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Review Article

Non-vitamin K antagonist oral anticoagulants for the prevention of recurrent venous thromboembolism

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ABSTRACT

Venous thromboembolism (VTE) is associated with a risk of recurrence that depends on factors specific to index event and patient. A first unprovoked VTE increases the risk of a recurrent event, particularly during the first year after anticoagulation cessation. Determining a strategy for the long-term prevention of recurrent VTE poses challenges that stem from a lack of agreement on recommended therapy duration and varying treatment burden for the patient. Oral anticoagulants, including vitamin K antagonists and non-vitamin K antagonist oral anticoagulants (NOACs), are the main treatment options for the long-term prevention of recurrent VTE. However, the risk of VTE recurrence must be balanced against the risk of bleeding in each patient. Phase III clinical trials have evaluated rivaroxaban, apixaban and dabigatran for extended treatment and prevention of VTE versus placebo, and versus warfarin in the case of dabigatran. Compared with placebo treatment, each NOAC showed superior efficacy together with an acceptable safety profile during extended treatment periods of 6–18 months. Patients receiving long-term NOAC therapy will still require regular risk factor assessment, but these agents may permit longer treatment duration with an improved benefit–risk profile.

Contents

Abbreviations: ACCP, American College of Chest Physicians; ASA, acetylsalicylic acid; bid, twice daily; BMI, body mass index; CI, confidence interval; CrCl, creatinine clearance; DVT, deep vein thrombosis; ESC, European Society of Cardiology; ISTH, International Society on Thrombosis and Haemostasis; LMWH, low molecular weight heparin; NICE, National Institute for Health and Care Excellence; NOAC, non-vitamin K antagonist oral anticoagulant; NR, not reported; OAC, oral anticoagulant; od, once daily; OR, odds ratio; PE, pulmonary embolism; RRR, relative risk reduction; UFH, unfractionated heparin; 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), and the recurrence of VTE after initial treatment, represents a major demand on healthcare systems [1,2]. VTE can impair an individual patient's quality of life and is potentially life threatening. Epidemiological studies from across Europe demonstrated an incidence of 1–2.5 cases of VTE per 1000 persons per year [3,4], whereas data from US communities showed a slightly lower average annual incidence of 0.7–1.2 cases per 1000 persons per year [5,6]. Global figures demonstrate annual incidences of 0.75–2.7 cases per 1000 persons per year [7]. The risk of VTE recurrence is highest during the first 12 months after the initial event, and this risk levels off with time, although it never falls to zero [8]. Reported recurrence rates are variable and depend on the periods and the populations assessed. VTE recurrence rates of 8.6–10.1% have been shown 6 months after a first VTE episode [8,9], and rates of 7–12.9% were found across the general population after one year [8,10,11]. The risk of developing recurrent VTE is higher in certain patient populations. For patients with active cancer, for instance, the risk of VTE recurrence was shown to be higher than for patients without concomitant malignancy [8,10,11]. The risk of recurrence is generally higher in patients with unprovoked (idiopathic) VTE than in those with a provoked index event (associated with risk factors such as surgery, hospitalisation or pregnancy) [12]. DVT confined to the distal veins (isolated distal or calf DVT or muscular) [13] is associated with an estimated 50% lower risk of VTE recurrence compared with proximal DVT and PE [14].

Anticoagulation therapy has been the mainstay of treatment and secondary prevention of VTE for >50 years. The current arsenal of anticoagulants consists of vitamin K antagonists (VKAs), heparin derivatives and the non-VKA oral anticoagulants (NOACs) rivaroxaban, apixaban, dabigatran and edoxaban. Owing to the nature of anticoagulation, however, treatment is inherently associated with a risk of bleeding, and treating physicians and patients are faced with a constant dilemma of weighing the risk of VTE recurrence against the risk of bleeding. An annual risk of 1.2–12% has been reported for major bleeding related to VKA therapy during treatment and secondary prevention of VTE [15–20]. Similar or lower rates have been demonstrated for the NOACs in phase III clinical trials [15–18].

NOACs offer advantages over VKA therapy owing to their simple, fixed dosing regimens. Unlike VKAs, NOACs do not require routine anticoagulation monitoring, and the extent of drug–drug and food–drug interactions is limited compared with VKAs [21,22]. For the treatment and secondary prevention of VTE, the NOACs have demonstrated similar or better outcomes profiles in phase III studies [16–18,23–27].

Studies of extended anticoagulant therapy have been conducted for rivaroxaban, apixaban and dabigatran with the aim of assessing the efficacy and safety of long-term treatment regimens for 6–18 months beyond the initial treatment period, compared with placebo [23,26,28]. In addition, dabigatran has been compared with warfarin in an active-control study [26]. In clinical practice, it is important to assess the benefits and risks of any long-term anticoagulant therapy to improve the management of patients who are at risk of recurrent VTE. One way to assess the potential benefit of extended anticoagulation is to compare the estimated number of potentially fatal recurrent venous thromboembolic events avoided with the estimated number of fatal bleeding events that may have resulted from extended anticoagulation over a certain period [14]. However, it is equally important to first identify those patients who are in need of extended or even life-long anticoagulation, and to understand the relevant safety considerations when making treatment decisions.

This review examines current guideline recommendations for VTE treatment and prevention, particularly in relation to how risk factors may affect decisions on the length of treatment with NOACs. Practical considerations during long-term use of NOACs for the management of VTE are also discussed.

2. Materials and methods

Current relevant European and North American guidelines were reviewed including the American College of Chest Physicians (ACCP), the European Society of Cardiology (ESC), the International Society on Thrombosis and Haemostasis (ISTH) and the UK National Institute for Health and Care Excellence (NICE) [14,29–32] in addition to all relevant published randomised phase III clinical studies on extended NOAC treatment [23,26,28].

3. Length of treatment

The ACCP, the ESC, the ISTH and NICE have all published recent recommendations on the duration of anticoagulation in VTE treatment and secondary prevention that are specific to patients with provoked VTE, unprovoked VTE and patients with concomitant cancer [14,29–32].

Guidelines largely agree on a 3-month treatment duration for provoked index events, although recommendations considering extended anticoagulation if the index event was a life-threatening PE or extensive DVT exist [14,29,32–34]. The guidelines are, however, less definitive in their guidance on unprovoked VTE and VTE with concomitant cancer (Table 1) [14,29,32,33]. All guidelines recommend a minimum duration of 3 months of anticoagulation for unprovoked VTE, but decisions on continuation or halting of treatment are largely dependent on regular individual risk factor assessment [14,29–31]. Minor differences exist with regard to the level of detail presented by the individual guidelines and on the use of risk factor assessments. The ACCP guidelines recommend indefinite treatment for an unprovoked VTE beyond 3 months if the patient's risk of bleeding is low or moderate [14], whereas the ESC guidelines recommend extended treatment in patients with a first episode of unprovoked VTE who are at a low risk of bleeding [29]. The ESC guidelines further recommend indefinite treatment for patients with a second episode of unprovoked PE regardless of the risk of bleeding [29].

Similar to the approach for determining therapy length for preventing VTE recurrence after an unprovoked index event, the guidelines on anticoagulation duration in patients with concomitant cancer recommend consulting individual risk factors to guide treatment decisions. The high risk of VTE recurrence and bleeding in cancer patients is reflected in the recommendations. Although the ACCP guidelines suggest treatment beyond 3 months even in patients at a high risk of bleeding [14], the ESC guidelines suggest consideration of indefinite anticoagulation for patients with PE and cancer [29]. The ISTH offers a dedicated set of guidelines for the treatment and prevention of VTE in this particular patient subgroup (Table 1) [32].

At present, there are no recommendations available for the treatment of recurrent provoked VTE, recurrent unprovoked VTE with a very long interval between the two events (e.g. >10 years) or mixed events (i.e. unprovoked and recurrent provoked).

The key message across all available guidelines is that regular risk factor assessment, in consideration with the patient's preferences, is the basis for all decision-making and may also offer a starting point on how to manage patients with these conditions [14,29–31].

4. Long-term treatment strategies for venous thromboembolism

4.1. Vitamin K antagonists

VKAs have been the standard of care for long-term prevention of secondary VTE for decades and continue to be widely recommended for this indication in patients with both provoked and unprovoked VTE [29–31]. The ACCP guidelines acknowledge that VKAs are still widely used for the extended treatment of VTE; however, they now suggest the use of NOACs over VKAs for long-term VTE treatment [14]. A recent meta-analysis comparing the efficacy and safety of oral anticoagulants and antiplatelet agents for the secondary prevention of VTE suggested that VKAs are highly effective in reducing recurrent VTE (8.8% reduction