Original Article

Dabigatran versus Warfarin in Patients with Atrial Fibrillation: A Randomized Controlled Trial

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ABSTRACT

Introduction: The risk of stroke as well as mortality is increased with atrial fibrillation. When compared to control medication, vitamin K antagonists like warfarin lower the risk of stroke and mortality but raise the risk of bleeding. Consequently, people with atrial fibrillation who are greater susceptible to stroke are advised to take warfarin. Even with warfarin, many people still don't have enough anticoagulation. New anticoagulant medications that are efficient, secure, and easy to use are therefore required.

Objective: To compare the efficacy and safety of dabigatran, at dose of 110 mg twice daily versus warfarin.

Materials and Method: 100 Patients were randomized either to Group D or W using web generated random numbers with 50 patients in each group. Patients in group D were given dabigatran tablets at dose of 110 mg twice BD. Patient in group W were given warfarin tablet at dose of 5 mg once daily. Outcomes measures included major bleeding rates, ischemic stroke incidences, recurrent thromboembolism incidences, and TTR (the period of time in therapeutic range of INR within 2.0 to 3.0) in 12 months.

Results: Incidence of major bleeding was lower in patients receiving dabigatran as compared to patients on warfarin therapy and the difference became significant at 12 months ($p<0.05$). Patients receiving dabigatran anti-coagulation therapy spent more time in therapeutic range of INR as compared to patients receiving warfarin with statistically significant difference ($p<0.0001$). There was total 13 events of stroke in warfarin group as compared to only 3 events in dabigatran group. However, the difference between group W and D was not significant at this sample size ($p>0.05$).

Conclusion: In our study, dabigatran had better efficacy and safety with less incidence of major bleeding, stroke, thromboembolism, and patients spending more time in therapeutic range of INR as compared to warfarin group.

Keywords: Dabigatran, Warfarin, Atrial Fibrillation, INR, Stroke, Major Bleeding.

INTRODUCTION

The risk of stroke as well as mortality is increased with atrial fibrillation. When compared to control medication, vitamin K antagonists like warfarin lower the risk of stroke and mortality but raise the risk of bleeding. [1] Consequently, people with atrial fibrillation who are greater susceptible to stroke are advised to take warfarin. [2]

Due to cardiac emboli that frequently accumulate in the left atrial appendage as a consequence of blood stasis, atrial fibrillation (AF) is a significant risk indicator for ischemic stroke. Stroke from these emboli typically results in a more debilitating stroke than stroke from other causes. [3-5]

Due to their numerous food-drug and drug-drug interacions, vitamin K antagonists are difficult to administer and necessitate regular laboratory testing. As a result, they are rarely utilized and are frequently discontinued when they are used. [6, 7] Even with warfarin, many people still don't have enough anticoagulation. [8] New anticoagulant medications that are efficient, secure, and easy to use are therefore required.

Additionally, they work best when the international normalized ratio (INR) indicates that the anti-coagulation is between two and three; it is widely acknowledged that adequate anti-coagulation requires a time in the therapeutic range (TTR) >70%, and individuals with inadequate control are more likely to experience severe bleeding or a fatal thromboembolic event. [9, 10]

In an effort to get around the problems with warfarin, a new class of oral anti-coagulant medications known as novel oral anti-coagulants—more recently renamed direct oral anti-coagulants, or DOACs—was created. [11]

Oral dabigatran etexilate is a prodrug that is a reversible direct thrombin inhibitor. It hinders the stability of thrombus development by preventing the conversion of fibrinogen to fibrin by blocking thrombin, the last stage of the clotting cascade. [12] Since the degree of anti-coagulant action and dabigatran plasma concentration are directly proportional, direct blockage of this last step of coagulation causes anti-coagulation within hours.

On the other hand, warfarin inhibits the liver's production of vitamin K-dependent clotting factors indirectly, which takes several days to manifest as anti-coagulation. It takes the elimination of circulating coagulation components to fully manifest its anti-coagulant effects. [13]

Dabigatran has been evaluated in a pilot trial involving patients with atrial fibrillation and in a study for the prevention of venous thromboembolism, in which doses of 150 mg twice daily and 220 mg once daily, respectively, were promising.[14, 15] We performed randomized controlled trial to compare the efficacy and safety of dabigatran, at dose of 110 mg twice daily versus warfarin.

MATERIALS AND METHODS

This was an open label, parallel group randomized controlled trial conducted on patients with atrial fibrillation from February 2023 to January 2024 in NMCH, Patna (a tertiary care hospital in eastern India). The study was conducted as per recommendations of GCP (Good Clinical Practice) after getting approval from IEC (Institutional Ethics Committee) and written informed consent was taken from patients with AF after providing and explaining participant information sheet.

Inclusion Criteria:

Patients with arial fibrillation as per electrocardiography and having at least one of following parameters:

- History of previous episode of stroke or TIA (transient ischemic attack)
- LVEF (left ventricular ejection fraction) < 40%
- NYHA class II or higher symptoms of cardiac failure
- Age ≥ 18 years
- Age between 18 and 74 years with type 2 diabetes mellitus, hypertension, or CAD (coronary artery disease)

Exclusion Criteria:

Patients with severe cardiac valve disease, patients having stroke within 14 days or history severe stroke within 6 months of enrollment, any disorder or condition with elevated risk of hemorrhage, patients with a creatinine clearance < 30 ml/minute, or patients having liver dysfunction, or pregnancy & lactation.

100 Patients were randomized either to Group D or W using web generated random numbers with 50 patients in each group.

Patients in group D were given dabigatran tablets at dose of 110 mg twice BD. Patient in group W were given warfarin tablet at dose of 5 mg once daily.

Doses of anticoagulation therapy was adjusted based on ACC (American College of Cardiology) guidelines. [16]

The main outcome of our study was the incidence of severe bleeding within three months of enrolment. Major bleeding was defined by the ISTH (International Society on Thrombosis and Haemostasias) as having one of the following characteristics: [17]

- Bleeding that is life-threatening
- Bleeding in a critical organ or region (intracranial, intraspinal, intraocular, retro-peritoneal, intraarticular, pericardial, or intramuscular along with compartment syndrome)
- Bleeding that causes a drop in haemoglobin levels of more than 2 g/dL or necessitates the administration of more than two units of PRBC (packed red blood cells).

To prevent any misunderstandings, a 48-hour window was provided for the drop in hemoglobin.

Secondary outcomes included major bleeding rates with follow-up periods of six and twelve months, ischemic stroke incidences within this time frame, recurrent thromboembolism incidences within the time frame, and TTR (the period of time in therapeutic range of INR within 2.0 to 3.0) in 12 months.

The total number of recorded INR values divided by the number of readings in the normal range yielded the TTR, which was then translated to a percentage. [18] In the study period, patients who experienced significant bleeding or had any other contraindication to the study medicines were excluded.

Stroke was identified as a focal neurological dysfunction with a non-traumatic origin and was categorized as either ischemic or of unspecified type, with a confirmatory diagnosis done using a chart evaluation and ICD 9 and 10 codes. [19, 20] Using a chart examination of ICD 9 and 10 codes, a confirmatory diagnosis of thromboembolism was done and it was determined as a fatal or non-fatal pulmonary embolism or deep vein thrombosis.

Statistical Analysis:

Data from patients receiving warfarin or dabigatran therapy were presented in tabular form using Microsoft Excel 365 and transferred to SPSS version 24 for further statistical analysis. Continuous data such as age, weight, CHA2DS2-VASc, TTR and eGFR were expressed as mean ± SD (standard deviation). Statistical significance of difference in continuous data between warfarin and dabigatran group was evaluated by unpaired t-test. Categorical data, including gender, CKD stage, usage of concurrent medication, and outcome measures, were reported as percentages and frequencies and then compared by chi-square or Fisher's exact test. A p-value of less than 0.05 was taken as cut-off for statistical significance.

RESULTS

50 patients received 1 year of pharmacotherapy with warfarin in group W whereas 50 patients received dabigatran. The baseline demographic and clinical characteristics of dabigatran and warfarin group is given in table 1.

Table 1: Comparison of baseline demographic and clinical characteristics between dabigatran and warfarin group

Variables	Group W (n=50)	Group D (n=50)	P-Value
Age in years, (mean ± SD)	61.58 ± 10.33	61.76 ± 12.76	0.94
CHA_2DS_2-VASc, (mean ± SD)	3.77 ± 1.34	3.71 ± 1.29	0.82
HAS-BLED Score (mean ± SD)	3.09 ± 0.24	3.01 ± 0.26	0.11
Creatinine Clearance (mean ± SD)	67.38 ± 10.46	71.49 ± 11.83	0.69
Aspirin, n	41	43	0.78
Statins, n	28	30	0.84
P2Y12 inhibitors, n	35	36	>0.99
Proton pump inhibitors, n	33	35	0.83
Sex, n			
Male	27	26	>0.99
Female	23	24	

At baseline, both dabigatran and warfarin groups were comparable with respect to age, sex, creatinine clearance, use of concomitant medication, HAS-BLED score, weight and CHA2DS2-VASc with no statistically significant difference between them (P>0.05).

Table 2: Comparison of Incidence of Stroke and Thromboembolism between Group W and Group D

Time Period	Group W n (%, N=50)	Group D n (%, N=50)	P-Value (Fisher's Exact Test)
0-3 Months	6 (8.00)	2 (4.00)	0.27
3-6 Months	5 (6.00)	1 (2.00)	0.20
6-12 Months	2 (2.00)	0 (0.00)	0.49

There was total 13 events of stroke in warfarin group as compared to only 3 events in dabigatran group. However, the difference between group W and D was not significant at this sample size (p>0.05).

Table 3: Comparison of Incidence of Major Bleeding between Group W and Group D

Time Period	Group W n (%, N=50)	Group D n (%, N=50)	P-Value
0-3 Months	9 (14.00)	3 (8.00)	0.12
3-6 Months	5 (8.00)	1 (2.00)	0.20
6-12 Months	7 (14.00)	0 (0.00)	**0.01**

Incidence of major bleeding was lower in patients receiving dabigatran as compared to patients on warfarin therapy and the difference became significant at 12 months (p<0.05).

Table 4: Comparison of TTR (Time in Therapeutic Range of INR) between Group W and Group D at Baseline

	Group W	Group D
Number of Patients (N)	50	50
Mean TTR in Percentage	47.66	63.49
Standard Deviation (SD)	8.03	5.96
Difference in Mean	-15.83	
95% Confidence interval (Difference of Mean)	-18.6365 to -13.0235	
P Value (Unpaired t-test)	**<0.0001**	

Patients receiving dabigatran anti-coagulation therapy spent more time in therapeutic range of INR as compared to patients receiving warfarin with statistically significant difference (p<0.0001).

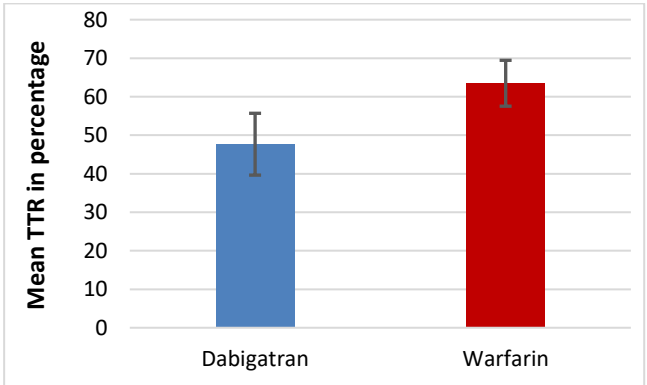

Figure 1: Comparison of TTR between Dabigatran and Warfarin

DISCUSSION

In this randomized controlled trial, we have compared the efficacy and safety of warfarin versus dabigatran in patients of non-valvular atrial fibrillation in tertiary care hospital of Bihar. Dabigatran was found to have better efficacy with respect to the risks of stroke, thromboembolism, major bleeding, and time in therapeutic range.

In our study, dabigatran had better efficacy and safety with less incidence of major bleeding, stroke, thromboembolism, and patients spending more time in therapeutic range of INR as compared to warfarin group.

In common clinical practice, the relative safety and efficacy of dabigatran vs warfarin seem to have been less explored. [21] Dabigatran 150 mg lowered the likelihood of stroke or systemic embolism in the RE-LY trial, which compared it to warfarin, while maintaining a comparable risk of significant bleeding. Comparing our results to those of apixaban, we observed an identical likelihood of stroke or systemic embolism with a decreased risk of serious bleeding. [22]

Numerous observational studies have consistently demonstrated dabigatran's equivalent efficacy to vitamin K antagonists; however, the conclusions concerning major bleeding risk have been less apparent. The majority of research revealed that the likelihood of major bleeding was comparable between warfarin and dabigatran, and that the event rates in dabigatran groups were significantly lower.[23-30]

Research has indicated that dabigatran carries a notably reduced risk when compared to vitamin K antagonists. [29, 30] The discrepancies observed in the outcomes may stem from variations in the research populations, time periods, and patient counts involved in the investigation.

Dabigatran was linked to a lesser likelihood of major bleeding among people under 75 years old, but a risk comparable to warfarin in patients over 75 years old, according to both RE-LY and a cohort study. As a result, studies involving older people are more probable to reveal a greater relative risk of dabigatran in comparison to warfarin. [22, 27]

The lower overall effectiveness and increased safety of dabigatran in our research may be explained by a lower incidence of dose reduction, but only a small proportion of the participants (<10%) received the 75 mg dose, which is in line with earlier findings from the ORBIT-AF registry. [31]

The twice-daily dose schedule of dabigatran may contribute to its benefits. The anticoagulant effect of dabigatran is less variable when taken twice daily due to its elimination half-life from 12 to 17 hours. This is particularly true when contrasted to the unpredictable anticoagulant effect of warfarin. Warfarin affects coagulation in a wide sense by blocking factors "II, VII, IX, and X" as well as proteins C and S. Dabigatran may be effective against thrombosis by selectively blocking just thrombin. This may be achieved while maintaining various other haemostatic processes within the coagulation system, thus reducing the risk of bleeding. [32]

CONCLUSION

In our study, dabigatran had better efficacy and safety with less incidence of major bleeding, stroke, thromboembolism, and patients spending more time in therapeutic range of INR as compared to warfarin group. The evidence generated in this study recommends for multi-centred randomized controlled trial with enough sample size and power to compare incidence of stroke or thromboembolism between various direct oral anti-coagulants in eastern India (particularly Bihar).

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