Duración óptima de la prevención secundaria en tromboembolismo venoso

Optimal duration of secondary prevention of VTE

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Recurrent venous thrombosis may occur within the first few days or weeks, but also after several months or years after the index event. Observational studies have reported that up to 40% of patients will experience a recurrence after 8 to 10 years[1]. The incidence rate of recurrent VTE was estimated to be about 5.0% patient-years, being highest during the first 6 months (11.0% patient-years) and then decreasing with a plateau at 2.2% patient-years between 4 and 10 years after the index event[2]. Recurrence rates are highest in patients with permanent predisposing factors, such as active cancer, and lowest in patients with major, removable predisposing factors such as surgery[3,4]. In between, there are several subgroups of patients including those with chronic inflammatory diseases, patients with non-surgical removable risk factors such as hormonal therapy or acute medical illness, and patients with unprovoked VTE[5]. It was proposed that a recurrence rate of 5% at one year and of 15% at five years after stopping anticoagulant therapy can be considered acceptable to justify discontinuation of vitamin K antagonists (VKAs), whereas higher recurrence rates should mandate continuation of treatment[6].

Randomized controlled trials have shown that all patients benefit from a minimum of three months of anticoagulant therapy[7]. After this period, guidelines suggest that patients with major transient risk

factors such as surgery, trauma, or hospitalization for an acute medical illness can safely discontinue treatment, while for all other patients indefinite treatment duration should be considered[4].

Decision on treatment extension should be based on a careful assessment of risks and benefits of anticoagulation, thus balancing the risk of recurrence with the risk of bleeding complications after the first 3 months of therapy. In the main clinical trials comparing extended duration of treatment with VKAs with no extended treatment for the secondary prevention of VTE, cumulative rates of major bleeding ranged from 0.4% to 3.0% after 1 year and continued to increase with further extension of treatment to up to 8.6% at 4 years[8-14]. Although recurrence rates after stopping treatment appear to be higher than major bleeding rates, case-fatality rate for major bleeding in patients taking warfarin for more than three months was shown to be higher than case-fatality rate of recurrent venous thromboembolism. A pooled analysis of randomized controlled trials and prospective cohort studies reported a case-fatality rate for major bleeding of 9.1% in patients taking VKAs for more than three months[15]. Conversely, the case-fatality rate for recurrent VTE after discontinuation of VKAs was 3.6% in another systematic review of randomized clinical trials and prospective cohort studies[16]. Thus, bleeding events are associated with at least 3 times higher risks of mortality than recurrent VTE and this needs to be taken into account when deciding treatment duration.

To improve treatment decisions, management strategies and clinical prediction, rules have been proposed to allow individual prediction of recurrence or bleeding complications. The detection of a negative D-dimer at the end of anticoagulant treatment in patients with unprovoked VTE is associated with a low risk of recurrence, and this risk remains in particular low when D-dimer remains negative for up to 3 months after treatment withdrawal[17,18]. The absence of residual vein obstruction on compression ultrasonography at the end of anticoagulant treatment was also proposed as a marker of low risk of recurrent VTE, but the clinical utility of this test remains uncertain[19]. A number of prediction rules were also proposed, which combined clinical and laboratory predictors of recurrent VTE and aimed to identify individual patients at low risk of recurrence who can safely withhold anticoagulant treatment. In the HERDOO2 score, sex, age, signs of post-thrombotic syndrome, D-dimer, and obesity were identified as independent predictors and included in a clinical prediction rule that was able to identify a subgroup of women (but not men) with a very low risk of recurrence[20]. The Vienna score is based on a nomogram which calculates the individual risk of recurrence at 12 and 60 months, based on sex, extension of DVT, PE and D-dimer[21]. Finally, the DASH score includes D-dimer, age, sex, and the use of hormonal therapy[22]. Unfortunately, none of these scores is sufficiently accurate to be routinely applied in clinical practice. A number of bleeding risk scores have also been proposed[4,23-25], but none predicted better than chance after external validation[26].

The results of extended treatment studies with the direct oral anticoagulants (DOACs) suggest that these compounds are highly effective as compared to placebo and have good safety profiles. In the studies with the DOACs, major bleeding rates were lower than bleeding rates observed with VKAs in previous studies and ranged between 0.1% and 0.9% after approximately one year of treatment[27-30]. In particular, a 50% dose reduction after the first 6 months of treatment for apixaban and rivaroxaban was shown to possibly improve the safety profile of anticoagulant treatment[29,30].

In conclusion, the optimal duration of secondary prevention of venous thromboembolism should take into account the presence or absence of major provoking factors at the time of the index event and of bleeding risk factors at the time of possible treatment discontinuation. After a minimum of 3 months, patients at low risk of recurrence such as patients with venous thromboembolism secondary to trauma, surgery, acute medical illness, or hormonal therapy should stop treatment, whereas patients with permanent risk factors (e.g. cancer) or with unprovoked venous thromboembolism should possibly continue for an indefinite period of time. The decision to stop or continue anticoagulant treatment remains difficult in the absence of adequate clinical prediction rules and should take into account patient preferences.

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