary Events (GRACE) showed that more than half (53.6%) of ACS patients were re-hospitalized at least once during the 5-year follow-up period after discharge.[4] The mechanisms by which antiplatelet drugs interfere with platelet activation and aggregation involve targeting enzymes or receptors that are critical for the synthesis or action of important mediators of these functional responses.[5]All traditional nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, are inhibitors of platelet COX-1. However, whereas aspirin permanently inactivates the enzyme, other NSAIDs act as reversible inhibitors. The interaction of ADP with one of its platelet receptors, P2Y12, can be blocked irreversibly by the active metabolites of thienopyridines (ticlopidine, clopidogrel, and prasugrel) or antagonized reversibly by novel drugs (cangrelor, ticagrelor).[6]The complementary

mechanisms of action of clopidogrel and aspirin have led to testing of the efficacy and safety of their combination in several high-risk settings.[7,8] The relative risk reduction of major vascular events associated with the combination of clopidogrel and aspirin, compared with aspirin alone, was relatively modest and inconsistent. The additional benefit of dual antiplatelet therapy versus aspirin alone was only a fraction of the benefit achieved by aspirin versus placebo in the same clinical settings[9], raising the possibility that the role of ADP in atherothrombosis may have been underestimated on the basis of clopidogrel trials because of incomplete and variable blockade of ADP-induced platelet aggregation by the drug.[10] To test the hypothesis that ticagrelor plus aspirin is safe and superior to clopidogrel plus aspirin for reducing thromobotic cardiovascular diseases and stroke recurrence in Indian patients study was done.

## METHODOLOGY

A prospective, observational clinical study was carried out in the Department of General Medicine, of a tertiary care teaching hospital, Haldia, West Bengal. Permission from the Institutional Ethics Committee was obtained before starting research work. Subjects and their accompanying family members was interviewed by pre-structured questionnaire, and past and present prescriptions and case notes, where available, was captured and reviewed. 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 observe the proceedings. Data regarding anti-platelet combination therapy and other pharmacotherapies were recorded. The prescription data was collected by me by clicking the picture by mobile outside the medical outpatient department in a separate room and interviewing the CAD patients without the knowledge of prescriber to avoid any bias after taking verbal consent and after due administrative and Institutional Ethics Committee permission.

**Inclusion Criteria**

1)Subjects who was suffering from cardiovascular disorders and prescribed antiplatelet drug (s) at Medicine O.P.D.

2)Adult patients ≥ 18 years of age and both the sexes was included

3)CAD patients with co-morbidities like diabetes mellitus, ischemic heart diseases, congestive heart failure and chronic renal diseases was also be included in the study

4)Those who understood the purpose of the study and are ready to provide information regarding their health status and those who signed an 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)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)

A total of 80 CAD patients under antiplatelet therapy was studied because time and facility constraints. Total 80 CAD patients were equally divided into 2 groups. About 40 subjects in each group, Group 1 [aspirin + clopidogrel] and group 2 [aspirin + ticagrelor] was studied. During their follow-up contacts at 2 months, 6 months, and 12 months, patients were asked to provide information regarding their current medications, any morbidity and their complications [if any]. Demographic parameters were analyzed by descriptive statistics.

## RESULTS

**Table 1: Demographic characteristics of study participants**

| Characteristic | Clopidogrel plus Aspirin (N = 40) [Group 1] | Ticagrelor plus Aspirin (N = 40) [Group 2] |
|---|---|---|
| Age [yrs] | 53.08±10.58 | 51.67±12.38 |
| Age groups | | |
| <40 yrs | 2 (5%) | 1 (2.5%) |
| 40-60 yrs | 26 (65%) | 28 (70%) |
| >60 yrs | 12 (30%) | 11 (27.5%) |
| Sex [M/F] | 33[ 82.5%]/7 [17.5%]; 4.71:1 | 31[77.5%]/ 9[22.5%]; 3.44:1 |
| Body mass index (Kg/m$^2$ ) | 24.9±2.3 | 25.7 ±1.9 |

**Table 2: Clinical characteristics of study participants**

| | | |
|---|---|---|
| Cardiovascular risk factors | | |
| Current smoker | 21 (52.5%) | 19 (47.5%) |
| Diabetes mellitus | 11 (27.5%) | 13 (32.5%) |
| Hypertension | 27 (67.5) | 29 (72.5%) |
| Dyslipidemia | 15 (37.5%) | 19 (47.5%) |
| Peripheral artery disease | 03 (7.5%) | 04 (10%) |
| Chronic renal disease | 02 (5%) | 01 (2.5%) |
| Atrial fibrillation | 03 (7.5%) | 04 (10%) |
| Congestive heart failure | 02 (5%) | 03 (7.5%) |
| Previous ischemic stroke | 03 (7.5%) | 05 (12.5%) |
| Previous TIA | 02 (5%) | 03 (7.5%) |
| Previous myocardial infarction | 02 (5%) | 02 (5%) |
| Prior coronary-artery bypass grafting | 04 (10%) | 03 (7.5%) |
| Median blood pressure (inter-quartile range) mm Hg* | | |
| Systolic | 158 (134.8–174) | 156 (130.5–172.0) |
| Diastolic | 88.6 (76–102.4) | 86.4 (78–96.6) |
| Index event | | |
| Unstable angina | 14 (40%) | 10 (25%) |
| Non–ST-segment elevation MI | 11 (27.5%) | 12 (30%) |
| ST-segment elevation MI | 15 (37.5%) | 16 (40%) |
| Others | - | 2 (5%) |

[Abbreviations: TIA, transient ischemic attack; *Presented as median value with first and third quartiles]

The baseline characteristics of the patients in the present study have been described and selected features are listed in [Table 1 & 2]. 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 53.08 years in group 1 and 51.67 years in group 2; 17.5 percent and 22.5% of the patients were women in group 1 and group 2 respectively. Majority of the participants were male in both the groups [group 1 (82.5%) & group 2 (77.5%)]. About 26 (65%) and 28 (70%) of the present cases series were at the age group of 40-60 years in group 1 and group 2 respectively. Average BMI was recorded more than 24.9±2.3 and 25.7 kg/m$^2$ in group 1 and group 2 respectively [Table 1].Hypertension was most common associated disorders in group 1 [27 (67.5%)] and group 2 [29 (72.5%)], which was followed by diabetes and dyslipidemia. Good number of study participants was chronic smokers 21 (52.5%) & 19 (47.5%) in group 1 and group 2 respectively. There were cases of previous ischemic stroke, previous TIA, previous myocardial infarction, and prior percutaneous coronary intervention/ PCI in both the groups [Table 2]. Median baseline SBP blood pressure was noted 158 and 156 mg Hg in the study groups. Percentage of index events for present study enrolment was unstable angina (40%/25%), non–ST-segment elevation MI (27.5%/30%), and ST-segment elevation MI (37.5%/ 40%) among the study groups [Table 2].

**Table 3: Concomitant medications taken by study participants**

| Characteristic | Clopidogrel plus Aspirin (N = 40) | Ticagrelor plus Aspirin (N = 40) |
|---|---|---|
| Diuretics | 07 (17.5%) | 08 (20%) |
| Nitrates | 08 (20%) | 10 (25%) |
| Calcium antagonists | 07 (17.5%) | 07 (17.5%) |
| Beta-blockers | 11 (27.5%) | 09 (22.5%) |
| Angiotensin II–receptor blockers | 09 (22.5%) | 10 (25%) |
| Angiotensin-converting–enzyme inhibitors | 10 (25%) | 12 (30%) |
| Other antihypertensive agents | 4 (10%) | 03 (7.5%) |
| Statins | 21 (52.5%) | 19 (47.5%) |
| Other lipid-lowering agents | 03 (7.5%) | 06 (15%) |
| Anti-diabetic medications | 11 (27.5%) | 13 (32.5%) |
| Proton pump inhibitor | 32 (80%) | 33 (82.5%) |
| H2 blockers | 06 (15%) | 07 (17.5%) |
| Previous anti-platelet therapy | 09 (22.5%) | 11 (27.5%) |

Concomitant medications taken by the patients are shown in Table 3. Almost all the patients (aside from those who died or dropped out) took aspirin and the either clopidogrel/ticagrelor drug in combination. Commonly used drugs were proton pump inhibitors (80%, 82.5%), ACE inhibitors (25%, 30%), ARBs (22.5%, 25%), beta blockers(27.5%, 22.5%), statins (52.5%, 47.5%) anti diabetics (27.5%, 32.5%) and nitrates (20% and 25%) in group 1 and group 2 respectively.

**Table 4: Safety and efficacy outcomes among participants in two groups**

| Outcome | Clopidogrel plus Aspirin (N = 40) No. of patients (%) | Ticagrelor plus Aspirin (N = 40) No. of patients (%) | P Value |
|---|---|---|---|
| **Primary end point** | | | |
| • Death from any cause | 5 (12.5%) | 4 (10%) | P = 0.7251 |
| • Death from cardiovascular causes | 3 (7.5%) | 3 (7.5%) | P = 1.0000 |
| • Myocardial infarction (non-fatal) | 3 (7.5%) | 3 (7.5%) | P = 1.0000 |
| • Stroke (fatal) | 2 (5%) | 1 (2.5%) | P= 0.5587 |
| • Ischemic stroke (nonfatal) | 0 | 0 | - |
| • Stroke (non-fatal) | 1 (2.5%) | 1 (2.5%) | P = 1.0000 |
| **Secondary efficacy end point** Hospitalization for unstable angina, transient ischemic attack, or revascularization | 5 (12.5%) | 4 (10%) | P = 0.7251 |
| **Safety end points** | | | |
| • Major bleeding | 2 (5%) | 1 (2.5%) | P= 0.5587 |
| • Moderate bleeding | 1 (2.5%) | 1 (2.5%) | P = 1.0000 |
| • Minor bleeding | 6 (15%) | 4 (10%) | P = 0.5017 |

Follow-up with respect to the primary efficacy end point (the first occurrence of myocardial infarction, stroke, or death from cardiovascular causes) was complete. With 12 months of follow-up, the rate of the primary event like death from any cause was 12.5% in the clopidogrel plus aspirin group and 10% in the ticagrelor plus aspirin group (relative risk, 1.5; 95 percent confidence interval, -12.3296% to 17.3928%; P = 0.7251) [Table 4].

**Table 5: Types of Bleeding among study participants**

| Bleeding Type | Mild | Moderate | Severe |
|---|---|---|---|
| Conjunctival | 0 | 0 | 0 |
| Epistaxis | 1 (2.5%) | 0 | 0 |
| Gastrointestinal | 3 (7.5%) | 1 (2.5%) | 1 (2.5%) |
| Gingival | 0 | 0 | 0 |
| Hemoptysis | 0 | 0 | 0 |
| Hematuria | 0 | 0 | 0 |
| Intracranial | 3 (7.5%) | 1 (2.5%) | 2 (5%) |
| Intraocular | 0 | 0 | 0 |
| Puncture site | 1 (2.5%) | 0 | 0 |
| Retroperitoneal | 0 | 0 | 0 |
| Surgical | 2 (5%) | 0 | 0 |
| Others | 0 | 0 | 0 |

The rate of the primary safety end point (severe bleeding according to the GUSTO definition) was 2.5% in the clopidogrel plus group 1 and 5% in group 2. The rate of moderate bleeding was 2.5% percent in the ticagrelor group and clopidogrel plus aspirin group. The total rate of intracranial hemorrhage was mild 7.5%, moderate 2.5% and severe 2.5% in the two treatment groups respectively [Table 5].

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

| Characteristics | Clopidogrel plus Aspirin (N = 40)[Group 1] | Ticagrelor plus Aspirin (N = 40)[Group 2] |
|---|---|---|
| Hypersensitivity reactions | 0 | 0 |
| Angioedema | 0 | 0 |
| Dyspnea | 3 (7.5%) | 2 (5%) |
| Headache | 1 (2.5%) | 2 (5%) |
| Cough | 3 (7.5%) | 2 (5%) |
| Dizziness | 2 (5%) | 3 (7.5%) |
| Nausea | 2 (5%) | 2 (5%) |
| Atrial fibrillation | 0 | 1 (2.5%) |
| New onset Hypertension | 2 (5%) | 2 (5%) |
| Non-cardiac chest pain | 2 (5%) | 1 (2.5%) |
| Diarrhea | 1 (2.5%) | 1 (2.5%) |
| Back pain | 0 | 1 (2.5%) |
| Hypotension | 3(7.5%) | 2 (5%) |
| Fatigue | 3 (7.5%) | 3 (7.5%) |
| Bradycardia | 1 (2.5%) | 1 (2.5%) |
| Increased serum uric acid | 3 (7.5%) | 1 (2.5%) |

About 7.5% and 5% 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 [Table 6]. Only few cases serum uric acid levels increased from baseline 7.5% and 2.5% in group 1 and group 2. Slight increased risk of bradycardic events 2.5% (e.g., patients who have sick sinus syndrome, 2nd or 3rd degree AV block) was observed in the both groups [Table 6].

## DISCUSSION

In the present study 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 53.08 years in group 1 and 51.67 years in group 2; 17.5 percent and 22.5% 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.[11] Study by Zhao Q *et al* revealed among 500 randomized patients (mean age, 63.6 years; women, 91 (18.2%), 461 (92.2%) completed the trial.[12] Majority of the participants were male in both the groups [group 1 77.5% & group 2 82.5%]. Hypertension was most common associated disorders in group 1 [27 (67.5%)] and group 2 [29 (72.5%)], which was followed by diabetes and dyslipidemia. Several modifiable conditions (cigarette smoking, obesity, hypertension, hyperlipidemia), disease states (diabetes mellitus, renal disease), and aging are associated with platelet activation and represent risk factors for atherothrombotic complications.[13]Patients with acute minor ischaemic stroke and transient ischaemic attack are at high risk of recurrent stroke and cardiovascular events.[14] The Clopidogrel in High-risk patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial indicated that combined clopidogrel and aspirin treatment is superior to aspirin alone in reducing the risk of stroke, but could increase the risk of non-intracranial haemorrhage.[15,16] A genetic sub-study of the Platelet Inhibition and Patient Outcomes (PLATO) trial indicated that ticagrelor is more efficacious than clopidogrel for acute coronary syndromes, regardless of CYP2C19 genotype, but was associated with an increased risk of haemorrhage in patients with a history of stroke.[17] With 12 months of follow-up, the rate of the primary event like death from any cause was 12.5% in the clopidogrel plus aspirin group and 10% in the ticagrelor plus aspirin group (relative risk, 1.5; 95 percent confidence interval, -12.3296% to 17.3928%; P = 0.7251) [Table 4]. The rate of the primary safety end point (severe bleeding according to the GUSTO definition) was 2.5% in the clopidogrel plus group 1 and 5% in group 2. The rate of moderate bleeding was 2.5% percent in the ticagrelor group and clopidogrel plus aspirin group. The total rate of intracranial hemorrhage was mild 7.5%, moderate 2.5% and severe 2.5% in the two treatment groups respectively [Table 5]. About 7.5% and 5% 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 [Table 6].As the benefits of aspirin in the secondary prevention of ischemic events are well established, guidelines recommend that a loading dose

of aspirin (162–325 mg) be administered as soon as possible following an ACS event.[17,18,19] The Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes (SOCRATES) trial revealed a trend towards better efficacy in reducing the risk of vascular events in the ticagrelor treated group than in the aspirin group in an Asian subpopulation. However, limited data are available on the safety and efficacy of ticagrelor for the treatment of stroke, compared with data for clopidogrel on a background of aspirin in patients with acute stroke.[20] The Dual Antiplatelet Therapy (DAPT) study showed that 30 months of treatment with clopidogrel or prasugrel plus aspirin reduced major CV event rates following coronary stent placement, compared with 12 months of treatment, although with an increased risk of bleeding and a suggestion of increased all-cause mortality (2.0 vs. 1.5%; HR 1.36, 95% CI 1.00–1.85; **p** = 0.05).[21] Current US guidelines for ACS broadly recommend that dual antiplatelet therapy be continued for 12 months after the index event, followed by aspirin monotherapy.[18] Dual antiplatelet therapy (DAPT) combining aspirin and a $P2Y_{12}$ receptor inhibitor has been consistently shown to reduce recurrent major adverse cardiovascular events (MACE) in patients with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI) for stable coronary artery disease (CAD) compared with aspirin monotherapy, but at the expense of an increased risk of major bleeding.[22] Based on limited evidence, 12 months duration of DAPT is currently recommended in patients with ACS irrespective of their management strategy, but large ongoing randomised trials are currently assessing the efficacy and safety of a short-term DAPT strategy (3–6 months) for patients with ACS undergoing PCI with newer generation DES. Finally, several ongoing, large-scale, randomised trials are challenging the current concept of DAPT by investigating $P2Y_{12}$ receptor inhibitors as single antiplatelet therapy and may potentially shift the paradigm of antiplatelet therapy after PCI in the near future[22].Wang Yilong et al study revealed the primary safety outcome (PLATO major haemorrhagic event) occurred in five patients (1.5%) in the ticagrelor/aspirin group and four (1.2%) in the clopidogrel/aspirin group (hazard ratio 1.27; 95% confidence interval 0.34 to 4.72).[23] Three patients (0.9%) in the ticagrelor/aspirin group and two (0.6%) in the clopidogrel/aspirin group had intracranial haemorrhage. However, the rate of any haemorrhagic events occurring was higher in the ticagrelor/aspirin group (22.3%) than in the clopidogrel/aspirin group (14.2%; 1.65, 1.15 to 2.37). All of the proportional hazard assumptions were met (P=0.99 for major haemorrhagic event and P=0.82 for any haemorrhagic events). Vranckx P *et al* study revealed that ticagrelor in combination with aspirin for 1 month followed by ticagrelor alone for 23 months was not superior to 12 months of standard dual antiplatelet therapy followed by 12 months of aspirin alone in the prevention of all-cause mortality or new Q-wave myocardial infarction 2 years after percutaneous coronary intervention.[24]

## CONCLUSION

In this study of patients with established atherothrombotic disease or at high risk for such disease, there was slightly higher but non-significant benefit associated with ticagrelor plus aspirin as compared with clopidogrel plus aspirin in reducing the incidence of the primary end point of myocardial infarction, stroke, or death from cardiovascular causes. There was a moderate, though not significant, benefit in reducing the secondary composite end point of myocardial infarction, stroke, and death from cardiovascular causes, or hospitalization for unstable angina, transient ischemic attack, or revascularization.

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**How to cite this Article:** Verma AK, Prasad MK. Evaluation of efficacy and safety of antiplatelet combinations [Clopidogrel plus Aspirin versus Ticagrelor plus Aspirin] in patient with the thromobotic cardiovascular diseases – An observational study. Asian Pac. J. Health Sci., 2020; 7(1):97-103.
**Source of Support:** Nil, **Conflict of Interest:** None declared.