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Comparative Study of Compliance and Factors Affecting Compliance among Commonly Used Drugs in Deep Vein Thrombosis Patients

Sajid Ali[1*], Kheraj Mal[2], Jaghat Ram[3], Rukhsana Malik[4], Muhammad Aslam Abbassi[5], Qararo Shah[6] and Ufn Sahrish[7]

[1]Department of Pharmacy, Shah Abdul Latif University (SALU), Khairpur, Sindh, Pakistan.
[2]National Institute of Cardiovascular Diseases (NICVD), Sukkur, Sindh, Pakistan.
[3]National Institute of Cardiovascular Diseases (NICVD) Satellite Center, Larkana, Sindh, Pakistan.
[4]Department of Pharmacology, People's University of Medical and Health Sciences for Women (PUMHSW), Nawabshah, Sindh, Pakistan.
[5]Department of Pharmaceutics, Faculty of Pharmacy, University of Sindh, Jamshoro, Sindh, Pakistan.
[6]Shaheed Mohtarma Benazir Bhutto Medical University (SMBBMU), Larkana, Sindh, Pakistan.
[7] Chandka Medical College at Shaheed Mohtarma Benazir Bhutto Medical University (SMBBMU), Larkana, Sindh, Pakistan.

Authors' contributions

This work was carried out in collaboration among all authors. Author SA designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors KM, JR, RM, MAA, QS and US managed the analyses of the study and managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objectives: The objective of current research was to identify the compliance of antithrombotic drug (heparin, warfarin and Rivaroxaban) and factors of non-compliance associated with heparin, warfarin and rivaroxaban.
Methodology: A cross-sectional, observational study was conducted on patients suffering from

**Corresponding author: E-mail: arslan.ahmer@gmail.com;*

Deep Vein Thrombosis (DVT) at government teaching hospital of Larkana. 348 DVT patients were selected by using online sample calculator software. Data was collected by using pre validated questionnaire after taking patient consent; finally the data was analyzed with statistical package of social sciences (SPSS) version 25.

Results: The compliance with rivaroxaban was present in 103 (80.5%) patients followed by heparin drug compliance in 95 (74.2%) DVT patients and warfarin drug compliance in 98 (76.6%) DVT patients. Non-compliance factors with rivaroxaban were; cost in 4 (16.0%) patients, polypharmacy in 6 (24.0%) patients, side effects in 4 (16.0%) patients and prolong therapy in 11 (44.0%) patients. Non-compliance factors with heparin were; monitoring in 13 (39.4%) patients, diet restriction in 6 (18.2%) patients, injectable in 10 (30.3%) patients and ADR in 4 (12.1%) patients. Non-compliance factors with warfarin were; cost in 4 (13.3%) patients, polypharmacy in 8 (26.7%) patients, prolong therapy in 5 (16.7%) patients and ADR in 13 (43.3%) patients.

Conclusion: This study concludes that rate of drug compliance was high in patients of DVT with rivaroxaban followed by warfarin and heparin, whereas long duration of therapy, polypharmacy, side effects of therapy, cost of therapy, continuous monitoring, injectables, diet restrictions and ADRs of therapy were the most commonly reported factors of non-compliance.

Keywords: Deep venous thrombosis; heparin; warfarin; rivaroxaban.

1. INTRODUCTION

Deep vein thrombosis (DVT) is simply defined as “Presence of a blood clot (commonly known as thrombus) in deep vein of legs or rarely in arms” [1]. Deep vein thrombosis is the cardiovascular disease in which one or more than one blood clot is formed in large veins of human body. Presence of single blood clot in vein is called formation of thrombus, whereas presence of multiple blood clot in vein is called formation of thrombi. Thrombus or thrombi are responsible for partial or complete blockage of blood circulation in veins. In majority of cases deep vein thrombosis is formed in legs but it can also be observed either in veins of arms or in mesenteric veins or in cerebral veins [1,2].

Anticoagulation is an important part of DVT therapy. Majority of the DVT patients are treated with oral anticoagulant drugs, whereas few patient requires combination therapy. Proximal deep veins are mostly affected in severe thrombus. In acute phase of disease these patients are treated with mechanical- and catheter-directed thrombolysis (CDT), which causes the rapid lysis of thrombus and decreases the risk of increased incidence of post-thrombotic syndrome [3,4]. Such procedures are often used to manage acute ischemia of the limbs due to arterial thrombosis, but there is an elevated risk of ischemia-reperfusion damage [5,6]. However, thrombolytic treatment is directly correlated with higher risk of bleeding that also increased the risk of mortality in patients of DVT [7-10].

The main objectives in management of DVT are; Inhibits pulmonary embolism (PE). Decrease the increasing rate of morbidity. Decrease the increasing risk of postphlebitic syndrome development. Heparin is most commonly used drug for treatment of DVT. It is a heterogeneous polysaccharide mixture containing different fragments of polysaccharide having different molecular weights but similar therapeutic activity. In normal mechanism, activated factor X act on prothrombin protein and convert it into its active form i.e., thrombin. Protein thrombin act on fibrinogen protein and convert it into its active form i.e., fibrin. It is long string protein that creates mesh like covering around wound or in blood vessels. These fibrin covering accumulates the platelets on its surface and form blood clot that stop or decreased the blood flow. Basically, heparin have two fragments i.e., high and low molecular weight. Although both fragments have similar therapeutic effects but different mode of action in treatment of DVT. High Molecular Weight Heparin (HMWH): These fragments produced their anticoagulant action by directly affecting the antithrombin III (ATIII) and inhibit the process of thrombin. Antithrombin III, primary anticoagulant of human body, inactivates the thrombin as well as suppresses the activated factor X activity in process of coagulation. Low Molecular Weight Heparin (LMWH): These fragments produced their anticoagulant action by directly affecting on activated factor X and inhibit their activity [11-13]. Unfractionated Heparin (UFH) is mostly used in hospitals not only for treatment of DVT but also for prevention of DVT. It is administered to patient either intravenously (IV) or subcutaneously (SC) for prevention. In

case of prevention, heparin is administered few hours before surgery whereas in case of treatment, heparin is administered few day after surgery. It is administered to patient IV for treatment. In case of treatment, initially patient treated with UFH in hospital and then after discharge treated either by LMWH or warfarin [11-14].

Warfarin is oral anticoagulant, most commonly used for long-term treatment to avoid the reoccurrence of clot during the management of DVT. It is blood thinner commonly advice during DVT management in home. Warfarin shows the anticoagulant action in human body by antagonizing the vitamin K as well as responsible for reduction of different factors that play direct or indirect key role in blood clotting. Warfarin directly act on vitamin K reductase enzyme i.e., vitamin K epoxide reductase complex 1 (VKORC1) and inhibit its activity resulting in formation of vitamin K in reduced form. VKORC1 is very important enzyme that play key role in activation of vitamin K in body and its reduction decreased the vitamin K in function form resulting in decreased synthesis of clotting factors. Depletion of functional vitamin K also decreased the glutamate residues carboxylation that not only results in decreased formation of different coagulation factors such as II, VII, IX, and X but also decreased the formation of anticoagulant proteins such as C and S. That finally, decreased the prothrombin levels and indirectly decreased the thrombin production and decreased the clotting of blood as shown in Fig. 1. It is administered orally once in a day. It is advised that it should be administered either in afternoon or in evening. Its effect vary from patient to patients and high depends upon patients like response of patient towards metabolism of drug or quantity of vitamin K taken by patient daily, genetics, presence of different vitamin K clotting factors and binding proteins, comorbidities, any sort of drug interaction or side effect [15-17].

Rivaroxaban is also an oral anticoagulant, most commonly used for management of DVT. It is not only used for treatment of DVT and PE but also used for preventing recurrent DVT and PE. Its mechanism of action is somehow to similar heparin. Rivaroxaban directly inhibit the activated factor X responsible for conversion of prothrombin into thrombin form, which act on fibrinogen and convert it into fibrin that form mesh around wound or in blood vessels and accumulates the platelets on its surface and form blood clot that stop or decreased the blood flow. Rivaroxaban directly inhibit the activated factor X and prevent the all mechanism resulting in decreasing the clot formation process [18-20]. It is administered orally in divided doses in a day. It is advised that it should be administered either in divided doses to maintain its concentration in blood for achieving therapeutic efficacy [18-20].

2. METHODOLOGY

A methodology of hospital based study on comparison of three main drugs used in the management of deep vein thrombosis in tertiary care hospital of Larkana, Sindh Pakistan were as follows; The research on patients of deep vein thrombosis was performed in medicine department of government tertiary care hospital of Larkana. According to Census 2017, Larkana is the fourth largest city of Sindh with population of 490,508. Basic health care facilities are very much poor and similar to other cities of Sindh. Government hospital of Larkana is the largest teaching hospital of Larkana, providing the basic health care facilities to peoples of Larkana city.

2.1 Design of Study

Design of current hospital based study was descriptive cross-sectional.

2.2 Sample Size

Sample size was calculated by using OpenEpi software. After entering the required information in software the answer was 348.

2.3 Sampling Method

Patients were selected from medicine department of hospital by using the non-probability purposive sampling technique.

2.4 Duration of Study

Data of 384 patients was collected within six months.

2.5 Inclusion Criteria

Only those patient were included in the research whose age was from 18-65 years and were diagnosed with DVT. Only those patients were included in the study who were treated either with Rivaroxaban or Heparin or Warfarin.

2.6 Data Collection Method

Patients of deep vein thrombosis who fulfilled the inclusion criteria of research were enrolled in research. A specially designed pre validated questionnaire was used for interviewing enrolled patients and for collection of data.

2.7 Statistical Analysis

Collected data was interpreted with latest version 25.0 of SPSS.

3. RESULTS

3.1 Compliance of Rivaroxaban

Drug compliance with rivaroxaban drug was present in 103 (80.5%) patients and non-compliance was present in 25 (19.5%) patients.

3.2 Factors of Non-compliance of Rivaroxaban

Common factors of non-compliance reported in DVT patients with rivaroxaban were; cost in 4 (16.0%) patients, polypharmacy in 6 (24.0%) patients, side effects in 4 (16.0%) patients and prolong therapy in 11 (44.0%) patients.

Table 1. Compliance of rivaroxaban

Rivaroxaban compliance					
Rivaroxaban		**Frequency**	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	Compliance	103	80.5	80.5	80.5
	Non-Compliance	25	19.5	19.5	100.0
	Total	128	100.0	100.0	

Table 2. Factors of non-compliance of rivaroxaban

Factors of Non-compliance					
Rivaroxaban		**Frequency**	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	Cost	4	16.0	16.0	16.0
	Polypharmacy	6	24.0	24.0	40.0
	Side effects	4	16.0	16.0	56.0
	Prolong therapy	11	44.0	44.0	100.0
	Total	25	100.0	100.0	

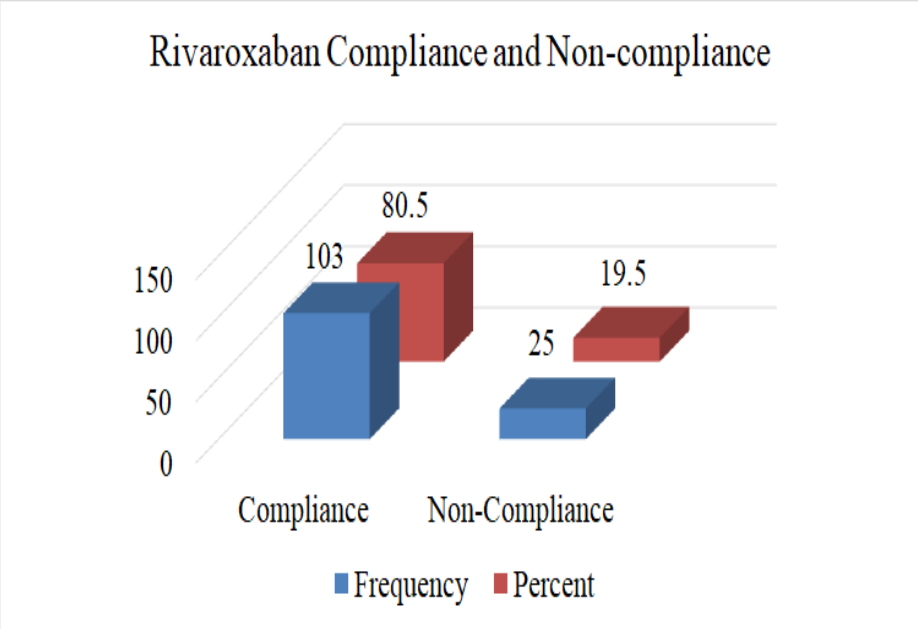

Fig. 1. Compliance of rivaroxaban

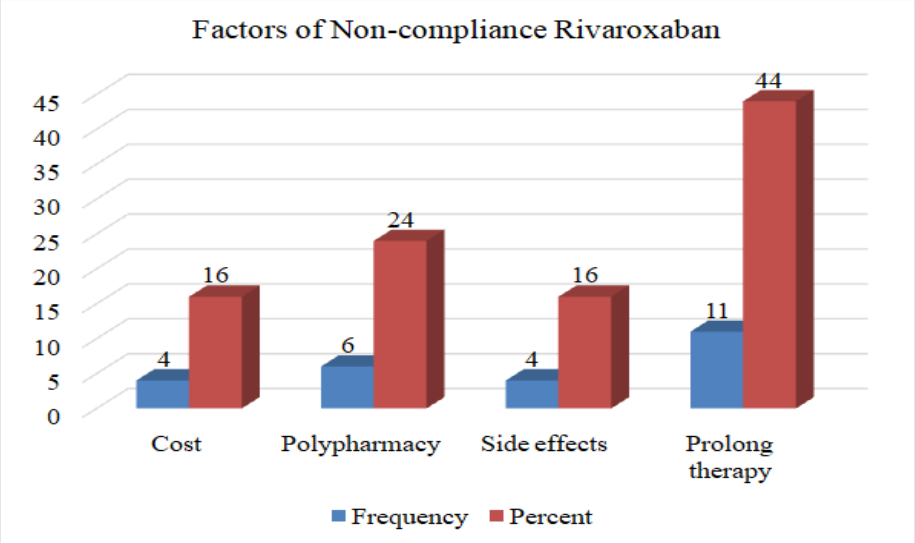

Fig. 2. Factors of Non-compliance of Rivaroxaban

3.3 Compliance of Heparin

Drug compliance with heparin drug was present in 95 (74.2%) patients and non-compliance was present in 33 (25.8%) patients.

3.4 Factors of Non-compliance of Heparin

Common factors of non-compliance reported in DVT patients with heparin were; monitoring in 13 (39.4%) patients, diet restriction in 6 (18.2%) patients, injectable in 10 (30.3%) patients and ADR in 4 (12.1%) patients.

3.5 Compliance of Warfarin

Drug compliance with warfarin drug was present in 98 (76.6%) patients and non-compliance was present in 30 (23.4%) patients.

Table 3. Compliance of heparin

Heparin compliance					
Heparin		**Frequency**	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	Compliance	95	74.2	74.2	74.2
	Non-Compliance	33	25.8	25.8	100.0
	Total	128	100.0	100.0	

Table 0. Factors of non-compliance of heparin

Factors of non-compliance					
Heparin		**Frequency**	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	Monitoring	13	39.4	39.4	39.4
	Diet Restriction	6	18.2	18.2	57.6
	Injectable	10	30.3	30.3	87.9
	ADR	4	12.1	12.1	100.0
	Total	33	100.0	100.0	

Table 5. Compliance of warfarin

Compliance					
Warfarin		**Frequency**	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	Compliance	98	76.6	76.6	76.6
	Non-Compliance	30	23.4	23.4	100.0
	Total	128	100.0	100.0	

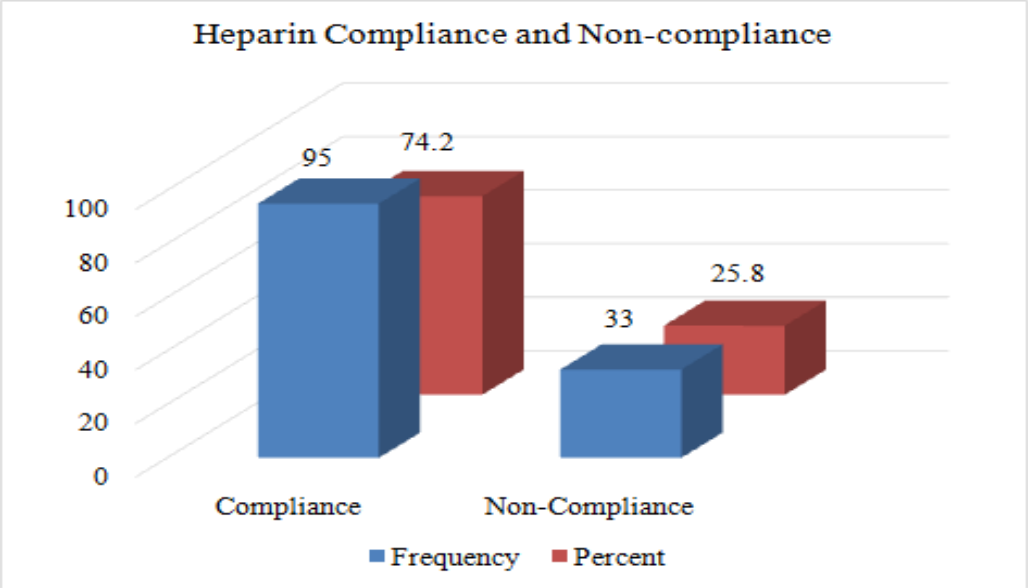

Fig. 3. Compliance of heparin

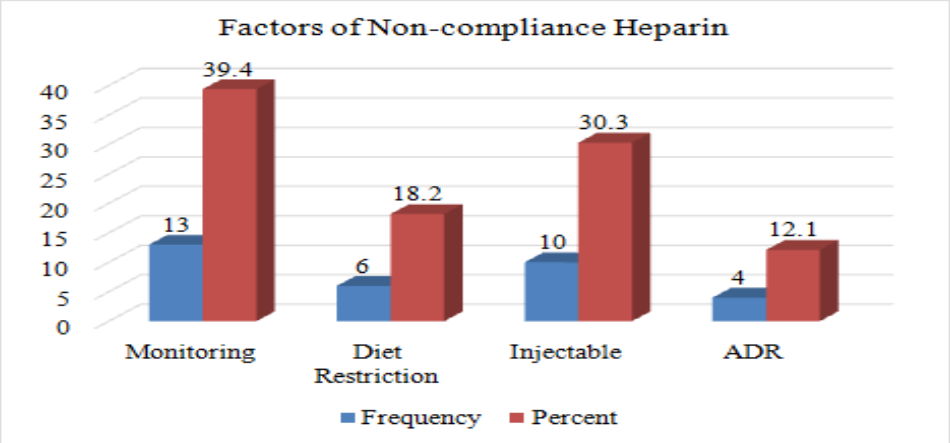

Fig. 0. Factors of Non-compliance of Heparin

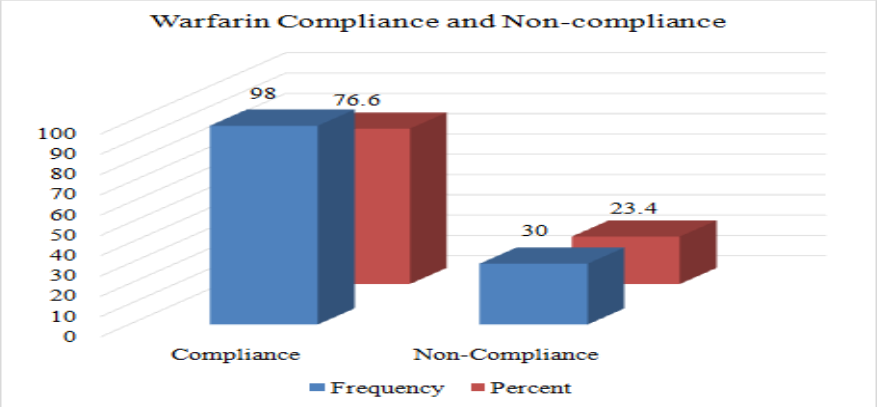

Fig. 5. Compliance of warfarin

3.6 Factors of Non-Compliance of Warfarin

Common factors of non-compliance reported in DVT patients with warfarin were; cost in 4 (13.3%) patients, polypharmacy in 8 (26.7%) patients, prolong therapy in 5 (16.7%) patients and ADR in 13 (43.3%) patients.

4. DISCUSSION

Therefore, current cross-sectional research was designed in setting of tertiary care hospital of Larkana, where diagnosed patients of DVT were enrolled from medicine department and evaluated for commonly reported clinical sign and symptoms of DVT, patients drug compliance with Heparin, Warfarin and Rivaroxaban drugs and associated non-compliance factors with these antithrombotic drugs.

In current research overall drug compliance with antithrombotic drugs was reported in 296 (77.1%) DVT patients, whereas drug compliance with rivaroxaban was present in 103 (80.5%) patients followed by heparin drug compliance in 95 (74.2%) DVT patients and warfarin drug compliance in 98 (76.6%) patients. A similar study by Kang, JM, et al.,[21] reported the overall drug compliance 93.8% with antithrombotic drugs, whereas drug compliance with rivaroxaban was 100.0% and warfarin drug compliance was 93.8% [28]. Similarly, different other studies such as; Lazo-Langner, A., et al., compared the heparin and rivaroxaban [20], Deitelzweig, S., et al, compared the warfarin and rivaroxaban [22], Al Khateep, Y. M., et al. compared the warfarin and rivaroxaban [23] and Piati, P. K., et al. compared the heparin, warfarin and rivaroxaban [24] and reported the higher drug compliance with rivaroxaban followed by heparin and warfarin [25-27].

Table 6. Factors of non-compliance of Warfarin

Factors of non-compliance					
Warfarin		**Frequency**	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	Cost	4	13.3	13.3	13.3
	Polypharmacy	8	26.7	26.7	40.0
	Prolong therapy	5	16.7	16.7	56.7
	ADR	13	43.3	43.3	100.0
	Total	30	100.0	100.0	

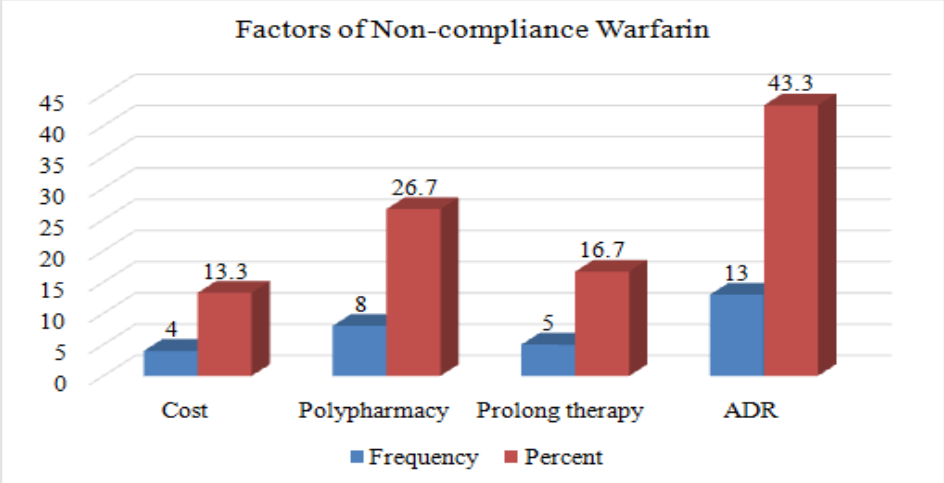

Fig. 6. Factors of non-compliance of warfarin

5. CONCLUSION

This study concludes that the rate of drug compliance was high with rivaroxaban followed by warfarin and heparin. Most commonly reported factor of non-compliance with rivaroxaban was long duration of therapy followed by polypharmacy, side effects of therapy and cost of therapy. Most commonly reported factor of non-compliance with heparin was continuous monitoring followed by injectables, diet restrictions and ADRs of therapy. Most

commonly reported factor of non-compliance with warfarin was ADRs of therapy followed by polypharmacy, long duration of therapy and cost of therapy.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline Patient's consent and ethical approval has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Lung, Blood Institute US. Introduction: Definitions of Deep Vein Thrombosis and Pulmonary Embolism. In, The Surgeon General's Call to Action to Prevent Deep Vein Thrombosis and Pulmonary Embolism. Rockville (MD): Office of the Surgeon General (US);2008.
2. Oklu R, Wicky S. Catheter-directed thrombolysis of deep venous thrombosis. In Seminars in Thrombosis and Hemostasis. Thieme Medical Publishers. 2013;39(04):446-451.
3. Ganguli S, Kalva S, Oklu R, Walker TG, Datta N, Grabowski EF, Wicky S. Efficacy of lower-extremity venous thrombolysis in the setting of congenital absence or atresia of the inferior vena cava. Cardiovascular and Interventional Radiology. 2012;35(5): 1053-1058.
4. Oklu R, Albadawi H, Jones JE, Yoo HJ, Watkins MT. Reduced hind limb ischemia-reperfusion injury in Toll-like receptor-4 mutant mice is associated with decreased neutrophil extracellular traps. Journal of Vascular Surgery. 2013;58(6):1627-1636.
5. Wicky S, Pinto EG, Oklu R. Catheter-directed thrombolysis of arterial thrombosis. In Seminars in thrombosis and hemostasis. Thieme Medical Publishers. 2013;39(4):441-445.
6. Enden T, Haig Y, Kløw NE, Slagsvold CE, Sandvik L, Ghanima W, Sandbæk G. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. The Lancet, 2012;379(9810):31-38.
7. Watson L, Broderick C, Armon MP. Thrombolysis for acute deep vein thrombosis. Cochrane Database of Systematic Reviews. 2016;11.
8. Bashir R, Zack CJ, Zhao H, Comerota AJ, Bove AA. Comparative outcomes of catheter-directed thrombolysis plus anticoagulation vs anticoagulation alone to treat lower-extremity proximal deep vein thrombosis. JAMA Internal Medicine. 2014;174(9):1494-1501.
9. Behravesh S, Hoang P, Nanda A, Wallace A, Sheth RA, Deipolyi AR, Oklu R. Pathogenesis of thromboembolism and endovascular management. Thrombosis;2017.
10. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2008;133(6):454S-545S.
11. Kearon C, Ginsberg JS, Julian JA, Douketis J, Solymoss S, Ockelford P, Gent M. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. JAMA. 2006;296(8):935-942.
12. García EMSN, Merino B, Taylor JH, Vizcaíno I, Vaquero C. Low-molecular-weight heparin for prevention of venous thromboembolism after varicose vein surgery in moderate-risk patients: a randomized, controlled trial. Annals of Vascular Surgery. 2013;27(7):940-946.
13. Antithrombotic drugs. Treatment Guidelines From The Medical Letter. 2011;9(110): 61–66.
14. Doliner B, Jaller JA, Lopez AJ, Lev-Tov H. Treatments to prevent primary venous ulceration after deep venous thrombosis. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2019;7(2), 260-271.
15. Lee S, Han J, Park RW, Kim GJ, Rim JH, Cho J, Kim JH. Development of a Controlled Vocabulary-Based Adverse Drug Reaction Signal Dictionary for Multicenter Electronic Health Record-Based Pharmacovigilance. Drug Safety. 2019;42(5):657-670.
16. Chokesuwattanaskul R, Thongprayoon C, Bathini T, Torres-Ortiz A, O'Corragain OA,

Watthanasuntorn K, Kröner PT. Efficacy and safety of anticoagulation for atrial fibrillation in patients with cirrhosis: A systematic review and meta-analysis. Digestive and Liver Disease. 2019;51(4): 489-495.

17. Predazzi IM, Mango R, Norata GD, Di Daniele N, Sergi D, Romeo F, Novelli G. Pharmacogenetics in cardiovascular disorders: an update on the principal drugs. American Journal of Cardiovascular Drugs, 13(2), 79-85.
18. Carter NJ, Plosker GL. Rivaroxaban: a review of its use in the prevention of stroke and systemic embolism in patients with atrial fibrillation. Drugs. 2013;73(7):715-739.
19. Burness CB, Perry CM. Rivaroxaban: a review of its use in the treatment of deep vein thrombosis or pulmonary embolism and the prevention of recurrent venous thromboembolism. Drugs, 2014;74(2):243-262.
20. Lazo-Langner A, Fleet JL, McArthur E, Garg AX. Rivaroxaban vs. low molecular weight heparin for the prevention of venous thromboembolism after hip or knee arthroplasty: a cohort study. Journal of Thrombosis and Haemostasis. 2014; 12(10):1626-1635.
21. Kang JM, Park KH, Ahn S, Cho S, Han A, Lee T, Min SK. Rivaroxaban after thrombolysis in Acute iliofemoral Venous thrombosis: A Randomized, open-labeled, Multicenter trial. Scientific Reports. 2019; 9(1):1-8.
22. Deitelzweig S, Kline J, Margolis JM, Raut M, Tran O, Smith D, Olson W. Comparison of rivaroxaban or warfarin use for venous thromboembolism on inpatient length of stay. Journal of the American College of Cardiology. 2016;67(13 Supplement):2065.
23. Al Khateep YM, Zaid NA, Salim OR. Comparative study of safety and effectiveness of rivaroxaban and warfarin in patients with acute deep venous thrombosis. The Egyptian Journal of Surgery, 2019;38(2):245.
24. Piati PK, Peres AK, de Andrade DO, Jorge MA, Toregeani JF. Analysis of recanalization of deep venous thrombosis: a comparative study of patients treated with warfarin vs. rivaroxaban. Journal Vascular Brasileiro. 2019;18.
25. Sharp CR, deLaforcade AM, Koenigshof AM, Lynch AM, Thomason JM. Consensus on the Rational Use of Antithrombotics in Veterinary Critical Care (CURATIVE): Domain 4—Refining and monitoring antithrombotic therapies. Journal of Veterinary Emergency and Critical Care, 2019;29(1):75-87.
26. Badjatiya A, Rao SV. Advances in Antiplatelet and Anticoagulant Therapies for NSTE-ACS. Current cardiology reports. 2019;21(1):3.
27. Mckenzie JA, Wilson-Clarke C, Prout J, Campbell J, Douglas RD, Gossell-Williams M. Improving warfarin therapy through implementation of a hospital-based pharmacist managed clinic in Jamaica. Pharmacy Practice (Granada). 2018;16(4).

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