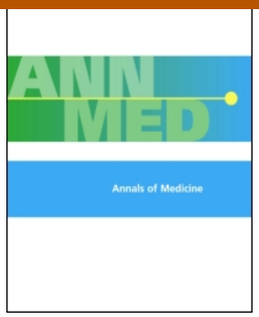

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Eduardo Peñaloza-Martínez, Pablo Demelo-Rodríguez, Marco Proietti, Guillermo Soria Fernández-Llamazares, Cristina Llamazares-Mendo, Luis Álvarez-Sala Walther, Alberto M. Marra & Jorge del Toro-Cervera

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Update on Extended Treatment for Venous Thromboembolism

Authors: Eduardo Peñaloza-Martínez[1], Pablo Demelo-Rodríguez[1,2,3], Marco Proietti[4,5,6], Guillermo Soria Fernández-Llamazares[1], Cristina Llamazares-Mendo[1], Luis Álvarez-Sala Walther[2,3], Alberto M. Marra[4,7], Jorge del Toro-Cervera[1,2,3]

(1) Venous Thromboembolism Unit. Internal Medicine Department. Hospital General Universitario Gregorio Marañón. Madrid, Spain

(2) School of Medicine. Universidad Complutense de Madrid. Spain

(3) Instituto de Investigaciones Sanitarias Gregorio Marañón

(4) IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy.

(5) Institute of Cardiovascular Sciences, University of Birmingham, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, United Kingdom.

(6) Department of Internal Medicine and Medical Specialties, Sapienza University of Rome, Rome, Italy.

(7) Pulmonary Hypertension Centre, Thoraxclinic at Heidelberg University Hospital, Heidelberg, Germany

Corresponding author:

Pablo Demelo-Rodríguez

Hospital General Universitario Gregorio Marañón, Madrid, Spain

Email: pbdemelo@hotmail.com

Abstract: The importance of assessing the probability of venous thromboembolism recurrence, a condition that includes deep vein thrombosis and pulmonary embolism, lies in the fact that it is the most important factor in deciding the duration of anticoagulant treatment. Risk of recurrence depends mostly on the presence of a risk factor for developing venous thromboembolism, with patients with unprovoked events being at the higher risk of recurrence. The risk of recurrence needs to be balanced with the risk of bleeding and the potential severity of these thrombotic and hemorrhagic events.

In patients with an unprovoked venous thromboembolism who complete treatment for the acute (first 10 days) and post-acute phase of the disease (from day 10 to 3-6 months), decision has to be made regarding prolonged antithrombotic therapy to prevent recurrences. The main goal of extended treatment is preventing recurrences with a safe profile in terms of bleeding risk. Many therapeutic options are now available for these patients, including antiplatelet therapy with aspirin or direct oral anticoagulants. Moreover, apixaban and rivaroxaban at prophylactic doses have demonstrated efficacy in preventing recurrences with a low risk of bleeding.

Keywords: anticoagulation; venous thromboembolism; bleeding.

Key Messages:

• Extending treatment (longer than 3 to 6 months) are challenging in patients with Venous Thromboembolism (VTE) and depend on the risk of venous thromboembolism recurrence, the bleeding risk and patient and physician preferences.

• Anticoagulation treatment should be stopped in patients with provoked VTE and in those with unprovoked VTE and a high bleeding risk after initial period of 3 to 6 months.

• There are some therapeutic alternatives (including Aspirin and low dose of some NOACs) to reduce venous thromboembolism recurrence risk in patients with unprovoked VTE and a low bleeding risk for extended treatment of VTE (after initial period of 3 to 6 months)

1. Introduction

Venous Thromboembolism (VTE) includes deep-vein thrombosis (DVT) and pulmonary embolism (PE), and represents the third cause of vascular disease-related deaths. The mainstay of treatment is anticoagulation, and current guidelines recommend to treat patients for 3 months or longer[1,2]. Decisions about extending treatment (longer than 3 to 6 months) are challenging and depend on the risk of venous thromboembolism recurrence once anticoagulation is stopped. It has been estimated in about 10% within the first year and 30% in the first five years in patients without reversible risk factors[3].

When considering extended anticoagulant therapy, a balance should be performed including the risk of VTE recurrence, the bleeding risk and patient and physician preferences. Vitamin K antagonist (VKA) therapy, as well as Non-vitamin K antagonist oral anticoagulants (NOACs) and aspirin, are effective for the prevention of VTE recurrence, but the inconvenience of laboratory monitoring in the case of VKA therapy and concerns about bleeding lead to reluctance to continue anticoagulation beyond the first 3-6 months. Aim of this review is to report the available evidences regarding the extended treatment for venous thromboembolism.

2. Evaluation of the risk of VTE recurrence

Calculating the likelihood of VTE recurrence is the most important factor to guide anticoagulant treatment duration. In this regard, it is important to classify the thrombotic event in unprovoked (formerly called idiopathic) or provoked.

An episode of VTE is considered unprovoked when a major trigger, usually environmental or acquired (such as surgery or immobilization) is not identified. However, this definition is not standardized, since there are minor or transient risk factors (RFs), such as hormonal treatment or minor thrombophilia, in which the associated VTE events are considered unprovoked or provoked according to different studies[4-7].

In this sense, a standardization of the terms has recently been proposed with the aim of improving clinical practice and research[4]. According to this proposal, the term 'unprovoked' rather than 'idiopathic' defines an episode of VTE in which there is no previous identifiable RFs while an episode is considered 'provoked' when it is preceded by a transient major, minor or persistent RF. Major RFs appear 3 months prior to the event; are associated with 50% less recurrence after

anticoagulation withdrawal in comparison with unprovoked events and increase the risk of a first episode of VTE more than 10 times. Examples of major RFs are major surgery or prolonged immobilization. Minor RFs appear in the 2 months previous to the episode of VTE and are associated with a 50% less recurrence after anticoagulation withdrawal in comparison with unprovoked events and increase the risk of a first episode from 3 to 10 times. An example of minor RFs is treatment with estrogens. Finally, persistent RFs would be active cancer, or those conditions that multiply at least 2 times the risk of VTE recurrence after anticoagulation withdrawal[4]. **Figure 1.**

VTE recurrence rate after treatment discontinuation for unprovoked events is as high as 10% after the first year reaching 30% after 5 years[5-7]. This recurrence rate is lower for provoked events caused by surgery (3% at 5 years) or a non-surgical RF (15% at 5 years)[5]. Patients with higher recurrence rate must be identified and separated from those with a single provoked VTE, in which the extension of anticoagulant treatment to more than 3-6 months is not necessary. The recurrence risk after anticoagulant discontinuation in unprovoked VTE does not vary depending on the duration of the anticoagulant treatment[8,9].

There are some additional factors that condition the risk of recurrence after a first episode of unprovoked VTE, which can help in the decision whether to prolong anticoagulant therapy after the initial period of 3-6 months, together with the estimation of the bleeding risk[10]. First, the previous history of VTE must be highlighted, since a previous episode of unprovoked VTE increases the risk of recurrence in 45% within 5 years[5]. Another factor would be older (or increasing) age, which multiplies by 1.7 the recurrence risk per each decade of life; male sex has an increased relative risk of 1.3-3.6 higher than females[11]. Obesity and post-thrombotic syndrome multiply recurrence risk by 2.6[12,13]. The index event has not shown to be a risk predictor, except in the case of distal DVT, which shows 51% less risk of recurrence when compared to proximal DVT[14]. Minor thrombophilias (heterozygosis for factor V Leiden and prothrombin G20210A) confer a minimal increase in relative risk of 1.4-1.7 so their presence should not condition treatment duration[15], while major thrombophilias (antithrombin III, C and S deficiencies) and antiphospholipid syndrome involve high recurrence risk and its presence might require indefinite anticoagulation. Residual venous thrombosis alone without post-thrombotic syndrome is not useful in predicting VTE recurrence[16].

D-dimer determination is perhaps the most useful laboratory test to predict recurrence but is not definitive. High concentrations of D-dimer one month after stopping anticoagulant treatment is associated with an increased risk of recurrent VTE[17,18]. Nevertheless, a normal concentration is not able to identify patients with low risk[19]. The combined use of D-dimer with other predictors, such as residual venous thrombosis (D-dimer and Ultrasonography in Combination Italian Study [DULCIS])[17] or the gender, has greater prediction ability than D-dimer alone. In fact, male gender and D-dimer are the risk predictors present in the 3 scales for prediction of VTE recurrence (D-dimer, Age, Sex male, Hormonal Therapy [DASH], Vienna Scale, and Hyperpigmentation, Edema or Redness, D-dimer, Obesity, Older age [HERDOO2]), which may be helpful, but only the HERDOO2 scale has been validated to guide treatment duration for women with unprovoked VTE[20], while for the other two models external validation is still needed[11].

3. Bleeding Risk Evaluation

The main limitation of long-term anticoagulation is bleeding risk, which is estimated globally in 2.06-2.24% (0.2-0.55% of fatal bleeding), which implies a mortality rate of 9.3-20.2% during the first 3 months[21-24]. After this period the risk of bleeding is 2.74 % per year, with a mortality rate of 2-18.2%[21-24]. The bleeding risk should be compared with the rate of fatal events due to recurrent VTE, which is estimated in 0.4% within the first 3 months, with a mortality rate of 11.3-16.1% (greater in pulmonary embolism than in DVT) and of 0.3% patients/year, being the mortality rate 2-3.6% after that time[21-24] . In the light of these data, it appears clear that the incidence and mortality of recurrent VTE seems to decrease over time while bleeding risk remains stable, therefore after the initial treatment period bleeding risk evaluation becomes as important as the recurrence one.

For the estimation of the bleeding risk, the American College of Chest Physicians (ACCP) used a model based on the number of predisposing bleeding factors in each patient, which can range from 1.6% to 12.8% in the first 3 months of anticoagulation and within 0.8% and more than 6.5% per year, after that period[2]. The only validated scale to evaluate the short-term (3 months) bleeding risk is RIETE (Registro Informatizado de Enfermedad Tromboembólica) score, a risk score based on six variables (age >75 years, recent bleeding, cancer, creatinine levels >1.2 mg/dl, anemia, or pulmonary embolism at baseline) that can identify VTE patients at low, intermediate, or high risk for major bleeding during the first three months of therapy[25]. There are no risk estimation scales for long-term

bleeding risk validated in patients with VTE, in opposition to the case of atrial fibrillation.

4. New therapeutic Options in Extended Treatment for VTE

The main available therapeutic options for extended treatment for VTE patients have been summarized in **Figure 2.**

As previously discussed, depending on the balance between individual VTE recurrence risk after discontinuation of anticoagulation and the bleeding risk while receiving treatment, prolonging anticoagulation into a secondary prevention (extended phase) may be justified after the initial treatment of acute and post-acute phase (3-6 months) for VTE.

The level of adherence to treatment guidelines for long-term management of VTE in the outpatient setting is unclear[26]. Factors that might limit the acceptance of extended anticoagulation include the current requirement for therapeutic monitoring and dietary restrictions with VKA, along with patients and clinicians perception of the bleeding risk associated with VKA anticoagulation[27].

More convenient anticoagulant agents with at least equivalent efficacy and safety may lead to more widespread acceptance of extended anticoagulation. Various strategies have been studied to reduce the cost, complexity, and toxicity of long-term anticoagulation therapy. Reduced-intensity warfarin proved to be less effective than standard intensity warfarin in randomized, controlled trials[28,29]. Other studies have evaluated different antithrombotic strategies in extended treatment and will be summarized in the following paragraphs.

Aspirin. The use of aspirin in the prevention of VTE recurrence was evaluated in two randomized clinical trials. The first one was the WARFASA trial[30], a multicenter, double-blinded trial that included patients with unprovoked VTE who had completed previously 6 to 8 months of treatment with oral anticoagulants. These patients were randomized to receive aspirin 100 mg per day vs placebo, during 2 years. VTE recurred in 28 of the 205 patients who received aspirin and in 43 of the 197 patients who received placebo (6.6% vs. 11.2% per year; HR 0.58; 95% confidence interval [CI], 0.36 to 0.93; p=0.02). The obtained outcomes showed that aspirin therapy reduced the rate of recurrence of VTE by about 40% compared to placebo, which suggests that it could be an interesting alternative to extended oral anticoagulant treatment for the prevention of VTE recurrences, with no increased risk for major bleeding or other adverse events compared to

placebo; some limitations should be considered regarding the bleeding risk (may be greater in real-world patients).

A second study was the ASPIRE trial[31] that included patients with a first episode of unprovoked VTE who had completed initial treatment with oral anticoagulants. They randomly assigned 411 patients to treatment with aspirin 100 mg a day and 411 patients to placebo for up to 4 years. VTE recurred in 73 of 411 patients assigned to placebo and in 57 of 411 assigned to aspirin (6.5% per year vs. 4.8% per year; HR with aspirin, 0.74; 95% confidence interval [CI], 0.52 to 1.05; p=0.09). showing that aspirin, as compared with placebo, did not significantly reduce the rate of recurrence of VTE, but it showed a significant reduction of 34% in the rate of major vascular events, with improved net clinical benefit and without increasing bleeding (rate of 0.6% per year with placebo vs. 1.1% per year with aspirin, p=0.22). It seems that patients who have had a first unprovoked event of VTE have an increased risk of arterial thrombosis and cardiovascular death. Aspirin has demonstrated to reduce the rate of these events, including stroke, myocardial infarction and cardiovascular death. As a limitation there were fewer recruited patients than initially planned. In contrast, the combined results of ASPIRE and WARFASA trials showed a highly significant reduction of 32% in the rate of VTE recurrence[31], providing significant evidence for the use of low dose aspirin therapy in the prevention of recurrent VTE and major vascular events in patients who have had a first episode of unprovoked VTE, considering aspirin as an alternative to anticoagulant treatment in the extended treatment of VTE.

Dabigatran. Dabigatran, a NOAC that is a direct thrombin inhibitor. It was evaluated for the secondary prevention of VTE in the RE-SONATE and RE-MEDY trials[32]. These double-blinded randomized trials compared dabigatran at a dose of 150 mg twice daily with warfarin (active-control study) or with placebo (placebo-control study) in patients with venous thromboembolism who had completed at least 3 initial months of therapy.

In the RE-MEDY trial (the active-control study) recurrent venous thromboembolism occurred in 26 of 1430 patients in the dabigatran group (1.8%) and 18 of 1426 patients in the warfarin group (1.3%) (HR with dabigatran, 1.44; 95% confidence interval [CI], 0.78 to 2.64; p=0.01 for non-inferiority), demonstrating that dabigatran 150 mg bid was non-inferior to warfarin in preventing VTE recurrence after 3–12 months of anticoagulant therapy. There was a significant reduction in major or non-major clinically relevant bleeding events with dabigatran compared with warfarin (HR 0.54; 95% CI, 0.41 to 0.71)

and an increase of major or clinically relevant bleeding when compared to placebo group (HR 2.92; 95% CI, 1.52 to 5.60; p<0.001). A higher incidence of acute coronary syndrome events was reported in patients receiving dabigatran in this study (0.9% vs 0.2% for warfarin; p = 0.02). A Limitation in trial design was reported due to the prespecified noninferiority margin for the hazard ratio that allowed an increase in risk by a factor of nearly 3 to be accepted as noninferior.

The RE-SONATE trial randomized 1,343 patients to dabigatran 150 mg (681 patients) or placebo (662 patients) for six months with extended follow-up to evaluate the long-term risk of recurrence (12 months after completion of study treatment) showing a 92 percent risk reduction for recurrent or fatal VTE with dabigatran versus placebo (three patients, 0.4 percent versus 37 patients, 5.6 percent; p<0.001 for superiority) with a higher rate of major or clinically relevant bleeding in the dabigatran group versus no treatment (36 patients, 5.3 percent versus 12 patients, 1.8 percent; p=0.001)

Apixaban. Apixaban is another NOAC, whose mechanism of action is the inhibition of factor Xa. The AMPLIFY-EXT trial[33] compared apixaban at 2 different doses (2.5 mg or 5 mg bid) for 12 months with placebo for secondary prevention of VTE after 6–12 months of initial anticoagulant treatment. Investigators selected both dosis on the basis that apixaban at 5 mg twice daily has been shown to be effective for the prevention of stroke in patients with atrial fibrillation, and at a dose of 2.5 mg twice daily, it has been shown to be effective for thromboprophylaxis after major orthopedic surgery.[34,35]

This randomized, double-blind study that included 2482 patients, showed that extended anticoagulation with apixaban at both doses reduced the risk of recurrent VTE without increasing the rate of bleeding. Concerning the recurrence of VTE or VTE-related death, it occurred in 73 of 829 patients (8.8%) receiving placebo, 14 of 840 patients (1.7%) receiving 2.5 mg of apixaban (reduction of 7.2%; 95% CI, 5.0 to 9.3; p<0.001); and 14 of 813 patients (1.7%) receiving 5 mg of apixaban (reduction of 7%; 95% CI, 4.9 to 9.1; p<0.001). The rates of major bleeding were similar for apixaban compared with placebo (2.5 mg group vs placebo: 0.2% vs 0.5%; RR 0.49; 95% CI 0.09–2.64; 5 mg group vs placebo: 0.1% vs 0.5%; RR 0.25; 95% CI 0.03–2.24). The rate of death from any cause was 1.7% in the placebo group, as compared with 0.8% in the 2.5-mg apixaban group and 0.5% in the 5-mg apixaban group, making AMPLIFY-EXT trial the first study of

secondary prevention of TVE that showed anticoagulant therapy to reduce the risk of all-cause mortality.

Edoxaban. Edoxaban is another NOAC approved for the treatment of VTE whose mechanism of action is the inhibition of factor Xa. The HOKUSAI-VTE study[36] (a randomized, double-blind, double-dummy trial designed to assess the efficacy and safety of edoxaban for the treatment of VTE), showed that a single daily dose of edoxaban was as effective and safer than warfarin after an initial course of heparin for 5 days (acute phase) in patients with VTE, but the decision to prolong treatment duration beyond 3 months (extended phase) and up to 12 months in the trial, was decided based on investigators discretion, to simulate clinical practice. The trial was not specifically designed to address edoxaban compared to warfarin or aspirin for the extended treatment of VTE. This limits the available data regarding edoxaban in this setting. However, a post-hoc analysis of HOKUSAI-VTE study[37], compared edoxaban with warfarin in those patients who continued therapy beyond 3 months and completed treatment for 12 months (40% of initially recruited patients); the incidence rate of recurrent VTE were 1.8% in the edoxaban group and 1.9% in the warfarin group (HR 0.97; 95% CI 0.69–1.37) and regarding major bleeding were 0.3% and 0.7%, respectively (HR 0.45; 95% CI 0.22–0.92). This provides additional data that edoxaban could be a safe alternative to warfarin for extended treatment in VTE.

Rivaroxaban. Rivaroxaban is another NOAC that acts by inhibiting factor Xa as well. The EINSTEIN EXT study[38] evaluated rivaroxaban for secondary VTE prevention after initial anticoagulant treatment for 6–12 months. Rivaroxaban 20 mg for an additional 6 or 12 months was associated with a significant 82% reduction in the relative risk of VTE recurrence compared with placebo, without a significantly increased risk of major bleeding~~,~~. A net clinical benefit, defined as the composite of the primary efficacy outcome or major bleeding, was observed with rivaroxaban compared with placebo (2.0% vs 7.1%, $p < 0.001$).

More recently, results from EINSTEIN CHOICE study[39] were published. In this randomized, double-blinded, phase 3 study, 3396 patients with venous thromboembolism were assigned to receive either once-daily rivaroxaban (at doses of 20 mg or 10 mg) or 100 mg of aspirin. All patients had completed 6 to 12 months of anticoagulation and duration of treatment was up to 12 months. Symptomatic recurrent fatal or nonfatal venous thromboembolism or unexplained death occurred in 17 of the 1107 patients (1.5%) assigned to receive 20 mg of rivaroxaban, in 13 of 1127 (1.2%) assigned to receive 10 mg of

rivaroxaban, and in 50 of 1131 (4.4%) assigned to receive aspirin (HR for 20 mg of rivaroxaban vs. aspirin, 0.34; 95% confidence interval [CI], 0.20 to 0.59; HR for 10 mg of rivaroxaban vs. Aspirin, 0.26; 95% CI, 0.14 to 0.47; P<0.001 for both comparisons). Major or clinically relevant nonmajor bleeding occurred in 3.3%, 2.4%, and 2.0% of the patients, respectively, with no differences between the 3 treatment groups. As limitation patients who required extended treatment with therapeutic doses of anticoagulant agents were excluded, therefore, it remains unknown whether the 10-mg dose of rivaroxaban would be sufficient to prevent recurrence in such patients. In summary, among patients with VTE the risk of a recurrent event was significantly lower with rivaroxaban at either a treatment dose (20 mg) or a prophylactic dose (10 mg) than with aspirin, without a significant increase in bleeding rates.

Thus, all direct oral anticoagulants evaluated for the secondary prevention of recurrent VTE appear to be effective agents for this indication, without an increased risk of bleeding compared to placebo (rivaroxaban and apixaban), lower bleeding risk than warfarin (dabigatran), lower major bleeding risk than warfarin (edoxaban), and similar bleeding risk than aspirin (rivaroxaban). The choice of agent is likely to be influenced by availability and individual patient characteristics or preferences. Extended treatment duration using NOACs (dabigatran, apixaban, edoxaban or rivaroxaban) for unprovoked VTE in clinical trials is up to 12 months and up to 4 years in the case of aspirin (ASPIRE Trial)[31]. After that period, a risk stratification should be performed at least annually to evaluate the risk of VTE recurrence and bleeding, and patient preference should also be adressed, in order to decide whether antithrombotic therapy should be continued.

5. Extended Treatment in Cancer-Associated Thrombosis

Several trials[40-44], have been conducted in patients with cancer for the treatment of cancer-associated thrombosis (CAT); these trials reported statistically significant reduction in VTE recurrence with LMWH when compared with heparin followed by VKA, without increased bleeding, for at least a 3 to 6-month treatment period (acute and postacute phase) and this data is summarized in previous guidelines for CAT treatment[45]. Because the burdensome of daily subcutaneous injections with LMWH and the absence of known benefit beyond 6 months, recently two clinical trials (HOKUSAI VTE Cancer and SELECT-D) comparing NOACs vs LMWH in extended treatment for CAT were performed[46,47]. The HOKUSAI VTE Cancer is a randomized, open-label, with a noninferiority design trial that compared oral edoxaban (60 mg once daily) or subcutaneous dalteparin,

given for at least 6 months and up to 12 months. The primary-outcome (a composite of recurrent VTE or major bleeding) occurred in 67 of the 522 patients (12.8%) in the edoxaban group and 71 of the 524 patients (13.5%) in the dalteparin group (HR of 0.97; 95% CI, 0.70 to 1.36; P=0.006 for noninferiority). Recurrent VTE occurred in 7.9% in the edoxaban group and in 11.3% in the dalteparin group (difference in risk, −3.4 percentage points; 95% CI, −7.0 to 0.2) but major bleeding occurred in 6.9% in the edoxaban group and in 4.0% in the dalteparin group (difference in risk, 2.9 percentage points; 95% CI, 0.1 to 5.6). Concluding that oral edoxaban was noninferior to subcutaneous dalteparin with respect to the composite outcome (recurrent venous thromboembolism or major bleeding), but the rate of major bleeding was higher with edoxaban than with LMWH[46].

Rivaroxaban at a dose of 15 mg twice daily for 3 weeks, then 20 mg once daily compared to dalteparin was evaluated in patients with CAT in the SELECT-D trial (randomized, multicenter and open-label). In this trial rivaroxaban was associated with relatively low VTE recurrence but higher major and clinically relevant nonmajor bleeding compared with LMWH, but the trial was designed to evaluate VTE recurrence over 6 months, limiting data on extendet treatment for CAT (longer than 6 months)[47].

A recent meta-analysis[48] concluded that NOACs (edoxaban and rivaroxaban) were more effective than LMWHs to prevent recurrent VTE but also were associated with a small but significantly increased risk of major bleeding, especially in the subgroup of patients with gastrointestinal cancer.

Thus, the optimal duration of anticoagulant therapy in patients with CAT is unknown, since evidence-based recommendations are lacking. Consensus guidelines generally suggest continuing anticoagulation treatment in patients with active cancer or receiving cancer treatment, with periodic reassessment of the risks and benefits[45,49]. LMWH continues to be the cornerstone of treatment in these patients, but NOACs (edoxaban and rivaroxaban) are also presented as an option to be considered in selected cancer patients.

6. Conclusion

Given the high rate of recurrence after an episode of unprovoked VTE, it is mandatory to individually balance the risk of bleeding and the risk of recurrence in these patients. In general terms, after a minimum period of 3-6 months

anticoagulant therapy should be stopped in patients with provoked VTE and those with unprovoked VTE and a high risk of bleeding. If bleeding risk is low or moderate, extended anticoagulation (over 6 months) should be considered. In selected cases, where the probability of recurrence is low due to the absence of additional risk factors (first episode of VTE, female sex, low D-dimer levels, absence of post-thrombotic syndrome, etc), and always after consulting the preferences of the patient, it may be appropriate to discontinue anticoagulation. Finally, in those patients with unprovoked VTE in whom anticoagulation is discontinued, aspirin reduces the risk of VTE recurrence (compared with placebo) although recurrence rates remain substantial; prophylactic doses of NOACs have some benefits (they do not require routine laboratory monitoring or dose adjustment and have fewer interactions with other drugs or food compared to warfarin) and are associated with a lower risk of most forms of bleeding with a significantly lower reduction in recurrent VTE when compared to aspirin (rivaroxaban) or placebo (rivaroxaban, apixaban).

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References:

1. Torbicki A, Perrier A, Konstantinides S, Agnelli G, Galie N, Pruszczyk, et al. Guidelines on the diagnosis and management of acute pulmonary embolism: the Task Force for the Diagnosis and Management of Acute Pulmonary Embolism of the European Society of Cardiology (ESC). Eur Heart J 2008;29:2276-315.

2. Kearon C, Akl EA, Comerota AJ, Prandoni P, Bounameaux H, Goldhaber SZ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis. 9th ed.: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141: Suppl:e419S-e494S.

3. Prandoni P, Noventa F, Ghirarduzzi A, Pengo V, Bernardi E, Pesavento R, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica 2007; 92: 199–205.

4. Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing GJ, Kyrle PA, et al. Categorization of patients as having provoked or unprovoked venous thromboembolism: Guidance from the SSC of ISTH. J Thromb Haemost. 2016;14:1480-3.

5. Del Toro-Cervera J, Demelo-Rodríguez P. Recurrence of venous thromboembolism. Rev Clin Esp. 2016;485-87.

6. Baglin T, Bauer K, Douketis J, Buller H, Srivastava A, Johnson G, et al. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: Guidance from the SSC of the ISTH. J Thromb Haemost. 2012;10:698-702.

7. Iorio A, Kearon C, Filippucci E, Marcucci M, Macura A, Pengo V, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: A systematic review. Arch Intern Med. 2010;170:1710-6.

8. Agnelli G, Prandoni P, Santamaria MG, Bagatella P, Iorio A, Bazzan M, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med. 2001;345:165-9.

9. Couturaud F, Sanchez O, Pernod G, Mismetti P, Jego P, Duhamel E, et al. Six months vs extended oral anticoagulation after a first episode of pulmonary embolism: The PADIS- PE Randomized Clinical Trial. JAMA. 2015;314:31-40.

10. Franco-Moreno AI, de Ancos-Aracil, García, Navarro MJ. Riesgo de recurrencia en el tromboembolismo venoso idiopático. Rev Clin Esp. 2016, 216:488-94.

11. Agnelli G, Becattini C. Risk assessment for recurrence and optimal agents for extended treatment of venous thromboembolism. Hematology Am Soc Hematol Educ Program. 2013;2013:471-7.

12. Eichinger S, Hron G, Bialonczyk C, Hirschl M, Minar E, Wagner O, et al. Overweight, obesity, and the risk of recurrent venous thromboembolism. Arch Intern Med. 2008;168:1678-83.

13. Stain M, Schonauer V, Minar E, Bialonczyk C, Hirschl M, Weltermann A, et al. The post-thrombotic syndrome: Risk factors and impact on the course of thrombotic disease. J Thromb Haemost. 2005;3:2671-6.

14. Boutitie F, Pinede L, Schulman S, Agnelli G, Raskob G, Julian J, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: Analysis of individual participants' data from seven trials. BMJ. 2011;342:d3036.

15. Ho WK, Hankey GJ, Quinlan DJ, Eikelboom JW. Risk of recurrent venous thromboembolism in patients with common thrombophilia: A systematic review. Arch Intern Med. 2006;166:729-36.

16. Carrier M, Rodger MA, Wells PS, Righini M, LE Gal G. Residual vein obstruction to predict the risk of recurrent venous thromboembolism in patients with deep vein thrombosis: A systematic review and meta-analysis. J Thromb Haemost. 2011;9:1119-25.

17. Palareti G, Cosmi B, Legnani C, Antonucci E, de Micheli V, Ghirarduzzi A, et al. D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: A management study. Blood. 2014;124:196-203.

18. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST Guideline and Expert Panel Report. Chest. 2016;149:315-52.

19. Kearon C, Parpia S, Spencer FA, Baglin T, Stevens SM, Bauer KA, et al. D-dimer levels and recurrence in patients with unprovoked VTE and a negative qualitative D-dimer test after treatment. Thromb Res. 2016;146:119-25.

20. Rodger MA, Le Gal G, Anderson DR, Schmidt J, Pernod G, Kahn SR, et al. Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study. BMJ. 2017;356:j1065.

21. Linkins LA, Choi PT, Douketis JD. Clinical impact of bleeding in patients taking oral anticoagulant therapy for venous thromboembolism: A meta-analysis. Ann Intern Med. 2003;139:893-900.

22. Carrier M, le Gal G, Wells PS, Rodger MA. Systematic review: Case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. Ann Intern Med. 2010;152:578-89.

23. Nieto JA, Solano R, Ruiz-Ribo MD, Ruiz-Gimenez N, Prandoni P, Kearon C, et al. Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: Findings from the RIETE registry. J Thromb Haemost. 2010;8:1216-22.

24. Lecumberri R, Alfonso A, Jimenez D, Fernandez Capitan C, Prandoni P, Wells PS, et al. Dynamics of case-fatality rates of recurrent thromboembolism and major bleeding in patients treated for venous thromboembolism. Thromb Haemost. 2013;110:834-43.

25. Ruiz-Gimenez N, Suarez C, Gonzalez R et al. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. Thromb Haemost. 2008;100:26-31.

26. Kahn SR, Springmann V, Schulman S, Martineau J, Stewart JA, Komari N, et al. Management and adherence to VTE treatment guidelines in a national prospective cohort study in the Canadian outpatient setting. The Recovery Study. Thromb Haemost. 2012;108:493-8.

27. Mas Dalmau G, Sant Arderiu E, Enfedaque Montes MB, Solà I, Pequeño Saco S, Alonso Coello P. Patients' and physicians' perceptions and attitudes about oral anticoagulation and atrial fibrillation: a qualitative systematic review. BMC Family Practice. 2017;18:3. doi:10.1186/s12875-016-0574-0.

28. Kearon C, Ginsberg JS, Kovacs MJ, et al. Comparison of low intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med. 2003;349: 631-9.

29. Ridker PM, Goldhaber SZ, Danielson E, Rosenberg Y, Eby CS, Deitcher SR, et al. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med. 2003;348:1425-34.

30. Becattini C, Agnelli G, Schenone A, Eichinger S, Bucherini E, Silingardi M, et al. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012;366:1959-67.

31. Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, et al; ASPIRE Investigators. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med. 2012;367:1979-87.

32. Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med 2013;368:X 709-18.

33. Agnelli G, Büller HR, Cohen A, Curto M, Gallus AS, Johnson M, et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med. 2013; 369:799-808.

34. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, et al. Apixaban in patients with atrial fibrilation. N Engl J Med 2011;364:806-17.

35. Raskob GE, Gallus AS, Pineo GF, Chen D, Ramirez LM, wright!!et al. Apixaban versus enoxaparin for thromboprophylaxis after hip or knee

replacement: pooled analysis of major venous thromboembolism and bleeding in 8464 patients from the ADVANCE-2 and ADVANCE-3 trials. J Bone Joint Surg Br. 2012;94:257-64.

36. Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp, Prins MH, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med. 2013;369:1406–15.

37. Raskob G, Ageno W, Cohen AT, Brekelmans MP, Grosso MA, Segers A, et al. Extended duration of anticoagulation with edoxaban in patients with venous thromboembolism: a post hoc analysis of the Hokusai-VTE study. Lancet Haematol. 2016;3:e228–36.

38. Bauersachs R, Berkowitz SD, Brenner B, Büller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363:2499-510.

39. Weitz JI, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. N Engl J Med 2017;376:1211-22.

40. Lee AY, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med. 2003;349:146–53.

41. Lee AY, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, et al. Tinzaparin vs warfarin for treatment of acute venous thromboembolism in patients with active cancer: a randomized clinical trial. JAMA 2015; 314: 677–86.

42. Hull RD, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. Am J Med. 2006;119:1062–72.

43. Meyer G, Marjanovic Z, Valcke J, Lorcerie B, Solal-Celigny P, Le Maignan C, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. Arch Intern Med. 2002;162:1729–35.

44. Deitcher SR, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. Clin Appl Thromb Hemost. 2006;12:389–96.

45. Farge D, Bounameaux H, Brenner B, Cajfinger F, Debourdeau P, Khoranna AA, et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. Lancet Oncol. 2016;17:452-e466.

46. Raskob GE, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med. 2018;378:615-24.

47. Young AM, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with wancer with venous thromboembolism: results of a randomized trial (SELECT-D). J Clin Oncol. 2018;36:2017-23.

48. Li A, Garcia DA, Lyman GH, Carrier M. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis. Thromb Res. 2018 Mar 2. [epub ahead of print].

49. Lee AYY. When can we stop anticoagulation in patients with cancer-associated thrombosis?. Hematology Am Soc Hematol Edu Program. 2017;2017:128-35.

Figures:

Figure 1. Venous thromboembolism according to different risk factors.

Figure 2. Duration of VTE therapy and therapeutic options. VTE: venous thromboembolism. RFs: risk factor DVT: Deep Vein Thrombosis. LMWH: low molecular weight heparin**.**