ARTIGO ORIGINAL ORIGINAL ARTICLE

NEW ORAL ANTICOAGULANTS (NOACS) ARE THE GOLD STANDARD IN VENOUS THROMBOEMBOLISM

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Abstract

Introduction: *Venous Thromboembolism (VTE) is an important cause of morbidity and mortality. The risk of recurrence could be very high without thromboprophylaxis. New oral anticoagulants (NOACs or DOACs) represent a new step in anticoagulation.*

Material and Methods: *We searched for papers with trials, systematic reviews and meta-analysis involving NOACs in the treatment and secondary prevention of VTE. We also searched for guidelines of two medical societies (American College of Chest Physicians and International Society of Thrombosis and Haemostasis - ISTH).*

Results: *Six RCT (randomized controlled trial) comparing NOACs with Warfarin shew a non-inferiority in relation with recurrent VTE and major bleeding. Two RCT (SELECT-D and Hokusay cancer) and one meta-analysis shew low recurrence rate of VTE in cancer patients and higher rate of bleeding, mainly in gastrointestinal and genitourinary cancers. There are two RCTs involving NOACs in treatment of patients with Antiphospholipid Syndrome (APS).*

Discussion: *NOACs shew non-inferiority over AVK. Guidelines of CHEST 2016 recommend NOACs for VTE treatment in no cancer patients, and Low Molecular Weight Heparin (LMWH) for cancer patients. ISTH suggest NOACs as the first option in VTE cancer patients with low risk of bleeding. A recent RCT shews no benefit and increased risk of vascular events in APS patients treated with NOACs. NOACs are the gold standard for VTE treatment and secondary prevention in no cancer patients. They could be the first option in cancer patients with low risk of bleeding.*

INTRODUCTION

Venous Thromboembolism (VTE), which includes Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE), is an important cause of morbidity and mortality. It is the third cause of cardiovascular death after myocardial infarction and stroke.[1] The incidence varies between[1-2] cases/1000/year for DVT and 0.5/1000/year for EP.

VTE is the number one preventable cause of death in hospitalized patients, and one of the most important causes of death related with the reason for hospitalization.[2]

After the first episode of VTE, the risk of recurrence could be of 30% after ten years without thromboprophylaxis. Most cases occur in first years after the event.[3]

There are several causes for VTE. Some of them are "provoked". In these cases, are included immobilization, cancer, surgery, trauma, thrombophilia acquired or genetic and hormonal supplementation. In other cases, there are no cause for the VTE (unprovoked).

History of cancer or active cancer is responsible for 10-20% of VTE cases[4], and cancer patients have an increased risk of bleeding related with anticoagulation compared with patients without cancer.[5]

During several decades, vitamin K antagonists (VKA) remained the only oral anticoagulant type. They are effective for treatment and prevention of VTE but have a high interpatient variable dose-response and high interactions with food and other drugs.[6] Dose of VKA are adjusted according to international normalized ratio (INR).

Low molecular weight heparins (LMWHs) solved some of the problems related with VKA, but have the disadvantage of parenteral administration.

New oral anticoagulants (NOACs or DOACs) represent a new step in anticoagulation. There are two groups of NOACs - Direct oral thrombin inhibitor (Dabigatran) and Direct oral factor Xa inhibitors (Rivaroxaban, Apixaban, Edoxaban and Betrixaban). They have the advantage of oral administration and a stable interpatient dose-response.

Recently were approved the reversal agents of NOACs. Idarucizumab is a direct inhibitor of Dabigatran and Andenaxet an antidote for factor Xa inhibitors.

The purpose of this paper is doing a revision of the latest evidence about the NOACs in the treatment of DVT and PE, and show the indications and contraindications of this drugs.

MATERIAL AND METHODS

In this non-systematic review, we searched for papers with trials involving NOACs in the treatment and secondary prevention of deep venous thrombosis or pulmonary embolism. We also searched for guidelines of two medical societies (American College of Chest Physicians and International Society of Thrombosis and Haemostasis) in this theme, meta-analysis and systematic reviews about NOACs in the treatment and prevention of VTE.

We analysed the evidence of NOACs in cancer patients, thrombophilia with antiphospholipid syndrome (APS), paediatric population, chronic kidney disease (CKD), obese patients, pregnancy and breast feeding.

Finally, we did a summary of the indications of NOACs in the treatment and secondary prevention of VTE.

RESULTS

The guidelines of CHEST 2016 recommend for VTE and no cancer a long-term treatment with NOACs with a Grade 2B over VKA and Grade 2C over LMWH.[7] This grade of recommendation was based in six randomized controlled trials (RCT) comparing NOACs with Warfarin, nine systematic reviews and six meta-analysis.[7] The RCTs involved Dabigatran (RE-COVER I and RE-COVER-II), Rivaroxaban (EINSTEIN DVT and EINSTEIN PE), Apixaban (AMPLIFY) and Edoxaban (HOKUSAY VTE)[8] with a non-inferiority in relation with recurrent VTE and major bleeding for all cases (Table 1). These trials involved a total of 26993 patients. The authors said that the risk reduction for VTE appears to be similar between NOACs and VKA, and seems to be similar between all NOACs. They also concluded that the risk of bleeding, particularly intracranial bleeding was inferior with NOACs comparing with VKA. Finally, they concluded that the risk of bleeding may be lower with Apixaban comparing with the other NOACs.[7] The sample size necessary for a superiority analysis would be overwhelming.

In terms of extension treatment in patients without cancer (after 3-6 months of VTE treatment), we have results of one RCT comparing Dabigatran vs Warfarin (REMEDY) that involved 2856 patients. This trial shewed that Dabigatran is effective as VKA in extended treatment for prevention of recurrent VTE and it has lower risk of major and clinically relevant non-major bleeding (CRNMB).[9]

There are more three RCTs (involving a total of 4208 patients) comparing NOACs with placebo in extended treatment for prevention of VTE. RESONATE study (Dabigatran 150mg twice-daily or placebo), EINSTEIN Extension (Rivaroxaban 20mg daily or placebo) and AMPLIFY-EXT (Apixaban 2.5mg twice-daily or placebo) shew that NOACs are effective in preventing recurrent VTE (reduction at least of 80%) without being associated with high risk of bleeding.[7]

Another RCT comparing Rivaroxaban or Aspirin in extended treatment for secondary prevention of VTE shew similar results with a dose of 10mg daily versus 20mg daily of rivaroxaban.[10]

The guidelines of CHEST 2016 recommend for VTE and cancer a LMWH over VKA (Grade 2B) and NOACs (grade 2C).[7] The different RCT involving NOACs versus VKA in VTE treatment included a very low number of patients with cancer (between 2 and 9%) and so they did not have power to show a non-inferiority of NOACs in cancer patients.

In 2018 were published two trials with NOACs in cancer. SELECT-D (406 patients) comparing Rivaroxaban 20mg daily or Dalteparin in treatment of VTE patients (symptomatic or incidental) with active cancer[11] shew a 6-months lower recurrence rate of VTE with Rivaroxaban (4% vs. 11% - with Hazard Ratio [HR] 0.43; 95% CI, 0.19 to 0.99) and higher rate of CRNMB (13 vs 4% with [HR]

Table 1 **Summary of RCT studies with NOACs vs. VKA in VTE acute Treatment**

NOAC	Studies	Patients	Outcomes (relative effect 95% CI)		
			All-cause mortality	Recurrent VTE	Major Bleeding
Dabigatran	RE-COVER I RE-COVER II	5107	RR 1.0 (0.67-1.5)	RR 1.12 (0.77-1.62)	RR 0.73 (0.48-1.10)
Rivaroxaban	EINSTEIN-DVT EINSTEIN-PE	8281	RR 0.97 (0.73-1.27)	RR 0.90 (0.68-1.2)	RR 0.55 (0.38-0.81)
Apixaban	AMPLIFY	5365	RR 0.79 (0.53-1.19)	RR 0.84 (0.6-1.18)	RR 0.31 (0.17-0.55)
Edoxaban	Hokusay-VTE	8240	RR 1.05 (0.82-1.33)	RR 0.83 (0.57-1.21)	RR 0.85 (0.6-1.21)

(Adapted from CHEST Guidelines 2016)[7]

3.76; 95% CI, 1.63 to 8.69). In this study, the most major bleedings or CRNMB were gastrointestinal and urologic and were more frequent in oesophageal and gastroesophageal cancers.

The Hokusay VTE Cancer study (1046 patients) comparing Edoxaban 60mg daily after 5 days with LMWH or Dalteparin in treatment of acute symptomatic or incidental VTE shew a non-inferiority in composite VTE recurrence and major bleeding during 12-months (12,8% vs. 13,5% [HR] 0.97; 95% CI, 0.7 to 1.36).[12] Major bleeding was significantly higher with Edoxaban, due to the higher rate of bleeding in patients with gastrointestinal cancer.

A systematic review and meta-analysis involving over 5000 patients with two RCT (SELECT-D and Hokusay VTE cancer study) and eleven cohort studies, most of them involving rivaroxaban, shewed that NOACs comparing with LMWH had lower 6-month recurrent VTE (risk ratio [RR] 0.65 (0.42-1.01)), higher CRNMB ([RR] 2.31 (0.85-6.28)) and major bleeding ([RR] 1.74 (1.05-2.88)) and no difference in mortality ([RR] 1.03 (0.85-1.26)).[13]

Venous Thromboembolism related with Thrombophilia is another important topic to review. There are two RCTs involving NOACs in treatment of patients with Antiphospholipid Syndrome (APS). RAPS Trial, comparing Rivaroxaban with Warfarin in patients with APS, recruited 116 patients and shew a higher endogenous thrombin potential (ETP) and a lower peak thrombin generation in rivaroxaban group. No thrombosis or major bleeding occurred.[14]

Recently was published TRAPS trial comparing Rivaroxaban (20mg daily) with Warfarin in high-risk patients with APS (triple positive antiphospholipid antibody test) and history of arterial or venous thrombosis.[15] This study was designed to enrol 537 patients but was stopped earlier (after 120 patients). There was an increased rate of arterial events (12% vs 0%) and major bleeding (7% vs 3%) in Rivaroxaban group. There were no venous events, but three of arterial events occurred in patients with previous VTE.

DISCUSSION

NOACs represent a new step in treatment of VTE. When we are talking about gold standard treatment, it is not just important to think in relevant scientific evidence that we have about the topic, but also the clinical judgment that we do and the patients values and preferences – Evidence Based Medicine.[16]

In terms of patients values and preferences, NOACs are effective, generally safe with low risk of bleeding, friendly with oral intake and, depending of countries, with low costs. In terms of clinical judgment, NOACs are effective, safe and allow long treatment with low risk of bleeding. In relation to relevant scientific evidence, as we said before, they have a non-inferiority to VKA and they have the advantage of no interpatient variable dose-response and low interactions with food and other drugs, as it was shown in different RCTs, systematic reviews and meta-analysis. So, in terms of VTE treatment in patients without cancer, NOACs are the gold standard.

VTE treatment in patients with cancer is not consensual. The guidelines of CHEST 20167 recommend LMWH as the first choice of treatment. In 2018 they were published two RCTs (SELECT-D and Hokusay VTE Cancer) and one meta-analysis that shew a lower or non-inferiority in rate of recurrent VTE with a higher rate of bleeding. The risk of bleeding was higher in oesophageal, gastrointestinal and genitourinary cancers.[11-13] In last year, International Society on Thrombosis and Haemostasis (ISTH) suggested NOACs as the first option in VTE cancer patients with low risk of bleeding, and LMWHs in patients with high risk of bleeding.[17] Also, they said that Rivaroxaban and Edoxaban are the only with RCT comparing NOACs with LMWH in cancer patients. Recently was presented in American Society of Hematology 60th Annual Meeting by Robert D. MacBane *et al*., the ADAM VTE Trial. This study included 300 patients with cancer and acute VTE (Apixaban vs. Dalteparin) and it shews a significantly lower VTE recurrence and similar rate of bleeding (major plus CRNMB) in Apixaban group.[18]

For the prevention of VTE in cancer patients, there are two trials with recent presentation results. The AVERT Trial included 574 patients receiving chemotherapy. It compared Apixaban (2.5mg twice-daily) with placebo for preventing VTE in high-risk ambulatory patients. It shews a significant lower rate of VTE episodes and higher major bleeding rate on Apixaban group.[19] The CASSINI Trial results were presented recently in American Society of Hematology 60th Annual Meeting by Khorana AA *et al*, and randomize 841 patients to compare rivaroxaban (10mg daily) with placebo for preventing VTE in high-risk patients.[19]

In terms of posology, we have two different groups of NOACs in initial treatment of VTE. Dabigatran and Edoxaban need an initial treatment of five to ten days with LMHW, and after that, a switch to NOAC (dabigatran 150mg twice daily or Edoxaban 60mg daily). Rivaroxaban and Apixaban do not need an initial treatment with LMHW, but have different doses in first days. VTE treatment with Rivaroxaban begins with 15mg twice daily during 21 days and switch to 20mg daily after that, while Apixaban begins with 10mg twice-daily during 7 days and switch to 5mg twice-daily after that. These doses are recommended for patients with normal renal function and weight (Table 2). Different schemes of posology are related with pharmacokinetic profile of medications and manufacturer believe that one daily regimen have better adherence than two daily. Related with this topic, recently was published a retrospective population-based cohort analysis involving 15254 that shew a decreased risk of recurrent VTE ($p<0.0001$) and major bleeding events ($p=0.0031$) in favour of Apixaban versus Rivaroxaban. Authors refer that this could be related with pharmacokinetic profile and posology regimen.[20]

After initial treatment (3 months), extended treatment should be evaluated in each case, based in the type

Table 2 **Summary of NOACs dose regimens in VTE Treatment**

NOAC	Initial Treatment	Long Treatment (at least 3 months)	Extended Treatment (more than 3-6 months)
LMHW initially then switch			
Dabigatran	LMWH 5-10 days	150mg 2id	150mg 2id
Edoxaban	LMWH 5-10 days	60mg id (>60kg) 30mg id (≤60kg)	60mg id (>60kg) 30mg id (≤60kg)
Single oral			
Rivaroxaban	15mg 2id (21 days)	20mg id	20mg id 10mg id (after 12 months)?
Apixaban	10mg 2id (7 days)	5mg 2id	2.5mg 2id

Doses need to be adjusted in function of Creatinine Clearance

of VTE (provoked or unprovoked), risk of recurrence VTE, risk of bleeding (low, moderate and high) and patient preferences.[7] Dose regimens are the same as in acute treatment for Dabigatran, Rivaroxaban and Edoxaban, and half of dose for Apixaban. As said previously, after twelve months of treatment, a trial shews similar results with Rivaroxaban 10mg or 20mg daily in thromboprophylaxis.[10]

Another point of discussion is the use of NOACs in thrombophilia (APS). Despite some good results of RAPS Trial, with no thrombosis or major bleeding episode, recently TRAPS Trial was prematurely terminated because of higher incidence of arterial events and major bleeding with Rivaroxaban. There were three patients with arterial thrombotic events and previous VTE. These results are opposite with some statements of other authors, in which recurrence happened in the same type of vessels (arteries or veins).[21] The authors of TRAPS Trial concluded that Rivaroxaban showed no benefit and increased risk.[15] One of the reasons appointed for this increased risk was a necessity of higher level of anticoagulation in patients with APS high risk.

One of the first concerns about NOACs was the lack of specific agents for reversal of direct oral anticoagulants. The nonspecific agents include prothrombin complex concentrate, recombinant activated factor VII and haemodialysis for dabigatran. In the last years was approved by FDA (Food and Drug Administration) and EMA (European Medicines Agency) a reversal direct agent of Dabigatran (Idarucizumab), and by FDA a reversal direct agent of direct oral factor Xa inhibitors (Andexanet alfa). The indications for use are restricted to patients with life threatening bleeding (eg, intracranial), critical organ or closed-space bleeding (eg, retroperitoneal, pericardial) and ongoing bleeding despite measures, or situations at high risk of bleeding like patients that need an emergent procedure or patients with expected long delay in spontaneous restoration of haemostasis (eg acute or chronic renal failure).

It is important refer some special populations. NOACs are contra-indicated in pregnancy, breast feeding, and chronic kidney disease in haemodialysis, and should not be used in extreme obese patients (Body Mass Index -BMI >40kg/m2 or >120kg).[22] Data regarding safety and efficacy are very limited in paediatric population.

We will have new data in the future about NOACs in cancer and thrombophilia.

The Caravaggio Study will randomize 1168 patients to show a non-inferiority of Apixaban versus Dalteparin for the treatment of acute VTE in patients with cancer.[23] Primary outcome will be recurrent VTE and primary safety outcome will be major bleeding after 6-months of treatment.

There is one trial in phase of recruitment in thrombophilia. ASTRO-APS will randomize patients with APS to compare Apixaban (2.5mg twice-daily) with Warfarin for the secondary prevention of thrombosis.

NOACs are the gold standard for VTE treatment and secondary prevention in no cancer patients, and in patients with weight inferior to 120kg and BMI inferior to 40kg/m^2.

NOACs could be the first option of treatment in cancer patients with low risk of bleeding (exclusion of oesophageal, gastrointestinal and genitourinary cancers). Probably could be a good option in paediatric population, but at this moment data regarding safety and efficacy are very limited.

In patients with Chronic Kidney Disease (CKD) with Clearance Creatinine (ClCr) of 15-30mg/dl, NOACs could not be the gold standard. In case of use, Rivaroxaban and Apixaban should be preferred and used with dose reduction. It patients with thrombophilia (APS) and VTE (without arterial thrombosis) could be used with caution.

NOACs are not indicated in patients with cancer and high risk of bleeding (oesophageal, gastrointestinal and genitourinary cancers), in patients with thrombophilia (APS) and arterial thrombosis with or without VTE and in extreme obese patients (weigh >120kg and BMI <40kg/m^2).

NOACs are contra-indicated in patients with CKD in haemodialysis or with ClCr <15mg/dl, in pregnancy and breast feeding.

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