New anticoagulants in critical care settings

Novos anticoagulantes em cuidados intensivos

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ABSTRACT

Thromboembolic events commonly occur in critically ill patients, and although they do not consistently present with specific signs and symptoms, they are associated with high morbity and mortality. Antithrombotic agents are the mainstay of the prevention and treatment of venous thromboembolism, and they are also used for stroke prevention in atrial fibrillation, embolism prevention in heart failure, and anticoagulation of prosthetic valves. These drugs have been combined with antiplatelet therapy for the prevention of secondary acute coronary syndrome. Antithrombotic agents such as Aspirin, clopidogrel, vitamin K antagonists and fondaparinux, an indirect Factor Xa inhibitor, are already incorporated into our clinical practice. New small-molecule, selective Factor Xa and thrombin inhibitors that simultaneously inhibit free plasma and clot-associated factor activities have received considerable attention recently. These new oral anticoagulants are in various phases of clinical development. dabigatran, rivaroxaban and apixaban are in more advanced phases of clinical development and are already available in a number of countries. This review article highlights the studies describing the use of these three anticoagulants in an intensive care setting.

Keywords: Anticoagulants; Antithrombotic; Intensive care; Critical care

INTRODUCTION

Critically ill patients should be monitored systematically for arterial or venous thromboembolic events, which are represented by a number of clinical conditions, including deep venous thrombosis (DVT), pulmonary embolism (PE), acute coronary syndromes (ACS) and, potentially, thromboembolic diseases such as atrial fibrillation (AF). Considering the relative prevalence of venous thromboembolic diseases in the intensive care unit (ICU setting), this review will focus on that pathology. Current data[1,2] indicates that, without appropriate anticoagulant prophylaxis, the incidence of DVT is approximately 60% in ICU patients. The risk factors associated with venous thromboembolism (VTE) in critically ill patients may be categorized as pre-existing or ICU-acquired factors. Pre-existing risks include recent surgery, trauma, burns, neoplasm, advanced age, cardiac or respiratory failure, acute myocardial infarction, previous thromboembolism, pregnancy, puerperium and estrogen therapy. ICU-acquired factors include indwelling central venous catheters, sepsis, sedation, neu-

romuscular blockade, and mechanical ventilation.[3] Anticoagulants are the mainstay of the prevention and treatment of thromboembolism. This class of drugs is also used for stroke prevention in AF patients, embolism prevention in heart failure patients and thrombus prevention in prosthetic valve patients.

At the end of the last century, Hoffman et al.[4] described a cell-based coagulation model that does not include activation of the coagulation cascade. Instead of depending on the pre-existing sequential model, this cell-based model describes three superimposed phases: initiation, amplification and propagation.

Initiation occurs in cells that express tissue factor, which is the main physiological trigger for coagulation. Vascular injury exposes plasma to tissue factor, which binds to Factor VII. This reaction activates Factors X and V and causes the generation of small amounts of thrombin.

This coagulation response is amplified on the platelet surface, rather than on the fibroblast where initiation occurs. As platelets adhere, the platelet surface-activated cofactors that amplify the stimulus are activated and accumulate locally. The thrombin produced in the initiation phase is a potent platelet activator. It causes several downstream events that activate platelets, as follows: phosphatidylserine exposure at the platelet membrane, Factor V extrusion from platelet granules, and Factor VIII activation. In a powerful positive feedback loop, the membrane-bound receptor complexes that include cofactors V and VIII boost subsequent thrombin generation near the platelet membranes. Propagation occurs when active proteases combine with their cofactors to form tenase and prothrombinase complexes on the platelet surfaces, which are physiologically optimized for hemostatic thrombin formation. Large amounts of thrombin then promote cleavage of fibrinogen to fibrin monomers that are then cross-linked by activated Factor XIII to strengthen the growing clot.

Several well-known anticoagulant drugs should be mentioned. Aspirin and clopidogrel are antiplatelet agents. Other anticoagulants include vitamin K antagonists (VKA) such as warfarin, indirect Factor Xa inhibitors (low molecular weight heparins, fondaparinux, idraparinux), oral direct factor Xa inhibitors (apixaban, edoxaban, rivaroxaban), and oral direct thrombin inhibitors (dabigatran and apixaban, among others) (Figure 1).[5-7]

The use of anticoagulant agents began in 1916 when the effects of the anticoagulant heparan sulfate (extracted from swine liver) were discovered by McLean.[8] Following this discovery, the mechanisms of coagulation were progressively elucidated, and potential atherothrombotic therapies were discovered. Later, in 1933, Karl Paul Link discovered dicoumarol, a VKA, that was initially used as rat venom. Dicoumarol was modified during the 1950s, and its derivative, hydroxycoumarin, was tested and used as a therapeutic oral anticoagulant in humans. For about 60 years, VKAs (mainly warfarin) have been used clinically for effective thromboembolic event prevention. Their universal use is limited, however, by a narrow therapeutic window, unpredictable pharmacodynamics and pharmacokinetics, significant drug interactions, need for frequent laboratory monitoring, food interactions, adverse bleeding events and, paradoxically, the possibility of inducing hypercoagulable states (e.g., warfarin-induced skin necrosis). These hypercoagulable states may lead to thrombogenic events or systemic hypercoagulability.[9-11] Additionally, barriers to appropriate use may be introduced by patient noncompliance with prescribing and monitoring. Appropriate monitoring of the international normalized rate (INR) is a mandatory element in managing VKA anticoagulation. However, INR measurements themselves are imperfect. The INR depends on measurements of prothrombin time (PT), a value that varies across laboratories due to different thromboplastin sensitivities. Because the INR is directly calculated from the PT (INR = PT/PTn),[ISI] this natural variance decreases confidence in the intrinsic stability of INR measurements.[12] The international sensitivity index (ISI),

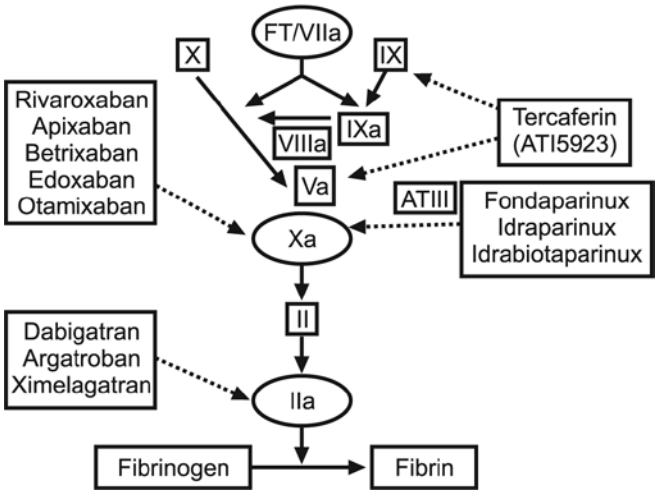

Figure 1- Anticoagulants' modes of action.

which reflects PT responsiveness to a given thromboplastin, may enable comparison of INR values obtained from different laboratories. However, the difficulty monitoring and the side effects described above limit the use of these drugs.[13,14]

Unfractionated heparin (UFH) is not as effective as warfarin, and it also has intrinsic limitations. It is given parenterally but, like warfarin, requires careful laboratory monitoring. In addition, it binds to plasma proteins and endothelial cells, worsens osteoporosis and increases the risk of thrombotic complications associated with heparin-induced thrombocytopenia (HIT).[15] Low molecular weight heparin (LMWH) was developed to avoid the practical limitations of warfarin and UFH. Indeed, LMWH was shown to be safe and effective. It does not require laboratory monitoring, and it has a longer half-life and a more predictable response. However, it requires parenteral dosing. Despite its improved safety profile, LMWH does not completely eliminate the risk of HIT, though its risk is lower than that of UFH.[16] In the last two decades, the development of synthetic compounds such as LMWH and pentasaccharides (fondaparinux) has prompted the quest for the ideal anticoagulant. The resulting new agents are more effective and are given as oral formulations on simple dosage schedules. Importantly, they have predictable pharmacokinetics and pharmacodynamics, and they do not have laboratory monitoring requirements.[17] Countless clinical trials have demonstrated encouraging results with selective Factor Xa and thrombin inhibitors. These are small molecules that concomitantly inhibit free plasma coagulation factors (FX and FII) but have little effect when these factors are bound. They do not require antithrombin (ATIII) for full effect. Among these new developing oral anticoagulants, dabigatran (oral direct thrombin inhibitor), rivaroxaban and apixaban (oral direct factor X inhibitors) are in Phase III clinical development and are already licensed in a number of countries,[18-20] including in Brazil (except for apixaban).

This review highlights the primary published trials describing the use of new anticoagulants in the intensive care unit setting.

Direct thrombin inhibitors (DTI)

DTIs block thrombin activity at two different sites: in free plasma and at the thrombus. Consequently, they prevent conversion of fibrinogen into fibrin, affecting the amplification and propagation of coagulation by reducing thrombin generation. Unlike UFH, which needs Serpin (ATIII) to amplify its effect, DTIs are not bound to plasma proteins and thus do not require ATIII. As a result, DTIs are stable in the plasma and do not require laboratory monitoring in patients with greater than 30 mL/kg/min creatinine clearance, even in obese and elderly patients. DTIs have a fast onset of action and are predominantly cleared by the kidneys. As they are not neutralized by Platelet Factor 4 (PF4), they prevent HIT, an adverse clinical syndrome resulting from heparin use that leads to development of temporary IgG/antiPF4/heparin antibodies.

This anticoagulant/antithrombotic class may be categorized in two groups: 1) those that bivalently bind to thrombin compounds (active site and exosite), such as hirudin and bivalirudin, and 2) those that univalently bind to thrombin (active site only), including ximelagatran (withdrawn from the market), argotraban (intravenous) and dabigatran (oral). Hirudin, bivalirudin and argatraban are exclusively parenteral drugs. They are approved for use in clinical conditions such as HIT, stroke prevention in AF, acute coronary syndromes and DVT prevention and treatment. Phase III trials have shown that ximelagatran is not inferior to VKAs for prevention of venous thromboembolism and stroke in patients with non-valvular AF. A previous study showed that it causes increased hepatotoxicity (odds ratio 6.73) and major cardiovascular events, although the study's statistical analysis was disputable due to an elevated non-inferiority power (non-inferiority, less than 1.4; actual, 2.0). The FDA (Food and Drug Administration) withdrew the product from the market in 2006.[21-23]

Dabigatran is an orally dosed, renally excreted DTI. After oral administration, dabigatran has a 12-17 hour half-life and 6% bioavailability, with peak plasma concentration within 2 hours of oral intake. It has few drug interactions, most of which involve cytochrome P450 enzymes. It was initially studied for prevention of thromboembolic events after major orthopedic surgeries (total hip and knee joints replacement surgeries) and for secondary prevention of stroke and VTE in non-valvular AF. This antithrombotic agent has been licensed clinically in Europe and Canada for postoperative VTE prevention after major orthopedic surgery (total hip or knee joints replacement) and for atrial fibrillation.[24,25] Although it has no relevant drug interactions, its use with quinidine, verapamil and clarithromycin is not advisable because dabigatran serum levels may

be increased; use with P-glycoprotein (P-gp) inducers such as rifampicin results in reduced activity. Its use is, however, becoming more common.[26]

Three significant Phase III studies describe the use of dabigatran for DVT prophylaxis after major orthopedic surgery (RE-MODEL, RE-MOBILIZE and RE-NOVATE). These studies demonstrated non-inferiority to LMWH for VTE prevention. Dabigatran was tested at 150 or 220 mg/day doses after total hip replacement surgery (RE-NOVATE, DTI versus enoxaparin 40 mg/day) or total knee replacement surgery (RE-MODEL, DTI versus enoxaparin 40 mg/day; and RE-MOBILIZE, versus enoxaparin 30 mg twice daily). The primary endpoint analyzed was combined DVT, PE and all-causes mortality. No increased hepatotoxicity was observed relative to LMWH. However, dabigatran is not recommended for liver dysfunction patients,[19] although there is evidence that the drug may be used in moderate liver dysfunction patients without affecting its pharmacodynamics or pharmacokinetics.[27] The RE-COVER trial evaluated 2,564 patients in a randomized, double-blind design comparing dabigatran (150 mg twice daily) and warfarin (for a target INR between 2 and 3) for prevention acute thromboembolic events (PE, DVT). The primary endpoints were new onset or recurrence of thromboembolic events and 6 months mortality; the safety evaluation addressed bleeding, ACS, and hepatotoxicity. In this study, dabigatran was shown to be non-inferior to warfarin for the treatment of acute thromboembolic events within 6 months. Two ongoing Phase III clinical trials (RE-SOLVE and RE-MEDY) are studying long term treatment and secondary VTE prevention.[28]

For AF, Phase II trials suggested that a 150 mg b.i.d. (twice daily) oral dose would be as effective and safe as VKAs. The RE-LY trial, a recently published Phase III, randomized, open-label trial, compared two dabigatran doses (110 mg b.i.d. and 150 mg b.i.d.) with warfarin dosed for a target INR 2.0-3.0. It assessed the reduction of strokes and embolic events as well as drug safety. A total of 18,113 subjects were enrolled, with a mean 24-month follow-up. Although RE-LY was described as a non-inferiority trial, superiority analysis revealed that dabigatran was as effective as warfarin and had fewer major bleeding events (3.36% versus 2.71%; p=0.003). The group that received dabigatran 150 mg b.i.d. also had a reduced occurrence of stroke/systemic embolism relative to patients who received warfarin, 1.11% versus 1.69% (CI 0.53 to 0.82; p<0.001; superiority). Dyspepsia was more frequent in the dabigatran group (12% versus 5.8%). Of note, there were no differences in liver function between the dabigatran and warfarin groups (2.1% versus 2.2%). These results were enthusiastically received by the scientific community. For the first time, an oral drug as safe and effective as warfarin but without warfarin's limitations was available. A RE-LY rollover study, the RELY-ABLE (Long Term Multi-Center Extension of Dabigatran Treatment in Patients with Atrial Fibrillation who Completed RE-LY Trial) is currently evaluating the safety of dabigatran over 28 months, and is scheduled to end in late 2011.[29] A specific antidote for dabigatrin is not available, and there are no methods for quantifying its efficacy. The management of bleeding events associated with dabigatran is similar to that of LMWH. Mild bleeding may be controlled by withholding one dose, given dabigatran's short half-life (12 to 17 hours). Supportive measures such as surgery, blood component transfusion, and hemodialysis may be indicated for more severe bleeding events. Preclinical trials suggested that the use of specific coagulation factors (activated recombinant Factor VII, prothrombin complex or activated charcoal) may reverse dabigatran's anticoagulant effects in imminent life-threatening situations, or when supportive measures do not sufficiently control bleeding.[30] Activated charcoal, charcoal filtration and hemodialysis are appropriate treatments for overdose events.[31]

INR monitoring has little sensitivity and is not recommended. The most sensitive tests for dabigatran's anticoagulant effect are thrombin time (TT), Ecarin Coagulation Time (ECT) and the thrombin inhibitor Hemoclot®, which is linearly correlated with the dabigatran plasma concentration.[31] However, in emergency conditions where ECT and Hemoclot® are not available, activated Partial Thromboplastin Time (aPPT) and TT are more accessible for assessment of dabigatran's anticoagulant effect even though aPPT is less sensitive for high dabigatran plasma concentrations. There is no data to support the use of activated clotting time (ACT) in this setting.[31]

Direct factor Xa inhibitors (DFXaI)

This antithrombotic class directly binds Factor Xa, requiring no antithrombin III involvement. Their antithrombotic action is Factor Xa-specific, without effects on other intrinsic/extrinsic coagulation pathways and without side effects such as thrombocytopenia.

DFXaI compounds are small molecule agents (low molecular weight) that can be administered orally. They are able to inactivate Factor Xa-related circulating forms (prothrombinase-Xa/Va complex). The inhibition is stochiometric, i.e., one DFXaI molecule inactivates one Factor Xa molecule. DFXaI is theoretically able to inhibit prothrombinase complex Factor Xa and clots bound to Factor Xa with improved clinical effectiveness (Figure 2).[32]

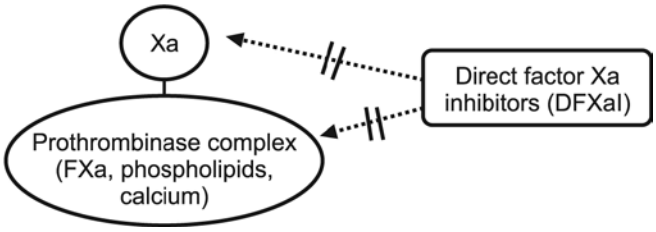

Figure 2 – Direct FXa inhibitors: binding to factor Xa site and clot prothrombinase complex.

Rivaroxaban

Rivaroxaban is an oxazolidione derivative that directly inhibits Factor Xa. It requires only one daily dose for effective treatment. It is used for VTE prevention after hip and knee joint replacement surgery and is approved in Brazil, Canada, the European Union and some Asian and African countries. Currently, rivaroxaban is the world's most studied DFXaI, with about 32,000 ongoing patients. In Phase I studies, 30 mg rivaroxaban was shown to inhibit thrombin for longer than 24 hours without affecting platelet, and it was associated with bleeding rates comparable to those of enoxaparin and lower than those of warfarin and direct thrombin inhibitors.[33-35] It is rapidly absorbed, has a 7-11 hours half-life and requires no weight or gender dosage adjustments. It is 66% cleared by liver and 33% cleared by the kidneys. It is predominantly metabolized by CYP3A4 enzymes. Coadministration with other drugs related to this pathway, such as ketoconazole/fluconazole, itraconazole, posaconazole, triazolics and protease inhibitors (as ritonavir) may increase its bioavailability and, consequently, bleeding. Moderate CYP3A4 and P-gp inhibitors like erythromycin can be used. Strong CYP3A4 inducers such as phenytoin, carbamazepine and phenobarbital may be used with caution. Patients with advanced liver disease, creatinine clearance below 30% and concurrent use of CYP3A4 inducers and/or inhibitors were excluded from the clinical trials. The Phase III set of trials RECORD (Regulation of Coagulation in Major Orthopedic Surgery Reducing Risk of DVT and PE) evaluated the use of rivaroxaban 10 mg once daily; these were double-blind trials including more than 12,500 patients undergoing total hip or knee joint replacement surgery. Rivaroxaban was superior to enoxaparin, with more than 50% reduction of the composite endpoint reflecting symptomatic VTE and death. However, the bleeding risk associated with rivaroxaban (0.7%) was higher than with enoxaparin (0.3%).[36-40] Other ongoing studies are evaluating this drug in other clinical conditions, including thromboembolic event therapy, stroke prevention in non-valvular AF, and secondary acute coronary syndrome prevention. Approximately 50,000 subjects will be involved in a clinical development program that will evaluate AF thromboembolic complications. For AF patients, the ROCKET AF (Rivaroxaban Once daily oral direct Factor Xa inhibition Compared with vitamin K antagonists for the prevention of stroke and Embolism Trial in Atrial Fibrillation) trial[41] is currently ongoing, with 15,000 patients in clinical follow-up. This is a non-inferiority, prospective, randomized, double-blind trial that compares the effectiveness and safety of a daily dose of 20 mg rivaroxaban with daily warfarin dosed for a target INR 2.0-3.0. The rivaroxaban dose was reduced to 15 mg for patients with moderate renal dysfunction. The drug was thus compared to the adjusted dose of warfarin indicated for stroke and systemic embolism prevention in non-valvular AF. Both therapies were given for an average of 18 months, with a minimum of 12 months, and some subjects were treated for longer than 24 months. Additionally, two Phase II trials were conducted in Japanese AF patients to identify ethnic differences in rivaroxaban safety and pharmacology. The studies failed to identify differences independent of factors like body surface area and eating habits.[42]

Apixaban

Apixaban is a potent DFXaI that is rapidly absorbed from the gastrointestinal tract and cleared by the kidneys (25-30%) and liver (65%) with a 9-14 hour half-life. The drug absorption is free of interference from food ingestion. Because apixaban, like rivaroxaban, is metabolized by the CYP3A4 enzymes, its metabolism is influenced by CYP3A4 inducers and inhibitors. After total hip and knee joint replacement surgery, Apixaban (2.5 mg b.i.d.) was as effective as subcutaneous enoxaparin (40 mg/day) for prevention of thromboembolic events and death, with similar bleeding rates. In the

ADVANCE 1 trial, which compared apixaban versus enoxaparin (30 mg b.i.d.), non-inferiority was not shown. However, VTE and death outcomes were similar, with fewer bleeding events in the apixaban group. The ADVANCE 2 trial[43] included 3,057 subjects undergoing total knee joint replacement surgery. Apixaban (2.5 mg b.i.d.) was more effective for both the primary and secondary endpoints than enoxaparin (40 mg/day), with similar safety results. Based on previous trials involving DVT and ACS patients, a 5 mg twice-daily dose was suggested for stroke prevention in AF patients. The ongoing ARISTOTLE[44] trial compares treatment of 18,000 patients with chronic, non-valvular atrial fibrillation with apixaban (5 mg orally, twice daily) or warfarin dosed for a target INR 2.0 to 3.0. The primary goal of this double-blind, parallel groups trial is to show non-inferiority of apixaban relative to warfarin. In another Phase III trial, the AVERROES trial, approximately 5,600 AF subjects with contraindications to VKA therapy were treated with apixaban (5 mg, oral, b.i.d.) or Aspirin for 36 months. This study's objective was to verify that this anticoagulant is more effective than acetylsalicylic acid (ASA – 81 to 324 mg) for stroke prevention in AF patients.[45]

Edoxaban

Edoxaban (DU-176b) is an oral competitive DFXaI with a 6-12 hour half-life and predominantly hepatic metabolism. It shares the DFXaI class drug interactions with CYP3A4 inhibitors and/or inducers. In *in vivo* studies,[46] Edoxaban dose-dependently inhibited thrombus formation in human volunteers, and its clinically effective dose did not significantly prolong bleeding time. Edoxaban (once or twice daily) was evaluated for stroke prevention in AF patients in Phase II studies[47] and was compared to standard therapy with Warfarin for 3 months. Clinically significant bleeding events were more frequent in patients receiving 30 and 60 mg edoxaban b.i.d. (7.8% and 10.6%) relative to warfarin (3.2%). The same edoxaban doses (30 and 60 mg) with once daily dosing led to clinically significant bleeding events at rates (3.0% and 4.7%) similar to warfarin (3.2%). A Phase III trial (ENGAGE-AF-TIMI48) is currently in process. It includes 16,500 subjects and compares low and high edoxaban doses with warfarin for 24 months in non-valvular AF. The dose is adjusted for renal dysfunction for patients with creatinine clearance between 30% and 50% and less than 50 kg body weight. Publication of its results is expected in 2011.

Betrixaban

Betrixaban is a direct FXa inhibitor with a 19-hour half-life and predominantly hepatic metabolism and biliary excretion. In a Phase II study[48] of DVT prevention in patients who underwent total knee joint replacement surgery, 15 mg or 40 mg of betrixaban were as effective as enoxaparin (30 mg b.i.d.) with similar bleeding rates at 14 days after surgery. The ongoing Phase II EXPLORE-Xa (Tolerability and Pilot Efficacy of Oral Factor Xa Inhibitor Betrixaban Compared to Warfarin) trial is evaluating stroke prevention in the presence of non-valvular AF. betrixaban is the only DFXaI for which a specific antidote was developed.[49] As with DTIs, other DFXaIs have no specific antidote available for use in cases of bleeding, overdose or non-elective surgery. The management of bleeding is not different from the management of bleeding resulting from LMWH, as described above. Recombinant Factor VII has limited effect on DxaI's anticoagulative effects. Preclinical studies have evaluated a recombinant FXa protein as an antidote for these agents with promising results.

Indirect factor Xa inhibitors (IFXaI)

Idraparinux is a parenteral, synthetic pentasaccharide that is similar to fondaparinux but has a different time course of action. Pentasaccharides were produced by synthesizing the smallest molecules that bind to ATIII heparin particles. Pentasaccharides bind to ATIII and, therefore, to FXa. They catalyze formation of an irreversible tertiary complex that in turn affects prothrombinase complex formation. After tertiary complex formation, the pentasaccharide may be released from the complex and can then either inhibit a new free plasma ATIII molecule or bind to a new prothrombinase complex. The precursor of pentasaccharides is fondaparinux[50-53], which was approved by the FDA (Food and Drug Administration), EMEA (European Medicines Agency) and the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária – ANVISA) for ACS, prophylaxis and therapy of DVT, TE, HIT and AF, as well as for pre-surgical bridging therapy.

Idraparinux is given subcutaneously and may be given every 7 days. It was initially evaluated in the Phase III trial AMADEUS for prevention of thromboembolic events in non-valvular AF. This study compared dose-adjusted VKAs (INR 2.0 to 3.0) with idraparinux (2.5 mg once a week). Thromboembolic events were reduced with this new therapy (HR 0.71

Table 1 – Primary new anticoagulant

Antthrombotic	Target	Study name	Clinical condition	Dose	Administration form	Renal excretion %	Half-life	Antidote	Clinical trial phase	Anticipated end	Reference number
Rivaroxaban	DFXaI			QD	PO	66	9-13		None		
		RECORD 1-4	DVTP						II/III	completed	36-40
		EINSTEIN-DVT	DVT						III	2011	33
		EINSTEIN-EXTENSION	DVT/PE						III	2011	36
		EINSTEIN-PE	PE						III	2011	34
		MAGELLAN	DVTP						III	2012	34
		ROCKET-AF	AF						III	2011	41
Apixaban	DFXaI			BID	PO	25	8-15h	None			
		ARISTOTLE/AVERROES	AF						III	2010	44
		ADVANCED 1	PTVP						III	completed	45
		ADVANCED 2	PTVP						III	completed	43
Edoxaban	DFXaI			QD	PO	62	6-12h	None			
		ENGAGE-AF-TIMI	AF						III	2011	48
Betrixaban	DFXaI			QD	PO	0	19h	None			
		EXPERT	DVTP						III	completed	48
		EXPLORE-AF	AF						III	2011	49
Dabigatran	DTI			BID	PO	80	12-14h	None			
		RE-MOBILIZE	DVTP						III	2009	24
		RE-MODEL	DVTP						III	2007	23
		RE-NOVATE	DVTP						III	2007	26
		RE-COVER	DVT						III	2009	28
		RE-LY	AF						III	2009	29
Idrabiotaparinux	IFXaI			Once a week	SC	100	130h		Avidin		
		BOREALIS-AF	AF							2012	56

QD – once daily dosing; BID – a twice daily dose; PO – oral; SC – subcutaneous; AF – atrial fibrillation; DVTP – deep venous thrombosis prophylaxis; DVT – deep venous thrombosis; PE – pulmonary embolism; IFXaI – indirect factor Xa inhibitor; DTI – direct thrombin inhibitor; DFXaI – direct factor Xa inhibitor.

[0.39-1.30] p=0.007, non-inferiority), but the clinically significant bleeding rate increased (HR 1.74 [1.47-2.06]; p=0.0001). No significant inter-groups difference was shown for mortality. However, bleeding-related complications limited its clinical use. The long half-life of idraparinux led to the development of a biotinylated version, idrabiotaparinux (SSR 126517). The biotinylation increases the drug's Avidin affinity; Avidin neutralizes idrabiotaparinux's anticoagulant effect by binding to is, leading to fast elimination as it causes this molecule to disassemble. The anticoagulant effects of idrabiotaparinux are similar to Idraparinux, but its anticoagulant effect may be completely reversed by Avidin parenteral infusion if necessary. The ongoing BOREALIS-AF (Evaluation of Weekly Subcutaneous Biotinylated Idraparinux Versus Oral Adjusted-dose Warfarin to Prevent Stroke and Systemic Thromboembolic Events in Patients with Atrial Fibrillation) trial is evaluating the effectiveness and safety of this idraparinux bioinylated form, and it is expected to end by 2012.[54-56]

CONCLUSION

Several anticoagulants are currently available for prophylaxis and therapy of intensive care unit thrombotic conditions. Unfortunately, an ideal anticoagulant, with predictable pharmacokinetics and pharmacodynamics, simple dosing, minimal drug interactions, specific antidotes and minimal need for laboratory monitoring, is not currently available. Newly developed anticoagulants, such as Factor Xa and direct thrombin inhibitors, are promising. However, new options that could offer an integral care alternative for critically ill patients and reduce the rate of adverse events are necessary. Definitive multi-center clinical trials are therefore warranted to support the safety of new anticoagulants in clinical practice.

RESUMO

Eventos tromboembólicos são complicações comuns em pacientes críticos. Podem apresentar sinais e sintomas pouco específicos e estão associados a um substancial aumento na morbimortalidade dos pacientes internados em unidades de terapia intensiva. Os agentes antitrombóticos são o pilar no tratamento e prevenção do tromboembolismo. Esta classe é também utilizada na prevenção do acidente vascular encefálico, na fibrilação atrial, na prevenção de eventos embólicos da insuficiência cardíaca, em pacientes com próteses valvares e têm sido associados a antiplaquetários na prevenção secundária da síndrome coronária aguda. Agentes antitrombóticos, como aspirina, clopidogrel, antagonistas da vitamina K e foundaparinux (inibidor indireto do fator Xa) já foram incorporados na prática clínica rotineira dos serviços de terapia intensiva. Recentemente, tem-se demonstrado grande interesse nos agentes que inibem seletivamente o fator Xa e a trombina. Estes apresentam estrutura molecular pequena e inibem simultaneamente o fator da coagulação livre no plasma e ligado ao trombo. Entre os novos anticoagulantes orais, dabigatran, rivaroxaban e apixaban são os que apresentam estudos clínicos em fases mais avançadas e uso na prática clínica já licenciado em alguns países. O objetivo desta revisão é salientar os principais estudos da literatura sobre novos anticoagulantes no cenário das unidades de terapia intensiva

Descritores: Anticoagulantes; Antitrombóticos; Cuidados intensivos; Cuidados criticos

REFERENCES

1. Geerts W, Selby R. Prevention of venous thromboembolism in the ICU. Chest. 2003;124(6 Suppl):357S-363S.
2. Fries D. [Anticoagulation in critically ill patient]. Wien Med Wochenschr. 2009;159(19-20):487-91. German.
3. Ribeiro MA, Netto PG, Lage SG. Desafios na profilaxia do tromboembolismo venoso: abordagem no paciente crítico. Rev Bras Ter Intensiva. 2006;18(3):316-9.
4. Hoffman M, Monroe DM 3rd. A cell-based model of hemostasis. Thromb Haemost. 2001;85(6):958-65
5. Padanilam BJ, Prystowsky EN. Atrial fibrillation: goals of therapy and management strategies to achieve the goals. Cardiol Clin. 2009;27(1):189-200, x. Review.
6. Richard T, Butaffuoco F, Vanhaeverbeek M. Clopidogrel plus aspirin in atrial fibrillation. N Engl J Med. 2009;361(13):1313; author reply 1314-5.
7. Harenberg J. New anticoagulants in atrial fibrillation. Semin Thromb Hemost. 2009;35(6):574-85.
8. McLean J. The discovery of heparin. Circulation. 1959;19(1):75-8.
9. Hirsh J, O'Donnell M, Eikelboom JW. Beyond unfractionated heparin and warfarin: current and future advances. Circulation. 2007;116(5):552-60.
10. Becattini C, Lignani A, Agnelli G. New anticoagulants for the prevention of venous thromboembolism. Drugs Des Devel Ther. 2010;4:49-60. Review.
11. Lopes RD, Piccini JP, Hylek EM, Granger CB, Alexander JH. Antithrombotic therapy in atrial fibrillation: guidelines translated for the clinician. J Thromb Thrombolysis. 2008;26(3):167-74.
12. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008;133(6 Suppl):160S-198S.
13. Mergenhagen KA, Sherman O. Elevated International Normalized Ratio after concurrent ingestion of cranberry sauce and warfarin. Am J Health Syst Pharm. 2008;65(22):2113-6.
14. Amouyel P, Mismetti P, Langkilde LK, Jasso-Mosqueda G, Nelander K, Lamarque H. INR variability in atrial fibrillation: a risk model for cerebrovascular events. Eur J Intern Med. 2009;20(1):63-9.
15. Hussey CV, Bernhard VM, McLean MR, Fobian JE. Heparin induced platelet aggregation: in vitro confirmation of thrombotic complications associated with heparin therapy. Ann Clin Lab Sci. 1979;9(6):487-93.
16. Weitz JI. Low-molecular-weight heparins. N Engl J Med. 1997;337(10):688-98. Erratum in: N Engl J Med. 1997;337(21):1567.
17. Bode C, Verheugt FW. The need for new oral anticoagulants in clinical practice: an introduction. J Cardiovasc Med (Hagerstown). 2009;10(8):593-4.
18. Harenberg J. Development of new anticoagulants: present and future. Semin Thromb Hemost. 2008;34(8):779-93.
19. Harenberg J, Wehling M. Current and future prospects for anticoagulant therapy: inhibitors of factor Xa and factor IIa. Semin Thromb Hemost. 2008;34(1):39-57.
20. Trimeche B, Bouraoui H, Mahdhaoui A, Ernez-Hajri S, Jeridi G. [Oral anticoagulants and atrial fibrillation]. Rev Med Interne. 2009;30(4):311-5. French.
21. Petersen P, Grind M, Adler J; SPORTIF II Investigators. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. J Am Coll Cardiol. 2003;41(9):1445-51.
22. Halperin JL; Executive Steering Committee, SPORTIF III and V Study Investigators. Ximelagatran compared with warfarin for prevention of thromboembolism in patients with nonvalvular atrial fibrillation: Rationale, objectives, and design of a pair of clinical studies and baseline patient characteristics (SPORTIF III and V). Am Heart J. 2003;146(3):431-8.
23. Samama MM, Gerotziafas GT. Newer anticoagulants in

2009. J Thromb Thrombolysis. 2010;29(1):92-104. Review.
24. Wolowacz SE, Roskell NS, Plumb JM, Caprini JA, Eriksson BI. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. Thromb Haemost. 2009;101(1):77-85.
25. Schulman S, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med. 2009;361(24):2342-52.
26. McBride BF. A preliminary assessment of the critical differences between novel oral anticoagulants currently in development. J Clin Pharmacol. 2005;45(9):1004-17.
27. Stangier J, Stähle H, Rathgen K, Roth W, Shakeri-Nejad K. Pharmacokinetics and pharmacodynamics of dabigatran etexilate, an oral direct thrombin inhibitor, are not affected by moderate hepatic impairment. J Clin Pharmacol. 2008;48(12):1411-9.
28. Baetz BE, Spinler SA. Dabigatran etexilate: an oral direct thrombin inhibitor for prophylaxis and treatment of thromboembolic diseases. Pharmacotherapy. 2008;28(11):1354-73.
29. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51. Erratum in: N Engl J Med. 2010;363(19):1877.
30. Wienen W, Stassen JM, Priepke H, Ries UJ, Hauel N. Effects of the direct thrombin inhibitor dabigatran and its orally active prodrug, dabigatran etexilate, on thrombus formation and bleeding time in rats. Thromb Haemost. 2007;98(2):333-8.
31. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, Clemens A. Dabigatran etexilate--a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost. 2010;103(6):1116-27.
32. Hammwöhner M, Smid J, Lendeckel U, Goette A. New drugs for atrial fibrillation. J Interv Card Electrophysiol. 2008;23(1):15-21. Review.
33. Piccini JP, Patel MR, Mahaffey KW, Fox KA, Califf RM. Rivaroxaban, an oral direct factor Xa inhibitor. Expert Opin Investig Drugs. 2008;17(6):925-37.
34. Haas S. Rivaroxaban--an oral, direct Factor Xa inhibitor: lessons from a broad clinical study programme. Eur J Haematol. 2009;82(5):339-49. Review.
35. Graff J, von Hentig N, Misselwitz F, Kubitza D, Becka M, Breddin HK, Harder S. Effects of the oral, direct factor xa inhibitor rivaroxaban on platelet-induced thrombin generation and prothrombinase activity. J Clin Pharmacol. 2007;47(11):1398-407. Erratum in: J Clin Pharmacol. 2008;48(11):1368.
36. Kakkar AK, Brenner B, Dahl OE, Eriksson BI, Mouret P, Muntz J, Soglian AG, Pap AF, Misselwitz F, Haas S; RECORD2 Investigators. Extended duration rivaroxaban versus short-term enoxaparin for the prevention of venous thromboembolism after total hip arthroplasty: a double-blind, randomised controlled trial. Lancet. 2008;372(9632):31-9.
37. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med. 2008;358(26):2776-86.
38. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W; RECORD1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med. 2008;358(26):2765-75.
39. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, Cushner FD, Lotke PA, Berkowitz SD, Bandel TJ, Benson A, Misselwitz F, Fisher WD; RECORD4 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet. 2009;373(9676):1673-80.
40. Van Thiel D, Kalodiki E, Wahi R, Litinas E, Haque W, Rao G. Interpretation of benefit-risk of enoxaparin as comparator in the RECORD program: rivaroxaban oral tablets (10 milligrams) for use in prophylaxis in deep vein thrombosis and pulmonary embolism in patients undergoing hip or knee replacement surgery. Clin Appl Thromb Hemost. 2009;15(4):389-94
41. ROCKET AF Study Investigators. Rivaroxaban-once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation: rationale and design of the ROCKET AF study. Am Heart J. 2010;159(3):340-347.e1.
42. Raghavan N, Frost CE, Yu Z, He K, Zhang H, Humphreys WG, et al. Apixaban metabolism and pharmacokinetics after oral administration to humans. Drug Metab Dispos. 2009;37(1):74-81.
43. Lassen MR, Raskob GE, Gallus A, Pineo G, Chen D, Hornick P; ADVANCE-2 investigators. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. Lancet. 2010;375(9717):807-15.
44. Lopes RD, Alexander JH, Al-Khatib SM, Ansell J, Diaz R, Easton JD, Gersh BJ, Granger CB, Hanna M, Horowitz J, Hylek EM, McMurray JJ, Verheugt FW, Wallentin L; ARISTOTLE Investigators. Apixaban for reduction in stroke and other ThromboemboLic events in atrial fibrillation (ARISTOTLE) trial: design and rationale. Am Heart J. 2010;159(3):331-9. Erratum in: Am Heart J. 2010;159(6):1162.

45. Carreiro J, Ansell J. Apixaban, an oral direct Factor Xa inhibitor: awaiting the verdict. Expert Opin Investig Drugs. 2008;17(12):1937-45.
46. Ogata K, Mendell-Harary J, Tachibana M, Masumoto H, Oguma T, Kojima M, Kunitada S. Clinical safety, tolerability, pharmacokinetics, and pharmacodynamics of the novel factor Xa inhibitor edoxaban in healthy volunteers. J Clin Pharmacol. 2010;50(7):743-53.
47. Hylek E. DU-176b, an oral, direct Factor Xa antagonist. Curr Opin Investig Drugs. 2007;8(9):778-83. Review.
48. Turpie AG, Bauer KA, Davidson BL, Fisher WD, Gent M, Huo MH, Sinha U, Gretler DD; EXPERT Study Group. A randomized evaluation of betrixaban, an oral factor Xa inhibitor, for prevention of thromboembolic events after total knee replacement (EXPERT). Thromb Haemost. 2009;101(1):68-76.
49. Lu G, Luan P, Hollenbach SJ, Abe K, DeGuzman FR, Siu G, et al. Reconstructed recombinant factor Xa as an antidote to reverse anticoagulation by factor Xa inhibitors. J Thromb Haemost. 2009;7(Suppl 2):OC-TH-107
50. Re G, Legnani C. Thrombocytopenia during fondaparinux prophylaxis: HIT or something different? Intern Emerg Med. 2010;5(4):361-3.
51. Schiele F. Fondaparinux and acute coronary syndromes: update on the OASIS 5-6 studies. Vasc Health Risk Manag. 2010;6:179-87.
52. Sharma T, Mehta P, Gajra A. Update on fondaparinux: role in management of thromboembolic and acute coronary events. Cardiovasc Hematol Agents Med Chem. 2010;8(2):96-103.
53. Ritt LEF, Flato UP, Guimarães HP, Avezum A, Piegas LS. Antitrombóticos nas síndromes coronarianas agudas: diretrizes atuais e novas evidências. Rev Bras Ter Intensiva. 2008;20(2):165-72.
54. Amadeus Investigators, Bousser MG, Bouthier J, Büller HR, Cohen AT, Crijns H, Davidson BL, et al. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. Lancet. 2008;371(9609):315-21. Erratum in: Lancet. 2008;372(9655):2022. Thorp-Pedersen, C [corrected to Torp-Pedersen, C].
55. Paty I, Trellu M, Destors JM, Cortez P, Boëlle E, Sanderink G. Reversibility of the anti-FXa activity of idrabiotaparinux (biotinylated idraparinux) by intravenous avidin infusion. J Thromb Haemost. 2010;8(4):722-9.
56. Harenberg J. Development of idraparinux and idrabiotaparinux for anticoagulant therapy. Thromb Haemost. 2009;102(5):811-5.