New oral anticoagulants - possible extension to other indications (Review)

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Abstract. Anticoagulant treatment is necessary in various conditions, with curative or preventive purposes. Until recently, the only oral anticoagulants available have been vitamin K antagonists. To overcome the disadvantages of the antivitamin K oral anticoagulants, new oral anticoagulants (NOACs) have been developed and included in clinical trials. After more than 60 years of using vitamin K antagonists, the introduction of NOACs represent a medical breakthrough, with promising prospects. Due to their promising results and better safety profile, NOACs have become an appealing alternative to vitamin K antagonists in a short period of time. NOACs have been approved for the prevention and treatment of venous thromboembolism and for the prevention of stroke in patients with nonvalvular atrial fibrillation. Starting with postoperative venous thromboprophylaxis after hip replacement surgery, NOACs have been approved also for other clinical situations. Rivaroxaban is the first oral anticoagulant approved to be used in combination with an antiplatelet agent to prevent atherothrombotic events in adults with coronary artery disease and/or peripheral artery disease. However, further investigation is needed to establish which group of patients would benefit most from this medical approach. Furthermore, preliminary studies have shown that NOACs seem to be a reasonable choice of anticoagulation for patients with cancer, but further studies are expected.

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1. Introduction

The anticoagulant treatment is used either to treat thrombotic events or to prevent them. Vitamin K antagonists have been for a long time the only option for oral anticoagulation. However, the treatment with vitamin K antagonists has some disadvantages that may have an impact on the patients' quality of life including requirement for frequent blood tests monitoring, dose changes according to the INR values, numerous drug-drug and drug-food interactions (1). As a result, solutions have been sought for a safer and more convenient oral anticoagulant treatment.

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After more than 60 years of using vitamin K antagonists, the introduction of new oral anticoagulants (NOACs) represent a medical breakthrough, with promising prospects. NOACs can be divided in two major categories, based on their mechanism of action: i) Direct thrombin inhibitors - Dabigatran; and ii) Direct factor X inhibitors - Rivaroxaban, Apixaban and Edoxaban5.

The first approved NOAC was Dabigatran (approved in 2008 by European Union and in 2010 by the Food and Drug Administration), followed closely by Rivaroxaban, Apixaban and Edoxaban (1).

The results of the studies so far encouraged the use of this new class of oral anticoagulants that proved at least non-inferiority compared to antivitamin K drugs regarding the prevention of thromboembolic events with lower bleeding rates (2). The main advantages of the NOACs compared to antivitamin K agents are the following: predictable pharmacokinetics and pharmacodynamics, rapid onset of action, rapid offset of action, short half-life, wide therapeutic window, few drug-drug and drug-food interactions, no need for laboratory monitoring (2).

Although all these properties make the NOACs an appealing alternative, there are also some disadvantages: high costs for both the anticoagulants and their available reversal agents (3), reversal agents not widely available (3), limited use in certain circumstances, such as patients with kidney or liver diseases (some NOACs are contraindicated, some require dose-adjustment), not approved during pregnancy (4), in children, in patients with mechanical mitral valve prosthesis, malignant diseases (5), antiphospholipid syndrome (2). Taking into account the positive results of the studies so far, it is reasonable that the interest of the research field in NOACs is increasing, with numerous ongoing studies. Furthermore, there is a tendency of widening the range of indications for NOACs (6).

2. NOACs current indications

The actual approved recommendations of NOACs are summarized in Table I (7-10).

3. Stable atherosclerotic vascular disease - prevention of major cardiac events

Coronary heart disease and peripheral arterial disease are frequently encountered pathologies, with atherosclerosis being the most frequent etiology. Patients with atherosclerotic disease have a high risk of major cardiac events (myocardial infarction, stroke) that can lead to death, so the secondary prevention is of great importance. Myocardial infarction and stroke occur frequently by atherosclerotic plaque rupture or by atherothrombosis, followed by embolization. Therefore, the best medical therapy includes plaque stabilization and prevention of thrombus formation. Statins are recommended for plaque stabilization and for reducing plaque progression. Regarding the prevention of thrombus formation, the cornerstone of the pharmacological approach remains a daily low-dose aspirin (11).

Single antiplatelet therapy is indicated indefinitely in all cases of carotid stenosis and in symptomatic lower extremities arterial disease, whereas dual antiplatelet therapy is recommended following revascularization for a limited period of time (depending on the situation) (12-14). Anticoagulant therapy is indicated only in the presence of coexisting conditions that require anticoagulation (e.g., atrial fibrillation) and may be temporarily associated with single antiplatelet therapy if there is recent revascularization (15).

Cardiovascular prevention in coronary artery disease - European Society of Cardiology guideline recommendations (16): The recommendations are similar to peripheral arterial disease. Statins and single antiplatelet therapy are indicated in all patients as prevention medication and dual antiplatelet therapy is reserved for acute coronary syndromes or for cases of stable coronary disease that have undergone percutaneous coronary intervention (PCI). In the latest guideline, there is no indication for oral anticoagulants in stable coronary artery disease (16,17).

The Warfarin Antiplatelet Vascular Evaluation (WAVE) trial tried to optimize the secondary prevention in patients with cardiovascular diseases and investigated the outcomes of associating warfarin with an antiplatelet agent compared to antiplatelet therapy alone, with the objective of lowering the risk of major cardiovascular events. Unfortunately, the results were not as expected, the aforementioned association showing no benefit and furthermore having a statistically significant higher risk of life-threatening bleeding complications (15).

4. New perspectives - reducing the risk of major cardiovascular events

The COMPASS trial evaluated the effectiveness of rivaroxaban in the secondary prevention in patients with chronic coronary artery disease or/and peripheral artery disease (18). In total, 27,395 patients with stable atherosclerotic vascular disease were enrolled and randomized to receive one of the three regimens: i) Rivaroxaban 2.5 mg twice daily plus Aspirin 100 mg once daily; ii) Rivaroxaban 5 mg twice daily plus Placebo; and iii) Aspirin 100 mg once daily plus Placebo.

The primary outcome was a composite of cardiovascular death, stroke and myocardial infarction (18). The secondary outcome was a composite of ischemic stroke, myocardial infarction, acute limb ischemia and cardiovascular death (18).

After a mean follow-up of 23 months, the study was stopped due to the superiority of the rivaroxaban and aspirin association. The rivaroxaban-plus-aspirin group compared to the aspirin-alone group showed a statistically significant reduction not only of the primary outcome, but also of the secondary outcome ($P<0.001$). On the other hand, the rivaroxaban-plus-aspirin group showed statistically significant higher rates of bleeding. Regarding stroke, the rivaroxaban-aspirin group showed a statistically significant lower rate of ischemic stroke and a non-significant higher rate of hemorrhagic stroke (18).

Based on this successful study, the combination of Aspirin 100 mg daily plus Rivaroxaban 2.5 mg twice daily for the prevention of atherothrombotic events in adults with coronary artery disease and/or peripheral artery disease was approved by the European Commission in August 2018 and by Federal Drug Administration in October 2018 (19).

Table I. Therapeutic indications for NOACs according to the European Medicines Agency (7-10).

NOAC	Recommendation
Rivaroxaban	Prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (such as congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke or transient ischaemic attack) Treatment of DVT and prevention of recurrent DVT and PE following an acute DVT in adults Co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome with elevated cardiac biomarkers
Apixaban	Prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery Prevention of stroke and systemic embolism in adult patients NVAF, with one or more risk factors (such as prior stroke or transient ischaemic attack; age ≥75 years; hypertension; diabetes mellitus; symptomatic heart failure NYHA Class ≥II) Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults
Edoxaban	Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors (such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack) Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults
Dabigatran	Primary prevention of venous thromboembolic events in adult patients who have undergone elective total-hip-replacement surgery or total-knee-replacement surgery Prevention of stroke and systemic embolism in adult patients with NVAF with one or more of the following risk factors: (previous stroke, transient ischaemic attack or systemic embolism; left ventricular ejection fraction <40%; symptomatic heart failure ≥NYHA class II; age ≥75 years; age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease or hypertension)

NOACs, new oral anticoagulants; NVAF, non-valvular atrial fibrillation; DVT, deep vein thrombosis; PE, pulmonary embolism; ASA, acetylsalicylic acid.

5. New perspectives - NOACs in patients with malignant diseases

The management of the anticoagulant treatment in this subgroup of patients is often a challenge for the clinician, as these patients have both an increased risk of bleeding, and an increased risk for thrombotic events. Currently, low-molecular-weight heparin is the recommended treatment for patients with cancer and venous thromboembolism. So far, NOACs have not been approved in patients with cancer due to insufficient data. However, recent studies suggest that NOACs could be a safe and efficient anticoagulant option.

The Hokusai VTE Cancer trial (20) is a randomized, controlled, open-label trial that compared a NOAC (edoxaban) with a low-molecular-weight heparin (dalteparin) for the treatment of venous thromboembolism in patients with cancer. In total, 1,050 patients with cancer and venous thromboembolism were randomly assigned to receive one of the following regimens (19): i) A low-molecular-weight heparin for at least 5 days, followed by oral edoxaban 60 mg once daily, or 30 mg once daily in patients with a creatinine clearance of 30-50 ml/min, or a body weight of 60 kg or less (20); and ii) Dalteparin 200 IU per kg per day subcutaneously for one month, followed by dalteparin 150 IU per kg per day subcutaneously.

The duration of treatment was 6-12 months (20). The primary outcome was a composite of recurrent venous thromboembolism or major bleeding (19). The conclusion of this trial involving patients with cancer-associated venous thromboembolism was that edoxaban was noninferior to dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding (20).

SELECT-D is a multicenter, randomized, open-label pilot study that included patients with active cancer and thrombosis (pulmonary embolism - either symptomatic, or incidental, or symptomatic lower-extremity proximal deep vein thrombosis) (21). It included 406 patients who were assigned to one of the following treatment regimens (21): i) Rivaroxaban 15 mg twice a day for 3 weeks, followed by rivaroxaban 20 mg daily up to 6 months; and ii) Dalteparin 200 IU per kg per day subcutaneously for one month, followed by dalteparin 150 IU per kg per day subcutaneously for 5 months.

The follow-up period was 2 years (21). The primary outcome of the trial was venous thromboembolism recurrence and the secondary outcomes were major bleeding and clinically relevant nonmajor bleeding. The conclusion of this study was that rivaroxaban, compared with dalteparin, lowers the recurrence rate of venous thromboembolism and raises the risk of bleeding in patients with cancer (20).

The ADAM-VTE study compared apixaban with dalteparin, in patients with cancer and associated venous thromboembolism (22). It included 287 patients who were assigned to one of the following treatment regimens (22): i) Apixaban 10 mg twice daily for 7 days followed by apixaban 5 mg twice daily up to 6 months; ii) Dalteparin 200 IU per kg per day subcutaneously for one month, followed by dalteparin 150 IU per kg per day subcutaneously for 5 months.

The primary outcome was major bleeding and secondary outcomes included venous thromboembolism recurrence and a composite of major bleeding plus clinically relevant non-major bleeding. The results of this study show statistically significant lower rates of venous thromboembolism recurrence in the apixaban-group and lower bleeding rates, but without statistical significance (21).

Supporting evidence regarding the use of apixaban in treating venous thromboembolism in patients with cancer is pending upon the ongoing study: CARAVAGGIO (23).

The AVERT study is a randomized, placebo-controlled, double-blind clinical trial that assessed the efficacy and safety of apixaban for thromboprophylaxis in patients with cancer (24). The selected patients were at an intermediate-to-high risk for venous thromboembolism (Khorana score ≥2) and were ambulatory patients initiating chemotherapy. The study included 563 patients who were assigned to one of the following treatment regimens: Apixaban 2.5 mg twice daily or placebo (23). The treatment period was 180 days and the patients were followed up for up to 210 days. The primary efficacy outcome was the first episode of major venous thromboembolism (proximal deep-vein thrombosis or pulmonary embolism) and the main safety outcome was major bleeding. The AVERT-study showed that apixaban at a dose of 2.5 mg twice daily resulted in a significantly lower risk of venous thromboembolism, but also in a significantly higher risk of major bleeding (24).

6. Conclusions

NOACs represent an appealing alternative to the antivitamin K oral anticoagulants (25,26). Currently, their indications are expanding (27), with many ongoing studies and promising results (28). Rivaroxaban is the first oral anticoagulant approved to be used in combination with an antiplatelet agent to prevent atherothrombotic events in adults with coronary artery disease and/or peripheral artery disease. However, further investigation is needed to establish which group of patients would benefit most from this medical approach. Furthermore, preliminary studies have shown that NOACs seem to be a reasonable choice of anticoagulation for patients with cancer, but further studies are expected.

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CLL, NB, AMAS, MR and MC collected, analyzed and interpreted the patient data regarding the new indications of new oral anticoagulants. CCD, OGB and SB substantially contribution to the conception of the work and interpretation of data; also, they drafted the manuscript and were major contributors in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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