Available online on 15.10.2024 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Copyright © 2024 The Author(s): This is an open-access article distributed under the terms of the CC BY-NC 4.0 which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited

Open Access Full Text Article

Review Article

A Review on Venous Thrombosis: Management with anticoagulants

Dr. P. Kishore Kumar *, Pasumala Varun, Thokala Ruchitha, Chinta Rohit Kumar, Dr. Tadikonda Rama Rao

CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad 501401, Telangana, India.

Article Info:

Article History:

Received 16 July 2024
Reviewed 25 Aug 2024
Accepted 20 Sep 2024
Published 15 Oct 2024

Cite this article as:

Kishore Kumar P*, Varun P, Ruchitha T, Rohit Kumar C, Rama Rao T, A Review on Venous Thrombosis: Management with anticoagulants, Journal of Drug Delivery and Therapeutics. 2024; 14(10)123-128. *DOI: http://dx.doi.org/10.22270/jddt.v14i10.6772*

*Address for Correspondence:

Dr. P. Kishore Kumar, CMR College of Pharmacy, Kandlakoya, Medchal, Hyderabad 501401, Telangana, India.

Abstract

Thrombosis is the most common condition and the world's leading cause of death due to blood clot development in blood arteries. Thromboembolism includes classification based on where the thrombus gets attached to the blood vessels. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two of the main causes of vascular death globally, making up venous thromboembolism (VTE). According to estimates, the yearly incidence rates of VTE in individuals with European ancestry vary from 104 to 183 per 100,000 person-years. Thrombus development and propagation are dependent upon the existence of anomalies in blood flow, blood vessel wall, and blood clotting components, which are together referred to as Virchow's triad. A comprehensive diagnostic approach, which includes clinical evaluation, D-dimer testing, ultrasonography, and lung scan, provided a non-invasive diagnosis for most outpatients with suspected venous thromboembolism. Anticoagulant medication is the primary and established treatment for people who have acute venous thromboembolism (VTE). Among the treatment options available, UFH & LMWH are found to be safe for the growing fetus as they appear to not cross the placenta. Oral anticoagulants targeting thrombin or factor Xa have been introduced, replacing vitamin K antagonists. In a study involving DOACs vs VKAs in patients with pre-existing heart conditions, patients receiving DOACs for non-valvular atrial fibrillation had predominantly superior efficacy and safety.

Keywords: Venous thromboembolism, Anticoagulants, Deep vein thrombosis, Pulmonary embolism, Thrombus

Introduction

Thrombosis:

Thrombosis, a disorder related to formation of clots in blood vessels, is the leading cause of mortality worldwide and has the highest prevalence among the diseases. WHO aims to reduce the incidence and mortality related to this because it can lead to other causes of death[1]. As a result of alterations in blood arteries, the illness mainly complicates in medical settings as myocardial infarction (5 instances per 1000 cases annually)[2], stroke (1.3–4.1 cases per 1000 cases annually)[3], or venous thromboembolism (1-3 occurrences per 1000 cases annually)[4]. Anticoagulants are employed for the prevention and treatment of venous thromboembolism, whereas antiplatelet medications are mostly utilized for the management of arterial thrombotic events, such as myocardial infarction and stroke. Anticoagulants hinder the process of coagulation, also known as secondary haemostasis, as indicated by their name[5].

Venous Thromboembolism:

It is a condition that occurs when blood clots are formed in veins which carry oxygenated blood to the heart. Venous Thromboembolism includes classification based on where the thrombus gets attached to the blood vessels. Deep vein thrombosis (DVT) and pulmonary embolism (PE) are two of the main causes of vascular death globally, making up venous thromboembolism (VTE)[6].

About two thirds of VTE episodes in clinical practice present as DVT, and one third as PE with or without DVT[7,8].

Other veins such as those in the upper extremities, cerebral venous sinuses, mesenteric, renal, and hepatic veins are less commonly affected by thrombosis. This VTE compendium also includes an entry on venous thromboembolism in unusual locations. Other veins such as those in the upper extremities, cerebral venous sinuses, mesenteric, renal, and hepatic veins are less commonly affected by thrombosis [9].

Deep Vein Thrombosis: Deep vein thrombosis typically originates in the calf region of the leg. Most thrombi often develop in the deep veins below the popliteal trifurcation, known as distal DVT. These thrombi are more likely to dissolve on their own without causing any symptoms[10,11]. Approximately 60-70% of patients with symptomatic venous thromboembolism (VTE) will develop deep vein thrombosis (DVT)[12]. Most patients present with symptoms when distal DVT spread to the popliteal and femoral veins and other proximal veins[10,11].

Deep vein thrombosis (DVT) can result in consequences such as post-thrombotic syndrome, pulmonary embolism (PE), and mortality[13] with untreated symptomatic proximal deep vein thrombosis (DVT) had a 50% probability of developing symptomatic pulmonary embolism (PE) within a period of 3 months[10,11]. A major consequence of DVT is post-thrombotic syndrome that occurs in 20–50% of patients and may result in permanent limb discomfort, swelling, heaviness, oedema, and leg ulcers[14,15]. Deep vein thrombosis (DVT) recurs in around 10% of patients, potentially leading to the development of severe post-thrombotic syndrome over a span of 5 years[10,11].

Pulmonary embolism: Common symptoms of pulmonary embolism (PE) include the sudden onset or development of difficulty breathing (dyspnea), chest discomfort, or persistent low blood pressure without any other identifiable cause[16].These symptoms are observed in around 30-40% of patients with venous thromboembolism (VTE)[17,18]. The survival rate for individuals with pulmonary embolism (PE) is lower compared to deep vein thrombosis (DVT) due to the fact that 25% of these patients experience abrupt mortality as their initial clinical presentation[19]. Without any additional therapy, the mortality rate for people identified with this illness might approach to 25% [20]. Nevertheless, the use of anticoagulant medication can take it down to 1.5%[21].

Risk Factors

The acquired risk factors for VTE include:

- Age > 40 years
- Bed rested patients
- Patients who had recent surgery
- Trauma
- Cancer patients
- Myocardial Infarction
- Ischemic Stroke
- Oral Contraceptives
- Hormone-replacement therapy
- Pregnant/ Postpartum mothers
- Prior history of VTE
- Long-lasting travellers
- Testing positive for antiphospholipid antibodies[22].

Thrombophilia refers to a collection of genetic abnormalities that increase the likelihood of experiencing thromboembolic events. The most well recognized factors contributing to thrombophilia include: factor V Leiden (resistance to activated protein C), prothrombin 20210A mutation, deficiency of protein C, lack of protein S, deficiency of antithrombin, elevated homocysteine levels, and abnormalities in the fibrinolytic system. Up to 33% of individuals with VTER and over 50% of patients with familial thrombosis may have a genetic susceptibility to thrombosis. Factor V Leiden detection is crucial for individuals who experience recurring episodes of venous thromboembolism (VTE), have other established reasons of thrombophilia, or belong to families with a high prevalence of VTE. Detecting deficiencies in protein C, protein S, and antithrombin is crucial in patients with a history of venous thromboembolism (VTE). These patients have a significantly higher risk, 8 to 10 times greater, of experiencing another VTE incidence. Prophylaxis against thrombosis should be employed consistently in all of these instances[22].

Incidence of VTE:

According to estimates, the yearly incidence rates of VTE in individuals with European ancestry vary from 104 to 183 per 100,000 person-years[23], which is comparable to the rates observed for stroke[24].The overall incidence of VTE may vary among African American communities based on their geographic location within the US, and it may be higher in African American populations[25] lower in Asian, Asian American, and Native American populations[26-28]. PE (with or without DVT) and DVT alone (without PE) have reported incidence rates that range from 29 to 78 and 45 to 117 per 100,000 person-years, respectively[29].

Pathophysiology

Understanding venous thromboembolism (VTE) requires the understanding of both the anatomy of deep veins and the physiology of the pulmonary system. Regarding the lower limbs, it is necessary to have knowledge of the femoral, iliac, and popliteal veins, while also recognizing the possibility of the upper limbs veins being affected (subclavian, axillary, and brachial). Although less frequent, VTE can also impact the superior vena cava, jugular veins, cerebral and cavernous sinuses, as well as retinal veins[30]. Thrombi seen in unusual locations should be examined to determine whether there are other possible causes or underlying disorders (such as Budd-Chiari syndrome with involvement of the hepatic or splenic veins). Superficial vein thrombosis, which is commonly caused by factors such as intravenous lines or cellulitis, generally does not require anticoagulant treatment [31]. The actual pathophysiology of venous thromboembolism goes as follows.

Thrombus development and propagation are dependent upon the existence of anomalies in blood flow, blood vessel wall, and blood clotting components, which are together referred to as Virchow's triad. Changes in blood circulation or the stagnation of venous flow typically arise during extended periods of inactivity or being restricted to a bed. Obstruction of the veins can occur due to external compression caused by enlarged lymph nodes, bulky tumors, or intravascular compression resulting from past blood clots. Through medicine, elevated levels of oestrogens, observed in women using oral contraceptives or undergoing hormone replacement treatment after menopause, have been linked to a threefold rise in the already minimal risk of venous thromboembolism. Malignancies, including adenocarcinomas and metastatic malignancies, are further linked to an elevated risk of venous

thromboembolism. Indeed, during the presentation, several cases of idiopathic venous thromboembolisms have shown hidden malignancies during further examination. Both pharmaceutical doses of oestrogens and cancer have the ability to activate the coagulation system [32].

Diagnosis

A comprehensive diagnostic approach, which includes clinical evaluation, D-dimer testing, ultrasonography, and lung scan, provided a non-invasive diagnosis for most outpatients with suspected venous thromboembolism. This technique demonstrated a high level of safety. For individuals with a low probability of developing venous thromboembolism (VTE), utilizing D-dimer as the primary diagnostic test decreases the necessity for imaging procedures. Imaging is necessary for individuals who are at a high risk of developing venous thromboembolism (VTE). The most proven procedures for diagnosing pulmonary embolism (PE) are ventilation-perfusion scanning and computed tomography pulmonary angiography. On the other hand, ultrasonography is used for diagnosing deep vein thrombosis (DVT) in the lower or upper extremities. Further investigation is required to explore novel diagnostic methods and verify the effectiveness of clinical decision guidelines for patients who are believed to have recurrent venous thromboembolism (VTE).

Treatment of Venous Thromboembolism

Anticoagulant medication is the primary and established treatment for people who have acute venous thromboembolism (VTE). Effective anticoagulation reduces the likelihood of recurring venous thromboembolism by almost 80%, bringing the risk down from 47% to 29% for untreated individuals to 5% from 7% for those who get treatment[33-36]. When receiving sufficient anticoagulant treatment (consisting of at least 5 days of heparin and 3 months of either oral anticoagulants with an international normalized ratio between 2.0 and 4.5, LMWH, or adjusted-dose subcutaneous unfractionated heparin), the likelihood of experiencing a fatal pulmonary embolism is extremely low. Specifically, the risk is 0.4% and 0.3% during and after treatment for deep vein thrombosis, and 1.5% and 0% during and after treatment for pulmonary embolism.

The American Society of Hematology issues guidelines for treatment of venous thromboembolism especially on dose selection, drug interaction management, INR testing, monitoring of anticoagulant responses etc. The guidelines for management of venous thromboembolism by ASH (available on the hematology.org website) state the following points for clinical practice for treatment of VTE. As of now, ASH 2019 guidelines are those latest ones available on the website of American Society of Hematology. Some of the key points regarding the treatment guidelines are as below.

Dose selection and managing VTE:

Several anticoagulants such as vitamin K antagonists (VKAs) (warfarin) and other options such as direct oral anticoagulants (DOACs) such as apixaban and rivaroxaban are first line drugs for VTE treatment. Here are few of the major points in the recommendations of anticoagulants in VTE treatment by ASH.

Anticoagulant therapy is strongly recommended for patients with PE and hemodynamic compromise. Patients with VTE who use a vitamin K antagonist (VKA) for secondary prevention should aim for an international normalized ratio (INR) range of 2.0 to 3.0, rather than a lower INR range. Patients with recurrent unprovoked VTE should receive indefinite anticoagulation. For simple deep vein thrombosis (DVT) and pulmonary embolism (PE) cases with minimal risk of complications, it is recommended to prioritize home therapy rather than hospital-based care. Additionally, when it comes to the first treatment of venous thromboembolism (VTE), direct oral anticoagulants are preferred over vitamin K antagonists (VKA)[37].

i. Dose selection in obese patients (BMI >30) must be done based on actual body weight for LMWH dose but not on maximum daily dose.

ii. For patients with renal insufficiency (CrCl < 30mL/min), anti-factor Xa monitoring is not required. Instead, should focus on dose adjustment or switching to an alternative with low clearance such as unfractionated heparin (UFH). In obese patients, body weight must be considered.

iii. Patient self-management (PSM): Patients who are on VKAs are recommended to test their INRs at home itself and adjust the dose based on the INR values obtained.

iv. For patients shifting from one class of anticoagulants to other, ASH suggests co-introducing DOAC and VKA together until the INR is in the therapeutic range. Consider the fact that DOACs can impact INR values.

v. Anticoagulant Management Services (AMS) can be utilized for patients which can reduce risk of PE and are on higher time in therapeutic range.

Planning invasive surgical treatment during anticoagulant therapy:

i. For patients with low to moderate risk of recurring VTE requiring VKA interruption for surgical procedure, ASH does not recommend using LMWH/UFH instead of VKAs as it increases the risk of bleeding.

ii. For surgery planned patients, DOAC testing may not be required prior to surgery but may be advisable for renal dysfunction patients.

When the patient is being involved in anticoagulant therapy monitoring for ADRs can be beneficial, patient must be provided with option of reversal of anticoagulants for the risk of bleeding and internal hemorrhage. For the bleeding risk patients, if the issue gets resolved, resumption of treatment may begin within 90 days rather than discontinuation[38].

Treatment guidelines in pregnant women:

Among the treatment options available, UFH & LMWH are found to be safe for the growing fetus as they appear to not cross the placenta. LMWH is the preferred pharmacological treatment for preventing VTE in pregnant individuals, as agreed upon by agreement. Low molecular weight heparin (LMWH) is supplied via subcutaneous injection and can be safely used in pregnant and nursing individuals[39].

There is insufficient evidence to support the safety of direct oral anticoagulant medicines (DOACs) for preventing venous thromboembolism (VTE) in pregnant women. However, the American College of Obstetricians and Gynecologists recommends that Direct Oral Anticoagulants (DOACs) may be a viable option for preventing blood clots in women who have just given birth and are not nursing. Low molecular weight heparin (LMWH) and unfractionated heparin are effective in reducing mortality and recurrence of venous thromboembolism (VTE) and are recommended therapy alternatives during pregnancy. Treatment of VTE in pregnancy requires at least 3 months of anticoagulant therapy. (6 months including postpartum period) [40].

Novel Anticoagulant Therapy:

Oral anticoagulants targeting thrombin or factor Xa have been introduced, replacing vitamin K antagonists. Clinical studies show similar efficacy in stroke prevention in atrial fibrillation and secondary prevention after acute coronary syndromes. These drugs may replace vitamin K antagonists in atrial fibrillation cases and post-acute coronary syndromes[41].

Initial treatment with Fondaparinux:

Fondaparinux is a parenterally administered factor Xa inhibitor that exhibits less variance in patient response than UFH, resulting in more steady effects. Fondaparinux does not need to be monitored; it is injected subcutaneously once day [(42)]. 7.5 mg is the standard dosage; however, patients weighing less than 50 kg or more than 100 kg should receive dosages of 5 mg or 10 mg, respectively [43].

Treatment with DOACs:

Current global clinical trials assessed DOACs, such as rivaroxaban and edoxaban, for the treatment of VTE, long-term prevention of recurrences, and prevention of cardiogenic cerebral embolisms in patients with postoperative primary VTE and atrial fibrillation [44,45].

In a study involving DOACs vs VKAs in patients with pre-existing heart conditions, patients receiving DOACs for non-valvular atrial fibrillation had predominantly superior efficacy and safety. Patients who were treated with DOACs for acute VTE had non-inferior efficacy, but an overall superior safety profile[46].

Oral anticoagulants have better patient safety benefitting risk to benefit with drop in stroke, haemorrhages and death whereas warfarin has been seen with increase of GI bleeding [47]. Oral Apixaban has been found to have less risk of internal bleeding and is usually the drug of choice as a DOAC in some cases [48].

However, in some case Enoxaparin was shown to have more potency than other drugs and can be used when needed [49].

With these newer drugs emerging into the treatment options, the factor Xa inhibitors tend to still be relevant and are effective in reducing thromboembolic attacks and events effectively [50].

Conclusion

Anticoagulants have emerged as go-to drugs for treatment of venous thrombosis and are found effective in decreasing the complications associated with thrombotic attacks. However, wider range of anticoagulant drugs available gives the flexibility of choosing the appropriate treatment based on the patient's condition. Adherence to the latest anticoagulant therapy guidelines in treatment of VTE by ASH, by clinicians can help in maximizing the patient's benefit. Appropriate dose selection along with consideration of other conditions such as pregnancy, risk of bleeding etc. can be appreciated if considered. VKAs, DOACs etc can be potent drug options that are effective in treatment of VTE. While considering all these guidelines, monitoring patient safety profile can be beneficial in averting anticoagulant induced adverse events such as severe thrombocytopenia, internal bleeding etc.

Acknowledgements

We would like to acknowledge Dr. K Geetha, co-ordinator of the Department of PharmD and Dr G Ramya Balaprabha, Hospital co-ordinator CMR College of pharmacy, for their time and efforts in making this publication possible.

Conflict of Interest

The authors have no conflicts of interest regarding this review article.

References

1. World Health Organization; 2023. Available at https://www.who.int/news-room/factsheets/detail/noncommunicable-diseases. Accessed September 16, 2023.

2. Fang J, Alderman MH. Dissociation of hospitalization and mortality trends for myocardial infarction in the United States from 1988 to 1997. Am J Med. 2002;113(2):208-214. https://doi.org/10.1016/S0002-9343(02)01172-5

3. Feigin VL, Lawes CM, Bennett DA, Anderson CS. Stroke epidemiology: A review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. Lancet Neurol. 2003;2(1):43-53. https://doi.org/10.1016/S1474-4422(03)00266-7

4. • White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107(suppl 1) -I-8. https://doi.org/10.1161/01.CIR.0000078468.11849.66

5. Mackman, N, Bergmeier, W, Stouffer GA, Weitz, J.I. Therapeutic strategies for thrombosis: New targets and approaches. Nat. Rev. Drug Discov. 2020; 19(5), 333-352. https://doi.org/10.1038/s41573-020-0061-0

6. Wendelboe AM, Raskob GE. Global Burden of Thrombosis: Epidemiologic Aspects. Circ. Res. 2016; 118:1340-1347. https://doi.org/10.1161/CIRCRESAHA.115.306841

7. Anderson FA, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE. A Population-Based

Perspective of the Hospital Incidence and Case-Fatality Rates of Deep Vein Thrombosis and Pulmonary Embolism: The Worcester DVT Study. Arch. Intern. Med. 1991;151:933-938. https://doi.org/10.1001/archinte.1991.00400050081016

8. Oger E. Incidence of venous thromboembolism: A community-based study in western France. Thromb Haemost. 2000;83(5):657-660. doi: 10.1055/s-0037-1613887. https://doi.org/10.1055/s-0037-1613887

9. Riva N. Cerebral and splanchnic vein thrombosis: Advances, challenges, and unanswered questions. J Clin Med. 2020;9(3):743. doi: 10.3390/jcm9030743. https://doi.org/10.3390/jcm9030743

10. Kearon C. Natural history of venous thromboembolism. Circulation. 2003;107(suppl 1)-I30. https://doi.org/10.1161/01.CIR.0000078464.82671.78

11. Ho WK. Deep vein thrombosis risks and diagnosis. Aust Fam Physician. 2010;39(7):468-474.

12. White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107(suppl 1)-I8. https://doi.org/10.1161/01.CIR.0000078468.11849.66

13. Scarvelis D, Wells PS. Diagnosis and treatment of deep-vein thrombosis. CMAJ. 2006;175(9):1087-1092. https://doi.org/10.1503/cmaj.060366

14. Snow V, Qaseem A, Barry P, et al. Management of venous thromboembolism: A clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2007;146(3):204-210. https://doi.org/10.7326/0003-4819-146-3-200702060-00149

15. Kahn SR. The post-thrombotic syndrome. Thromb Res. 2011;127(suppl 3)-S92. https://doi.org/10.1016/S0049-3848(11)70024-X

16. Agnelli G, Becattini C. Acute pulmonary embolism. N Engl J Med. 2010;363(3):210-274. https://doi.org/10.1056/NEJMra0907731

17. White RH. The epidemiology of venous thromboembolism. Circulation. 2003;107(suppl 1)-I8. https://doi.org/10.1161/01.CIR.0000078468.11849.66

18. McRae S. Pulmonary embolism. Aust Fam Physician. 2011;39(6):462-466.

19. Heit JA. Venous thromboembolism: Disease burden, outcomes and risk factors. J Thromb Haemost. 2005;3(8):1611-1617. https://doi.org/10.1111/j.1538-7836.2005.01415.x

20. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. Lancet. 1960;275(7138):1309-1312. https://doi.org/10.1016/S0140-6736(60)92299-6

21. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. JAMA. 1998;279(6):458-462. https://doi.org/10.1001/jama.279.6.458

22. Barczyk A, Pierzchała W. Risk factors of venous thromboembolism. Wiad Lek. 2001;54(5-6):311-324. PMID: 11556214.

23. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, Forcier A, Dalen JE. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: The Worcester DVT Study. Arch Intern Med. 1991;151(5):933-938. https://doi.org/10.1001/archinte.1991.00400050081016

24. Rothwell PM, Coull AJ, Giles MF, et al. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). Lancet. 2004;363(9425):1925-1933. https://doi.org/10.1016/S0140-6736(04)16405-2

25. Zakai NA, McClure LA, Judd SE, et al. Racial and regional differences in venous thromboembolism in the United States in 3 cohorts. Circulation. 2014;129(14):1502-1509. https://doi.org/10.1161/CIRCULATIONAHA.113.006472

26. Cheuk BL, Cheung GC, Cheng SW. Epidemiology of venous thromboembolism in a Chinese population. Br J Surg. 2004;91(3):424-428. https://doi.org/10.1002/bjs.4454

27. Klatsky AL, Armstrong MA, Poggi J. Risk of pulmonary embolism and/or deep venous thrombosis in Asian-Americans. Am J Cardiol. 2000;85(11):1334-1337. https://doi.org/10.1016/S0002-9149(00)00766-9

28. Hooper WC, Holman RC, Heit JA, Cobb N. Venous thromboembolism hospitalizations among American Indians and Alaska Natives. Thromb Res. 2002;108(5):273-278. https://doi.org/10.1016/S0049-3848(03)00058-6

29. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8):464-474. doi: 10.1038/nrcardio.2015.83. Epub 2015 Jun 16. PMID: 26076949; PMCID: PMC4624298. https://doi.org/10.1038/nrcardio.2015.83

30. Mackay JA, Lyman DT, Alizadeh H, et al. Venous thromboembolism: Risk assessment, prevention, and treatment. Am J Med. 2015;128(6):689.e1-689.e22. doi: 10.1016/j.amjmed.2015.06.039. https://doi.org/10.1016/j.amjmed.2015.06.039

31. Ashorobi D, Ameer MA, Fernandez R. Thrombosis. [Updated 2023 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538430/.

32. Turpie AGG. ABC of antithrombotic therapy: Venous thromboembolism: Pathophysiology, clinical features, and prevention. BMJ. 2002;325(7369):887-890. https://doi.org/10.1136/bmj.325.7369.887

33. Hull R, Delmore T, Genton E, Hirsh J, Gent M, Sackett D, McLoughlin D, Armstrong P. Warfarin sodium versus low-dose heparin in the long-term treatment of venous thrombosis. N Engl J Med. 1979;301(16):855-858. https://doi.org/10.1056/NEJM197910183011602

34. Lagerstedt C, Fagher B, Olsson CG, Öqvist B, Albrechtsson U. Need for long-term anticoagulant treatment in symptomatic calf-vein thrombosis. Lancet. 1985;326(8454):515-518. https://doi.org/10.1016/S0140-6736(85)90459-3

35. Kearon C, Hirsh J. Management of anticoagulation before and after elective surgery. N Engl J Med. 1997;336(21):1506-1511. https://doi.org/10.1056/NEJM199705223362107

36. Hirsh J. Heparin. N Engl J Med. 1991;324(22):1565-1574. https://doi.org/10.1056/NEJM199105303242206

37. Ortel TL, Neumann I, Ageno W, Beyth RJ, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S, Thurston C, Vedantham S, Verhamme P, Witt DM, Flórez ID, Izcovich A, Nieuwlaat R, Ross S, Schünemann HJ, Zhang Y. American Society of Hematology 2020 guidelines for management of venous thromboembolism: Treatment of deep vein thrombosis and pulmonary embolism. Blood Adv. 2020;4(22):5778-5811. https://doi.org/10.1182/bloodadvances.2020001830

38. Falanga A, Ay C, Di Nisio M, Gerotziafas G, Jara-Palomares L, Langer F, Lecumberri R, Mandala M, Maraveyas A, Pabinger I, Sinn M. Venous thromboembolism in cancer patients: ESMO Clinical Practice Guideline. Ann Oncol. 2023;34(5):452-467. https://doi.org/10.1016/j.annonc.2022.12.014

39. Greer IA, Nelson-Piercy C. Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: A systematic review of safety and efficacy. Blood. 2005;106(2):401-407. https://doi.org/10.1182/blood-2005-02-0626

40. American College of Obstetricians and Gynecologists' Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin No. 196: Thromboembolism in Pregnancy. Obstet Gynecol. 2018 Jul;132(1):e1-e17. https://doi.org/10.1097/AOG.0000000000002706

41. Coordinating Committee, De Caterina R, Husted S, Wallentin L, Andreotti F, Arnesen H, Bachmann F, Baigent C. New oral anticoagulants in atrial fibrillation and acute coronary syndromes: ESC Working Group on Thrombosis-Task Force on Anticoagulants

in Heart Disease position paper. J Am Coll Cardiol. 2012;59(16):1413-1425. https://doi.org/10.1016/j.jacc.2012.02.008

42. Nakamura M, Okano Y, Minamiguchi H, Munemasa M, Sonoda M, Yamada N, Hanzawa K, Aoyagi N, Tsujimoto H, Sarai N, Nakajima H, Kunieda T. Multidetector-row computed tomography-based clinical assessment of fondaparinux for treatment of acute pulmonary embolism and acute deep vein thrombosis in Japanese patients. Circ J. 2011;75(6):1424-32. https://doi.org/10.1253/circj.CJ-10-1036

43. Nakamura M, Yamada N, Ito M. Novel anticoagulant therapy of venous thromboembolism: Current status and future directions. Ann Vasc Dis. 2017;10(2):92-98. https://doi.org/10.3400/avd.ra.17-00015

44. Büller HR, Décousus H, Grosso MA, et al.; Hokusai-VTE Investigators. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369(14):1406-1415. https://doi.org/10.1056/NEJMoa1306638

45. Agnelli G, Buller HR, Cohen A, et al.; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808. https://doi.org/10.1056/NEJMoa1302507

46. Makam RCP, Hoaglin DC, McManus DD, Wang V, Gore JM, Spencer FA, et al. Efficacy and safety of direct oral anticoagulants approved for cardiovascular indications: Systematic review and meta-analysis. PLoS ONE. 2018;13(5) https://doi.org/10.1371/journal.pone.0197583

47. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365(10):883-891. https://doi.org/10.1056/NEJMoa1009638

48. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013;369(9):799-808. https://doi.org/10.1056/NEJMoa1302507

49. Guan Z, Wang R, Hussain RH, Fredenburgh JC, Jaffer IH, Weitz JI. Rivaroxaban and apixaban are less effective than enoxaparin for the prevention of catheter-induced clotting in vitro. J Thromb Haemost. 2023;21(1):76-82. https://doi.org/10.1016/j.jtha.2022.10.020

50. Weitz JI, Eikelboom JW. What is the future of factor XI inhibitors? Circulation. 2022;146(25):1899-1902. https://doi.org/10.1161/CIRCULATIONAHA.122.061132