New Oral Anticoagulants – What’s New? A Systematic Review

João Pedro Silva Santos
5rd year Medical Student, Bahiana School of Medicine, Salvador, Bahia, Brazil

Patricia Ramos Borges Ferracioli
Pathologist Doctor, Hospital Santo Amaro, Salvador, Bahia, Brazil

Wagner Ramos Borges
Professor Adjunct, Bahiana School of Medicine, Salvador, Bahia; PhD in Medicine, Bahia Federal University; Vascular Surgeon, Member of Brazilian Society of Angiology and Vascular Surgery and Brazilian College of Surgeon, Salvador, Bahia, Brazil

Abstract

Introduction: Anticoagulant therapy is defined as the standard prevention and treatment method for systemic thromboembolism. Thus, despite heparin and vitamin K antagonists being used as traditional methods, the new oral anticoagulants (NOACs), such as activated factor X inhibitors and direct thrombin inhibitors, have been emerged, based on their safety and efficacy analyses appropriate to clinical practice, in addition to its convenience in clinical management. Objectives: To evaluate anticoagulant therapy with the use of NOACs. Methods: This is a systematic review, using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria. Studies from the National Library of Medicine (PubMed.gov) and Embase databases were included, through randomized clinical trials (RCTs), published from 2011 until June 2021, which comprised the investigation question. Data were extracted about the NOACs, the conventional anticoagulant, use in renal patients, clinical outcomes and side effects. Results: 384 results were identified through the search strategy, proceeding to the analysis of 315 after exclusion of duplicates. Then, after the application of the eligibility criteria, 33 studies progressed to full reading and 18 were included in the qualitative analysis of the review. The included studies demonstrated the analysis of specific comorbidities, and most comprised the adult population and warfarin as a conventional anticoagulant used. Edoxaban was the most evaluated NOAC, being included in 7 studies. Bias analysis found 3 “low risk” studies and 7 overall “high risk” studies. Conclusion: The comparison of conventional therapy and NOACs demonstrates similarity in the efficacy clinical outcomes analyzed by the studies, with similar reductions of the risk of thromboembolic events. From the analysis of the occurrence of bleeding, NOACs represent reduced rates of such outcomes. Regarding the analysis of the risk of bias of the studies, 15 of the 18 studies analyzed were classified as “high risk of bias” or as “some concerns”, especially in the criteria of “missing outcome data. In general, although no methodologically strong evidence has been identified about NOACs, their use is a reasonable alternative to conventional therapy in clinical management.

Introduction
The scenario of anticoagulation therapy, with the suggestion of using new anticoagulants, has shown great advances in order to prevent the extension of the condition 1 and improve clinical pharmacological management. This development came mainly due to the various effects of anti-vitamins K, such as multiple drug interactions, bleeding and the need for laboratory
monitoring [2,3]. Thus, new classes of oral anticoagulants were developed: inhibitors of activated factor K, mainly warfarin, classically used in therapeutic intervention. [4,5]

Conventional treatment, with the use of low molecular weight and unfractionated heparin, with intravenous administration, in addition to vitamin K antagonists, such as warfarin, was the basis of anticoagulant treatment for a long time. [6] However, several obstacles in its way therapeutic use, such as those mentioned above, opened space for the use of new oral anticoagulants (NOACs), becoming the main acute and long-term treatment of venous thromboembolism [5], prioritizing more predictable pharmacokinetics, rapid onset of action and simplified administration. [7] Due to the growing use of direct oral anticoagulants in clinical practice, several studies have highlighted the advantages of this class of medications in relation to classic therapy.

From this perspective, clinical efficacy and safety studies have demonstrated the progress of new oral anticoagulants, with benefits in the rate of bleeding, reduction in the rate of recurrence and dosage comfort of the drug, in addition to there being no need for constant monitoring of the action of the drug [4,8], frequent characteristics of the class of vitamin K antagonists. Thus, the development of new scientific studies, such as RE-COVER [9] and HOKUSAI-VTE [10], provided advances in the treatment and prevention of new thromboembolic conditions, by revealing similarities in efficacy and superior safety of dabigatran and edoxaban, compared to conventional therapy.

Treatment with new oral anticoagulants presents evident efficacy and safety factors, so that the definition of their non-inferiority criteria has become noticeable in the current literature, in comparison with conventional therapy and its peculiarities that make clinical use difficult. In view of this, because it is a current issue and accompanied by scientific gaps, such as the limited use of NOACs in kidney patients and the absence of definitively effective antidotes, work those studies anticoagulant therapy with new oral anticoagulants is necessary.

Therefore, the present study aims to evaluate anticoagulant therapy using new oral anticoagulants, through a systematic review of the current literature, with the aim of answering the main questions regarding the subject.

Methods

The present study consists of a systematic review that aimed to evaluate anticoagulant therapy with the use of new oral anticoagulants, in the period between December 2020 and September 2021. The preparation of this study was based on the recommendations described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – PRISMA. [32]
researchers participated in evaluating the articles. There was no disagreement between the authors during the study inclusion period. The article collection and selection stage were carried out between 02/28/2021 and 03/28/2021.

The data collected and the information evaluated, through reading and recording the articles chosen according to the eligibility criteria, were population; type of new oral anticoagulant used; conventional anticoagulant used; time of medication use; dose of therapy; need to adjust doses for kidney patients; clinical outcomes; clinical outcome results; common and uncommon side effects.

In order to analyze the risk of bias of the articles selected for the study, the Cochrane platform for risk of bias in randomized clinical trials, RoB 2.0, was used, updated on August 22, 2019. In this way, 5 domains were evaluated Generators of bias in randomized controlled trials: randomization bias, bias due to deviations from intended interventions, bias due to missing outcome data, bias due to outcome measurements, bias due to selection of reported outcome. The risk of bias assessment was carried out by only 1 evaluator.

From the databases used, a total of 379 studies were found that included the search strategy. Among the 379 studies identified, 96 came from PUBMED and 283 from EMBASE. Additionally, 5 articles were identified from an active search in the article references, as it was deemed necessary to cover relevant studies that were cited in articles resulting from the collection in the aforementioned databases, resulting in 384 articles. Of these 384, 69 were excluded for being duplicates, totaling 315, where 107 were excluded for not covering the topic delimited by the research question, totaling 208 studies, selected for reading the title and abstract. By reading the abstracts, 116 articles were excluded because they were not randomized clinical trials, where 21 presented publications only on the rationale and/or design of a study, 28 retrospective observational studies, 17 cohort studies, 13 meta-analyses, 7 publications on protocol, 1 case-control and 19 were from other designs not mentioned above, totaling 92 articles. In the screening, 59 articles were excluded for not meeting the eligibility criteria, resulting in 33 articles that advanced to full reading. Of these 33, 15 were excluded for being incomplete, being summaries of works already evaluated, under different nomenclatures. Therefore, 18 articles were included for qualitative analysis of this review.

The studies included in the qualitative analysis were published between 2011 and 2021. All articles included the analysis of a specific comorbidity, in order to evaluate the use of new oral anticoagulants (NOACs) compared to conventional therapy. Among them, 17 articles addressed an adult or elderly population, with 1 article based on a pediatric population. Atrial fibrillation (AF) was the comorbidity analyzed in most articles, forming a total of 8 studies, with cerebral venous thrombosis (CVT), deep vein thrombosis (DVT) or pulmonary embolism (PE) being comorbidities evaluated in 7 studies, 2 studies evaluated populations with surgical valve implantation and 1 study included patients with antiphospholipid syndrome (APS), associated with arterial thrombosis or venous thrombosis. The distribution of NOACs was carried out in such a way that dabigatran was used in 2 studies, rivaroxaban in 6 studies, apixaban in 3 studies and edoxaban was the most evaluated, being included in 7 studies.

In the comparison carried out in randomized clinical trials, warfarin was the most used medication, being specified in 17 studies, which, together with NOACs, were used for a period that varied between 1 month and 3 years. The dosages used varied according to the population of each study, the associated comorbidity and the medication in use, so that the adjustment for renal patients was carried out in 12 studies, where 9 studies reduced the dosage by half to cover patients with clearance / reduced creatinine clearance. The presentation of primary clinical outcomes was distributed according to the comorbidity analyzed in each study, being differentiated into efficacy outcomes and safety outcomes. Efficacy was assessed mainly based on the occurrence of cerebrovascular accident (CVA) in 9 studies, recurrence of venous thromboembolism (VTE) or systemic embolic event in 16 studies and death from any cause was included in the efficacy outcome in 3 studies. The safety outcome was assessed based mainly on the occurrence of bleeding, so that the occurrence of major/significant bleeding or clinically relevant non-major bleeding was present in the 18 studies evaluated, with the occurrence of intracranial hemorrhage being assessed in one total of 2 studies.

**Discussion**

Anticoagulant therapy is frequently used in the prevention and treatment of thromboembolic events5, in order to mainly reduce morbidity and mortality associated with constant systemic conditions, such as pulmonary thromboembolism (PTE) and deep vein thrombosis (DVT). Therefore, the outpatient use of the therapy was in line with a notable scientific advance, through the reduction of multiple drug interactions, bleeding rates and laboratory monitoring that is unnecessary in new classes of anticoagulants, providing a more suitable profile for clinical and outpatient practice.

For a long time, anticoagulant treatment was based on classical therapy, based on the use of vitamin K antagonists. Heparin, which acts by inhibiting antithromboplastic, through antithrombin, and acts on
activated coagulation factors, such as Factor II, in low molecular weight or unfractionated forms, is a drug used mainly in initial therapy. In addition to heparins, the constant use of vitamin K antagonists was adopted, such as warfarin, which acts to inhibit vitamin K-dependent clotting factors, resulting in the synthesis of inactive forms of these proteins, presenting, within the therapy classical, as a gold standard. [11]

Unfractionated heparin has some advantages, such as a half-life of 90 minutes and its effect is reversed by protamine, but it can induce thrombocytopenia. [12]

Low molecular weight heparin, on the other hand, has a dosage based on weight and does not require routine monitoring. [13] Warfarin, in turn, can be used in long-term anticoagulation, is administered orally and has its effect reversed by vitamin K. However, the latter has interactions with other drugs, interactions with food and the risk of bleeding increases over time [12], limiting its therapeutic use.

The use of conventional therapy presents a high number of important functional limitations [4], such as those mentioned above. Thus, based on the classically used anticoagulation, it became possible to analyze an anticoagulant that could come closer to the ideal and simplify treatment, taking into account oral administration, low drug interactions, reduction in the occurrence of bleeding and reduced need for monitoring pharmacological action. [6]

Several studies demonstrate the management of classical therapy in hospitalized and outpatient patients, comparing it with the use of new oral anticoagulants. In the initial period of treatment, the medication was mainly used intravenously, using unfractionated heparin, or subcutaneously, using enoxaparin, nadroparin, dalteparin, tinzaparin or fondaparinux. [4] In the long-term period, in which the transition from intravenous therapy to oral therapy, the most studied drugs in this condition are vitamin K antagonists, with warfarin being the main representative of this category of drugs, which acts in the cyclic conversion of vitamin K [4,14] and inhibits the production of factors of coagulation II, VII, IX and X, taking approximately 36-72 hours for its anticoagulant effect to occur.

Due to their functional characteristics and limitations, a new class of anticoagulants was developed, with the aim of having a more practical and feasible pharmacological profile in clinical practice. [4][11]

Therefore, the class of new medications includes factor activated (rivaroxaban, apixaban and edoxaban) and direct thrombin inhibitors (dabigatran) [2–4], providing, among several factors, advances in the outpatient use of anticoagulation treatment. These new oral anticoagulants were the basis of scientific studies, being compared with the current treatment at the time. Dabigatran, a direct thrombin inhibitor, was the first to be analyzed in order to evaluate its role in venous thromboembolism (VTE). From RE-COVER, a randomized, double-blind trial involving patients with acute VTE, who received parenteral anticoagulant therapy, dabigatran 150 mg every 12 hours was used compared with warfarin, which had its dose adjusted to achieve the international normalized rate (INR) of 2.0 to 3.0. In this study, dabigatran showed efficacy for recurrence prophylaxis similar to that of warfarin (2.4% vs. 2.1%, p<0.001), in addition to demonstrating equivalence in terms of severe bleeding (1.6% vs. 1.9%) and superiority in the issue of any bleeding (16.1% vs. 21.9%), thus demonstrating a safety profile, as well as the joint analysis of the RE-COVER II study. [9,13,14,15]

Through the use of apixaban, a drug that inhibits activated factor studies, maintaining a comparative character similar to that of the EINSTEIN [18] study. Apixaban was administered 10 mg twice a day for seven days, followed by 5 mg twice a day for 6 months, comparing with conventional treatment (enoxaparin, followed by warfarin), from a sample of 5,395 patients with acute VTE. The study results showed a lower rate of severe bleeding (0.6% vs. 1.8%, p<0.001), in addition to a recurrence rate equivalent to conventional therapy (2.3% vs. 2.0%, p<0.001), 7%, p<0.001), denoting a pattern of similarity and/or superiority of the new anticoagulant drug. [16,17]

Through carrying out the aforementioned studies, the advantages of using new oral anticoagulants became scientific evidence, based on the effectiveness/safety relationship. [7] Therefore, the hypothesis that prioritizes the use of such drugs highlights their clinical benefits, the based on its similarity in efficacy compared to conventional therapy, superiority in safety and convenience in clinical use, without the need for laboratory monitoring, and the absence of interactions with different medications, characteristics common to the class of conventional therapy medications. [4]

Only the efficacy and safety outcomes in studies evaluating NOACs do not exhaust the topic regarding possible advantages in relation to traditional treatment. Regarding drug and food interactions, NOACs interact to a significantly lesser extent compared to warfarin, through their mechanism of resecreting P glycoprotein, which regulates the absorption of drugs into the bloodstream, which, together with cytochrome P450, it plays a fundamental role in the metabolism of rivaroxaban and apixaban. [7]

Although warfarin, in turn, is relatively effective and safe, this therapy has several drug and dietary interactions, making its therapeutic management difficult. [5]

In addition to the effects of NOACs having a limited reversal capacity, with the use of idarucizumab, for dabigatran, and andexanet alfa, for the other factor of...
the renal function of patients who have indications for anticoagulant therapy, becomes a primary factor in the therapeutic management of such patients. [7] Regarding the absence of the need for laboratory monitoring, NOACs have more predictable actions, eliminating coagulation tests for monitoring, in addition such tests do not have significant precision for factor.

Various factors influence the occurrence of complications during anticoagulant treatment, such as the associated comorbidity, the age group in question and the length of time the therapy has been used. In this view, in terms of the characteristics of each patient during therapy, the risk of bleeding, which is the main clinical safety outcome, fluctuates in a volatile manner, depending on each patient and the associated comorbidities. In this way, possible risk factors are analyzed, to stratify risks and benefits more efficiently. Anticoagulant medications are the basis of the treatment of venous thromboembolism. [5] Despite the therapeutic benefits, spontaneous bleeding related to such treatment is the major complication, associated with the presence of specific comorbidities, thus increasing the rate of morbidity and mortality associated with such condition. [18,19,20]

From the occurrence of the bleeding outcome, risk stratification becomes present, taking as evidence the degree of hemodynamic instability, the source or origin of the bleeding and the degree of blood loss. [21] Several factors that associate the severity of bleeding with the treatment of anticoagulation, aim to fill the gaps in reducing the risk of this outcome occurring, in addition to the variability of reported bleeding frequencies. [22]

Within this premise, a randomized clinical trial, characterized by being an open non-inferiority test, assigned patients with cancer and acute or incidental symptomatic venous thromboembolism to receive low molecular weight heparin for at least 5 days, followed by edoxaban, a dose of 60mg per day or subcutaneous dalteparin at a dose of 200 IU/kg of body weight, once a day for one month, followed by dalteparin at a dose of 150 IU/kg, once a day, with administration by, at least, 6 months, and up to 12 months. This study demonstrated that the use of edoxaban was not inferior to the use of dalteparin in terms of major bleeding and recurrence of venous thromboembolism in cancer patients. [23]

Because patients with cancer and venous thrombosis are more likely to develop recurrent thromboembolic complications [24,25], another study, which addresses subgroup analysis and a post-hoc analysis in patients with cancer in the HOKUSAI-VTE, randomized, double-blind and multicenter, concluded that edoxaban is as effective as warfarin in the anticoagulant therapy of patients with cancer and venous thromboembolism, in a safe manner, with the occurrence of clinically less significant bleeding. [26] Thus, several studies have shown that anticoagulant therapy, with new oral anticoagulants, is also effective in cancer patients, compared to conventional therapy, highlighting its therapeutic role in clinical practice.

Although oral anticoagulants increase the chance of bleeding, their use in patients with atrial fibrillation (AF) can reduce the risk of ischemic stroke [27], as well as in patients with acute non-cardioembolic stroke. [28-30] Dessa Thus, in a randomized clinical trial, patients with non-valvular atrial fibrillation who were at increased risk of stroke received rivaroxaban, with a daily dose of 20 mg, or warfarin with an adjusted dose. This study showed that rivaroxaban was not inferior to warfarin in preventing stroke or systemic embolism, in addition to there being no significant difference in the risk of major bleeding, but with a lower rate of intracranial and fatal bleeding with rivaroxaban. [29,31-35]

d vitamin K antagonist (warfarin or acenocoumarol), based on the rate of recurrence of thrombotic conditions (2.1% vs. 3.0%, p <0.001 ), in addition to reduced occurrence of serious bleeding (0.8% vs. 1.2%, p=0.21), where the comorbidity analyzed, like most studies included in the review, was venous thromboembolism (VTE). [18,36-43]

Regarding the clinical trials included, edoxaban was the most evaluated NOAC among them. The use of edoxaban in the HOKUSAI-VTE study, where the rate of VTE recurrence (3.2% vs. 3.5%, p<0.001) and the rate of clinically relevant bleeding (8.5% vs. 10.3%, p<0.004) of edoxaban in relation to warfarin, the similarity of efficacy and superiority in safety outcomes appears to present a pattern in the objects of comparative studies of NOACs and conventional therapy [10], just like the present study, showing consistent with a more accessible therapy, so as not to require frequent monitoring and dosage adjustments. [4] Therefore, it appears that the results are like publications on the subject.

The presence of specific comorbidities in the study of NOACs reflects the main indications for their clinical use. Therefore, the included studies mainly analyze comorbidities with high incidences in the population, such as atrial fibrillation and venous thromboembolism, to reflect the current literature. According to the analysis of comorbidities, one of the concerns linked to NOACs is their use in kidney patients, as chronic renal failure is a risk factor for VTE and the occurrence of bleeding. [19] Therefore, the need to reduce the dosage or the non-use of NOACs was reported and became a practice in studies that included patients with reduced creatinine clearance, using a reduced dosage (about 1/2 the dosage of patients with adequate creatinine clearance), especially when using of edoxaban. [7, 44-49]
The time of use of the anticoagulant drug is reported in three distinct phases: initial phase, long-term phase, and extended phase. [50] The period and need for anticoagulation is determined through the location of the thrombus (isolated distally vs. proximal), presence of any provocative factor and if there is recurrence, one must think about the risk of bleeding associated with the extensive period of anticoagulation. [8] In parallel with the literature, the variation between the period of 1 month to 3 years in the present study concerns the weighting between the risk of recurrence and risk of bleeding, where higher rates of bleeding were identified in extended phase therapies, compared to a lower rate of thromboembolic recurrence. [7]

In addition to the clinical outcomes listed in the trials and included in this review, variables that study factors that influence decision-making regarding its use and in clinical practice must be considered. In view of this, the occurrence of side effects to the use of NOACs is reported, where it is mainly based on cardiovascular events and bleeding in specific sites, such as the upper airways and gastrointestinal tract (GIT), in which dabigatran acts by increasing the risk of dyspeptic symptoms and, together with edoxaban and rivaroxaban, appears to be related to GIT bleeding outcomes. [9,19,51]

For methodological analysis, randomization measures, interventions, and results of RCTs can impact the reliability of scientific works. [52] In this regard, the non-inferiority RCTs analyzed in the review, which presented a randomized and double-blind design, with the elaboration of specific and standardized clinical outcomes, appear to present a reflection more consistent with current scientific evidence. However, although the studies promote an RCT design as a standard, the methodology and sample must be closer to reality, such as AMPLIFY [17] and HOKUSAI-VTE [10], which implemented comprehensive scale samples (n>5000). Regarding health interventions, RCTs and systematic reviews of these trials provide the most reliable evidence about their effects, minimizing the risk of bias, if there is a sufficient sample and randomization ensures that participants in the intervention and comparison groups are similar. [52]

The results obtained in the present study clarify the advantages of using NOACs, compared to conventional therapy, to provide information about non-inferiority in terms of efficacy and superiority in the safety of their clinical use, in addition to particularities of use in renal patients, time of use linked to the occurrence of bleeding and recurrence of thromboembolic events and the possibility of side effects in its therapeutic use. **Conclusion**

Several specific comorbidities are analyzed separately in the studies included in the review. The clinical outcomes adopted by the studies showed similarities between the NOACs group and the conventional treatment group, mainly using warfarin. Regarding the occurrence of complications, specifically thromboembolic events and bleeding, such outcomes appear to represent lower rates in the population using NOACs, compared to conventional therapy, demonstrating the establishment of a noticeable advantage in their clinical use.

In general, the heterogeneity found in the bias domains and the high index of moderate or high risk of bias in the articles promote a reduction in confidence in the evidence analyzed, mainly through the characterization of most studies as “some concerns” and “high risk of bias”, due to the need for a larger sample size and the lack of a structured methodology in terms of results and intended interventions.

However, the development of strategies and new treatment options have led to advances towards a safer and more effective option, pointing to benefits in the use of NOACs in terms of a simpler and more accessible clinical practice. Furthermore, it is interesting that these studies use standardized clinical outcomes, to provide a reliable interpretation of reality. Therefore, studies are needed to evaluate anticoagulant therapy with new oral anticoagulants, to prioritize the benefits of treatment.

**Financial support**

None.

**Conflicts of interest**

No conflicts of interest declared concerning the publication of this article.

**References**


