

New Anticoagulants in the Treatment of VTE

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Abstract

Low molecular weight heparins (LMWHs) and vitamin K antagonists make up the cornerstone of therapy for patients with venous thromboembolism (VTE) but have drawbacks making their use difficult in daily practice. Current research focuses on the development of new anticoagulant drugs that could be administered orally at a fixed dose, with fewer food and drug interactions and no need for monitoring or dose adjustment. Several new drugs are tested in noninferiority trials, either as a single-drug approach treatment (e.g., rivaroxaban or apixaban), or after an initial course of LMWH (e.g., dabigatran or edoxaban). Published clinical trials demonstrate that rivaroxaban and dabigatran are noninferior to conventional treatment in patients with VTE. Several issues remain challenging for physicians, such as the lack of antidote and of routinely available monitoring tests. To what extent new anticoagulant drugs will change clinical practice is not yet well defined. They may facilitate outpatient management of VTE. They might also improve the risk–benefit balance of prolonged anticoagulation and therefore modify the optimal duration of anticoagulation in VTE patients.

Keywords

- ▶ venous thromboembolism
- ▶ anticoagulants
- ▶ therapeutics
- ▶ review

Anticoagulant therapy is the cornerstone of the management of patients with venous thromboembolism (VTE), with several objectives: (1) to avoid the extension of the thrombotic process, (2) to stabilize the thrombus and prevent its migration from lower limb veins to the lungs, (3) to prevent VTE recurrence, and (4) to prevent long-term complications of VTE (eg, postthrombotic syndrome and chronic thromboembolic pulmonary hypertension). Current anticoagulant therapy mainly relies on heparins and on vitamin K antagonists (VKAs). Over the last decades, several major improvements in anticoagulant therapy strongly modified the management of VTE patients. However, currently available drugs are inconvenient to use. Current research focuses on the development of new anticoagulant drugs that could be administered orally, with a wide therapeutic window allowing their administration at a fixed dose, with a rapid onset of action and a short half-life, fewer food and drug interactions, and no need for monitoring or dose adjustment.

Limitations of Current Drugs

Unfractionated Heparin

Parenteral unfractionated heparin (UFH), low molecular weight heparin (LMWH), and fondaparinux are fast-acting anticoagulant drugs used to prevent thrombus extension at the initial treatment phase. UFH is the only anticoagulant treatment that has been evaluated against placebo in the landmark randomized, controlled trial published by Barritt and Jordan in 1960.¹ Heparin is a mixture of glycosaminoglycans with heterogeneous size, anticoagulant activity, and pharmacokinetic properties. Extracted from porcine intestine, not all heparin molecules possess the pentasaccharide sequence that provides the anticoagulant activity through binding to antithrombin. Heparin increases the natural anticoagulant activity of antithrombin against circulating coagulation factors IIa (thrombin) and Xa. It may be administered intravenously or subcutaneously.²

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Heparin has several severe adverse effects. Apart from bleeding, heparin's main adverse effects include osteoporosis and heparin-induced thrombocytopenia (HIT), requiring regular platelet count monitoring during treatment. It is necessary to monitor the anticoagulant activity of UFH using biological tests, and to perform subsequent frequent dose adjustments. Indeed, the length of heparin chains is also associated with variable protein and cell binding and variable means of elimination: longer chains have a tissue clearance, whereas shorter chains have renal clearance. These variations in pharmacokinetics necessitate monitoring the anticoagulant activity of UFH using biological tests. On the other hand, the tissue clearance makes the use of UFH possible under activated partial thromboplastin time (aPTT) monitoring in patients with severe renal failure.

Low Molecular Weight Heparin

Low molecular weight heparins (LMWHs) are derived from UFH by depolymerization. Their pharmacokinetics are more predictable, allowing the use of a once- or twice-daily subcutaneous (SC) fixed dose according to the patient's weight, with no need to monitor the anticoagulant activity. LMWHs have a predominant anti-Xa activity, with a variable anti-IIa activity depending on the type of LMWH. The risk of osteoporosis and of HIT is lower with LMWH as compared with UFH; therefore platelet monitoring is not required. LMWHs have replaced UFH in the initial management of most patients with VTE. On the other hand, LMWHs are mainly eliminated through the kidney, limiting their use in patients with severe renal failure.²

Fondaparinux

Fondaparinux is an antithrombin dependent synthetic pentasaccharide with an exclusive anti-Xa activity. Fondaparinux has several advantages over LMWH: (1) it is a synthetic drug, (2) it has a fixed SC therapeutic dose for patients with body weights between 50 and 100 kg, and (3) it does not require biological monitoring for either efficacy (anticoagulant activity) or safety (platelet count) concerns. *Unlike heparins, fondaparinux has no specific antidote.* Nonspecific drugs may be used if an urgent reversal is needed, such as recombinant activated factor VII. Similar to LMWHs, the renal clearance of fondaparinux contraindicates its use in patients with severe renal failure.

Vitamin K Antagonists

Vitamin K Antagonists Cannot Be Used Alone at the Acute Phase of VTE

Administered orally, VKAs inhibit the synthesis of coagulation factors by the liver. They inhibit the synthesis of factors II, VII, IX, and X, as well as that of natural anticoagulants proteins C and S. Unlike heparins, they have no activity on activated coagulation factors. This, along with the long half-life of factor II (i.e., prothrombin), is responsible for a delayed onset of action and precludes their use alone in patients with acute VTE. An overlap between fast-acting parenteral anticoagu-

lants and oral VKAs is necessary at initiation of anticoagulant therapy.³

VKAs Have a Narrow Therapeutic Window and a Large Inter- and Intraindividual Variability Over Time

Interindividual variability is explained by important variations in genes involved in the metabolism of vitamin K and of VKAs, whereas intraindividual variability over time is explained by numerous drug and food interactions, as well as comorbidities. Thus *VKA efficacy needs to be monitored according to the international normalized ratio (INR)*. The therapeutic target range for VTE is between 2.0 and 3.0.⁴ Under- and overdosing expose patients to the risks of recurrent VTE and of bleeding, respectively. *VKAs have a long duration of action.* This is an issue in case of bleeding or when an invasive procedure needs to be performed. However, when urgent reversal is needed, for example, in patients with bleeding or a need for urgent surgery, the use of vitamin K and prothrombin complex concentrates allows prompt restoration of hemostasis. Vitamin K can also be used to correct high INR values.⁴

VKAs Are Less Efficient than LMWH in Patients with Cancer

The fact that VKAs are less efficient than LMWHs⁵ may be due to an increased risk of both bleeding and clotting in these patients, as well as to difficulties in daily VKA management (food and drug interactions, nausea and thrombocytopenia on chemotherapy, etc.).

VKAs Should Not Be Used in Pregnant Women

VKA exposure during the first trimester increases the risk of malformation. During the third trimester, it increases the risk of bleeding. Theoretically, VKAs may be used during the second trimester, but this is often inconvenient.

Patients on Long-Term VKAs Have a High Risk of Bleeding

Current estimates of optimal duration for oral anticoagulant therapy (OAT) are based on the risk of recurrent VTE after OAT discontinuation but also on the risk of bleeding during long-term OAT.⁶

New Oral Anticoagulant Drugs

Pharmacology

New drugs under development have the potential to act on two distinct targets: (1) activated thrombin for orally available dabigatran etexilate and (2) activated factor Xa for oral rivaroxaban, apixaban, or edoxaban. Orally administered prodrug dabigatran etexilate is rapidly converted by esterases to the active drug dabigatran, which acts as a direct inhibitor of thrombin. The family of oral direct factor Xa inhibitors comprises several drugs: rivaroxaban, apixaban, and edoxaban. In contrast with heparin that acts through antithrombin on activated factor X and factor II, and in contrast with VKAs that inhibit the synthesis of coagulation factors (II, VII, IX, and X) by the liver, these drugs have a direct effect on coagulation factors independent from antithrombin. Both anti-IIa and

Table 1 New Oral Anticoagulant Regimens as Evaluated in Clinical Trials

Drug	Commercial Name	Target	Time to Peak (h)	Half-Life (h)	Bioavailability (%)	Renal Excretion (%)	Drug Interactions
Dabigatran	Pradaxa (Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT)	Factor IIa	1.5	14–17	8	>80	P-glycoprotein
Rivaroxaban	Xarelto (Janssen Pharmaceuticals, Titusville, NJ)	Factor Xa	2–3	7–11	80	33	CYP3A4 P-glycoprotein
Apixaban	Eliquis (Pfizer, New York, NY; Bristol-Myers Squibb, New York, NY)	Factor Xa	3	8–14	66	25	CYP3A4 P-glycoprotein
Edoxaban	–	Factor Xa	4	8–11	45	35	CYP3A4 P-glycoprotein

anti-Xa are active not only on circulating coagulation factors but also on coagulation factors within the thrombus.

The main pharmacokinetic characteristics of new oral anticoagulants (NOACs) are displayed in ►Table 1.

These new drugs may be less affected by diet and genetics and have fewer drug interactions compared with VKAs.⁷ Drug interactions occur through two major mechanisms: interac-

tion with cytochrome P450 (CYP) enzyme CYP 3A4 or P-glycoprotein (P-gp). A nonexhaustive list of the main interacting medications is displayed in ►Table 2. The clinical relevance of these interactions remains to be determined, but physicians should be cautious when prescribing NOACs. A recent cross-sectional study in patients admitted with atrial fibrillation revealed that more than 40% of them were

Table 2 New Anticoagulant Drugs' Interactions

CYP3A4 Inhibitors		P-glycoprotein	
Strong/moderate:	ritonavir, indinavir, nelfinavir Erythromycin, telithromycin, clarithromycin Fluconazole, ketoconazole, itraconazole nefazodone bergamottin quercetin aprepitant verapamil chloramphenicol	P-gp substrates	quinidine, propafenone, dronedarone atorvastatin, simvastatin, lovastatin diltiazem, verapamil, nicardipine, bepridil celiprolol, talinolol, carvedilol digoxin, amprenavir, saquinavir, indinavir, nelfinavir, ritonavir cyclosporine, tacrolimus sirolimus, prednisolone, dexamethasone terfenadine, fexofenadine cimetidine, ranitidine erythromycin, rapamycin levofloxacin, sparfloxacin, anthracyclines, taxanes loperamide, domperidone, phenytoin, morphine
Weak	cimetidine buprenorphine cafestol		
Unknown	Amiodarone, ciprofloxacin, cyclosporine Diltiazem, imatinib, Echinacea, enoxacin Ergotamine, metronidazole, mifepristone norfloxacin tofisopam delavirdine, efavirenz, nevirapine gestodene Mibefradil saquinavir fluoxetine/norfluoxetine, fluvoxamine	P-gp inhibitors	Quinidine Verapamil Amiodarone Erythromycin Clarithromycin ketoconazole itraconazole ritonavir

receiving at least one P-gp-affecting drug.^{7a} Drug interactions may be even more important with some drugs, for example,azole antimycotics, human immunodeficiency virus protease inhibitors such as ritonavir, among others, that simultaneously impact CYP 3A4 and P-gp.

Clinical Development

The first stage of clinical development focused on primary prevention of VTE in surgical patients. For treatment of VTE, the new drugs either challenge both LMWHs and VKAs (single-drug approach, e.g., rivaroxaban or apixaban), or only challenge VKAs (e.g., dabigatran or edoxaban) after an initial course of LMWH.

Results of Clinical Trials

Dabigatran

The phase 3 RE-COVER trial evaluated dabigatran etexilate for the treatment of acute symptomatic VTE [proximal deep venous thrombosis (DVT) or pulmonary embolism (PE)], in a randomized, double-blind, noninferiority trial [noninferiority margin hazard ratio (HR) 2.75] with warfarin as the comparator after an initial course of parenteral anticoagulant therapy.⁸ Oral dabigatran was given at a fixed dose of 150 mg twice daily for 6 months following initial parenteral therapy given for a median duration of 9 days. The primary outcome was the 6-month incidence of recurrent VTE and of VTE-related deaths, confirmed following central adjudication. The primary outcome was confirmed in 2.4% of 1274 patients randomly assessed to dabigatran and 2.1% of 1265 patients randomly assigned to warfarin (hazard ratio with dabigatran of 1.1, 95% CI 0.65 to 1.84). Major and clinically relevant nonmajor bleeding occurred significantly less frequently in patients on dabigatran: 5.6% in the dabigatran group, and 8.8% in the warfarin group (HR 0.63; 95% CI 0.47 to 0.84). There was no difference in the risk of major bleeding. Dyspepsia was more frequent in the dabigatran group (2.9% vs 0.6%, $p < 0.001$).⁸ In contrast with patients exposed to ximelagatran, there was no evidence of hepatic toxic effects associated with dabigatran. The results of a second trial with the same study design will soon be available (RE-COVER 2 study www.clinicaltrials.gov; NCT00680186).

Rivaroxaban

The phase 3 EINSTEIN-DVT trial compared rivaroxaban 15 mg twice a day for 3 weeks followed by 20 mg once daily for 3, 6, or 12 months, to LMWH and VKA for treatment of symptomatic DVT in a noninferiority (noninferiority margin HR 2.0), open-label, randomized trial.⁹ The primary outcome was the incidence of symptomatic recurrent VTE, recurrent DVT, nonfatal and fatal PE, confirmed following central adjudication. The primary outcome was observed in 2.1% of 1731 patients randomly assigned to rivaroxaban and 3.0% of 1717 patients randomly assigned to warfarin (HR with rivaroxaban of 0.68; 95% CI 0.44 to 1.04), confirming noninferiority. There was no difference in either the risk of major bleeding or the risk of major and clinically relevant nonmajor bleeding: 8.1% in both groups (HR 0.97; 95% CI 0.76 to 1.22). No difference in

any adverse events was found between the two groups.⁹ The ongoing EINSTEIN-PE study (www.clinicaltrials.gov; NCT00439777) has the same design but includes patients with symptomatic PE with or without DVT. The study has been completed, but no results are yet available.

Apixaban

The phase 3 AMPLIFY-VTE study (www.clinicaltrials.gov; NCT00643201) compares apixaban 10 mg twice a day for 7 days, followed by 5 mg twice a day for 6 months to LMWH and VKA for treatment of patients with proximal DVT or PE, in a randomized, double-blind, noninferiority trial. The study is still ongoing.

Edoxaban

The phase 3 HOKUSAI study (www.clinicaltrials.gov; NCT00986154) compares edoxaban 60 mg once daily for 3, 6, or 12 months (30 mg only in patients with body weight below 60 kg, creatinine clearance 30 to 50 mL/min or concomitant use of potent P-gp inhibitors) to VKA, after an initial course of parenteral anticoagulant therapy for treatment of patients with proximal DVT or PE, in a randomized, double-blind, noninferiority trial. The study is still ongoing.

Results of Clinical Trials—Extended Therapy

The duration of anticoagulant treatment for a first unprovoked VTE is unclear. This long-term decision should be based on balancing the long-term mortality risk from recurrent VTE, largely preventable with oral anticoagulant therapy, against the long-term mortality risk of major bleeding, the principal complication of oral anticoagulant therapy.⁶ Four clinical trials evaluated the NOACs for long-term therapy of VTE after a 6-month initial course of anticoagulation. These studies used as a comparator either warfarin in patients deemed at high risk of recurrent VTE, or placebo in patients with no indication for long-term warfarin therapy.

Versus Placebo

Dabigatran

The phase 3 RE-SONATE study evaluated dabigatran etexilate for the long-term treatment of VTE in a randomized, double-blind superiority trial with placebo as the comparator after a 6- to 18-month course of anticoagulant therapy.¹⁰ Oral dabigatran was given at a fixed dose of 150 mg twice daily for an additional period of 6 months. The primary outcome was the 6-month incidence of recurrent VTE and related deaths, confirmed following central adjudication. The primary outcome was confirmed in 0.4% of 681 patients randomly assigned to dabigatran and 5.61% of 662 patients randomly assigned to placebo (HR with dabigatran 0.08; 95% CI 0.02 to 0.25). Clinically relevant bleeding occurred significantly more frequently in patients on dabigatran: 5.3%, versus 1.8% in the placebo group (HR 2.9; 95% CI 1.5 to 5.6). There was no difference in the risk of major bleeding or the risk of cardiovascular events.¹⁰

Rivaroxaban

The phase EINSTEIN-EXTENSION trial compared rivaroxaban 20 mg once daily for 6 or 12 months, to placebo for long-term treatment of VTE after 6 to 12 months of anticoagulant therapy in a double-blind, randomized superiority trial.⁹ The primary outcome was the incidence of symptomatic recurrent VTE. The primary outcome was observed in 1.3% of 602 patients randomly assigned to rivaroxaban and 7.1% of 594 patients randomly assigned to placebo (HR with rivaroxaban 0.19; 95% CI 0.09 to 0.40). Major or clinically relevant nonmajor bleeding occurred significantly more frequently in patients on rivaroxaban: 6.0%, versus 1.2% in the placebo group (HR 5.2; 95% CI 2.3 to 11.7).

Apixaban

The phase 3 AMPLIFY-EXTENSION study (www.clinicaltrials.gov; NCT00633893) compares two dosages of apixaban: 5 mg twice a day or 2.5 mg twice a day, to placebo for a 12-month extended anticoagulant treatment of VTE, in a randomized, double-blind trial. The study is still ongoing.

Versus Warfarin

Dabigatran

The RE-MEDY study evaluated dabigatran etexilate for the long-term treatment of VTE in a randomized, double-blind superiority trial with warfarin as the comparator after a 3- to 12-month course of anticoagulant therapy.¹¹ Oral dabigatran was given at a fixed dose of 150 mg twice daily for an additional period of 6 to 36 months. The primary outcome was the incidence of recurrent VTE and related deaths, confirmed following central adjudication. The primary outcome was confirmed in 1.8% of 1430 patients randomly assigned to dabigatran and 1.3% of 1426 patients randomly assigned to warfarin (HR with dabigatran 1.44; 95% CI 0.73 to 2.61). Bleeding occurred significantly less frequently in patients on dabigatran: 19.4%, versus 26.2% in the warfarin group (HR 0.7; 95% CI 0.7 to 0.9). However, there was a statistically significant increase in the risk of acute coronary syndrome (ACS) in the dabigatran arm: 0.9% versus 0.2% in the warfarin arm, $p = 0.02$.¹¹

To summarize, the results of clinical trials using NOACs indicate that we might be able to replace VKAs in the treatment of patients with VTE. Moreover, two drugs (rivaroxaban and apixaban) also challenge LMWHs for the initial treatment of VTE and hence might replace both LMWH and VKA in the management of VTE. Advantages of the NOACs are their ease of use: no need for initial parenteral drug administration (for rivaroxaban and apixaban), same dose for all patients, no need for monitoring and dose adjustment, no need for platelet monitoring. On the other hand, disappointingly, the NOACs provide no clear benefits in terms of efficacy or safety.

For long-term therapy, clinical trials comparing NOACs to placebo are disappointing; although NOACs reduce the risk of recurrent VTE, they increase the risk of bleeding. One may regret that a reduced dose of dabigatran or of rivaroxaban has not been tested in clinical trials. This strategy had successfully

been tested for the direct thrombin inhibitor ximelagatran (withdrawn from the market a few years ago for hepatic toxicity) in the THRIVE III trial. After 6 months of therapy with 36 mg twice a day, a regimen of 24 mg twice a day allowed a significant reduction in the risk of recurrent VTE with no significant increase in the risk of bleeding.¹² A reduced dose is currently under investigation with apixaban in the AMPLIFY-EXTENSION trial.

Challenges in the Development of NOACs: From Clinical Trials to Practice

To better understand the ongoing developments, some issues need to be addressed in regard to study methods and interpretation.

Are Noninferiority Trials an Acceptable Design in VTE Treatment Studies?

The clinical studies of new anticoagulant drugs for VTE treatment did not demonstrate any improvement in efficacy as compared with existing therapies. In fact, all these clinical studies were designed as noninferiority trials.⁸ A noninferiority margin is determined that corresponds to the maximum loss of efficacy leading to a conclusion of noninferiority. The definition of this margin is a matter of controversy. A consensus is that the margin should ensure that the tested drug preserves at least three quarters of the efficacy of the reference treatment as compared with placebo. This accepted potential loss in efficacy needs to be offset by a better safety or ease of use. Furthermore, the per protocol analysis is important in a noninferiority trial because the intention to treat analysis favors the noninferiority. Admittedly, the intention to treat analysis remains the main analysis because it preserves the benefit of patients' randomization. Finally, there is a debate as to whether a double-blind or an open-label design should be used in noninferiority trials.¹³ Although open-label trials are "closer to reality," the double-blind design is crucial to ensure that the placebo effect—which may strongly favor the noninferiority—is similar in the two arms.

Do Patients Included in These Trials Reflect VTE Patients Seen in Daily Practice?

Patients included in clinical trials should have characteristics similar to those of patients in whom the treatment will be used in clinical practice. This has been an issue in recent trials on NOACs. Most trials had many exclusion criteria that selected patients with a lower risk of bleeding and of recurrent VTE. Drug interactions were limited and under close control. As a result, the mean age of patients included in these trials is at least 10 years younger than that of real-life patients. The need for a signed informed consent impedes the inclusion of patients with impaired cognitive function, though VTE mainly affects elderly patients with a different risk profile. Close monitoring of patients included in these clinical trials was different from routine care. Finally, few cancer patients and no patients with severe renal or hepatic failure were included. This raises issues on the extrapolation of the results to the general population. This also means that many patients

will continue to receive VKA due to contraindications to the use of NOACs.

Should DVT and PE Patients Be Evaluated Separately?

DVT and PE are two different clinical manifestations of VTE. However, these two conditions have a different prognosis. The short-term risk of VTE-related death appears much higher in patients treated for PE than in patients treated for DVT.¹⁴ At discontinuation of anticoagulant therapy, the risk of recurrent VTE might be higher in patients initially treated with DVT, but this increased risk might be counterbalanced in terms of prognosis by the fact that patients tend to experience recurrence at the same site as their initial episode of VTE.¹⁵ Hence, the risk-benefit balance of anticoagulant therapy may differ between patients with DVT or with PE. This may be true for initial therapy as well as for the optimal duration of anticoagulation.

Will Patients' Management Be Really Simpler?

Even if new anticoagulant drugs will simplify management of patients with VTE, regimens evaluated in clinical trials widely differ between drugs. Some include a pretreatment with LMWH, whereas others don't. Moreover, some drugs are prescribed at a higher dose for a variable period of time (e.g., 3 weeks for rivaroxaban, 1 week for apixaban). Finally, a lower dose is evaluated in a subgroup of fragile patients only for edoxaban (—Table 3). Furthermore, regimens may vary according to NOACs' indications or to geographic regions. In patients with moderate renal failure, a dose adjustment was tested for rivaroxaban in patients with atrial fibrillation but not in patients with VTE.

One of the main concerns for physicians is the lack of a specific antidote. Although the short half-life of the new anticoagulant drugs limits the need for antidote use, rapid reversal is necessary in patients with life-threatening bleeding or those requiring rapid surgical intervention. Some antidotes are under development, such as modified factor Xa with no catalytic activity for anti-Xa drugs,¹⁶ and selective antibody directed against dabigatran for dabigatran.¹⁷ Dabigatran may also be eliminated by hemodialysis. Nonspecific

antidotes, such as prothrombin complex concentrates (PCCs) or recombinant activated factor VIIa may be used in this indication, even though, to date, no clinical trial evaluating such drugs and using clinical end points is available. Moreover, the efficacy of PCC may differ between anti-Xa and anti-IIa reversal.¹⁸

No monitoring tests are currently available for the new anticoagulant drugs. Usual hemostatic parameters are modified under NOACs with no demonstrated correlation between the magnitude of the variation in hemostatic parameters and the risk of thrombosis or bleeding. The efficacy and safety of the NOACs were demonstrated in clinical trials in which no monitoring or dose adjustments were performed. However, it might be useful to appraise the anticoagulant activity in treated patients in case of recurrent VTE or bleeding events, and before an invasive procedure. Some biological tests are currently under development, such as calibrated prothrombin time for anti-Xa¹⁹ and ecarin- or thrombin-clotting time for anti-IIa.²⁰ These tests may be of interest should they demonstrate a correlation not only with drug plasma concentration but also with clinical outcomes and with an improved management of invasive procedures.

Moreover, the lack of monitoring suppresses a potential compliance assessment tool, INR monitoring. The latter gives feedback to patients on the way they manage their therapy. Finally, unlike VKAs whose action lasts several days, the short half-life of NOACs might render crucial the day-to-day compliance to the treatment. Evaluation of both patients' NOACs compliance and quality of life will be important. It is likely that educational efforts will need to be maintained or even reinforced in the future anticoagulant era.

Other Challenges

The concomitance of both the venous thromboembolic and the atherothrombotic risks is frequent and raises concerns on the need for an association between NOACs and antiplatelet agents. VKAs and therapeutic doses of LMWH are efficient in preventing both arterial and venous thromboses. As a matter of fact, in patients with arterial disease and an indication for anticoagulant therapy, the European Society of Cardiology

Table 3 New Anticoagulant Drugs' Regimens

Drug	LMWH Pretreatment?	Regimen	Regimen, Extended Treatment
Dabigatran	Yes	150 mg twice a day	150 mg twice a day
Rivaroxaban	No	15 mg twice a day × 3 weeks, then 20 mg once daily	20 mg once daily
Apixaban	No	10 mg twice a day × 7 days, then 5 mg twice a day*	5 mg twice a day or 2.5 mg twice a day*
Edoxaban	Yes	60 mg once daily;* Dose reduction: 30 mg once daily in patients with body weight < 60 kg, GFR 30–60 mL/min, P-gp inhibitors use	60 mg once daily* Dose reduction: 30 mg once daily in patients with body weight < 60 kg, GFR 30–60 mL/min, P-gp inhibitors use

* Study results not available.

GFR, glomerular filtration rate; P-gp, P-glycoprotein.

2010 guidelines recommend combining antiplatelet agents with VKA only in particular settings (e.g., recent ACS or coronary stenting).²¹ Whether this remains true for patients started on NOACs is unknown. The increased risk of ACS in the dabigatran arm of clinical trials comparing dabigatran to VKAs might indicate that oral direct anti-IIa does not protect against atherothrombotic complications to the same extent that VKAs do. Of note, an increased risk of ACS has not been observed in clinical trials assessing anti-Xa drugs, whereas it had already been observed with a previous anti-IIa (ximelagatran). The risk-benefit balance of the association between NOACs and AAP (antiplatelet agents) remains to be studied.

Using an oral drug with no initial injections, allowing an easier outpatient management and a wider therapeutic window could lead to “trivialization” of anticoagulation and to changes in clinical practice. One might fear that the availability of NOACs leads to an overdiagnosis and overuse of anticoagulants in patients with suspected VTE.

Which Drug Should We Prefer in Patients with VTE?

Importantly, all the NOACs have been tested either versus LMWH/VKA or versus VKA alone, but no direct comparison between drugs is available. Inferring indirect comparisons from reported differences in study conclusions should be avoided, and specific clinical trials are needed to better define indications for each one of these drugs. Should the results of ongoing trials confirm their efficacy and safety, rivaroxaban and apixaban are appealing in the management of VTE patients since they challenge both the LMWH and VKA and avoid the need for bridging from parenteral to oral therapy. Currently published clinical trials evaluating NOACs for an extended duration of treatment are disappointing. Reduced doses of anticoagulants (e.g., apixaban) should be tested for this indication.

UFH and VKA remain the only option for patients with renal failure (creatinine clearance below 30 mL/min), mechanical valve replacement, or severe VTE. LMWHs remain the best treatment for patients with cancer- or pregnancy-associated VTE.

Conclusion

The NOACs represent a true therapeutic revolution by way of their oral administration, rapid onset of action, fixed dose, no need for monitoring and dose adjustment thanks to predictable pharmacokinetics and pharmacodynamics, no risk of heparin-induced thrombocytopenia, and low levels of food or drug interaction. They may replace both short-acting parenteral heparins and VKAs and facilitate early discharge or outpatient care of selected VTE patients. However, the previous example of ximelagatran emphasized the need for caution. Nonetheless, the results of several clinical trials on various new drugs with different mechanisms of action (anti-Xa, anti-IIa), in thousands of patients during several months allow us to be optimistic. The first published studies suggest that most of them may be noninferior to conventional therapeutic strategies in terms of both efficacy and safety. Of note, new drugs have not yet been fully evaluated in several

subgroups of patients frequently encountered in daily practice: patients with atherothrombotic disease, cancer, and the elderly. Furthermore, the risk-benefit balance may not be different enough to lead to major modifications in treatment duration or indication. Physicians should recognize the need for continued education for patients using NOACs. The lack of monitoring of NOACs suppresses the feedback of INR. Evaluation of both treatment compliance and quality of life in patients receiving NOACs will be important. Several issues remain unsolved, including the lack of an antidote, management of invasive procedures, and the risk-benefit of the association of NOACs with antiplatelet agents. NOACs render the outpatient management of VTE easier, but they might trivialize anticoagulant therapy (overdiagnosis, reduced compliance) and expose more patients to the risks of these treatments.

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