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The role of new oral anticoagulants in orthopaedics: an update of recent evidence

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Abstract Rivaroxaban, dabigatran, apixaban and edoxaban are the four available new oral anticoagulants (NOAC) which are currently approved for venous thromboembolism prophylaxis after total hip and knee replacement. Large phase 3 and phase 4 studies comparing NOAC with low molecular weight heparins have shown similar results regarding the efficacy and safety of these two categories of anticoagulants. Management of bleeding complications is a matter of great significance. Three reversal agents have been developed: idarucizumab, andexanet alfa and ciraparantag. Idarucizumab is now commercially available. Regarding the perioperative management of NOAC, two main scientific groups have published their own recommendations. The European Heart Rhythm Association recommends 48-h period of stoppage preoperatively for factor Xa inhibitors and at least 3 or 4 days for dabigatran, while the French Study Group on Thrombosis and Haemostasis recommends 5-day discontinuation for all NOAC. Conventional clot tests can only be used as rough indicators for laboratory assessment of the activity of NOAC. Specific laboratory tests have been developed for more accurate measurements of NOAC blood levels, including a dilute thrombin time test (Hemoclot test) and the ecarin clot test for dabigatran and chromogenic anti-factor Xa assays for direct factor Xa inhibitors. Due to the beneficial properties of NOAC, these drugs are gaining ground in daily orthopaedic practice, and many studies are being conducted in order to extend the indications of these anticoagulants agents.

Keywords New oral anticoagulants · Orthopaedics · Reversal agents · Laboratory assessment · Perioperative management

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Background

Venous thromboembolism (VTE), including both deep vein thrombosis (DVT) and pulmonary embolism (PE), is a serious and life-threatening complication after major orthopaedic surgeries. Without VTE prophylaxis, the incidence of symptomatic VTE after major orthopaedic surgery is considered to be up to 4.3% in the first 35 postoperative days [1, 2]. It is estimated that in 2030, the annual number of performed total hip arthroplasties (THA) and total knee arthroplasties (TKA) will be 570,000 and 3.48 million, respectively [3]. These huge numbers emphasize the need for new, simple and effective methods of thromboprophylaxis.

The traditional anticoagulants which are used for the prevention of VTE in orthopaedics include unfractioned heparin (UFH), low molecular weight heparins (LMWH), vitamin K antagonists (VKA) and aspirin. In 2005, a new

synthetic pentasaccharide factor Xa inhibitor called fondaparinux was approved for the prevention of VTE after major orthopaedic procedures. Despite the wide use of all these agents, each one of them has certain disadvantages. VKA, for example, have a delayed onset of action and a narrow therapeutic window; LMWH are administrated subcutaneously, and they may result in HIT (heparin-induced thrombocytopenia); and fondaparinux is not recommended for patients <50 kg and >75 years [4–6]. All these disadvantages lead to low compliance of patients and orthopaedic surgeons with the recommended thromboprophylaxis guidelines.

During the last decade, a growing trend for the use of new anticoagulants has been evolved. The new oral anticoagulants (NOAC) intervene in the cascade of coagulation and inhibit its pathways through two different mechanisms (Fig. 1). Currently, the use of these new anticoagulants comes with some scepticism, mainly about their safety.

The three oral anticoagulants which are mainly used in orthopaedics today are rivaroxaban, dabigatran and apixaban. Recently, three phase 3 trials regarding the use of a fourth oral anticoagulant called edoxaban after THA, TKA and hip fracture surgeries have been published [7–9]. Rivaroxaban, apixaban and edoxaban are direct factor Xa inhibitors, while dabigatran is a direct thrombin inhibitor (Table 1). Rivaroxaban and apixaban are approved by the European Medicines Agency (EMA) and by the US Food and Drug Administration (FDA) for thromboprophylaxis after TKA and THA, while dabigatran has not been approved in USA yet. Edoxaban has been approved in Japan since 2011 for the prevention of VTE following major orthopaedic procedures, but not yet in USA and Europe.

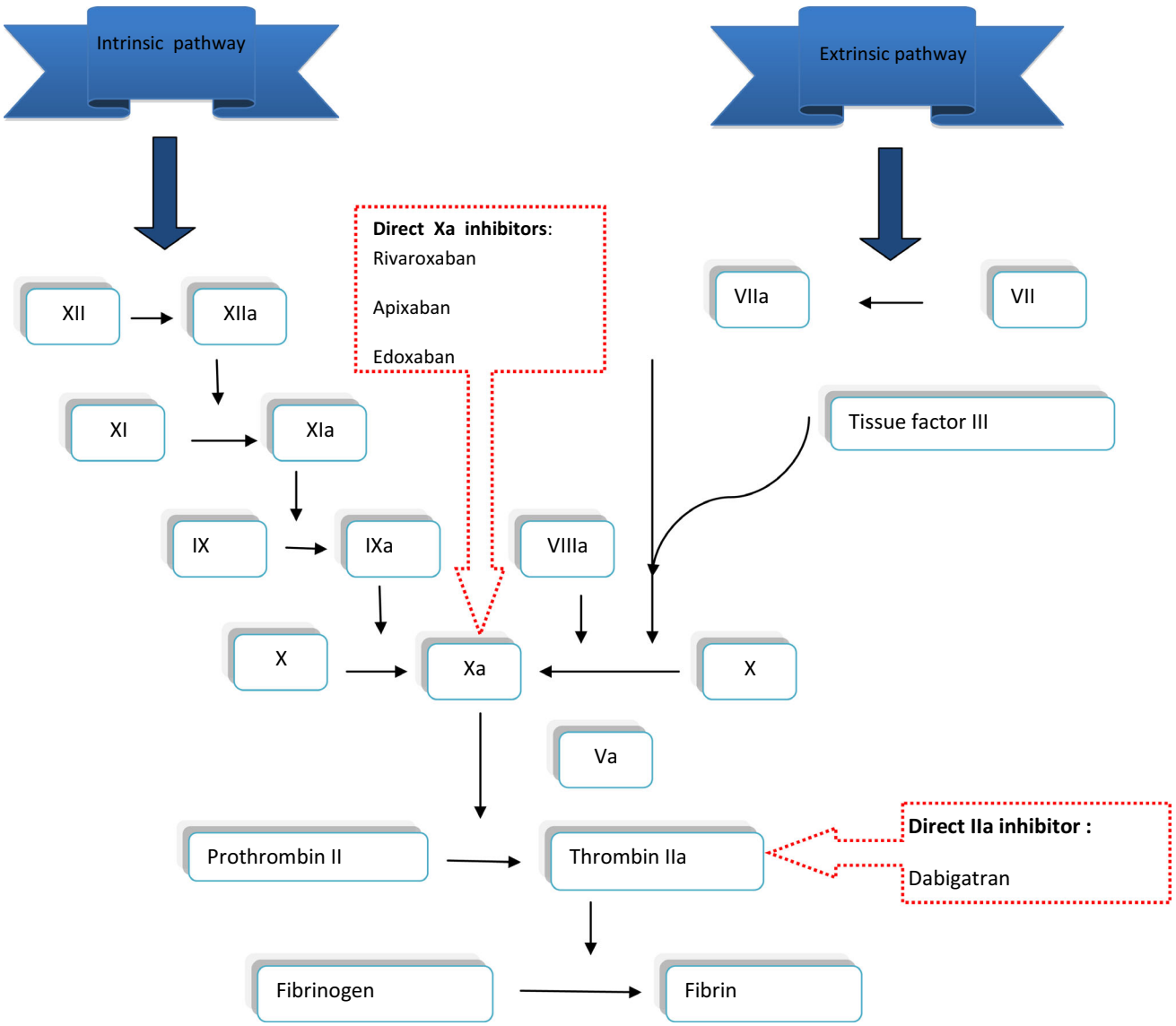

Fig. 1 Anticoagulation mechanism of action of NOAC

Table 1 Chemical and pharmacological properties of direct oral anticoagulants

NOAC	Rivaroxaban	Dabigatran	Apixaban	Edoxaban
Target molecule	Xa	IIa	Xa	Xa
Dosage	10 mg × 1	220 mg × 1 (150 mg CrCl 30–50 ml/min)	2.5 mg × 2	30 mg × 1
1st dose postoperatively	6–10 h 10 mg	1–4 h 110 mg (75 mg CrCl 30–50 ml/min)	12–24 h 2.5 mg	6–24 h 30 mg
Bioavailability	80%	6%	50%	60%
$T_{1/2}$ (h)	9–13	12–14	8–15	9–11
Renal excretion	66%	80%	25%	35%
Drug interactions	Inhibitors and inducers CYP3A4, P-gp	Inhibitors and inducers P-gp	Inhibitors and inducers CYP3A4, P-gp	Inhibitors and inducers P-gp

NOAC are now included in clinical practice guidelines for thromboprophylaxis after orthopaedic surgeries by several scientific organizations such as the American College of Chest Physicians (ACCP), the American Academy of Orthopaedic Surgeons (AAOS), the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN) and the Australian National Health and Medical Research Council (NHMRC), though these recommendations mainly refer to prophylaxis after hip and knee replacement [1, 10–13] (Table 2).

Main text

Rivaroxaban

Rivaroxaban, a direct factor Xa inhibitor, is one of the new oral anticoagulants approved by FDA in 2011 and also by EMA in 2008 for the prevention of VTE after THA and TKA in a dose of 10 mg, 6–10 h postoperatively after cautious haemostasis has been obtained.

Intestinal transport of rivaroxaban is carried out through a transporter protein, called P-glycoprotein (P-gp), and is metabolized in liver by cytochrome P450 enzymes (CYP3A4/5 and CYP2J2). Approximately 66% of the drug is renally excreted (about 36% of which is excreted as intact product), and the rest is excreted through faeces as unchanged product[14]. Rivaroxaban reaches peak concentration in blood and has its maximum anti-factor Xa action (20–80%) 2–3 h after administration, and its half-life elimination time is 9–13 h [14–17]. Use of rivaroxaban in patients with CrCl < 30 ml/min (severe renal impairment) has not been studied, while in patients with mild or moderate renal insufficiency, its use is not contraindicated. Rivaroxaban is also contraindicated in patients suffering from moderate to severe hepatic insufficiency which results

Table 2 Current thromboprophylaxis guidelines including NOAC

Guidelines	Total knee arthroplasty		Total hip arthroplasty	
	NOAC	Duration	NOAC	Duration
ACCP	Rivaroxaban Dabigatran Apixaban	10–14 days*	Rivaroxaban Dabigatran Apixaban	10–14 days*
AAOS	Unable to recommend specific anticoagulants instead of others	Duration must be individualized but at east for 10 days	Unable to recommend specific anticoagulants instead of others	Duration must be individualized but at east for 10 days
NICE	Rivaroxaban Dabigatran Apixaban	10–14 days	Rivaroxaban Dabigatran Apixaban	28–35 days
SIGN	Rivaroxaban Dabigatran	The ideal duration is not established	Rivaroxaban Dabigatran	The ideal duration is not established
NHMRC	Rivaroxaban Dabigatran	Until 14 days	Rivaroxaban Dabigatran	Until 35 days

* It is recommended to extend duration of thromboprophylaxis up to 35 days

in higher concentration levels, and consequently in higher prolongation of PT.

In general, rivaroxaban does not interact with other, widely used drugs. No drug–drug interaction has been observed in co-administration with aspirin, naproxen, digoxin, atorvastatin, H2 antagonists and antacids, though in a recent study co-administration with NSAID's was found to lead to increased postoperative haemorrhage. Drugs that inhibit the enzyme CYP3A4 and the protein P-gp result in higher levels of rivaroxaban and consequently increase the risk of bleeding. Such drugs are various anti-fungals like ketoconazole and HIV protease inhibitors. Conversely, drugs that induce CYP3A4 and P-gp have the opposite effect in the activity of rivaroxaban [18].

Regarding the use of rivaroxaban in orthopaedics, four major phase 3 randomized clinical trials (RECORD—Regulation of Coagulation in Orthopaedic Surgery to Prevent DVT and PE) and recently one phase 4 study (XAMOS) have been conducted [19–23]. The purpose of all these studies was to compare the efficacy and safety of rivaroxaban to those of enoxaparin in prevention of VTE. Two phase 3 studies (RECORD 1,2) were including patients after THA, and the other two were including patients after TKA (RECORD 3,4). In all these 4 trials, a superiority of rivaroxaban compared to enoxaparin in prevention of VTE after TKA and THA was found, something that is also evident in several meta-analyses of these studies. Another outcome of these trials was that the incidence of postoperative bleeding in patients who received rivaroxaban was increased, though this increase was not statistically significant [24–27]. Conversely, there are meta-analyses of these trials which showed that this superior efficacy of rivaroxaban in prevention of VTE (including fatal events) was due to prevention of DVT only, while as far as the incidence of PE or postoperative death is concerned, the rates were similar for rivaroxaban and enoxaparin [27–29].

Recently, the first real-world phase 4 trial about the efficacy and the safety of rivaroxaban after THA and TKA was published (XAMOS). This study, as well as other real-world studies, confirmed the successful profile of rivaroxaban. Interestingly, in some of these studies rivaroxaban was found to be even safer, or at least had similar safety compared to LMWH concerning major bleeding events [30–34]. On the other hand, there are 7 other real-world studies which found that rivaroxaban resulted in a higher incidence of postoperative haemorrhage (either major or minor) and in more surgical site complications such as haematoma, wound dehiscence, superficial infection and even periprosthetic infection which often led to a second operation [35–41].

Rivaroxaban is the only new oral anticoagulant the safety and efficacy of which have been evaluated after other orthopaedic procedures, apart from joint replacement. In the XAMOS extended study, the efficacy and safety of rivaroxaban in patients after hip and lower limb fracture surgery were assessed. Rivaroxaban had similar efficacy and safety in prevention of VTE compared to that of other types of anticoagulants [42]. In another study, in which rivaroxaban was compared with LMWH in patients after lumbar spine surgery, rivaroxaban showed to be as efficient and safe as LMWH [43]. The ERIKA trial is a recently published phase 2 trial evaluating the efficacy of rivaroxaban after knee arthroscopy. The results of the study showed that a 7-day course of rivaroxaban is safe and efficient, though a larger trial is needed to verify these results [44].

To sum up the results of all these studies, many outcomes seem to be controversial and inconclusive, especially concerning the safety of rivaroxaban. Nevertheless, all studies agree about the superior or at least similar efficacy of rivaroxaban compared to enoxaparin in prevention of VTE, and consequently many of these studies conclude that the comparative results between the pros and cons of rivaroxaban are in favour of its use [45]. The proven efficacy of rivaroxaban led this drug to be a widely accepted option for thromboprophylaxis, despite the slightly increased risk of postoperative bleeding and wound complications.

Dabigatran

Dabigatran has a different mechanism of anti-thrombotic action compared to rivaroxaban. It is a direct inhibitor of thrombin and subsequently inhibits the formation of fibrinogen to fibrin, as well as the accumulation of platelets. Dabigatran has been approved in Europe since 2008 for the prevention of VTE after THA and TKA in a dosage of 220 mg (110 mg on the day of surgery, 1–4 h postoperatively). For patients with moderate renal insufficiency, $\geq$75 years or for those receiving amiodarone or quinidine, a reduced dosage of 150 mg (75 mg on the day of surgery) is recommended. Dabigatran is now approved for thromboprophylaxis after THA and TKA in more than 100 countries, but not in USA yet.

It is administrated as a prodrug, the dabigatran etexilate, which is hydrolysed and converted to its active form, dabigatran. Dabigatran is metabolized through liver microsomal carboxylesterases, and the transporter protein P-glycoprotein (P-gp) also participates in its absorption process. Contrary to rivaroxaban, the enzymes of cytochrome P450 do not have a role in metabolism of dabigatran. It has a mean terminal half-life of 12–14 h, peak blood concentrations are being reached 2 h after consumption, and about 80% of the drug is renally excreted. In patients with moderate renal insufficiency

(30 ml/min < CrCl < 50 ml/min), half-life time is prolonged to 27–28 h and a decreased dose of 150 mg/day is recommended, while in patients with severe renal insufficiency (CrCl < 30 ml/min), dabigatran is contraindicated. It is also contraindicated in patients with doubled levels of liver enzymes [46]. Dabigatran interacts with drugs that inhibit the transporter protein P-gp, and so co-administration with these drugs results in increased blood concentrations of dabigatran. On the other hand, drugs like rifampicin and phenytoin have the reverse effect [47].

Four major randomized clinical trials and several meta-analyses of these trials have been conducted regarding the efficacy and safety of dabigatran in prevention of VTE after THA and TKA (RENOVATE, RENOVATE 2, REMODEL and REMOBILIZE) [48–51]. These 4 trials showed that dabigatran in a dose of 220 mg has similar efficacy when compared to 40 mg of enoxaparin in prevention of VTE, but not when compared to the North American dosage of enoxaparin which is 30 mg twice daily. The incidence of postoperative bleeding was similar for the two drugs [6, 52].

Wolowacz et al. [53] in a recent meta-analysis of the REMODEL, REMOBILIZE and RENOVATE trials supported the individual results of these studies about the efficacy and safety of dabigatran, though he mentioned that the heterogeneity of these studies may not allow to reach safe conclusions. A recent pooled analysis of RENOVATE and RENOVATE II studies by Eriksson et al. [52] also added to the evidence base for the safe and efficient use of dabigatran. To date, a certain number of real-world studies have been conducted about the use of dabigatran, though not as many as for rivaroxaban. The largest real-world observational study including 5292 patients after THA and TKA was recently published. The results of this study confirmed the successful outcomes of dabigatran in a real-world orthopaedic setting [54]. In some of these real-world studies, the efficacy of dabigatran was found to be similar to that of LMWH with even lower rates of postoperative bleeding, while that of other dabigatran resulted in a higher incidence of VTE [55–57]. Furthermore, some studies showed that dabigatran may lead to a higher incidence of wound leakage subsequently resulting in an increased length of stay, but this was not evident in other studies [56, 58, 59].

It seems that the current body of the literature about the efficacy and safety of dabigatran is somewhat controversial. While most studies agree that dabigatran has similar efficacy with enoxaparin in prevention of VTE (at least for the dosage of 220 mg) with concomitant similar safety regarding postoperative haemorrhage, there are some studies that link dabigatran to various postoperative complications such as wound bleeding and secretion.

Apixaban

Apixaban, like rivaroxaban, is another direct factor Xa inhibitor. It was approved by the European agency (EMA) in 2011 and recently in 2014 by the US organization (FDA) as a prophylactic agent for the prevention of VTE after THA and TKA in a dose of 2.5 mg every 12 h, with the first dose received 12–24 h postoperatively.

Although it would be more than expected for apixaban to have similar pharmacokinetic properties with those of rivaroxaban, this is not totally true [60]. Its bioavailability after oral administration is 50%, and peak concentrations in blood are being achieved 3–4 h after administration. The half-life elimination time is 8–15 h, while only 25% of the drug is renally excreted. Nevertheless, in patients with severe renal insufficiency (CrCl < 15–30 ml/min), apixaban must be used very cautiously, while in patients with CrCl < 15 ml/min, apixaban is contraindicated as well as in patients with severe hepatic insufficiency [60, 61]. Metabolism of apixaban is achieved through the transporter protein P-gp and the cytochrome P450 enzyme CYP3A4. Subsequently, drugs that induce or inhibit the activity of those also affect the activity of apixaban.

Three major phase 3 clinical trials (ADVANCE 1, ADVANCE 2 and ADVANCE 3) as well as many reviews and meta-analyses concerning the use of apixaban after TKA and THA have been conducted [62–64]. These three trials confirmed the safe and efficient use of apixaban in patients after TKA and THA for the prevention of VTE. A worthy mentioned point of these studies is that the European dosage of enoxaparin (40 mg daily) showed to be less effective than apixaban, while this was not true for the North American regime (30 mg twice a day) which was used in ADVANCE 1 study. This increased dose of enoxaparin, though, led to higher rate of postoperative bleeding.

Another interesting outcome was noted in many meta-analyses, in which apixaban appeared to be more effective only in the prevention of DVT, and not in PE [28, 65, 66]. Furthermore, Villa et al. [67] based on his meta-analysis considered that the results of the phase 3 clinical trials do not support the undeniable superiority of apixaban compared to enoxaparin and additionally that there was a trend for a higher incidence of PE and deaths in the enoxaparin group. In conclusion, apixaban seems to be more safe and effective than enoxaparin (at least for the European dosage) in prevention of VTE after THA and TKA, with some concerns about its efficacy in prevention of PE [68, 69].

Edoxaban

Edoxaban is the newest oral anticoagulant which has been used for the prevention of VTE after joint replacement and

hip fracture surgery. It is also a factor Xa inhibitor and so far has been approved in USA and Europe (2015) to reduce the risk of stroke and dangerous blood clots (systemic embolism) in patients with atrial fibrillation. Although similar approval has not been obtained for the prevention of VTE after major orthopaedic procedure, edoxaban has been used for this cause in Japan and other Asian countries in a dose of 30 mg once daily, 6–24 h after the surgery.

Edoxaban is mainly metabolized by hydrolysis, and its intestinal transport also occurs through P-gp. The bioavailability of edoxaban is approximately 60%. Unlike rivaroxaban and apixaban, only a slightest portion of the drug is metabolized by cytochrome P450 [70]. Drug interactions occur only after concomitant use with P-gp inhibitors and inducers. Edoxaban has a half-life of approximately 9–11 h, while peak concentrations in plasma are being reached 1–2 h after administration. About 35% of the elimination of the drug occurs through kidneys, and the rest is excreted through faeces. Most of the drug is excreted unchanged. A dose reduction is recommended in patients with moderate renal impairment (CrCl $<$ 50 ml/min) [15, 70].

Three phase 3 clinical trials about the use of edoxaban for the prevention of VTE after knee and hip replacement, as well as after hip fracture surgery have been conducted [7–9]. Edoxaban showed to be more effective than enoxaparin for the prevention of VTE after TKA and THA. Additionally, adequate prophylaxis after hip fracture surgery was achieved with edoxaban. The incidence of bleeding events in these studies was lower for edoxaban after THA and hip fracture surgery, but not after TKA. Nevertheless, the safety of edoxaban after TKA was statistically similar to that of enoxaparin. All these phase 3 trials enrolled substantially lower number of patients compared to the phase 3 trials of the other NOAC, and also the total duration of thromboprophylaxis was shorter. Another concern is the fact that these studies were conducted mainly in Japan, where the somatometric characteristics of the population are different to those of Western population.

Although the use of edoxaban after major orthopaedic procedures based on the results of current studies seems promising, larger studies including patients from Western countries are needed in order to reach safe conclusions.

Management of bleeding

Management of bleeding complications includes general measurements, administration of coagulation factors and administration of drug-specific reversal agents. General measurements consist of drug discontinuation, administration of activated charcoal (if last dose $<$2 h), mechanical compression, surgical haemostasis, replacement of fluids and RBC transfusion. Coagulation factors can be administrated in the form of FFP (fresh frozen plasma), although this has several disadvantages. These disadvantages can be overcome with the use of prothrombin complex concentrates (PCC) and recombinant-activated factor VII. Three different PCC products (a 3-factor PCC, a 4-factor PCC and an activated PCC) and one recombinant-activated factor VII are commercially available [71, 72]. Today, the 4-factor PCC is mainly used, while the results of the rest PCC and rFVIIa remain unclear.

The last category of drugs includes three new agents: idarucizumab, andexanet alfa and ciraparantag. Idarucizumab is a humanized mouse monoclonal antibody fragment that binds specifically to dabigatran. It is the first of the specific reversal agents approved by FDA (October 2015) and EMA (November 2015) [73]. Andexanet alfa is the second specific reversal agent which is used for reversion of the anti-thrombotic activity of factor Xa inhibitors like rivaroxaban and apixaban. It is a recombinant modified factor Xa molecule. This modification results in lack of its coagulation activity, but the native structure of the molecule remains and so it can bind directly to factor Xa inhibitors [74]. Two parallel phase 3 trials showed that andexanet alfa effectively reversed the anticoagulant activity of factor Xa inhibitors, without clinical toxic effects [75]. A phase 4 study (ANNEXA-4) has been designed, and its results in the real-world environment will provide vital information about the efficacy and safety of this antidote. Ciraparantag is the newest agent of this category and has the advantage that can neutralize the activity of all classes of NOAC as well as of UFH, LMWH and fondaparinux. This universal antidote is a small, synthetic, water-soluble molecule that binds to direct inhibitors of factor Xa and IIa [74]. These three agents look promising, but the relatively small number of enrolled patients in phase 2 and 3 trials emphasizes the need for real-world studies [75].

Laboratory assessment

Regarding the laboratory assessment of the activity of NOAC, conventional clot tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and thrombin time (TT) can only be used as rough indicators, because they lack sensitivity and the relationship of the values of these tests with the levels of blood concentrations is not linear (Table 3). The PT test can only be used to detect levels in blood and to roughly quantify the activity of rivaroxaban and edoxaban, while TT and aPTT tests can be used for dabigatran detection, as normal values of these tests suggest absence or low levels of dabigatran. The

Table 3 Laboratory assessment of NOAC

Test	Rivaroxaban	Dabigatran	Apixaban	Edoxaban
PT	Rough indicator	Unsuitable assay	Unsuitable assay	Rough indicator
aPTT	Unsuitable assay	Rough indicator	Unsuitable assay	Unsuitable assay
TT	Unsuitable assay	Rough indicator	Unsuitable assay	Unsuitable assay
Specialized test	Chromogenic anti-factor Xa assays	Hemoclot test Ecarin clot test	Chromogenic anti-factor Xa assays	Chromogenic anti-factor Xa assays

Table 4 Recommendations about preoperative discontinuity of NOAC

NOAC	EHRA	French study group
Rivaroxaban	≥48 h	5 days
Dabigatran	CrCl ≥80 ml/min ≥48 h	5 days
	CrCl 50–80 ml/min ≥72 h	
	CrCl 30–50 ml/min ≥96 h	
Apixaban	≥48 h	5 days
Edoxaban	≥48 h	–

sensitivity of these tests is even lower for apixaban, so they are not suitable for the assessment of its blood levels. Certain laboratory tests have been developed for more accurate measurements of NOAC blood levels. For dabigatran, these tests include a dilute thrombin time test (Hemoclot test) and the ecarin clot test. Ecarin clot test is highly sensitive with linear response to dabigatran, but very costly. For direct factor Xa inhibitors, the most useful and sensitive tests are the drug-specific chromogenic anti-factor Xa assays which can accurately quantify drug levels [15, 60].

Perioperative management

The perioperative management of NOAC is another matter of great significance. The anticoagulant activity of NOAC (which have a relatively short half-time, closed to 12 h) almost disappear after 4–5 half-times [76]. Perioperative management of NOAC must be based on certain factors, such as the patient's and procedure's risks of thrombosis and bleeding, patient's comorbidities (mainly renal insufficiency), and the pharmacokinetic properties of each agent [77, 78]. The European Heart Rhythm Association (EHRA) guidelines and the French Study Group on Thrombosis and Haemostasis guidelines are the two mostly referred recommendations (Table 4). According to EHRA, at least 48-h period of stoppage is recommended for factor Xa inhibitors, while at least 3 or 4 days of discontinuation is usually recommended for dabigatran [79]. The French Study Group on Thrombosis and Haemostasis provides a more conservative approach and recommends a mandatory 5-day stoppage for all NOAC [80]. The postoperative administration of NOAC can be initiated after 48–72 h, as long as appropriate haemostasis has been achieved.

Conclusions

New oral anticoagulants will have a more leading role in prevention of VTE after orthopaedic procedures in future, which is additionally shown from the fact that constantly more and more scientific groups and national orthopaedic societies include these agents in their thromboprophylaxis guidelines. The obvious advantage of NOAC compared to LMWH is the oral route of administration and thus the better compliance of the patients, as well as the avoidance of constant laboratory monitoring which is necessary for VKA. On the other side, there are certain disadvantages regarding the use of NOAC, such as the interactions with more drugs compared to LMWH, and the fact that they are mainly renally excreted so they may not be indicated for patients with renal impairment. Another disadvantage of NOAC is the relative lack of antidote in case of bleeding complications, though a great research is currently being carried out.

In conclusion, rivaroxaban seems to have an advantage over dabigatran and apixaban as far as the efficacy in prevention of VTE is concerned, but this comes with the cost of its higher risk of bleeding. Dabigatran has similar efficacy and safety with LMWH, while regarding the safety and efficacy of apixaban, studies showed that it has a lower rate of bleeding events and is also more efficient compared to at least the European dosage of enoxaparin. More level 4 studies are needed in order to reach a safe conclusion about in which side the balance between pros and cons of use of NOAC leans, but certainly the future seems promising for this new category of anticoagulants.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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