Review Article
Volume 10:7, 2020
DOI: 10.37421/jccr.2020.10.1365

Clinical Case Reports

ISSN: 2165-7920 Open Access

Developing Deep Venous Thrombosis while on Rivaroxaban: A Review of Rivaroxaban

Rasha A. Al-Khafaji*

Department of Cardiology, Endocrinology and Nephrology, Nordsjælland (North Zealand) University Hospital, Hillerød and Frederikssund, Denmark

Abstract

Rivaroxaban is a Direct Oral Anticoagulant (DOAC), which has six licensed indications, including the use for prevention of stroke and systemic embolism with non-valvular Atrial Fibrillation (AF) and the treatment of Venous Thromboembolism (VTE). The pharmacokinetics and the pharmacogenetics of rivaroxaban are reviewed by the author because of a previously reported case of a 43-year-old Caucasian female, who was diagnosed with popliteal and calf Deep Venous Thrombosis (DVT) while on anticoagulation treatment in the form of rivaroxaban 20 mg PO daily. This treatment was started because of a previously verified bilateral Pulmonary Embolism (PE) 5 months earlier. Rivaroxaban is more frequently used in clinical practice, and many physicians are aware that rivaroxaban requires adaptation mainly on the patient's renal function. However, there is still a need to increase awareness of rivaroxaban's interactions with drugs that share its pathways when the hepatic *CYP450 and/or P-gp/BCRP* are involved. These pathways are utilized by several medications, which are used in cardiovascular and neurological diseases, and the treatment of infections. These interactions can result in under or overexposure to rivaroxaban, which both effects can be detrimental. The author makes several cautious suggestions to decrease the incidence of under/overexposure of rivaroxaban. Physicians, including primary care physicians, could receive a clinical course focusing on DOACs for anticoagulation treatment or direct clinical training within a short-term Anticoagulation Team (ACT) stewardship program concerning adequate prescriptions of rivaroxaban/DOAC as well as their interactions. Also, patients who are elderly and/or with polypharmacy while taking rivaroxaban require more frequent controls. Furthermore, research exploring the effects of *ABCG1, ABCG2, CYP3A4, CYP3A5*, and Drug-Drug Interactions (DDI), is warranted. Finally, there is a need to identify a validated method for measuring rivaroxaban in primary care.

Keywords: *ABCG1* • *ABCG2* • Anti-factor Xa assays • *CYP3A4* • Direct Oral Anticoagulant (DOAC) • Drug-Drug Interaction (DDI) • Pharmacogenomics • Recurrent VTE

Introduction

A detailed description of the clinical presentation and the analysis of this previously reported case could be found in Al-Khafaji et al. [1]. A 43-year-old Caucasian female was on a full anticoagulation therapy by using rivaroxaban (Xarelto) 20 mg PO daily due to a previously verified bilateral (PE) 5 months earlier, when she presented to the Accident & Emergency Room (A and E) on the third day of her symptoms as a referred case by the general practitioner for a suspected DVT due to slight right leg swelling. The patient had BMI> 37, a Wells' score of 2 (Moderate risk), and a negative high-quality D-dimer test. The only medication at the time of the presentation was Rivaroxaban 20 mg daily in the last four months. A complete right lower limb Doppler Ultrasound (US) was scheduled by the author, revealing thrombosis in the popliteal and calf veins.

Rivaroxaban belongs to the Direct Oral Anticoagulant (DOAC) group, also known as non-vitamin K oral anticoagulants (NOACs), which includes factor Xa inhibitors: Apixaban (Eliquis®), Edoxaban (Savaysa, Lixiana), and rivaroxaban (Xarelto), and direct thrombin inhibitors: Dabigatran (Pradaxa®) and argatroban [2]. Rivaroxaban (Xarelto; Bayer HealthCare) became the first direct inhibitor of factor Xa to be approved for clinical use in 2008 [3]. Rivaroxaban has six licensed indications, including prophylaxis of atherothrombotic events in acute coronary syndrome, four different dosages, and at least five possible durations of therapy [4,5].

***Address for Correspondence:** Al-Khafaji RA, Department of Cardiology, Endocrinology and Nephrology, Nordsjælland (North Zealand) University Hospital, Hillerød and Frederikssund, Denmark, E-mail: rasha.alkhafaji2@gmail.com, ORCID: https://orcid.org/0000-0003-4577-562X*

Received 15 June 2020; **Accepted** 02 July 2020; **Published** 09 July 2020

Literature Review

Rivaroxaban is approved with other DOACs such as apixaban and dabigatran in many countries in adult patients for thromboprophylaxis after elective hip or knee replacement surgery, prevention of stroke and systemic embolism with non-valvular atrial fibrillation (AF), for the treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE), and prevention of recurrent DVT and PE [5-13]. Prevention of stroke in AF was by far the most prevalent indication for prescribing a DOAC [14].

Rivaroxaban's mechanism of action

Hemostatistically, an activated factor X (Xa) is at the convergence point of the intrinsic and extrinsic coagulation pathways, and it directly converts prothrombin to thrombin via the prothrombinase complex, leading to fibrin clot formation and platelet activation [3,8,15]. But, factor X's activity can be markedly suppressed without affecting hemostasis [3]. Therefore, factor X represents an ideal target to prevent thrombosis without inducing systemic hypocoagulation and unintended bleeding complications. Constant scientific research has led to improved understanding of coagulation pathways and led to the development of several new parenterally or orally active agents that specifically target single blood coagulation factors [7]. Rivaroxaban inhibits prothrombinase and free and clot-bound Factor Xa activity reversibly [9,15], thus effectively blocking thrombin generation [3,6,8,13,15]. Also, rivaroxaban increases clot permeability and degradability [15].

Why Rivaroxaban and DOACs?

Low-Molecular-Weight Heparins (LMWH)s and Vitamin K Antagonist (VKA)s are still the basis of contemporary thromboprophylaxis and treatment in

many countries [3,6]. Both Unfractionated Heparin (UFH) and Low-Molecular-Weight Heparins (LMWH) are indirect anticoagulants, and their activity is mediated by inhibiting plasma cofactors and to a lesser extent for UFH, heparin cofactor II. UFH has an anti-Xa to an anti-IIa ratio of 1:1, while LMWHs have ratios from 2:1 to 4:1, depending on the molecular weight distribution of the preparation [3]. LMWHs have replaced UFH due to superior pharmacokinetics and a lower risk of bleeding than UFH [3]. But, they both are inconvenient, especially in an out-patient setting [3,16]. Warfarin is an oral anticoagulant, which is a prototype Vitamin K Antagonist (VKA). VKAs interfere with the γcarboxylation of glutamate residues in Factors II, VII, IX, and X [3,6,16]. VKAs have a slow onset of action; interact with food and drugs, which creates intra-individual variations, and requires constant monitoring through normalized ratio (INR) range, usually 2.0-3.0, and thus probable dose adjustment. These unpredictable pharmacokinetics and pharmacodynamics are both costly and practically challenging [3,9,14,16,17]. Also, warfarin is affected by common genetic polymorphisms, particularly in *CYP2C9* and *VKORC1*. Unpredictability has led they have a narrow therapeutic window [3,9,16,17]. Thus, warfarin imposes a heavy burden on healthcare systems and patients. But, warfarin is the only anticoagulant approved for use by the Food and Drug Administration (FDA) in individuals with mechanical heart valves [9] (Figure 1). On the other hand, rivaroxaban, which belongs to the Direct Oral Anticoagulant (DOAC) group, has several qualities that make it effective for short and long term usage [3]. It has predictable, dose-dependent pharmacokinetics, relatively short half-life; 5-9 h in healthy young subjects and 11-12 h in elderly subjects, rapid onset of action, plasma rivaroxaban levels and inhibition of Factor Xa are closely correlated, wide therapeutic window, a better efficacy/safety ratio, fewer food and drug interactions, and it does neither require routine monitoring nor routine dose adjustment, which may also increase patient's compliance. Also, a dual-route of elimination; the liver metabolizes 2/3 while 1/3 is excreted unaltered by the kidneys [3,6-9,11,16] (Figure 1). Bodyweight, gender, and ethnicity had no clinically relevant effects on rivaroxaban pharmacodynamics [15].

However, the latter view was not shared with other studies, as it will be shown later in this review. DOACs are effective in treating VTE and safer in terms of bleeding than VKAs [17]. Despite the factor Xa inhibitors are emerging as a popular alternative to the use of VKA, there are several withdrawals to the use of DOACs. They are the high cost, and that caution must be taken in case of renal and liver impairment. They are also contraindicated in pregnancy and lack clinical efficacy in thromboprophylaxis in patients with mechanical valves [18]. Age, weight, renal function, compliance, the risk of thromboembolism, and the risk of bleeding should be considered when prescribing one of the DOAC as well as the patient's financial ability [18]. This review reveals that other factors should also be considered when prescribing one of the DOACs.

Rivaroxaban, Apixaban and VTE

The superiority of apixaban and rivaroxaban compared to dabigatran and edoxaban in treating VTE is that they do not need to be preceded with "lead-in" anticoagulation by unfractionated heparin or Low-Molecular-Weight Heparin (LMWH) before initiating therapy. Therefore, apixaban and rivaroxaban are now increasingly being used for acute VTE compared with VKAs and other DOACs [10]. In a metaanalysis directly comparing apixaban to rivaroxaban in patients with acute VTE, it was found that there is no difference in rates of recurrent VTE. However, in the rivaroxaban group, both major bleeding and minor bleeding events were significantly higher [10]. In this metanalysis, it was also found that on average, 345 patients would have to receive apixaban (instead of rivaroxaban) for one additional patient not to have the study outcome of major bleeding (number needed to harm) [10]. It has been reported that there is less gastrointestinal bleeding with apixaban [10], and it is favored in patients with Chronic Kidney Diseases (CKD) [9,10]. This meta-analysis is, therefore, in favor of using apixaban to treat VTE in patients with a history of gastrointestinal bleeding, current heavy menses, or CKD. It also shows that patients taking long-term rivaroxaban will likely benefit if they switch to apixaban if they can adhere to the twice-daily dosing. Therefore, discussing the options of anticoagulation between these agents with the patients is necessary [10].

Hospitalized patients for stroke, heart failure, respiratory insufficiency, infections and inflammatory disease have a high risk for VTE [19]. Identification of the patient's risk to develop VTE through validated risk scores such as IMPROVE and elevated d-dimer levels aid in identifying patients who could benefit from thromboprophylaxis during hospitalization. The risk for developing VTE after discharge continues up to 6 weeks, but thromboprophylaxis is rarely continued after hospital discharge. Rivaroxaban was explored for this purpose in a clinical trial by giving it in prophylactic dosage for 45 days after hospital discharge. It was not associated with a significantly lower risk of symptomatic VTE and death due to PE than placebo. Both apixaban and rivaroxaban efficacy could be affected by potent inducers of both CYP3A4 and P-gp, such as Carbamazepine (CZP), therefore considering an alternative drug to CZP where possible when these anticoagulants are to be used [20]. More details of Drug-drug interactions are provided in this review.

Rivaroxaban and Age, Ethnicities and Body Mass Index (BMI)

When choosing any of the DOACs, the dosage should consider patient-specific factors including age, weight, renal function, serum creatinine, concomitant medications, and the cause for prescribing the drug [14]. If the patient was already started on a DOAC before hospital admission, it is

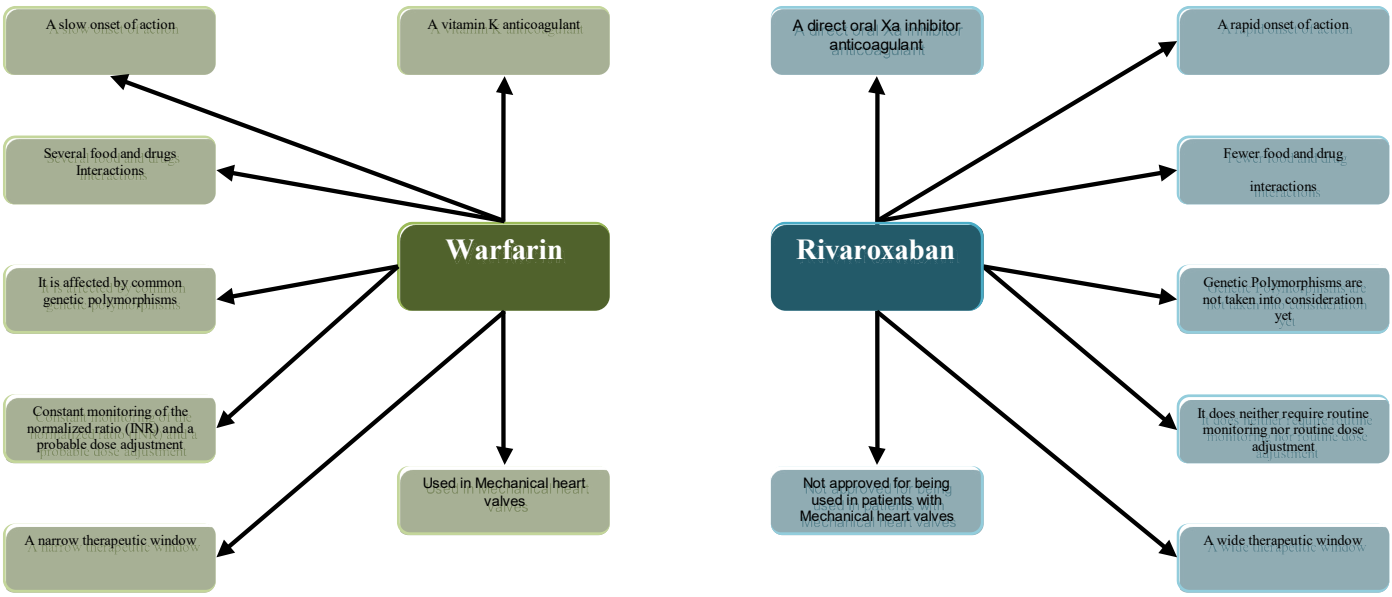


Figure 1. A comparison between Rivaroxaban and Warfarin. Several differences exist between these two oral anticoagulants; here, some of these differences are illustrated.

necessary to consider the patient's characteristics that may have changed in the time between the initiations until the new admission [14].

Rivaroxaban and Age

Age is insufficient to explain an increase of rivaroxaban's exposure on its own, but overexposure may occur based on a decrease in renal function seen with aging [8]. Systemic exposure to rivaroxaban is increased in elderly patients aged 75 years compared to younger patients following a single dose of rivaroxaban 10 mg. But despite this, rivaroxaban dosages do not need adjustment according to age, because this effect was attributed to a reduced renal function in older patients rather than the effect of age itself [15]. By contrast, Wu et al. [7] reported a clinical case of a 67-year-old female with a normal kidney and liver function tests and normal platelet counts, who was treated with a normal dose of rivaroxaban for Pulmonary Embolism (PE) and bilateral intermuscular veins DVT. However, she developed rare abnormal prolongation coagulation tests of PT, aPPT, and gastrointestinal and gum bleeding after 24 hours of administration [7]. Current guidelines recommend that using DOAC, including rivaroxaban do not require coagulation monitoring, but a small number of patients may develop routine coagulation test changes and bleeding during rivaroxaban therapy, especially in the elderly [7].

Rivaroxaban and BMI

The peak plasma concentration, distribution, and the half-life of rivaroxaban are not affected by high body weight [17]. The National Institutes of Health define obesity as having a BMI between (30-40 kg/m^2) while 'extreme obesity' as having a BMI of >40 kg/m^2 [21]. Higher weight individuals may have increased (Volume distribution) Vd levels of rivaroxaban, although the clinical significance of this is unknown [21]. The clinical importance of considering the BMI is that it raises concerns about underdosing of DOAC in patients at the extremes of obesity [21]. These concerns are based on reduced peak concentrations and shorter half-lives occurring with increasing weight [21]. Unlike edoxaban, there are no recommendations to adjust the dose according to bodyweight when prescribing rivaroxaban [22]. Although a lower bodyweight (B50 kg) significantly increased Cmax by 24%, this was not considered clinically relevant, and no dosage adjustment was thought necessary [15]. In the Dresden NOAC Registry (NCT01588119) [23], a non-interventional registry with 3432 enrolled patients, which rivaroxaban users represented 61.3%, it was found that there is no indication that high BMI is associated with inferior NOAC effectiveness or safety [23]. DOACs are safe and effective in obese patients with BMI ≤4 0 kg/m^2 or body weight ≤ 120 kg according to the conclusion of the Scientific and Standardization Committee (SSC) of the International Society of Thrombosis and Haemostasis (ISTH) [24]. If DOACs are used in a patient with a BMI of >40 kg m2 or weight of >120 kg, it is suggested that it should be supplied with measurements of the anticoagulant activity including anti-Xa according to the Scientific and Standardization Committee (SSC) of the International Society of Thrombosis and Haemostasis (ISTH) [22,24].

Rivaroxaban and Ethnicity

Rivaroxaban is approved for anticoagulation therapy in Japan since 2012, but at present, it is approved and prescribed at a lower dose because of the unique pharmacokinetics in Japanese patients compared to Caucasian patients [13]. Healthy Japanese volunteers had a 20-40% higher exposure than other ethnicities, but this difference was reduced when values were adjusted for bodyweight [15]. The dosage in Japan for preventing stroke and Systemic Embolism (SE) in Japanese patients is 15 mg once daily in patients with creatinine clearance [CrCl] ≥ 50 mL/min or 10 mg once daily in those with CrCl 30-49 mL/min) [12]. Bleeding risk and anticoagulant treatment in the Asian population have been recognized as different from those of the Western population [25].

Rivaroxaban's absorption and distribution

Rivaroxaban is not a pro-drug and has a rapid bioavailability [2]. Rivaroxaban is lipophilic and has a limited aqueous solubility, which can explain its increased bioavailability with a fed state for doses at 20 mg. There is a decreased bioavailability of rivaroxaban at high doses due to dissolution-limited absorption, which can explain the reduced risk of unintentional overdosing [8,9,15]. Thus, it is recommended that rivaroxaban doses of 15 and 20 mg are taken with food [15]. Dialysis is not expected to remove rivaroxaban [15] because of its binding to plasma proteins. Serum albumin is the most significant protein binding for rivaroxaban [2,5,9,15].

The Possible causes of Underdosing/Overdosing of Rivaroxaban

A stepwise clinical approach is necessary when evaluating the presence of a possible Underdosing/Overdosing of rivaroxaban. The following sections highlight how to approach these presentations to identify the probable underlying cause.

Compliance

Because of the pharmacokinetics and pharmacodynamics of rivaroxaban that it does not require routine monitoring or routine dose adjustment, it may have increased compliance. Pharmacokinetic and pharmacodynamic have improved, for example, the therapeutic compliance of elderly patients with PE as compared to warfarin. Therefore, it is expected to become also a favorable choice for the treatment of PE in elderly patients [16]. It is recommended that rivaroxaban doses of 15 and 20 mg are taken with food [15]. One of the most common causes of failure of any clinical treatment is non-compliance, which may alter the overall pharmacokinetics and the plasma concentrations of the prescribed agents [26]. Unlike warfarin, which could be controlled by regular INR measurements, under coagulation in DOACs would be challenging to confirm even if the patient has taken the medication because of tests such as an anti-Xa measurement for (rivaroxaban, apixaban or edoxaban) are not widely used. Also, there are neither validated tests nor expected therapeutic ranges for these tests [27]. The consequences of non-adherence in the case of DOAC, even if missing a single dose, can result in more significant consequences than VKA because of the relatively short half-lives, as demonstrated in the introduction (Figure 1). Therefore compliance is very critical to provide protection from stroke and VTE [27,28].

Accurate intake of rivaroxaban

Rivaroxaban is not a pro-drug and has a rapid bioavailability [2]. Rivaroxaban is lipophilic and has a limited aqueous solubility, which can explain its increased bioavailability with a fed state for doses at 20 mg. There is a decreased bioavailability of rivaroxaban at high doses due to dissolution-limited absorption, which can explain the reduced risk of unintentional overdosing [8,9,15]. Thus, it is recommended that rivaroxaban doses of 15 and 20 mg are taken with food [15]. Dialysis is not expected to remove rivaroxaban [15] because of its binding to plasma proteins. Serum albumin is the most significant protein binding for rivaroxaban [2,5,9,15].

Rivaroxaban and Dosage

The majority of cases with inappropriate prescription of DOACs were due to underdosing according to their corresponding Summary of Product Characteristics (SmPC) [14]. The complexity of appropriate DOAC dosing contributes to the prescribing errors [14]. In a retrospective cohort study, which enrolled 772 to study the appropriateness dosing of (DOACs) before and during hospital admission in the UZ Brussel in 2016, it showed that rivaroxaban (375 patients; 48.6%) was the most frequently prescribed DOAC, followed by apixaban (290 patients; 37.6%) and dabigatran (107 patients; 13.9%) [14].

Unlike apixaban, which necessitates a dose reduction only when at least 2 out of the 3 following factors are met: serum creatinine: 1.5 mg/dL, weight: 60 kg, and/or age 80 years [14] rivaroxaban requires adaptation mainly on the patient's renal function. In general, physicians tend to prescribe subtherapeutic doses than the recommended doses of anticoagulation because of fear from bleeding events or to refrain from anticoagulation initiation in high-risk patients [14]. Using evidence-based clinical evaluation scales such as the HAS-BLED can help physicians in their assessment [14]. In the previously mentioned study [14], underdosing was more common in the apixaban group (24.5%) while it was (12.8%) for rivaroxaban [14].

The presence of other diseases

Hepatic impairment, whether mild, moderate, or severe, results in overexposure at varying degrees [15]. Renal clearance of rivaroxaban is decreased in patients with moderate hepatic insufficiency [15].

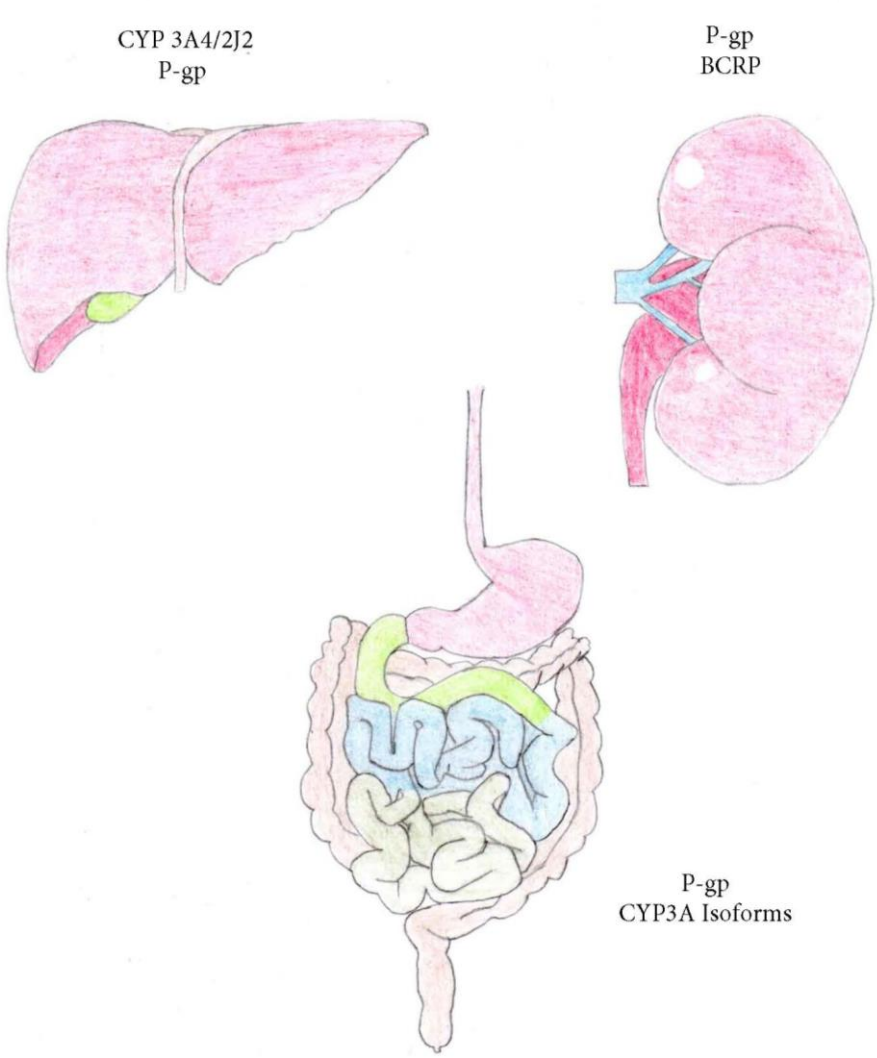
Pharmacogenetics and drug interactions

Pharmacogenetics plays a role in distribution, metabolism, and excretion (Figure 2). All DOACS are substrates of P-glycoprotein [22]. Apixaban and rivaroxaban are also substrates of cytochrome P450 (*CYP3A4*) [5,22], dabigatran is not [22]. Rivaroxaban is metabolized by both cytochrome P450 enzymes and CYP independent mechanisms. Oxidative biotransformation by *CYP3A4* accounted for 18%, and *CYP2J2* accounted for 14% of the total rivaroxaban elimination [8,13,15]. While non-CYP-mediated hydrolysis of the amide bonds accounted for 14% of total rivaroxaban elimination [8,15]. *CYP450s* has a high degree of polymorphism, which expectedly leads to inter-individual variability [8]. Also, this enzyme is inhibited by drugs; for example, it is inhibited strongly by ketoconazole and ritonavir, resulting in increased exposure of rivaroxaban with concomitant administration with such inhibitors [8,13,15]. 66% of rivaroxaban's clearance is renal, while 28% is fecal/biliary. The multidrug efflux transporter P-glycoprotein (permeability glycoprotein), which is also abbreviated as P-gp or Pgp, plays a vital role in the clearance of rivaroxaban. The P-gp's function differs according to its histological distribution (Figure 2). In the small intestine, it is responsible for opposing absorption of rivaroxaban. Therefore its inhibition results in increased absorption and thus rivaroxaban overexposure [29]. Active renal excretion of rivaroxaban is through the transporters P-gp [29] and Breast Cancer Resistance Protein (BCRP) [8,13,15]. Thus inhibiting them through drugs could also result in overexposure [8]. In the hepatobiliary system, P-glycoprotein binds to rivaroxaban and facilitates its gastrointestinal excretion [29].

Drug-Drug Interactions

The basis of DDI with concomitant use of Rivaroxaban

Although rivaroxaban has fewer drug-drug interactions as compared to VKA, it does not mean it is free from such interactions (Table 1). Assessment of the clinical significance of a potential interaction between drugs generally is complex, especially in patients, who are in multiple medical therapies as in cancer patients, elderly, and heart failure patients [22]. Understanding the possible interactions is very important because of the increased incidence of polypharmacy [25]. Therefore, the concomitant use of rivaroxaban, and these drugs is highly likely [13,29] (Table 1). *CYP3A4, CYP2J2*, and the transport proteins P-gp and BCRP (*ABCG2*) are involved in the elimination of rivaroxaban [13]. (Pharmacogenetics section). Therefore, in theory, drug-drug



Note: P-gp or Pgp; Permeability Glycoprotein, and also known as multidrug resistance protein 1 (MDR1), or ATP-binding cassette sub-family B member 1 (ABCB1), or cluster of differentiation 243 (CD243). BCRP; Breast Cancer Resistance Protein.

Note: This figure is adapted from Galgani A, Palleria C, Iannone L et al. Pharmacokinetic Interactions of Clinical Interest Between Direct Oral Anticoagulants and Antiepileptic Drugs. Front Neurol. 2018;9:1067 [2]. The figure is hand-drawn by Haider A. Al-Khafaji.

Figure 2. Rivaroxaban's pharmacokinetic pathways.

interaction is possible between rivaroxaban and drugs which are substrates for, or inhibitors of *CYP3A4* and/or *CYP2J2*, and the transport proteins P-gp and BCRP (*ABCG2*). Despite there are known interactions, but these interactions are not necessarily clinically relevant [13]. Rivaroxaban does not interact to a clinically relevant extent with substrates for, or inhibitors of, *CYP3A4* and/ or P-gp, unless the agent strongly inhibits both CYP3A4 and P-gp/ BCRP (*ABCG2*) as in ketoconazole or antiprotease inhibitors [13,30]. Rivaroxaban can be administrated in combination with moderate inhibitors of *CYP450* enzymes and p-gp [18]. This view is not shared by other studies, as shown later. The concomitant use of drugs such as rifampicin, carbamazepine, phenytoin, and possibly phenobarbital will cause strong induction of *CYP3A4*, which metabolizes rivaroxaban and apixaban and thus subsequently decrease their effects [9,15]. Drugs; azole antimycotics such as ketoconazole, fluconazole, clarithromycin, erythromycin and HIV protease inhibitors, such as ritonavir increase anticoagulant effects in rivaroxaban [9,15,22], Edoxaban is much less dependent on *CYP3A4* metabolism, but it is a substrate for the P-glycoprotein (P-gp) efflux transporter as other DOACs. Dabigatran is not metabolized via the *CYP3A4* pathway [22,31]. But both edoxaban and Dabigatran must be preceded with "lead-in" anticoagulation by UFH or LMWH before the initiation with dosage. Overexposure to rivaroxaban has been reported in a 65-year-old man in the form of hemoptysis, epistaxis, pulmonary hemorrhage and intracranial hemorrhage in the left frontal lobe, with bilateral frontal subarachnoid hemorrhage after starting clarithromycin while already taking rivaroxaban 20 mg/d, which was initiated for VTE prophylaxis four months prior to this clinical presentation [29]. Clarithromycin is a strong inhibitor of *CYP3A4* and P-glycoprotein [29]. The result of anti-factor Xa level, which was taken 33 hours after the last dose of rivaroxaban, was elevated (537 µg/L).

Medications used in cardiovascular diseases

Many patients are likely receiving other medications used for cardiovascular diseases when they are also using rivaroxaban. For example, one of the indications to use rivaroxaban in clinical practice is the prevention of stroke in

Table 1 Examples of Drugs That May Interact With Rivaroxaban

Drug	Mechanism	Effect	Action
Drugs used in	**Infections**		
Clarithromycin	A strong inhibitor of CYP3A4 only, but also reported possessing weak to moderate P-gp inhibitory potential [13]. Another publication reported it to be a moderate CYP3A4 and p-gp inhibitors [18]. Finally, another study reported that Clarithromycin was a strong inhibitor of both CYP3A4 and P-glycoprotein [29].	Overexposure to Rivaroxaban [29] Another study: clinical impact is not clearly defined [18]	There is a conflict in what is recommended. Coadministration is not recommended [29] while in another publication: it can be coadministered with rivaroxaban as their clinical impact is not clearly defined [18]. The online drug interaction checker provided in the text states that there is a potential for serious interaction. The author of this review suggests not to coadminister.
Erythromycin	Is a moderate CYP inhibitor and weak to moderate P-gp inhibitor [13]. Another publication reported it to be a moderate CYP3A4 and p-gp inhibitors [18].	Interactions were not considered clinically significant because they were similar in magnitude to the inter-individual variability expected for rivaroxaban in patients [13]. A different source indicated that it causes overexposure [29].	There is a conflict in what is recommended: Use with caution and monitor closely. A lower dose of rivaroxaban is advisable [29], while another publication states it can be coadministered with rivaroxaban as the clinical impact is not clearly defined [18]. The online drug interaction checker provided in the text states that significant interaction is possible. The author of this review suggests not to coadminister
Fluconazole	Is a strong inhibitor of CYP2C9 (rivaroxaban is not metabolized via CYP2C9), a moderate inhibitor of CYP3A4, and also reported potentially to inhibit BCRP (ABCG2) [13].		Use with caution and monitor closely. A lower dose of rivaroxaban is advisable [29], while another study suggested that it should be avoided [25].
Ketoconazole and ritonavir*	Strong inhibitors of CYP3A4/2J2, P-gp, and BCRP (ABCG2) [13].	Ketoconazole leads to an increase in exposure with a higher effect with a higher dose of ketoconazole (400 mg versus 200 mg) [13].	Do not prescribe [38].
Drug	**Mechanism**	**Effect**	**Action**
Drugs used	**In Cardiological**	**Diseases**	
Amiodarone	Amiodarone and its main metabolite *N*-desethylamiodarone (NDEA) inhibit CYP3A4 (irreversibly and reversibly) and P-gp [32].	Increase exposure of rivaroxaban	- Close monitoring. - Clinical cases of possible exposure have been reported [5,25,33]. - Decrease the dose to 10 mg rivaroxaban in the presence of mild or moderate Renal Impairment when coadministered both drugs [32].
Antiplatelets	Rivaroxaban pharmacokinetics were not altered to a clinically relevant extent by coadministration with platelet aggregation inhibitors	Both drugs have the potential to cause bleeding. Therefore the combination increases the incidence of bleeding [14].	- In acute coronary syndrome, they may be coadministered [15]. - One in four DOAC patients receiving DAPT (Dual antiplatelet therapy) presented with bleeding [14].
Atorvastatin	Is a substrate of CYP3A4/P-gp	Does not have significant interaction with rivaroxaban [13,25]	They could be coadministered [13,25]
Digoxin	A substrate for P-gp	Does not have significant interaction with rivaroxaban and might be considered safe [13,25]	They could be coadministered [13,25]
Drug	**Mechanism**	**Effect**	**Action**
Drugs	**used in Neurology**		
Carbamazepine	Is a strong inducer of CYP 3A4 isoenzymes and P-gp transporter [20].	Decrease the level of rivaroxaban, which causes an undercoagulable state.	Close monitoring [2]. Use warfarin with INR monitoring as an alternative for anticoagulation therapy [20].
Levetiracetam	A potential effect on P-gp activity (Induction)	Does not have significant interaction with rivaroxaban.	They could be co-administrated [2]. But again, the author states that an effect on CYP has not been shown but, since this AED may induce Pg-p activity, and is a substrate itself of this transporter, its safety in patients taking DOACs still needs to be demonstrated [2].

Midazolam	Is a substrate for CYP3A4 only [13].	Does not have significant interaction with rivaroxaban and vice-versa.	They could be coadministered [13].
Phenytoin	Is a combined strong CYP3A4 and P-gp inducer [31,20].	Decrease the level of rivaroxaban, which causes an undercoagulable state.	Close monitoring [31]. Coadministration should be avoided [2]. Use warfarin with INR monitoring as an alternative for anticoagulation therapy [2, 20].
Zonisamide	Is a weak inhibitor of P-gp *in vitro* study, but they do not significantly affect CYP3A4, CYP1A2, and CYP2D6 activity *in vitro* [2].	Does not have significant interaction with rivaroxaban	They could be coadministered [2].

Notes: **Ritonavir, is both an inducer as well as an inhibitor, which creates an unpredictable effect on CYP3A metabolism [26]. A table of AEDs Interactions and P-gp or CYP3A4/3A5 and CYP2J2 systems are provided by Galgani A et al. [2]. A table giving examples of drugs, scenarios, and suggested management is also provided by Fralick M et al. [29].

patients with atrial fibrillation, and it could be used as well in acute coronary syndrome. Therefore, it is highly likely that patients with these conditions are taking concomitant cardiovascular medications, such as digoxin and statins [13] (Table 1). Amiodarone and its main metabolite N-desethylamiodarone (NDEA) inhibit *CYP3A4* (irreversibly and reversibly) and P-gp [32]. Thus, amiodarone increases blood levels of rivaroxaban by altering drug metabolism [5,25,29]. Age and renal insufficiency produced clinically significant increases in rivaroxaban's exposure with amiodarone coadministration [32]. A study [32] which employed Physiologically-Based Pharmacokinetic (PBPK) modeling to simulate the prospective (DDIs) between rivaroxaban and amiodarone, found that the extent of DDI was not clinically significant despite there was an increase in systemic exposure of rivaroxaban (20 mg once daily, days 1 to 20) when coadministered with loading doses of amiodarone 200 mg three times daily (t.i.d.) (days 5 to 20) in healthy subjects [32]. Conversely, there was a clinically significant increase in rivaroxaban exposure when there were combined effects of amiodarone and mild and moderate Renal Impairment (RI) [32]. A revised rivaroxaban dose of 10 mg in the presence of coadministration of amiodarone and mild or moderate RI yielded comparable systemic exposures to those achieved at the therapeutic 20 mg dose in young [32]. With systematic PBPK-guided dose reduction of rivaroxaban in the presence of concomitant amiodarone, the extent of pharmacokinetic DDIs is minimized while anticoagulant efficacy is likely preserved [32]. Baig et al. [5] reported based on an assessment by Roussel Uclaf Causality Assessment Method (RUCAM) a probable occurrence of acute liver failure with rivaroxaban therapy, which was initiated for prevention of thromboembolism in an 89-year-old woman with a history of atrial fibrillation and biventricular congestive heart failure with a LVEF 25%. The patient's chronic amiodarone dose had been increased from 200 mg to 400 mg daily because of paroxysmal atrial fibrillation, suspected secondary to frequent mode switching noted on the pacemaker's reading before initiation with rivaroxaban. After 1-week therapy with rivaroxaban, she developed symptoms, signs, and biochemical findings of acute liver failure. The possibility of rivaroxaban-amiodarone interaction as a cause of acute liver failure in the reported cases could not be completely ruled out [5].

In a classic example, an 87-year-old man was reported to have developed a spontaneous cardiac tamponade due to a haemopericardium. The patient was already on rivaroxaban 20 mg daily as thromboprophylaxis due to paroxysmal atrial fibrillation. The patient was started on amiodarone 200 mg daily for four months prior to this acute admission and had a history of pulseless ventricular tachycardia with an implantable cardiac defibrillator *in situ* and non-ischemic cardiomyopathy [33]. A retrospective cohort study looked into the association between the use of at least 1 DOAC prescription of dabigatran, rivaroxaban, or apixaban for nonvalvular atrial fibrillation with and without concurrent medications and the risk of major bleeding in 91 330 patients from the Taiwan National Health Insurance database in the period (01.01.2012 – 31.12.2016 [25]. It found that there were rarely combinations between antifungals and DOACs, but that does not exclude the bleeding risk of such a combination [25]. The combination of the antiarrhythmic amiodarone was common in clinical practice, but this study observed that there was more bleeding incidence when this combination coexists and it was associated with an adjusted incidence rate difference for major bleeding of 13.94 events per 1000 person-years, which probably exceeds any benefit that such a combination could deliver [25]. In almost one-third of all hospital admissions, the combination of DOACs with antiplatelet drugs is quite common [14]. Rivaroxaban pharmacokinetics were not altered to a clinically relevant extent by coadministration with platelet aggregation inhibitors (e.g., clopidogrel), NSAIDs (e.g., aspirin or naproxen), but they do increase the incidence of bleeding; therefore caution is needed. In acute coronary syndrome, they may be coadministered [15]. A retrospective cohort study involving 772 in the UZ Brussel in 2016 showed that at least one in four DOAC patients receiving DAPT (Dual antiplatelet therapy) presented with bleeding [14].

Medications used in neurological disease

A history of stroke accounts for about 30-40% of acquired epilepsy in the elderly; therefore, the combined use of antiepileptic drugs and anticoagulants is common in clinical practice [2,31]. Phenobarbital, phenytoin, and carbamazepine are more likely to reduce the anticoagulant effect of DOACs (especially rivaroxaban, apixaban, and edoxaban) because the older Antiepileptic Drugs (AED)s most important pharmacokinetics involve cytochrome P450 (CYP) [2]. Carbamazepine, phenytoin, and phenobarbital are inducers of several cytochrome P450 (CYP) enzymes such as *CYP1A2, CYP2C9, CYP2C19, and CYP3A4*, but also of Uridine Diphosphate Glucuronosyltransferase (UGT) system and epoxide hydrolase [2]. Several clinical cases, which involve their coadministration, could be found within the same publication as a summary [2]. Becerra et al. [31] reported an interaction between phenytoin and rivaroxaban in a 48-year-old woman, who was admitted due to cerebral venous thrombosis, bilateral PE, and left lower limb DVT and was later operated for a low-grade gastrointestinal stromal tumor of the gut. She was receiving phenytoin 100 mg three times daily (t.i.d.), and the patient's anticoagulation therapy shifted from enoxaparin 60 mg twice daily (b.i.d.) to rivaroxaban 15 mg b.i.d on day 5. The First peak anti-Factor Xa was 70 ng/ml (reference value: 100–300 ng/ml), and a week later, the anti-Xa levels were 90 ng/ml. Due to concerns about thrombosis progression, the patient was switched to dabigatran [31]. The authors, therefore, suggested that either monitoring serum levels of DOACs or considering other therapeutic options [31]. Other similar clinical cases could be found within the same publication as a summary [31].

Newer AEDs have a limited enzyme-inducing potential compared with older-generation compounds, but some of them are involved in metabolic modifications. There are a few newer AEDs, which are neither affecting CYP nor P-gp significantly, such as lamotrigine, or pregabalin, thus could be used safely. Although the effects of Zonisamide on P-gp are not well-known, it does not significantly affect *CYP3A4, CYP1A2*, and *CYP2D6* activity *in vitro*; therefore, it could be coadministered. Levetiracetam exerts only a potential effect on P-gp activity, and thus it might be safe as well. A table of AEDs Interactions and P-gp or *CYP3A4/3A5* and *CYP2J2* systems is provided by Galgani et al. [2]. Carbamazepine (CZP) is a widely used anticonvulsant for the treatment of epilepsy, bipolar disorders, and trigeminal neuralgia [20]. Because of being a strong inducer of CYP 3A4 isoenzymes and P-gp transporter, it can reduce the plasma concentrations and efficacies of substrate drugs using these mechanisms [20]. Based on the previous, starting anticoagulants in patients using AED, especially phenytoin, carbamazepine, phenobarbital, or valproate, requires extra caution [2]. Also, the coexistence of polypharmacy or taking a combination of two or more of these AEDs at the same time due to pharmaco-resistant epilepsy further complicates predicting their effect on drug metabolism. Epileptic patients are also at a higher risk of bleeding due to traumatic injury. Also, the lack of widespread validated methods in measuring the *in vivo* antithrombotic effects of DOACs, and especially for those acting on factor Xa, makes the use of warfarin, and individual dose tailoring based on the INR values a reasonable choice to be considered [2,20].

Polymorphisms and genetic variations

Because of the favorable pharmacokinetics of the DOACs as compared

to VKA and LMWH, there is an increase in their prescription in clinical practice [18]. With more research being conducted, it shows that DOACs are affected by genetic variations [18].

Cytochrome 450: A total of 70-80% of all drugs in clinical use are biotransformed by enzymes belonging to the CYP1, 2, and 3 families [34]. The CYP3A subfamily is especially prominent in these metabolic activities. CYP3A4 is both the most abundant and the most versatile human drug-metabolizing enzyme because it contributes to the metabolism of one-half of all drugs in clinical use [26,35]. Therefore the cytochromes P450 (CYPs) constitute the major enzyme family in drug pharmacokinetics and are a major source of variability [34]. The effects of pharmacogenetics on Warfarin are well known. Genetic variation caused by nucleotide polymorphisms (SNPs) in *CYP2C9* and *VKORC1* genes can explain the inter-individual variability in plasma levels of warfarin that have been associated with bleeding episode. The best predictor of warfarin dose is the genotype of VKORC1 (Vitamin K Epoxide Reductase Complex Subunit 1) gene, which provides instructions for making a vitamin K epoxide reductase enzyme. This is responsible for the conversion of vitamin epoxide to vitamin K, and it accounts for 25% of the interindividual variation [9]. In regards to P450 type 2C9 (*CYP2C9*), which is responsible for the metabolism of warfarin, it accounts for 10% of the interindividual variation and three alleles are identifiable of P450 type 2C9 (CYP2C9); *CYP2C9*2* and *CYP2C9**3 are both poor metabolizers while the *1 allele is the wild type [9]. The frequency of such alleles has shown ethnic variation [9]. A reduction in the clearance of S-warfarin leading to overanticoagulation has been seen in the presence of genetic variants CYP2C9*2 and CYP2C9*3, while the presence of VKORC1 genetic variants 1639 G>A and 1172 C>T causes increased sensitivity to warfarin [18]. Clinical trials illustrating the clinical benefit of genotype-guided warfarin therapy has been conducted [18].

Not every identified genetic variation involving the genes that could be involved for rivaroxaban's pathways can lead to clinical significance. For example, *CYP2J2*7,* –76G>T (rs890293) results in decreased expression of this enzyme, but no conclusive clinical associations [34], *CYP3A4*1B*; –392A>G (rs2740574), probably has no effect on transcription but it is observed that it can increase prostate cancer disease progression, *CYP3A4*22*; 15389 C>T (rs35599367) results in decreased expression & activity and results in a decrease in the metabolism of simvastatin and increase the lipid-lowering response, it also decreases the daily-dose requirement for tacrolimus, an immunosuppressive drug that is used in organ transplant [34]. Gene function is based not only on DNA sequence but also on other heritable changes termed epigenetics come into play. Thus, potential contributors to the substantial variability in CYP3A activity may include genetic, environmental, pathological, hormonal, and dietary factors such as grapefruit [26]. Epigenetics affect gene regulatory mechanisms through DNA methylation, histone protein modification, and microRNAs (miRNAs). miR-27b, for example, showed direct regulation for *CYP1B1* and *CYP3A4* while miR-148a influenced CYP3A4 and CYP2B6 expression through the nuclear receptor, the xenosensor pregnane X receptor (PXR, NR1I2) [34]. Functional gene duplications are rare among CYPs 2J2, and 3A4, and the term "rapid metabolizer" should only be used in the context of phenotypic differences [34]. Higher clearance has been reported for several CYP3A4 drugs such as erythromycin, verapamil, cyclosporine in females [35]. The hormonal status, especially in an adult woman, is complex and further altered by contraceptive agents or hormone replacement therapy. The effect of the natural and the pharmacological hormonal environment of women on CYP3A activity, and the clearance of its substrates have not been well established [26]. Women can metabolize some drugs more quickly than men [34], especially those that are substrates of the major drug-metabolizing cytochrome P450, CYP3A4 [34,35]. In analyzing 94 surgical liver samples, it was found that female liver samples had a 2-fold higher *CYP3A4* levels than the male samples [35].

ABCB1 (P-gp)+ABCB2 (BCRP): Some of the inter-individual variability of DOACs can be attributed to the alteration of genetic variants of gene loci and drug-drug interactions [18]. Dabigatran is affected by Single Nucleotide Polymorphisms (SNPs) in CES1 and ABCB1 because they contribute to altering the drug's peak to levels of clinical significance [18]. SNPs in ABCB1 are implicated in the alteration of rivaroxaban plasma drug levels and apixaban [18]. ABCB1 encodes for P-gp and ABCG2 encodes for BCRP. The latter and the former are responsible for the active renal secretion of rivaroxaban [18,36]. The ABCB1 gene is located on chromosome 7 and is composed of 29 exons in a 251.3-kb genomic region [36]. The three most common SNPs in the coding region are rs1128503 (1236 C>T, Gly412Gly), rs2032582 (2677 G>T, Ala893Ser) and rs1045642 (3435 C > T, Ile1145Ile) [37]. They are in strong linkage disequilibrium and present a minor allelic frequency around 50% in the Caucasian population [37]. ABCB1 gene encodes the P-glycoprotein (P-gp), a 170 kDa transmembrane transporter, and exists in the xenobiotic barriers including the placenta, blood-brain barrier, and the blood-testis barrier, etc. [26,37] (Figure 2). As stated previously, the functionality of the P-gp depends on its histological location; presence in the hepatocyte enhances biliary excretion. In the brush border of proximal tubule cells it enhances renal excretion while it presence in the apical membrane of enterocytes it limits absorption [37] (Figure 2). rs2032582 (C.2677G>T) and rs1045642 (C.3435C>T) are among the 100 polymorphisms of ABCB1 that have been shown to affect rivaroxaban metabolism [18,36]. These 2 polymorphisms are frequently documented to exist as haplotypes, which if homozygous, the patient can have a higher plasma level of rivaroxaban and subsequent bleeding. Their frequencies could range from 2-90% across populations and they exhibit large interethnic differences [36].

The effects of Genetics were illustrated in a reported clinical case of a 79-year-old man who developed severe iron deficiency anemia, which subsequently led to STEMI [36]. This anemia was probably because of chronic gastrointestinal bleeding secondary to overexposure of rivaroxaban given at 20 mg PO. This patient had a genotype of TT for the c.2677G>T Single Nucleotide Polymorphism (SNP) and TT for the c.3435C>T SNP. Also, CYP3A4/5 phenotyping showed moderately decreased enzymatic activity [36]. These combined genetic changes led to the estimated half-life of rivaroxaban increasing by threefold in the reported patient [36]. However, this explanation was contradicted by the work done by Sennesael et al. [37] who concluded that the ABCB1 1236 C > T-2677G > T-3435C > T and 1199 G > A SNPs had no significant influence on the intracellular accumulation of rivaroxaban when compared to the wild-type protein [37]. But, their work confirmed the role of ABCB1 in transporting the drug. They [37] attributed the finding found by Ing et al. [36] to being coincidental because of the relatively high frequency of the homozygous genotype because it is expected that up to 25% of the population of Caucasian origin is 2677-3435TT [37]. In addition, the simvastatin received by the patient could be attributed to the finding because it inhibits CYP3A4 enzyme and the ABCB1 and ABCG2 transporters. Finally, this patient was presented with moderate renal impairment [37]. The impact of inhibition of ABCB1 alone could not have a high significance because rivaroxaban is also substrate for the ABCG2 transporter, known as protein (BCRP), and the cytochrome P450 (CYP) 3A4/3A5 enzyme. The active renal secretion by ABCB1 and ABCG2 accounts for 30% [37] while the hepatic transformation by *CYP3A4/3A5* accounts for 18% of total drug elimination [37].

How to Detect Rivaroxaban?

Laboratory assessment of Rivaroxaban

Rivaroxaban is a factor Xa inhibitor, therefore, the PT/international normalized ratio [INR] for VKA and activated Partial Thromboplastin Time (PTT) for heparin could not be used for monitoring exposure or overdose of rivaroxaban [6] (Figure 1). The anti-Factor Xa chromogenic assays (with the use of rivaroxaban calibrators and controls) are proposed to be able to measure the entire range after therapeutic dosing and results are expressed as rivaroxaban concentration (μg/l) [6]. The normal trough level of anti-factor Xa, typically measured 24 hours after drug administration, ranges from 8 to 150 μg/L [29]. There are many practical limitations of this assay in clinical practice, such as the measured concentration is a quantitative measurement and does not assess the qualitative anticoagulation activity of the rivaroxaban. In a normal renal clearance, the rivaroxaban's concentration will be high in the period 2-4 hours after drug administration compared with 12-24 hours after dosing [5,6,15]. Furthermore, the test is not routinely available at most clinical centers [6,7]. If a qualitative assessment of rivaroxaban's presence is needed, the PT test is suitable, provided that a rivaroxaban-sensitive reagent is used [6,7,15]. Prothrombin Time (PT) is a blood test that measures how long it takes

blood to clot. Normal PT can indicate intact hemostatic function. Excessive rivaroxaban may cause PT prolongation as seen in the case reported by Wu et al. [7], and the case reported as a summary by Horn J and Hansten P [38] which reported a patient on HIV medication; etravirine, ritonavir, darunavir, raltegravir, and tenofovir/ emtricitabine developed thigh swelling with anemia and hypotension after 24 hours from initiating rivaroxaban 10 mg daily following a total hip replacement. Elevated rivaroxaban plasma concentration was also confirmed [38]. Limitations of this are that the rivaroxaban has a minimal effect at 24 hours post-dosing on PT. PT is not specific for Factor Xa and can be influenced by other disease conditions, such as some types of cancers, Hodgkin's disease, and liver disease [6]. Moderate hepatic impairment also leads to a moderate increase in inhibition of factor Xa activity and prolongation of PT [15]. Registering the time of drug administration and blood sampling time is necessary for PT and anti-Factor Xa assays [6].

Thromboelastography (TEG) Test and Rivaroxaban

TEG is a method designed to monitor and analyze the entire coagulation process in real-time, and some parameters can be obtained within 10 minutes [39]. The benefits of viscoelastic testing are that it is rapid and uses reliable techniques, which can guide hemostatic therapy in bleeding patients, such as in major heart and liver transplant surgeries, or cases of acute bleeding caused by trauma or Postpartum Hemorrhage (PPH) [39]. Using TEG as guidance can reduce the transfusion of platelets and/or RBCs and/or plasma [39]. Also, it enables individualized therapy by targeting the actual deficiencies of each patient [39]. Therefore, it is of use in assessing the coagulation status of stroke patients and monitoring patients with congenital bleeding disorders [39]. TEG, therefore, can decrease the hospital stay; reduce complications and costs [39]. The R-value in the TEG test identifies the time needed for a clot formation to start. Therefore it reflects the coagulation factor activity. Thus, a prolonged R time should be treated with plasma. In a study assessing the effect of DOAC by using the TEG®6s, the R-value demonstrated a significant correlation with DOAC concentrations. Also, the R-value had enough sensitivity and specificity to detect low DOAC concentrations. Therefore, this can be potentially used in presurgical patients receiving DOAC, including situations prior to cardioconversion or radiofrequency ablation procedures [40]. But this study was limited in terms that the R-value was measured only 3-time points over 3 hours rather than more time points over 12 to 24 hours and only on nine healthy young males [40]. This study reflected that DOACs primarily affect the whole blood clotting time [40].

Discussion

Rivaroxaban is being used for six different indications, and more physicians are prescribing it, but real-world data of patients with diverse demographics and clinical characteristics using DOACs are still needed. Because of the increased incidence of the concomitant use of rivaroxaban with medications used in cardiovascular and neurological diseases, and infections, understanding the Drug-Drug Interaction (DDI) of this type of polypharmacy is very important. The author shares the conclusion of Oladiran et al. [33] in that most physicians are aware of adjusting rivaroxaban's dose in renal impairment, but there is still a need to increase awareness of rivaroxaban's interactions with drugs that share its pathways where the hepatic *CYP450* and/or P-gp/BCRP are involved. By receiving a clinical course focusing on DOACs for anticoagulation therapy or direct clinical training within a short-term Anticoagulation Team (ACT) stewardship program can physicians, including primary care physicians, could be more educated with regards to the adequate prescription of rivaroxaban/DOAC. It is also possible to use an online drug checker in daily practice to identify interactions and suggestions if internet services are available. The provided online drug checker has been used by the author also to check the drugs written in the table within this review. Therefore the author does suggest a possible use of this application or any available validated application for this purpose.

https://www.webmd.com/interaction-checker/default.htm

Consulting a pharmacist and/or a physician who specializes in this field can also be an alternative if available. In our center, patients who start on Anticoagulation Therapy (ACT) generally should be seen within the first month of ACT at the anticoagulation therapy clinic of our hospital. Then these patients, unless they require closer monitoring of their ACT, should be seen again in the third month of their ACT, if it is a DOAC, at their own General Practitioner (GP). The follow up after that, if it is a DOAC, should be done by their GP once every year. The author suggests that a more frequent follow up for those patients who are elderly and/or have polypharmacy could be warranted to ensure compliance, doses, and check for DDI when taking DOACs. The previously reported patient [1] was assessed to be compliant and was receiving an accurate dose of 20 mg for the treatment of a previously PE at the time of presentation with no other medications. TEG test was not done, and anti-Factor Xa chromogenic assays are unavailable in the center. On a consented follow-up, the tests for both thrombophilia and Antiphospholipid Syndrome (APS) were negative, and she was not under investigation for cancer because of a lack of clinical suspicion. Is it possible that this patient is a “rapid metabolizer”? Because the patient has a female gender, which according to Wolbold et al. [35] a female exhibits 2-fold higher *CYP3A4* levels in the liver, or maybe she has rare functional gene duplications in CYPs 2J2, or 3A4. The patient being a rapid metabolizer is a valid question.

Conclusion

In conclusion, whether the pharmacokinetics and or/ pharmacogenetics involved in rivaroxaban pathways have created a state of decreased anticoagulation and “rivaroxaban failure” is a question that remains unfortunately unanswered. Clinical cases involving drug-rivaroxaban interactions, which resulted in overexposure with subsequent bleeding, or recurrent VTE while in a fully anticoagulated rivaroxaban/DOAC dose, have begun to appear in the literature. However, only through reporting more clinical cases in different contexts, is it possible to obtain enough online data. This data can be used for research analysis, provide more input to the guidelines, and subsequently improve clinical practice when prescribing rivaroxaban/DOACs. There are currently few studies looking into the pharmacogenetics involved in rivaroxaban pathways. Therefore more studies exploring these aspects are warranted. Finally, there is a need to identify a validated method for measuring rivaroxaban in primary care. The absence of such a test can affect clinical decision and management, as seen in the case reported by Fralick et al. Could the TEG test in a patient taking rivaroxaban be used effectively to indicate that the patient is on proper anticoagulation therapy and exclude a state of decreased anticoagulation? This question is intriguing and does warrant a study

Acknowledgement

The author thanks the two anonymous reviewers for their careful reading of the manuscript and insightful suggestions. The author also thanks Haider A. Al-Khafaji for drawing Figure 2 in this review and free of charge.

Funding

This presented review is a non-commercial review. Neither funding nor financial support have been provided for neither researching this review nor its publication. It represents the scientific and clinical interests of the author.

Ethics

The summary of the clinical case provided and cited in this review is from a previously published work, which the patient’s oral consent for that publication of the case details was witnessed by documenting it in the patient’s official electronic system.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Rasha A Al-Khafaji and Louise Schierbeck. “Deep Venous Thrombosis in a Patient with a Moderate Pretest Probability and a Negative D-Dimer Test: A Review of the Diagnostic Algorithms.” *J Blood Med* 11 (2020): 173-184.
2. Alessandro Galgani, Caterina Palleria, Luigi Francesco Iannone and Giovambattista De Sarro, et al. “Pharmacokinetic Interactions of Clinical Interest between Direct Oral Anticoagulants and Antiepileptic Drugs.” *Front Neurol* 9 (2018): 01.
3. Elisabeth Perzborn, Susanne Roehrig, Alexander Straub and Dagmar Kubitza, et al. “The Discovery and Development of Rivaroxaban, an Oral, Direct Factor Xa Inhibitor.” *Nat Rev Drug Disc* 10 (2010): 61-75.
4. Sue, Wakelin. "Primary-Care Overprescribing of Rivaroxaban in Patients without Atrial Fibrillation.” *Clin Pharmacist* 10 (2018): 01.
5. Muhammad Baig, KennethJ Wool, JewellH Halanych and RehanA Sarmad. “Acute Liver Failure after Initiation of Rivaroxaban: A Case Report and Review of the Literature.” *North Am J Med Sci* 7 (2015): 407.
6. Meyer Samama, Geneviève Contant, Theodore E Spiro and Elisabeth Perzborn, et al. “Laboratory Assessment of Rivaroxaban: A Review.” *Thrombosis J* 11 (2013): 11.
7. Hai-Di Wu, Hong-Yan Cao, Zi-Kai Song and Shuo Yang, et al. “Considerations for Routine Coagulation Monitoring with Rivaroxaban: A Case Report and Review of the Literature.” *World J Clin Case* 7 (2019): 382-388.
8. Sosipatros, Bratsos. “Pharmacokinetic Properties of Rivaroxaban in Healthy Human Subjects.” *Cureus* 11 (2019): 5484.
9. Nishank Jain and Robert F. Reilly. “Clinical Pharmacology of Oral Anticoagulants in Patients with Kidney Disease.” *Clin J Am Soc Nephrol* 14 (2018): 278-287.
10. Madan Raj Aryal, Rohit Gosain, Anthony Donato, Han Yu, et al. “Systematic Review and Meta-analysis of the Efficacy and Safety of Apixaban Compared to Rivaroxaban in Acute VTE in the Real World.” *Blood Adv* 3 (2013): 2381-2387.
11. Adam Cuker, Deborah M. Siegal, Mark A. Crowther and David A. Garcia. “Laboratory Measurement of the Anticoagulant Activity of the Non–Vitamin K Oral Anticoagulants.” *J Am College Cardiol* 64 (2014): 1128-1139.
12. Hiroaki Shimokawa, Takeshi Yamashita, Shinichiro Uchiyama and Takanari Kitazono, et al. “The Expand Study: Efficacy and Safety of Rivaroxaban in Japanese Patients with Non-valvular Atrial Fibrillation.” *Int J Cardiol* 258 (2018): 126-132.
13. Wolfgang Mueck, Dagmar Kubitza and Michael Becka. “Co-administration of Rivaroxaban with Drugs that Share its Elimination Pathways: Pharmacokinetic Effects in Healthy Subjects.” *Brit J Clin Pharmacol* 76 (2013): 455-466.
14. Souad Moudallel, Stephane Steurbaut, Pieter Cornu and Alain Dupont. “Appropriateness of DOAC Prescribing before and during Hospital Admission and Analysis of Determinants for Inappropriate Prescribing.” *Front Pharmacol* 9 (2018): 1.
15. Celeste B. Burness and Caroline M. Perry. “Rivaroxaban: A Review of Its Use in the Treatment of Deep Vein Thrombosis or Pulmonary Embolism and the Prevention of Recurrent Venous Thromboembolism.” *Drugs* 74 (2014): 243-262.
16. Zi-Kai Song, Hongyan Cao, Haidi Wu and Qi Wei, et al. “Current Status of Rivaroxaban in Elderly Patients with Pulmonary Embolism (Review).” *Exp Therapeut Med* 26 (2020): 2817-2825.
17. Kakkos Sant, Kirkilesis Gaun and Tsolakis Iiner. “Editor's Choice-Efficacy and Safety of the New Oral Anticoagulants Dabigatran, Rivaroxaban, Apixaban, and Edoxaban in the Treatment and Secondary Prevention of Venous Thromboembolism: A Systematic Review and Meta-analysis of Phase III Trials.” *Euro J Vasc Endovasc Surg* 48 (2014): 565-575.
18. Sri H. Kanuri and Rolf P. Kreutz. “Pharmacogenomics of Novel Direct Oral Anticoagulants: Newly Identified Genes and Genetic Variants.” *J Personalized Med* 9 (2019): 7.
19. Alex C. Spyropoulos, Walter Ageno, Gregory W. Albers and Gregory C. Elliott, et al. “Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness.” *New Eng J Med* 379 (2018): 1118-1127.
20. Hadley Bortz, Carmela E. Corallo and Huyen Tran. “Increasing Understanding Regarding the Risk of Concomitant Use of Carbamazepine and Direct Oral Anticoagulants.” *J Pharm Pract* 32 (2018): 123-125.
21. Martin, Kevin. “Use of the Direct Oral Anticoagulants in Obese Patients: Guidance from the SSC of the ISTH.” *J Thrombo Haemost* 14 (2016): 1308-1313.
22. Carrier Marc and Blais Nion. “Treatment Algorithm in Cancer-associated Thrombosis: Canadian Expert Consensus.” *Curr Oncol* 25 (2018): 329-337.
23. Tittl Luise and Endig Sandra. “Impact of BMI on Clinical Outcomes of NOAC Therapy in Daily Care: Results of the Prospective Dresden NOAC Registry (NCT01588119).” *Int J Cardiol* 262: 85-91.
24. Alex C. Spyropoulos, Veronica Ashton, Yen-Wen Chen and Bingcao Wu, et al. “Rivaroxaban *versus* Warfarin Treatment among Morbidly Obese Patients with Venous Thromboembolism: Comparative Effectiveness, Safety, and Costs.” *Thrombo Res* 182 (2018): 159-166.
25. Shang-Hung Chang, I-Jun Chou, Yung-Hsin Yeh and Meng-Jiun Chiou, et al. “Association between Use of Non-Vitamin K Oral Anticoagulants with and without Concurrent Medications and Risk of Major Bleeding in Nonvalvular Atrial Fibrillation.” *JAMA* 318 (2017): 1250.
26. Cotreau Monette, Von Moltke Lisa and Greenblatt David. “The Influence of Age and Sex on the Clearance of Cytochrome P450 3A Substrates.” *Clin Pharmacokinet* 44 (2005): 33-60.
27. Marc A. Rodger, Sebastien Miranda, Aurelien Delluc and Marc Carrier. “Management of Suspected and Confirmed Recurrent Venous Thrombosis while on Anticoagulant Therapy.” *Thrombo Res* 180 (2005): 105-109.
28. Leah B. Hatfield, Mark L. Plaster and Zaffer M Qasim. “Recurrent VTE despite Anticoagulation.” *J Thrombosis Haemost* 7 (2017): 01.
29. Michael Fralick, David N. Juurlink and Theodore Marras. “Bleeding associated with Coadministration of Rivaroxaban and Clarithromycin.” *Canadian Med Ass J* 188 (2016): 669-672.
30. Sam, Schulman. “How I Treat Recurrent Venous Thromboembolism in Patients Receiving Anticoagulant Therapy.” *Blood* 129 (2017): 3285-3293.
31. Ana F. Becerra, Tomas Amuchastegui and Aldo H. Tabares. “Decreased Rivaroxaban Levels in a Patient with Cerebral Vein Thrombosis Receiving Phenytoin.” *Case Rep Hematol* 2017 (2017): 1-3.
32. Eleanor Jing Yi Cheong, Janice Jia Ni Goh, Yanjun Hong and Pipin Kojodjojo, et al. “Rivaroxaban with and without Amiodarone in Renal Impairment.” *J Am Coll Cardiol* 71 (2018): 1395-1397.
33. Oreoluwa Oladiran, Jared Segal, Ifeanyi Nwosu and Salik Nazir. “A Rare Case of Spontaneous Cardiac Tamponade Induced by Concomitant Use of Rivaroxaban and Amiodarone.” *Case Rep Cardiol* 2018 (2018): 1-4.
34. Ulrich M. Zanger and Matthias Schwab. “Cytochrome P450 Enzymes in Drug Metabolism: Regulation of Gene Expression, Enzyme Activities, and Impact of Genetic Variation.” *Pharmacol Therapeut* 138 (2018): 103-141.
35. Renzo Wolbold, Kathrin Klein, Oliver Burk and Andreas K. Nüssler, et al. “Sex is a Major Determinant of CYP3A4 Expression in Human Liver.” *Hepatol* 38 (2003): 978-988.

36. Kuntheavy Ing Lorenzini, Youssef Daali, Pierre Fontana and Jules Desmeules, et al. "Rivaroxaban-Induced Hemorrhage Associated with ABCB1 Genetic Defect." *Front Pharmacol* 7 (2016): 01.

37. Anne-Laure Sennesael, Nadtha Panin, Christelle Vancraeynest, Lionel Pochet, et al. "Effect of ABCB1 Genetic Polymorphisms on the Transport of Rivaroxaban in HEK293 Recombinant Cell Lines." *Sci Rep* 8 (2018): 1.

38. John R. Horn and Philip D. Hansten. "The Dangers of Drug Interactions with Doacs." *Pharm Times* 2017: 01.

39. João D. Dias, Angela Sauaia, Hardean E. Achneck, Jan Hartmann, et al. "Thromboelastography-guided Therapy Improves Patient Blood Management and Certain Clinical Outcomes in Elective Cardiac and Liver Surgery and Emergency Resuscitation: A Systematic Review and Analysis." *J Thromb Haemost* 17 (2019): 984-994.

40. Ramin Artang, Maren Anderson and Jorn D. Nielsen. "Fully Automated Thromboelastograph TEG 6s to Measure Anticoagulant Effects of Direct Oral Anticoagulants in Healthy Male Volunteers." *Res Pract Thromb Haemost* 3 (2019): 391-396.

How to cite this article: Rasha A Al-Khafaji. "Developing Deep Venous Thrombosis while on Rivaroxaban: A Review of Rivaroxaban." Clin Case Rep 10 (2020): 1365. DOI:10.37421/jccr.2020.10.1365