Direct-acting Oral Anticoagulants: An Overview

Hatem H. Salem
Department of Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia

Correspondence: Prof. Hatem H. Salem, Department of Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Clayton, Victoria, Australia. E-mail: hatem.salem@monash.edu

ABSTRACT

In today’s practice, an increasing number of patients are prescribed anticoagulant therapy. Short-term anticoagulation as a primary or secondary prophylaxis of thrombosis is standard of care in many clinical indications. In addition, there has been a significant increase in the number of patients receiving long-term full therapeutic anticoagulation, particularly among patients with atrial fibrillation and those with venous thrombosis having a high risk of recurrence. Therefore, clinicians and patients warmly accepted the timely introduction of non-Vitamin K antagonists to clinical practice. Anticoagulants such as anti-Xa and antithrombin have been found to be effective and safe as compared with the standard of care using low-molecular-weight heparin and warfarin. Importantly, the new anticoagulants exhibit rapid onset of action and do not require regular monitoring, making them convenient and user-friendly. Another interesting and consistent observation is that the new anticoagulants have a lower incidence of intracranial bleeding as compared with warfarin therapy. However, before prescribing these drugs, clinicians should check and periodically monitor the renal function of their patients, particularly when new drugs known to affect renal function are introduced. Clinicians should also be aware that these new anticoagulants cannot be considered as a replacement for warfarin in all indications. For example, warfarin remains the drug of choice in patients with prosthetic valves and in those suffering from the antiphospholipid syndrome. Finally, clinicians should be aware and adhere to the appropriate indications for the use of these new anticoagulants and use them at their approved dosage.

Key words: Anticoagulant therapy, direct-acting oral anticoagulants, non-Vitamin K antagonists

INTRODUCTION

For decades, clinicians had to contend with heparin and warfarin as the only two anticoagulants available for the large number of patients presenting with a variety of thrombotic disorders. Heparin, which can only be used parenterally, was discovered over 100 years ago.[1] Warfarin, on the other hand, was discovered during the course of investigating a fatal bleeding disorder, known as “sweet clover disease,” that afflicted cattle.[1] This disease threatened the cattle industry in the United States and was caused by cattle feeding on coumarin-rich grass.

The pioneering work of Dr. Karl Paul Link, a biochemist, led to the discovery of dicumarol as the agent responsible for the “sweet clover disease.” This, subsequently, led to the identification of coumarin as an oral anticoagulant.[2] In 1945, Dr. Link got the idea of using coumarin as a rodenticide (to kill rats and mice). They developed a more active form of the drug and named it warfarin as their research work was supported by the Wisconsin Alumni Research Foundation, and “arin” is the chemical structure that the drug belongs to. Soon thereafter, it was discovered that the effects of warfarin can be fully reversed with Vitamin K. This was a critical discovery in...
reassuring the regulators of the safety of the medication and was instrumental in allowing the registration of the drug for use in humans.\[1\]

The discovery of heparin and warfarin paved the way for the widespread application of anticoagulant therapy in a large number of thrombotic disorders. Today, close to 1% of the population in the Western world is receiving anticoagulant therapy for the prevention or treatment of thrombosis.\[3\] Until recently, warfarin was the only available oral anticoagulant. Extensive clinical research on the optimum way to use warfarin has allowed for its wide application, but despite this, the drug remains difficult and complex to use. The primary problem with warfarin relates to its narrow therapeutic window and the unpredictability of its pharmacokinetics and pharmacodynamics. Many factors affect the absorption and clearance of the drug. Equally, the effects of the drug are very much influenced by dietary factors and other medications. This unpredictability, coupled with the narrow therapeutic window, demanded that patients receiving this treatment underwent regular monitoring to ensure that they were within the “therapeutic range.”\[4\] Despite careful and close monitoring, it is estimated that patients are in the “therapeutic range” only 40% of the time, with 50% of the time being over- or under-anticoagulated.\[4\] Patients who are under-anticoagulated are at risk of thrombotic events, whereas in patients who are over-anticoagulated, bleeding is a major concern. In this regard, it is noteworthy that warfarin is the drug most responsible for iatrogenic admissions to hospital.\[5\]

Not surprisingly, clinicians longed for more effective and safer anticoagulants. An ideal anticoagulant was viewed as one that was predictable in its effects, reliable, fast acting, had a wide therapeutic window and did not require monitoring.

The past 50 years have also witnessed a thorough understanding of the coagulation factors, their biochemical structure and the way they work. Despite the complexity of blood clotting, we have come to appreciate that in the coagulation reaction, two enzymes, namely, thrombin and factor X\(_2\), play a pivotal role in clot formation. The molecular structure of these enzymes was also determined, enabling scientists to develop chemical structures that occupy the active site of these enzymes, thereby blocking their activities. This work, which spanned over 30 years, resulted in the discovery of a significant number of new oral anticoagulants. These new drugs are small molecules, readily bioavailable and act by binding in the active site of either thrombin or X\(_2\), thereby directly inhibiting the coagulation mechanism. Newly developed drugs have undergone extensive clinical studies, which has resulted in their registration in most countries across the world.\[6-8\]

Several acronyms have been used to refer to these drugs. When first released, they were referred to as novel oral anticoagulants (NOACs). However, with the passage of time, the drugs were no longer “novel” and were referred to as direct-acting oral anticoagulants (DOACs) or target-specific oral anticoagulants. The acronym NOACs had a short revival on the basis that it referred to non-Vitamin K antagonists’ oral anticoagulants. More recently, the International Society of Haemostasis and Thrombosis has reviewed all the acronyms and recommended that the drugs be referred to as DOACs. There was a concern that the NOAC abbreviation could potentially be interpreted as “no” anticoagulation, and thus, DOAC was selected as the most appropriate acronym.\[9\]

With the development of new oral anticoagulants, for the first time in decades, clinicians have a smorgasbord of anticoagulants to choose from. However, it is important to bear in mind that the collective experience with these new anticoagulants is relatively small as compared with warfarin, and like many new drugs, we do not have the complete knowledge and understanding of their potential side effects. Therefore, it is important to be cautious and careful in prescribing these new agents and to ensure that the correct dose for the indication is used. In this article, I will review the commonly used new oral anticoagulants, presenting evidence for their use in different clinical settings.

**ANTITHROMBINS**

Ximelagatran was the first oral thrombin inhibitor to be developed and marketed. The drug was registered for use as an anticoagulant in several European countries on the basis of strongly positive clinical data. Unfortunately, the drug had to be withdrawn soon after its registration due to significant hepatic toxicity observed in several patients.\[6\] Soon thereafter, dabigatran etexilate was the second thrombin inhibitor developed. Dabigatran etexilate is a prodrug that is converted to the active form dabigatran by esterases widely available in the blood and liver.\[7\] The active drug binds to the active site of thrombin, completely inhibiting its enzymatic activity. Dabigatran is the only oral antithrombin available for clinical use. It has relatively low bioavailability, with only
6.5% of the drug being absorbed, while the bulk of the ingested dose is eliminated in feces. Dabigatran has a half-life of 14–17 h, with 80% of the absorbed drug being cleared by the kidney. Patients with impaired renal function rapidly accumulate the drug. The drug is very rapidly absorbed, with a $C_{\text{max}}$ of 2 h. If required, the effect of the drug can be readily reversed using a monoclonal antibody idarucizumab.\textsuperscript{[8]}

**ANTI-FACTOR X\textsubscript{A}**

Several anti-X\textsubscript{A} drugs have been synthesized and assessed in extensive clinical studies. The two most widely available drugs are rivaroxaban and apixaban. Both these drugs target the active site of factor X\textsubscript{A} and inhibit its ability to cleave prothrombin to form thrombin.

Rivaroxaban is a direct-acting drug that is 80% bioavailable. The drug is primarily metabolized by the liver. Although only 30% of the drug is excreted unchanged in the urine, care is needed in patients with renal impairment. Dose reduction when the creatinine is between 30 and 50 ml/min is required. The drug is rapidly absorbed with a $C_{\text{max}}$ of 2 h and a half-life of 5–9 h. This half-life is more prolonged in older individuals (approximately 9–13 h).\textsuperscript{[7]}

Apixaban is the second anti-X\textsubscript{A} registered in many countries. This drug has a 50% bioavailability and is rapidly absorbed, with a $C_{\text{max}}$ of 3 h. Approximately 27% of the drug is excreted unchanged by the kidney. Similar to rivaroxaban, despite the limited renal excretion, dose reduction is recommended if the creatinine clearance is reduced.\textsuperscript{[7]}

**CLINICAL APPLICATION OF DIRECT-ACTING ORAL ANTICOAGULANTS**

All DOACs have undergone very similar clinical development programs. In the first instance, the drugs were examined as thromboprophylactic agents for patients undergoing hip or knee arthroplasty. This was followed by clinical studies in patients with deep vein thrombosis (DVT) and pulmonary embolism (PE) as well studies in patients with atrial fibrillation (AF). I will briefly review the various studies that have led to the registration of the drugs in various clinical indications.

**Venous thromboembolism prophylaxis in hip and knee arthroplasty**

The reason initial studies focused on these patients are the high frequency of venous thrombosis in patients undergoing joint arthroplasty.

Dabigatran was evaluated in four studies: RE-MODEL\textsuperscript{[10]} and RE-MOBILIZE\textsuperscript{[11]} for patients undergoing knee replacement surgery and RE-NOVATE I\textsuperscript{[12]} and RE-NOVATE II\textsuperscript{[13]} for patients undergoing hip replacement surgery. In all four studies, the comparator was enoxaparin, the most widely used thromboprophylactic agent at the time and the gold standard for thromboprophylaxis. Dabigatran was used at a dose of either 150 or 220 mg once a day, with half the first dose given 1–4 h postoperatively and the full dose first administered the day after surgery. Enoxaparin was started the evening before surgery at a dose of 40 mg/day in all countries participating in the study, except in the United States. In studies carried out in the United States, the dose of enoxaparin was 30 mg twice daily, which was consistent with the clinical practice in the country. All studies were designed to be noninferiority studies. The results confirmed that dabigatran was not inferior to enoxaparin for the prevention of venous thrombosis in patients undergoing hip or knee arthroplasty and that there was no difference in the bleeding side effects (both major and minor) between dabigatran and enoxaparin. The studies also found the optimum duration of thromboprophylaxis to be 15 and 30 days for patients undergoing knee replacement surgery and hip replacement surgery, respectively.

Rivaroxaban was evaluated in a similar set of studies: RECORD 1\textsuperscript{[14]} and RECORD 2\textsuperscript{[15]} (hip replacement studies) and RECORD 3\textsuperscript{[16]} and RECORD 4\textsuperscript{[17]} (knee replacement studies). In all these studies, rivaroxaban was used at a fixed dose of 10 mg/day, starting 6–8 h after wound closure. In RECORD 1 and 2, enoxaparin was used as the comparator at a dose of 40 mg/day, starting 12 h presurgery and restarting 6–8 h postwound closure. The duration of anticoagulant administration was 10–14 days in RECORD 2 and 31–39 days in RECORD 1. In terms of studies for patients undergoing knee replacement surgery, RECORD 4 was carried out in the United States and the comparator was enoxaparin 50 mg bd, while RECORD 3 was carried out in countries other than the United Sates and the comparator was enoxaparin 40 mg daily. Once again, the first dose of rivaroxaban was administered 6–8 h postwound closure, whereas enoxaparin was first administered 12 h presurgery in RECORD 3 and 12 h postsurgery in RECORD 4. In all the studies, rivaroxaban was demonstrated to be superior as compared with enoxaparin in the prevention of venous thromboembolism (VTE) and mortality. There was no difference in major bleeding in the different arms of all studies. This was the first demonstration of enhanced clinical efficacy with no increase in the risk of major bleeding.
Apixaban was also studied in patients undergoing hip and knee arthroplasty. The dose of apixaban in all studies was 2.5 mg bd. In the ADVANCE 1 study, apixaban was compared with enoxaparin 30 mg bd, while in the ADVANCE 2 study, apixaban was compared with enoxaparin 40 mg daily. The ADVANCE 5 study enrolled patients that underwent total hip replacement and the comparator was enoxaparin 40 mg/day. In all studies, apixaban was initiated 12–24 h postoperatively. Enoxaparin, when used at 30 mg bd, was started at the same times as apixaban. However, when the drug was used at 40 mg daily, the first dose was administered 12 h preoperatively. In ADVANCE 2 and 3, apixaban was found to be superior than enoxaparin (40 mg daily) in terms of efficacy, with a similar safety profile, whereas in ADVANCE 1, enoxaparin (30 mg bd) demonstrated similar efficacy as apixaban, with no statistically significant difference in the safety profile.

**Summary of the orthopedic thromboprophylaxis studies and their impact on clinical practice**

It has been demonstrated that dabigatran at a dose of 150 or 220 mg, administered at half dose within 1–4 h of surgery and daily thereafter, has a similar efficacy and safety profile to enoxaparin. On the other hand, rivaroxaban and apixaban, administered 6–8 h and 12–24 h postoperatively, respectively, proved to be superior to the standard dose of enoxaparin (40 mg daily, first dose given 12 h presurgery). Furthermore, both drugs demonstrated a similar safety profile to enoxaparin. Rivaroxaban and apixaban were similar in terms of efficacy and safety to enoxaparin administered at a dose of 30 mg bd.

As a result of these studies and the clear superiority of apixaban and rivaroxaban as thromboprophylactic agents, there has been a significant shift in the way patients are being managed. While some clinicians continue to use enoxaparin as their thromboprophylactic agent of choice, evidence suggests that for optimum results, the drug should be administered twice daily at a dose of 50 mg. This is clearly a demanding situation, given the optimum duration of thromboprophylaxis (10–14 days for knee replacement and 30 days for hip replacement surgery). The oral route of administration of rivaroxaban and apixaban has resulted in an increasing number of clinicians shifting their practice to these drugs in preference to enoxaparin. Dabigatran has not enjoyed similar success given that its efficacy is comparable with that of enoxaparin and the need to initiate treatment at half the dose within 1–4 h of surgery.

**TREATMENT OF VENOUS THROMBOEMBOLISM**

When managing acute VTE, we recognize the following three distinct treatment phases:

1. **Acute treatment:** This is the early phase when patients first present. The patients are highly thrombogenic, and a more intense anticoagulation regimen is needed in this phase. This phase lasts a minimum of 7 days from presentation.

2. **Long-term treatment:** Following the acute/early phase, patients progress to the long-term treatment of venous thrombosis. In this phase, the dose of anticoagulation is slightly moderated. This phase lasts 3–6 months.

3. **Extended treatment:** Patients deemed of the need for more prolonged treatment are referred to as being in the extended phase of anticoagulation therapy. In this phase, many trials have used a prophylactic dose of anticoagulation.

**Dabigatran for the treatment of venous thromboembolism: Acute and long-term studies**

In all studies in patients with VTE, the dose of dabigatran used was 150 mg 12 hourly. The RE-COVER I study randomized patients with confirmed VTE to receive 6 months of treatment with dabigatran or “standard of care” (heparin, low molecular weight or unfractionated, followed by warfarin). Patients randomized to the dabigatran arm received low-molecular-weight heparin in the acute phase of treatment for a period of 10–14 days before dabigatran was commenced. Patients were evaluated after 6 months of treatment. In this study, a fixed dose of dabigatran was as effective as warfarin, with a similar safety profile. The key difference between the two arms of the study is the need to continuously monitor and modify the dose of warfarin, whereas dabigatran was used at a fixed unmonitored dose.

The results of RE-COVER I were confirmed in the second study, RE-COVER II. Both studies had identical protocols.

**Dabigatran in the extended treatment of venous thromboembolism**

Two studies (RE-MEDY and RE-SONATE) examined the efficacy of dabigatran in extended treatment. All patients completed 3–6 months of their venous thrombosis treatment before being eligible for enrolment in the extended treatment studies. In the RE-MEDY study, patients were blindly randomized to receive dabigatran.
or warfarin over an 18-month period. The results of this study confirmed that dabigatran was not inferior to warfarin in preventing VTE recurrence.[22] In the second study, RE-SONATE, eligible patients were blindly assigned to dabigatran or placebo. As expected, patients on dabigatran fared much better, with a significant reduction in the incidence of VTE as compared with the placebo arm of the study.[23]

The dabigatran studies cited above confirmed the efficacy and safety profile of dabigatran in the long-term and extended treatment of VTE. The only bleeding that was noted more commonly in dabigatran users was gastrointestinal bleeding; however, compared with warfarin, the difference was not statistically significant. It is important to note that in the dabigatran treatment studies (RE-COVER 1 and 2), the early (acute) treatment of VTE was performed using a low-molecular-weight heparin and dabigatran was first introduced in the long-term treatment phase.

Rivaroxaban in the treatment of venous thromboembolism

The EINSTEIN DVT and EINSTEIN PE studies were open-label studies where patients with proven DVT or PE were randomized to rivaroxaban or “standard of care” (low-molecular-weight or unfractionated heparin followed by warfarin).[24,25] Rivaroxaban was administered at a dose of 15 mg twice daily for the first 3 weeks (the acute phase) followed by 20 mg daily for 3–12 months. In the two studies (EINSTEIN DVT and EINSTEIN PE), rivaroxaban was confirmed to be noninferior to warfarin in terms of efficacy, with similar rates of major and clinically relevant nonmajor bleeding.

At the end of the EINSTEIN DVT/PE studies, patients were given the opportunity to enroll in a separate study, the EINSTEIN-extension study.[26] Here, patients were randomized to ongoing rivaroxaban treatment at a dose of 20 mg daily or placebo. Rivaroxaban treatment was associated with an 82% relative risk reduction in the recurrence of VTE as compared with placebo. The authors of the study concluded that approximately 15 patients needed to be treated to prevent one recurrent VTE event. This is clearly a very significant and important finding, particularly in view of the low incidence of observed major bleeding (0.7%).

Apixaban in the treatment of venous thromboembolism

In the AMPLIFY trial, patients with VTE were randomized to receive apixaban or “standard of care” (low-molecular-weight or unfractionated heparin followed by the warfarin therapy).[27] The dose of apixaban was 10 mg twice daily for the 1st week (acute phase of treatment), reducing to 5 mg twice daily in the long term (6 months). The results of this study confirmed that apixaban was not inferior to standard of care but, importantly, was much safer with a significant lower rate of major bleeding.

In a separate study (AMPLIFY-extension), patients who completed at least 6 months of anticoagulation for a VTE were randomized to receive either placebo or one of the two doses of apixaban (2.5 mg bd or 5 mg bd).[28] Recurrent DVT- and VTE-related mortality was reduced from 8.8% in the placebo arm to 1.7% in the two apixaban arms of the study. The rate of major bleeding was not different across the three studies.

Summary of venous thromboembolism treatment studies

The studies detailed above have all confirmed that the new anticoagulants have an efficacy and safety profile similar to that of warfarin in the treatment of VTE. Importantly, the new drugs were used at a fixed dose and without regular laboratory testing. However, it is important to bear in mind that if using dabigatran, a lead-in period of treatment of 10–14 days with low-molecular-weight heparin is required and that dabigatran cannot be used upfront in patients with VTE. The situation is different for apixaban and rivaroxaban, where studies have clearly shown that both drugs can be used upfront in the treatment of patients with VTE. Once again, it is important to bear in mind that the initial treatment of patients with VTE requires the use of these drugs at a higher dose as compared with the dose used in the long-term phase of treatment.

PREVENTION OF THROMBOEMBOLISM IN PATIENTS WITH ATRIAL FIBRILLATION

To date, warfarin has been the only drug available to prevent thromboembolic events in patients with AF. The need for constant monitoring, change of dose as well as the various drug–drug and food–drug interaction has made it difficult for clinicians to recommend anticoagulation to all patients at risk of thromboembolic events, particularly elderly patients. Not surprisingly, the introduction of the new anticoagulants used at a fixed dose and without monitoring was highly anticipated. Three pivotal studies were performed, namely, the RELY study[29] (dabigatran vs. warfarin), the ROCKET study[30] (rivaroxaban vs. warfarin) and the ARISTOTLE study[31] (apixaban vs.
warfarin), all of which enrolled very large number of patients (>10,000) and had very similar design.

In the RELY study, dabigatran was used at two doses: either 150 or 110 mg administered twice daily. Patients receiving the 150 mg dose had superior outcomes in terms of thromboembolic events compared with warfarin, whereas those receiving the 110 mg had similar outcomes compared with warfarin. As expected, the bleeding in patients receiving 110 mg was significantly less than in patients on warfarin, whereas patients receiving the 150 mg dose had similar bleeding events as warfarin. One key point is that both doses of dabigatran were associated with a very significant reduction in intracranial hemorrhage as compared with warfarin [0.23% and 0.3% (110 mg and 150 mg, respectively)], and 0.74% for warfarin).[29]

The ROCKET study randomized patients with AF to receive rivaroxaban or warfarin. The dose of rivaroxaban was 20 mg daily, unless the creatinine clearance was 30–49 ml/min, where the dose was reduced to 15 mg daily. In this study, rivaroxaban was shown to be noninferior to warfarin in the prevention of embolic events. Although bleeding events were the same in the two arms of the study, warfarin usage was associated with a significant higher rate of intracranial hemorrhage compared with rivaroxaban (0.8% vs. 0.4%). This is very similar to the results observed in the RELY study.

In the ARISTOTLE study, apixaban was compared with warfarin in a similar cohort of patients with AF. Apixaban was used at a dose of 5 mg twice daily, with the dose reduced to 2.5 mg twice daily in patients with two or more of the following: aged >80 years, weight of ≤60 kg and a serum creatinine of ≥1.5 mg/dL (133 μmol/L). In this study, apixaban demonstrated similar efficacy but was much safer than warfarin both in terms hemorrhagic stroke and major bleeding.

**Conclusion of the studies on new anticoagulants in patients with atrial fibrillation**

All studies have confirmed that the new anticoagulants used at a fixed dose are as effective as warfarin in the prevention of embolic events in patients with AF. The only drug that was superior to warfarin was dabigatran when used at a dose of 150 mg twice daily. One very important lesson that emerged from all these studies is that warfarin has a propensity to cause the development of intracranial hemorrhage, a feature not shared to the same extent by the new drugs. This makes the new drugs a very attractive proposition for the long-term treatment of patients with AF, given the very serious outcome and poor prognosis of patients who succumb to complicating intracranial bleeding.

**PERIOPERATIVE MANAGEMENT OF PATIENTS ON NEW ANTICOAGULANTS**

All three drugs discussed in this review have relatively short half-lives. If a patient receiving a DOAC is planned for surgery, it is important to stop the drug for an appropriate period of time to enable it to be cleared presurgery.[30] In patients with a normal renal function who are to undergo a planned surgery that poses mild-to-moderate risk of bleeding, it is sufficient to stop the drug 1 day preoperatively. Patients undergoing surgery where the risk of bleeding is high or when any bleeding is undesirable should have their anticoagulants ceased 48 h preoperatively. In select patients (those with renal impairment creatinine clearance 30–50 ml/min), the anticoagulant should be ceased 3–4 days preoperatively. In some situations, it may be necessary/desirable to assess patients preoperatively for residual anticoagulant activity. This can be done using an anti-X assay for rivaroxaban and apixaban or a dilute thrombin time for dabigatran.

**SITUATIONS WHERE DIRECT-ACTING ORAL ANTICOAGULANTS SHOULD NOT BE USED**

The new drugs have been around for a relatively short period of time as compared with warfarin and heparin. Thus, our knowledge and experience with these drugs is limited. However, it is now clear that warfarin continues to be the drug of choice in patients with prosthetic valves. A study on the application of dabigatran in patients with mechanical valves has clearly shown that dabigatran should not be used in these patients.[32] Other situations where warfarin will continue to be used (until new data emerge) include patients with moderate-to-severe renal impairment (creatinine clearance < 50 ml/min), those with severe antiphospholipid syndrome and poorly compliant patients. Patients in whom the venous thrombosis is driven by a cancer represent a special category of thrombosis and are best treated with low-molecular-weight heparin.[33]

**REVERSAL OF DIRECT-ACTING ORAL ANTICOAGULANTS**

With the increasing use of DOACs, there will be many instances when prompt reversal of anticoagulant activity will be required. Although the half-lives of the drugs are relatively short as compared with warfarin, there is still...
a need for prompt reversal in situations of significant bleeding, in patients unable to clear the drug (for example, deteriorating renal function) or in cases of overdose.

Over the past 5 years, scientists have been actively pursuing the discovery and clinical development of specific antidotes to DOACs. Idarucizumab is a novel humanized mouse monoclonal antibody that binds dabigatran and promptly reverses its anticoagulant effect.\[^8\] A 5 g intravenous infusion of this antibody resulted in the normalization of dilute thrombin time in 98% and 93% of the two groups studied. This dabigatran antagonist has now been approved by several regulatory agencies and is available for clinical use. For the reversal of factor X\(_a\) antagonists, scientists have followed a factor X\(_a\) decoy strategy. Andexanet alfa is an inactive heavy chain of factor X\(_a\) that binds the factor X\(_a\) inhibitors and clears them from the circulation. Andexanet has been shown to effectively reverse the anticoagulant activity of both rivaroxaban and apixaban.\[^54\] It is currently in a phase III clinical trial program.

**OVERALL CONCLUSIONS**

Since their introduction over the past decade, the new anticoagulants have progressively replaced warfarin in several indications. The convenience of using these drugs has enabled practitioners to prescribe anticoagulation to patients who were unable to undergo this treatment previously. Unfortunately, the lack of head-to-head comparison of the new drugs makes it impossible to decide if one is better than the other. Finally, clinicians should be reminded that anticoagulant drugs are potentially dangerous, and for the minimization of side effects, particularly bleeding, patients should be carefully instructed on the appropriate usage of the medication. The indication and safety of ongoing anticoagulant therapy should always be reviewed, and periodic assessment of renal function is essential to minimize overdose with these medications.

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**Conflicts of interest**

There are no conflicts of interest.

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