

Which patients with venous thromboembolism should receive non-vitamin K antagonist oral anticoagulants? The majority

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Anticoagulation plays a crucial role in the management of venous thromboembolism (VTE), in order to prevent extension or embolization of the thrombus, recurrence and chronic sequelae, such as the post-thrombotic syndrome and thromboembolic pulmonary hypertension¹. The treatment of VTE traditionally involves an initial phase of parenteral anticoagulation (unfractionated heparin, low molecular weight heparin or fondaparinux), overlapped and followed by vitamin K antagonists, which constitute the mainstay of the long-term and extended treatment². Recently, non-vitamin K antagonist oral anticoagulants (NOA), the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitors apixaban, edoxaban and rivaroxaban, have been proposed as alternatives to the current standard of care for VTE treatment^{2,3}. In addition to well-known practical advantages, the NOA have shown similar efficacy and an improved safety profile when compared to standard treatment in phase III clinical trials. Thus, NOA can simplify the therapeutic management of VTE and suit the majority of patients with VTE.

The pharmacological properties of NOA and their ease of use might have important implications in clinical practice. NOA have a rapid onset of action and reach peak plasma concentration in approximately 2 hours⁴, thereby overcoming the need for initial parenteral anticoagulation. Two of them, apixaban and rivaroxaban, are administered with a single drug approach, with higher doses during the acute phase (1 to 3 weeks) in order to prevent early VTE recurrence⁵. Similarly, NOA have a rapid offset of action, thereby allowing rapid reversal of coagulation when needed. Finally, due to the predictable pharmacokinetic response, minimal food and drug interactions and the wider therapeutic window, compared to vitamin K antagonists, they can be administered in fixed doses and routine laboratory monitoring is not required⁴. As a result, NOA can simplify the initial treatment of VTE. Patients suitable for home treatment, i.e. the majority of patients with deep vein thrombosis and patients with low-risk pulmonary embolism, can be easily treated as outpatients also during the initial phase, without the need for burdensome parenteral therapy or frequent blood tests. Patients admitted to hospital can be discharged early,

without needing to wait for the International Normalised Ratio to reach the therapeutic range.

The NOA show a particularly favourable safety profile, especially in specific subgroups of fragile patients, and a consistent efficacy profile in higher risk patients such as patients with pulmonary embolism.

A systematic review of 69 studies, mainly randomised, controlled trials, reported that conventional anticoagulant treatment is hampered by a risk of major bleeding complications of approximately 2%, with a case-fatality rate of 11%, during the first 6 months of treatment⁶. The risk is even higher when considering real-life patients enrolled in registries⁷. The results of the randomised, controlled trials comparing NOA with standard treatment have shown a consistent reduction of the risk of major bleeding of about 40% and of the risk of fatal bleeding and non-fatal intracranial haemorrhages of more than 60%⁸. Ongoing registries are evaluating whether their benefit is also present in real-life, clinical practice⁹.

The risk of bleeding complications with any anticoagulant treatment is known to be greater in certain subgroups of patients, such as the elderly, patients with renal impairment or patients with active cancer¹⁰. Approximately 20% of the population enrolled in the EINSTEIN trials comparing rivaroxaban with parenteral treatment and vitamin K antagonists consisted of "fragile" patients, defined as aged >75 years, creatinine clearance <50 mL/min or body weight ≤50 kg¹¹. In this subgroup, the rates of recurrent VTE and major bleeding were higher than in non-fragile patients, but the use of rivaroxaban resulted in a significant reduction of major bleeding complications, compared to standard therapy (1.3% vs 4.5%, respectively; hazard ratio [HR]: 0.27, 95% confidence interval [CI]: 0.13-0.54)¹¹. Similarly, in the HOKUSAI study edoxaban was associated with a significantly lower risk of major and clinically relevant non-major bleeding, compared to warfarin, in patients with a creatinine clearance 30-50 mL/min, body weight ≤60 kg or receiving potent P-glycoprotein inhibitors (7.9% vs 12.8%, respectively; HR 0.62, 95% CI: 0.44-0.86)¹². These results suggest that fragile patients can probably benefit the most from NOA. However, physicians need to take careful account of renal function, and the use of NOA should be

discouraged in patients with severe renal failure (defined by a creatinine clearance <30 mL/min).

Another difficult subgroup is represented by cancer patients, who have an increased risk of both bleeding and recurrent VTE compared to non-cancer patients. Anticoagulation is cumbersome in cancer patients because of the frequent need for interruptions, such as in the case of invasive procedures or chemotherapy-induced thrombocytopenia, and because of several drug-drug interactions¹⁰. There is preliminary evidence that the efficacy and safety of NOA might be comparable to those of vitamin K antagonists also in this population¹³, although cancer patients enrolled in randomised, clinical trials were relatively healthy, hence not fully representative of everyday clinical practice. Furthermore, no comparison is currently available between NOA and low molecular weight heparin, the current standard of treatment for VTE in patients with cancer.

Finally, the efficacy of NOA has been confirmed in patients with pulmonary embolism, who were the specific focus of the EINSTEIN-PE trial¹⁴ and who represented approximately one third of the populations of the other studies^{12,15,16}. Although only patients with hemodynamically stable pulmonary embolism were eligible for these studies, the HOKUSAI trial also provided information about patients with pulmonary embolism and evidence of right ventricular dysfunction (defined by an N-terminal pro-brain natriuretic protein level ≥ 500 pg/mL), in whom edoxaban was associated with a lower incidence of recurrent VTE than standard treatment (3.3% vs 6.2%, respectively; HR 0.52, 95% CI: 0.28-0.98)¹².

NOA have emerged as an advantageous therapeutic strategy for long-term, secondary prevention of VTE. Extended treatment is recommended for patients at a significant risk of recurrence, such as patients with unprovoked thrombotic events, when the risk of bleeding is acceptable². However, balancing the benefits and disadvantages of extended anticoagulation is difficult.

NOA can overcome some of the drawbacks of vitamin K antagonists, mainly the need for periodic laboratory monitoring and dose adjustments, and the consequent burden for patients. For the extended treatment of VTE, NOA have been compared mainly to placebo, since the trials included patients who had already received active treatment for at least 6 months and for whom there was clinical equipoise regarding the need to continue anticoagulant therapy. As expected, NOA were superior to placebo in the prevention of recurrent VTE and major bleeding complications were slightly increased, although not exceeding 1%¹⁷⁻¹⁹.

Of note, in the AMPLIFY-EXT trial, two different dosages of apixaban (2.5 mg and 5 mg twice daily) were compared to placebo¹⁸. Low- and high-dose of

apixaban had similar efficacy, with a more than 60% relative risk reduction of the primary outcome, recurrent VTE and overall mortality, and an approximately 80% relative risk reduction of recurrent VTE and VTE-related death, compared to placebo. Apixaban 2.5 mg showed similar rates of the composite safety outcome, major and clinically relevant non-major bleeding, compared to placebo (3.2% vs 2.7%, respectively; relative risk 1.20, 95% CI: 0.69-2.10) and a trend towards fewer bleeding complications, compared to apixaban 5 mg (3.2% vs 4.3%, respectively; relative risk 0.74, 95% CI: 0.46-1.22)¹⁸. The availability of two different dosing regimens, both safe, effective and easy to use, will allow the drug dosage to be adapted to the risk of bleeding of each single patient.

Dabigatran was the only NOA that was directly compared to warfarin for the long-term secondary prevention of VTE in the RE-MEDY trial, in which it was shown to have similar efficacy and be associated with less major or clinically relevant bleeding (5.6% vs 10.2%, respectively; HR 0.54, 95% CI: 0.41-0.71)¹⁹. Hence, NOA showed several advantages during the secondary prevention of VTE, making the extended treatment phase feasible for a greater number of patients.

In conclusion, the majority of VTE patients can be treated safely and effectively with NOA. The only exceptions today are patients with severe renal failure and patients with active cancer, at least until additional data become available for this latter group. Thanks to their pharmacological properties, the direct oral anticoagulants are easier to use and have several advantages for patients and for the health care system. Positive findings from randomised, controlled trials place them as valid alternatives to the current standard of care for both acute and extended treatment of VTE. Careful pharmacovigilance, through registries or phase IV trials, is needed in order to confirm these results in real-life clinical practice.

Conflicts of interest

NR has no relevant conflicts to declare in relation to this paper. WA has participated in advisory boards for Bayer HealthCare, Boehringer Ingelheim, Bristol-Myers Squibb-Pfizer and Daiichi Sankyo, and has received travel or research support from Bayer HealthCare, GlaxoSmithKline, Pfizer-BMS, Daiichi Sankyo, and Boehringer Ingelheim.

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