DOI: https://doi.org/10.2298/SARH200116063A
UDC: 616.14-005.6/.7-089.168; 615.273

REVIEW ARTICLE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Prevention of venous thromboembolism with rivaroxaban and apixaban in orthopedic surgery

Nebojša Antonijević[1,2], Vladimir Kanjuh[1,3], Ivana Živković[2], Ljubica Jovanović[2], Miodrag Vukčević[1,4], Milan Apostolović[1,5]

[1]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[2]Clinical Center of Serbia, Clinic for Cardiology, Belgrade, Serbia;
[3]Serbian Academy of Science and Arts, Committee on Cardiovascular Pathology, Belgrade, Serbia;
[4]Zemun Clinical Hospital Centre, Belgrade, Serbia;
[5]Banjica Institute for Orthopedic Surgery, Belgrade, Serbia

SUMMARY

Numerous limitations and side effects of standard anticoagulants require administering new anticoagulant drugs. New peroral anticoagulants of Factor Xa inhibitor group have more advantages, the key ones being: substantial reductions in specific nutrition limitations and drug interaction, no need for routine laboratory monitoring and greatly improved therapy predictability. Rivaroxaban, a selective peroral Factor Xa inhibitor is more effective compared with enoxaparin for venous thromboembolism (VTE) prophylaxis in major orthopedic interventions. Though several single trials demonstrated no difference in hemorrhagic complications, certain meta-analyses with rivaroxaban showed a higher incidence of hemorrhage. Apixaban, a peroral reversible inhibitor of factor Xa approved for the prevention of VTE, compared with European-approved doses of enoxaparin has the efficacy almost equal to the North-American-approved enoxaparin doses without a significant difference in bleeding rates, though ADVANCE I study points towards lower bleeding rates in patients treated with apixaban.

To clarify the contradictory results of the recent meta-analysis related to the comparison between the stated factor X inhibitors and various comparator enoxaparin regimens as well as related to the risk for symptomatic PTE and total bleeding events following major orthopedic surgery, new research will be required. Specificities of rivaroxaban and apixaban, already constituting, according to modern recommendations, an integral part of the VTE prophylaxis protocols after major orthopedic interventions, will enable the establishment of personalized protocols aimed at developing an improved safety profile of each individual patient.

Keywords: prevention; venous thromboembolism; rivaroxaban; apixaban

INTRODUCTION

Prevention of venous thromboembolism (VTE) as a common denominator of deep vein thrombosis (DVT) and/or pulmonary thromboembolism (PTE) as a significant cause of vascular mortality, posttromboflebitis syndrome, chronic thromboembolic pulmonary hypertension, recurrent VTE has great medical, social, and economic significance [1–4]. Like unfractionated heparin (UFH) low molecular weight heparins (LMWH) reduce the risk of VTE at least 60% compared to patients without thromboprophylaxis, but are not convenient for outpatients as they require subcutaneous administration [5, 6]. The incidence of heparin thrombocytopenia, as a serious adverse effect of the applied anticoagulant therapy, is approximately 3–5% in patients treated with UFH in orthopedic surgery and about 0.9% in patients treated with LMWH [7–12].

Oral anticoagulant therapy with vitamin K antagonists (VKA) has many limitations: unpredictability of action, narrow therapeutic window, delayed onset of action, postponed action after discontinuation of therapy, numerous interactions with food and drugs, variable therapeutic effects, and a relatively small percentage of patients in the predicted therapeutic range [13].

The use of heparin anticoagulants is also restricted by the necessity of parenteral administration, the risk of heparin thrombocytopenia with possible potentially endangering thromboses and osteoporosis [14].

In spite of the use of standard, recommended prophylactic anticoagulant regimens with low doses of UFH as well as LMWH, warfarin or recombinant hirudin, the incidence of DVT, confirmed by venography, still ranges 16–30% [15].

Factor X is a well-targeted place for the action of anticoagulant drugs and the primary site of coagulation cascade amplification being positioned at the point of convergence of the external and internal coagulation pathway (Scheme 1) [16, 17]. Direct Xa factor inhibitors such as rivaroxaban and apixaban are not dependent on antithrombin and do not inhibit only the free factor Xa but also factor Xa bound to the complex of prothrombinase on the platelet membrane, and therefore have more advantages even in relation to indirect Factor Xa inhibitors such as fondaparinux and LMWH [16, 18].

Received • Примљено: January 16, 2020
Accepted • Прихваћено: August 17, 2020
Online first: September 9, 2020

Correspondence to:
Nebojša ANTONIJEVIĆ
Pasterova 2
11000 Belgrade, Serbia
drantoni@gmail.com

RIVAROXABAN

Pharmacotherapy group and Anatomical Therapeutic Chemical classification

Rivaroxaban belongs to the B01AF subgroup of direct factor Xa inhibitors within the B01A group of antithrombotic drugs [19].

A brief history of the drug

The synthesis of rivaroxaban was achieved under the program "Factor Xa" launched in 1998 by Bayer [20]. In the group of new direct factor Xa inhibitors, rivaroxaban was firstly approved for clinical use in the prevention of VTE in adults undergoing total knee replacement (TKR) and total hip replacement (THR) in 2008 in the EU and Canada [20]. The Food and Drug Administration (FDA) approved rivaroxaban for the prevention of DVT in patients undergoing TKR and THR in 2011 [20].

Pharmacodynamics

Mechanism of action

Rivaroxaban is a highly selective, direct Xa factor inhibitor with oral bioavailability. Rivaroxaban blocks the free factor Xa and the clot connected factor Xa as well as the activity of the prothrombinase complex [18]. The inhibition of factor Xa interrupts the intrinsic and extrinsic cascade pathway of blood coagulation, preventing the formation and development of thrombus. Rivaroxaban does not inhibit thrombin and has no effect on platelets.

Pharmacokinetics

Rivaroxaban causes dose-dependent inhibition of factor Xa and achieves its maximum effect after 1–4 hours following administration [2]. Bioavailability is high, 80–100%.

Due to reduced absorption of rivaroxaban in the distal gastrointestinal tract, the administration of the drug distal to the stomach is avoided [21]. The presence of food delays, the time until the maximum concentration of the drug (T_{max}) is reached and increases the maximum drug concentration (C_{max}) and the area under the curve (AUC) at a dose > 10 mg [22].

Distribution of rivaroxaban is achieved by binding to albumin in 92–95%, and the volume of distribution is 50 liters [21]. The drug cannot be eliminated by hemodialysis due to a high degree of binding to plasma proteins [18].

Biotransformation and elimination: two thirds of the applied drug undergo metabolic degradation, with renal and fecal elimination equally. A third of the administered dose is excreted unchanged in urine following active renal secretion [21].

Metabolism of rivaroxaban is mediated by CYP3A4/5 and CYP2J2 isoenzymes and CYP-independent mechanisms. Rivaroxaban is a substrate for P-glycoprotein (P-gp) [21].

After oral administration the half-life of the drug is 5–9 hours in the young, and 11–13 hours in the elderly [21].

Interactions

The bioavailability of rivaroxaban is increased with the concomitant use of CYP3A4/P-gp inhibitors, such as ketoconazole or HIV protease inhibitors (e.i. ritonavir), which may cause higher concentrations of rivaroxaban and hemorrhage and the concomitant administration of these drugs may be considered contraindicated. Concomitant use of strong CYP 3A4 inducers such as rifampicin, carbamazapine, phenytoin, St. John's Wort can significantly decrease the concentration of rivaroxaban and reduce its anticoagulant effects [21, 22, 23].

Clinical pharmacology

Dosing and indications

Elective TKR and THR require the administration of 10 mg daily rivaroxaban for the primary prevention of VTE. The initial dose is taken 6–10 hours after surgery. Recommended thromboprophylaxis duration is five weeks for THR and two weeks for TKR [21].

Efficacy

In Regulation of **C**oagulation in Orthopedic Surgery to Prevent DeepVenous Thrombosis and Pulmonary Embolism (RECORD) I–III trials, rivaroxaban dose of 10 mg once daily was compared to enoxaparin in a single daily dose of 40 mg, while in the RECORD IV trial enoxaparin at a dose of 30 mg twice daily was administered [24]. The occurrence of DVT, symptomatic or venographically proven asymptomatic, non-fatal PTE and all-cause mortality were registered as the primary efficacy outcome, while the occurrence of major bleeding was monitored as the primary safety outcome.

In the RECORD I, non-inferiority/superiority study examining a group of 4591 patients with THR and treated with the anticoagulants 35 days, it was demonstrated within the primary efficacy outcome that the listed adverse events were registered at significantly lower degree in patients treated with rivaroxaban 10 mg compared to enoxaparin at a dose of 40 mg once daily (1.1% *vs*. 3.7%, $p < 0.001$) [24, 25]. Major episodes of VTE were also lower in the group of patients treated with rivaroxaban compared to enoxaparin (0.2% *vs*. 2.0%, $p < 0.001$). The incidence of major bleeding did not significantly differ between groups (0.3% and 0.1% respectively).

In RECORD II, superiority trial, performed on 2551 patients after THR, rivaroxaban at a dose of 10 mg was administered for 31–39 days, and enoxaparin for 10–14 days. Primary efficacy outcome was revealed in 2% of treated patients with rivaroxaban compared to 9.3% treated with enoxaparin ($p < 0.0001$), without significant difference in bleeding [24, 25].

In the RECORD III, non-inferiority/superiority trial, 2531 patients undergoing TKR were randomized to

thromboprophylaxis with rivaroxaban at a dose of 10 mg once daily and enoxaparin at a dose of 40 mg once daily subcutaneously for 10–14 days in both groups. Within the primary efficacy outcome, significantly lower incidence of adverse events in patients treated with rivaroxaban compared to those treated with enoxaparin (9.6% *vs*. 18.9%, $p < 0.001$) was shown, with comparable rates of significant bleeding [24, 25].

In the RECORD IV randomized non-inferiority/superiority study, which examined 3148 patients after TKR, unlike RECORD III study, the active comparator enoxaparin was administered in the dosage regimen of 30 mg twice daily. The primary efficacy outcome was registered in 6.9% of patients treated with rivaroxaban, as opposed to 10.1% of those treated with enoxaparin ($p = 0.012$), without significant difference in the incidence of major bleeding (0.7% *vs*. 0.3%, respectively) [24, 25].Briefly, single daily oral administration of rivaroxaban was more effective than enoxaparin in North American and European doses in the prevention of VTE after major orthopedic interventions [25].

For orthopedic patients who will not be operated having various forms of immobilizations, the results of the MAGELLAN and MARINER trials are of clinical importance [26, 27]. In the MAGELLAN study with hospitalized medically ill patients, rivaroxaban 10 mg daily was non-inferior to enoxaparin 40 mg daily, while rivaroxaban during 35 days was superior to enoxaparin (administered for 10 days) for the prevention of VTE [26]. In the MARINER study with medically ill patients at increased risk for VTE, after discharge thromboprophylaxis with rivaroxaban 10 mg daily resulted in lower incidence of non-fatal VTE compared to placebo (0.18% *vs*. 0.42%; HR 0.44; 95% CI, 0.22–0.89). Composite of symptomatic VTE or VTE-related death and major bleeding rates were comparable between rivaroxaban and placebo [27]. FDA approved rivaroxaban 10 mg once daily in acutely ill, hospitalized patients at increased risk of VTE, but not at high risk of bleeding [28].

Safety of rivaroxaban administration

Cumulative analysis of all four RECORD studies registered a greater incidence of significant ("major") and clinically relevant ("non-major") bleeding in the rivaroxaban treated group compared to enoxaparin [24]. In RECORD trials calculation of bleeding did not include bleeding from the site of surgery, although it may contribute to major bleeding, wound infection, and the need for reoperation [23, 24].

Rivaroxaban was demonstrated to be more effective than enoxaparin, but with a significantly higher rate of major and clinically relevant "non-major" bleeding [25]. By reviewing 89 publications, rivaroxaban was found to be non-inferior to enoxaparin in thromboprophylaxis after major orthopedic surgery [18]. A meta-analysis of eight randomized clinical studies with 15,596 patients after elective hip and knee surgery showed that patients treated with rivaroxaban had a lower rate of VTE and a lower overall mortality by 44% (RR 0.56; 95% CI 0.39–0.80) compared to enoxaparin. However, prophylaxis with rivaroxaban caused an increased risk of major bleeding by 65% (RR 1.65; 95% CI 0.93–2.93) and clinically relevant bleeding by 21% (RR 1.21; 95% CI 0.98–1.5), which was not statistically significant [29].

Contraindications for the use of rivaroxaban are the following: hypersensitivity to the active substance, clinically significant active bleeding, liver disease associated with coagulopathy and clinically significant bleeding risk, renal insufficiency defined by creatinine clearance < 15 ml/min, concomitant therapy with anticoagulant drugs, pregnancy and lactation [21, 24].

APIXABAN

Pharmacotherapy group and Anatomical Therapeutic Chemical classification

Apixaban belongs to the B01AF subgroup of direct factor Xa inhibitors within the B01A group of antithrombotic drugs [19].

A brief history of the drug

Since 2007, the synthesis of apixaban has been achieved in collaboration with Bristol-Myers Squibb and Pfizer [30]. It has been approved in Europe since 2012 for the prevention of VTE after THR and TKR. The FDA approved apixaban to reduce the risk of thrombosis after THR and TKR in 2014.

Pharmacodynamics

Mechanism of action of the drug

Apixaban is an oral, selective, reversible, direct factor Xa inhibitor that blocks the central protease of the coagulation pathway of factor X, common for the intrinsic and extrinsic pathway of the coagulation cascade. Apixaban inactivates the free factor Xa, the clot-connected factor Xa and prothrombinase complex, responsible for the conversion of prothrombin into thrombin, thereby reducing the formation of thrombin, but not affecting the existing levels of thrombin [31]. Apixaban incompletely inhibits thrombin production by reversibly binding to factor Xa, allowing the formation of a small amount of thrombin needed for the physiological regulation of haemostasis. Consequently, apixaban has a lower risk of bleeding compared with direct thrombin inhibitors [31].

Pharmacokinetics

After oral administration, the maximum concentration of apixaban is achieved after 3–4 hours, and stable concentrations are expected on the third day. Absolute bioavailability is around 50% for doses up to 10 mg [32]. Food intake does not affect AUC or C_{max} of apixaban at a dose of 10 mg, thus the drug can be administred regardless of the meal [32].

Apixaban is 87% bound to plasma proteins, and the volume of distribution is 21 L (Table 1) [32].

Table 1. Pharmacokinetic characteristics of new anticoagulant drugs

Characteristics	RIVAROXABAN	APIXABAN
Absorption	High bioavailability 80–100%	Medium bioavailability 50%
Half-life	5–9 h*/11–13 h**	12 h (8–15 h)
Renal elimination	33%	27%
Hepatic elimination	67%	73%

*generally in young healthy individuals
**generally in the elderly

It is eliminated by multiple pathways (urinary in 27%, non-renal pathways in 73%, mainly fecal and by bile) [32]. The drug metabolism is mediated by CYP3A4/5 and partly via CYP1A2, 2C8, 2C9, 2C19, and 2J2 isoenzymes [32]. The total clearance is 3.3 L/h and the half-life is 12 hours [32].

Intereactions

Multiple elimination pathways suggest that the potential for the interaction of apixaban and other drugs is relatively low [31]. The concomitant use of potent CYP3A4 and P-gp inhibitors, such as azole antimycotics (e.i. ketoconazole, itraconazole, etc.) and HIV protease inhibitors (e.i. ritonavir) are not recommended, while inducers such as phenytoin, carbamazepine, phenobarbital and St. John's wort can be used with increased caution because they decrease the plasma concentration of apixaban and reduce its effect [31].

Clinical pharmacology

Dosage and indications

Apixaban is indicated for primary VTE prophylaxis after THR and TKR at a dose of 2.5 mg twice a day, with a first dose intake 12–24 hours after surgery. The recommended therapy after THR is 32–38 days, and after TKR 10–14 days [32].

Efficacy

ADVANCE-I (Apixaban Dose Orally *vs*. ANtiCoagulation with Enoxaparin), a randomized non-inferiority study performed in 3195 patients after TKR, compared the administration of apixaban at a dose of 2.5 mg twice daily to enoxaparin 30 mg twice a day during 10–14 days. The incidence of total VTE and all-cause mortality (primary efficacy outcome) was comparable in both investigated groups with a similar frequency (9% *vs*. 8.8%) [24, 25].

In the ADVANCE II randomized non-inferiority study involving 3057 patients after TKR apixaban at a dose of 2.5 mg twice daily (initiated 12–24 hours after surgery) was compared to enoxaparin in European doses, 40 mg once daily (introduced 12 hours preoperatively). The primary efficacy outcome (total VTE and all-cause mortality) was observed at a significantly lower rate in patients treated with apixaban compared to enoxaparin (15.1% *vs*. 24.4%, p = 0.001, respectively).

In ADVANCE III study, prophylaxis of VTE in patients undergoing THR, primary outcome was registered in 1.4% of patients treated with apixaban and 3.9% treated with enoxaparin in European doses of 40 mg daily (p < 0.001) [33].

Concerning the previous studies on the efficacy of apixaban in the prevention of VTE, one can conclude that the superiority and comparable safety profile of apixaban versus European doses of enoxaparin (40 mg once daily) was demonstrated, but apixaban was not effective enough compared to the North American doses of enoxaparin (30 mg twice daily) [25]. Efficacy of apixaban at a dose of 2.5 mg twice daily in the prevention od VTE in patients undergoing THR and TKR in ADVANCE II and ADVANCE III were not followed by significant increase in the degree of major and clinically relevant bleeding [34].

The results of the meta-analysis of Gómez-Outes et al. [35], indicated that rivaroxaban had a significantly lower risk of symptomatic VTE compared to enoxaparin (RR 0.48; 95% CI; 0.31–0.75; p = 0.001); compared to insignificant decrease with apixaban (RR 0.82; 95% CI; 0.41–1.64; p = 0.57) and dabigatran (RR 0.71; 95% CI; 0.23–2.12, p = 0.54), with more frequent clinically relevant bleeding with rivaroxaban (RR 1.25; 95% CI 1.05–1.49, p = 0.01) and dabigatran, but less often with apixaban (RR 0.82; 95% CI; 0.69–0.98; p = 0.03). Another meta-analysis with 20 studies and 38,507 patients demonstrated a risk of total VTE significantly lower with apixaban (RR 0.62; 95% CI; 0.47–0.81, p = 0.001) and rivaroxaban (RR 0.7; 95% CI 0.6–0.81, p < 0.001) compared to enoxaparin [36].

Risk of VTE and total mortality is significantly reduced by both rivaroxaban (RR 0.56; 95% CI 0.39–0.80, p = 0.002), and apixaban (RR 0.63; 95% CI 0.42–0.95; p = 0.03) [35]. When data obtained for total symptomatic VTE were analyzed separately for symptomatic DVT and pulmonary embolism, both rivaroxaban (RR 0.4; 95% CI 0.22–0.72; p = 0.002) and apixaban (RR 0.41; 95% CI 0.18–0.95; p = 0.04) significantly reduced the risk of DVT [35].

In the meta-analysis of Gómez-Outes et al. [35], apixaban significantly increased the risk of symptomatic PTE following knee arthroplasty compared to enoxaparin (RR 2.56, 95% CI 1.1–5.98; p = 0.03), unlike rivaroxaban showing an insignificant trend in the reduction of symptomatic PTE (RR 0.89; 95% CI 0.3–2.67, p = 0.84). However, meta-analysis of Ma et al. [37] on six randomized studies with 13,790 patients pointed out that there was no significant difference in the incidence of PTE after knee arthroplasty between apixaban and enoxaparin, (RR 2.0; 95% CI, 0.97–4.12, p = 0.06) as well as between apixaban and enoxaparin in larger North American prophylactic doses of 30mg b.i.d. (RR 1.65; 95% CI, 0.77–3.54, p = 0.2). In addition, the same meta-analysis did not find significant difference between rivaroxaban and enoxaparin in the incidence of pulmonary embolism [37].

Safety profile of apixaban

The rate of all-bleeding and major bleeding of ADVANCE-I, was lower in patients treated with apixaban compared to

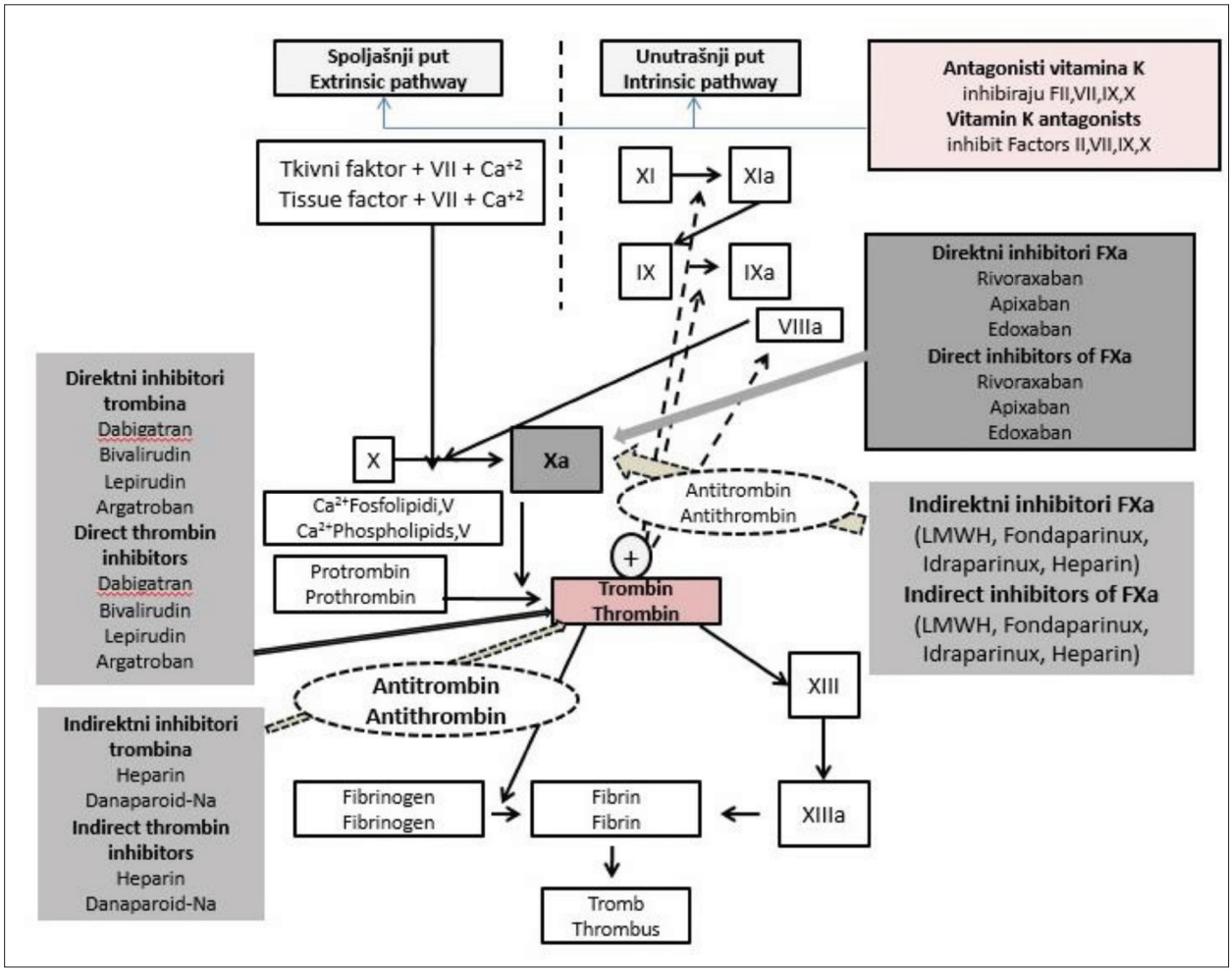

Figure 1. The mechanism of action of anticoagulant drugs

enoxaparin, with the difference even becoming significant for composite of major and clinically relevant non-major bleeding (2.9% *vs.* 4.3%, p = 0.03) [24, 25].

ADVANCE II and ADVANCE III study showed a comparable rate of bleeding in the group treated with apixaban and enoxaparin, also in the case of significant bleeding [23, 33].

The duration of prophylaxis with apixaban was consistent with guidelines, 32–38 days after hip surgery and 10–14 days after knee surgery [33].

When compared to enoxaparin administered at a dose of 30 mg b.i.d. subcutaneously and commenced 12–24 hours after surgery, in patients with elective hip operation in ADVANCE I study, apixaban showed that it did not meet the criteria of non-inferiority compared to enoxaparin but that it had a lower rate of bleeding [32]. ADVANCE trials with apixaban included bleeding from the site of the surgical incision [25].

The results of comparison between apixaban 2.5 mg b.i.d. for 30 days and enoxaparin 40 mg q.d. for 6–14 days in thromboprophylaxis of non-surgical patients (ADOPT study – Apixaban Dosing to Optimize Protection from Thrombosis), indicated that there was no statistically significant difference in the rate of symptomatic DVT but showed significantly higher degree of major bleeding in apixaban group [38].

When major and non-major clinically relevant bleeding in patients treated with apixaban and enoxaparin are analyzed separately, only trends towards fewer bleeding in patients treated with apixaban are observed [38]. In comparison with enoxaparin, the risk of significant major or clinically relevant non-major bleeding is higher with rivaroxaban (RR 1.52; 95% CI; 1.14–2.02, p = 0.004), while comparable bleeding rates with apixaban and enoxaparin were demonstrated after arthroplastic surgery [36, 39].

Apixaban is contraindicated in patients with allergy to apixaban and substances present in the form of a final drug, those with severe hepatic impairment followed by coagulopathy and clinically relevant bleeding risk, and clinically significant active bleeding [32, 33]. Apixaban is not recommended in severe renal insufficiency with creatinine clearance < 15 ml/min. Caution is advised in patients with creatinine clearance of 15–30 ml/min [33].

The advantages of rivaroxaban and apixaban over other drugs from the same Anatomical Therapeutic Chemical group

Oral administration is the advantage of rivaroxaban and apixaban compared with indirect factor Xa inhibitors (fondaparinux, LMWH and UFH) requiring parenteral administration [31]. A lower number of interactions with drugs and foods, the absence of the need for routine laboratory monitoring and a more stable and predictable therapeutic effect have advantages over VKA [13, 32]. Direct inhibitors directly bind to the catalytic site of factor Xa (rivaroxaban and apixaban), while indirect inhibitors (fondaparinux, LMWH, and idraparinux) bind to antithrombin and potentiate antithrombin mediated anti-Xa activity [31].

Section from the guidelines for the prevention of vte with focus on Rivaroxaban and apixaban

In addition to the previously known drugs (i.e. VKA, LMWH), apixaban, dabigatran, rivaroxaban and fondaparinux are recommended for patients undergoing elective knee arthroplasty at least 10–14 days and for elective hip artoplasty 35 days optimally, according to American College of Chest Physicians guidelines, Thrombosis Canada and National Institute for Health and Care Excellence guidelines [23, 40, 41].

The development of anticoagulant drugs of higher quality enables, depending on the characteristics of the patients and the particular pharmacokinetic properties of each drug, better therapy individualization than before the appearance of new anticoagulants. The most important pharmacokinetic characteristics of these new anticoagulant drugs are provided in Table 1 [21, 32, 42, 43].

In the event of moderate bleeding caused by the use of apixaban and rivaroxaban, local hemostasis measures and standard general hemorrhage measures with supstitution of certain blood products are taken. In case of a life-threatening bleeding for patients treated with rivaroxaban and apixaban, andexanat alfa, a first-in-class recombinant modified factor Xa protein, has been approved in Europe and the USA for reversal of anticoagulant activity [44, 45]. Currently, the use of andexanet alfa is limited due to the availability and cost. Prothrombin complex concentrate, activated prothrombin complex concentrate, and recombinant activated factor VIIa may be also administered [45].

CONCLUSION

In conclusion, rivaroxaban, a selective oral factor Xa inhibitor, is more effective than enoxaparin administered in both of the mentioned regimens in VTE prophylaxis in major orthopedic interventions. Although some studies state that there is no difference in the incidence of hemorrhagic complications, certain meta-analyses have shown a greater incidence of haemorrhage with rivaroxaban. Apixaban, an oral reversible factor Xa inhibitor, has proved more effective in the prevention of VTE compared to European doses of enoxaparin, and almost as effective as North American doses. No significant differences in bleeding rates have been identified, although one study (ADVANCE I) indicates a lower incidence of bleeding in those treated with apixaban [24].

New research is required in order to clarify the contradictory results of certain statistical analyzes in recent meta-analyses comparing the mentioned factor X inhibitors and the different regimens of comparator enoxaparin, related to the risk of symptomatic PTE and overall bleeding after major orthopedic surgeries [35, 36, 37].

It remains a challenge for future studies and clinical practice to determine the place of factor Xa inhibitors, rivaroxaban and apixaban in the prophylaxis of VTE, to define undoubted benefits and to remedy their deficiencies, bearing in mind the pharmaco-economic aspect and the unavoidable social dimension of VTE as one of the leading causes of mortality and morbidity in the world.

NOTE

This paper is an integral part of the project: Research of pathological and morphological lesions of: congenital and acquired heart diseases (and their pulmonary circulation), myocardium and coronary blood vessels, Department of Medical Sciences of the Serbian Academy of Sciences and Arts and the project 173008 from 2011: "Complex diseases as a model system for research the modulation phenotype-structural analysis of molecular biomarkers" under the auspices of the Ministry of Science of the Republic of Serbia.

Conflict of interest: None declared.

REFERENCES

1. Dahl OE. New oral antithrombotics: focus on dabigatran, an oral, reversible direct thrombin inhibitor for the prevention and treatment of venous and arterial thromboembolic disorders. Vascular Health and Risk Management. 2012;8:45–57.
2. Fisher WD. Impact of venous thromboembolism on clinical management and therapy after hip and knee arthroplasty. Can J Surg. 2011;54(5):344–51.
3. Mitić-Milikić M, Vukčević M. Current views on the diagnosis of pulmonary thromboembolism. Vojnosan Pregled. 2004;61(2):187–91.
4. Stevanović M, Apostolović M, Stojsavljević J, Vučković V, Krneta O. Intraoperativne i postoperativne komplikacije pri ugradnji totalne endoproteze kuka. Acta Orthopaedica Iugoslavica. 1998;39(2):161–4.
5. Hunt BJ. The prevention of hospital – acquired venous thromboembolism. Br J Haematol. 2009;144(5):642–52.
6. Huisman MV, Quinlan DJ, Dahl OE, Schulman S. Enoxaparin versus dabigatran or rivaroxaban for thromboprophylaxis after hip or knee arthroplasty: Results of separate pooled analyses of phase III multicenter randomized trials. Circ Cardiovasc Qual Outcomes. 2010;3(6):652–60.
7. Antonijević NM, Radovanović N, Obradović S, Vucelić D, Stojanović B, Miković D, et al. Obstacles in the diagnostics and therapy of heparin-induced thrombocytopenia. Srp Arh Celok Lek. 2010;138 Suppl 1:69–73.
8. Antonijevic NM, Milosevic R, Perunicic J, Stanojevic M, Calija B, Vasiljevic Z. Need for more intensive treatment of patients with acute pulmonary embolism caused by heparin- induced thrombocytopaenia Type II. Eur Heart J. 2005;26(24):2745–6.

9. Antonijević N, Stanojević M, Perunicić J, Djokić M, Miković D, Kovac M, et al. Thrombocytopenia induced by type II heparin and myocardial infarction: 2 case reports. Srp Arh Celok Lek. 2004;132(1–2):33–7.
10. Antonijević N, Stanojević M, Milosević R, Miković D, KovacM, Terzić B, et al. Heparin-induced type II thrombocytopenia--new views on diagnosis and therapy. Med Pregl. 2003;56(5–6):247–50.
11. Antonijević NM, Jovanović L, Djordjević V, Zivković I, Vukcević M, Apostolović M, et al. Contemporary approach to primary prophylaxis of venous thromboembolism regarding the impact of risk factors on anticoagulation therapy duration. Srp Arh Celok Lek. 2014;142(3–4):249–56.
12. Antonijevic N, Stanojevic M, Milosevic R, Djordjevic V, Jaukovic M, Vukcevic V, et al. Combined thrombophilic risk factors and essential thrombocythemia in patient with recurrent venous thromboembolic episodes-thirty-three-year follow-up. J Thromb Thrombolysis. 2005;19(2):93–5.
13. Hull R. Oral Antithrombotic Inhibitors: Dabigatran Etexilate, Meeting an Unmet Need? Clin Appl Thromb Hemost. 2009;15 Suppl 1:5S–8S.
14. Gray E, Mulloy B, Barrowcliffe TW. Heparin and low-molecular-weight heparin. Thromb Haemost. 2008;99(5):807–18.
15. Lassen MR, Bauer KA, Eriksson BI, Turpie AG. Eur Pentasaccharide Elective Surgery Study (EPHESUS) Steering Committee. Postoperative fondaparinux versus preoperative enoxaparin for prevention of venous thromboembolism in elective hip replacement surgery: a randomized double-blind comparison. Lancet. 2002;359(9319):1715–20.
16. Eikelboom JW, Weitz JI. New anticoagulants. Circulation. 2010;121(13):1523–32.
17. Sasaki H, Ishida K, Shibanuma N, Tei K, Tateishi H, Toda A, et al. Retrospective comparison of three thromboprophylaxis agents, edoxaban, fondaparinux, and enoxaparin, for preventing venous thromboembolism in total knee arthroplasty. Int Orthop. 2014;38(3):525–9.
18. Thomas TF, Ganetsky V, Spinler SA. Rivaroxaban: an oral factor Xa inhibitor. Clin Ther. 2013;35(1):4–27.
19. Guidelines for ATC classification and DDD assignment 2013. Available from: http://www.whocc.no/filearchive/publications/1_2013guidelines.pdf
20. Misselwitz F, Berkowitz SD, Perzborn E. The discovery and development of rivaroxaban. Ann N Y Acad Sci. 2011;1222:64–75.
21. Summary of Product Characteristics – Xarelto®. Bayer plc. Available from: https://www.medicines.org.uk/emc/product/6402/smpc on 20/08/2018. [last updated 18 July 2018]
22. Kubitza D, Becka M, Zuehlsdorf M, Mueck W. Effect of food, an antacid, and the H2 antagonist ranitidine on the absorption of BAY 59-7939 (rivaroxaban), an oral, direct factor Xa inhibitor, in healthy subjects. J Clin Pharmacol. 2006;46(5):549–58.
23. NICE Clinical Guidline Issue date March 2018 (National Institute For Health and Clinical Exellence) London; www. nice.org.uk; 2018;1–43.
24. Ufer M. Comparative efficacy and safety of the novel oral anticoagulants dabigatran, rivaroxaban and apixaban in preclinical and clinical development. Thromb Haemost. 2010;103(3):572–85.
25. Huisman MV. The proof for new oral anticoagulants: clinical trial evidence. Eur Orthop Traumatol. 2011;2(1–2):7–14.
26. Cohen AT, Spiro TE, Büller HR, Haskell L, Hu D, Hull R, et al. Rivaroxaban for thromboprophylaxis in acutely ill medical patients. N Engl J Med. 2013;368(6):513–23.
27. Spyropoulos AC, Ageno W, Albers GW, Elliott CG, Halperin JL, Hiatt WR, et al. Rivaroxaban for Thromboprophylaxis after Hospitalization for Medical Illness. N Engl J Med. 2018;379(12):1118–27.
28. Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202439s029lbl.pdf (2019, accessed 31 December 2019).
29. Cao YB, Zhang JD, Shen H, Jiang YY. Rivaroxaban versus enoxaparin for thromboprophylaxis after total hip or knee arthroplasty: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol. 2010;66(11):1099–108.
30. Hanna MS, Mohan P, Knabb R, Gupta E, Frost C, Lawrence JH. Development of apixaban: a novel anticoagulant for prevention of stroke in patients with atrial fibrillation. Ann N Y Acad Sci. 2014;1329(1):93–106.
31. Kim S. Apixabane: A new oral direct Xa infibitor. PharmaNote. 2012;27(4):1–9.
32. Summary of Product Characteristics – Eliquis®, Bristol-Myers Squibb-Pfizer. Available from: https://www.medicines.org.uk/emc/product/4756/smpc on 20/08/2018. [last updated 16 August 2018]
33. RADAR NPS (Rational Assessment of Drug and Research). Available from: http://www.nps.org.au/health_professionals/publications/nps_radar/2012/january_2012.
34. Eriksson BI, Bauer KA, Lassen MR, Turpie AG; Steering Committee of the Pentasaccharide in Hip-Fracture Surgery Study. Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after hip-fracture surgery. N Engl J Med. 2001;345(18):1298–304.
35. Gómez-Outes A, Terleira-Fernández AI, Suárez-Gea ML, Vargas-Castrillón E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. BMJ. 2012;344:e3675.
36. Feng W, Wu K, Liu Z, Kong G, Deng Z, Chen S, et al. Oral direct factor Xa inhibitor versus enoxaparin for thromboprophylaxis after hip or knee arthroplasty: Systemic review, traditional meta-analysis, dose-response meta-analysis and network meta-analysis. Thromb Res. 2015;136(6):1133–44.
37. Ma G, Zhang R, Wu X, Wang D, Ying K. Direct factor Xa inhibitors (rivaroxaban and apixaban) versus enoxaparin for the prevention of venous thromboembolism after total knee replacement: A meta-analysis of 6 randomized clinical trials. Thromb Res. 2015;135(5):816–22.
38. Goldhaber SZ, Leizorovicz A, Kakkar AK, Haas SK, Merli G, Knabb RM, et al. ADOPT Trial Investigators. Apixaban versus enoxaparin for thromboprophylaxis in medically ill patients. N Engl J Med. 2011;365(23):2167–77.
39. Yu Z, Shan P, Yang X, Lou XJ. Comparison of efficiency and safety of rivaroxaban, apixaban and enoxaparin for thromboprophylaxis after arthroplastic surgery: a meta-analysis. Biosci Rep. 2018;38(6):BSR20180423.
40. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149(2):315–52.
41. THROMBOPROPHYLAXIS: ORTHOPEDIC SURGERY. http://thrombosiscanada.ca/wp-content (2018, accessed December 2019)
42. Arixtra: EPAR – product information. Available from: www.ema.europa.eu
43. Pradaxa: EPAR – product information. Available from: www.ema.europa.eu
44. Heo Y. Andexanet Alfa: First Global Approval. Drugs. 2018;78(10):1049–55.
45. Galliazzo S, Donadini MP, Ageno W. Antidotes for the direct oral anticoagulants: What news? Thromb Res. 2018;164 Suppl 1:S119–23.

Превенција венског тромбоемболизма ривароксабаном и апиксабаном у ортопедској хирургији

Небојша Антонијевић[1,2], Владимир Кањух[1,3], Ивана Живковић[2], Љубица Јовановић[2], Миодраг Вукчевић[1,4], Милан Апостоловић[1,5]

[1]Универзитет у Београду, Медицински факултет, Београд, Србија;
[2]Клинички центар Србије, Клиника за кардиологију, Београд, Србија;
[3]Српска академија наука и уметности, Одбор за кардиоваскуларну патологију, Београд, Србија;
[4]Клиничко-болнички центар Земун, Београд, Србија;
[5]Институт за ортопедску хирургију „Бањица", Београд, Србија;

САЖЕТАК

Бројна ограничења и нежељена дејства стандардних антикоагулантних лекова намећу потребу за применом нових антикоагулантних лекова. Перорални антикоагулантни лекови из групе инхибитора фактора *Xa* имају више предности, од којих су најважније непостојање посебних ограничења у исхрани, значајно мањи број интерреакција са лековима, рутинска примена без посебног лабораторијског мониторинга, стабилнији и предиктабилнији терапијски ефекат. Ривароксабан, селективни перорални инхибитор фактора *Xa*, ефикаснији је од еноксапарина у профилакси венског тромбоемболизма при великим ортопедским интервенцијама. И поред тога што поједине студије наводе да нема разлике у настанку хеморагијских компликација, одређене метаанализе са ривароксабаном показале су већу учесталост хеморагија. Апиксабан, перорални реверзибилни инхибитор фактора *Xa*, показао се ефикаснијим у превенцији венског тромбоемболизма у односу на европске дозе еноксапарина, а готово је подједнако ефикасан као северноамеричке дозе. Нису утврђене значајније разлике у степену крварења, мада студија *ADVANCE-I* указује на мању учесталост крварења код оних лечених апиксабаном. Ради разјашњења контрадикторних резултата у новијим метаанализама у односу на поређење наведених инхибитора фактора *X* и различитих режима компаратора еноксапарина, као и у односу на ризик за симптоматски плућни тромбоемболизам и укупна крварења после великих ортопедских операција, биће неопходна нова истраживања. Специфичности ривароксабана и апиксабана, који према савременим препорукама већ чине саставни део протокола профилаксе венског тромбоемболизма у великим ортопедским интервенцијама, омогућиће успостављање персонализованих протокола како би се успоставио бољи сигурносни профил код сваког болесника.

Кључне речи: превенција; венски тромбоемболизам; ривароксабан; апиксабан