



An Observational Study Comparing Effectiveness and Safety of Dabigatran versus Warfarin in Patients of Non Valvular Atrial Fibrillation in a Tertiary Care Hospital of West Bengal

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Abstract

Objectives: *This study aims to evaluate effectiveness and safety of dabigatran versus warfarin in patients of non valvular atrial fibrillation in clinical practice in a tertiary care hospital of west Bengal, India by comparing the number of ischaemic stroke, bleeding events and other adverse events.*

Methods: *A prospective longitudinal observational study was conducted over 16 months (January 2018-April 2019). The study population comprised patients diagnosed of non valvular atrial fibrillation, receiving either dabigatran or warfarin with CHA2DS2-VASC SCORE ≥ 2 and patients of hyperthyroidism, treated for last one year, presenting with persistent atrial fibrillation in euthyroid state. They were divided into two groups & followed for 1 year to observe number of ischaemic strokes, thromboembolic events, bleeding events. After baseline investigations, in warfarin group INR was checked until stable therapeutic range (2-3) reached, then every 2nd monthly both groups are followed. Relevant statistical tests were utilized for data analysis.*

Results: *Total 150 patients were studied. Only 2 patients (2.7%) out of 74 patients in dabigatran showed event of ischaemic stroke and in warfarin group the number of ischaemic events were 8 (10.5%) out of 76 patients. So numerically dabigatran more effectively can prevent ischaemic stroke (p value 0.098). 2 patients (2.7%) in group A and 4 patients (5.3%) in group B were having minor bleeding episodes (p value 0.681).*

Conclusion: *Dabigatran 110 mg twice daily dose seems better than warfarin INR adjusted dose regarding effectiveness and safety profile in non valvular atrial fibrillation in Indian perspective in absolute number of ischaemic stroke and bleeding episodes.*

Keywords: *Non valvular atrial fibrillation, CHA2DS2-VASc score, Warfarin, Dabigatran, INR.*

Introduction

A cardiac arrhythmia is defined as an alteration of the electrical rhythm of the heart. Among the pathologic types of supraventricular arrhythmias

the ATRIAL FIBRILLATION is the most common cardiac arrhythmia. Atrial fibrillation is characterised by disorganized, rapid, irregular atrial electrical activity with abnormal atrial

contraction and with an variable ventricular rate that is originated from atrio ventricular nodal conduction. The prevalence rises with increasing age, and more than 95% of atrial fibrillation patients are more than 60 years of age¹.

Non-Valvular atrial fibrillation means atrial fibrillation without any rheumatic mitral stenosis, a mechanical or bio prosthetic heart valve, or mitral valve repair². Atrial fibrillation increases the risks of stroke and thromboembolic events. So anticoagulation is the mainstay of stroke prevention therapy specially vitamin k antagonist warfarin. Thus a risk score has been validated to identify the patients, who can be better benefitted from anticoagulant or antiplatelet drugs. This CHA2DS2-VASC score has a broader range including congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke, vascular disease, age 65-74 years, female sex³. And those patients having score of ≥ 2 are categorized as high risk patients and needs aggressive management with anticoagulant drugs like vitamin k antagonist or novel oral anticoagulant (NOAC). Warfarin has potential risk to use due to bleeding chance and drug interactions requiring frequent coagulation monitoring. In case of non valvular atrial fibrillation, the newer anti-coagulants like direct thrombin inhibitor DABIGATRAN is also used as well as vitamin k antagonist. It does not need regular monitoring and has few drug interactions.

Dabigatran has shown to be non- inferior to warfarin in studies evaluating the prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation, thus leads to the US FDA approval for this indication⁴. Dabigatran has also been demonstrated its effectiveness in the prevention of venous thromboembolism in patients undergoing total hip and knee replacement surgery and prevention of recurrent venous thromboembolism. Though there were many studies comparing effectiveness and safety of dabigatran versus warfarin in non valvular atrial fibrillation outside India, in Indian perspective such studies are lacking⁵.

This study might shed some light on the effectiveness of fixed dose dabigatran regarding prevention of thromboembolism in non valvular atrial fibrillation and thus might contribute in patient outcome by selecting most appropriate anti-thrombotic agent as per the situation.

Materials and Method

The study was carried out for a period of 16 months starting from January 2018 to April 2019. The study population included all patients attending the department of cardiology, who are diagnosed by attending cardiologist with non valvular atrial fibrillation and received anticoagulation therapy with warfarin or dabigatran with CHA2DS2 –VASC SCORE ≥ 2 & patients of hyperthyroidism, who were treated for last one year for thyrotoxicosis, now presented with persistent atrial fibrillation even in euthyroid state. A total of 162 patients with newly diagnosed non valvular atrial fibrillation were included in the study, but 12 patients had discontinued their treatment in the very first week. So ultimately 150 patients included in the study, 74 in dabigatran treated group and 76 in warfarin treated group. The other drugs that were prescribed, not considered in this study as they were present in both the groups.

Exclusion criteria were as follows-

- Patients of valvular atrial fibrillation
- Patients with prosthetic heart valve
- Patients receiving other anticoagulant or antithrombotic drugs along with dabigatran or warfarin
- Those undergone any surgical procedure to control atrial fibrillation
- Stroke within last 14 days or severe stroke within 6 months
- Any major surgery within previous month
- Known Haemorrhagic disorder or bleeding diathesis
- Pregnancy and lactation
- Active liver disease
- Creatinine clearance < 30 ml/min
- Patients with active hyperthyroidism

- Patients who are unwilling to participate in this study

This study was designed to evaluate both effectiveness and safety of dabigatran versus warfarin in case of non valvular atrial fibrillation in Indian perspective.

With a clearance from institutional ethics committee and approval from The West Bengal University of Health Sciences, written informed Consent had been taken from patients or near relatives of patients in case of critical patients. (consents were in three different languages like Bengali, Hindi and English). Patients were randomly prescribed warfarin and dabigatran by the attending cardiologist as per his choice. Those, who are receiving dabigatran, were designated as group A and those, receiving warfarin were designated as group B. On first visit, a thorough general and systemic examination was done & all baseline laboratory data were noted like reports of ECG, Echocardiography, reports of liver function test, kidney function tests, thyroid function test and INR and they were asked a few questions from the standardised questionnaire. Patients were prescribed either Dabigatran Etxilate 110 mg twice daily or Warfarin 1 mg once daily orally.

During the course of treatment with warfarin, patients were followed up at first once weekly up to the period until the INR value reaches within desired and stable therapeutic range for first time (INR 2-3). Then the patients were examined at 1st month, 2nd month and thereafter every 2nd monthly. During every follow up INR, Liver enzymes like SGPT, SGOT and kidney function like serum Creatinine was recorded strictly.

Where as in the dabigatran group, patients were followed up every 2nd monthly. During follow up, liver enzymes like SGPT and SGOT and kidney function i.e. serum Creatinine was noted regularly. The patients were observed for one year and during this period following parameters are noted-

Primary Outcome

- Number of stroke or systemic embolism or myocardial infarction following intake of

these drugs in dabigatran and warfarin groups.

- Number of bleeding episodes during intake of these drugs in this groups.

Secondary Outcome

- Any adverse drug reaction noted during this period.

Results & Analysis

Total study population comprised of 26 to 90 years age group. Among them 137 patients out of 150 (91.3%) were of 46-90 years age group. Total 82 patients (54.67%) were female. Among baseline co morbidities, total 92 (61.3%) patients were hypertensive, 63 (42%) patients were of diabetes mellitus, 7 (4.66%) were of hyperthyroidism. Maximum patients i.e 87 (59.3%) were of persistent atrial fibrillation and rest were of paroxysmal type.

Primary Outcome

Cardio embolic stroke occurred in 2 patients receiving dabigatran 110 mg dose (2.7%) and in 8 patients of warfarin treated group (10.5%). The p value was 0.098, relative risk was 0.2568 and 95% confidence interval is 0.056-1.17. During the follow up period, no other thromboembolic events, myocardial infarction or death occurred.

Table 1: Distribution of number of cardioembolic stroke after intervention in two study population

Serial no.	Study groups	Number of ischaemic stroke
1	Group A(n=74)	2(2.7%)
2	Group B(n=76)	8 (10.5%)
3	Total (n=150)	10 (6.67%)

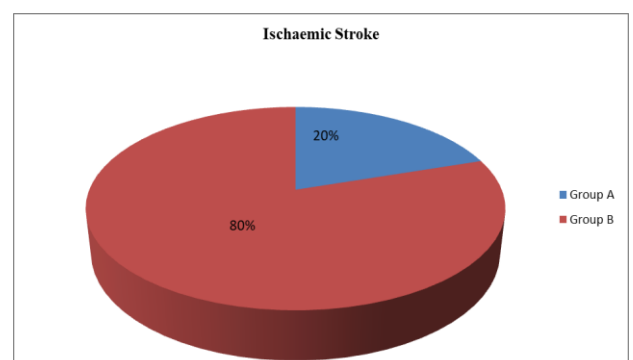


Figure 1: distribution of ischaemic stroke events in two study population

No major bleeding episodes occurred during follow up period. But few minor bleeding episodes like epistaxis, gum bleeding, petechiae etc. occurred in both groups. In dabigatran treated group A, 2 patients were presented with minor bleeding (2.7%) and in warfarin treated group B, 4 patients (4%) developed minor bleeding episodes.

Table 2: Distribution of number of minor bleeding event in two study population

Serial no.	Study groups	Number of minor bleeding events
1	Group A (n=74)	2(2.7%)
2	Group B (n=76)	4(5.3%)
3	Total (n=150)	6(4%)

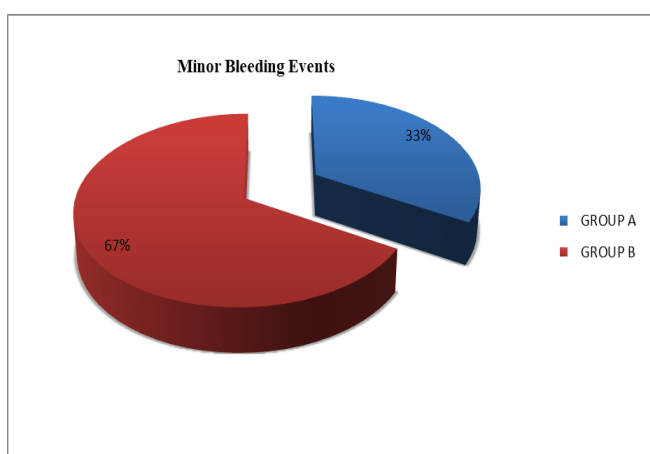


Figure 2: distribution of minor bleeding events in two study population

Nausea was not statistically significant in two groups (p=0.744). Vomiting was not statistically significant in two groups (p=0.617). In group-A, 19 (25.7%) patients had dyspepsia and in group-B, 6 (7.9%) patients had dyspepsia. This association was statistically significant (p=0.003). Upper abdominal pain was not statistically significant in two groups (p=0.439). Petechiae/ecchymosis was not statistically significant in two groups (p=0.245).

Adverse reactions	Group A (n=74)	Group B (n=76)	Total (n=150)
Nausea	5(6.8%)	4(5.3%)	9(6%)
Vomiting	2(2.7%)	1(1.3%)	3(2%)
Dyspepsia	19(25.7%)	6(7.9%)	25(16.7%)
Upper abdominal pain	4(5.4%)	2(2.6%)	6(4%)
Petechiae	0	3(3.9%)	3(2%)

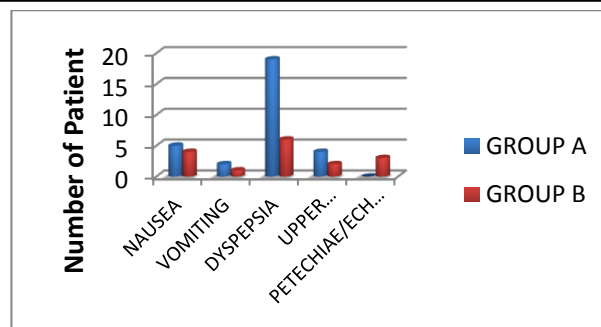


Figure 3: Distribution of different adverse drug reactions over 12 months in two study groups

Statistical Analysis

Data was entered in to MS EXCEL sheet and was analysed by using statistical software SPSS version 17.0. The continuous data was presented by mean ± SD and categorical data was presented by frequency with their relative percentage. Data was tested for normality by using Kolmogorov smirnov test. The association between the variables was tested by using chi square test or fisher`s extract test as per applicability. The mean was compared by using independent t test and median was compared by using Mann Whitney U test as per applicability of the data.. P-value ≤ 0.05 was considered for statistically significant.

Discussion

Comparison was done in between fixed dose regimen of dabigatran 110 mg twice daily with INR adjusted dose of warfarin, in patients who had non valvular atrial fibrillation and were at risk of stroke. Dabigatran dose seems better than warfarin with respect to numerical numbers of primary efficacy outcome of stroke as well as safety outcomes i.e. bleeding events. In the present study, Only 2 patients (2.7%) out of 74 patients in group A showed event of ischaemic stroke and in group B the number of ischaemic events were 8 (10.5%) out of 76 patients. So numerically dabigatran more effectively can prevent ischaemic stroke but there is no statistically significant difference between this two groups (p value 0.098). Patients with features of cardio embolic stroke presented in the department, a CT scan and echocardiography was done to locate the primary source of thrombus.

Patients of confirmed cardio embolic stroke were advised for admission in the hospital for further treatment.

There was total 10 events of cardio embolic stroke among 150 patients i.e. 6.67% per year in the present study population. Among them 7 patients were female, 8 patients had a history of old stroke, all of them were hypertensive and aged more than 65 years, 3 of them were diabetic. So all of them had multiple co morbidities which increases the CHA2DS2-VASC score ≥ 4 and predisposed to high risk of stroke incidence.

According to ACC/AHA 2014 recommendations³, the annual stroke risk is 4% per year with a CHA2DS2-VASC score of 4 and increases with increasing score i.e. 6.7% and 9.8% per year with a CHA2DS2-VASC score of 5 and 6 respectively. In the RELY trial⁶, the number of first ischaemic stroke and embolism was only 3% among patients treated with 110 mg dabigatran group and it was 3.4% in case of warfarin INR adjusted treated group. And there was no statistically significant difference (p value 0.27) but numerically dabigatran treated group showed less events than warfarin treated group. This is similar with the present study finding.

In another prospective nationwide cohort study in Denmark⁷, there was no statistically significant difference between two groups regarding ischaemic stroke and embolism events, which was similar to our present study.

In another study design including health insurance database⁸, it was shown that numerically more stroke prevention in dabigatran treated group compared to warfarin treated group, but there was no statistically significant relation. The present study is corroborative with this study.

A comparative observational study including database in 2015⁹ had revealed a similar type of results i.e. same rate of ischaemic stroke reduction between dabigatran treated and warfarin treated groups (p value 0.06).

Regarding safety of anticoagulant drugs, we had assessed that by comparing number of bleeding events occurred in both study population during

study period. But no major bleeding episode was noted during this follow up period of one year. Only 27 patients (18%) out of 150 patients had a has bled score of 3 and only 5 patients (3.3%) out of 150 patients had a has bled score of 4.

And among the study population, 2 patients (2.7%) in group A and 4 patients (5.3%) in group B were having minor bleeding episodes, for which there was no need to stop the study drug. There was no statistically significant difference between these groups (p value 0.681).

In RELY trial⁶, among 18113 patients major bleeding occurred more in warfarin treated group as compared to dabigatran 110 mg treated group (p value 0.003).and minor bleeding was also less in dabigatran 110 mg group (14.62% /year) than warfarin group (18.15%/ year). So treatment with dabigatran 110 mg was associated with lower bleeding rates. So present study finding partially corroborate with this finding.

In another study in Denmark⁷, from the registry of medicinal products it was noted that number of major bleeding both intra cranial as well as gastro intestinal bleeding was lower in dabigatran 110 mg group as compared to warfarin. So this study finding partially similar to our present study. But as the study population was so small with a shorter study period, so probably the major bleeding events were nil in present study.

The benefit of dabigatran may explained by pharmacokinetics. Since it has an elimination half-life of 12-17 hours, twice daily regimen reduces variability in anticoagulation effect, as compared to warfarin, which is difficult to control.as dabigatran specifically inhibit thrombin, it may have antithrombotic efficacy while preserving other haemostatic process in coagulation system and thus reduce risk of bleeding.

In this present study, dyspepsia was significantly more frequent in patients given dabigatran than following warfarin use (p value 0.003, 25.7% vs 7.9% respectively). There was no significant difference in occurrence of incidence of nausea, vomiting, upper abdominal pain, hypersensitivity or petechiae/ecchymosis.

In RELY trial ⁶, among 18113 patients, dyspepsia was more frequent in dabigatran 110 mg group (11.8%) as compared to warfarin group (5.8%). So the present study finding correlates with this study.

In Asian population in a study ¹⁰, it was found that commonest adverse effect was dyspepsia in dabigatran group (3.9%) as compared to warfarin (0.4%).

In a cross sectional cohort study with 103 patients treated with dabigatran ¹¹, it was found that 33% of them developed dyspepsia and that was the major side effect. So this study finding was similar our present study though the study design was different.

In US a quantitative benefit-harm and economic analysis study in 2010 ¹², among 50,000 patients the main incidence of adverse event was dyspepsia in dabigatran 110 mg group (11.8%) as compared to warfarin (5.8%). This finding was matched with our study.

There may be a possible explanation for this side effect. Dabigatran needs low pH for enhanced absorption. so the capsules contain dabigatran coated pellets with a tartaric acid core. This acidity may enhance the dyspepsia symptom.

Conclusion

Dabigatran 110 mg twice daily dose seems better than warfarin INR adjusted dose regarding effectiveness and safety profile in non valvular atrial fibrillation in Indian perspective in absolute number of ischaemic stroke and bleeding episodes. The incidence of dyspepsia was significantly high with dabigatran .There was no other significant difference in other adverse drug reactions. Further large scale multi centric studies are necessary to corroborate these findings in similar population and to provide new concepts for management of non valvular atrial fibrillation.

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