Comparing Apixaban vs Rivaroxaban for Atrial Fibrillation Patients: An Effectiveness and Safety Analysis

Ghaida Fahad S Mubki [1*], Mohmad Saad M Al Karani [1], Ahmed Saeed Abdullah [1], Tahani Mahmoud M Riyahi [1], Reem Abdulaziz Abdullah [1], Maha Mubarak Hamas Alotaibi [1], Amal Abdullah Faraj Hassan [2], Ahmed awad ali Zahrani [3], Nada Abdulrahman Hamad Altooq [1], Anfal Khalid Zain Bajamal [1], Nada saleh mohammad aldahaiman [1], Sajeda Qasim Abdulaziz Binjumaiah [1], Afaf Eesa Alsaggar Alenizi [1]

Abstract

Atrial fibrillation (AF) is a common problem with the way the heart beats that makes you more likely to have a stroke or a systemic embolism. People with AF need anticoagulation treatment to make sure they don't have a stroke. Direct oral anticoagulants (DOACs) are now the most popular choice since they are safe, effective, and simple to use. People with AF are often given apixaban and rivaroxaban as DOACs, but there is ongoing discussion about how well and safely they work compared to each other. These studies include randomized controlled trials, observational studies, and meta-analyses. The goal of the review is to give a full picture of how well and safely apixaban and rivaroxaban work for people with AF. We check how well it works by looking at things like the number of deaths, strokes, and major bleeds. We also look at events that are important for safety, such as blood in the brain or intestines. We also talk about the treatments that can be chosen, like the type of patient, dose plans, and cost. Aside from being safer than other blood thinners, apixaban and rivaroxaban both work well to stop strokes. In real life, though, small differences in the risk of bleeding and other side effects could change the medicine that is chosen. Before doctors can pick the best anticoagulation treatment for AF patients that will improve their health and quality of life, they need to know a lot about how apixaban and rivaroxaban compare in terms of how well they work and how safe they are.

Keywords: Apixaban, Rivaroxaban, Atrial fibrillation (AF), Direct oral anticoagulants.

Significance | Apixaban, Rivaroxaban, Atrial fibrillation (AF), Direct oral anticoagulants.

*Correspondence. Ghaida Mubki, Ministry of Health of Saudi Arabia, Riyadh, Saudia Arabia.
E-mail: Ghaidaz99@hotmail.com

Editor Md Shamsuddin Sultan Khan, And accepted by the Editorial Board Apr 02, 2024 (received for review Feb 28, 2024)

Introduction

Around 1% of adults in North America experience atrial fibrillation (AF) (Miao et al., 2020) . Up to 20% of people with AF may get ischemic stroke, which can result in significant disability (Chen et al., 2021; Yang et al., 2020) morbidity, and mortality. Oral anticoagulants reduce the likelihood of stroke and other systemic emboli by as much as 70% and are advised for the majority of patients with AF (Hill et al., 2020). Direct oral anticoagulants (DOACs) are being increasingly favored over warfarin due to their enhanced effectiveness (Fu et al., 2024; Rutherford et al., 2020), safety, and user-friendly nature. Apixaban and rivaroxaban are the predominant choices for treating AF among the four approved DOACs(Yang et al., 2020). This review aims to compare Apixaban

Author Affiliation.
[1] Ministry of Health of Saudi Arabia, Riyadh, Saudia Arabia.
[2] Diploma in Pharmacy, Apartment 2, Building 4.07, King Abdullah Financial District, Riyadh, Al-Sibai Institute in Riyadh.
[3] Diploma in Pharmacy, Apt 201, Bulding 3, Next to Al Rajhi Transfers, Al Faisaliah, Taif, Saudi Arabia, Taif university.

Please cite this article.
Ghaida Fahad S Mubki 1*, Mohmad Saad M Al Karani et al. (2024). Comparing Apixaban vs Rivaroxaban for Atrial Fibrillation Patients: An Effectiveness and Safety Analysis, Journal of Angiotherapy, 8(4), 1-13, 9633

and Rivaroxaban for AF Patients. The ARISTOTLE (Apixaban Versus Warfarin in Patients With AF) trial found that patients who were randomly assigned to apixaban had reduced occurrences of stroke (Bonde et al., 2020), hemorrhage, and all-cause death (Aslan & Yildirim, 2022). The ROCKET-AF trial shown that rivaroxaban was equally effective as warfarin in preventing strokes in patients with nonvalvular AF. Additionally, rivaroxaban was found to have a decreased incidence of intracranial and fatal hemorrhage compared to warfarin (Lin et al., 2020). Randomized trials directly comparing apixaban with rivaroxaban have not yet been concluded, however they are currently in progress (Perreault et al., 2021).

Apixaban may have a lower risk of stroke and embolic events (Perreault et al., 2021) (hazard ratio [HR], 0.77 [95% CI, 0.56 to 1.06]) and a reduced risk of major bleeding (HR, 0.68 [CI, 0.52 to 0.90]) compared to rivaroxaban (O'Kane et al., 2022). The reduced peak anti-factor Xa levels observed in patients treated with apixaban could potentially contribute to the decreased incidence of major bleeding (Perreault et al., 2022). Conversely, the elevated trough levels of apixaban may be responsible for the lower occurrence of stroke and systemic embolism (Grymonprez et al., 2023). These suggested mechanisms are reinforced by a recent examination of individuals with nonvalvular AF, which demonstrated a decrease in the highest level of prothrombin time (a measurement linked to anticoagulant activity)(Stanifer et al., 2020) and an increase in the lowest level of prothrombin time when comparing apixaban to rivaroxaban (Jaksa et al., 2022). Apixaban is perhaps a safer and more efficacious option compared to rivaroxaban for the treatment of nonvalvular AF (Abdullah et al., 2021).

AF is a significant worldwide public health issue due to its rising prevalence (Agnelli et al., 2020) and its correlation with heightened risks of stroke, dementia, heart failure, and mortality (Healey et al., 2024). Vitamin K antagonists (VKAs) have traditionally been the primary treatment for preventing strokes in patients with (AF) (Stanifer et al., 2020). However, their effectiveness is hindered by several problems, including potential interactions with other drugs, a narrow range of safe and effective dosages (Ray et al., 2021), and the requirement for lifelong monitoring of anticoagulation levels due to significant variations between patients and even within individual patients (Pokorney et al., 2022).

A significant constraint of Warfarin is the restricted duration inside the therapeutic range (TTR) that can be measured by INR (McBane II et al., 2020). Randomized control trials have determined that the International Normalized Ratio (INR) fell within the desired range of around 36-68% (Koehl et al., 2020). Aspirin and clopidogrel have been utilized as alternative options to warfarin for the purpose of preventing strokes (Zeitouni et al., 2020). A meta-analysis of six trials has demonstrated that aspirin decreased the likelihood of stroke by 22%. Currently in progress A clinical research investigating the combined use of aspirin and clopidogrel demonstrated a 28% reduction in the risk of stroke (Zeitouni et al., 2020). However, this treatment also resulted in an elevated risk of significant bleeding both within and outside the brain (Stanifer et al., 2020).

I. Apixaban: General aspects and mechanism of action

Apixaban is a drug that can suppress factor Xa **(Fernandez et al., 2020)**, which is a key component in blood clotting. It does this by directly and specifically targeting factor Xa and can be reversed if needed (Wang et al., 2023). Pre-clinical investigations have thoroughly examined its efficacy in preventing arterial and venous thrombosis (Dawwas et al., 2022). Apixaban is highly effective in preventing both arterial and venous thrombosis when administered at levels that maintain hemostasis (Mavrakanas et al., 2020). It is a powerful inhibitor of both free and cell-bound factor Xa and activated prothrombinase. Apixaban rapidly inhibits factor Xa (Mamas et al., 2022), although it does not directly affect platelet aggregation (Mamas et al., 2022). However, it indirectly inhibits this process by lowering thrombin synthesis (Rutherford et al., 2020).

Factor Xa is a desirable target for anticoagulation (Woller et al., 2022) as it plays a crucial role in the coagulation cascade and regulates the production of thrombin (Figure 1) (Piccini et al., 2022). Activation of a single molecule of factor Xa results in the production of 1000 molecules of FIIa (Chiv et al., 2024). Factor Xa inhibition reduces the generation of thrombin, but does not impact its activity (Piccini et al., 2022), therefore maintaining hemostasis and perhaps decreasing the risk of bleeding in clinical settings (Lau et al., 2022). Factor Xa inhibitors may be more effective and safer than thrombin due to the limited roles of factor Xa outside the coagulation cascade (Hanni et al., 2020).

II. Pharmacokinetics

Apixaban exhibits high bioavailability (Wetmore et al., 2022), with pre-clinical research indicating that it achieves its maximum plasma concentration around 3 hours after being administered (Whitehouse et al., 2022). Its estimated bioavailability is roughly 43-46% (Whitehouse et al., 2022). Apixaban's absorption remains unaffected by the presence of meals (Labovitz et al., 2021). The metabolism of apixaban has been shown to involve O-demethylation, hydroxylation, and sulfation of hydroxylated O-dimethyl apixaban (Labovitz et al., 2021). The estimated terminal half-life of apixaban is 8-13 hours. Apixaban does not significantly inhibit or induce cytochrome P450 enzymes (Geisler et al., 2023), which reduces the likelihood of drug-drug interactions (Jakowenko et al., 2020). The results of experiments using human cDNA-expressed P450 enzymes and P450 enzyme inhibitors showed that the main enzyme responsible for the oxidative metabolism of apixaban is CYP3A4/5, with a smaller contribution from CYP1A2 and CYP2J2 (Jakowenko et al., 2020).

Based on these findings, it is expected that CYP3A4 and CYP3A5 play a significant role in the metabolism of apixaban (Bonde et al.,

2020). Apixaban undergoes metabolism mostly in the liver and intestines (Cohen et al., 2021), as evidenced by its metabolism in human intestinal microsomes but not in kidney microsomes (Cohen et al., 2021). Pre-clinical research have shown that apixaban has several mechanisms by which it is eliminated (Cohen et al., 2021). Apixaban is mostly eliminated through the kidneys, with approximately 25% of the drug being excreted in the urine (Agnelli et al., 2022). Additionally, a significant portion (55%) of the drug is eliminated through the feces (Mahe et al., 2022), and biliary excretion also plays a role in the drug's elimination (Mokadem et al., 2021). Apixaban may be a more effective treatment choice for those with liver or kidney problems due to its ability to be eliminated through several pathways (Mokadem et al., 2021).

Dabigatran, which received FDA approval for the prevention of stroke in individuals with AF Rivaroxaban Chen et al. (2021)), which has been recently approved by the FDA as an alternative anticoagulant for patients with AF (McBane II et al., 2024), is excreted through the kidneys to the extent of 80%. It has a dual mode of elimination (McBane II et al., 2024), with one-third of the active drug being excreted unchanged through the kidneys Attelind et al. (2022), while the remaining two-thirds are eliminated by the liver (Xu et al., 2023). Apixaban is a comparatively safer choice for individuals with renal insufficiency when compared to the other two newer anticoagulants (Healey et al., 2024). This is due to its ability to be eliminated by numerous pathways (de Vries et al., 2020). Contrary to dabigatran, the absorption of this medication is not influenced by the presence of meals (Jansson et al., 2020).

III. Apixaban for prevention in AF

The AVERROES trial, released in February 2011, was the initial significant clinical study that examined the effectiveness of apixaban in comparison to aspirin for preventing strokes in individuals with AF (Rutherford et al., 2020). The study was a randomized, multicenter, double-blind clinical trial involving 5599 patients with AF who had a higher risk of stroke and were not good candidates for VKA therapy (Mamas et al., 2022). The majority of participants in the apixaban group were administered a dosage of 5 mg twice daily (Mavri et al., 2021). Approximately 6% of the patients in the apixaban group had their dosage decreased to 2.5 mg twice daily (Fralick et al., 2020).

Additionally, the study also assessed secondary outcomes such as overall mortality and hospitalization resulting from cardiovascular causes (Stanifer et al., 2020). The main safety measure examined in the study was major bleeding, which was defined as clinically evident bleeding accompanied by one or more of the following criteria: a decrease in hemoglobin level of 2 g per deciliter or more within 24 hours de Vries et al. (2020), bleeding necessitating transfusion of 2 or more units of packed red blood cells, any bleeding at critical sites (such as intracranial, intraspinal, intraocular(Bonde et al., 2020), intraarticular, intraocular, pericardial, intramuscular with compartment syndrome, or retroperitoneal), or fatal bleeding (Labovitz et al., 2021)).

IV. Future of Apixaban

Based on the positive results of the AVERROES and ARISTOTLE trials, apixaban shows potential as a new and effective anticoagulant for preventing stroke in patients with AF (Mokadem et al., 2021). Across the different major categories of patients (Ansell et al., 2022), there was a consistent and sustained drop in primary efficacy outcomes. Apixaban demonstrates a favorable side-effect profile (Chen et al., 2021), as seen by a decreased rate of discontinuation compared to warfarin. Apixaban demonstrates superior efficacy compared to warfarin in preventing strokes (McBane II et al., 2024), while also significantly reducing the risk of bleeding. Presently, there exist two substitute oral anticoagulants to warfarin (Miao et al., 2020), namely the direct thrombin inhibitor dabigatran and the factor Xa inhibitor rivaroxaban (Attelind et al., 2022). The FDA advisory group recently endorsed Rivaroxaban as a prospective treatment for stroke prevention in people with AF ((Xu et al., 2023). Each of these medicines, such as apixaban, has the significant benefit of convenience as they do not necessitate anticoagulation monitoring (Healey et al., 2024).

The Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY) assessed the efficacy of dabigatran (de Vries et al., 2020). The trial found that the 150 mg twice daily dose of dabigatran reduced the occurrence of stroke and systemic embolism, while maintaining a comparable rate of bleeding (Jansson et al., 2020). However, it is important to note that dabigatran was associated with a higher incidence of gastrointestinal bleeding Rutherford et al. (2020). Dabigatran was also observed to have a greater incidence of dyspepsia (11.8% of patients in the 110 mg dose group (Mamas et al., 2022), 11.3% of patients in the 150 mg dose group) compared to warfarin (5.8% of patients) (Mavri et al., 2021).

This could be due to the composition of dabigatran, which has a tartaric acid component that enhances absorption in the intestines (Fralick et al., 2020). The best bioavailability of dabigatran demands a low pH (Ray et al., 2021), which may also contribute to a higher occurrence of gastrointestinal bleeding. Apixaban demonstrated a reduced incidence of gastrointestinal bleeding compared to warfarin (Ray et al., 2021), and this lower bleeding rate was consistently observed across different age groups. Apixaban is excreted by the kidneys at a rate of around 25% (McBane II et al., 2020), while dabigatran is excreted at a rate of 80% (Koehl et al., 2020). This indicates that apixaban may be a comparatively safer anticoagulant for people with kidney problems (Zeitouni et al., 2020).

V. Real-World Use of Apixaban for Stroke Prevention in Atrial Fibrillation

The introduction of nonvitamin K antagonist oral anticoagulants (NOACs) has significantly changed the use of oral anticoagulant (OAC) therapy for stroke prevention in AF(de Vries et al., 2020). These NOACs offer comparable effectiveness, safety, and convenience compared to vitamin K antagonists like warfarin (de Vries et al., 2020). There are currently four NOACs (novel oral anticoagulants) approved for clinical usage (Fernandez et al., 2020). These include dabigatran, a direct thrombin inhibitor, as well as rivaroxaban, apixaban, and edoxaban, which are oral factor Xa inhibitors (Wang et al., 2023). The prevalence of postmarketing observational real-world studies (RWS) has closely mirrored the chronological order in which these medications were introduced to the market. Relative to clinical trials (Dawwas et al., 2022), real-world studies (RWS) use smaller, less carefully chosen groups of participants (Mavrakanas et al., 2020), which aids in comprehending the impact of NOACs in particular clinical scenarios or condition (Bonde et al., 2020).

However, a significant number of patients who are suitable candidates for the use of NOACs are prescribed a lower dosage, which is not in accordance with the recommended dosage stated on the prescription for this reduced dosage treatment (Cohen et al., 2021). According to the analysis conducted in the ORBIT-AF II, 9.4% of patients received insufficient doses of NOACs (novel oral anticoagulants), with up to 11.8% of apixaban users being prescribed reduced doses (W. Ageno et al., 2021). The use of reduced doses was found to be linked to a higher occurrence of major adverse outcomes(Walter Ageno et al., 2021). A larger percentage of patients receive treatment with the reduced dose, and findings indicate that treating patients with apixaban at a reduced dose is linked to poorer outcomes (Agnelli et al., 2022).

The surprise discovery was that a lower dosage of apixaban proved to be more effective than dabigatran (Mahe et al., 2022). There is a scarcity of evidence about direct or indirect comparisons of different lower dose NOACs (Mokadem et al., 2021), hence these findings must be evaluated with caution. It is important to take into account the fact that published research are based on real-world observations (Ansell et al., 2022), which means that there may still be some remaining factors that could influence the results (Chen et al., 2021). In addition, patients who are prescribed a low or reduced dose in RWS may be older and frailer due to the presence of various comorbidities (McBane II et al., 2024).

VI. Effectiveness and Safety of Apixaban in over 3.9 Million People with Atrial Fibrillation

Anticoagulation is the primary focus for preventing stroke in individuals with AF and is a key aspect of the recommended care of AF according to guidelines (Miao et al., 2020). The effectiveness of direct-acting oral anticoagulants (DOACs) compared to warfarin has been the subject of significant interest during the past decade (Attelind et al., 2022). DOACs have generally, but not always, shown favorable results in terms of stroke and death Xu et al. (2023). Currently, direct oral anticoagulants (DOACs) are preferred over warfarin for preventing strokes in patients with AF because they have a better safety record in terms of cerebral hemorrhage (all DOACs) and severe bleeding (certain DOACs) Healey et al. (2024). Nevertheless, reaching a consensus on the most advantageous Direct Oral Anticoagulant (DOAC) in terms of both effectiveness and safety is difficult, mostly due to the absence of trials directly comparing these medications Healey et al. (2024)

There is a large amount of real-world data available on the safety, and to a lesser extent, the effectiveness of DOACs Piccini et al. (2022). However, the differences in the groups of people studied, the criteria used to include or exclude participants, and the statistical methods employed have led to conflicting results and various unresolved concerns (Mentias et al., 2020).

Moreover, our comprehension of the possible influence of geographical region, study design, and age on these outcomes is insufficient (Al Sulaiman et al., 2022). By addressing these deficiencies in the existing body of data, healthcare providers and patients will be able to make more informed decisions based on solid evidence when choosing a direct oral anticoagulant (DOAC) for stroke prevention in individuals with AF (O'Kane et al., 2022)

The objective of this systematic review and meta-analysis was to evaluate the efficacy and safety of apixaban ((Gulilat et al., 2020), the most frequently prescribed direct oral anticoagulant (DOAC), with other DOACs and vitamin K antagonists (VKA) such as warfarin (Xu et al., 2023). Initially, our objective was to ascertain whether apixaban had superior efficacy (in terms of reducing stroke and mortality) and safety (in terms of reducing severe bleeding) compared to dabigatran (Suzuki et al., 2020).rivaroxaban (Lau et al., 2020), edoxaban, and VKAs for patients diagnosed with AF (Grymonprez et al., 2023).

VII. Role of rivaroxaban in the management of atrial fibrillation

AF continues to be the most common long-lasting abnormal heart rhythm that causes substantial illness and death (Guimarães et al., 2020). Estimates indicate that its prevalence is on the rise (Bonaca et al., 2020). AF is a persistent condition that leads to the stagnation of blood in the left atrium (Connolly et al., 2022).

This condition is closely linked to a higher likelihood of developing blood clots in the left atrium (De Vriese et al., 2021), which can then travel to the brain and cause a stroke or blockage in the systemic arteries (Ramacciotti et al., 2022). The primary objectives of treating AF are to prevent thromboembolic consequences (Ramacciotti et al., 2022), such as stroke or systemic embolism (SE), and to relieve symptoms. Current guidelines advise that the management of

patients with AF should consider their specific requirements and preferences, with clinicians providing patients with a customized care plan (Ray et al., 2021). This is a method of stroke prevention that is focused on evaluating and managing risks, as well as a thorough examination of the available solutions for preventing blood clots (Ashton, Kerolus-Georgi, et al., 2021).

Non-vitamin K oral anticoagulants (NOACs), such as rivaroxaban, apixaban, edoxaban, and dabigatran, are drugs that inhibit factor Xa or directly inhibit thrombin (Male et al., 2020). These drugs have predictable effects on the body and do not require monitoring (Ashton, Mudarris, et al., 2021). As a result, they are a highly appealing alternative to vitamin K antagonists (VKA). Since being introduced in the UK in 2008 (Planquette et al., 2022), primarily for preventing blood clots in deep veins, prescriptions for NOACs have considerably risen (Planquette et al., 2022). As a result, NOACs now make up the bulk of prescriptions for oral anticoagulants (Esmaeili et al., 2021). In 2015, Non-Vitamin K Oral Anticoagulants (NOACs) comprised 56.5% of all prescriptions for Oral Anticoagulant (OAC) medications (Esmaeili et al., 2021). Among the NOACs, rivaroxaban was the most commonly given, followed by apixaban and dabigatran (Spyropoulos et al., 2020).

VIII. Mode of action of rivaroxaban

Rivaroxaban is an oral anticoagulant that directly inhibits factor Xa (Spyropoulos et al., 2020). Factor Xa is generated through both the intrinsic and extrinsic coagulation pathways and serves as the step that limits the rate of thrombin production (Figure 2) (Bainey et al., 2020). Factor Xa is potentially a superior target compared to thrombin due to its limited involvement in processes other than coagulation (Ageno, Beyer Westendorf, et al., 2022). Consequently, inhibiting factor Xa may result in a reduced occurrence of adverse effects (Speed et al., 2020). Rivaroxaban functions as an anticoagulant by specifically, directly, and reversibly obstructing free and clot-associated factor Xa in human plasma, without attaching to antithrombin (Fernandez et al., 2021). This leads to the suppression of the transformation of factor II (prothrombin) into factor IIa (thrombin) (Young et al., 2020). Rivaroxaban exhibits a selectivity that is 100,000 times greater for factor Xa compared to other biological proteases (Rutherford et al., 2020) including thrombin plasmin, factor VIIa, factor IXa, and activated protein C (Ageno, Bertù, et al., 2022). It does not directly affect platelet aggregation (Samama et al., 2020). Rivaroxaban is very tolerable, exhibiting a consistent pharmacokinetic profile, and does not require laboratory monitoring (Samama et al., 2020).

IX. Pharmacodynamics

Rivaroxaban demonstrates excellent tolerability in healthy human individuals, exhibiting a prompt initiation of its effects and a direct relationship between dosage and its pharmacodynamics and pharmacokinetics (Tittl et al., 2021). Studies published over ten years ago indicate that rivaroxaban at doses ranging from 5 to 80 mg inhibits factor Xa by 20% to 61% (Bonde et al., 2020)

The highest level of inhibition was observed between 1 and 4 hours after injection, and these effects persisted for a duration of 5 to 12 hours (De Vriese et al., 2021). Both prothrombin time (PT) and activated partial thromboplastin time (aPTT) were shown to be extended in a manner that depended on the dosage (De Vriese et al., 2021). The PT was extended by a factor of 1.3–2.6 compared to the initial value, while the aPTT was extended by approximately 1.5 times compared to the initial value (Jansson et al., 2020) . The aforementioned values were attained within a time frame of 1 to 4 hours subsequent to the administration of rivaroxaban (Jansson et al., 2020).

X. Pharmacokinetics

Rivaroxaban is promptly and nearly completely absorbed upon oral treatment (Ray et al., 2021). The 10 mg tablet dose achieves peak plasma concentrations (Cmax) and has a bioavailability of 80%–100% (Chen et al., 2021). Food intake at this dose did not have an impact on the area under the curve (AUC) (Rutherford et al., 2020). However, the rate at which a 20 mg pill is absorbed and becomes available for use by the body seems to decrease when taken without food (Rutherford et al., 2020). Nevertheless, while the body is in a fed state, the concentration of rivaroxaban tends to increase (Hill et al., 2020). The pharmacokinetics of rivaroxaban do not seem to be influenced by the specific type of food ingested. Roughly 90% of rivaroxaban is bound to proteins, and its volume of distribution is approximately 1.36 liters per kilogram (Lin et al., 2020)

Rivaroxaban undergoes hepatic metabolism mostly by cytochrome P450 isoenzyme 3A4, without significant formation of active circulating metabolites (Alberts et al., 2020). The excretion of this substance occurs through two modes: renal elimination and a minor quantity through the fecal and biliary channels (Hanon et al., 2021). Around 14% to 31% of the medication is eliminated in the urine without undergoing any changes (Escobar-Cervantes et al., 2023). The elimination half-life of Rivaroxaban, administered at dosages ranging from 5 mg daily to 30 mg twice daily, is 5-9 hours (Rivera-Caravaca et al., 2023). Rivaroxaban, when given to patients who are over 75 years old, have renal insufficiency (creatinine clearance below 50 mL/minute), low body weight (less than 50 kg) (Rivera-Caravaca et al., 2023). or moderate hepatic disease (Child-Pugh class B), has been found to result in decreased renal clearance (Matoba et al., 2021). Higher concentration (AUC), and increased factor Xa inhibition (Lau et al., 2022) This suggests that dosage adjustments may be required for these patients (Hernandez et al., 2020).

This molecule exhibits selective, reversible, and direct binding to the active site of factor Xa (Costa et al., 2020), thereby inhibiting its interaction with substrates. This molecule is the sole representative

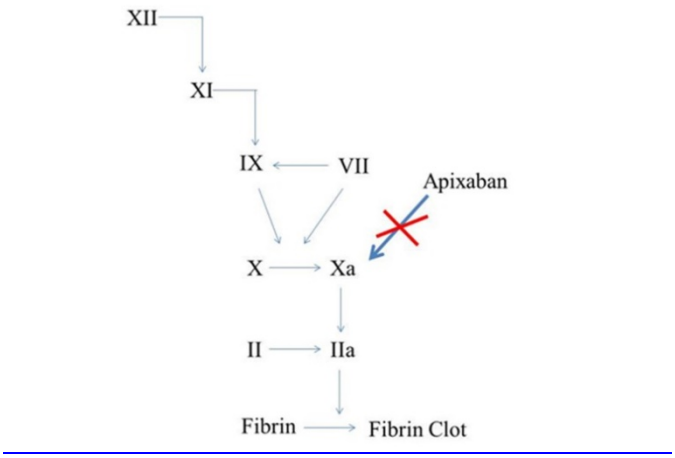

Figure 1. Mechanism of action of Apixaban in the coagulation cascade.

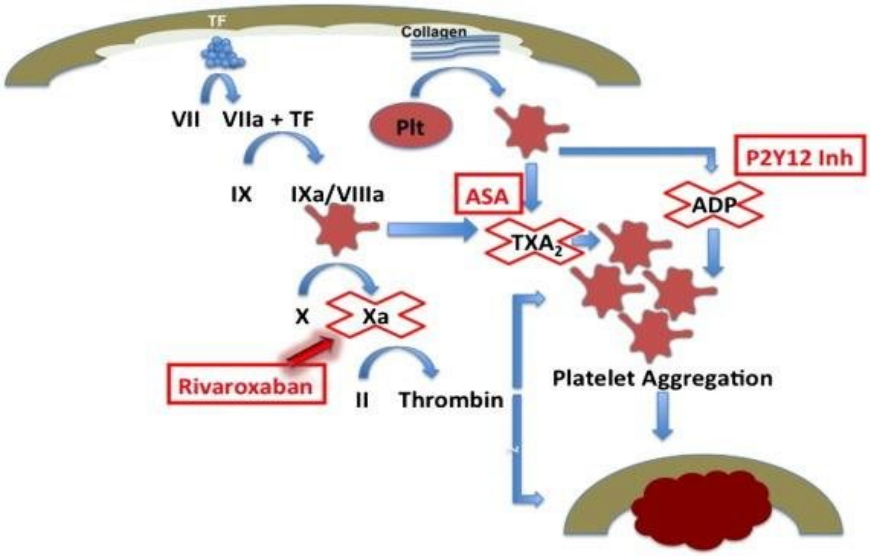

Figure 2. Mode of action of rivaroxaban

of a novel category of compounds called oxazolidinediones (Mentias et al., 2020), which have exceptionally high bioavailability. Rivaroxaban is a compound that is processed by the P-glycoprotein system and is moved across cell membranes (Weir et al., 2020). Rivaroxaban is not known to induce or inhibit any CYP system, but it is metabolized by CYP3A4 and CYP2J2 (Miao et al., 2020). Therefore, when potent inhibitors of these systems and of P-glycoprotein (such as ketoconazole, itraconazole, or ritonavir) are used together with rivaroxaban, it leads to a 2.5-fold increase in the bioavailability of rivaroxaban (Guimaraes et al., 2021). When rifampicin, a potent inducer of these enzymatic systems, was introduced (Guimarães et al., 2020), the bioavailability decreased by 50%. Food consumption leads to a delay in the time it takes for the drug to reach its highest concentration in the blood (by approximately 4 hours) and an increase in the highest concentration reached (by around 30%) (Tittl et al., 2021). Due to the fact that renal excretion is the primary method of eliminating rivaroxaban from the body, it is advisable to exercise caution when the creatinine clearance is less than 50 mL per minute (Bonde et al., 2020). It is recommended to administer a dose of 15 mg twice day during the initial weeks of treatment (De Vriese et al., 2021), followed by a daily dose of 15 mg afterward (Hua et al., 2021).

Another factor influencing the removal of rivaroxaban from the body through the kidneys is the decrease in kidney function that occurs with advancing age (Hua et al., 2021). Although aged patients have been found to have a two-fold increase in terminal elimination half-life (Fralick et al., 2020), there is no suggested need to alter the dosage based on age (Ray et al., 2021). The available research indicates that there is a clear and direct relationship between the way the body processes rivaroxaban and its effectiveness as an anticoagulant (Ray et al., 2021). Therefore, there is no specific guideline recommending regular monitoring of rivaroxaban medication (Rutherford et al., 2020).

XI. Rivaroxaban as an oral anticoagulant for stroke prevention in atrial fibrillation

AF is the prevailing heart arrhythmia and a significant risk factor for stroke and systemic embolism (Rutherford et al., 2020). The incidence of AF in the general population of developed countries ranges from 1.5% to 2.0% (Hill et al., 2020). In the United States alone, over 2 million individuals are impacted by this disorder (Lin et al., 2020). Individuals who are 40 years or older have a 25% chance of acquiring AF (Alberts et al., 2020). The typical age of patients with AF is between 75 and 85 years (Hanon et al., 2021) , and the occurrence of AF is around 10% in individuals aged 85 years and beyond. Patients with AF have a risk of stroke that is five times higher than that of the general population (Escobar-Cervantes et al., 2023). Furthermore, AF is linked to a threefold rise in the occurrence of congestive heart failure, a risk that is particularly elevated in individuals aged 80 years and above (Rivera-Caravaca et al., 2023).

Individuals with AF have a worse outlook when it comes to stroke, with a higher rate of medical and neurological problems and a greater risk of death throughout their hospital stay compared to individuals without AF(Konicki et al., 2020). Following an AF-related stroke, over 50% of patients experience mortality within a year (Matoba et al., 2021). Additionally, among patients with AF who were hospitalized due to their first ischemic stroke, 60% of strokes resulted in disability and 20% were fatal (Lau et al., 2022). Due to the significant rise in the likelihood of stroke in patients with AF (Spyropoulos et al., 2020), anticoagulants that focus on various elements in the coagulation cascade, such as the vitamin K antagonist (VKA) warfarin, have become the primary treatment for preventing stroke in people with nonvalvular AF (Ercisli et al., 2021). Nevertheless, warfarin is linked to numerous constraints, such as the requirement for frequent coagulation monitoring (Ercisli et al., 2021). The impact of warfarin is modified by a multitude of interactions with food and drugs, as well as genetic variations, which can lead to an unpredictable reaction (Ageno, Beyer Westendorf, et al., 2022).

As a result, target-specific oral anticoagulants have been developed, such as rivaroxaban (Speed et al., 2020), apixaban, edoxaban, and dabigatran etexilate (Fernandez et al., 2021), which specifically inhibit Factor Xa or thrombin (Young et al., 2020).

Rivaroxaban directly hinders the activity of Factor Xa, which is present in both free form and linked to blood clots (Rutherford et al., 2020). This action effectively stops the creation of new blood clots and prevents existing blood clots from growing larger (Ageno, Bertù, et al., 2022). Rivaroxaban is quickly absorbed from the gastrointestinal system and achieves maximum levels in the bloodstream within 2-4 hours (Samama et al., 2020). The maximum suppression of Factor Xa activity, extension of prothrombin time (PT; using a sensitive thromboplastin reagent) (Bonaca et al., 2020), and elongation of activated partial thromboplastin time (which is less predictable) all take place around 2-3 hours after administration (Connolly et al., 2022). However, the measurements can differ depending on the reagents employed (De Vriese et al., 2021). Rivaroxaban exhibits a half-life of 5–9 hours in individuals who are in good health (Ramacciotti et al., 2022), but in older patients, the half-life extends to 11–13 hours (Ray et al., 2021).

In addition, rivaroxaban has consistent pharmacokinetics and pharmacodynamics, and it has little interactions with both food and drugs (Ashton, Kerolus-Georgi, et al., 2021). Rivaroxaban is eliminated from the body by two different processes. One-third of the drug is excreted in the urine without any changes, (Male et al., 2020), while two-thirds undergo metabolic breakdown in the liver

(Ashton, Mudarris, et al., 2021). Half of the breakdown products are eliminated through the kidneys(Petzold et al., 2020), while the other half are eliminated through the hepatobiliary route (Planquette et al., 2022). Rivaroxaban has a high oral bioavailability of 80% to 100% at dosages of 2.5 mg and 10.0 mg (Connor et al., 2020), regardless of whether it is taken on an empty stomach or with food. This high bioavailability remains consistent even at a dose of 15.0 mg (Esmaeili et al., 2021). The bioavailability and absorption of rivaroxaban decrease as the dosage increases (Spyropoulos et al., 2020); however, this decline is less significant when the dose is consumed alongside meal(Spyropoulos et al., 2020).

AF continues to be a substantial healthcare burden (Ercisli et al., 2021), and it is projected to rise as the aging population of wealthy countries grows (Bainey et al., 2020). There is a demand for an oral anticoagulant that is both efficient and convenient, and does not necessitate regular monitoring of blood clotting, dosage modifications, (Ageno, Beyer Westendorf, et al., 2022) or dietary limitations. Rivaroxaban provides a therapy alternative and is approved in the United States and the European Union for preventing stroke and systemic embolism in people with nonvalvular AF (Speed et al., 2020). Rivaroxaban, at a dosage of 20 mg once daily (or 15 mg once daily for individuals with a creatinine clearance of 30-49 mL/minute)(Speed et al., 2020), demonstrated noninferiority to warfarin in preventing stroke and systemic embolism in patients with nonvalvular AF and a moderate-to-high risk of stroke(Escobar-Cervantes et al., 2023). The incidence of severe bleeding, both major and nonmajor, was comparable between the two therapy groups (Escobar-Cervantes et al., 2023). However, the rivaroxaban group saw considerably fewer cases of intracranial hemorrhage (ICH) and fatal bleeding episodes compared to the warfarin group (Konicki et al., 2020). Analyses conducted on specific patient subgroups (Matoba et al., 2021), such as those with moderate renal impairment, elderly patients aged 75 years or older (Lau et al., 2022), patients with a history of myocardial infarction, and patients with a history of stroke or transient ischemic attack (TIA) (Hernandez et al., 2020), have confirmed the overall findings of the ROCKET AF study (Costa et al., 2020). These analyses have shown that rivaroxaban is a suitable alternative to warfarin for reducing the risk of stroke and systemic embolism in a diverse range of patients with AF Although there is clear guidance on the use of rivaroxaban for preventing strokes in patients with nonvalvular AF (Weir et al., 2020). There are still outstanding questions regarding the best timing to start the treatment after a stroke (Miao et al., 2020).

The GARFIELD (Global Anticoagulant Registry in the FIELD)(Guimaraes et al., 2021) registry is a comprehensive multinational database that gathers information on the real-life care and outcomes of patients who have recently been diagnosed with nonvalvular AF (Guimarães et al., 2020). This registry has the potential to offer useful knowledge regarding the most effective approaches and treatment choices for certain subgroups of patients (Tittl et al., 2021).

XII. Association of Rivaroxaban vs Apixaban With Major Ischemic or Hemorrhagic Events in Patients with AF

Approximately 3 million to 6 million individuals in the United States are affected with AF (Bonde et al., 2020), and it is anticipated that these figures will increase to 6 million to 16 million by the year 2050 (De Vriese et al., 2021). AF significantly amplifies the likelihood of stroke by a factor of 5 and is estimated to be responsible for 15% of all strokes (Hua et al., 2021). Consequently, the administration of anticoagulant medication to prevent ischemic strokes is an essential aspect of managing this long-term condition (Jansson et al., 2020). Direct oral anticoagulants are the recommended anticoagulants for individuals with AF (Fralick et al., 2020) due to their more predictable pharmacokinetics, greater simplicity of use, and equally good or superior clinical outcomes compared to vitamin K antagonists (Ray et al., 2021). Out of the four medicines in this category that have been approved for treatment in AF in the United States (Chen et al., 2021), rivaroxaban and apixaban are currently responsible for the majority of direct oral anticoagulant prescriptions. These two pharmaceuticals are given more often than warfarin(Rutherford et al., 2020) .

The efficacy and safety of direct oral anticoagulants are intricately linked to plasma concentrations. Insufficient plasma concentrations fail to effectively prevent ischemic strokes or systemic embolisms (Rutherford et al., 2020), while excessively high concentrations elevate the risk of serious bleeding. Apixaban and rivaroxaban are reversible inhibitors of activated factor X (Xa) with similar elimination half-lives (Hill et al., 2020). However, apixaban requires twice-day dosing, while rivaroxaban only needs to be taken once daily (Lin et al., 2020). Therefore, there is a significant increase in the difference between the highest and lowest levels of rivaroxaban concentrations (Alberts et al., 2020). This raises concerns about the effectiveness and safety of this medication (Hanon et al., 2021). The contrasting clinical outcomes of rivaroxaban and apixaban could have significant health implications for the large population of patients who rely on these medications for long-term stroke prevention (Escobar-Cervantes et al., 2023).

Conclusion

This review looks at apixaban and rivaroxaban for people with AF and finds that both are good at lowering the risk of stroke, systemic embolism, and big bleeding events. However, apixaban is seen as a better choice because it works better at stopping big bleeding events, especially intracranial hemorrhage. It also has a more stable anticoagulant effect and less fluctuation in plasma levels, which makes it less likely that someone will take too little or too much.

However, treatment choices should be based on the patient's unique needs and preferences. This includes renal function, cost, and patient adherence. There needs to be more real-world data and long-term follow-up studies to confirm the results of the comparative effectiveness and safety studies. In conclusion, apixaban may have a better safety record with fewer problems with bleeding. Doctors should carefully compare the pros and cons of each drug.

Author contributions

G.F.S.M. contributed to the conceptualization of the review and provided expertise in pharmacy practice. M.S.MA.K. and S.Q.A.B. participated in literature review, data synthesis, and manuscript drafting. A.S.A.A. provided critical insights into pharmacological aspects. T.M.M.R. assisted in data collection, organization, and formatting. R.A.A.A. and M.M.H.A. contributed to manuscript editing, revision, and ensuring clarity. A.A.F.H. and A.E.A.A. provided expertise in pharmacy practice and contributed to the discussion. A.A.A.Z. assisted in literature search, data collection, and organization. N.A.H.A. contributed to the critical review and provided feedback. A.K.Z.B. and N.S.M.A. contributed to the literature review and manuscript drafting. All authors read and approved the final version of the review.

Acknowledgment

The authors thanked the Department.

Competing financial interests

The authors have no conflict of interest.

References

Abdullah, H. M., Ullah, W., Jafar, M. S., van Zyl, M., Saeed, R., Alam, M., Alraies, M. C., & Fischman, D. L. (2021). Safety and efficacy of apixaban, rivaroxaban, and warfarin in end-stage renal disease with atrial fibrillation: a systematic review and meta-analysis. Cardiovascular Revascularization Medicine, 30, 26-32.

Ageno, W., Bertù, L., Bucherini, E., Camporese, G., Dentali, F., Iotti, M., Lessiani, G., Parisi, R., Prandoni, P., & Sartori, M. (2022). Rivaroxaban treatment for six weeks versus three months in patients with symptomatic isolated distal deep vein thrombosis: randomised controlled trial. bmj, 379.

Ageno, W., Beyer Westendorf, J., Contino, L., Bucherini, E., Sartori, M. T., Senzolo, M., Grandone, E., Santoro, R., Carrier, M., & Delluc, A. (2022). Rivaroxaban for the treatment of noncirrhotic splanchnic vein thrombosis: an interventional prospective cohort study. Blood advances, 6(12), 3569-3578.

Ageno, W., Vedovati, M. C., Cohen, A., Huisman, M., Bauersachs, R., Gussoni, G., Becattini, C., & Agnelli, G. (2021). Bleeding with apixaban and dalteparin in patients with cancer-associated venous thromboembolism: results from the Caravaggio study. Thrombosis and haemostasis, 121(05), 616-624.

Ageno, W., Vedovati, M. C., Cohen, A., Huisman, M., Bauersachs, R., Gussoni, G., Becattini, C., & Agnelli, G. (2021). Bleeding with Apixaban and Dalteparin in Patients with Cancer-Associated Venous Thromboembolism: Results from the Caravaggio Study. Thromb Haemost, 121(5), 616-624. https://doi.org/10.1055/s-0040-1720975

Agnelli, G., Becattini, C., Meyer, G., Muñoz, A., Huisman, M. V., Connors, J. M., Cohen, A., Bauersachs, R., Brenner, B., & Torbicki, A. (2020). Apixaban for the treatment of venous thromboembolism associated with cancer. New England Journal of Medicine, 382(17), 1599-1607.

Agnelli, G., Muñoz, A., Franco, L., Mahé, I., Brenner, B., Connors, J. M., Gussoni, G., Hamulyak, E. N., Lambert, C., & Suero, M. R. (2022). Apixaban and dalteparin for the treatment of venous thromboembolism in patients with different sites of cancer. Thrombosis and haemostasis, 122(05), 796-807.

Al Sulaiman, K., Badreldin, H. A., Korayem, G. B., Alenazi, A. A., Alsuwayyid, F., Alrashidi, A., Alhijris, M., Almutairi, F., Alharthi, F., & Vishwakarma, R. (2022). Evaluation of Apixaban safety and effectiveness in morbidly obese patients with atrial fibrillation: a retrospective cohort study. Thrombosis Journal, 20(1), 25.

Alberts, M., Chen, Y.-W., Lin, J. H., Kogan, E., Twyman, K., & Milentijevic, D. (2020). Risks of stroke and mortality in atrial fibrillation patients treated with rivaroxaban and warfarin. Stroke, 51(2), 549-555.

Ansell, J., Bakhru, S., Laulicht, B. E., Tracey, G., Villano, S., & Freedman, D. (2022). Ciraparantag reverses the anticoagulant activity of apixaban and rivaroxaban in healthy elderly subjects. European heart journal, 43(10), 985-992.

Ashton, V., Kerolus-Georgi, S., & Moore, K. T. (2021). The pharmacology, efficacy, and safety of rivaroxaban in renally impaired patient populations. The Journal of Clinical Pharmacology, 61(8), 1010-1026.

Ashton, V., Mudarris, L., & Moore, K. T. (2021). The pharmacology, efficacy, and safety of rivaroxaban in obese patient populations. American Journal of Cardiovascular Drugs, 21(3), 283-297.

Aslan, O., & Yildirim, S. (2022). Rivaroxaban and apixaban in patients with atrial fibrillation; a real-world data. Turkish Journal of Medical Sciences, 52(4), 948-957.

Attelind, S., Hallberg, P., Wadelius, M., Hamberg, A.-K., Siegbahn, A., Granger, C. B., Lopes, R. D., Alexander, J. H., Wallentin, L., & Eriksson, N. (2022). Genetic determinants of apixaban plasma levels and their relationship to bleeding and thromboembolic events. Frontiers in Genetics, 13, 982955.

Bainey, K. R., Welsh, R. C., Connolly, S. J., Marsden, T., Bosch, J., Fox, K. A., Steg, P. G., Vinereanu, D., Connolly, D. L., & Berkowitz, S. D. (2020). Rivaroxaban plus aspirin versus aspirin alone in patients with prior percutaneous coronary intervention (COMPASS-PCI). Circulation, 141(14), 1141-1151.

Bonaca, M. P., Bauersachs, R. M., Anand, S. S., Debus, E. S., Nehler, M. R., Patel, M. R., Fanelli, F., Capell, W. H., Diao, L., & Jaeger, N. (2020). Rivaroxaban in peripheral artery disease after revascularization. New England Journal of Medicine, 382(21), 1994-2004.

Bonde, A. N., Martinussen, T., Lee, C. J.-Y., Lip, G. Y., Staerk, L., Bang, C. N., Bhattacharya, J., Gislason, G., Torp-Pedersen, C., & Olesen, J. B. (2020). Rivaroxaban versus apixaban for stroke prevention in atrial fibrillation: an instrumental variable analysis of a nationwide cohort. Circulation: Cardiovascular Quality and Outcomes, 13(4), e006058.

Chen, C., Cao, Y., Zheng, Y., Dong, Y., Ma, J., Zhu, W., & Liu, C. (2021). Effect of rivaroxaban or apixaban in atrial fibrillation patients with stage 4–5 chronic kidney disease or on dialysis. Cardiovascular Drugs and Therapy, 35, 273-281.

Chiv, R., Beradid, S., Suissa, S., & Renoux, C. (2024). Effectiveness and Safety of Edoxaban Compared With Apixaban in Elderly Patients With Nonvalvular Atrial Fibrillation: A Real-World Population-Based Cohort Study. Stroke.

Cohen, A. T., Pan, S., Byon, W., Ilyas, B. S., Taylor, T., & Lee, T. C. (2021). Efficacy, safety, and exposure of apixaban in patients with high body weight or obesity and venous thromboembolism: insights from AMPLIFY. Advances in Therapy, 38, 3003-3018.

Connolly, S. J., Karthikeyan, G., Ntsekhe, M., Haileamlak, A., El Sayed, A., El Ghamrawy, A., Damasceno, A., Avezum, A., Dans, A. M., & Gitura, B. (2022). Rivaroxaban in rheumatic heart disease–associated atrial fibrillation. New England Journal of Medicine, 387(11), 978-988.

Connor, P., Sánchez van Kammen, M., Lensing, A. W., Chalmers, E., Kállay, K., Hege, K., Simioni, P., Biss, T., Bajolle, F., & Bonnet, D. (2020). Safety and efficacy of rivaroxaban in pediatric cerebral venous thrombosis (EINSTEIN-Jr CVT). Blood advances, 4(24), 6250-6258.

Costa, O. S., Beyer-Westendorf, J., Ashton, V., Milentijevic, D., Moore, K. T., Bunz, T. J., & Coleman, C. I. (2020). Effectiveness and safety of rivaroxaban versus warfarin in obese nonvalvular atrial fibrillation patients: analysis of electronic health record data. Current Medical Research and Opinion, 36(7), 1081-1088.

Dawwas, G. K., Leonard, C. E., Lewis, J. D., & Cuker, A. (2022). Risk for recurrent venous thromboembolism and bleeding with apixaban compared with rivaroxaban: an analysis of real-world data. Annals of internal medicine, 175(1), 20-28.

de Vries, T. A., Hirsh, J., Xu, K., Mallick, I., Bhagirath, V. C., Eikelboom, J. W., Ginsberg, J. S., Kruger, P. C., & Chan, N. C. (2020). Apixaban for stroke prevention in atrial fibrillation: why are event rates higher in clinical practice than in randomized trials?—a systematic review. Thrombosis and haemostasis, 120(09), 1323-1329.

De Vriese, A. S., Caluwé, R., Van Der Meersch, H., De Boeck, K., & De Bacquer, D. (2021). Safety and efficacy of vitamin K antagonists versus rivaroxaban in hemodialysis patients with atrial fibrillation: a multicenter randomized controlled trial. Journal of the American Society of Nephrology, 32(6), 1474-1483.

Ercisli, M. F., Lechun, G., Azeez, S. H., Hamasalih, R. M., Song, S., & Aziziaram, Z. (2021). Relevance of genetic polymorphisms of the human cytochrome P450 3A4 in rivaroxaban-treated patients. Cellular, Molecular and Biomedical Reports, 1(1), 33-41.

Escobar-Cervantes, C., Díez-Villanueva, P., Bonanad Lozano, C., Reino, A. P., Almendro-Delia, M., Facila, L., Valle, A., & Suárez, C. (2023). Vascular protection with rivaroxaban in the comprehensive management of atrial fibrillation. Expert review of cardiovascular therapy, 21(11), 791-802.

Esmaeili, S., Abolmaali, M., Aarabi, S., Motamed, M. R., Chaibakhsh, S., Joghataei, M. T., Mojtahed, M., & Mirzaasgari, Z. (2021). Rivaroxaban for the treatment of cerebral venous thrombosis. BMC neurology, 21, 1-6.

Fernandez, S., Lenoir, C., Samer, C. F., & Rollason, V. (2021). Drug-drug interactions leading to adverse drug reactions with rivaroxaban: A systematic review of the literature and analysis of VigiBase. Journal of Personalized Medicine, 11(4), 250.

Fernandez, S., Lenoir, C., Samer, C., & Rollason, V. (2020). Drug interactions with apixaban: a systematic review of the literature and an analysis of VigiBase, the World Health Organization database of spontaneous safety reports. Pharmacology research & perspectives, 8(5), e00647.

Fralick, M., Colacci, M., Schneeweiss, S., Huybrechts, K. F., Lin, K. J., & Gagne, J. J. (2020). Effectiveness and safety of apixaban compared with rivaroxaban for patients with atrial fibrillation in routine practice: a cohort study. Annals of internal medicine, 172(7), 463-473.

Fu, E. L., Desai, R. J., Paik, J. M., Kim, D. H., Zhang, Y., Mastrorilli, J. M., Cervone, A., & Lin, K. J. (2024). Comparative safety and effectiveness of warfarin or rivaroxaban versus apixaban in patients with advanced CKD and atrial fibrillation: nationwide US cohort study. American Journal of Kidney Diseases, 83(3), 293-305. e291.

Geisler, T., Keller, T., Martus, P., Poli, K., Serna-Higuita, L. M., Schreieck, J., Gawaz, M., Tünnerhoff, J., Bombach, P., & Nägele, T. (2023). Apixaban versus aspirin for embolic stroke of undetermined source. NEJM evidence, 3(1), EVIDoa2300235.

Grymonprez, M., De Backer, T. L., Bertels, X., Steurbaut, S., & Lahousse, L. (2023). Long-term comparative effectiveness and safety of dabigatran, rivaroxaban, apixaban and edoxaban in patients with atrial fibrillation: A nationwide cohort study. Frontiers in pharmacology, 14, 1125576.

Guimaraes, H. P., e Silva, P. G. d. B., Liporace, I. L., Sampaio, R. O., Tarasoutchi, F., Paixão, M., Hoffmann-Filho, C. R., Patriota, R., Leiria, T. L., & Lamprea, D. (2021). A randomized clinical trial to evaluate the efficacy and safety of rivaroxaban in patients with bioprosthetic mitral valve and atrial fibrillation or flutter: rationale and design of the RIVER trial. American heart journal, 231, 128-136.

Guimarães, H. P., Lopes, R. D., de Barros e Silva, P. G., Liporace, I. L., Sampaio, R. O., Tarasoutchi, F., Hoffmann-Filho, C. R., de Lemos Soares Patriota, R., Leiria, T. L., & Lamprea, D. (2020). Rivaroxaban in patients with atrial fibrillation and a bioprosthetic mitral valve. New England Journal of Medicine, 383(22), 2117-2126.

Gulilat, M., Keller, D., Linton, B., Pananos, A. D., Lizotte, D., Dresser, G. K., Alfonsi, J., Tirona, R. G., Kim, R. B., & Schwarz, U. I. (2020). Drug interactions and pharmacogenetic factors contribute to variation in apixaban concentration in atrial fibrillation patients in routine care. Journal of Thrombosis and Thrombolysis, 49, 294-303.

Hanni, C., Petrovitch, E., Ali, M., Gibson, W., Giuliano, C., Holzhausen, J., Makowski, C., Pallisco, A., Patel, N., & Sutter, D. (2020). Outcomes associated with apixaban vs warfarin in patients with renal dysfunction. Blood Advances, 4(11), 2366-2371.

Hanon, O., Vidal, J.-S., Pisica-Donose, G., Orvoën, G., David, J.-P., Chaussade, E., Caillard, L., de Jong, L. W., Boulloche, N., & Vinsonneau, U. (2021). Bleeding risk with rivaroxaban compared with vitamin K antagonists in patients aged 80 years or older with atrial fibrillation. Heart, 107(17), 1376-1382.

Healey, J. S., Lopes, R. D., Granger, C. B., Alings, M., Rivard, L., McIntyre, W. F., Atar, D., Birnie, D. H., Boriani, G., & Camm, A. J. (2024). Apixaban for stroke prevention in subclinical atrial fibrillation. New England Journal of Medicine, 390(2), 107-117.

Hernandez, A. V., Bradley, G., Khan, M., Fratoni, A., Gasparini, A., Roman, Y. M., Bunz, T. J., Eriksson, D., Meinecke, A.-K., & Coleman, C. I. (2020). Rivaroxaban vs. warfarin and renal outcomes in non-valvular atrial fibrillation patients with diabetes. European Heart Journal-Quality of Care and Clinical Outcomes, 6(4), 301-307.

Hill, N. R., Sandler, B., Bergrath, E., Milenković, D., Ashaye, A. O., Farooqui, U., & Cohen, A. T. (2020). A systematic review of network meta-analyses and real-world evidence comparing apixaban and rivaroxaban in nonvalvular atrial fibrillation. Clinical and Applied Thrombosis/Hemostasis, 26, 1076029619898764.

Hua, Y., Sun, J.-Y., Su, Y., Qu, Q., Wang, H.-Y., Sun, W., & Kong, X.-Q. (2021). The safety and efficacy of rivaroxaban compared with warfarin in patients with atrial fibrillation and diabetes: a systematic review and meta-analysis. American Journal of Cardiovascular Drugs, 21, 51-61.

Jakowenko, N., Nguyen, S., Ruegger, M., Dinh, A., Salazar, E., & Donahue, K. R. (2020). Apixaban and rivaroxaban anti-Xa level utilization and associated bleeding events within an academic health system. Thrombosis research, 196, 276-282.

Jaksa, A., Gibbs, L., Kent, S., Rowark, S., Duffield, S., Sharma, M., Kincaid, L., Ali, A. K., Patrick, A. R., & Govil, P. (2022). Using primary care data to assess comparative effectiveness and safety of apixaban and rivaroxaban in patients with nonvalvular atrial fibrillation in the UK: an observational cohort study. BMJ open, 12(10), e064662.

Jamieson, M. J., Byon, W., Dettloff, R. W., Crawford, M., Gargalovic, P. S., Merali, S. J., Onorato, J., Quintero, A. J., & Russ, C. (2022). Apixaban use in obese patients: a review of the pharmacokinetic, interventional, and observational study data. American Journal of Cardiovascular Drugs, 22(6), 615-631.

Jansson, M., Själander, S., Sjögren, V., Renlund, H., Norrving, B., & Själander, A. (2020). Direct comparisons of effectiveness and safety of treatment with Apixaban, Dabigatran and Rivaroxaban in atrial fibrillation. Thrombosis Research, 185, 135-141.

Koehl, J. L., Hayes, B. D., Al-Samkari, H., & Rosovsky, R. (2020). A comprehensive evaluation of apixaban in the treatment of venous thromboembolism. Expert Review of Hematology, 13(2), 155-173.

Konicki, R., Weiner, D., Herbert Patterson, J., Gonzalez, D., Kashuba, A., Cao, Y. C., Gehi, A. K., Watkins, P., & Powell, J. R. (2020). Rivaroxaban precision dosing strategy for real-world atrial fibrillation patients. Clinical and Translational Science, 13(4), 777-784.

Labovitz, A. J., Rose, D. Z., Fradley, M. G., Meriwether, J. N., Renati, S., Martin, R., Kasprowicz, T., Murtagh, R., Kip, K., & Beckie, T. M. (2021). Early apixaban use following stroke in patients with atrial fibrillation: results of the AREST trial. Stroke, 52(4), 1164-1171.

Lau, W. C., Cheung, C.-L., Man, K. K., Chan, E. W., Sing, C. W., Lip, G. Y., Siu, C.-W., Lam, J. K., Lee, A. C., & Wong, I. C. (2020). Association between treatment with apixaban, dabigatran, rivaroxaban, or warfarin and risk for osteoporotic fractures among patients with atrial fibrillation: a population-based cohort study. Annals of internal medicine, 173(1), 1-9.

Lau, W. C., Torre, C. O., Man, K. K., Stewart, H. M., Seager, S., Van Zandt, M., Reich, C., Li, J., Brewster, J., & Lip, G. Y. (2022). Comparative effectiveness and safety between apixaban, dabigatran, edoxaban, and rivaroxaban among patients with atrial fibrillation: a multinational population-based cohort study. Annals of internal medicine, 175(11), 1515-1524.

Lin, S. Y., Kuo, C. H., Yeh, S. J., Tsai, L. K., Liu, Y. B., Huang, C. F., Tang, S. C., & Jeng, J. S. (2020). Real-world rivaroxaban and apixaban levels in asian patients with atrial fibrillation. Clinical Pharmacology & Therapeutics, 107(1), 278-286.

Mahe, I., Agnelli, G., Ay, C., Bamias, A., Becattini, C., Carrier, M., Chapelle, C., Cohen, A. T., Girard, P., & Huisman, M. V. (2022). Extended anticoagulant treatment with full-or reduced-dose apixaban in patients with cancer-associated venous thromboembolism: rationale and design of the API-CAT study. Thrombosis and haemostasis, 122(04), 646-656.

Male, C., Lensing, A. W., Palumbo, J. S., Kumar, R., Nurmeev, I., Hege, K., Bonnet, D., Connor, P., Hooimeijer, H. L., & Torres, M. (2020). Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial. The Lancet Haematology, 7(1), e18-e27.

Mamas, M. A., Batson, S., Pollock, K. G., Grundy, S., Matthew, A., Chapman, C., Manuel, J. A., Farooqui, U., & Mitchell, S. A. (2022). Meta-analysis comparing apixaban versus rivaroxaban for management of patients with nonvalvular atrial fibrillation. The American journal of cardiology, 166, 58-64.

Matoba, T., Yasuda, S., Kaikita, K., Akao, M., Ako, J., Nakamura, M., Miyauchi, K., Hagiwara, N., Kimura, K., & Hirayama, A. (2021). Rivaroxaban monotherapy in patients with atrial fibrillation after coronary stenting: insights from the AFIRE trial. Cardiovascular Interventions, 14(21), 2330-2340.

Mavrakanas, T. A., Garlo, K., & Charytan, D. M. (2020). Apixaban versus no anticoagulation in patients undergoing long-term dialysis with incident atrial fibrillation. Clinical Journal of the American Society of Nephrology, 15(8), 1146-1154.

Mavri, A., Vene, N., Božič-Mijovski, M., Miklič, M., Söderblom, L., Pohanka, A., Malmström, R. E., & Antovic, J. (2021). Apixaban concentration variability and relation to clinical outcomes in real-life patients with atrial fibrillation. Scientific Reports, 11(1), 13908.

McBane II, R. D., Loprinzi, C. L., Zemla, T., Tafur, A., Sanfilippo, K., Liu, J. J., Garcia, D. A., Heun, J., Gundabolu, K., & Onitilo, A. A. (2024). Extending Venous Thromboembolism Secondary Prevention with Apixaban in Cancer Patients. The EVE Trial. Journal of Thrombosis and Haemostasis.

McBane II, R. D., Wysokinski, W. E., Le-Rademacher, J. G., Zemla, T., Ashrani, A., Tafur, A., Perepu, U., Anderson, D., Gundabolu, K., & Kuzma, C. (2020). Apixaban and dalteparin in active malignancy-associated venous thromboembolism: The ADAM VTE trial. Journal of Thrombosis and Haemostasis, 18(2), 411-421.

Mentias, A., Heller, E., & Vaughan Sarrazin, M. (2020). Comparative effectiveness of rivaroxaban, apixaban, and warfarin in atrial fibrillation patients with polypharmacy. Stroke, 51(7), 2076-2086.

Miao, B., Sood, N., Bunz, T. J., & Coleman, C. I. (2020). Rivaroxaban versus apixaban in non-valvular atrial fibrillation patients with end-stage renal disease or receiving dialysis. European journal of haematology, 104(4), 328-335.

Mokadem, M. E., Hassan, A., & Algaby, A. Z. (2021). Efficacy and safety of apixaban in patients with active malignancy and acute deep venous thrombosis. Vascular, 29(5), 745-750.

O'Kane, C. P., Avalon, J. C. O., Lacoste, J. L., Fang, W., Bianco, C. M., Davisson, L., & Piechowski, K. L. (2022). Apixaban and rivaroxaban use for atrial fibrillation in patients with obesity and BMI≥ 50 kg/m2. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 42(2), 112-118.

Perreault, S., Cote, R., Dragomir, A., White-Guay, B., Lenglet, A., & Dorais, M. (2022). Effectiveness and safety of low-dose versus standard-dose rivaroxaban and apixaban in patients with atrial fibrillation. Plos one, 17(12), e0277744.

Perreault, S., Dragomir, A., Cote, R., Lenglet, A., White-Guay, B., De Denus, S., Schnitzer, M. E., Dubé, M. P., Brophy, J. M., & Dorais, M. (2021). Comparative effectiveness and safety of high-dose rivaroxaban and apixaban for atrial fibrillation: A propensity score-matched cohort study. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 41(4), 379-393.

Petzold, T., Thienel, M., Dannenberg, L., Mourikis, P., Helten, C., Ayhan, A., M'Pembele, R., Achilles, A., Trojovky, K., & Konsek, D. (2020). Rivaroxaban reduces arterial thrombosis by inhibition of FXa-driven platelet activation via protease activated receptor-1. Circulation Research, 126(4), 486-500.

Piccini, J. P., Caso, V., Connolly, S. J., Fox, K. A., Oldgren, J., Jones, W. S., Gorog, D. A., Durdil, V., Viethen, T., & Neumann, C. (2022). Safety of the oral factor Xla inhibitor asundexian compared with apixaban in patients with atrial fibrillation (PACIFIC-AF): a multicentre, randomised, double-blind, double-dummy, dose-finding phase 2 study. The lancet, 399(10333), 1383-1390.

Planquette, B., Bertoletti, L., Charles-Nelson, A., Laporte, S., Grange, C., Mahé, I., Pernod, G., Elias, A., Couturaud, F., & Falvo, N. (2022). Rivaroxaban vs dalteparin in cancer-associated thromboembolism: a randomized trial. Chest, 161(3), 781-790.

Pokorney, S. D., Chertow, G. M., Al-Khalidi, H. R., Gallup, D., Dignacco, P., Mussina, K., Bansal, N., Gadegbeku, C. A., Garcia, D. A., & Garonzik, S. (2022). Apixaban for patients with atrial fibrillation on hemodialysis: a multicenter randomized controlled trial. Circulation, 146(23), 1735-1745.

Ramacciotti, E., Agati, L. B., Calderaro, D., Aguiar, V. C. R., Spyropoulos, A. C., de Oliveira, C. C. C., Dos Santos, J. L., Volpiani, G. G., Sobreira, M. L., & Joviliano, E. E. (2022). Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. The lancet, 399(10319), 50-59.

Ray, W. A., Chung, C. P., Stein, C. M., Smalley, W., Zimmerman, E., Dupont, W. D., Hung, A. M., Daugherty, J. R., Dickson, A., & Murray, K. T. (2021). Association of rivaroxaban vs apixaban with major ischemic or hemorrhagic events in patients with atrial fibrillation. Jama, 326(23), 2395-2404.

Rivera-Caravaca, J. M., Sanchez, M. A., Fernández, M. S., Rafols, C., Barón-Esquivias, G., Ynsaurriaga, F. A., Freixa-Pamias, R., Goya, I. L., Rodríguez, J. M. V., & Pérez-Cabeza, A. I. (2023). Adverse Clinical Outcomes and Associated Predictors in Rivaroxaban-Treated Atrial Fibrillation Patients With Renal Impairment. The American Journal of Cardiology, 203, 122-127.

Rutherford, O.-C. W., Jonasson, C., Ghanima, W., Söderdahl, F., & Halvorsen, S. (2020). Comparison of dabigatran, rivaroxaban, and apixaban for effectiveness and safety in atrial fibrillation: a nationwide cohort study. European Heart Journal-Cardiovascular Pharmacotherapy, 6(2), 75-85.

Samama, C. M., Laporte, S., Rosencher, N., Girard, P., Llau, J., Mouret, P., Fisher, W., Martínez-Martín, J., Duverger, D., & Deygas, B. (2020). Rivaroxaban or enoxaparin in nonmajor orthopedic surgery. New England Journal of Medicine, 382(20), 1916-1925.

Speed, V., Green, B., Roberts, L. N., Woolcombe, S., Bartoli-Abdou, J., Barsam, S., Byrne, R., Gee, E., Czuprynska, J., & Brown, A. (2020). Fixed dose rivaroxaban can be used in extremes of bodyweight: a population pharmacokinetic analysis. Journal of Thrombosis and Haemostasis, 18(9), 2296-2307.

Spyropoulos, A. C., Ageno, W., Albers, G. W., Elliott, C. G., Halperin, J. L., Hiatt, W. R., Maynard, G. A., Steg, P. G., Weitz, J. I., & Lu, W. (2020). Post-discharge prophylaxis with rivaroxaban reduces fatal and major thromboembolic events in medically ill patients. Journal of the American College of Cardiology, 75(25), 3140-3147.

Stanifer, J. W., Pokorney, S. D., Chertow, G. M., Hohnloser, S. H., Wojdyla, D. M., Garonzik, S., Byon, W., Hijazi, Z., Lopes, R. D., & Alexander, J. H. (2020). Apixaban versus warfarin in patients with atrial fibrillation and advanced chronic kidney disease. Circulation, 141(17), 1384-1392.

Suzuki, S., Yamashita, T., Akao, M., Okumura, K., & investigators, J.-E. A. (2020). Clinical implications of assessment of apixaban levels in elderly atrial fibrillation patients: J-ELD AF registry sub-cohort analysis. European Journal of Clinical Pharmacology, 76, 1111-1124.

Tittl, L., Marten, S., Naue, C., & Beyer-Westendorf, J. (2021). 5-year outcomes from rivaroxaban therapy in atrial fibrillation: Results from the Dresden NOAC Registry. Thrombosis Research, 202, 24-30.

Wang, T. Y., Svensson, L. G., Wen, J., Vekstein, A., Gerdisch, M., Rao, V. U., Moront, M., Johnston, D., Lopes, R. D., & Chavez, A. (2023). Apixaban or warfarin in patients with an On-X mechanical aortic valve. NEJM evidence, 2(7), EVIDoa2300067.

Weir, M. R., Ashton, V., Moore, K. T., Shrivastava, S., Peterson, E. D., & Ammann, E. M. (2020). Rivaroxaban versus warfarin in patients with nonvalvular atrial fibrillation and stage IV-V chronic kidney disease. American heart journal, 223, 3-11.

Wetmore, J. B., Herzog, C. A., Yan, H., Reyes, J. L., Weinhandl, E. D., & Roetker, N. S. (2022). Apixaban versus warfarin for treatment of venous thromboembolism in patients receiving long-term dialysis. Clinical Journal of the American Society of Nephrology, 17(5), 693-702.

Whitehouse, K. R., Avula, D., Kahlon, T., Costelle, D., Dunbar-Matos, C., Pahwa, S., Trivedi, J. R., & Slaughter, M. S. (2022). Apixaban: Alternative anticoagulation for HeartMate 3 ventricular assist device. ASAIO Journal, 68(3), 318-322.

Woller, S. C., Stevens, S. M., Kaplan, D., Wang, T.-F., Branch, D. W., Groat, D., Wilson, E. L., Armbruster, B., Aston, V. T., & Lloyd, J. F. (2022). Apixaban compared

with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial. Blood Advances, 6(6), 1661-1670.

Xu, Y., Chang, A. R., Inker, L. A., McAdams-DeMarco, M., Grams, M. E., & Shin, J.-I. (2023). Associations of apixaban dose with safety and effectiveness outcomes in patients with atrial fibrillation and severe chronic kidney disease. Circulation, 148(19), 1445-1454.

Yang, L., Brooks, M. M., Glynn, N. W., Zhang, Y., Saba, S., & Hernandez, I. (2020). Real-world direct comparison of the effectiveness and safety of apixaban, dabigatran, rivaroxaban, and warfarin in Medicare beneficiaries with atrial fibrillation. The American Journal of Cardiology, 126, 29-36.

Young, G., Lensing, A. W., Monagle, P., Male, C., Thelen, K., Willmann, S., Palumbo, J. S., Kumar, R., Nurmeev, I., & Hege, K. (2020). Rivaroxaban for treatment of pediatric venous thromboembolism. An Einstein-Jr phase 3 dose-exposure-response evaluation. Journal of Thrombosis and Haemostasis, 18(7), 1672-1685.

Zeitouni, M., Giczewska, A., Lopes, R. D., Wojdyla, D. M., Christersson, C., Siegbahn, A., De Caterina, R., Steg, P. G., Granger, C. B., & Wallentin, L. (2020). Clinical and pharmacological effects of apixaban dose adjustment in the ARISTOTLE trial. Journal of the American College of Cardiology, 75(10), 1145-1155.