Original Article

Dabigatran: Clinical correlation of drug and its dose with risk of stroke and bleeding

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Abstract

Background: Dabigatran is the first oral direct thrombin inhibitor which is endorsed by Food and Drug Administration in the prevention of embolic events in patients with nonvalvular atrial fibrillation. Suitable dose of the drug for the patient is selected based on CHA2DS2-VASc score and HAS-BLED score.

Aim: To determine and compare the risk of occurrence of stroke and bleeding after the initiation of dabigatran therapy in patients prescribed with this drug.

Methods: Patients with more than 18 years who were prescribed with dabigatran during 2017-2019 in a tertiary care hospital were selected for the study. Most of the patient's prescriptions contained an antiplatelet, so a comparison was made between the clinical outcomes of patients given with dabigatran alone and dabigatran with an antiplatelet because antiplatelet can have effects on the safety as well as efficacy profile of dabigatran.

Results: Out of 75 patients enrolled in the study, 42 patients were in the dabigatran with the antiplatelet group and 33 were in the dabigatran alone group. In both the groups, there was a significant reduction in CHA_2DS_2-VASc score, i.e., 2.58 ± 1.32–1.94 ± 1.21 in dabigatran-treated patients within 6 months, and the score was lowered from 3.76 ± 1.22 to 2.92 ± 1.22 in other groups. The mean value of the HAS-BLED score of dabigatran was reduced from 1.15 ± 0.83 to 0.84 ± 0.78 and that of dabigatran with antiplatelet group from 2.10 ± 0.94 to 1.74 ± 0.92.

Conclusion: It was observed that within 6 months, both the treatment groups showed a reduction in the risk scores. The dabigatran group had lower background risks of stroke and bleeding in comparison to the dabigatran plus antiplatelet group.

Keywords: Antiplatelet, bleeding risk, dabigatran, oral anticoagulant, thromboembolic events

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INTRODUCTION

Dabigatran is a novel oral anticoagulant (NOAC), indicated by the Food and Drug Administration (FDA) to prevent and treat a range of thromboembolic events, which exerts its action via the blockade of central elements of the coagulation cascade.[1] Conventionally used Vitamin K antagonist (VKA) warfarin was later replaced with NOACs because of its rapid onset of action, few drug interactions, specific coagulation enzyme target, and predictable pharmacokinetics. VKA has several drawbacks

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which limit the long-term application of these drugs due to their narrow therapeutic index, drug interactions, and risk of bleeding.[2,3] The term novel was initially applied to dabigatran during 2010 when it was introduced to the US market. The approved indications are prevention of stroke and systemic embolism in nonvalvular atrial fibrillation, deep-vein thrombosis, and pulmonary embolism. The recommended dose is 150 mg twice daily, in definite cases, a reduced dose of 110 mg or 75 mg is preferred based on CHA_2DS_2-VASc and HAS-BLED score.[4,5]

CHA_2DS_2-VASc score

CHA_2DS_2-VASc score is often used for stroke risk calculation in atrial fibrillation patients. It has a score range of (0-9) and based on this score, the patient was categorized into low risk (0-1), moderate risk (2-3), and high risk (≥4).[6] Depending on the score, therapy could be initiated as follows, i.e., if the CHA_2DS_2-VASc score is 0, then there is no need of an antithrombotic therapy, if the score is 1, then antithrombotic therapy with oral anticoagulation or antiplatelet therapy is preferred and if the CHA_2DS_2-VASc score is >2, then oral anticoagulation is recommended.[7]

HAS-BLED score

The HAS-BLED system calculates the major bleeding risk. Based on this score, patients were categorized into low risk (<3 range) and high risk (≥3) patients. High risk indicates potential risk for bleeding and may require closer observation for the occurrence of adverse events.[6,8,9]

Even though dabigatran was approved by the FDA in 2010, Indian studies related to its safety profile are rare. The existing studies were based on the comparison of dabigatran with warfarin. Hence, this study mainly focused on assessing the risk for occurrence of bleeding and stroke associated with the use of dabigatran and dabigatran with antiplatelet, in a tertiary care hospital setting through 6 months follow-up.

From the Western studies, it was found that dabigatran 110 mg was associated with lower risk of major hemorrhage and 150 mg was associated with lower rate of stroke or embolism.[10] Hence, we analyzed whether the above findings are applicable in the Indian population.

In this study, one of our main objectives was to compare different doses of dabigatran such as 75 mg, 110 mg, and 150 mg for the comparison of risk scores, and such a comparison is not available elsewhere, especially with 75 mg. Efficacy and safety concerns when dabigatran given along with an antiplatelet were also determined in this study. In the case of methodological approach, we select patients prescribed with dabigatran in a hospital setting, whereas all available studies are mostly clinical trials. Comparison between different doses done in result helps to choose the best dose based on the risk scores.

METHODS

It was a retrospective longitudinal hospital based study conducted in a tertiary care hospital in the southern part of India. The patients who were initiated with dabigatran from March 2017 to March 2019 were selected and followed for 6 months. Institutional Review Board and Institutional Ethics Committee (Reg no: RAJH/2019/007) approval were obtained before the initiation of the study.

Patients with more than 18 years who were initiated with the drug during the study period were included in the study. However, patients who had chronic kidney disease (increased bleeding risk because of accumulation of drug), malignancy and those who were reluctant to participate in follow-up were excluded from the selected population.

The data were collected using the electronic medical database. A total of 105 patients initiated with dabigatran were identified from the database. However, only 75 patients fitted into the inclusion criteria and were eligible for the study. The remaining patients were excluded from the study for the following reasons such as 15 patients were with chronic kidney disease, 9 patients had malignancy, and 6 patients were reluctant to participate in the study.

Patient consent for participation was obtained before the commencement of the study. The demographic details, comorbid conditions, concurrent drug use, and details regarding antiplatelet therapy were collected from patient profiles. After collecting the required data, telephonic interviews of the patients were conducted to collect the missed data that were not available from the database. Risk of bleeding and risk of occurrence of stroke were calculated based on HAS-BLED Score and CHA_2DS_2-VASc score before the initiation of dabigatran therapy, and the same was repeated at 6-month interval. Comparison of scores obtained before initiation of therapy to that of 6 months posttherapy was made among different doses of dabigatran. Similarly, the dabigatran alone group was compared with dabigatran with the antiplatelet group for more accurate results in terms of improvement in the risk scores [Figure 1].

Data storage and analysis were performed using Microsoft Excel and IBM SPSS (Statistical Package for the Social

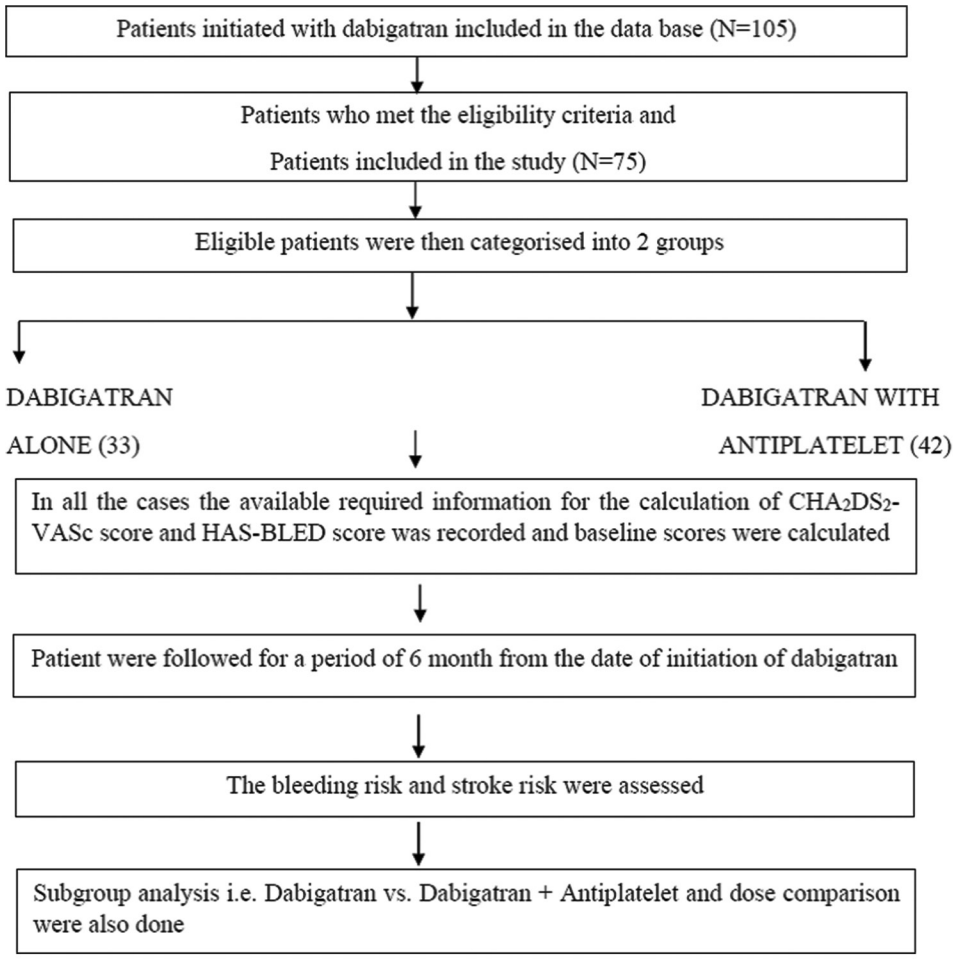

Figure 1: Flow chart of the study methodology

Sciences) 25. The risk for the occurrence of stroke and bleeding were the parameters analyzed between groups before initiation and after 6 months of therapy. Inferential tests were applied, and all the *P* values were two-tailed with a significance level of 5%.

RESULTS

Risk calculations in dabigatran users

Stroke risk

The CHA_2DS_2-VASc score for Dabigatran and Dabigatran with antiplatelet users in the initial and the 6 months are depicted in Table 1. The total number of high-risk patients in each dose was reduced in both groups after initiation of therapy. After 6 months, it was found that 110 mg of both the groups had an increase in the number of moderate-risk patients and a decrease in high-risk patients.

When comparing the CHA_2DS_2-VASc scores at initial and 6 months [Table 2] within the comparing groups, it is evident that the patients were showed an improvement in terms of their stroke risk. In the dabigatran alone group,

Table 1: CHA_2DS_2-VASc score of dabigatran users at 0th month and 6th month (dose-wise categorization)

	75 mg, *n* (%)	110 mg, *n* (%)	150 mg, *n* (%)	Total, *n* (%)
Dabigatran (0th month)	*n*=4	*n*=10	*n*=19	*n*=33
Low	0	1 (10)	5 (26.3)	6 (18.18)
Moderate	2 (50)	5 (50)	10 (52.63)	17 (51.5)
High	2 (50)	4 (40)	4 (21.06)	10 (30.3)
Dabigatran+antiplatelets	*n*=6	*n*=34	*n*=2	*n*=42
Low	0	1 (2.95)	0	1 (2.38)
Moderate	4 (66.6)	16 (47)	2 (100)	22 (52.3)
High	2 (33.3)	17 (50)	0	19 (45.2)
Dabigatran (6th months)	*n*=4	*n*=10	*n*=19	*n*=33
Low	0	3 (30)	8 (42.1)	11 (33.3)
Moderate	3 (75)	6 (60)	8 (42.1)	17 (51.5)
High	1 (25)	1 (10)	3 (15.78)	5 (15.15)
Dabigatran+antiplatelets	*n*=6	*n*=34	*n*=2	*n*=42
Low	1 (16.6)	3 (8.82)	0	4 (9.52)
Moderate	4 (66.6)	22 (64.7)	2 (100)	28 (66.66)
High	1 (16.6)	9 (26.47)	0	10 (23.8)

18.18% of patients in the low-risk group initially were increased up to 33.3%. In the case of the moderate-risk group, no change has occurred and high-risk groups showed a reduction from 30.3% to 15.15% at 6 months. Similarly, in dabigatran with antiplatelet group, 2.38% of

Table 2: Comparison of CHA_2DS_2-VASc score (initial versus 6th month)

Drugs	Number of patients (m onths)		Mean score (months)		*P*
	0, *n* (%)	6, *n* (%)	0	6	
Dabigatran					
Low	6 (18.18)	11 (33.3)	2.58±1.32	1.94±1.21	0.002
Moderate	17 (51.5)	17 (51.5)			
High	10 (30.3)	5 (15.15)			
Dabigatran with antiplatelets					
Low	1 (2.38)	4 (9.52)	3.76±1.22	2.92±1.22	0.000
Moderate	22 (52.3)	28 (66.66)			
High	19 (45.2)	10 (23.8)			
Comparison of dabigatran versus dabigatran with antiplatelet, *P*			0.000	0.001	

patients were increased up to 9.52% in low-risk group. Furthermore, patients in moderate (52.3%to 66.66%) and high risk (45.2% to 23.8%) groups showed improvement in their scores. The mean value of CHA_2DS_2-VASc score of dabigatran at the initial period was found to be 2.58 ± 1.32 and it was reduced to1.94 ± 1.2. In dabigatran with the antiplatelet group also there was a reduction of mean score from 3.76 ± 1.22 to 2.92 ± 1.22. In both groups, there was a significant decrease in the CHA_2DS_2-VASc score caused by the treatment given ($P = 0.002$ and $P = <0.05$). Furthermore, we could see that the risk of stroke score was higher in dabigatran with antiplatelet when compared to dabigatran alone.

Bleeding risk

The risk of bleeding at the initial and 6 months was assessed through HAS-BLED score and is elaborated in Table 3. In the dabigatran group, initially, there were 31 patients with low risk and only 2 with high risk of bleeding. Dabigatran with the antiplatelet group had 30 patients and 12 patients with low and high risk, respectively. At 6 months, a total of 32 and 36 patients were added to the low-risk classes of dabigatran and the other groups, respectively. Among different doses of dabigatran in dabigatran alone group, one patient, each from 150 mg and 110 mg dose, had a bleeding risk reduction from high-risk category to low risk category within 6 months of initiation of therapy. Similarly, in dabigatran with the antiplatelet group, 5 patients given with 110 mg dose had a risk reduction from high to low and one patient from 75 mg also showed risk reduction within 6 months.

In the comparison of the risk of bleeding at initial and 6th month [Table 4] using HAS-BLED scores, it is noticeable that patients showed a reduction in their bleeding risk. In dabigatran group, 93.9% of patients in low-risk group increased up to 96.9%. In high -risk group, 6.1% of patients were reduced to 3.03%. In dabigatran with the antiplatelet group, 71.4% of patients in the low group were increased up to 85.7% and 28.5% of patients in high-risk group were reduced up to 14.2%. After

Table 3: HAS-BLED score of dabigatran users in 0th month and 6th month (dose wise categorization)

	75 mg, *n* (%)	110 mg, *n* (%)	150 mg, *n* (%)	Total, *n* (%)
Dabigatran (0th month)	*n*=4	*n*=10	*n*=19	*n*=33
Low	4 (100)	9 (90)	18 (94.7)	31 (93.9)
High	0	1 (10)	1 (5.27)	2 (6.1)
Dabigatran+antiplatelets	*n*=6	*n*=34	*n*=2	*n*=42
Low	2 (33.3)	26 (76.4)	2 (100)	30 (71.4)
High	4 (66.6)	8 (23.5)	0	12 (28.5)
Dabigatran (6th month)	*n*=4	*n*=10	*n*=19	*n*=33
Low	3 (75)	10 (100)	19 (100)	32 (96.9)
High	1 (25)	0	0	1 (3.03)
Dabigatran+antiplatelets	*n*=6	*n*=34	*n*=2	*n*=42
Low	3 (50)	31 (91.1)	2 (100)	36 (85.7)
High	3 (50)	3 (8.83)	0	6 (14.2)

HAS=Hypertension abnormal renal/liver function stroke, BLED=Bleeding labile INRs elderly drug therapy or alcohol intake

initiation of dabigatran therapy, the patients were closely monitored because of the risk of potential bleeding, each parameter of HAS-BLED scores, such as blood pressure, abnormality in renal or liver function, stroke, bleeding events, labile INR, concomitant use of drugs like NSAIDS were checked frequently at each patient visit and all these were under control which leads to an improvement in the HAS-BLED score. The mean value of the HAS-BLED score of dabigatran at the initial period was found to be 1.15 ± 0.83 and it was reduced to 0.84 ± 0.78. Similarly, in the dabigatran with antiplatelet group, there was a reduction of mean score from 2.10 ± 0.94 to 1.74 ± 0.92. Even though mean score at baseline was high in dabigatran with antiplatelet group, because of the complications, both the drugs are given. However, in both groups, there was a significant decrease in the HAS-BLED score caused by the treatment given ($P = 0.026$ and $P = 0.002$).

DISCUSSION

In patients taking dabigatran for its approved indications, the clinical efficacy and safety of the drug at different doses can be assessed by determining the risk of stroke and risk of bleeding using the appropriate scores. As a subgroup analysis, we also evaluated the risk of stroke and bleeding of dabigatran, when it was given alone and in combination

Table 4: Comparison of HAS-BLED score (initial versus 6th month)

Drugs	Number of patients (months)		Mean score (months)		*P*
	0, *n* (%)	6, *n* (%)	0	6	
Dabigatran					
Low	31 (93.9)	32 (96.6)	1.15±0.83	0.84±0.78	0.026
High	2 (6.1)	1 (3)			
Dabigatran with antiplatelets					
Low	30 (71.4)	36 (85.7)	2.10±0.94	1.74±0.92	0.002
High	12 (28.5)	6 (14.2)			
Comparison of dabigatran versus dabigatran with antiplatelet, *P*			0.000	0.000	

HAS=Hypertension abnormal renal/liver function stroke, BLED=Bleeding labile INRs elderly drug therapy or alcohol intake

with an antiplatelet. Randomized evaluation of long-term anticoagulation therapy (RE-LY) compared between Dabigatran 110 mg and 150 mg and the outcomes were constant with better efficacy of D150, less major bleeding with D110, and low intracerebral hemorrhage rates for both doses.[10] In this comparative analysis of dabigatran at different doses and dabigatran along with an antiplatelet in the Indian population, we found that initiation of dabigatran has resulted in a significant reduction in the risk scores, the patients who showed high risk of stroke at the time of commencement of therapy was moved to either moderate- or low-risk categories within 6 months of therapy without a significant increase in the bleeding risk as well. Among the available doses of dabigatran such as 150 mg, 110 mg, and 75 mg, an appropriate dosage for the patient was selected based on the risk scores. The results of the study showed 110 mg was more frequently prescribed and it exhibited efficacy in terms of stroke prevention that is almost similar to that of 150 mg without causing much increase in bleeding risk.

The concomitant use of antiplatelet therapy with dabigatran or warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial suggests that concomitant antiplatelet use leads to a significant rise in the overall risk of major bleeding when combined with an oral anticoagulant.[11,12]

The key findings of our study underline that the Dabiagatran was prescribed based on risk calculations with respect to CHA_2DS_2–VASc score (stroke risk) and HAS-BLED score (bleeding risk). Within 6 months, both the treatment groups showed a reduction in the risk scores, especially with 110 mg of dabigatran.

Limitations of the study

Instead of comparing dabigatran with other oral anticoagulants which has been trialed across the world, our study was done with each dose of the drug as well as with its concomitant use along antiplatelet. We came across certain limitations which could not be neglected. They include.

- If this was a multicenter study, instead of a single center, more patients could be enrolled. Number of patients prescribed with dabigatran in our hospital was enough to conduct a study, but many of them were fallen under exclusion criteria
- Equal number of patients should have been included within each dose because one of our objectives was to compare different doses of dabigatran. Due to the small sample size available, we could not incorporate the equal number of participants
- Some information was missing since the assessment of data was made through the hospital database, for example, over the counter medications such as nonsteroidal anti-inflammatory drugs, which should be considered in the HAS-BLED score
- Our study might have the potential for a selection bias as the patients were selected in a nonrandomized manner.

CONCLUSION

It was observed that within 6 months, both the treatment groups showed a reduction in the risk score. In comparison with dabigatran with antiplatelet group, dabigatran group had lower background risks of stroke and bleeding. It was a practice that elderly patients and patients with other risk factors such as the risk of bleeding, a low dose will be prescribed because of safety concerns. Hence, it was necessary to know whether the prescribed dose is effective as well as safe in such patients. Similarly, in the case of dabigatran with an antiplatelet group, it was given to comorbid patients, so it could not be solely said that because of the presence of the antiplatelet the risk increases. However, in both treatment groups, the risk of stroke has been reduced by the initiation of therapy, along with that risk of bleeding resulted from anticoagulant therapy is also low.

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Conflicts of interest

There are no conflicts of interest.

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