Assessment of Safety and Efficacy Outcomes of Patients Receiving Dabigatran in A Tertiary Care Hospital: A Retrospective Longitudinal Study

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ABSTRACT

OBJECTIVE -To assess the efficacy and safety outcomes of patients associated with the use of different doses of dabigatran and dabigatran with an antiplatelet in a tertiary care hospital. **METHODS -**A retrospective longitudinal hospital-based study was conducted and patients who were initiated with dabigatran at doses of 75,110 and 150 mg for non-valvular atrial fibrillation, stroke, deep vein thrombosis, and pulmonary embolism from March 2017 to 2019 were enrolled and followed for one year. Patients with end-stage renal disease, malignancy, and those who were reluctant to follow up were excluded from the study. Using the electronic medical database, all the required information was collected and evaluated for the occurrence of outcomes such as bleeding events, other adverse drug reactions, readmissions, effectiveness in the prevention of stroke, and DVT/PE, and survival analysis. **RESULTS -**A total of 75 patients were selected in which 33 patients were categorized into the dabigatran group and the remaining 42 into the dabigatran with the antiplatelet group. From the dabigatran group and dabigatran with an antiplatelet, 33.3 % and 40.47% experienced bleeding respectively. Other adverse event occurrences were 45.45% and 73.80% in the dabigatran and dabigatran with antiplatelet groups respectively. Readmission was higher with dabigatran along with antiplatelet. Effectiveness in stroke prevention was 100 % in the dabigatran group and 88.09 % in the dabigatran with an antiplatelet group. DVT/PE prevention was controlled in both the groups100%). In survival analysis 92% were alive and 8 % got expired. **CONCLUSION -**Major bleeding events were more evident in dabigatran with an antiplatelet group at 110 mg. Dabigatran with an antiplatelet at 110 mg dose was associated with a higher number of other adverse events as well as readmission rates. Effectiveness in stroke prevention was higher with the dabigatran group and DVT/PE prevention was controlled in both groups.

INTRODUCTION

Novel oral anticoagulants (NOACs) are the mainstay of management of thromboembolic events which are indicated by the FDA to prevent and treat a range of thromboembolic events which exert its action via the blockade of central elements of the coagulation cascade. The main indications comprise deep vein thrombosis, pulmonary embolism, atrial fibrillation, and stroke [1]. The term novel was initially applied to dabigatran during the period 2010 when it was introduced to the US market. Conventionally used vitamin K antagonist warfarin was later replaced with NOACs. These novel agents mainly include dabigatran (Pradaxa) approved by the U.S. Food and Drug Administration (FDA) in 2010, rivaroxaban (Xarelto) approved in the year 2011, apixaban (Eliquis) cleared in 2012 and, edoxaban (Savaysa) which is approved in 2011. Compared to VKAs, NOACs offer simplification of long-term anticoagulation therapy because of less frequent dose adjustments along with intermittent INR monitoring. Advantages of NOACS include the rapid onset of action, few drug interactions, specific coagulation enzyme targets and, predictable pharmacokinetics [2]. Vitamin K antagonist has several drawbacks imminent to the long-term application of these drugs due to their narrow therapeutic index, drug interactions, and risk of bleeding. To overcome these downsides NOACs are being evolved [3].

Dabigatran is the first oral direct thrombin inhibitor that is endorsed by the FDA in the prevention of embolic events in patients with non-valvular atrial fibrillation. It has a less antagonistic effect on thrombin-mediated platelet aggregation. The recommended dose is 150 mg twice daily, indefinite cases a reduced dose of 110 mg is recommended, particularly in patients with moderate renal impairment and geriatric patients who are at risk of bleeding [4,5]. In patients with normal renal function, levels of dabigatran will fall to 25% of steady-state concentration after 24 hours and to 6.25 % after 48 hours. At recommended therapeutic doses, dabigatran prolongs the coagulation markers like activated partial thromboplastin time (aPPT), Ecarin clotting time (ECT), and Thrombin time (TT.) aPPT provides an approximation of dabigatran's anticoagulant effect. In the RE-LY trial, the median trough aPPT in patients who received150 mg dose was 52 seconds [6]. NOAC versus warfarin for stroke prevention in patients with AF proved that NOAC is superior to warfarin in the evention of stroke and embolism in patients with AF along with a significant reduction in intracranial hemorrhage which leads to an overall reduction in mortality. [7] Efficacy and safety of direct oral anticoagulants for cardiovascular indications proved that NOAC had predominantly superior efficacy and safety in non-valvular atrial fibrillation and non-inferior

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efficacy in case of acute VTE.[8] NOACs versus warfarin for stroke prevention in NVAF proved that NOACs are superior to warfarin in stroke prevention in patients with NVAF, reduction of bleeding events, and convenience in usage.[9] Non-Vitamin K antagonist oral anticoagulant comparison versus warfarin in AF patients with intracerebral hemorrhage proved that NOACs were associated with a lower risk of ischemic stroke and recurrent stroke compared with warfarin.[10] Clinical effectiveness of NOACs versus warfarin in older patients with AF and ischemic stroke proved that NOAC use at discharge was associated with better long-term outcomes compared to warfarin in patients with AF and IS [11].

Complications associated with the use of dabigatran mainly include bleeding, which can be major or minor. Major bleeding based on the level of Hb, transfusion rate, and hemorrhage from a critical anatomical site. Minor bleeding includes GI bleeding, gum bleeding, ecchymosis, hematoma, bleeding from the nose and eyes. Other associated complications are esophageal injury, impairment of liver and kidney function, cardiac abnormalities, and allergic reactions. Dosing is mainly based on CHAD-VASc and HAS-BLED scores. CHA_2DS_2-VASc score used for stroke risk stratification in atrial fibrillation (AF) patients and HAS-BLED for the assessment of bleeding risk [7].

From the baseline study, we realized dabigatran is better, so we focused on dabigatran, which has a rapid onset of action, few drug interactions, and predictable pharmacokinetics and we ought to know which dose is appropriate and have the lowest risk and the safety and efficacy outcomes of dabigatran and dabigatran with antiplatelet.

MATERIALS AND METHODS:

METHOD

STUDY DESIGN

A retrospective longitudinal hospital-based study.

STUDY PARTICIPANTS

 Patients who were initiated with dabigatran for non-valvular atrial fibrillation, stroke, deep vein thrombosis, and pulmonary embolism from March 2017 to 2019 were enrolled and followed for one year. Patients with more than 18 years who were initiated with dabigatran during the period March 2017 to March 2019 were included in the study. Patients who had the end-stage chronic renal disease (CrCl<30 ml/mint), malignancy patients, patients who

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were reluctant to follow up / were not willing to participate in follow-up were excluded from the study.

METHODOLOGY

A total of 150 patients initiated with dabigatran at doses of 75,110 and 150 mg were included in the database and only 120 were fitted into the inclusion criteria and eligible for the study. Of 150 patients, 15 were excluded due to chronic kidney disease, 9 due to malignancy, and 6 were reluctant to follow up. Among 120 patients, 75 patient data was collected and categorized into two arms as dabigatran and dabigatran with antiplatelet with 33 and 42 participants respectively. The data was collected using the electronic medical database. The suitable patients were determined from the database using the specific unique health identification number (UHID) and the required data such as demographic details (age, sex, weight, contact number, past medical history, past medication history, etc.), details regarding antiplatelet therapy, safety, efficacy outcomes were collected with the help of a data collection form. The risk of bleeding and occurrence of stroke was determined based on HAS-BLED Score and CHA2DS2-VASc score before initiation of dabigatran therapy and the same was repeated at 6-month intervals. The patient admissions during the follow-up period (reason for hospitalization) and survival details (vascular and all-cause mortality) till the end of the study period were also assessed.

STUDY OUTCOMES

The study was mainly focused on safety and efficacy outcomes in dabigatran-treated patients. The safety outcomes of dabigatran at different doses (75mg, 110mg, and 150mg) in each indication are bleeding (major or minor), other adverse effects, hospitalizations, and survival. Efficacy outcomes include the effectiveness in stroke prevention as well as DVT/PE prevention.

Primary safety outcome - Bleeding or Hemorrhage**.**

Major bleeding: Drop-in hemoglobin level of at least 2g/dl or transfusion of at least 2 units of packed blood cells or hemorrhage from a critical anatomical site.

Minor bleeding: Includes gastrointestinal bleeding (indicated by melena implying upper GI bleed and hematochezia implying lower GI bleed), gum bleeding, ecchymosis, hematoma, hemarthrosis, hemoptysis, hematuria, or bleeding from other sites like eyes, nose, etc.

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Efficacy outcome: Occurrence or recurrence of stroke/Thromboembolic events, Recurrence of DVT, PE.

Secondary outcomes

Other adverse events, hospitalization, and survival.

STATISTICAL ANALYSIS

The data were presented either as the mean ± standard deviation (SD) or the number of patients and percentage. Data storage and analysis were performed using Microsoft Excel and IBM SPSS 25. The Kaplan-Meier curve was used to represent the survival data of dabigatran-treated patients. All the p values were two-tailed and a significance level of 5% was used.

RESULT AND DISCUSSION

RESULTS

1. Safety Outcomes

1. 1 Bleeding

Bleeding events were considered as the important parameter of the safety outcomes of Dabigatran. Major and minor bleeding data regarding different doses in the Dabigatran group and Dabigatran with an antiplatelet group are elaborated in Table 1.1. In the Dabigatran group, major bleeding was highest with 150 mg and lowest with 75 mg. But minor bleeding was highest with 110 mg and 75 mg equally. In the other group (with antiplatelet), 110 mg had the highest major bleeding rates and also there were no minor bleeding events with 75 mg and 150 mg. In total, 11 (33.3%) patients experienced bleeding in the Dabigatran group and 17(40.47%) patients in Dabigatran with the antiplatelet group. In the comparison of both groups, there is a significant difference (P-0.002) in the bleeding rates between Dabigatran and the Dabigatran with antiplatelet groups**.**

Readmission for bleeding within 1 year of initiation of therapy was much more evident in the combination group than in the dabigatran alone group. Only one patient among the study participant needed to discontinue the dabigatran therapy due to bleeding. 5 patients in the dabigatran group and 17 patients in the dabigatran with the antiplatelet group had greater than or equal to 2 g/ dl decrease in Hb and 1 patient each in both the groups required to have a

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transfusion of > 2 units of packed red blood cells due to bleeding. The GI bleeding was more evident in the form of Malena.

Table No. 1: Occurrence of bleeding in dabigatran and dabigatran with an

BLEEDING	DABIGATRAN				DABIGATRAN WITH ANTIPLATELETS			
	75mg (N=4)	110mg (N=10)	150mg (N=19)	**Total (N=33)**	75 mg (N=6)	110 mg (N=34)	150 mg (N=2)	**Total (N=42)**
Major	1 (25%)	2 (20%)	3(15.78%)	**6(18.18%)**	1(16.16%)	13(38.2%)	2 (100%)	**16(38.09 %)**
Minor	2 (50%)	2 (20%)	1(5.26%)	**5(15.15%)**	0	1 (2.94%)	0	**1(2.38%)**

1.2. Other adverse events

Dabigatran with antiplatelet therapy is associated with higher incidences of other adverse events than dabigatran alone. Other adverse events mainly comprise liver abnormalities, kidney problems, electrolyte imbalances, GI problems, etc. 15 ADR associated with dabigatran alone and 31 with dabigatran and antiplatelet therapy. Electrolyte imbalances mainly include hypokalemia and hyponatremia. Liver and kidney problems mainly include elevation of liver enzymes as well as renal function. Dermatological disorders reported with combination therapy include Acneiform eruptions, Melasma, Erythema multiform, and hyperpigmented patches. When comparing the doses most of the adverse events were reported with dose 110 mg and the least number of adverse events with 150 mg in the category of dabigatran with antiplatelet therapy. In dabigatran therapy, 150 mg is associated with the highest number of events and 75 mg with the least number of events. When comparing both the groups, 45.45% of patients experienced ADR in the dabigatran group, and 73.80% of patients experienced adverse events in the dabigatran with an antiplatelet therapy group. There are no significant differences exist between the experienced ADR in both groups.

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Table No. 2: Comparison of other adverse events between dabigatran and dabigatran with antiplatelet groups

Other ADR	DABIGATRAN				DABIGATRAN WITH ANTIPLATELET				
	75mg (N=4)	110mg (N=10)	150mg (N=19)	Total (N=33)	75mg (N=6)	110mg (N=34)	150mg (N=2)	Total (N=42)	
Liver problems	-	-	1 (5.3%)	1 (3.03%)	-	4 (11.76%)	-	4 (9.5%)	P VALUE: 0.620
Kidney problems	1(25%)	1(10%)	1 (5.3%)	3(9.09%)	1 (16.6%)	1 (2.94%)	2 (100%)	4 (9.5%)	
Skin disorders	-	-	2 (10.5%)	2(6.06%)	2 (33.3%)	2 (5.88%)	1 (50%)	5(11.9%)	
Vision problems	-	-	1 (5.3%)	1(3.03%)	2 (33.3%)	-	-	2(4.76%)	
GI problems	-	-	2 (10.5%)	2(6.06%)	2 (33.3%)	6 (17.64%)	-	8(19.04%)	
Electrolyte abnormalities	2(50%)	2(20%)	1 (5.3%)	5(15.2%)	1 (16.6%)	5 (14.7%)	-	6(14.3%)	
Others	-	-	1 (5.3%)	1(3.03%)	-	2 (5.88%)	-	2 (4.76%)	

1.3. Hospital Readmissions

Hospital readmissions due to adverse events associated with dabigatran are higher in dabigatran-antiplatelet combination therapy compared to dabigatran alone treatment. The common reasons for readmissions include hyponatremia, gastrointestinal disturbances, recurrent stroke, etc. Most of the cases were reported in the combination category under 110 mg and electrolyte abnormality and recurrent stroke is one of the highlighting reasons for readmission. 21 patients got readmitted in the category of dabigatran with antiplatelet from 42 patients and 1 case of readmission from 33 cases in dabigatran alone category due to anemia**.** It is evident that 3.03% got readmitted during the study period in the dabigatran category and 50% of subjects got admitted in dabigatran with an antiplatelet group.

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Table No. 3: Comparison of hospital readmission between dabigatran and dabigatran with antiplatelet

DRUG (N)	HOSPITAL READMISSIONS	P VALUE
DAB IGATRAN	1(3.03%)	
DABIGATRAN WITH ANTIPLATELET	21(50%)	.002

1:4 Survival Analysis

Figure 1.4 explains the survival data of subjects during the study period and the reason for mortality is categorized into all-cause mortality and mortality due to cardiovascular associated causes. From the total number of patients i.e. Out of 75 patients, 4 patients were dead during the study period due to all-cause mortality and 2 died due to cardiovascular mortality. A total of 6 deaths were reported throughout our study, it was found that only 1 death (all-cause mortality) was associated with the dabigatran group at a dose of 75 mg (25%). The remaining 5 were related to dabigatran with an antiplatelet group in which 4(Two all-cause mortality and two CV-related mortality) with 110mg (11.77%) and 1 (all-cause mortality) with 75 mg (2.95%). From the figure1.4, the first death is reported during the 9th month of the study period due to all-cause mortality. The remaining deaths were reported during the 12th month, 15th month, 17th month, 19thmonth, and the final death is reported during 24 months. Out of the total subjects enrolled in the study, 92% of them were alive and 8 % got expired during the study period. Mortality due to all causes includes accidents, age-related death, etc. and more death occurred in the 110 mg group. The range of survival time is 16 months and the mean is 11.7-20.23.
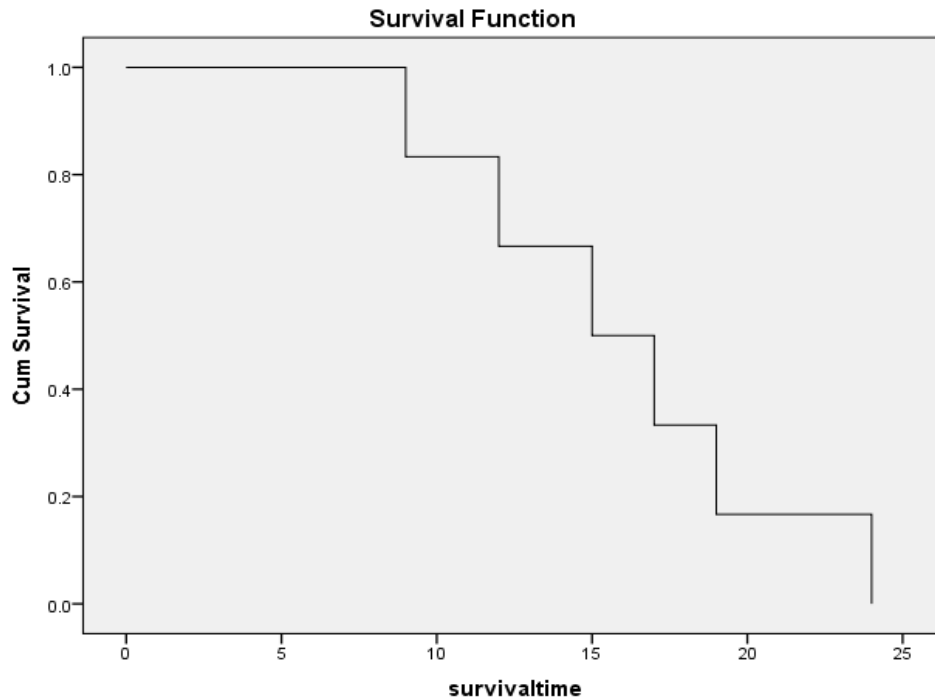
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Figure No. 1: Kaplan Meier plot for survival data

2. Efficacy outcomes

The effectiveness of Dabigatran was analyzed in terms of stroke prevention and DVT/PE control as shown in Table 2. In the Dabigatran group, there was complete stroke prevention and in Dabigatran with an antiplatelet group, stroke prevention was 88.09%. DVT/PE was completely controlled in both groups. Among the total 42 patients of Dabigatran with an antiplatelet group, 5 experienced recurrent stroke where the Dabigatran group had a complete stroke prevention profile. From the data assessed, there were no significant differences (P= 0.327) between the Dabigatran alone and Dabigatran with the antiplatelet group regarding the effectiveness parameters (stroke prevention, DVT/PE control).

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Table No. 4: Comparison of Effectiveness in preventing stroke and DVT/PE in dabigatran and dabigatran with the antiplatelet group

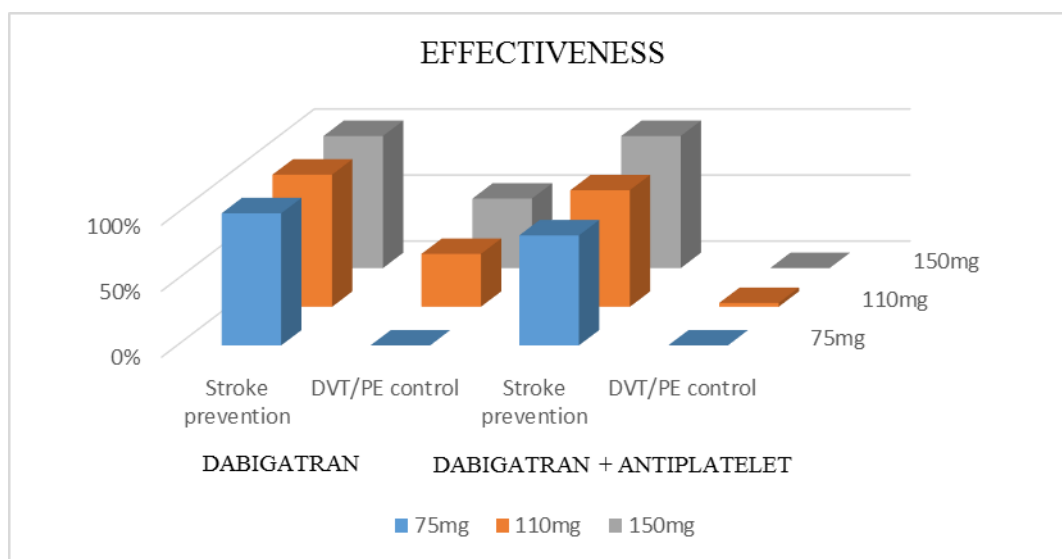| EFFECTI VENESS	DABIGATRAN ALONE				DABIGATRAN WITH ANTIPLATELETS				P VALUE: 0.327
	75mg (N=4)	110mg (N=10)	150mg (N=19)	**Total (N=33)**	75 mg (N=6)	110 mg (N=34)	150 mg (N=2)	**Total (N=42)**	
Stroke prevention	4 (100%)	10(100 %)	19(100 %)	**33(100%)**	5(83. 3%)	30(88.2 %)	2(100 %)	**37(88.1%)**	
DVT /PE control	0	4(40%)	10(52.6 %)	**14(100%)**	0	1(2.9%)	0	**1 (100%)**	

Figure No. 2: Effectiveness of Dabigatran in both treatment groups in stroke prevention and DVT/PE control

DISCUSSION

The key findings of this retrospective longitudinal study are following. Bleeding events were considered as a prominent parameter that measures the safety of Dabigatran. Although previous dose comparison studies concluded that 110 mg had lower rates of major bleeding, we had major bleeding events associated with 110 mg of Dabigatran [13]. It was also evident that bleeding events were higher in the Dabigatran with an antiplatelet group in comparison

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with the other. Thus for total bleeding events, results showed a significant statistical difference between both the groups.

The effectiveness of Dabigatran was measured using stroke prevention as well as DVT/PE control. In RELY trial, it was concluded that Dabigatran 150 mg was associated with a lower risk of stroke [14], likewise in our study, total patients in the Dabigatran group were prevented from recurrent stroke and had a complete DVT/PE control throughout the study period. Although there is no significant statistical difference between the groups, recurrent stroke events had occurred in Dabigatran with antiplatelet therapy especially with 110 mg.

In our study, we also assessed other adverse events experienced by the patients during the study period. The finding revealed that dabigatran with antiplatelet is associated with higher complications. Dabigatran with antiplatelet is associated with a higher number of liver problems, kidney problems, skin reactions, GI disturbances, electrolyte abnormalities when compared to the dabigatran group. These observations were consistent with the result of a previous study [12].

The reason for readmissions between both groups was analyzed in our study. We found that readmission was higher for dabigatran with the antiplatelet group due to electrolyte abnormality, GI problems, recurrent stroke, etc. A retrospective cohort study to determine the incidence and severity of bleeding events requiring hospitalization among AF patients receiving antiplatelet or anticoagulants found that anticoagulation with dabigatran was associated with an overall increased occurrence of bleeding requiring hospital readmission and GI problems was more prevalent with dabigatran and antiplatelet [15]. This was also considered to be one of the added strengths of our study since the data regarding the readmissions were limited.

In our Analysis, 92% of patients survived and 8 % of them decreased during the study period. The main reasons behind mortality are all-cause mortality and cardiovascular mortality. Out of 75 patients, 6 of the patients expired and 5 of them died due to all causes, and 1 due to cardiovascular mortality. Even though 6 were expired, 5 of them come under the category of dabigatran with antiplatelet, which denotes that this group is associated with an increased risk of mortality than dabigatran alone treatment. A systemic review and meta-analysis of dabigatran etexilate and risk of MI, other CV events, major bleeding, and all-cause mortality found that dabigatran is associated with significantly increased risk of MI and this increased

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risk should be considered taking into account the overall benefit in terms of major bleeding and all-cause mortality [16].

Instead of comparing Dabigatran with other oral anticoagulants which have been trialed across the world, our study aimed to assess the safety and efficacy within each dose of the drug as well as with its concomitant use along with antiplatelet. Certain limitations have come across and this includes,

- The number of patients prescribed with Dabigatran was enough to conduct a study, many of them were fallen under exclusion criteria. If this was a multicenter study, instead of a single-center, more patients could be enrolled.

- Since one of our objectives was to compare different doses of dabigatran, an equal number of patients should have been included within each dose. Due to the small sample size available, we could not incorporate an equal number of participants.

- Data collection via hospital databases leads to some missing information.

CONCLUSION

The occurrence of major bleeding among the different doses of dabigatran,110 mg is the most frequently prescribed dose, and even though it was having a lower risk of bleeding when compared to dabigatran 150 mg as per the previous studies, dabigatran 110 mg can also possess the significant risk of major bleeding. The risk of bleeding is further increased when the drug is given with an antiplatelet. Even though there was no significant difference between the occurrence of stroke and thromboembolic events (DVT and PE) in both the group, stroke reduction was better in the dabigatran group than with dabigatran and antiplatelet group. Occurrence of other complications was reported in each of the treatment groups and the rate of occurrence was found to be more in the dabigatran with an antiplatelet group. In survival analysis, only 20% mortality has occurred among the study participants. Skin reactions such as acneiform eruptions, problems with vision, esophagitis were the side effects of dabigatran that we're able to found from the study participants.

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