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Review article

New oral anticoagulants and their reversal agents

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Abstract

Atrial fibrillation is a commonly encountered pathology in medical practice, and its prevalence has shown a continuous rise over the past years. Atrial fibrillation has a significant impact on patients' quality of life, not only due to the standard anticoagulant treatment with vitamin K antagonists that require close monitoring and dose adjustment, but also due to the fragile equilibrium between hemorrhagic and thrombotic risks. The introduction of new oral anticoagulants (NOACs) in the treatment guidelines for atrial fibrillation has improved the quality of life, as NOACs do not require close monitoring or dose adjustments. However, even if the safety profile of the NOACs regarding the hemorrhagic risk is superior to vitamin K antagonists, the problem raised by an unexpected hemorrhage (e.g. severe hemorrhage after an accident) and the need for efficient hemostasis in a chronic anticoagulated patient has remained unsolved. To find a solution for this problem, reversal agents for NOACs have been developed and tested, and two of them, idarucizumab and andexanet-alpha, have already been approved by the FDA, thus making NOACs increasingly appealing as a choice of anticoagulation treatment.

Keywords : atrial fibrillation, new oral anticoagulants, idarucizumab, andexanet-alpha

Highlights

- ✓ Long-term oral anticoagulant therapy includes vitamin K antagonists and new oral anticoagulants (NOACs).
- ✓ The introduction of NOACs in the treatment guidelines for atrial fibrillation has improved the quality of life of patients, as they do not require close monitoring or dose adjustments.
- ✓ NOACs are divided into two broad categories, depending on the mechanism of action: substances that directly inhibit the activity of thrombin (e.g. dabigatran) and substances that directly inhibit activated factor X (e.g. rivaroxaban, apixaban, edoxaban).

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Introduction

Atrial fibrillation – epidemiological data

Atrial fibrillation is a frequent pathology in medical practice, which despite treatment and careful management, remains the primary cause of heart failure, stroke, and even sudden death (1-3).

Epidemiological data show a rise in the prevalence and incidence of this pathology (1). This could be due to easier detection of atrial fibrillation, access to ECG devices, and the possibility of ECG-Holter monitoring, thus discovering paroxysmal atrial fibrillation episodes otherwise undiagnosed.

Global life expectancy has grown significantly between the years 1970 and 2015 (4), in some countries even up to 20 years, with average life expectancy around 80 years at the European level (5). This implies a global increase in the prevalence of the elderly population, as well as of the chronic diseases associated with ageing, that increase the risk of developing atrial fibrillation (e.g. hypertension, ischemic heart disease, valvular diseases, etc.). Atrial fibrillation in Europe is estimated at 3% in adults older than 20 years, with an expected number of 14-17 million patients by 2030 in the European Union (6-8).

Anticoagulant medication in patients with atrial fibrillation

A major complication of atrial fibrillation is the increased risk of stroke. An essential objective in the treatment of atrial fibrillation is the prevention of stroke by using oral anticoagulant therapy (9). Long-term oral anticoagulant therapy includes vitamin K antagonists and new oral anticoagulants that should be personalized for each patient according to comorbidities in order to achieve a balance between thrombotic and hemorrhagic risk (10).

The decision to anticoagulate a patient should take into consideration two scores for the assessment of thrombotic risk and hemorrhagic risk (9).

The CHA2DS2-VASC score evaluates the risk of stroke in patients with non-valvular atrial fibrillation. CHA2DS2-VASC is calculated adding the points according to the presence of some major risk factors for stroke (Table 1). Anticoagulation therapy should be reconsidered in patients with a CHA2DS2-VASC score ≥ 1 and is indicated at a score ≥ 2 (11, 12).

Table 1. CHA_2DS_2-VASC score

Points	CHA_2DS_2-VASC
1	Congestive heart failure
1	Hypertension
2	Age ≥ 75 years
1	Diabetes mellitus
2	Stroke/ Transient Ischemic Attack/ Thromboembolic event
1	Vascular disease (prior Myocardial Infarction, Peripheric Arterial Disease or Aortic Plaque)
1	Age 65 to 74 years
1	Sex category (female sex)

The HAS-BLED (Table 2) score assesses hemorrhagic risk. A high score is not a contraindication for anticoagulant treatment, but rather indicates the need for accurate detection and subsequent removal of the modifiable hemorrhagic risk factors. Modifiable hemorrhagic risk factors are uncontrolled arterial hypertension (especially a systolic blood pressure > 160 mmHg), a labile INR or a therapeutic INR in less than 60% of the time, usage of medication that predisposes to bleeding, or excess alcohol usage (13, 14).

Table 2. HAS-BLED score.

Points	HAS-BLED
1	Hypertension (uncontrolled, systolic blood pressure >160 mmHg)
1	Abnormal renal function
1	Abnormal liver function
1	Stroke
1	Bleeding
1	Labile INR
1	Age > 65 years
1	Prior alcohol (≥ 8 drinks/week) or drug usage history
1	Medication usage predisposing to bleeding (antiplatelet agents, NSAIDs)

Discussions

According to the latest European Society of Cardiology guideline, oral anticoagulant therapy is recommended only in non-valvular atrial fibrillation and is not recommended in patients with valvular atrial fibrillation (atrial fibrillation in patients with mitral stenosis or prosthetic valve) (8). In deciding the anticoagulant treatment, the comorbidities of the patient play a very important role (15-17).

New oral anticoagulants

These molecules have been developed because of the multiple disadvantages of vitamin K antagonists. Vitamin K antagonists (warfarin, acenocoumarol) have a long duration of action, with a long half-life and an unpredictable anticoagulant effect that requires careful and constant monitoring by checking the value of INR and adjusting doses accordingly. New oral anticoagulants have been synthesized as a higher-safety therapeutic option. These are divided into two broad categories, depending on the mechanism of action: substances that directly inhibit the activity of thrombin (e.g. dabigatran) and substances that directly inhibit activated factor X (e.g. rivaroxaban, apixaban, edoxaban). These new classes of anticoagulants have the advantage of a more predictable anticoagulant effect, fixed doses, and not requiring INR monitoring. In addition, studies have demonstrated the superior safety profile of the new anticoagulants compared to warfarin in the case of non-valvular atrial fibrillation (18). NOACs offer a superior safety profile compared with cumarinic anticoagulants in patients who need surgical interventions, with a shorter presurgery interrupting period.

Dabigatran, the first approved NOAC, was introduced following the results of the RE-LY study (18). The dose of dabigatran is 110 mg twice daily or 150 mg twice daily, the study demonstrating that both doses are non-inferior to warfarin. Compared to warfarin, dabigatran 110 mg, administered twice daily, demonstrated a lower rate of major hemorrhage, with similar per cent of stroke or systemic embolism (18). Administered 150 mg twice daily, dabigatran had similar major bleeding rates to warfarin, but lower rates of stroke or systemic embolism (18). The daily dose of dabigatran depends on the age and comorbidities of the patient. Treatment with dabigatran has been associated with a higher rate of digestive hemorrhage and dyspeptic symptoms. A possible explanation may be the tartaric acid, a component of the capsule, which is intended to provide a lower pH and better absorption at the digestive level (18). Dabigatran has predominantly renal elimination (80%); it is not recommended in patients with a creatinine clearance (CrCl) between 30-59 mL/min and is contraindicated in patients with CrCl less than 30mL/min (19, 20).

Rivaroxaban, according to the ROCKET-AF study, is also non-inferior to warfarin, with similar rates of stroke and systemic embolism prevention and of hemorrhagic risk (21). However, in the group of patients treated with rivaroxaban, a lower incidence of intracranial hemorrhage was observed and a greater frequency of digestive hemorrhage. The usual dose of rivaroxaban is a single dose of 20 mg per day or 10 mg/day for patients with a CrCl of 15-49 mL/min (21, 22).

Apixaban has been shown in the ARISTOTLE study to be superior to warfarin regarding stroke prevention (18). Compared to warfarin, apixaban had lower rates of bleeding of any type, both intracranial hemorrhages and gastrointestinal bleeding, and is the only NOAC that shows significantly lower rates of all types of bleeding (23). Also, the group of patients treated with apixaban had a lower incidence of myocardial infarction than the group treated with warfarin. This result could be an advantage of apixaban compared to dabigatran, which had a higher incidence of myocardial infarction compared to the warfarin-treated group. The standard dose of apixaban is 5 mg twice daily, apixaban being the NOAC with the lowest percentage of renal elimination (25%) (23). A lower dose to 2.5 mg twice daily is recommended if at least two of the three criteria are present: age > 80 years, weight < 60 kg or serum creatinine > 1.5 mg/dL (24).

The latest NOAC is *edoxaban*, which was compared to warfarin in the ENGAGE-AF-TIMI study (25). Edoxaban has two dose regimens: high (a single daily dose of 60 mg) or low (a single daily dose of 30 mg). Edoxaban proved to be non-inferior to warfarin regarding the prevention of ischemic stroke and systemic emboli, with a higher incidence of ischemic stroke when taken in a low-dose regimen, and a lower incidence when taken in the high-dose regimen (25). Both dose regimens demonstrate a significant decrease in bleeding complications, both intracranial hemorrhages and fatal hemorrhages, the only exception

being gastrointestinal hemorrhages that have a higher frequency only in the high-dose regimen group (25). An important drug interaction occurs with glycoprotein P inhibitors, such as verapamil or quinidine, so, in case of concomitant medication with these drugs, the dose of edoxaban should be reduced by half. Edoxaban is not recommended in patients with CrCl <30 mL/min. Doses should be adjusted for patients with a CrCl between 15-49 mL/min, at 30 or 15 mg per day (25, 26).

All NOACs have demonstrated a superior safety profile or at least non-inferior to warfarin regarding hemorrhagic risk, and are at least non-inferior to warfarin in the prevention of ischemic stroke and systemic embolism. However, the frequency of digestive hemorrhage was higher in patients treated with dabigatran, rivaroxaban, or edoxaban compared to patients treated with warfarin, apixaban being the NOAC with the lowest frequency of all types of hemorrhage, including gastrointestinal bleedings (27).

The NOACs are not recommended in patients with severe renal dysfunction. A major drawback has been, until recently, the lack of an antidote, with the impossibility of stopping the anticoagulant effect in case of severely fatal bleeding (for example following severe trauma, the need of an emergency or urgent operation, etc.) (28, 29). Numerous surgical interventions, especially pelvic surgery, in both men and women, even not major, are associated with intraoperative blood losses (30). Elimination of NOACs is realized at the renal level, so kidney function must be carefully monitored during treatment with NOACs by monitoring the serum creatinine, both preoperative and postoperative (31).

New perspectives in the acute treatment of hemorrhage in patients taking NOACs: reversal agents Idarucizumab and Andexanet Alpha

To counter the anticoagulant effects of NOACs in case of acute bleeding, the reversal agents idarucizumab and andexanet alpha were recently introduced on the market.

Idarucizumab is a monoclonal antibody that acts against dabigatran and was introduced on the market following the results of a REVERSE-AD study (32). Idarucizumab is given in a total dose of 5 g, divided into two 50 mL bolus infusions, over 10-15 minutes. Its effect is fast, the median time to reversing the effect being 2.5 hours (33). Idarucizumab has been approved in Europe and is indicated in life-threatening bleedings or emergency surgery, in patients with chronic anticoagulant therapy with dabigatran (34).

In patients receiving preprocedural idarucizumab, efficient periprocedural hemostasis was obtained in 93.4% of the cases (33). In addition, administration of idarucizumab does not expose to an additional procoagulant post-administration risk, the risk depending on the pre-existing risk factors of each patient. Only 4.8% of patients had thrombotic events within 30 days after idarucizumab administration (33). Idarucizumab can be administered regardless of the renal function, without the need for dose adjustment. One drawback is the lack of data regarding the use of idarucizumab in patients younger than 18 years old and in pregnant women.

Also, immunogenic reactions may occur after administration of idarucizumab. So far, no allergic reactions to idarucizumab have been reported, but some cases of immunogenic reactions with anti-idarucizumab antibodies production have been reported, without affecting the response in case of a future administration (34). However, the data regarding these situations is limited and remains the subject of future studies.

Andexanet Alfa is a recombinant modified human factor Xa molecule and is the second reversal molecule, recently approved by the FDA, against rivaroxaban and apixaban. According to the Andexanet-Alfa 4 study, it demonstrated its efficacy on both rivaroxaban and apixaban, without significant adverse effects (35). Andexanet Alfa was administered depending on the last dose of anticoagulant taken by the patient: if the last dose was administered more than 7 hours before, then 400 mg of Andexanet Alfa had been given as a bolus, followed by 480 mg during 2 hours infusion. If the last dose of anticoagulant was taken less than 7 hours or if the last dose was unknown, then 800 mg of Andexanet Alfa had been given as a bolus, followed by 960 mg during 2 hours infusion (35). Effective hemostasis was reached 12 hours after infusion with Andexanet Alfa, being present in 79% of the study population. At 30 days post-administration, thrombotic events occurred in 18% of patients, and the mortality rate was 15% (35).

Ciraparantag is a new reversing agent, which is the subject of the currently undergoing study "Phase 2 Placebo-Controlled, Single-Site, Single-Blind Study of Rivaroxaban Reversal by Ciraparantag as Measured by WBCT" (36). Ciraparantag is a water-soluble molecule

that binds heparin and direct factor Xa and IIa inhibitors, which had promising results in phase I studies, managing to reverse anticoagulation due to edoxaban after a dose of 100-300 mg (36).

Conclusions

NOACs have entered the clinical practice, being recommended by international guidelines, demonstrating their efficacy and superior safety profile compared to warfarin. The emergence and approval of the new molecules, idarucizumab and andexanet alfa, solve one of the most important drawbacks of NOACs, the absence of a reversal agent, and provides the opportunity for better control of life-threatening bleedings or uncontrollable hemorrhages in emergency surgeries, for patients who follow chronic treatment with NOACs (37, 38).

Conflict of interest disclosure

The authors declare that there are no conflicts of interest to be disclosed for this article.

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