IJBPAS, May, 2024, 13(5): 2141-2153

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

WARFARIN AND DABIGATRAN FOR THE TREATMENT OF ACUTE DEEP VEIN THROMBOSIS: COMPARISON OF SAFETY AND EFFICACY

SUTHAR JV[1*], PATEL S[2], SHAH B[3]

1: Dept. of Pharmacology & Clinical Pharmacy, Ramanbhai Patel College of Pharmacy, Charotar University of science and Technology, Changa - 388 421, Gujarat, India

2: M.Pharm Student, Dept. of Pharmacology & Clinical Pharmacy, Ramanbhai Patel College of Pharmacy, Charotar University of science and Technology, Changa - 388 421, Gujarat, India

3: Vascular Surgeon, Sheth H. J. Mahagujarat Hospital. Nadiad-38700, Gujarat, India

***Corresponding Author: Dr. Jalpa V. Suthar: E Mail: jalpasuthar.ph@charusat.ac.in**

Received 15th May 2023; Revised 16th July 2023; Accepted 24th Aug. 2023; Available online 1st May 2024

https://doi.org/10.31032/IJBPAS/2024/13.5.7997

ABSTRACT

The direct oral thrombin inhibitor dabigatran has a predictable anticoagulant effect and may be an alternative therapy to warfarin for patients who haveacute venous thromboembolism. This study aimed to compare the safety and efficacyof Dabigatran vs Warfarin in patients with deep vein thrombosis (DVT). An ambispective study was conducted on patients with DVT. Patients were randomly received dabigatran or warfarin for treatment of DVT by the doctor. Demographic details, drug treatment, medical history, presenting complaints, and diagnosis were recorded in CRF. Descriptive statistical analysis was done using MS Excel. In total, 60 patients with DVT were divided into 2 treatment groups (30 to dabigatran and 30 to warfarin). The duration of treatment was 6 months. The majority of the 32 (53.4%) had Poplitial femoral DVT. Dabigatran treatment group 26 (86.6%) showed better recanalization at the end of the 6-month treatment duration while in Warfarin there were 15 (50%) patients. Except for patients who had pulmonary embolism even on treatment, all of the safety and efficacy parameters had shown significant differences ($p < 0.05$). In acute DVT, dabigatran showed significant evidence of clinical safety and efficacy compared to warfarin with a better safety profile and no laboratory monitoring.

Keywords: Deep Vein Thrombosis, Safety, Efficacy, Dabigatran, Warfarin

INTRODUCTION

Venous thromboembolism (VTE) is a disease comprised of two conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). DVT is a blood clot (thrombus) that most often affects regions of stasis inside the veins of the lower leg or thigh. PE occurs when a portion of a clot detaches, moves, and lodges in the pulmonary arteries, causing life-threatening conditions **[1]**. The thromboembolic disease has emerged as one of the most important issues confronting doctors, and it continues to be a major concern for most general and orthopedic surgeons **[2]**. Isolated deep vein thromboses (DVTs) account for nearly two-thirds of thromboembolic disease cases, with proximal DVTs accounting for 80 percent **[3]**.

DVT affects 1 to 2 individuals per 1000 people per year, or 300,000 to 600,000 people in the United States every year **[4]**. DVT is more common as people get older, with prevalence ranging from 1 in 10,000 in people under the age of 20 to 1 in 100 in people over the age of 80 **[5]**. DVT affects the lower extremities the most, but it can also affect the upper extremities **[6, 7]**. Women are more likely to be affected when they are younger, but this ratio reverses as they get older[8]. Black people have a higher probability risk of occurrence than Asians, but overall Asians have a lower rate **[9]**.

DVT can result in significant morbidity in the form of leg pain or swelling. Untreated DVT can lead to Pulmonary Embolism, which can be fatal. Anticoagulant treatment, fortunately, decreases both the morbidity and mortality associated with this condition **[10, 11]**. Anticoagulation is the cornerstone of DVT treatment, intending to avoid PE and thrombosis recurrence. Anticoagulant treatment is very effective at preventing repeated VTE, but it is also linked to a higher risk of bleeding complications**[12, 13]**. Each year, major bleeding events may occur in 1% to 3% of patients taking Vitamin K Antagonists (VKAs), compared to a 30% lower relative risk of major bleeding with Direct Oral Anticoagulants (DOACs) **[14, 15]**.

Patients with DVT that have a contraindication to anticoagulation and are scheduled for follow-up should consider retrievable inferior vena cava filters **[15]**. Endovascular or surgical clot removal is needed for all patients with phlegmasia cerulea dolens, whereas selected DVT patients are candidates for endovascular thrombus removal to avoid post-thrombotic syndrome complications **[11]**. Compression therapy can be used to treat established post-thrombotic syndrome, but it is unlikely to prevent the syndrome from developing in the same place **[15]**.

DOACs are a new class of anticoagulants that have recently been introduced into clinical practice for the acute and long-term treatment of DVT. Since DOAC are given in a fixed dose and do not need routine monitoring, they make DVT treatment much simpler **[1]**. Anticoagulation with DOACs has several advantages, including ease of administration, fewer medication and dietary interactions, and predictable pharmacokinetic properties that do not need clinical monitoring **[16]**. The development of DOACs, which do not require routine coagulation monitoring and can be started without initial parenteral treatment **[12]**. For several years, the standard treatment option was an oral VKA, such as warfarin. This regimen is highly effective in both treating and preventing recurrent DVT. VKAs' limitations include drug exposure variability, a narrow therapeutic window, numerous drug and food interactions, a relatively high rate of bleeding complications, and the need for routine coagulation monitoring. Hence, all of which have complicated use of this agents and poor patient compliance. As a consequence, these drawbacks have been overcome with the approval of the newer DOACs. As a result, experts are looking for new DOACs that are both safe and effective alternatives to warfarin.

In Clinical Practice, doctors prescribed various treatment modalities for the management of DVT. The major concern is about safety and efficacy with Pharmacoeconomics of the various treatment approaches. Tablet dabigatran (110 mg) is usually prescribed twice a day and showed better anticoagulation effect with safety over other medications and there is no need for treatment monitoring **[17]**. Hence, the present study is planned to compare the safety and efficacy of dabigatran vs. warfarin in patients with DVT.

METHODOLOGY

An Ambispective study was carried out at the vascular surgery department of Sheth H. J. Mahagujarat Hospital, Nadiad. The data were collected from January 2018 to December 2020 as a retrospective period and February 2021 to March 2021 as a prospective period. Institutional Ethics Committee (Approval No. approved the study CHA/IEC/ADM/20/07/622.3).

The patients attending OPD and the inpatient Department of Vascular Surgery for the treatment of Deep Vein Thrombosis (DVT) were enrolled in the study **[Figure 1]**. All patients with acute deep vein thrombosis and attending to the vascular department of the hospital were included in the study. The patients with pulmonary embolism, pregnancy-associated with deep vein thrombosis, post-varicose sclerotherapy associated deep vein thrombosis, patients who have undergone

thrombectomy and followed by 6-month anticoagulation treatment, and patients who have undergone thrombolysis and followed by 6-month anticoagulation treatment were excluded from the study.

A total of 60 patients with deep vein thrombosis was enrolled and further randomly divided into 2 treatment groups. Total 30 patients were assigned Dabigatran medication while the other 30 patients were assigned Warfarin medication. Tablet Dabigatran was given as 110mg dose twice a day whereas Tablet Warfarin was given as 5mg dose once a day.

The data such as medical records, electronic reports, Follow-up doppler reports, and documentation of discharge of the patient were recorded in Case Record Form (CRF). Additionally, details like demographic parameters and patient's history such as age, gender, presenting complaints, diagnosis, drugs prescribed, and dosage were also recorded. Other parameters that were evaluated immediately as well as on monthly time interval during the study. It included after the start of treatment immediate symptomatic recovery time (loss of edema, loss of venous congestion, improve SpO_2 /breathlessness), doppler test at the interval of 2-month, 3-month, 6 months to check the recanalization rate (% vessel recanalize), the reappearance of symptoms, bleeding and total cost of therapy.

Descriptive statistical analysis was carried out using Microsoft Office Excel. Data were expressed as numbers and percentages. Data of two treatment groups were analyzed and compared by performing a T-test between both the treatment groups. A *p*-value less than 0.05 was considered Significant.

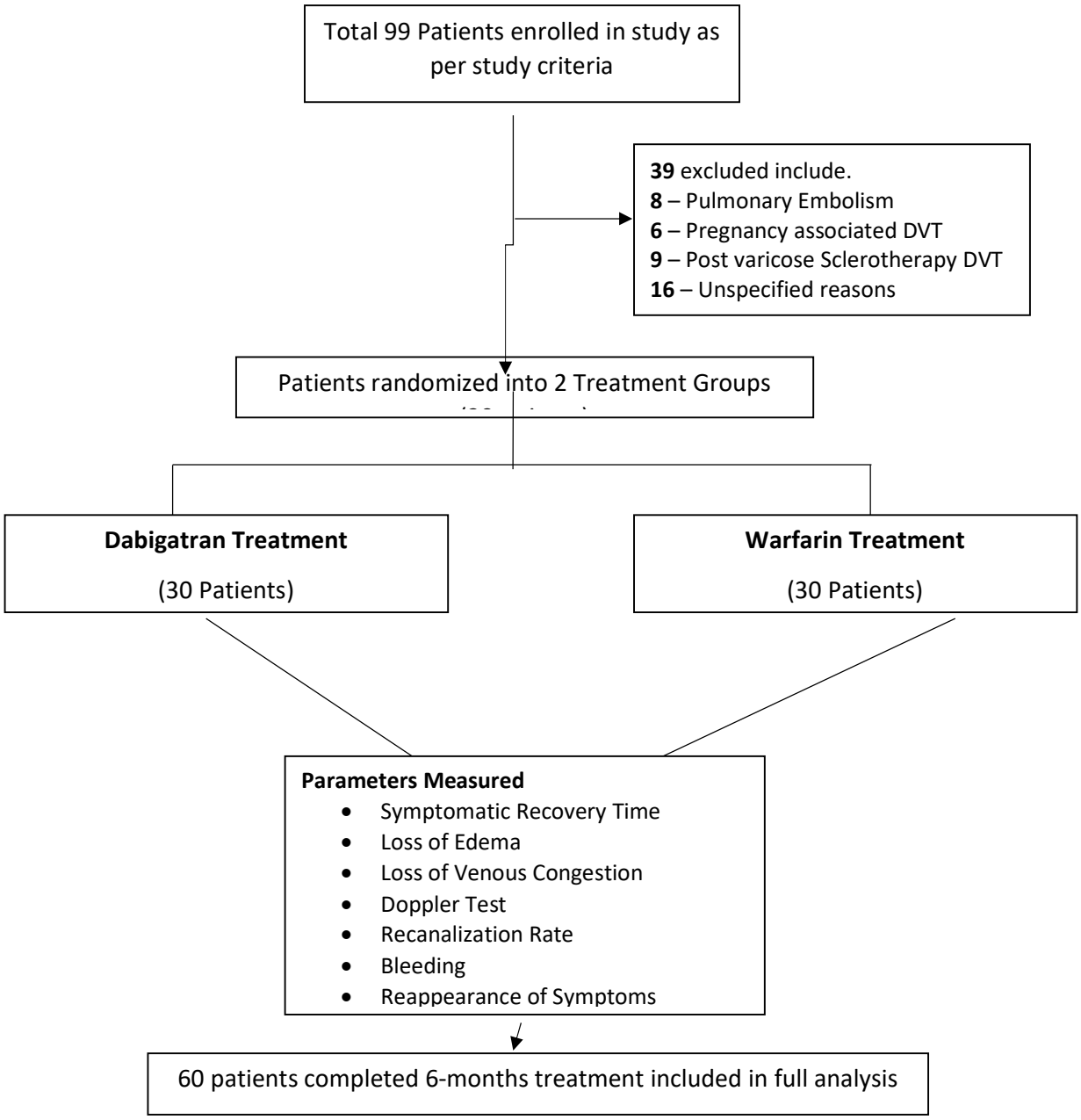

Figure 1: Patient enrolment process

RESULTS:

A total of 60 patients with deep vein thrombosis was enrolled and further randomly divided into 2 treatment groups i.e., 30 patients in the Dabigatran treatment group and 30 patients in the Warfarin treatment group.

Out of the total 60 patients, the highest number (n=15, 26%) of patients were presented in the age group 31-40 years. The mean age range was found 29±20.6 years with a minimum of 14 years of age and a maximum of 84 years **[Figure 2]**. The female patients (37, 62%) suffered higher

as compared to male (23, 38%) patients in the study.

The majority of patients 50 (83.3%) complained of pain in the calf at the time of the hospital visit, followed by Mild to Moderate edema 25 (41.6%) and Tense edema-Phlegmasia alba dolens 20 (33.3%). Few patients had complaints of Cellulites 5 (8.3%) and Breathlessness 2 (3.3%) reported at the time of presentation. A maximum number of patients 37 (62%) were presented to the hospital within 7-14 days from the day of onset of the symptom followed by 15 (25%) patients after 14 days and 8 (13%) patients visited between 0-7 days. There are two types of DVT most commonly observed in the study. Out of the total, the majority of them had Poplitial Femoral DVT accounting for 32 (53.4%) and 28 (46.6%) patients had Iliac Femoral DVT type **[Table 1]**.

Doppler test was carried out in all patients with DVT at the interval of 1st, 3rd, and 6th months of the period. At the end of the 6th month, in the dabigatran group, a total of 26 (86.6%) patients showed better recanalization, whereas only 15 (50%) patients showed good recanalization in the warfarin treatment group.

According to the cost-benefit analysis in Pharmacoeconomics, the loss of human workdays indicated the inability to work due to the presence of disease which affects the overall earning of the patient. In the study, the loss of human workdays was categorized as 0-7 days, 7-14 days, 14-21 days, and >21 days. After the onset of symptoms, in the dabigatran treatment group majority of the patients, 17 (56.8%) lost 7-14 days. Wherein the warfarin treatment group majority of patients 20 (66.6%) lost 14-21 days. The average loss of workdays was 10 days and 18 days in the dabigatran and warfarin treatment group respectively **[Table 1]**.

Dosage regimen and cost of therapy were evaluated in both groups. Tablet dabigatran, a 110 mg twice a day regimen has cost around 326 INR for 10 tablets. Whereas Tablet warfarin 5 mg is prescribed once a day and the cost per strip of 10 tablets is 35 INR. The cost of Dabigatran is higher as compared to warfarin but the treatment with dabigatran is better in terms of safety, effectiveness, and patient compliance because there is no need for frequent blood investigations monitoring. In the treatment with warfarin, every 15 days blood monitoring is required of PT-INR levels which adds extra cost into the treatment **[Table 1]**.

Comparison between both the Treatment Groups:

The safety and efficacy of the treatment were evaluated by measuring reappearance of symptoms, pulmonary embolism, bleeding, and failure in recanalization. In the dabigatran treatment group, only one

patient showed reappearance whereas 4 patients showed failed recanalization. Moreover, warfarin treatment group patients showed bleeding and complications with treatment. The outcome parameters of both treatment groups were compared using a T-test and the level of significance was checked. All the parameters showed significant differences (p <0.05) except pulmonary embolism even on medications parameter **[Table 2]**.

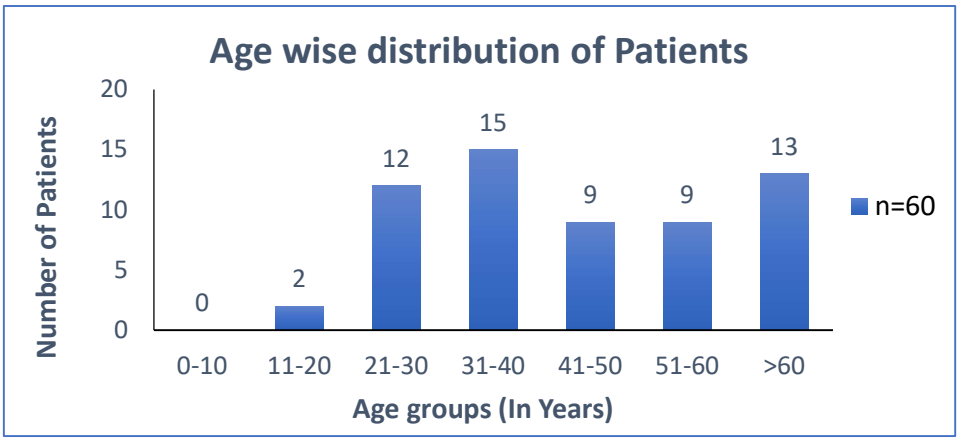

Figure 2: Age Group Distribution of DVT patients

Table 1: Demographic and performance characteristic of patients

Sr. No.	Parameters	Dabigatran group (N=30)	Warfarin group (N=30)
		No. of Patients (n, %)	
1	Age groups (years)		
	11-20	1 (3.3%)	1 (3.3%)
	21-30	6 (20%)	6 (20%)
	31-40	8 (26.6%)	7 (23.3%)
	41-50	4 (13.3%)	5 (16.6%)
	51-60	5 (16.6%)	4 (13.3%)
	>60	6 (20%)	7 (23.3%)
2	Gender Distribution:		
	Male	10 (33.4%)	13 (43.3%)
	Female	20 (66.6%)	17 (56.7%)
3	Complains and Presentation:		
	Tense edema-Phlegmasia alba dolens	11 (36.6%)	9 (30%)
	Mild to moderate edema	10 (33.4%)	15 (50%)
	Cellulites	3 (10%)	2 (6.6%)
	Pain in calf	23 (76.6%)	27 (90%)
	Breathlessness	1 (3.3%)	1 (3.3%)
4	Time of Presentation:		
	0-7 days	5 (16.6%)	3 (10%)
	7-14 days	17 (56.7%)	20 (66.6%)
	>14 days	9 (30%)	6 (20%)
5	Types of DVT:		
	Iliac Femoral DVT	15 (50%)	13 (43.3%)
	Poplitial Femoral DVT	13 (43.3%)	19 (63.3%)
6	Loss of Human Work Days:		
	0-7 days	10 (33.3%)	1 (3.3%)
	7-14 days	17 (56.8%)	4 (13.3%)
	14-21 days	2 (6.6%)	20 (66.6%)
	>21 days	1 (3.3%)	5 (16.8%)
	Average loss of work days	10 days	18 days
7	Total Cost of Therapy:	11,736 INR	4,230 INR

Table 2: Comparison of treatment outcome parameters among both the treatment groups

Sr. No.	Safety and Efficacy Parameters	Dabigatran (N=30)	Warfarin (N=30)	P-value
1	1st month Doppler Recanalization >30%	20 (66.6%)	6 (20%)	0.0014*
2	3rd month Doppler Recanalization >50%	25 (83.3%)	13 (43.3%)	0.0097*
3	6th month Doppler Recanalization >70% to near-total	26 (86.6%)	15 (50%)	0.0018*
4	Patients who had Reappearance of Symptoms even on Medications	1 (3.3%)	5 (16.6%)	0.0087*
5	Patients who had Pulmonary Embolism even on Medications	0 (0%)	2 (6.6%)	0.15
6	Patients who had Bleeding	0 (0%)	3 (10%)	0.0077*
7	Patients who failed proper recanalization and needs repeat extended Medications	4 (13.3%)	15 (50%)	0.018*

*** P-value <0.05 is considered significant using paired T-test.**

DISCUSSION

In the present study, a total of 60 patients having deep vein thrombosis were enrolled in the study, they were randomly prescribed dabigatran or warfarin by the doctor. A total of (13, 21.6%) patients were in the geriatric age group (>60 years). Approximately 50% of patients were in the age group of 21-40 years. A similar result was shown in a study conducted by Naess *et al*18 and Silverstein *et al* [19] which states during childbearing years, the incidence rate in women was twice the rate of incidence in men, but after 60 years the rate was slightly higher in men. Hence, the prevalence of DVT increases with the increase in age. In the study, female predominance (37, 62%) in DVT was observed. Females (55%) had a higher prevalence of DVT as compared to males were also reported by Jose *et al* **[20]**.

In the present study, clinical presentations associated with DVT were included like "Pain in calf accounting (50, 83.3%)" followed by "Mild to moderate edema (25, 41.6%)", and "Tense edema-Phlegmasia alba dolens (20, 33.3%)". A very few patients reported "Cellulites (5, 8.3%)" and "Breathlessness (2, 3.3%)". Similar findings were reported by Rutherford *et al* **[21]**.

All the patients attending the hospital were categorized according to the duration of complaints, and among them (37, 62%) patients had complaints between 7-14 days. A very a smaller number of patients reported hospital within 7 days of complaints. The reason behind the delay in the time of presentation at the hospital may include negligence to visit the hospital and seek proper treatment and inappropriate diagnosis at GP stated by Jose *et al* **[20]**.

The literature review suggested that poplitial femoral DVT and Iliac femoral DVT were majorly diagnosed among other types of DVTs **[22]**. Similarly, in this study, poplitial femoral DVT (32, 53.4%) and Iliac femoral DVT (28, 46.6%) patients were found.

The Recanalization rate was measured in both the group of patients to compare the percentage of recanalization rate. Overall, the dabigatran treatment group showed better results as compared to the warfarin treatment group. Out of a total of 30 patients in dabigatran, at 1st-month 20 (66.6%) patients showed good doppler recanalization rate followed by 25 (83.3%) in 2nd-month and 26, (86.6%) at 3rd-month doppler recanalization rate". On the other side, in the warfarin group, at "1st-month doppler recanalization rate showed (6, 20%)" followed by "2nd-month doppler recanalization rate (13, 43.3%)" and "3rd-month doppler recanalization rate (15, 50%)".

The number of "patients who had reappearance of symptoms even on medications was only (1, 3.3%) in case of dabigatran whereas (5, 16.6%) patients in case of warfarin". A similar study finding reported by Goldhaber *et al* **[23]** showed overall risk recurrence was higher in patients who were treated with warfarin as compared to dabigatran. Hence, there are chances of treatment failure with warfarin medication and requires further interventions.

Total (2, 6.6%) patients were reported pulmonary embolism even on medication in the warfarin group and no patients in the dabigatran group reported pulmonary embolism even on medications. A similar study reported by Schulman *et al* **[24]** showed that the warfarin treatment group was more prevalent to have pulmonary embolism even on medication as compared to the dabigatran treatment group. Hence, dabigatran has lower chances of complications. Additionally, the bleeding events associated with medications was in (3, 10%) patients in warfarin group whereas there zero patient complained bleeding event in dabigatran group. A similar study carried out by Wang *et al* **[25]** studies showed (29%) of patients with warfarin had bleeding issues vs 16% of patients with dabigatran.

In the study, recanalization failure and requirement of extended medication were evaluated in both groups after providing treatment for 6 months. In the dabigatran group (4, 13.3%) patients and warfarin group (15, 50%) patients reported failed recanalization and needed extended medications. In the warfarin group, the majority of failure in recanalization was reported with further complications. Similarly, Schulman *et al* **[24]** showed the majority of patients in the warfarin treatment group needed further medication interventions.

The average loss of human workdays associated with DVT was evaluated in the study to determine the cost-benefit analysis. In the dabigatran treatment group, an average of 10 days of loss of human work was observed while an average of 18 days loss was found in the warfarin treatment group. Most people are fully healed from a deep vein thrombosis within a few weeks up to a month reported by Jennifer *et al* **[26]**. In the study, the total cost of therapy among both the treatment group was also evaluated to determine the economic burden. In the Dabigatran vs warfarin treatment, 110 mg twice a day and 5 mg once a day respectively were prescribed as a dosage regimen for 6 months of duration. In the treatment of warfarin, additionally every 15 days routine blood monitoring test like prothrombin time – International normalized ratio (PT-INR) was required to monitor treatment outcome. However, in the dabigatran treatments group, no routine blood monitoring is required. For dabigatran, a total cost 11,736 INR, (dollar currency) and for warfarin, a total costs 4,230 INR additionally monitoring charges required for the duration of 6 months treatment. A similar pharmacoeconomic comparison was reported by Buttorff *et al*. and Martin *et al* **[27, 28]**.

The limitations of the study, as it was carried for shorter time duration the sample size was small. The compliance was recorded on the basis of symptoms improvement and personal interaction with doctor.

CONCLUSION:

The study supported the use of dabigatran as an oral anticoagulant regimen for patients presenting with symptomatic acute DVT. The safety and efficacy of dabigatran are higher in terms of lower risk of bleeding, improved recanalization rate, and better symptomatic control as compared to warfarin in DVT. Dabigatran is a more convenient treatment option for patients and health care providers than warfarin because it does not require regular blood-coagulation monitoring. The cost of dabigatran is higher as compared to warfarin but due to wider safety, efficacy, and patient compliance, dabigatran is a better drug of choice. The findings of the study provided evidence of clinical safety and efficacy in the management of patients with DVT.

REFERENCES:

[1] Ogbonna KC, Dixon DL. Critical appraisal of dabigatran in the treatment of deep vein thrombosis and pulmonary embolism. J Blood Med 2015; 6: 177–84.

[2] Kouka N, Nass L, Feist W. Pharmacological and Non-Pharmacological Management Methods of DVT and Pulmonary Embolism. Compression Therapy Concepts, 2004.

[3] White RH. The epidemiology of venous thromboembolism. Circulation, 2003.

[4] Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol 2015; 12: 464–74.

[5] Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population-based study. Arch Intern Med, 1998.

[6] Delluc A, Le Mao R, Tromeur C, Chambry N, Rault-Nagel H, Bressollette L. Incidence of upper-extremity deep vein thrombosis in western France: A community-based study. Haematologica 2019; 104: 29–31.

[7] Grant JD, Stevens SM, Woller SC, Lee EW, Kee ST, Liu DM. Diagnosis and management of upper extremity deep-vein thrombosis in adults. Thromb Haemost 2012; 108: 1097–108.

[8] Heit JA. The epidemiology of venous thromboembolism in the community. Arteriosclerosis, Thrombosis, and Vascular Biology, 2008.

[9] White RH, Zhou H, Romano PS. Incidence of idiopathic deep venous thrombosis and secondary thromboembolism among ethnic groups in California. Ann Intern Med 1998; 128: 737–40.

[10] Lensing A, Prandoni P, Prins M, Lancet HB-T, 1999 U. Deep-vein thrombosis. Lancet 1999; 353: 479–86.

[11] Osman AA, Ju W, Sun D, Qi B. Deep venous thrombosis: a literature review. Int J Clin Exp Med 2018; 11: 1551–61.

[12] Imberti D, Pomero F, Benedetti R, Fenoglio L. Safety and efficacy of direct oral anticoagulants for extended treatment of venous thromboembolism. Intern Emerg Med 2016; 11: 895–900.

[13] Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016; 149: 315–52.

[14] Piran S, Schulman S. Treatment of bleeding complications in patients on anticoagulant therapy. Blood 2019; 133: 425–35.

[15] Liu D, Peterson E, Dooner J, Baerlocher M, Zypchen L, Gagnon J. Diagnosis and management of iliofemoral deep vein thrombosis: Clinical practice guideline 2015; 187: 1288–96.

[16] Coulis AA, Mackey WC. A Review of the Efficacy and Safety Profiles of the Novel Oral Anticoagulants in the Treatment and Prevention of Venous Thromboembolism. Clin Ther 2018; 40: 2140–67.

[17] US-FDA [Internet]. US-FDA. 2015 [cited 2021 Jul 25]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022512s007lbl.pdf

[18] Næss IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: A population-based study. J Thromb Haemost 2007; 5: 692–9.

[19] Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ. Trends in the incidence of deep vein thrombosis and pulmonary embolism: A 25-year population-based study. Arch Intern Med 1998.

[20] Ferro JM, Coutinho JM, Dentali F, Kobayashi A, Alasheev A, Canhão P. Safety and Efficacy of Dabigatran Etexilate vs Dose-Adjusted Warfarin in Patients with Cerebral Venous Thrombosis: A Randomized Clinical Trial. JAMA Neurology 2019; 76: 1457–65.

[21] Cronenwett J, Johnston K. Rutherford's vascular surgery E-book, 2014.

[22] Walker R. Clinical pharmacy and therapeutics E-Book, 2011.

[23] Goldhaber SZ, Schellong S, Kakkar A, Eriksson H, Feuring M, Kreuzer J. Treatment of acute pulmonary embolism with dabigatran versus warfarin: A pooled analysis of data from RE-COVER and RE-COVER II. Thromb Haemost 2016; 116: 714–21.

[24] Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H. Dabigatran versus Warfarin in the Treatment of Acute Venous Thromboembolism. NEJM 2009; 361: 2342–52.

[25] Wang S V., Franklin JM, Glynn RJ, Schneeweiss S, Eddings W, Gagne JJ. Prediction of rates of thromboembolic and major bleeding outcomes with dabigatran or warfarin among patients with atrial fibrillation: New initiator cohort study. BMJ 2016; 353.

[26] Robinson J. After Deep Vein Thrombosis: What to Expect in Recovery [Internet]. 2020 [cited 2021 May 14]. Available from: https://www.webmd.com/dvt/happens-after-dvt

[27] Buttorff C, Ruder T, Bauman M. Multiple Chronic Conditions in the United States. Multiple Chronic Conditions in the United States, 2017.

[28] Martin AB, Hartman M, Lassman D, Catlin A. National health care spending in 2019: Steady growth for the fourth consecutive year. Health Aff 2021; 40: 14–24.