A Study on the Effectiveness of Mono and Dual Antiplatelet Therapy in Secondary Prevention of Vascular Events

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Research Article

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Abstract

Stroke or a cerebrovascular accident is the sudden death of brain cells due to the inadequate blood flow. The WHO clinically defines stroke as ' the rapid development of clinical signs and symptoms of a focal neurological disturbance lasting more than 24 hours or leading to death with no apparent cause other than vascular origin'. The study was aimed to determine whether addition of aspirin to clopidogrel could have a greater benefit than clopidogrel alone in prevention of secondary vascular events in patients after TIA or ischemic stroke. It was a retrospective observational study with duration of six months. The study was conducted in the Department of Neurology, Kovai Medical Center and Hospital, a multi speciality hospital in Coimbatore,Tamil Nadu. Among the stroke patients, visiting the neurology clinic, 34.2 % of patients had recurrence of vascular events. The mean age of the study population was found to be 61.36 years. The age of onset of the study population was found to be varying from 41 to 90 years. About 31% of the total study population, were under the age group of 61-70 and they constituted the highest percentage.29% were found to be in the 51-60 age group.20% of total patients were under the age group of 71-80.In the age group of 41-50,the percentage was 14% and 6% were noted in 81-90 age group. In the total study population, 86.8 % were having hypertension as the risk factor.52.6 % patients were identified to be having diabetes and 34.2 % of patients had a previous history of stroke.Out of the total study population, 36 patients had ischemic stroke as the qualifying event and 2 patients were having Transient Ischemic Attack. The event rate for ischemic stroke in dual therapy group was found to be 35.48 % and 0.2% for TIA. The frequency of primary endpoint event was found out from the plot between the follow up period in months and number of patients at risk. The number of primary endpoints was found to increase in the follow up period in patients receiving dual therapy whereas in mono therapy there was only a small rise in the frequency of primary endpoint event. The event rates were more in patients under dual therapy. The primary events were found to have a significant association with gender, risk factors and therapy. No bleeding complications were observed in the study population.

Introduction

Stroke, or a cerebrovascular accident is the sudden death of brain cells due to the inadequate blood flow. The WHO clinically defines stroke as ' the rapid development of clinical signs and symptoms of a focal neurological disturbance lasting more than 24 hours or leading to death with no apparent cause other than vascular origin'. Stroke is a clinical syndrome which can be sub divided into two broad categories according to its pathophysiology. Ischaemic strokes which are caused by either cerebral thrombosis or embolism accounting for 50-85% of all strokes worldwide and Haemorragic strokes caused by subarachnoid haemorrhage or intracerebral haemorrhage and which account for 1%-7% and 7%-27% respectively of all strokes worldwide.

The extent and site of brain injury indicates the effect of stroke but the clinical symptoms alone cannot accurately predict its underlying causes. Stroke symptoms involve speech impairment, memory loss, acute onset of unilateral paralysis, loss of vision, speech impairment, impaired reasoning ability, coma or death. It is found that one third of all strokes are preceded by Transient Ischemic attacks (TIAs), also called mini strokes, which are able to temporarily interrupt blood flow to the brain.

Up to 90% of all strokes are found to be ischemic in nature, while 10% resulting from intracerebral hemorrhage or subarachnoid hemorrhage . The majority of ischemic strokes are found to be of arterial origin such as atherothrombosis — which is a generalized, diffuse and progressive polyvascular disease. In most of acute ischemic strokes, unstable angina, acute MI, sudden cardiac death, and peripheral arterial disease (PAD), atherothrombosis have a key role. (Balucani et al.,2010)

The most widely used system of aetiological ischaemic stroke classification is Trial of Org 10172 in Acute Stroke Treatment (TOAST) .The TOAST classification system has five categories: 1) large-artery atherosclerosis 2) cardioembolism 3) small-artery occlusion (lacune) 4) stroke of other determined etiology and 5) stroke of undetermined etiology. (Wolf and Hennerici , 2011)

Antiplatelet therapy remains the cornerstone of therapy for treatment and secondary prevention because the pathophysiology of stroke involves atherosclerotic plaque disruption and subsequent thrombosis. Aspirin exerts its antiplatelet action by irreversibly inhibiting the cyclooxygenase enzyme, blocking the prostaglandin mediated pathway of platelet activation. Ticlopidine and clopidogrel,both thienopyridines which are structurally related and acts by selectively inhibiting adenosine diphosphate–induced platelet aggregation. Dipyridamole have both potent vasodilator and antiplatelet activity and act by by inhibiting phosphodiesterases or blocking uptake of adenosine.Epoprostenol ,another potent vasodilator is given to prevent platelet loss during renal dialysis.Glycoprotein (GP) IIb-IIIa antagonists which involves a complex platelet glycoprotein IIb- IIIa complex and mediates platelet aggregation via the binding of adhesive proteins such as fibrinogen and von Willebrand factor (vWF).Abciximab is a human-murine chimeric monoclonal antibody Fab fragment which binds to the complex GP IIb-IIIa with high affinity.Eptifibatide,Tirofiban and lamifiban are competetive inhibitors of the GP IIb IIIa complex.(Bennett and Brown 2003)

For preventing recurrent vascular events in patients with a history of stroke or TIA, antiplatelet therapy has been proven to be the best strategy available. The advantages of secondary stroke prevention associated with aspirin, other antiplatelet agents such as clopidogrel and combinations of antiplatelet drugs like aspirin and extended-release dipyridamole in preliminary therapy has been recognized by the Current clinical practice guidelines by American Heart Association (AHA), American Stroke Association (ASA), American College of Chest Physicians (ACCP), American Academy of Neurology (AAN), European Stroke Organization (ESO) and European Society of Cardiology (ESC).There has been great developments for the past two decades in antithrombotic agents for secondary stroke prevention. (Diener and Wong, 2008)

A series of trials in stroke prevention with antiplatelets have been carried out in past few years.CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial has shown that clopidogrel can better reduce the rate of ischaemic events and vascular events than aspirin. Randomised controlled trials in patients with coronary manifestations of atherothrombosis(CURE, CREDO) findings showed the sustained benefit of clopidogrel over the standard treatment including aspirin. The therapeutic benefits were all achieved along with an acceptable increase in the risk of major bleeding complications. Thus, these trials gave the motivation to undertake MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients), to find out whether aspirin added to clopidogrel would further reduce the risk of recurrent ischaemic vascular events in high-risk patients after transient ischaemic attack or ischaemic stroke. (Diener et al., 2004)

Patients who survive a stroke or TIA are especially vulnerable to recurrent cerebrovascular events and most likely to suffer other forms of cardiovascular disease, including coronary artery disease, congestive heart failure, atrial fibrillation and peripheral vascular disease. The long term stroke recurrence risk ranges from 4-12% annually with a particularly heightened risk in first 6 months after an event.These conditions predispose to high term mortality after stroke. Studying the effectiveness of mono and dual antiplatelet therapy will help in improving drug use and thereby increasing the quality of life in stroke patients.

The study was aimed to determine whether addition of aspirin to clopidogrel could have a greater benefit than clopidogrel alone in prevention of secondary vascular events in patients after TIA or ischemic stroke.

Material and Method

Study design: It was a retrospective observational study with duration of six months.

Study setting: The study was conducted in the Department of Neurology, Kovai Medical Centre and Hospital, a multi speciality hospital in Coimbatore, Tamil Nadu.

Study period: The study was conducted over a period of six months from June 2011 to December 2011.

Study population: A total of 38 subjects were included in this study.

Study criteria
Inclusion criteria
Patients of age > 40 years who are diagnosed with stroke and treated with mono and dual antiplatelet therapy.

Exclusion criteria
a) Patients who are less than 40 years of age.
b) Patients who are diagnosed with hemorrhagic stroke.

Sources of data
The data were collected from patients's case reports and treatment charts**.**

Study protocol
Patients who met the study criteria were included in the study.Ethical committte approval was obtained from Kovai Medical Center and Hospital.Records of patients on antiplatelet therapy from January 2009 to January 2010 were studied.Demographic characteristics of the patient including age,sex,occupation,smoking habits were collected.The other necessary findings like type of stroke,history of stroke,past medication history,type of antiplatelet therapy prescribed,number of reccurrences were noted from patient's case reports and treatment charts.Data was entered in the data entry sheet.Analysis was based on the first occurrence of an event in the primary endpoint at any point during the follow-up period.The follow up period was taken as 18 months.

Statistical analysis
Demographic characteristics of the study population were expressed in percentage. Relative risks and associations were determined by using the 'chi-square test'. Values of P ≤ 0.05 were considered to be significant**.**

Results

In this retrospective study, the effectiveness of mono and dual antiplatelet therapy in secondary prevention of vascular events was evaluated in a total of 38 patients with ischemic stroke, during the period June 2011 to December 2011.

Among the stroke patients, visiting the neurology clinic , 34.2 % of patients had recurrence of vascular events. The mean age of the study population was found to be 61.36 years. In the population identified, the number of male patients were found to be 30 and female patients were 8 (Table 1).

The age of onset of the study population was found to be varying from 41 to 90 years. About 31% of the total study population, were under the age group of 61-70 and they constituted the highest percentage.29% were found to be in the 51-60 age group.20% of total patients were under the age group of 71-80.In the age group of 41-50,the percentage was 14% and 6% were noted in 81-90 age group. (Table 2).

Mean age of patients taking dual therapy was found to be 61 and mean age in mono group was 64. In dual therapy group, 31% had Ischemic stroke as qualifying event compared to 5 % in monotherapy.

TABLE 1: Gender wise distribution of total study population

Sl.No	Gender	Percentage of patients
1.	Male	79%
2.	Female	21%

TABLE 2: Age wise distribution of the study population

Sl.No	Age group	Percentage of patients
1.	41-50	14
2.	51-60	29
3.	61-70	31
4.	71-80	20
5.	81-90	6

In the male study population, 86.6 % were prescribed dual therapy and 13.3 were prescribed with monotherapy (Table3,.In the female group, 87.5 % were prescribed with dual therapy and 12.5 % were given monotherapy.(Table 4).

In the total study population, 86.8 % were having hypertension as the risk factor.52.6 % patients were identified to be having diabetes and 34.2 % of patients had a previous history of stroke.(Table 5).

TABLE 3: Type of Antiplatelet prescribed.
MALE

Sl.No	Antiplatelet prescribed	Percentage of patients
1.	DUAL	86.6
2.	MONO	13.3

TABLE 4: Type of Antiplatelet prescribed.
FEMALE

Sl.No	Antiplatelet prescribed	Percentage of patients
1.	DUAL	87.5
2.	MONO	12.5

The mean age of the patients being prescribed dual therapy was found out to be 60.93 and mean age of the patients taking monotherapy was found to be 64.2 (Table 6).According to TOAST classification,2% were found to be having cardioembolism, 20% were having large artery atherothrombosis,12 % with small vessel occlusion in dual therapy group.20 % had cardioembolism and 60 % had small vessel occlusion in mono group.(Table 7,)

Previous ischemic stroke, hypertension, diabetes, hypercholestrerolemia were found to be the most common risk factors in the population studied. Previous ischemic stroke were reported in 12 % of

327

dual therapy group and 1% in mono group. Hypertension was found in 30 % of dual group and 3 % of mono group. Diabetes was found to be a risk factor in 16% of dual therapy patients and 4% in monogroup. Hypercholesterolaemia was identified as risk factor in 19% of dual group and 4 % of mono group.11% of dual therapy patients and 2 % of mono therapy patients were smokers. (Table 8)

TABLE 5: Risk factors and medical history

Sl.No	Risk factors	percentage of patients
1.	Hypertension	86.8
2.	Diabetes	52.6
3.	Previous ischemic stroke	34.2

TABLE 6: Base line characteristics

	DUAL	MONO
MEAN AGE	60.93	64.2
QUALIFYING EVENT		
IS	31(93.9)	5(1)
TIA	2(6)	0
TOAST CLASSIFICATION		
Cardioembolism	2(6)	1(20)
Large-artery atherosclerosis	20(60.6)	0
small-vessel occlusion	12(36.3)	3(60)
stroke of other determined cause	-	-
undetermined cause	-	-
RISK FACTORS AND MEDICAL HISTORY		
Previous IS	12(36.3)	1(20)
Hypertension	30(90.9)	3(60)
Diabetes	16(48.4)	4(80)
Hypercholester olaemia	19(57.5)	4(80)
Past or current smoker	11(33.3)	2(40)

TABLE 7:TOAST CLASSIFICATION

TOAST CLASSIFICATION	DUAL	MONO
Cardioembolism	2(6)	1(20)
Large-artery atherosclerosis	20(60.6)	0
small-vessel occlusion	12(36.3)	3(60)

	stroke of other determined cause	-	-
	undetermined cause	-	-

TABLE 8: Risk factors and medical history

Sl.No	Risk factors	DUAL (33)	MONO (5)
1.	Previous IS	36.3	20
2.	Hypertension	90.9	60
3.	Diabetes	48.4	80
4.	Hypercholesterolaemia	57.5	80
5.	Past or current smoker	33.3	40

Out of the total study population, 36 patients had ischemic stroke as the qualifying event and 2 patients were having Transient Ischemic Attack. The event rate for ischemic stroke in dual therapy group was found to be 35.48 % and 0.2% for TIA. The event rate for TIA was found to be 0.5 % in dual group. The event rate was found to be 31.2 % in dual therapy group in patients whose age is greater than 61 and 41.1% in patients of age greater than or equal to 61 compared to the 33.3 % in mono group. The event rate in dual therapy group for males was found to be 42.3 % and 0.25 % in mono group. The event rate in dual therapy group for females was found to be 14.2 %.In patients having hypertension 0.4 % event rate was noted in dual therapy compared to 33.3 % in monotherapy. Diabetes patients had 0.25 % event rate in dual therapy and 0.25 % in monotherapy. Event rate in patients with previous ischemic stroke was found to be 1% in dual therapy and 1 % in monotherapy.(Figure 9).

FIGURE 9: Frequency of primary endpoint event
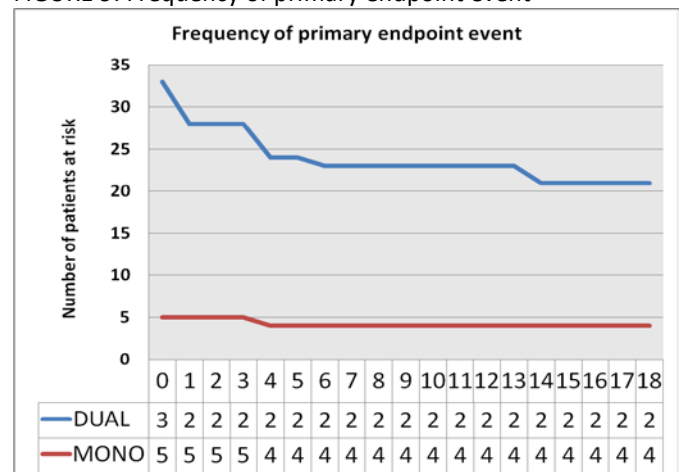
The frequency of primary endpoint event was found out from the plot between the follow up period in months and number of patients at risk. The number of primary endpoints was found to increase in the follow up period in patients receiving dual therapy

whereas in mono therapy there was only a small rise in the frequency of primary endpoint event.

Univariate analysis of factors affecting primary endpoint showed that there was an association between recurrence and factors like gender, hypertension, previous ischemic stroke, antiplatelet therapy. Out of the total study population,8 patients having age less than 61 had recurrence with a p value < 0.20.In the age group ≥ 61, five patients were found to have recurrence.12 male patients and 1 female patient were found to have recurrence with a p value < 0.01.In patients with hypertension,13 cases of recurrences were found with a p value < 0.01.In patients with diabetes,5 cases were recorded with a p value < 0.7.In dual therapy group 12 cases of recurrences were noted compared to 1 case in mono therapy group with a p value <0.01.(Table 10)

TABLE 9: Rates of primary endpoint event

		number(n)	EVENT RATE (%) DUAL	EVENT RATE (%) MONO
qualifying event	IS	36	35.48	0.2
	TIA	2	0.5	0
Age(years)	<61	18	31.2	0
	≥61	20	41.1	33.3
Sex	Female	8	14.2	0
	Male	30	42.3	0.25
Hypertension	No	5	0	0
	Yes	33	0.4	33.3
Diabetes	No	18	47	0
	Yes	20	0.25	0.25
Previous IS	No	25	0	0
	Yes	13	1	1

The relative risk for recurrence were found out in the study population. In patients having ischemic stroke the relative risk of monotherapy was found to be 1.7742 times than that of dual therapy. The relative risk was found to be the same for both mono and dual therapy in patients having TIA. Relative risk with mono therapy was .9412 times than dual therapy in patients of age < 61 and 1.2353 times in age ≥ 61.In male patients, relative risk with monotherapy was

1.6923 times than with dual therapy and in females it was found to be 0.7500 times. Patients with hypertension had 0.9744 times the risk and those with previous ischemic stroke had 1.2821 times risk than with dual therapy. The relative risk in patients having diabetes was found to equal in both dual and mono therapy.(Table 11)

TABLE 10: Univariate analysis of factors affecting primary event

		Recurrence	Non recurrence	P value
Age < 61		8	15	< 0.20
Age ≥ 61		5	10	
Male		12	18	
Female		1	7	< 0.01
Hypertension	YES	13	20	< 0.01
	NO	0	5	
Previous IS	YES	13	0	< 0.01
	NO	0	25	
Diabetes	YES	5	11	< 0.7
	NO	8	10	
Therapy	MONO	1	4	< 0.01
	DUAL	12	21	

TABLE 11: Relative risk

	Relative risk	95% CI	P value
Ischaemic stroke	1.7742	0.2886 - 10.9086	0.5361
TIA	1.0000	0.104 - 9.6139	1.0000
Age < 61	1.9412	0.141 - 26.7183	0.6200
Age ≥ 61	1.2353	0.2261 - 6.7498	0.8073

Male	1.6923	0.2924 - 9.7948	0.5570
Female	0.7500	0.04558 - 12.3407	0.8404
Hypertension	0.9744	0.41 - 2.3153	0.9531
Previous IS	1.2821	0.5717 - 2.8748	0.5465
Diabetes	1.0000	0.1499 - 6.6709	1.0000

Discussion

Stroke, or a cerebrovascular accident is the sudden death of brain cells due to the inadequate blood flow. Approximately, 20 million people suffer from stroke each year and out of these 5 million will not survive.85% of global deaths from stroke occurs in developing countries. It also causes functional impairments, 20% survivors require institutional care after 3 months and disability occurs in 15-30% (Balucani, et al.,2010). Ischemic stroke is found to be the principal universal cause of disability in the developed world, and the third leading cause of mortality. It is expected that 8–12% of individuals are found to die within the first 30 days of their initial stroke, and patients who survive the initial attack face an enlarged risk of successive vascular events and stroke, as approximately one-quarter of all strokes occurring each year are found to be recurrent. 21.5% of patients are found to be experiencing either a recurrent stroke or a transient ischemic attack (TIA) within the first year following the initial attack.(Diener and Wong, 2008). However, our results showed that out of the total patients, 34.2 % had recurrence of vascular events.

Official census data from the United Kingdom in 1981, 1991, and 2001 have persistently shown inequalities in ischemic stroke mortality among the South Asian population. According to the 3 cross-sectional studies based on the national census data in the United Kingdom, the average standard mortality ratios (SMR) in South Asians were 55% and 41% higher in males and females, respectively when compared with the white population. The average SMR for the South Asians between the ages of 20 and 69 years was 155 for males and 141 females. Although rates of mortality from stroke have been declining in the UK population as a whole between 1970 to 1992, among South Asians, the rate of decline was 10 times less than the white population.(Gunarathne et al., 2009). In our study the age of the study population varied from 41 to 90 years and the mean age of the study population was found to be 61.36 years. In the population identified, the number of male

patients were found to be 78.94% and female patients were 21 %.

A randomized, double-blind, placebo-controlled trial revealed that the most prevalent risk factors at randomization were hypertension (78%), diabetes mellitus(68%),and hypercholesterolemia (56%). 26% of patients had previous ischemic stroke and 19% had transient ischemic attack. Most patients (n=6033;79%) had one additional risk factor, as defined in the inclusion criteria at study entry, and 1496 (20%) had two or more. No imbalance in baseline characteristics was recorded between the two groups (Diener et al.,2004).In our total study population,86.8 % were having hypertension as the risk factor.52.6% patients were identified to be having diabetes and

34.2 % of patients had a previous history of stroke. Previous ischemic stroke, hypertension, diabetes, hypercholesterolemia were found to be the most common risk factors in the population studied. Previous ischemic stroke were reported in 12 % of dual therapy group and 1% in mono group. Hypertension was found in 30 % of dual group and 3 % of mono group. Diabetes was found to be a risk factor in 16% of dual therapy patients and 4% in monogroup. Hypercholesterolemia was identified as risk factor in 19% of dual group and 4 % of mono group.11% of dual therapy patients and 2 % of mono therapy patients were smokers.

The only 2 South Asian studies that classified their stroke population according to the TOAST taxonomy found a higher prevalence of lacunar strokes (42.7% and 68%) compared with large vessel infarctions (26% and 10%). In our study, according to TOAST classification,2% were found to be having cardioembolism, 20% were having large artery atherothrombosis,12 % with small vessel occlusion in dual therapy group. 20% had cardioembolism and 60 % had small vessel occlusion in mono group. (Gunarathne et al., 2009).

Of the 700,000 strokes that occur yearly in the United States, 200,000 are recurrent events. The risk of recurrent stroke has been reported as 11.5% at 7 days, 6% to 15% at 30 days, and 18.5% at 3 months. Following a transient ischemic attack (TIA), the estimated risk of recurrent stroke was 8% at 7 days, 11.5% at 1 month, and 17.3% at 3 months. However, in our study, out of the total study population, 36 patients had ischemic stroke as the qualifying event and 2 patients were having Transient Ischemic Attack. The event rate for ischemic stroke in dual therapy group was found to be 35.48 % and 0.2% for TIA. The event rate for TIA was found to be 0.5 % in dual group (Kiwon etal., 2007).

In a MATCH trial conducted in 507 centres , the estimated event rate per year for first occurrence of the primary endpoint was 12·7%, consistent with the protocol hypothesis; the on-treatment analysis was consistent with the intention-to-treat analysis (relative risk reduction 9·5%, 95% CI −2·0 to 19·6). Examination of the event rates for the primary endpoint in different predefined patient subgroups indicated a slight favour for adding aspirin to clopidogrel compared with placebo to clopidogrel in most subgroups . No interactions were reported between covariates and treatment effect, apart from patient age (p=0·012 for interaction between age and treatment effect (Diener et al.,2004). In our study,the relative risk for recurrence were found out in the study population. In patients having ischemic stroke the relative risk of monotherapy was found to be 1.7742 times than that of dual therapy. The relative risk was found to be the same for both mono and dual therapy in patients having TIA. Relative risk with mono therapy was .9412 times than dual therapy in patients of age < 61 and 1.2353 times in age≥ 61.In male patients, relative risk with monotherapy was 1.6923 times than with dual therapy and in females it was found to be 0.7500 times. Patients with hypertension had 0.9744 times the risk and those with previous ischemic stroke had 1.2821 times risk than with dual therapy. The relative risk in patients having diabetes was found to equal in both dual and mono therapy.

Conclusion

The aim of the study was to determine whether addition of aspirin to clopidogrel could have a greater benefit than clopidogrel alone in prevention of secondary vascular events in patients after TIA or ischemic stroke. Out of the total patients, 34.2 % of patients had recurrence of vascular events. 36.3 % patients reached the primary endpoint in the group receiving dual therapy compared to 20% in the monotherapy group. 31% in dual therapy group had Ischemic stroke as qualifying event compared to 5 % in monotherapy.

Our study focused on the prevalence of risk factors in patients with recurrence of vascular events. Risk factors found were previous ischemic stroke in 12 % of dual therapy group and 1% in mono group. Hypertension was found in 30 % of dual group and 3 % of mono group. Diabetes was risk factor in 16% of dual therapy patients and 4% in monogroup Hypercholesterolemia was found in 19% of dual group and 4 % of mono group11% of dual therapy patients and 2 % of mono therapy patients were smokers.

According to TOAST classification,2% were having cardioembolism,20% were having large artery atherothrombosis,12 % with small vessel occlusion in dual therapy group.20 % had cardioembolism and 60 % had small vessel occlusion in mono group.

In our study, we also observed the prescribing trends in patients and dual therapy was found to be more prominent than monotherapy. Dual therapy did not appear to have any added advantage over monotherapy .The event rates were more in patients under dual therapy. The primary events were found to have a significant association with gender, risk factors and therapy. No bleeding complications were observed in the study population.

Acknowledgement

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests