WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 11, Issue 17, 765-774. Review Article ISSN 2277– 7105

A SYSTEMATIC REVIEW ON SAFETY AND EFFICACY OF DABIGATRAN VS RIVAROXABAN

V. Sanghavi*, Gayathri M.[1], Ramya V.[2], Pavithra G.[3], Merlin Jose[4] and Monica B.[5]

*Assistant Professor, Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode- 637205, Namakkal Dist., Tamil Nadu, India.

[1,2,3,4,5]Doctor of Pharmacy-Intern, Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode- 637205, Namakkal Dist., Tamil Nadu, India.

Article Received on
05 November 2022,

Revised on 25 Nov. 2022,
Accepted on 15 Dec. 2022,

DOI: 10.20959/wjpr202217-26553

***Corresponding Author**
V. Sanghavi
Assistant Professor, Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode- 637205, Namakkal Dist., Tamil Nadu, India.

ABSTRACT

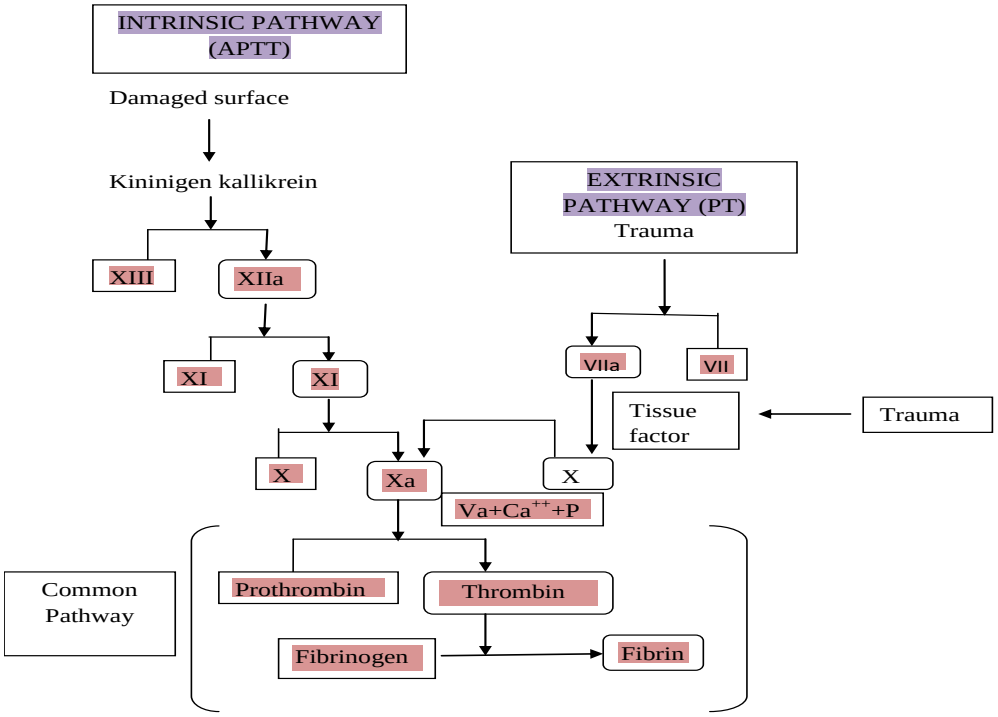
Anticoagulants are the primary treatment for patients suffering from atrial fibrillation (AF) and are used to prevent stroke and systemic embolism. Direct factor Xa inhibitors, such as Rivaroxaban, are taken orally, whereas direct thrombin inhibitors, such as Dabigatran, are given intravenously. Compared to Rivaroxaban, Dabigatran (150 mg BID) significantly reduced the risk of stroke and systemic embolism, as well as hemorrhagic stroke. When compared to Rivaroxaban, Dabigatran (110 mg BID) was associated with lower significant hemorrhage and cerebral bleeding. Major risk bleeds were significantly higher with Rivaroxaban than with Dabigatran, as were all-cause mortality and gastrointestinal bleeding.

KEYWORDS: Rivaroxaban, Dabigatran, Atrial Fibrillation, Stroke.

INTRODUCTION

Anticoagulants are the backbone of care for patients with atrial fibrillation (AF) or flutter in order to prevent stroke and systemic embolism. Additionally, they can be utilized to treat different thrombus formation conditions as well as to prevent and treat venous thromboembolism (VTE). This class of medications needs to be used with caution because an overdose can induce bleeding or insufficient clot prevention.[1] To prevent and treat venous and arterial thromboembolic disorders, parenteral anticoagulants acting by blocking vitamin

K-dependent coagulation factors, such as unfractionated (UFH), low molecular weight heparins (LMWHs), or fondaparinux, as well as oral anticoagulants, have been utilized (vitamin K antagonists, VKAs). Direct Oral Anti-Coagulants, sometimes known as "DOACs," are anticoagulant pharmacotherapies that are used to avoid thrombosis in a number of cardiovascular conditions. DOACs are divided into two groups: oral direct factor Xa inhibitors (such as rivaroxaban, apixaban, edoxaban, and betrixaban) and direct thrombin inhibitors (such as dabigatran).[2]



[Factor VII – Proconvertin, VIIa- Recombinant factor, X – Stuart prower factor, Xa – Serine protease, XI – Plasma thromboplastin antecedent, XIII – Fibrin Stabilizing factor.

Rivaroxaban

Class: Factor Xa inhibitors, Anticoagulants, Blood Modifier agent.

MOA: Rivaroxaban serves as an anticoagulant by selectively inhibiting factor Xa without the requisite for a cofactor (e.g., anti-thrombin III). Rivaroxaban inhibits prothrombinase activity and unbound factor Xa. It indirectly prevents thrombin-induced platelet aggregation by reducing the production of thrombin by inhibiting factor Xa, which also suppresses thrombin production.

USES: Atrial fibrillation, myocardial infarction, stroke, Congenital heart disease, Deep venous thrombosis, Pulmonary embolism, Venous thromboembolism.

Dose

- Acute coronary syndrome - 2.5 to 5 mg twice daily orally
- Atrial fibrillation - 20 mg once daily orally
- Stroke and myocardial infarction: 2.5 mg taken twice day in order to 75–100 mg of aspirin taken once daily, with or without food.
- Deep vein thrombosis (15 mL/min or higher creatinine clearance) 15 mg orally two times a day for 21 days, subsequently 20 mg once daily orally.
- Pulmonary embolism (15 mL/min or higher) 15 mg orally two times a day for 21 days followed by 20 mg orally once daily

Adverse reactions

1. Cardiovascular: Syncope
2. Gastrointestinal: Gastrointestinal hemorrhage, Upper gastrointestinal bleeding
3. Hematologic: Hematoma, Major (Stroke prevention in nonvalvular atrial fibrillation, pulmonary embolism.
4. Immunologic: Angioedema

Contraindications

1. Active bleeding from a pathogen
2. Anaphylaxis or other severe hypersensitivity reaction to rivaroxaban

Monitoring index values

1. Prothrombin time (PT), INR, or activated partial thromboplastin time monitoring for rivaroxaban's anticoagulant impact (aPTT)
2. Implementing the HAS-BLED risk score in high-risk individuals at each and every orders visit to monitor bleeding risk(blood pressure, abnormal kidney and hepatic function, stroke, bleeding, labile Internationalised Normal Rations, and drugs or alcohol)
3. In patients receiving treatment for VTE and having a CrCl of 15 to 30 mL/min, pay special attention and assess blood loss as away.
4. Hematocrit and haemoglobin.[3]

Pharmacoeconomics:[4]

Drug	Strength	Dosage Form	Cost ($)	Daily Usage On Average	The Average Cost of Daily	The Cost of Treatment

					Drug Usage ($)	Course ($)
Rivaroxaban	10 mg 15 mg 20 mg	Tablet	2.8400	15 mg twice daily for three weeks, then 20 mg once daily	2.84 to 5.68	3 months: 315 6 months: 571

Dabigatran

CLASS: Direct thrombin inhibitors.

MOA: Dabigatran, the substance in dabigatran etexilate that is the active ingredient, and its acyl glucuronides function as direct thrombin inhibitors that are competitive and prevent the synthesis of thrombi. The anticoagulant dabigatran and its acyl glucuronides inhibit both free and clot-bound thrombin as well as thrombin-induced platelet aggregation.

Indication

Stroke and systemic embolism (S/SE) in patients with nonvalvular atrial fibrillation (AF), Deep Vein Thrombosis (DVT), Pulmonary embolism.

Doses

- ✓ Twice-daily use of 150 mg for atrial fibrillation.
- ✓ **Heparin-induced thrombocytopenia (HIT) -** Acute HIT with thrombosis: 150 mg twice daily after 5 days or longer of treatment with a parenteral non-heparin anticoagulant. Until platelet count recovery, take 150 mg orally twice daily for acute isolated HIT (HIT without thrombosis).
- ✓ **Pulmonary embolism:** 110 mg orally 1–4 hours following surgery; 220 mg orally once daily for 28–35 days after hemostasis is achieved.

Dosage Adjustments

- Treatment of DVT - CrCl less than 50 mL/min- Avoid coadministration
- Stroke and systemic embolism prophylaxis in non-valvular atrial fibrillation - CrCl 15 to 30 mL/min- 75 mg orally twice day.

Adverse Effects

1. Cardiovascular: Nonvalvular Atrial Fibrillation, Myocardial Infarction, DVT, Pulmonary Embolism
2. Internal organs: Internal bleeding, upper gastrointestinal bleeding
3. Hematology: Major Hemorrhage (Adult, DVT and pulmonary embolism, nonvalvular atrial fibrillation, Thrombosis
4. Epidural hematoma and intracranial bleeding in the neurological system
5. Alveolar Hemorrhage
6. Respiratory : Hemorrhage, Alveolar

Contraindications

A serious hypersensitive reaction is a contraindication (eg, anaphylactic reaction or anaphylactic shock)

Monitoring Variables

1. Tests of renal function
2. High-risk patients' bleeding risk can be assessed using the HAS-BLEED risk score at every follow-up.
3. Hematocrit/hemoglobin.
4. Prothrombin time, thrombin time, and activated partial thromboplastin time (aPTT) should only be used as qualitative assays to determine whether an anticoagulant effect exists.[3]

Anticoagulant Comparison Chart.[5]

Generic	Dabigatran	Rivaroxaban
FDA approval What conditions is this drug approved for?	Deep venous thrombosis, Pulmonary embolism, Venous thromboembolism.	Stroke and systemic embolism (S/SE) in patients with nonvalvular atrial fibrillation (AF), Deep Vein Thrombosis (DVT), Pulmonary embolism
Dose	150 mg BID	20 mg OD
Mechanism	Oral direct thrombin inhibitor	Oral direct factor Xa inhibitor
Adverse event	Hemorrhage	Hemorrhage
Laboratory monitoring	Thrombin time Ecarin clotting time	Anti-factor Xa
Metabolism	Activation by esterases renal	Hepatic (CYP3A4-major) renal
Excretion	80% renal	2/3 liver, 1/3 renal
Renal impairment	Use 75mg twice daily if CrCl=15-30mL/minm^2	Use 15mg daily if CrCl=30-49mL/minM^2 avoid use if CrCL <30mL/minm^2
Hepatic impairment	N/A	Avoid use in moderate or severe

Drug interaction	P-glycoprotein inhibitors or inducers	CYP3A4 inhibitors or inducers-P-glycoproteins inhibitors or inducers
Special considerations	Intestinal absorption is pH dependent and is reduced in patients taking proton pump inhibitors.	Higher levels expected in patients with renal or hepatic failure.

Comparative effectiveness of rivaroxaban and dabigatran

Dabigatran (150 mg BID) substantially diminished the occurrence of hemorrhagic stroke, non-disabling stroke, systemic embolism, and stroke contrasted to rivaroxaban. There were no discernible changes in the ability of apixaban and dabigatran (both doses), rivaroxaban, or rivaroxaban plus dabigatran 110 mg BID to prevent stroke and systemic embolism. The new OACs and the ischemic stroke showed no discernible differences.

Comparison of dabigatran and rivaroxaban's relative safety[6]

Apixaban considerably reduced major bleeding compared to rivaroxaban and dabigatran 150 mg BID, but did not significantly vary from dabigatran 110 mg BID. The amount of extracranial and gastrointestinal bleeding was also significantly different between apixaban and dabigatran 150 mg BID. There were no appreciable differences between dabigatran 110 mg BID and apixaban in terms of safety endpoints. Apixaban had less severe or clinically significant bleeding as compared to rivaroxaban. Systemic embolism increased when apixaban was taken in place of rivaroxaban. Apixaban had less substantial or clinically significant bleeding as compared to rivaroxaban. Systemic embolism was more frequent with apixaban than with rivaroxaban. Cerebral haemorrhage and severe haemorrhage were both reduced after taking dabigatran 110 mg BID when compared to rivaroxaban.

Guidelines of Dabigatran

According to the 2019 Focused Update of the 2014 guidelines for the management of atrial fibrillation from the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Rhythm Society (HRS), dabigatran has a class 1 recommendation (level of evidence A) for the treatment of non-valvular atrial fibrillation and is preferred over warfarin, like other DOACs. Warfarin has been demonstrated to be either non-inferior or inferior to dabigatran in preventing stroke and systemic embolism. It also has a minimized risk of catastrophic bleeding.[7]

Dabigatran and other DOACs are advocated over warfarin (Grade 2B) in the American College of Chest Physicians' 2016 guidelines for the treatment of acute VTE in patients

without cancer, and they recommend three months of treatment for the management of DVT and PE (Grade 1B)[10] In accordance with the 2020 VTE guidelines published by the American Society of Hematology, DOACs are recommended over VKAs (conditional recommendation based on intermediate certainty in the evidence), and individuals with low creatinine clearance, moderate to severe liver disease, or antiphospholipid syndrome are not eligible for this recommendation. This tribunal does not endorse one DOAC over another and instead gives a conditional recommendation based on scant data.[8]

For patients with eGFR > 30 mL/min and 75 mg twice day for those with eGFR 15-29 mL/min, respectively, are the FDA-approved dosages of dabigatran for atrial fibrillation. Real-world evidence strongly reject the use of DOACs in patients with end-stage renal disease (ESRD). In light of the results of the RE-COVER, RE-COVER II, RE-MEDY, and RE-SONATE trials, the FDA approved dabigatran 150 mg BID (after 5–10 days of parenteral anticoagulation) for the treatment of DVT and PE in patients with eGFR > 30 mL/min and discouraged use in those with eGFR 30 mL/min.[9]

Guidelines of Rivoroxaban

According to the most recent American College of Cardiology (ACC), American Heart Association (AHA), and Heart Rhythm Society (HRS) 2019 focused update on 2014 guidelines, rivaroxaban has a class 1 recommendation and level of evidence B for nonvalvular atrial fibrillation with a CHA2DS2-VASc score of two or higher in men and three or higher in women.[9] Rivaroxaban and other DOACs have a prior class 1 recommendation with the level of evidence B in the 2014 ACC/AHA/HRS recommendations for nonvalvular atrial fibrillation with a CHA2DS2-VASc score of 2 or greater in both males and females.[9]

The 2014 ACC/AHA/HRS guidelines for nonvalvular atrial fibrillation had a prior class 1 recommendation for rivaroxaban and other DOACs with the level of evidence B and a CHA2DS2-VASc score of 2 or more in both males and females.[9] The recommended dosage of rivaroxaban in the acute DVT and acute PE studies was 15 mg twice day for three weeks, then 20 mg daily. Warfarin was evaluated versus low molecular weight heparin for an average of 8 days before it was therapeutic with an INR level below 2. In the continued therapy group, a 20 mg daily dose of rivaroxaban was contrasted with a placebo. The trials show that rivaroxaban is a single medicine that is both secure and effective for treating

venous thrombosis and venous thromboembolism.[10,11] this led to the FDA's 2012 approval of rivaroxaban.[12]

Pocket Guidelines to Physicians

If Rivaroxaban is taken concurrently with Enoxaparin, Warfarin, Apixaban, Argatroban, Dabigatran Etexilate, or Fondaparinux, there may be an increased risk of bleeding. The probability of bleeding doubles when dabigatran and aspirin are taken simultaneously. Contrarily, dabigatran exposure is increased when ticagrelor and dabigatran are combined, particularly in individuals with renal impairment. Concurrent use should be avoided in patients with severe renal impairment (CrCl, 15 to 30 mL/min). Compared to dabigatran, which is excreted 80% in the kidneys, rivaroxaban is excreted at a rate of 2/3 in the liver and 1/3 in the kidneys. Continuous monitoring of creatinine clearance is necessary when taking either Rivaroxaban or Dabigatran. Compared to Dabigatran's 6% bioavailability, rivaroxaban's ranges from 60 to 80%.

INR readings of 0.2 to 1.2 were classed as normal, while readings of 1.3 to 1.4 were classified as abnormal. INR levels greater than 1.4 were regarded as high.[13]

Recent studies have found high INR levels as high as over with dabigatran, particularly in older patients with impaired renal function[8]. As a result, each patient's serum creatinine level needs to be checked before dabigatran is prescribed. After that, elderly and those with unstable renal function should have their creatinine levels evaluated at least once a year and on a regular basis, respectively.[14]

CONCLUSION

This study demonstrated that rivoroxaban is equally effective at preventing ischemic strokes and thromboembolism as dabigatran. When compared to dabigatran, rivoroxaban significantly increased major risk bleeding, all-cause mortality, and gastrointestinal bleeding ((GIB)). Due diligence should be put into weighing the benefits and risks of using Rivaroxaban, including the individual's risk of GIB. Dabigatran and rivaroxaban both had increased bleeding risks when used to prevent strokes in adults with atrial fibrillation, according to recent real-world evidence.

REFERENCE

1. Tsai HO. Pharmacological Review of Anticoagulants. Anticoagulation Drugs-the Current State of the Art., 2019 Sep 4.
2. Chen A, Stecker E, A. Warden B. Direct oral anticoagulant use: a practical guide to common clinical challenges. Journal of the American Heart Association, 2020 Jul 7; 9(13): e017559.
3. www.Micromedex.com.
4. Parsi K, van Rij AM, Meissner MH, Davies AH, Maeseneer MD, Gloviczki P, Benson S, Bottini O, Canata VM, Dinnen P, Gasparis A. Triage of patients with venous and lymphatic diseases during the COVID-19 pandemic–The Venous and Lymphatic Triage and Acuity Scale (VELTAS): A consensus document of the International Union of Phlebology (UIP), Australasian College of Phlebology (ACP), American Vein and Lymphatic Society (AVLS), American Venous Forum (AVF), European College of Phlebology (ECoP), European Venous Forum (EVF), Interventional Radiology Society of Australasia (IRSA), Latin American Venous Forum, Pan-American Society of .... Phlebology, 2020 Sep; 35(8): 550-5.
5. Pell JP, McIver B, Stuart P, Malone DN, Alcock J. Comparison of anticoagulant control among patients attending general practice and a hospital anticoagulant clinic. British journal of general practice, 1993 Apr 1; 43(369): 152-4.
6. Lip GY, Larsen TB, Skjøth F, Rasmussen LH. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. Journal of the American College of Cardiology, 2012 Aug 21; 60(8): 738-46.
7. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Journal of the American College of Cardiology, 2019 Jul 9; 74(1): 104-32.
8. Ortel TL, Neumann I, Ageno W, Beyth R, Clark NP, Cuker A, Hutten BA, Jaff MR, Manja V, Schulman S, Thurston C. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood advances, 2020 Oct 13; 4(19): 4693-738.
9. Ogbonna KC, Dixon DL. Critical appraisal of dabigatran in the treatment of deep vein thrombosis and pulmonary embolism. Journal of blood medicine, 2015; 6: 177.

10. Buller, H.R., Lensing, A.W., Prins, M.H., Agnelli, G., Cohen, A., Gallus, A.S., Misselwitz, F., Raskob, G., Schellong, S. and Segers, A., A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the Einstein–DVT Dose-Ranging Study. *Blood, The Journal of the American Society of Hematology*, 2008; *112*(6): 2242-2247.(9)
11. Einstein Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. New England Journal of Medicine, 2010 Dec 23; 363(26): 2499-510.(10)
12. Reis A. Prevention and treatment of venous thromboembolism: the place of new oral anticoagulants. Revista Portuguesa de Cardiologia: Orgao Oficial da Sociedade Portuguesa de Cardiologia= Portuguese Journal of Cardiology: an Official Journal of the Portuguese Society of Cardiology, 2012 Apr 1; 31: 45-50.(11).
13. Rivaroxaban and its Effect on International Normalised Ratio-A Prospective Study of 28 Hip and Knee Arthroplasty Patients 1Cheng Hong Yeo, 2V. Eranki, 3A. Pillai and 2G. Morrison(12)
14. Ciurus T, Sobczak S, Cichocka-Radwan A, Lelonek M. CARDIAC SURGERY New oral anticoagulants–a practical guide. Kardiochirurgia i Torakochirurgia Polska/Polish Journal of Thoracic and Cardiovascular Surgery, 2015; 12(2): 111-8.