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COMPARATIVE STUDY ON BLEEDING COMPLICATION OF CLOPIDOGREL VERSUS TICAGRELOR IN PATIENTS WITH ACUTE CORONARY SYNDROME

Anjali Jayakumar, Archa Rajendran, Salabha Ann Mathew, Raina Sebastian, Dr.S.Haja Sherief, Dr.T.Sivakumar

Nandha College of Pharmacy, Erode, Tamil Nadu, India.

Abstract:

Background: *In the Platelet Inhibition and Patient Outcome (PLATO) trial, ticagrelor compared with clopidogrel reduced the primary composite end point of death from vascular causes, myocardial infarction or stroke after ACS, but increase the risk of bleeding complications.*

Objective: *To evaluate the safety outcome in patients on clopidogrel and ticagrelor, to assess the severity of bleeding based on TIMI and CRUSADE score and to determine the impact of bleeding complications on mortality.*

Methods and Results: *In this prospective observational study, we studied 200 acute coronary syndrome patients with co-morbidities. The primary end point was occurrence of any type of bleeding, and is determined as per international bleeding criteria's TIMI and CRUSADE.*

Both clopidogrel and ticagrelor induced bleeding cases were reported. The incidence of overall bleeding was higher in patients taking ticagrelor compared to those taking clopidogrel in patients with acute coronary syndrome.

Conclusion: *In patients with acute coronary syndrome with or without ST segment elevation, treatment with ticagrelor as compared with clopidogrel significantly reduce the rate of death from vascular causes, myocardial infarction or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure related bleeding.*

Keywords: *Acute coronary syndrome, ST elevated myocardial infarction, Non-ST elevated myocardial infarction, Clopidogrel, Ticagrelor*

Corresponding author:

Anjali Jayakumar,
Pharm.D intern,
Nandha College of Pharmacy,
Erode,Tamil Nadu,India
Mob: 9744995642
Email:anjalijayakumar24@gmail.com

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INTRODUCTION:

In patients who have acute coronary syndrome with or without ST segment elevation, current clinical practice guidelines recommend dual antiplatelet treatment with aspirin and clopidogrel [1]. Antiplatelet agents are used for the treatment and prevention of ischemic events in patients with established artherothrombosis or with risk factors for vascular diseases [2].

Bleeding has become an important health and economic problem and has an incidence of 2- 17% in acute coronary syndrome patients taking clopidogrel and ticagrelor. Bleeding significantly influences both the short term and long term prognosis.

In the DISPERSE trial, there was an increase in the risk of minor bleeding with ticagrelor compared to clopidogrel, but very few major bleeding events were reported.

The incidence of total major bleeding (using either the PLATO or TIMI definitions) was not significantly increased with the use of ticagrelor compared with clopidogrel.

Ticagrelor, a reversible and direct acting oral antagonist of the adenosine diphosphate receptor P2Y12 provides faster, greater and more consistent P2Y12 inhibition than clopidogrel [3]. In a dose guiding trial, there was no significant difference in the rate of bleeding with the use of ticagrelor at a dose of 90 mg or 180 mg twice daily and the rate with the use of clopidogrel at a dose of 75 mg daily [4].

Thrombolysis in Myocardial Infarction (TIMI) is an internationally accepted bleeding criteria used to determine ischemic events or mortality in patients with unstable angina or NSTEMI or STEMI [5]. Can rapid Risk stratification of Unstable angina patients Suppress ADverse outcome with Early implementation of ACC/AHA guidelines .It is a prediction tool for estimating the baseline risk of major bleeding in patients with acute coronary syndrome [6].

We conducted a study to determine the incidence, clinical impact of bleeding complication in a population of acute coronary syndrome patients and the ability to predict those events using risk score. A group of patients at higher risk of bleeding complications can be identified according to known risk factors and a risk scoring system can be developed and then may focus more on preventive measures that should help to reduce the incidence of bleeding.

MATERIALS AND METHODS:

The study is a single centered prospective observational study with a sample of 200(male-79.5% and female-20.5%) from 1st February 2017 to 31st July 2017 and the follow up period ended in September. The study was approved by institutional ethics committee, G.Kuppusamy Naidu Memorial Hospital, Coimbatore after submitting the proposal.

Patients were eligible for enrollment if they were hospitalized for an acute coronary syndrome, with or without ST segment elevation and unstable angina. Major exclusion criteria were patients taking anticoagulants like warfarin, acunocumerol etc., patient those who are not willing to consent and concomitant therapy with a strong cytochrome P450 3A inhibitor or inducer.

Patients were randomly assigned to receive ticagrelor or clopidogrel .Ticagrelor was given in a loading dose of 180 mg followed by a dose of 90 mg. Clopidogrel was given in a loading dose of 300 mg followed by 75 mg. For these assigned patients the risk of bleeding will be assessed by TIMI bleeding score and CRUSADE bleeding criteria. Then the cases with high risk of bleeding were reported to the physician thereby dosage adjustment and combination monotherapy were done for these patients. These patients were followed up during hospital stay and 1 month follow up post discharge through phone call, thus comparing the clinical outcome of clopidogrel and ticagrelor and assessing whether the patient contribute to mortality.

The primary safety end point was the first occurrence of any type of major bleeding. Additional safety end points included minor bleeding such as hematochezia, hematuria and macular bleed. Chi square test was used to compare the risk of bleeding in patients taking clopidogrel and ticagrelor.

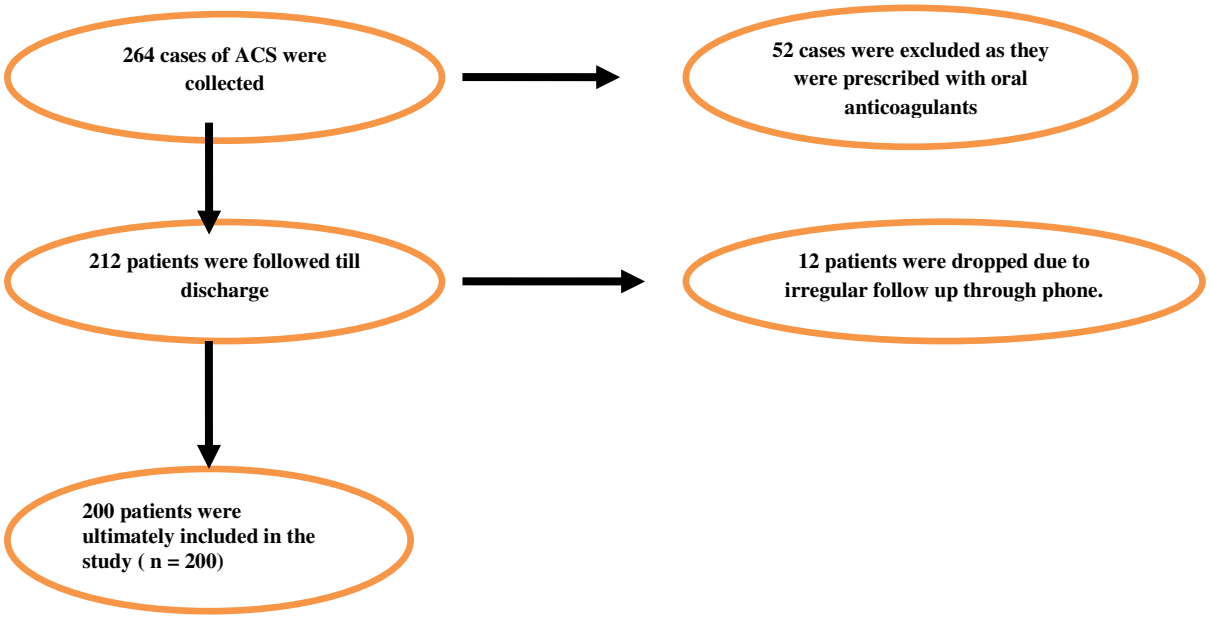

Figure No.1. Flow chart showing study sample selection

RESULTS:

Study patients

We recruited 264 patients with acute coronary syndrome. The follow up period ended in September 2017. About 77.5% patients received 75 mg clopidogrel and 22.5% patients received 90 mg ticagrelor.

Bleeding

Ticagrelor and clopidogrel groups did not differ significantly with regards to the rate of major bleeding as per the study (4.5% and 3.5%). There was a significant difference in the rate of major bleeding analyzed as per TIMI and CRUSADE bleeding criteria.

Table No.1.Categorisation of patients based on TIMI bleeding criteria

Category	No of patients (n=200)	Percentage (%)
Low risk	80	40%
Moderate risk	100	50%
High risk	20	10%
Total	200	100%

Table. No. 2.Categorisation of patients based on CRUSADE bleeding criteria

Category	**No of patients (n=200)**	**Percentage (%)**
Very low risk	5	2.5%
Low risk	49	24.5%
Moderate risk	80	40%
High risk	40	20%
Very high risk	26	13%
Total	200	100%

With ticagrelor as compared to clopidogrel there were more episodes of hematuria (ticagrelor -2, clopidogrel -1) and macular bleed (clopidogrel 1, ticagrelor- 0).However the major gastrointestinal bleeding occurs.

Discontinuation of the study drug due to adverse events occurred more frequently with ticagrelor than with clopidogrel.The levels of creatinine increased slightly more during the treatment period with ticagrelor than with clopidogrel.

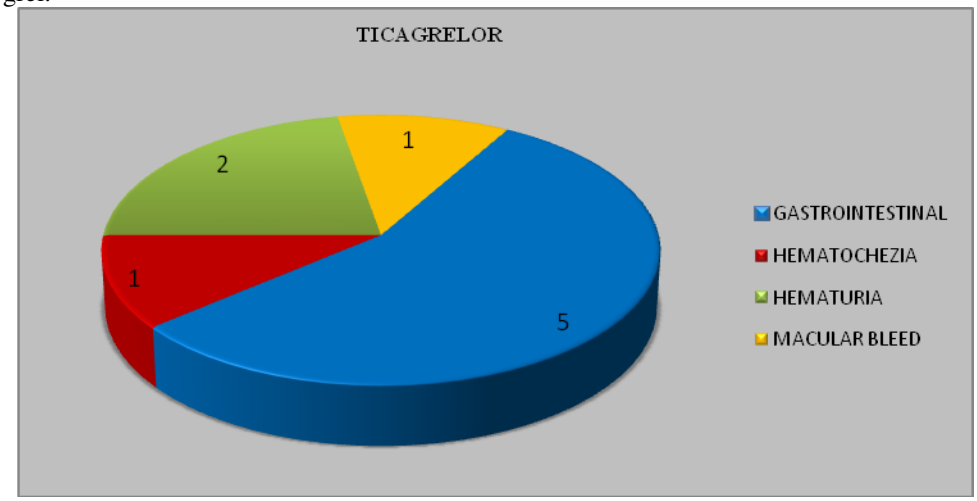

Figure.No.2.Categorisation of patients based on types of bleeding induced ticagrelor

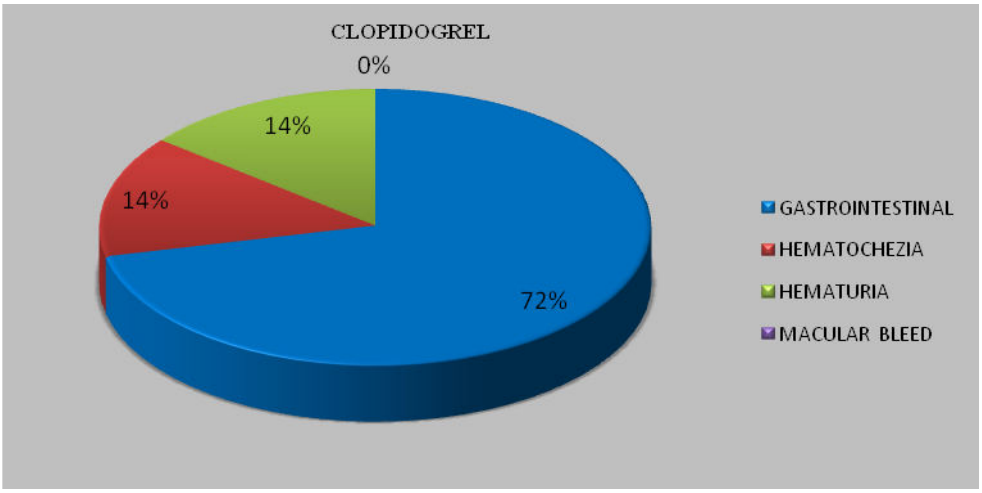

Figure.No.3.Categorisation of patients based on types of bleeding induced by clopidogrel

DISCUSSION:

The study shows that treatment with ticagrelor as compared with clopidogrel in patients with acute coronary syndrome significantly reduced the rate of death from vascular causes, myocardial infarction or stroke. A similar benefit was seen for individual components of death from vascular causes and myocardial infarction but not for stroke. The beneficial effects of ticagrelor were achieved without a significant increase in the rate of major bleeding.

The benefits of ticagrelor over clopidogrel were seen in patients who had an acute coronary syndrome with or without ST segment elevation.

The incremental reduction in the risk of coronary thrombotic events with ticagrelor is with more intense P2Y12 inhibition [7]. Treatment with ticagrelor was also associated with an absolute and relative reduction in the rate of death. This survival benefit from more- intense platelet inhibition with ticagrelor is consistent with reduction in the mortality rate obtained by means of platelet inhibition with aspirin in patients who had acute coronary syndrome and with clopidogrel in patients who had myocardial infarction with ST-segment elevation (Antithrombotic Trialists' Collaboration.2002).

Since P2Y12 inhibition with ticagrelor is reversible, the antiplatelet effect dissipates more rapidly than with the thienopyridine which are irreversible P2Y12 inhibitors. Although the rate of bleeding events were not lower with ticagrelor than with clopidogrel the more intense platelet inhibition with ticagrelor was not associated with an increase in the rate of major bleeding. The rare episodes of gastrointestinal bleeding were often fatal and were equal in both ticagrelor and clopidogrel groups.

The study concluded that patients who had acute coronary syndrome with or without ST segment elevation, treated with ticagrelor as compared with clopidogrel, significantly reduced the rate of death from vascular causes, myocardial infarction or stroke without an increase in the rate of overall bleeding complications.

At the same time, TIMI and CRUSADE were compared to analyze the better predictor of bleeding complication. From the above mentioned comparison CRUSADE was found to be better predictor of bleeding complication than TIMI.

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