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Review Article

Extended non-vitamin K antagonist oral anticoagulation therapy for prevention of recurrent venous thromboembolism

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ABSTRACT

Evidence from the use of traditional therapy (low-molecular-weight heparin/vitamin K antagonists) for venous thromboembolism (VTE) treatment and prevention suggests that extending treatment beyond the acute phase reduces recurrence. More recently, several non-vitamin K antagonist oral anticoagulants (NOACs) have been approved in the acute setting; accumulating evidence suggests continuing treatment with these agents beyond 12 months offers additional benefits to patients with VTE.

This review examines the evidence for NOAC use in longer-duration anticoagulation treatment, and discusses guidelines from major societies. Clinical data from the phase III extension studies for apixaban, dabigatran and rivaroxaban are presented, and the clinical and economic costs and benefits are examined. Evidence from other therapy areas utilising extended treatment regimens highlights the possible impact of factors relevant to extended anticoagulation therapy. Phase IV studies of NOACs are presented.

US and European guidelines advise long-term therapy in certain instances, taking into account evidence on NOAC use in VTE accumulated recently. They support NOAC use where they have been selected as the initial therapy choice and therapy needs to be extended beyond 3 months. The phase III extension studies demonstrate the benefits of extended NOAC use versus treatment cessation, with reduced recurrence rates versus placebo, although associated with a potential moderate increase in bleeding risk. Phase IV data are also emerging, with the recent XALIA study showing that a broad range of patients with VTE can benefit from continued rivaroxaban treatment; ongoing research will yield data on long-term use of the other NOACs in routine clinical practice.

Contents

Abbreviations: ACCP, American College of Chest Physicians; Bid, twice daily; CI, confidence interval; DVT, deep-vein thrombosis; ESC, European Society of Cardiology; LMWH, low-molecular-weight heparin; NICE, National Institute for Health and Care Excellence; NOAC, non-vitamin K antagonist oral anticoagulants; od, once daily; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

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1. Introduction

Venous thromboembolism (VTE), comprising deep-vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common cardiovascular disease [1]. The incidence rate among the general population is 1–2 cases per 1000 people, and the risk of VTE recurrence increases with advancing age [2,3]. Standard therapy for treatment and prevention of VTE has historically involved heparin/fondaparinux followed by and overlapping with a vitamin K antagonist (VKA) [4]. Recently, several non-VKA oral anticoagulants (NOACs; apixaban, dabigatran, edoxaban and rivaroxaban) have been approved in this setting, after the respective phase III and extension trials demonstrated the efficacy and safety of these agents in VTE treatment and prevention of recurrent events [5–11].

2. Rationale for extended treatment

Duration of anticoagulation can be categorised into initial treatment, lasting 3–6 months, and long-term treatment lasting beyond 3–6 months (although there is variation between authors on these terms, e.g. some describe therapy beyond 3 months with no scheduled stop date as extended therapy) [4,12]. There is a strong rationale for anticoagulation treatment beyond the acute phase in many patients with VTE, because the risk of recurrent VTE after stopping anticoagulation treatment is high, particularly for unprovoked DVT (~40% at 10 years) (Fig. 1) [13]. Extended warfarin treatment for 12 months versus 3 months after unprovoked proximal DVT was associated with a reduced rate of VTE recurrence; furthermore, this clinical benefit was not maintained after cessation of anticoagulation treatment at 12 months [14]. Similar outcomes have been seen for patients with PE receiving warfarin versus placebo for 18 months after completing 6 months of VKA treatment. Again, the clinical benefit did not persist after cessation of treatment at 18 months [15]. Long-term low-intensity warfarin (target international normalised ratio of 1.5–2.0) for treatment of unprovoked VTE also reduced rates of the composite endpoint of recurrent VTE, major haemorrhage and death versus placebo; the randomised trial was terminated early by an independent safety monitoring board because the benefits were so pronounced in the absence of any obvious harms [16]. However, there are currently no studies supporting the safety and efficacy of extended anticoagulant treatment beyond 2 years, although the risk of recurrence has been shown to decrease after 5 years (Fig. 1) [13]. This suggests that the net clinical benefit of extended anticoagulation may be different for the first 5 years compared with the period thereafter. Physicians should be aware of this possibility when considering whether to treat patients for an indefinite period.

The relative effectiveness of standard treatments has also been compared, with some studies showing a similar impact between low-molecular-weight heparin (LMWH) and VKAs on recurrent VTE rates [17]. However, patient demographics and clinical characteristics may also influence treatment effectiveness in extended or long-term anticoagulation. In patients with VTE and cancer, which is a major risk factor for recurrent VTE, extended treatment with LMWH reduced rates of recurrent VTE (although not mortality) versus VKAs [18]. Other agents have also been tested for extended anticoagulation. The Van Gogh Extension study compared 6 months of treatment with the Factor Xa inhibitor idraparinux with placebo in patients who had previously completed 6 months of anticoagulation therapy [19]. Rates of recurrent VTE were lower in the idraparinux group; however, there was a higher rate of major bleeding with idraparinux than with placebo.

These findings highlight that there is a good basis for extended or long-term anticoagulation treatment in VTE. Given the clear benefits shown with standard therapeutic options, looking at the potential role for the NOACs in these settings is of interest. This review will discuss the current guidelines, phase III data, risks and benefits, and evidence from routine clinical practice relating to anticoagulation beyond the acute phase with the NOACs.

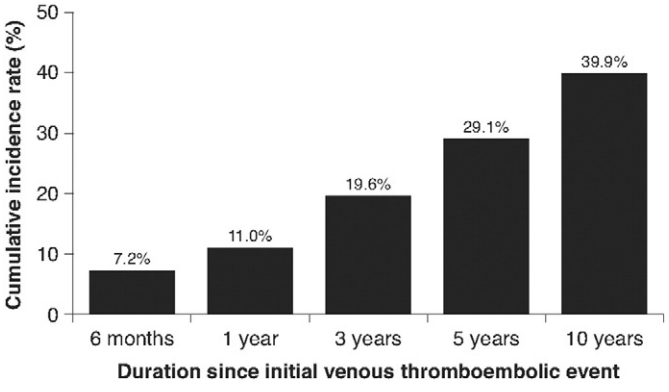

Fig. 1. VTE recurrence risk in patients with unprovoked DVT. DVT, deep-vein thrombosis; VTE, venous thromboembolism [Single column].

3. Evidence for non-vitamin K antagonist oral anticoagulants for long-term anticoagulation

Most evidence regarding the rationale for extended treatment has been derived from studies using VKAs [13,14,16]; however, of the four NOAC extension studies reported to date, only one has compared a NOAC with a VKA [11]. The American College of Chest Physicians (ACCP) guidelines recommend extended anticoagulation in certain patients [4,20]. The decision depends on whether the DVT is proximal or distal, whether the patient has active cancer and whether VTE was provoked (e.g. as a result of surgery or a non-surgical transient risk factor). For example, extended or longer-term treatment is advised for a first unprovoked proximal VTE provided the patient's bleeding risk is low or moderate; in patients with a higher bleeding risk, anticoagulation is only recommended for 3 months. The strength of these recommendations also varies: the former advice is given an evidence rating of 2B, meaning that it is only a weak recommendation based on moderate-quality evidence; however, the latter is graded as 1B, meaning that although the evidence quality is moderate, the strength of the recommendation is high.

The ACCP makes specific therapy recommendations for extended anticoagulation. The 2012 guidelines generally favoured the use of a VKA over LMWH for patients without cancer, and LMWH over VKAs for patients with cancer; VKAs were recommended over dabigatran or rivaroxaban (apixaban and edoxaban were not approved for VTE treatment and prevention at the time of publication of these ACCP guidelines) in patients with or without cancer, owing to the paucity of post-authorisation data. The recent 2016 update accounts for the interim accumulation of evidence on the NOACs in this setting [20]. The update advises that NOACs are preferred to VKAs for the first 3 months of treatment in patients with DVT of the leg or PE with no cancer. For patients with cancer-associated thrombosis, LMWH is advised over VKAs or the NOACs. For extended or long-term therapy beyond 3 months, it is recommended to continue with the initial therapy choice. In most cases, anticoagulation for 3 months is advised over long-term treatment (no scheduled stop date). The exceptions to this are patients with: a first unprovoked proximal DVT of the leg or PE and a low or moderate bleeding risk, a second unprovoked VTE and a low or moderate bleeding risk and patients with cancer-associated thrombosis. Owing to the lack of head-to-head comparisons between the NOACs and an insufficient amount of indirect evidence, the guidelines do not state a preference for a specific NOAC; instead, they advise that drug-specific adverse events, local cost/coverage issues and patient preference should be considered as factors influencing NOAC choice.

In Europe, the European Society of Cardiology (ESC) published guidelines in 2014 for the acute management of PE [21]. These also