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Efficacy and Safety of Dual Antiplatelet Therapy in High-Risk, Post-Percutaneous Coronary Intervention Patients beyond One Year

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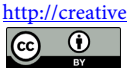


Abstract

Background: Individuals with coronary artery disease (CAD) who have undergone a percutaneous coronary intervention (PCI) are at an increased risk for adverse coronary events. Management with dual antiplatelet therapy (DAPT) has been indicated in this group, however, DAPT significantly increases the risk of bleeding. **Objectives:** This study aimed to evaluate aspirin versus clopidogrel and aspirin on major adverse cardiac and cerebrovascular events (MACCE) and risk of bleeding in individuals already on DAPT for one year after undergoing PCI. **Methods:** This was a single-center, double-arm, interventional, prospective study. A total of 956 individuals who had undergone PCI and were on DAPT for a year were enrolled. After calculating DAPT scores, individuals with DAPT scores ≥2 were assigned to the aspirin and clopidogrel group, and those with DAPT scores <2 were prescribed aspirin alone. The participants were followed for one year to collect data on incidences of MACCE and significant bleeding. **Results:** The group on clopidogrel and aspirin demonstrated a significantly lower rate of MACCE when compared to those on aspirin alone (p = 0.003). However, stent thrombosis, stroke, and myocardial infarction (MI) did not significantly differ in an inter-group comparison. The rate of moderate bleeding was greater in the clopidogrel group; however, the difference was not found to be statistically significant (p = 0.19). Conclusions: Continuing DAPT for a period between 12 and 24 months after PCI in individuals with a DAPT score ≥2 had favorable outcomes in reducing coronary adverse events without resulting in significant bleeding.

Keywords

Aspirin, Clopidogrel Drug-Eluting Stents, Dual Antiplatelet Therapy,

Percutaneous Coronary Intervention

1. Introduction

Individuals with percutaneous coronary intervention (PCI) for coronary artery disease (CAD) show a drastic improvement with drug-eluting stents (DES). However, to avoid stent thrombosis and reduce adverse cardiac outcomes after DES, dual antiplatelet therapy (DAPT) is recommended. This therapy uses a P2Y12-receptor inhibitor with aspirin. Balancing the bleeding risk associated with DAPT and the cardiovascular risk in its absence poses a clinical dilemma [1]. A large-scale trial on participants having completed a year of DAPT after DES compared the effects of aspirin with prolonging DAPT for 18 months. Extended DAPT was associated with a lesser risk of stent thrombosis and MACCE, however, it increased bleeding. Mortality was higher due to non-cardiovascular reasons such as bleeding, cancer, or trauma [1].

Aspirin and clopidogrel are the two most commonly administered antiplatelet drugs effective in the prevention of cardiovascular disease (CVD). Their combination exhibits synergistic effects as they have different mechanisms of action. Aspirin non-selectively and irreversibly inhibits cyclooxygenase (COX) and prevents thromboxane A2 (TXA2) (a potent platelet agonist) production. Clopidogrel (a second-generation thienopyridine) is converted into its active thiol form by cytochrome P450 enzymes. It works by binding irreversibly to the adenosine diphosphate (ADP)-P2Y12 receptor on platelets. Aspirin and clopidogrel demonstrate long-lasting antiplatelet activity. However, up to 83% of individuals are resistant to aspirin, and 4% - 30% of individuals are resistant to clopidogrel. Therefore, there is variability in their efficacy among individuals [2].

Variations in platelet aggregation during antiplatelet therapy have been demonstrated. Individuals who do not achieve adequate platelet inhibition following aspirin and clopidogrel therapy are at risk for adverse ischemic events. Conversely, some individuals respond excessively to antiplatelet drugs and present an increased risk of bleeding. Genotypical characteristics of individuals may be responsible for this phenomenon [3]. Conflicting results on various anti-platelet drugs necessitate more studies in this regard to provide personalized treatment options to individuals who have undergone PCI. Thus, this 12-month-long prospective study compares the use of continued DAPT (aspirin with clopidogrel) with that of aspirin alone in individuals on DAPT following PCI in the past year.

2. Method

2.1. Study Population

Individuals (N = 956) who underwent PCI at LPS Institute of Cardiology, Kanpur, and had completed a year after treatment were included in the study.

2.2. Study Design

A prospective, double-arm, interventional study.

3. Inclusion Criteria

Individuals >18 years of age, who had undergone stent placement after PCI between October 2015 and December 2016 were included. Individuals who had been on DAPT following PCI without any adverse effects were included.

4. Exclusion Criteria

1) Individuals with stents >4.0 mm or <2.25 mm.
2) Pregnant women.
3) Individuals contraindicated for prolonged DAPT.
4) Individuals requiring surgery that needs antiplatelet therapy to be discontinued within 30 months after enrollment.
5) Individuals with a low life expectancy of <2 years.
6) Individuals on warfarin or similar anticoagulant therapy.
7) Individuals allergic to one of the components or drugs.
8) Individuals with both bare metal stents and DES at the index procedure.

5. Ethics Statement

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. All participants gave informed consent prior to their participation in the study, and strict confidentiality of their personal information was maintained throughout the research process.

6. Procedure

Individuals after completing a year of DAPT following the index procedure and who were event-free were randomized to either group I (aspirin and clopidogrel) or group II (placebo and aspirin) based on DAPT scores [4]. Aspirin and clopidogrel (group I) as DAPT were administered to individuals with a DAPT score of ≥2 and those with a DAPT score <2 received aspirin and placebo (group II) along with other optimum medication for a year (**Table 1**).

Table 1. Calculation of DAPT scores is based on the following parameters.

Parameter	Score
Age ≥75 years	−2
Age 65 - 75 years	−1
Age <65 years	0
Current cigarette smoker	1
Diabetes	1

Continued

MI at presentation	1
Prior PCI or prior MI	1
Stent diameter	1
Paclitaxel-eluting stent	1
CHF or LVEF <30%	2
Saphenous vein graft PCI	2

CHF: Chronic heart failure; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction; PCI: Percutaneous coronary intervention.

The primary efficacy endpoint was the occurrence of MACCE, (stent thrombosis, stroke, myocardial infarction (MI), and death between 12 to 24 months after the procedure) and all-cause mortality. Standard criteria for the diagnosis of stent thrombosis, MI, and stroke were used.

7. The Academic Research Consortium Definitions Are Provided below

7.1. Definite Stent Thrombosis

Partial or total thrombotic occlusion confirmed angiographically or pathologically, in the peri-stent area and an additional criterion, which could be an acute ischemic symptom, ECG changes, or elevated cardiac biomarker.

7.2. Probable Stent Thrombosis

Unexplained incidence of death <30 days after stent implantation or myocardial infarction associated with reported acute ischemia in the area of the implanted stent not possessing an angiographically confirmed stent thrombosis or any other cause.

7.3. Possible Stent Thrombosis

Death after 30 days due to unexplained reasons.

According to standard diagnostic criteria, stroke was defined, including clinical assessment and imaging studies.

Bleeding was graded into mild, moderate, and severe as per the simplified Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) criteria.

8. GUSTO Bleeding Criteria

1) Severe or life-threatening: Substantial hemodynamic compromise requiring treatment due to intracerebral hemorrhage.

2) Moderate: No hemodynamic compromise but requiring blood transfusion.

3) Mild: Bleeding present but not meeting the above criteria.

Follow-up was carried out in the 3rd, 6th, and 12th months. At every follow-up, clinical examination, blood investigations, electrocardiogram, complete blood count, random blood sugar, and renal function test were performed. Other specific investigations such as troponin level, computed tomography scan, and repeat angiogram, were carried out when needed. At the end of one year of enrollment, inter-group comparisons were made for the endpoints.

9. Statistical Analysis

The comparison of clinical characteristics was carried out using a chi-squared test and student's t-test for qualitative and continuous variables, respectively. Results with values of $p < 0.05$ were considered significant.

10. Results

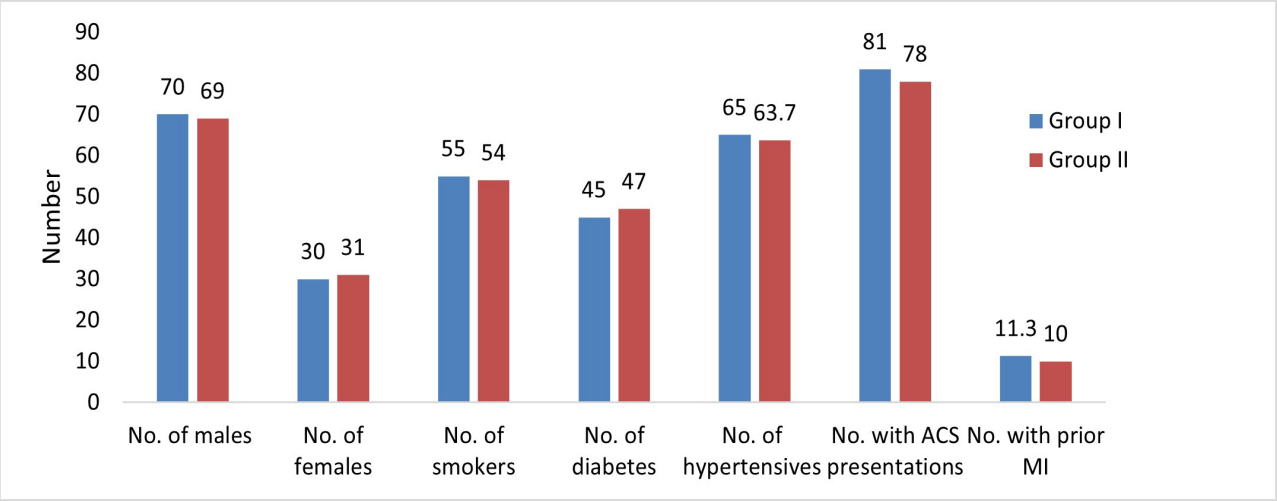
The number of patients enrolled in the study was 956, with 469 of the study participants continuing DAPT and 487 participants being administered placebo + aspirin. Baseline characteristics were matched (Table 2, Figure 1).

After following up for one year, numbers of ischemia & bleeding and deaths were observed (Figure 2).

Table 2. Baseline characteristics.

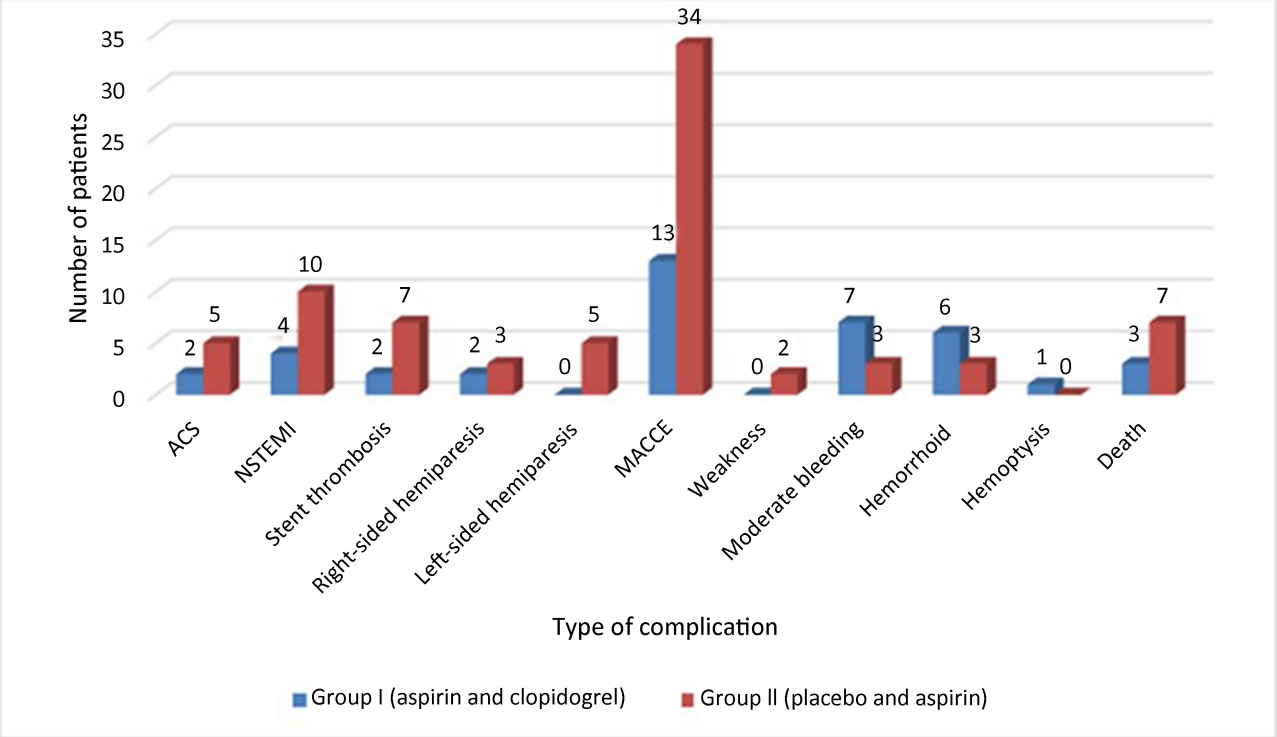
Parameter	Group I (N = 469)	Group II (N = 487)
Mean age	52.5	51.2
Number of males	70	69
Number of females	30	31
Mean body weight	52	53.5
Number of smokers	55	54
Number of diabetics	45	47
Number of hypertensives	65	63.7
Number with ACS presentations	81	78
Number with prior MI	11.3	10
Mean stent length	28.5 mm	31.3 mm
Mean stent diameter	2.8 mm	2.9 mm
Mean LVEF	39%	40%

ACS: Acute coronary syndrome; LVEF: Left ventricular ejection fraction; MI: Myocardial infarction.



ACS: Acute coronary syndrome; MI: Myocardial Infarction.

Figure 1. Matching of baseline characteristics between group I and group II.



ACS: Acute coronary syndrome; MACCE: Major adverse cardiac and cerebrovascular events; NSTEMI: Non-ST-elevation myocardial infarction.

Figure 2. Number of complications in both groups.

Patients with DAPT after one year had a lower number of major adverse cardiac events (MACE). Out of 469 patients from the DAPT arm (group I), only 13 (2.7%) experienced a MACCE. In the placebo group (group II), out of 487 patients, the total number of patients who suffered a MACCE was 34 (6.9%) with a significant p-value of 0.003. Myocardial infarction (MI) without mortality was reported in 6

(1.2%) patients of the DAPT arm (group I). In the placebo arm (group II), MI without mortality was reported in 15 patients, which was 3% of the total patients in group II. Inter-group comparison of the results showed that MI without mortality did not significantly differ between the groups (p = 0.06). Stroke was reported in 2 (0.4%) out of 469 patients in the DAPT arm (group I). In the placebo arm (group II), stroke was reported in 5 (1.2%) patients. The differences between the two groups were not statistically significant (p = 0.29).

Stent thrombosis was reported in 2 (0.42%) patients out of a total of 469 patients in group I. In the placebo arm (n = 487), only 7 (1.4%) patients developed stent thrombosis in group II. No statistically significant inter-group differences in stent thrombosis (p = 0.05).

The total number of deaths reported in the DAPT arm (group I) was 3 (0.6%) in group I whereas 7 (1.4%) in group II. Death was reported in 7 patients out of 487 in the placebo arm, which was around 1.4% of patients in group II. The differences between the two groups were not statistically significant (p = 0.05).

Continued use of aspirin and clopidogrel (group I) compared to aspirin and placebo (group II) reduced the incidence of MACCE significantly (2.7% vs. 6.9%, p = 0.003). However, the incidences of stroke (0.4% vs 1.2%), stent thrombosis (0.42 vs. 1.4%), and MI (1.2% vs 3%) showed no significant difference. Moderate bleeding was higher in the clopidogrel group (1.4% vs 0.6%), though this again, was not statistically significant (p = 0.19).

11. Discussion

CAD mortality is due to complications such as MI, arrhythmia and heart failure (HF). Atherosclerotic plaques in coronary vessels lead to stenosis and ischemia, or rupture and thrombosis, ultimately resulting in MI. Chronic ischemia and MI further precipitate HF and may lead to death. Management of CAD is directed at reducing symptoms of angina and preventing MI and death. Medical treatment aims at alleviating angina and stabilizing atherosclerotic plaques. Invasive procedures such as PCI are necessary to re-establish blood supply to ischemic areas [5].

The American Heart Association (AHA) guidelines of 2011 recommended the use of P2Y12-receptor antagonists and aspirin (DAPT) for at least a year following DES [6]. In individuals having undergone PCI, DAPT is necessary to avoid ischemia and stent thrombosis. However, choosing an appropriate antiplatelet agent is challenging as they must reduce thrombosis without causing significant bleeding [7].

The bleeding risk appears to be proportional to the length of treatment. Although shortening DAPT to 6 months could reduce bleeding, extending DAPT beyond a year significantly decreased ischemic events among individuals who managed a year of DAPT without bleeding [8]. Thus, it is essential to ascertain the risk-to-benefit ratio of DAPT. By optimizing patient selection, DAPT could be successfully used to reduce ischemia without causing bleeding [6]. It is necessary to weigh the bleeding risk before deciding the treatment duration [8]. For this, the

DAPT score may be used.

The current study found that group I on clopidogrel and aspirin showed a greater benefit on MACCE than group II who were on aspirin and placebo (p = 0.003). Inter-group differences in stent thrombosis and MI were not observed. Moderate bleeding was slightly higher in the clopidogrel group (p = 0.19). This study encourages the continuation of DAPT in individuals with a DAPT score ≥2 without much risk of significant bleeding.

In comparison with previous studies like the DAPT study, which was one of the largest studies, this study demonstrated reduced thrombotic events in post-PCI patients continuing DAPT beyond one year, selected on the basis of DAPT score. Though MI, all-cause mortality, stroke, and stent thrombosis were reduced, this decrease was not statistically significant. In this study, MACEs were reduced significantly. Therefore, the patients with a DAPT score ≥2 benefited by continuing therapy beyond one year.

In this study, bleeding risk was assessed with a simple GUSTO criterion as it is easy to use and has been used in previous studies. Although no major bleeding events were reported in this study, moderate bleeding events were observed. Despite the number of moderate bleeding events being higher in the DAPT arm compared with the placebo arm, the results were not statistically significant.

The findings of this study are in accordance with the results reported in different systematic reviews. A meta-analysis and systematic review of 24 randomized controlled trials (RCTs) involving 79,073 patients revealed that prolonged DAPT beyond one year after DES placement significantly reduces MI incidence compared to 12-month DAPT, midterm DAPT, and short-term DAPT followed by either aspirin or P2Y12 inhibitor monotherapy [9]. Another recent network meta-analysis analyzing 27 RCTs involving 79,880 patients was conducted to compare different DAPT regimes after coronary drug-eluting stenting. It was found that the short-term DAPT followed by P2Y12 inhibitor monotherapy (S-DAPT + P2Y12) demonstrated the lowest bleeding risk (OR = 0.36, 95%CI: 0.26 - 0.49), whereas long-term DAPT (L-DAPT) presented the highest bleeding risk. In terms of MI, stent thrombosis, and cardiovascular and cerebrovascular adverse events, L-DAPT proved to be the most effective regimen with odds ratios of 1.82 (95%CI: 1.49 - 2.21), 2.18 (95%CI: 1.45 - 3.28), and 1.28 (95%CI: 1.12 - 1.45) respectively [10].

To summarize, this study reinforces that extended DAPT, guided by the DAPT score, effectively reduces thrombotic events in high-risk patients post-PCI without significantly increasing bleeding risks.

11.1. Strengths of the Study

The study is well powered, and baseline characteristics were adequately matched, strengthening the validity. The one-year follow-up allows for the observation of long-term effects. Alternately, the study provides valuable data on the effectiveness of DAPT in the Indian population, adding to its real-world relevance.

11.2. Limitations of the Study

The study has certain limitations. It did not account for inter-individual variability, affecting the generalizability of the results. The findings may be region-specific and not applicable beyond the Indian context. The study's scope on bleeding risks is limited, as moderate bleeding events were observed but not statistically significant, requiring more detailed analysis. Since this study was conducted at a single center, this may further limit the applicability of the results.

12. Conclusion

This study indicates that extended DAPT, guided by the DAPT score, effectively reduces MACCEs in high-risk patients who have undergone PCI without significantly increasing bleeding risks.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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