ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 6, Issue – 3, May – 2021 , Page No. : 161 - 169

Comparison of Gastrointestinal Bleeding Among ACS Patients under Short Term and Long Term Duration of Dual- Antiplatelet Therapy

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Citation this Article: Ms. Sidhi Sunil, Ms. Haritha Rajmohan, Ms. Anjali R, Dr. Praveen Chacko, Dr. Sherin Alexander, Mr. Phillip Jacob, Dr. Sofi Binu, "Comparison of Gastrointestinal Bleeding Among ACS Patients under ShortTerm and Long Term Duration of Dual- Antiplatelet Therapy", IJMSIR- May - 2021, Vol – 6, Issue - 3, P. No. 161 – 169.

Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Background: Antiplatelet therapy has improved the prognosis of atherothrombosis, including stable coronary heart disease (CHD), acute coronary syndrome (ACS), ischemic stroke, and peripheral arterial disease (PAD). However, they are associated with bleeding complications especially gastrointestinal (GI) bleeding. Dual antiplatelet therapy with aspirin and clopidogrel or one of the newer agents is associated with GI bleeding complications. Patients with complaints of GI bleeding have different levels of severities which are categorized using many types of risk scoring systems. Compared the percentage of GI bleeding among patients on the short-term and long-term duration of DAPT using the Glasgow-Blatchford bleeding score (GBS).

Methodology: A Retrospective study of 6 months was analyzed among 508 patients of a tertiary care hospital inThiruvalla who were under the cardiology department between January 2015 and December 2018 and those receiving dual antiplatelet therapy. The main outcome measurement was patients with or without symptoms of GI bleeding such as reduction of Hb level, melena, and led to a gastroenterology consultation, and even the physician identified complications thus causing an alteration in the DAPT regimen.

Result: Data were collected from medical records. 9 cases of GI bleeding were observed during the follow-

up period. Among the 508 cases, Comparing the duration of DAPT, predisposition of GI bleeding risk was more among long term duration were 15.2% (36 subjects) compared to short duration 4.8% (13 subjects) and GI bleeding was seen only among long term duration 1.8%(9 subjects). The Short Term Therapy of DAPT was more usedin the age group of ≤59 years and Long Term Therapy of DAPT was more used among the age group of ≥60 years and observed that the use of Short Term and Long Term Dual Antiplatelet Therapy was found approximately similar among male and female subjects.

Conclusion: In our study, it was found that 1.8% of gastrointestinal bleeding in patients due to DAPT. A short duration of DAPT considerably reduced the rate of major bleeding event and might be safer with similar rates of repeated thrombotic complications as compared to the long duration of therapy. The chances for bleeding were seen in the prolonged duration of therapy, where all the bleeding cases were under the prolonged duration of DAPT. A shorter DAPT duration significantly reduced the rate of major bleeding events.

Keywords: Dual antiplatelet therapy (DAPT), Gastrointestinal Bleeding, Coronary artery disease (CAD), Short Term Therapy, Long Term Therapy, Aspirin, Clopidogrel.

Introduction

The word acute coronary syndrome covers a broad spectrum of clinical situations, from unstable angina to ST- segment elevation myocardial infarction (STEMI). These are, with uncommon exceptions a consequence of the acute thrombus formation related to a disrupted coronary atherosclerotic plaque. [(1)]Currently, dual antiplatelet therapy (DAPT) is recommended for the treatment and prevention of the complications of vascular events both during short- and long-term treatment in patients with the atherothrombotic disease. However, antiplatelet therapy is associated with bleeding complications and gastrointestinal bleeding has been reported as one of the most common causes of life-threatening complications. [(2)] The mechanisms of the ability of aspirin to induce GI bleeding involve the suppression of gastroduodenal prostaglandin synthesis and it increases with increasing doses of aspirin. The mechanism behind the action of clopidogrel with regard to the GI endothelium is unclear. [(3)] Clopidogrel administration was associated with a 20% relative risk reduction of a composite endpoint of cardiovascular death, nonfatal MI, or stroke compared with placebo. There was more major GI bleeds in the clopidogrel plus aspirin compared with aspirin alone (75–325 mg/day). The major overall bleeding rates for the combined use of low-dose (less than 100 mg/day) aspirin plus clopidogrel were lower than for using aspirin alone at higher doses (200 mg/day). In patients with high-risk ACS, 1 year of therapy with clopidogrel plus aspirin results in greater life expectancy than aspirin alone. Patients treated with combined therapy experienced a non-significant trend toward an increase in major bleeding. Therefore, the increased risk of bleeding complications associated with combined treatment may be influenced by the sequence of drug addition. [(4)]

The present study aims to compare the gastrointestinal bleeding among patients with Acute Coronary Syndrome under short term and long term duration of Dual-antiplatelet therapy using the GB score. Besides, we also assess the safety of DAPT across various time durations.

Methodology

a) **Study Design:** Retrospective observational study

b) **Study Site:** The study was conducted in the cardiology department of Believers Church Medical CollegeHospital (BCMCH), Thiruvalla.

c) **Study Period:** 6 months (November 2019 to April 2020)

d) **Study Approval:** This study was approved by the Institutional Human Ethics Committee of Believers Church Medical College Hospital, Thiruvalla.

e) **Inclusion Criteria**

1. Age above 18yrs.
2. Patients under Dual-antiplatelet therapy.
3. Patients who were on regular follow-up.

f) **Exclusion Criteria**

1. Patients previously diagnosed with GI disorder.
2. Patients with anticoagulant therapy.
3. Patients who have any hepatic dysfunction.

g) **Study Variables**

- Demographic profile: Name, Age, Gender, Date of prescription.
- All details regarding diagnosis, comorbidities.
- Details of Prescription: Brand/Generic name, Dosage, Route, Frequency, and Duration.

h) **Data Collection Tool:** Pre-designed validated data collection form was used.

i) **Data Collection Procedure:** All patients satisfying the study criteria were enrolled in the study. The required data were retrieved and entered into the pre-designed data collection proforma. Patients were assessed for any symptoms of GI bleeding, or any gastroenterology consultations. The patients were classified based on the risk severity using GB score.

j) **Data Analysis:** The data collected were entered in Microsoft excel-2010 version and statistically analyzed. Results were presented in tabular form and presented as frequency and percentage.

Results

a) Distribution of age group

Table 1: Distribution of age group

Sn.	Age groups	Total number of subjects	Subjects with Short TermTherapy	Subjects with Long Term Therapy
		Frequency	Percentage	Percentage
l	<60	302	65.6%	34.43%
2	≥60	206	36%	64.07%

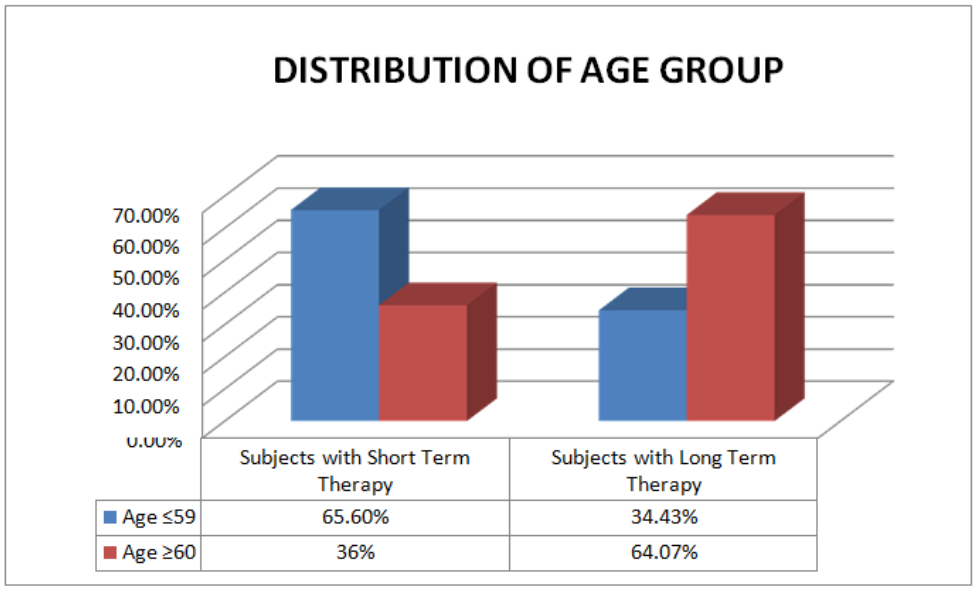

Fig. 1: Distribution of patients based on age group

Table 1/Figure 1 Shows the age group distribution of the patients. Among 508 study population, the Short Term Therapy of DAPT was more used in the age group of <60 (65.6%) and Long Term Therapy of DAPT was more used among the age group of ≥60 (64.07%).

a) Distribution of gender

Table 2: Distribution of gender

Sn.	Gender	Total numberof subjects	Subjects with ShortTerm Therapy	Subjects with LongTerm Therapy
		Frequency	Percentage	Percentage
1	Male	375	54%	46.13 %
2	Female	133	53%	47.4 %

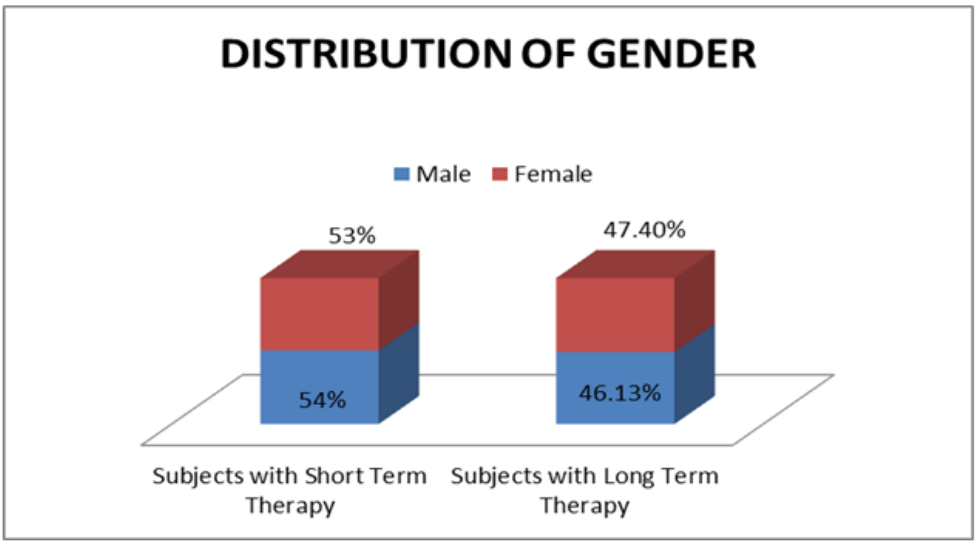

Figure 2: Distribution of gender

Table 2/Figure 2 Illustrates the distribution of patients based on gender. Among 375 male subjects, 54% were taken Short Term DAPT and 46.13% were taken Long Term DAPT. Among 133 female subjects, 53% were

taken Short Term DAPT and 47.3% were Long Term DAPT. So the use of Short Term and Long Term Dual Antiplatelet Therapy was found approximately similar among male and female

Distribution of duration of dual antiplatelet therapy

Table 3: Distribution of duration of DAPT

Sn.	Duration of DAPT	Total number ofsubjects	Subjects with GI Bleeding Risk	Subjects with GI Bleeding
		Frequency	Frequency	Frequency
1	Short	272	13	0
2	Long	236	36	9
Total		508	49	9

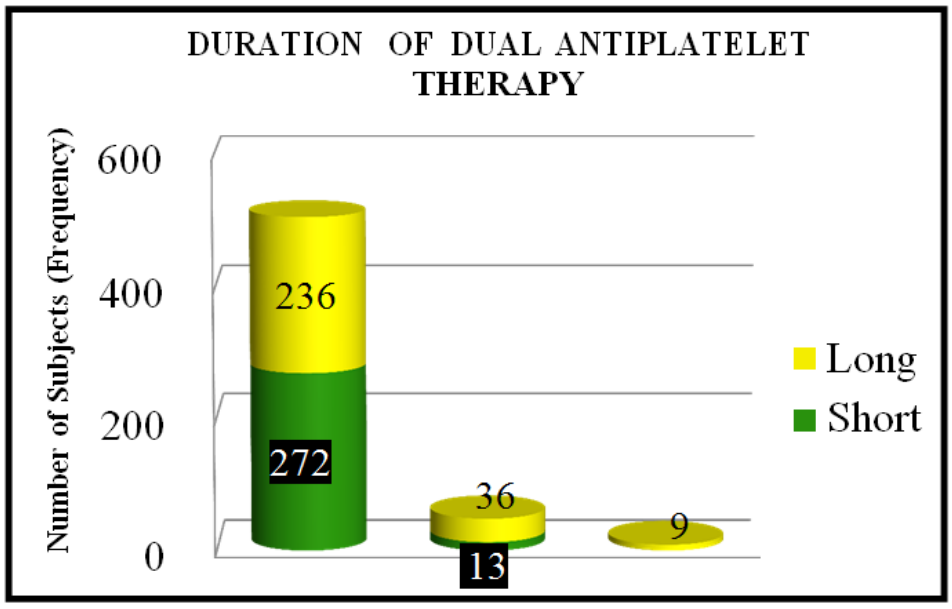

Figure 3: Distribution of duration of DAPT

Table 3/Figure 3 Demonstrates the distribution of duration of DAPT, Predisposition of GI bleeding risk was more among long term duration were 15.2% (36 subjects) compared to short duration was 4.8% (13 subjects) and GI bleeding was seen only among long term duration was 1.8% (9 subjects).

1. Distribution of general management

Table 4 : Distribution of general management

Sn.	Management	Drugs	Frequency	Percentage
1	Combination to singletherapy	Clopidogrel 75 mg	36	63
2	Dose reduction	Aspirin 75 mg and Clopidogrel75 mg	20	34
3	Alternative drugs	Ticagrelor	2	3
Total			58	100

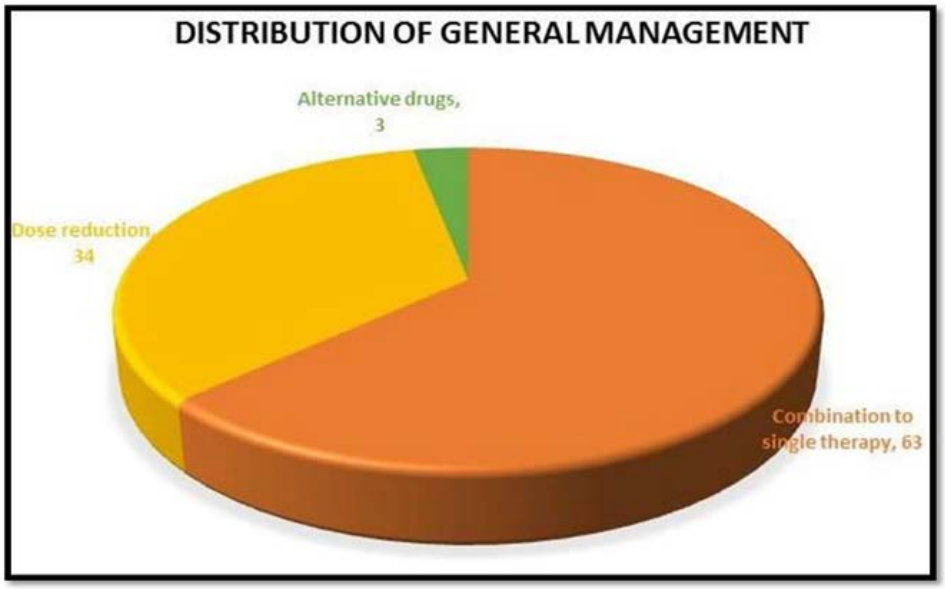

Figure 4 : Distribution of general management

Table 4/Figure 4 Explains the distribution of general management provided. Out of 58 GI bleeding risk patients, switching dual antiplatelet therapy to single antiplatelet therapy was more (63%), followed by dose reduction (34%), and the least shown was switching to alternative drugs (3%).

Discussion

The objective of the study was to compare the gastrointestinal bleeding among patients under short term and long term duration of Dual-antiplatelet therapy using the Glasgow-Blatchford bleeding score (GBS) and also find the various methods used in the management of gastrointestinal bleeding due to Dual-antiplatelet therapy. The study population entailed of 500 samples. The study was a hospital based retrospective observational study. The data of patients were collected from November 2019 to April 2020 in the department of cardiology of BCMCH and then the data entered into a predesigned data collection proforma.

Age wise distribution among 508 total patients based on the short term and long term duration of Dual-antiplatelet therapy use, the Short Term Therapy of DAPT were more used in the age group of <60 (65.6%) and Long Term Therapy of DAPT were more used among the age group of ≥60 (64.07%).In a study conducted by L Seung-Yul et. al. using 6 randomized trials that compared short-term (≤ 6 months) and long-term (12 months) DAPT, individual participant data meta-analysis was performed in elderly patients (≥ 65 years of age) showed that in the younger patients (<65 years of age, n= 6,152), short-term DAPT was related with a higher risk of the major result. In elderly patients (n= 5,319) however, the risk of primary outcome did not significantly differ between patients receiving short-term and long-term. Short-term DAPT was associated with a significant decrease in major bleeding compared with long-term DAPT in the total group, and particularly in elderly patients. [5]

The gender distribution of patients based on the use of Short Term and Long Term Dual Antiplatelet Therapy. Among 375 male subjects, 54% were taken Short Term DAPT and 46.13% were taken Long Term DAPT. Among 133 female subjects, 53% were taken Short Term DAPT and 47.3% were Long Term DAPT. So the use of Short Term and Long Term Dual Antiplatelet

Therapy was found approximately similar among male and female subjects. A study conducted by M Verdoia et.al. entailed 1500 acute coronary syndrome patients in a prospective, multicenter, randomized study considered for gender differences with short-term v/s 12 months dual antiplatelet therapy in patients with the ACS. The study shows that a 3 months Dual Antiplatelet Therapy offers similar results as compared to a standard 12 months Dual Antiplatelet Therapy at 2-years follow-up in both male and female gender .They concluded that equivalent rates of survival, MI, stent thrombosis, stroke, and bleeding events were detected with the two DAPT strategies, with no impact of gender.[6]

The distribution of duration of DAPT, predisposition to develop GI bleeding was more among long term duration were 15.2% (36 subjects) compared to short duration were 4.8% (13 subjects). A more extended long term DAPT administration provides benefits in ischemic events, but with excess in hemorrhagic complications, with overall neutral effects on mortality. In a similar study M. Verdoia et.al. They included 3 RCTs and sub- analyses from 8 RCTs, with a total of 17,941 patients. A shorter DAPT duration significantly reduced the rate of major bleeding events (short 1.5%, vs. long 1.9%).The reduction in bleeding events was more significant in trials evaluating long DAPT duration. They concluded a short duration of DAPT could be safer with similar proportions of recurrent thrombotic complications as compared to the standard 12 months, and similar mortality. Also does not provide any survival benefit, but is associated with a significant reduction in major bleeding complications. [7]

Out of 58 GI bleeding risk patients, switching dual antiplatelet therapy to single antiplatelet therapy(63%) was more, followed by dose reduction(34%), and the least shown was switching to alternative drugs(3%). Lanas et.al. explained that with alteration for multiple risk factors, it was found that the relative risk for upper gastrointestinal bleeding was 3.7% for low-dose aspirin, 2.8% for clopidogrel and 16.4% for the combination (aspirin plus clopidogrel). Also in a multicenter randomized double-blinded trial by F Amico et.al. explained ticagrelor was found to be superior to clopidogrel for the reduction of death from vascular causes, myocardial infarction, or stroke. A similar benefit was seen for the individual components of death and myocardial infarction but no benefit from stroke. This benefit was attained without a significant increase in bleeding. The benefit was the same in the short-term (days 0 to 30 days) and in the longer term (days 31 to 360). This benefit appears to be prevalent over the whole ACS spectrum of patients, regardless of being managed medical or invasive management. Ticagrelor is the first and only oral antiplatelet agent, FDA approved to demonstrate superior reduction for CV death vs. clopidogrel at 12 months. In a study by S. Yusuf et.al. showed that the bleeding rates were 4.9%, 3.5% , and 2.5% when the dose of aspirin was 300 mg, 100-300 mg , and <100 mg, respectively.[8, 9, 10]

Conclusion

Acute Coronary Syndrome is a term that incorporates unstable angina, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). A patient with an ACS most commonly presents with a single, ruptured atherosclerotic plaque in one major coronary artery, they may present with more than one ruptured plaque and multiple active lesions in more than one coronary artery, which predisposes the patient to a worse prognosis. (11)

Dual antiplatelet therapy (DAPT), consisting of the combination of aspirin and a platelet $P2Y_{12}$ inhibitor, is the cornerstone of pharmacological treatment aimed at preventing atherothrombotic complications in patients with a variety of coronary artery disease (CAD) manifestations . [12] A Class I recommendation (should be given) in most clinical settings is made for at least 6–12 months of DAPT (depending on the setting), and a Class II b recommendation is made for prolonged DAPT beyond this initial 6- to 12-month periodically.[13,14,15,16]The use of antiplatelet agents is narrow by bleeding complications, most of which arise from the upper gastrointestinal (UGI) tract. Upper gastrointestinal (UGI) bleeding is a recurrent cause of emergency admission and hospitalization. Gastrointestinal bleeding remains a concern while prescribing dual antiplatelet drugs. Likewise, even if not discussed herein, non-GI life-threatening bleeding complications (e.g. intracranial hemorrhage) are also considered.

From our study, we were able to compare the gastrointestinal bleeding among patients under short term and t long term duration of Dual-antiplatelet therapy and observed that GI bleeding was more among long term duration were 15.2% (36 subjects) compared to short duration were 4.8% (13 subjects). Chances for bleeding were seen in the long term duration of therapy, where all the bleeding cases were under the long term duration of DAPT. While considering the age distribution, the Short Term Therapy of DAPT was more used in the age group of ≤59 (65.6%) and Long Term Therapy of DAPT was more used among the age group of ≥60 (64.07%) and found that Short-term DAPT was associated with a significant decrease in major bleeding associated with long-term DAPT in the overall group, and particularly in elderly patients. Also found that even though the patients using Short Term and Long Term DAPT were was found approximately similar among male and female subjects. Legitimize further research on gender-specific distribution is required to determine the possible targets for future tailored dual antiplatelet therapies. A short duration of DAPT significantly reduced the rate of major bleeding events and could be safer with similar rates of repeated thrombotic complications as compared to the standard 12 months, and similar mortality. The chances for bleeding were seen in the prolonged duration of therapy, where all the bleeding cases were under the prolonged duration of DAPT. The percentage of dose reduction was found to be 34%, the percentage of switching from combination to single antiplatelet therapy was seen as 63% ,and opting for alternative drugs was done 3%.

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