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RESEARCH ARTICLE

Comparison of clopidogrel with aspirin versus aspirin alone for the secondary prevention of atherothrombotic events

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Abstract

Background: Dual antiplatelet therapy with clopidogrel plus low dose aspirin has not been studied in broad population of patients at high risk for atherothrombotic events.

Method: We randomly assigned 232 patients with either clinically evident cardiovascular and cerebrovascular atherothrombotic events to receive clopidogrel (75mg per day) plus aspirin (75mg per day) or aspirin (75mg per day) and followed them for a period of 12 months. The primary efficacy end point was composite of first occurrence of myocardial infarction (nonfatal), ischemic stroke (nonfatal), death due to cardiovascular/cerebrovascular causes.

Results: The rate of primary efficacy end point was 6.19 percent in clopidogrel plus aspirin group and 8.92 percent in aspirin alone group. (Relative risk: 0.69; 95 percent Confidence Interval: 0.27 - 1.75; p = 0.30). The rate of secondary efficacy end point was composite of first occurrence of myocardial infarction (nonfatal), ischemic stroke (nonfatal), hospitalization for angina or transient ischemic attack (TIA) was 15.04 percent in the clopidogrel plus aspirin and 18.75 percent in the aspirin (Relative risk: 0.80; 95 percent Confidence Interval: 0.44 – 1.48; p = 0.28). The rate of bleeding was 6.19 percent in the clopidogrel plus aspirin and 4.46 percent in the aspirin (Relative risk: 1.38; 95 percent confidence interval: 0.45-4.24; p=0.39). The rate of adverse events was 11.50 percent in the clopidogrel plus aspirin and 7.14 percent in aspirin (Relative risk:1.61; 95 percent confidence interval: 0.69-3.73; p=0.18).

Conclusion: Clopidogrel plus aspirin was not significantly more effective than aspirin alone for the secondary prevention of atherothrombotic events in patients with myocardial infarction or unstable angina (who have already completed 12 months of dual antiplatelet therapy), stable angina, ischemic stroke or transient ischemic attack.

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INTRODUCTION

Atherosclerotic vascular disease has propensity to cause arterial thrombosis, a sequence that has been characterized as an "atherothrombotic" process (Ruggeri, 2002; Fuster et al., 2005). Coronary and cerebrovascular atherothrombotic disorders are leading causes of death and disability in the world (Lopez and Murray, 1998). Their prevalence is increasing; they are significantly undertreated, and better means of prevention are needed (Bhatt et al., 2006a). Available antithrombotic therapy is safe and efficient but the morbidity and mortality due to atherothrombosis is still unacceptably high (Juan et al., 2004).

Platelets have been shown to play a central role in the pathogenesis of atherothrombosis (Ruggeri, 2002; Fuster et al., 2005). Intravascular thrombosis is initiated by platelet adhesion and aggregation and is completed by the formation of fibrin. Thus Platelets participate in pathological thrombosis that leads to myocardial infarction, stroke and peripheral vascular thrombosis (Brunton et al., 2011).

Prevention of platelet aggregation can prevent thrombus formation (Satoskar et al., 2011). Potent inhibitors of platelet function have been developed in recent years. These drugs act by discrete mechanisms; thus, in combinations, their effects are additive or synergistic. Their availability has led to a revolution in cardiovascular medicine. In patients with previous vascular events, the use of antiplatelet agents for secondary prevention is well established (Brunton et al., 2011).

A number of studies support the benefits of antiplatelet agents, which are used in the secondary prevention of myocardial infarction and stroke. Long term treatment with an antiplatelet agent after ST-segment elevation myocardial infarction (STEMI) is associated with 25% reduction in the risk of recurrent infarction, stroke, or cardiovascular mortality. (Fauci et al., 2008)

The platelet active drugs inhibit different steps in either platelet activation or platelet recruitment. The prostaglandin thromboxane A_2 is an arachidonate product that causes platelets to change shape, release their granules, and aggregate. Drugs that antagonize this pathway interfere with platelet aggregation. Aspirin is the prototype of this class of drugs, which inhibits the enzyme cyclooxygenase and reduces production of thromboxane A_2. (Zehnder et al., 2007).This interferes with the formation of thrombi. Aspirin is a cornerstone of treatment in cardiovascular disease (Goldman et al., 2007)

Clopidogrel is a thienopyridine that irreversibly inhibits adenosine diphosphate $P2Y_{12}$ receptor on platelet, thus reducing platelet aggregation by inhibiting ADP pathway of platelet (Zehnder et al., 2007). The trial CAPRIE (1996) conducted by Gent M et al. (Gent et al., 1996) concluded that long term administration of clopidogrel in patients with atherosclerotic vascular disease is more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction or death due to vascular events. There were no significant differences between the two drugs in terms of safety. Thus, clopidogrel is an effective alternative to aspirin for use in atherothrombotic disease (Brunton et al., 2011).

Clopidogrel combined with aspirin reduces death and coronary ischemic events in patients with acute coronary syndrome and also reduces the risk of thrombus formation in patients undergoing implantation of stent in coronary artery (Fauci et al., 2008). This suggests the synergistic actions of the two drugs, as might be expected from their distinct mechanisms of action.

Aspirin inhibits only the cyclooxygenase pathway leaving the adenosine diphosphate (ADP) $P2Y_{12}$ receptor unaffected. Moreover aspirin resistance has been noted in the research studies (Kour et al., 2006).This suggests that addition of clopidogrel to aspirin may be beneficial.

While combined treatment with clopidogrel and aspirin for at least a year is recommended in patients with acute coronary syndrome and following implantation of a drug eluting stent; studies have not shown any benefit of routine addition of clopidogrel to aspirin in patients with chronic stable Ischemic heart disease (Fauci et al., 2008).

In light of this, we thought it is worthwhile to evaluate the efficacy and safety of clopidogrel and aspirin combination for the secondary prevention of atherothrombotic events and to compare with aspirin monotherapy.

This aim of study was to compare the efficacy and safety of clopidogrel and aspirin combination with aspirin alone for the secondary prevention of atherothrombotic events.

MATERIAL AND METHODS

This study was conducted at the Medicine Department of tertiary care teaching hospital. This was a prospective, randomized, open-labelled, study for evaluation of efficacy and safety of clopidogrel plus aspirin as compared with aspirin alone for secondary prevention in patients with previous atherothrombotic events.

The study was approved by Institutional Ethics Committee and written informed consent was obtained from all the patients enrolled in the study.

Patients were eligible to enroll in the trial if they were 40 years of age or older and had one of the following conditions: myocardial infarction (MI) or unstable angina (who have already completed 12 months of dual antiplatelet therapy), stable angina, ischemic stroke or transient ischemic attack (TIA) within previous three months of an event.

Patients were excluded if they had history of acute coronary syndrome (myocardial infarction or unstable angina) of $\leq$ 12 months from the occurrence of an event and the patient with recent stent implantation or undergoing stent implantation. Patients with history of intracranial haemorrhage, systemic bleeding, bleeding diathesis or coagulopathy were also excluded. Patients with known valvular heart disease, patients having current peptic

ulceration, patients on long term nonsteroidal anti-inflammatory drugs, patients scheduled for major surgery or vascular surgery, patients with severe comorbid conditions such as moderate or severe kidney or liver disease, leukaemia, lymphoma, malignant tumours were excluded.

Eligible patients were randomly assigned either to clopidogrel (75 mg per day) plus aspirin (75 mg per day) or aspirin (75 mg per day). All the patients also received other concurrently required medications such as hypolipidemic drugs, antihypertensive drugs, antidiabetic drugs, etc.

Study treatment was started on the day of randomization and continued for 12 months. After randomization, follow up visits were scheduled at 1, 3, 6, 9, and 12 months. These visits were supplemented by follow up telephonic calls to the patients. During these follow up visits patient's compliance was assessed, adjustment of other concurrently required medication was done if required, interventions, outcome events and adverse events were recorded.

Primary efficacy end point

Composite of first occurrence of myocardial infarction (nonfatal), ischemic stroke (nonfatal), death due to cardiovascular/cerebrovascular causes.

Secondary efficacy end point

Composite of first occurrence of myocardial infarction (nonfatal), ischemic stroke (nonfatal), death due to cardiovascular/cerebrovascular causes, and hospitalization for angina pectoris or transient ischemic attack (TIA).

Safety end point

Safety was evaluated by recording incidence as well as severity of bleeding and any other adverse events in each group of patients throughout the follow up period. Bleeding was evaluated according to the 'Global Utilization of strategies to Open Occluded Coronary Arteries' (GUSTO) criteria (Rao et al., 2006, 2007) GUSTO criteria for classifying the severity of bleeding is as follows; 1) Severe or life threatening bleeding such as intracranial haemorrhage or bleeding that causes substantial hemodynamic compromise requiring blood or fluid replacement, along with inotropic support, or surgical intervention. 2) Moderate bleeding which needs blood transfusion but does not result in hemodynamic compromise and does not require other interventions. 3) Minor bleeding that neither requires transfusion nor cause haemodynamic compromise.

Statistical analysis

Efficacy end point (primary and secondary), safety end point and other adverse events in clopidogrel plus aspirin group and in the aspirin alone group were analyzed by Pearson's chi square test. Analysis was based on the first occurrence of an event at any point during the follow up period. Patients lost to follow up were not included in the analysis. $P < 0.05$ is considered significant to show a statistical difference between the two groups.

RESULTS

A Total of 232 patients were enrolled in trial (December 2010 to December 2012). Of these, 116 patients were assigned to clopidogrel plus aspirin and 116 patients to aspirin. Three patients in the clopidogrel plus aspirin group and four patients in the aspirin alone group were lost to follow up. These patients were excluded from analysis. At 12 months follow up, data was available for 113 patients in the clopidogrel plus aspirin group and 112 patients in the aspirin alone group, which was analyzed for efficacy and safety end points.

There were in all 3 deaths in clopidogrel plus aspirin group; 2 deaths due to cardiovascular cause and 1 death due to non-cardiovascular cause. In the aspirin group, there were 5 deaths in all; 3 deaths due to cardiovascular cause and 2 deaths due to non-cardiovascular cause. All these patients were included in the efficacy and safety analysis (Fig 1).

Baseline characteristics of patients included in both the groups were comparable at baseline as regards to demographic characteristics when analyzed by 'Z test for the difference between two means. Similarly when analyzed by 'Z' test for the difference between proportions, both the groups were found to be comparable at baseline with respect to number of patients included as per inclusion criteria, their clinical characteristics as well as other concurrent medications received by them (Table 1).

With a follow up of 12 months, the rate of primary efficacy end point [composite of first occurrence of myocardial infarction (nonfatal), ischemic stroke (nonfatal), and death due to cardiovascular cause] was 6.19% in the clopidogrel plus aspirin group and 8.92% in the aspirin alone group. (Relative risk: 0.69; 95% CI: 0.27 - 1.75; $p = 0.30$). There was no statistically significant difference between the two groups as regard to the rate of primary efficacy end point ($p > 0.05$) (Table 2).

There was one death due to non-cardiovascular cause in the clopidogrel plus aspirin group as compared to two deaths in the aspirin alone group. The difference between the two groups with respect to deaths due to non-cardiovascular causes was not statistically significant as shown in the Table 3.

There were 6 (5.30%) patients hospitalized for angina in clopidogrel plus aspirin group; as compared to 9 (8.03%) patients in aspirin alone group. 4 (3.54%) patients were hospitalized for transient ischemic attack (TIA) in clopidogrel plus aspirin group; as compared to 2 (1.78%) patients in aspirin alone group.

The rate of the secondary efficacy i.e. [composite of first occurrence of myocardial infarction (nonfatal), ischemic stroke (nonfatal), death due to cardiovascular cause, hospitalization for angina or transient ischemic attack (TIA)] was 15.04% in the clopidogrel plus aspirin group as compared to 18.75% in the aspirin alone group. (Relative risk: 0.80; 95% CI: 0.44 – 1.48; p = 0.28). There was no statistically significant difference between the two groups as regard to the rate of secondary efficacy end point (p > 0.05) (Table 4))

There was not a single event of major or moderate bleeding in either of the two groups; however minor bleeding such as epistaxis, gastrointestinal bleeding and hematuria occurred in patients of both the groups. The overall incidence of bleeding (composite of epistaxis, gastrointestinal bleeding, and hematuria) was 6.19% in the clopidogrel plus aspirin group and 4.46% in the aspirin alone group. (Relative risk: 1.38; 95% CI: 0.45 – 4.24; p = 0.39). The difference in the overall incidence of bleeding between the two groups was not statistically significant. (p>0.05) (Table 5).

The other adverse events found in patients of both the groups were gastric upset, diarrhoea, and rash. The overall incidence of other adverse events (composite of gastric upset, diarrhoea, and rash) was 11.50% in the clopidogrel plus aspirin group and 7.14% in the aspirin alone group. (Relative risk: 1.61; 95 % CI: 0.69 – 3.73; p = 0.18).

The incidence of adverse events was relatively less in aspirin alone group as compared with clopidogrel plus aspirin group; however, the difference in the overall incidence of adverse events between the two groups was not statistically significant (p > 0.05) (Table 6).

DISCUSSION

This study was conducted with aim of comparing the efficacy and safety of clopidogrel and aspirin combination with that of aspirin alone for the secondary prevention of atherothrombotic events. Patients with myocardial infarction or unstable angina (who have already completed 12 months of dual antiplatelet therapy), stable angina, ischemic stroke or transient ischemic attack (TIA) within previous three months of an event were included in the study.

We excluded the patients with acute coronary syndrome (myocardial infarction or unstable angina) of ≤ 12 months from an event, patients with recent stent implantation or undergoing stent implantation; as dual antiplatelet therapy is indicated in these patients for up to 12 months from the occurrence of an event (Fauci et al., 2008; Sweetman, 2007;Mehta et al., 2001, Chen et al., 2005;Sabatine et al., 2005)

Patients enrolled in this study either received clopidogrel (75 mg per day) plus aspirin (75 mg per day) or aspirin (75 mg per day).

Similar doses have been used in several studies comparing efficacy and safety of clopidogrel and aspirin combination with aspirin alone in such as recent clinical trials MATCH (Diener et al., 2004), COMMIT (Chen et al., 2005), CHARISMA (Bhatt et al. 2006b), ACTIVE (Connolly et al., 2009) etc.

All the patients in this study continued to receive other concurrently required medications such as atorvastatin, β-blocker, ACE inhibitor, nitrates, diuretics, antidiabetic drugs, etc.

The two groups were comparable at baseline as regards to demographic characteristics, number of patients included as per inclusion criteria, their clinical characteristics as well as other concurrent medications received by them.

Therefore, the difference in the incidence of efficacy end point and safety end point, if any between the study groups can be attributed to the difference in the study drugs used.

In our study, we found that, at the end of follow up i.e.12 months from the day of randomization, there was no significant benefit associated with clopidogrel plus aspirin combination when compared with aspirin alone in reducing the incidence of the primary end point (composite of first occurrence of myocardial infarction, ischemic stroke and death from cardiovascular cause).

Similarly, there was no significant benefit found with clopidogrel plus aspirin combination therapy when compared with aspirin alone, in reducing the secondary efficacy end point (composite of first occurrence of myocardial infarction, ischemic stroke, death from cardiovascular cause, hospitalization for angina, or transient ischemic attack).

In our study, safety of dual antiplatelet therapy (clopidogrel plus aspirin) in comparison with aspirin monotherapy was assessed in terms of incidence of bleeding and other adverse events in both the groups.

In our study, we used 'The Global Use of Strategies to Open Occluded Coronary Arteries' (GUSTO) bleeding criteria for assessment of severity of bleeding based on the finding in the study, which compared another

bleeding criteria 'Thrombolysis in Myocardial Infarction' (TIMI) and found that the risk association persisted only with 'GUSTO', while the 'TIMI' correlation did not reach significance. The authors recommended that future clinical trials should consider using a combination of the GUSTO bleeding scale and the need for transfusion to assess bleeding complications (Roa et al., 2006, 2007).

In the present study, there was not a single event of major or moderate bleeding found in either of the two groups. Minor bleeding such as epistaxis, gastrointestinal bleeding and hematuria occurred in both the groups. The other adverse events such as gastric upset, diarrhea, and rash occurred in both the groups. The difference in the incidence of bleeding and other adverse events between the two groups was not statistically significant.

In this study, the rationale for combining two antiplatelet agents with different mechanisms of action is based on the possibility of obtaining additive effects in preventing vascular recurrences in patients with clinically evident atherothrombotic events.

In the trial CAPRIE (Gent et al., 1996) clopidogrel was found to be superior than aspirin in reducing the risk of death from vascular causes, myocardial infarction, and ischemic stroke. After CAPRIE, other clinical trials have lent the evidence which supports the use of dual antiplatelet therapy in patients with acute coronary syndrome and in those undergoing percutaneous coronary interventions (Yusuf et al., 2001; Steinhubl et al., 2002; Chen et al., 2005;Sabatine et al., 2005).

However studies have not shown any benefit of the routine addition of clopidogrel to aspirin in patients with chronic stable ischemic heart disease (Fauci et al., 2008).

CHARISMA trial (Bhatt et al., 2006b) in patients with symptomatic vascular disease (including a history of MI and stable angina) or multiple risk factors showed that clopidogrel plus aspirin was not more effective than aspirin alone in reducing the rate of vascular events in patients with clinically evident atherothrombotic disease or multiple risk factors.

In the trial CHARISMA, after the analysis of results only in patients with clinically evident atherothrombosis i.e. excluding the group of high risk patients, it was found that, clopidogrel plus aspirin combination is marginally better than aspirin alone. However, authors have suggested that since this finding is based on subgroup analysis, it should be interpreted with caution and this finding requires further study.

Thus, the finding in our study that clopidogrel plus aspirin is not more effective than aspirin alone is in consistence with the overall finding of CHARISMA trial; however it differs with the result of subgroup analysis of this trial.

In CHARISMA trial, though severe bleeding was comparable in both the groups, clopidogrel plus aspirin was associated with a significant increase in the rate of moderate bleeding; while in our study the difference between the incidence of bleeding in two groups was not statistically significant. In CHARISMA trial patients were followed up for 28 months, whereas in our study, the follow up period was 12 months.

The MATCH (Diener et al., 2004) trial has evaluated combination of clopidogrel and aspirin in comparison with clopidogrel monotherapy therapy for secondary prevention of stroke. The researchers concluded that there was no demonstrable benefit of adding clopidogrel to aspirin for secondary prevention of stroke.

Our study finding is in concurrence with the finding of MATCH trial, that the combination of clopidogrel and aspirin is not more effective than aspirin monotherapy for the secondary prevention of atherothrombotic events.

However in MATCH trial, life threatening bleedings and major bleedings were higher in the group receiving aspirin and clopidogrel versus clopidogrel alone, which is in contrast to our study results, where we found that the two treatments do not differ with respect to the occurrence of bleeding events.

The other difference being that MATCH trial was conducted only in patients with cerebrovascular events i.e. stroke and TIA; whereas in our study, patients with both cardiovascular and cerebrovascular events were enrolled. Duration of follow up in MATCH trial was 18 months; whereas in our study, we followed up the patients for 12 months. MATCH trial compared efficacy and safety of clopidogrel plus aspirin with clopidogrel alone whereas we compared efficacy and safety of clopidogrel plus aspirin with that of aspirin alone.

Kennedy J et al. (Kennedy et al., 2007) in the FASTER trial concluded that, immediately after TIA or minor stroke, patients are at high risk of stroke, which might be reduced by using clopidogrel in addition to aspirin. The haemorrhagic risk of the combination of aspirin and clopidogrel do not seem to offset this potential benefit. However in this trial follow up period was 90 days; whereas in our study, patients were followed up for a period of 12 months. Thus, the finding in our study is based on use of antiplatelet therapy for a longer duration i.e. for 12 months.

A systematic review and meta-analysis by Geeganage CM et al (Geeganage CM et al. 2012) comparing the safety and efficacy of dual versus mono antiplatelet therapy in patients with acute ischemic stroke or TIA found that Dual antiplatelet therapy appears to be safe and effective in reducing stroke recurrence and combined vascular events in patients with acute ischemic stroke or transient ischemic attack as compared with monotherapy. Our

findings differ with this meta-analysis since we found dual antiplatelet therapy and monotherapy have similar efficacy.

In the trials, CURE (Mehta et al., 2001) conducted in patients with acute coronary syndrome, COMMIT (Chen et al., 2005) conducted in acute myocardial infarction and CLARITY-TIMI-28 (Sabatine et al., 2005) conducted in patients undergoing per cutaneous intervention, it was found that, clopidogrel plus aspirin combination is superior over aspirin alone in reducing major cardiovascular event. Whereas in the trials REAL-LATE and ZEST-LATE (Park et al., 2010) conducted in patients with drug eluting stent, there was no benefit found with clopidogrel and aspirin combination therapy when given for more than 12 months.

In our study, we found that clopidogrel plus aspirin do not offer any additional benefit over aspirin alone for the secondary prevention of atherothrombotic events and the incidence of bleeding and other adverse events was similar in both the groups.

Thus, we conclude that, combination of clopidogrel and aspirin is not significantly more effective than aspirin alone for the secondary prevention of atherothrombotic events in patients with myocardial infarction or unstable angina (who have already received 12 months of dual antiplatelet therapy), stable angina, stroke, or transient ischemic attack. Similarly, the two treatments do not differ as regard to safety considering bleeding and other adverse events.

The results and conclusions of our study are based on the findings where the patients were followed up for 12 months. The results and inference could differ if similar studies are conducted for longer duration.

Figure 1: Study profile

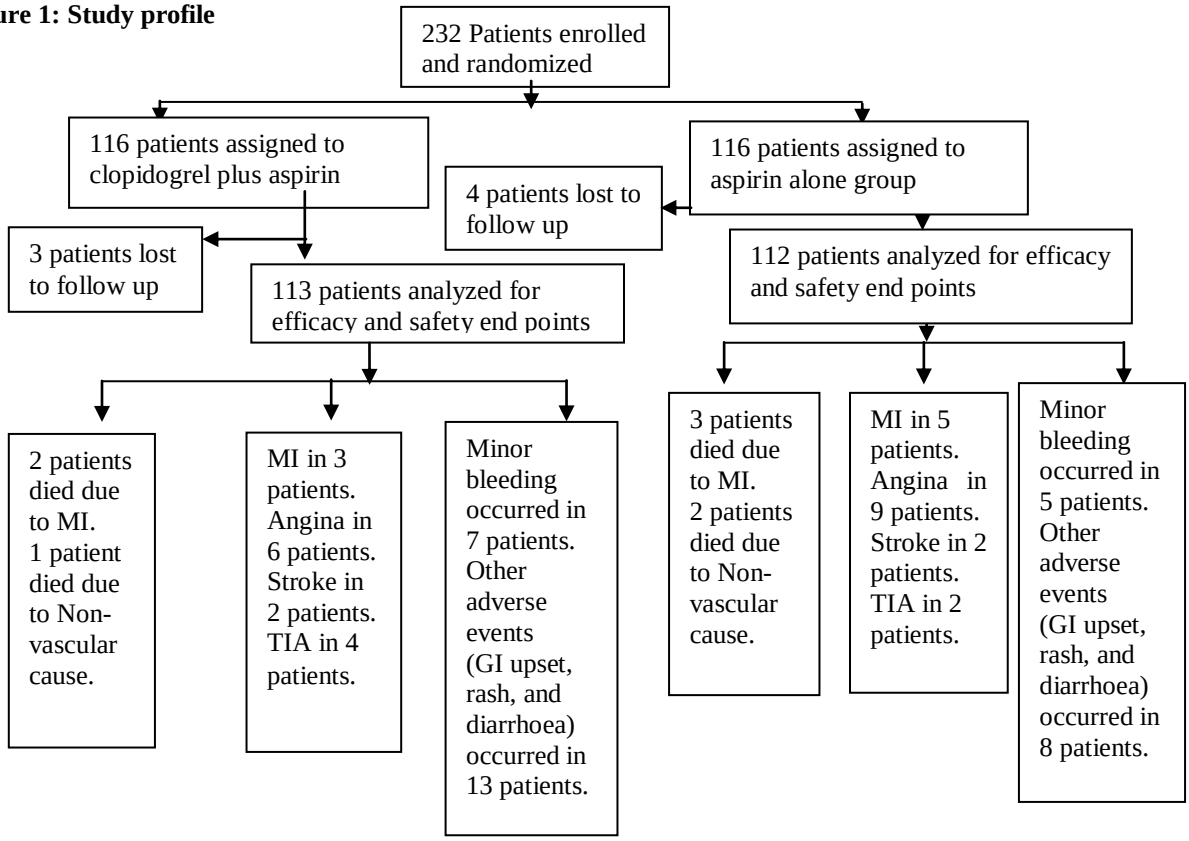

Table 1: Baseline demographic characteristics, inclusion subgroups, clinical characteristics, and other concomitant medications.

Characteristics	Clopidogrel plus Aspirin (n=113)	Aspirin alone (n=112)
	No. of Patients (%)	No. of Patients (%)
A) Demographic characteristics		
i) Mean age (year) ± SD	55.31 ± 12	56.46 ± 13.74
ii) Mean weight (kg) ± SD	60.5411.41	57.83 ± 12.32
i) Males	73 (64.60)	69 (61.60)
ii) Females	40 (35.39)	43 (38.39)
B) Inclusion subgroup		
i) Myocardial infarction	33 (29.20)	31 (27.67)
ii) Angina	49 (43.36)	51 (45.53)
iii) Ischemic stroke	27 (23.89)	25 (22.32)
iv) Transient ischemic attack	4 (3.53)	5 (4.46)
C) Clinical characteristics		
i) Congestive heart failure	20 (17.69)	17 (15.17)
ii) Hypertension	86 (76.10)	82 (73.21)
iii) Diabetes mellitus	11 (9.73)	13 (11.60)
D) Concomitant medications		
i) Atenolol	46 (40.70)	42 (37.50)
ii) Amlodipine	37 (32.74)	33 (29.46)
iii) Enalapril	82 (72.56)	79 (70.53)
iv) Nitrates	69 (61.06)	73 (65.17)
v) Diuretics-	22 (19.46)	18 (16.07)
vi) Atorvastatin	73 (64.60)	75 (60.95)
vii) Antidiabetic (Metformin and or Glibenclamide)	11 (9.73)	13 (11.60)

Values are expressed as Mean ± Standard deviation or number (%)

Table 2: Primary efficacy end point

Primary efficacy end point	Clopidogrel plus Aspirin (n=113)	Aspirin alone (n=112)	Relative Risk 95% CI	p Value
	No. of Patients (%)	No. of patients (%)		
Myocardial Infarction	3 (2.65)	5 (4.46)	0.59 (0.14 – 2.42)	0.35
Ischemic stroke	2 (1.77)	2 (1.78)	0.99 (0.14 – 6.91)	0.68
Vascular Death	2 (1.77)	3 (2.68)	0.66 (0.11 – 3.87)	0.49
Total	7 (6.19)	10 (8.92)	0.69 (0.27 – 1.75)	0.30

Vascular death – cardiovascular death (death due to myocardial infarction) CI – Confidence interval

Table 3: Death due to non-cardiovascular causes

Events	Clopidogrel plus Aspirin (n=113)	Aspirin alone (n=112)	Relative Risk 95% CI	P value
	No. of patients (%)	No. of patients (%)		
Non vascular death	1 (0.88)	2 (1.78)	0.49 (0.04-5.38)	0.49

Non-vascular death – Death not due to cardiovascular/cerebrovascular cause
CI – Confidence interval

Table 4: Secondary efficacy end point

Secondary efficacy end point	Clopidogrel plus Aspirin (n=113)	Aspirin alone (n=112)	Relative Risk 95% CI	p Value
	No. of Patients (%)	No. of patients (%)		
Myocardial Infarction	3 (2.65)	5 (4.46)	0.59 (0.14 – 2.42)	0.35
Ischemic stroke	2 (1.77)	2 (1.78)	0.99 (0.14 – 6.91)	0.68
Vascular Death	2 (1.77)	3 (2.68)	0.66 (0.11 – 3.87)	0.49
Angina	6 (5.30)	9 (8.03)	0.66 (0.24-0.79)	0.29
TIA	4 (3.54)	2 (1.78)	1.98 (0.37 – 10.60)	0.34
Total	17 (15.04)	21 (18.75)	0.80 (0.44- 1.48)	0.28

TIA – Transient ischemic attack CI – Confidence interval

Table 5: Bleeding events

Bleeding events	Clopidogrel plus Aspirin (n=113)	Aspirin alone (n=112)	Relative Risk 95% CI	p Value
	No. of Patients (%)	No. of patients (%)		
A) Major bleeding	0	0	-	-
B) Moderate bleeding	0	0	-	-
C) Minor bleeding				
i) Epistaxis	3 (2.65)	2 (1.78)	1.48 (0.25 – 8.72)	0.5
ii) GI bleed	2 (1.77)	2 (1.78)	0.99 (0.14 – 6.91)	0.68
iii) Hematuria	2(1.77)	1 (0.89)	1.98 (0.18-21.55)	0.50
Total	7 (6.19)	5 (4.46)	1.38 (0.45 – 4.24)	0.39

GI bleed – Gastrointestinal bleeding CI – Confidence interval

Table 6: Other adverse events

Secondary efficacy end point	Clopidogrel plus Aspirin (n=113)	Aspirin alone (n=112)	Relative Risk 95% CI	p Value
	No. of Patients (%)	No. of patients (%)		
Gastric upset	6 (5.30)	4 (3.57)	1.48 (0.43-5.12)	0.37
Diarrhea	4 (3.53)	2 (1.78)	1.98 (0.37-10.60)	0.34
Rash	3 (2.65)	2 (1.78)	1.48 (0.25-8.72)	0.50
Total	13 (11.50)	8 (7.14)	1.61 (0.69-3.73)	0.18

CI – Confidence interval

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