Review Article

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Prevention of recurrent deep-vein thrombosis

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Abstract:

The aim of this review is to outline recent randomized controlled trials and strategies that have tested various methods that aim to reduce the risk of recurrent venous thromboembolism (VTE) after the completion of anticoagulant therapy. Aspirin reduced VTE recurrence by approximately 30% (hazard ratio [HR], 0.68; 95% confidence interval [CI] 0.51–0.90) without any increase in bleeding. Dabigatran was effective in reducing VTE (HR, 0.08; 95% CI, 0.02–0.25) but carried a lower risk of major or nonmajor clinically relevant bleeding than warfarin but a higher risk than placebo: 5.3% in the dabigatran group and 1.8% in the placebo group (HR, 2.92; 95% CI, 1.52–5.60). Rivaroxaban was effective in reducing VTE (HR, 0.18; 95% CI, 0.09–0.39) but carried a higher risk of major or nonmajor clinically relevant bleeding than placebo: 6.0% in the rivaroxaban group and 1.2% in the placebo group (HR, 5.19; 95% CI, 2.3–11.7). Apixaban at either treatment dose (5 mg) or a thromboprophylactic dose (2.5 mg) reduced the risk of recurrent VTE from 8.8% in the placebo group to 1.7% in the apixaban group (Relative risk reduction of 81%) ($P < 0.001\%$) without increasing the rate of major bleeding. Sulodexide reduced the risk of recurrence (HR, 0.49; 95% CI 0.27–0.92), without any increase in bleeding risk. Residual thrombus and elevated D-dimer are markers for increased risk of recurrence. Their presence when combined with other risk factors enables one to stratify patients into high, intermediate, or low risk of recurrence of VTE. Other markers enable one to stratify patients into high, intermediate, and low risk for bleeding. On the basis of the balance of risks for recurrence and bleeding, one can advise patients on the need for secondary prevention and the most suitable medication.

Keywords:

Apixaban, aspirin, dabigatran, rivaroxaban, venous thromboembolism

Introduction

Recurrence of deep-vein thrombosis (DVT) or pulmonary embolism (PE) after completion of conventional oral anticoagulation therapy (low-molecular-weight heparin for 5 days followed by Vitamin K antagonists [VKAs] for 3, 6, or 12 months) is high. For patients with unprovoked DVT, the incidence of recurrence is 11% at 1 year, 30% at 5 years, and 40% at 10 years. For patients with provoked DVT, the recurrence rate is approximately half of the above values.[1] Recurrence of PE and DVT, leading to PE are life-threatening and recurrence of DVT may result in severe postthrombotic syndrome and reduced quality of life.[2] The aim of this review is to outline recent randomized controlled clinical trials and strategies that have tested various methods that aim to reduce the risk of recurrence of venous thromboembolism (VTE).

Aspirin Trials

Two randomized controlled trials (WARFASA and ASPIRE) have tested the efficacy of aspirin in preventing DVT recurrence. In the first study (WARFASA),[3] 402 patients who had completed 6–18 months of oral anticoagulant treatment for a first unprovoked DVT were randomly assigned to aspirin, 100 mg daily, or placebo for 2 years. During treatment, 23 patients taking

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aspirin and 39 taking placebo had a recurrence (5.9% vs. 11.0% per year; hazard ratio [HR], 0.55; 95% confidence interval [CI], 0.33–0.92). Adverse events were similar in the two groups. In the second study (ASPIRE),[4] 882 patients who had completed oral anticoagulant treatment for a first unprovoked DVT were randomly assigned to aspirin, 100 mg daily, or placebo for 4 years. During treatment, 57 patients taking aspirin and 73 taking placebo had a recurrence (4.8% vs. 6.5% per year; HR, 0.74; 95% CI, 0.52–1.05). Adverse events were similar in the two groups.

In a pooled analysis of both studies, the DVT recurrence rate was 13.8% in the aspirin groups and 19.1% in the placebo groups (HR, 0.68; 95% CI 0.51–0.90) ($P = 0.007$).[3]

Dabigatran

Dabigatran was compared to warfarin in one study and to placebo in the second study of patients who had completed treatment for unprovoked DVT (RE-SONATE study).[5]

In the active-control study, which involved 2856 patients, recurrent VTE occurred in 1.8% of patients in the dabigatran group and 1.3% of patients in the warfarin group (HR with dabigatran, 1.44; 95% CI, 0.78–2.64; $P = 0.01$ for noninferiority). Major bleeding occurred in 0.9% of patients in the dabigatran group and 1.8% of patients in the warfarin group (HR, 0.52; 95% CI, 0.27–1.02). Major or clinically relevant bleeding was less frequent with dabigatran (HR, 0.54; 95% CI, 0.41–0.71).

In the placebo-control study, which involved 1343 patients, recurrent VTE occurred in 0.4% of patients in the dabigatran group and 5.6% of patients in the placebo group (HR, 0.08; 95% CI, 0.02–0.25; $P < 0.001$). Major bleeding occurred in two patients in the dabigatran group (0.3%) and no patient occurred in the placebo group. Major or clinically relevant bleeding occurred in 5.3% of patients in the dabigatran group and 1.8% of patients in the placebo group (HR, 2.92; 95% CI, 1.52–5.60).

It was concluded that dabigatran was effective in the extended treatment of VTE and carried a lower risk of major or clinically relevant bleeding than warfarin but a higher risk than placebo.

Rivaroxaban

An open-label, randomized, event-driven, noninferiority study was performed that compared oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with subcutaneous enoxaparin initially, followed by a VKA (either warfarin or acenocoumarol) for 3, 6, or 12 months in patients with acute, symptomatic DVT (EINSTEIN Investigators 2010).[6]

In parallel, a double-blind, randomized, event-driven superiority study was performed. This study compared rivaroxaban alone (20 mg once daily) with placebo for an additional 6 or 12 months in patients who had completed 6–12 months of treatment for VTE.[6]

The study of rivaroxaban for acute DVT included 3449 patients in which 1731 given rivaroxaban and 1718 given enoxaparin plus a VKA. Rivaroxaban had noninferior efficacy with respect to the primary outcome (36 events [2.1%] vs. 51 events with enoxaparin-VKA [3.0%]; HR, 0.68; 95% CI, 0.44–1.04; $P < 0.001$). The principal safety outcome occurred in 8.1% of the patients in each group.

In the continued-treatment study, which included 602 patients in the rivaroxaban group and 594 in the placebo group, rivaroxaban had superior efficacy (8 events [1.3%] vs. 42 with placebo [7.1%]; HR, 0.18; 95% CI, 0.09–0.39; $P < 0.001$). Four patients in the rivaroxaban group had nonfatal major bleeding (0.7%) versus none in the placebo group ($P = 0.11$). Major or clinically relevant bleeding occurred in 6.0% of patients in the rivaroxaban group and 1.2% of patients in the placebo group (HR, 5.19; 95% CI, 2.3–11.7).

It was concluded that rivaroxaban offered a simple, single-drug approach to the short-term and continued treatment of venous thrombosis that may improve the benefit-to-risk profile of anticoagulation.

Apixaban

A double-blind study involving 2486 patients compared two doses of apixaban (2.5 and 5 mg, twice daily) with placebo in patients with VTE who had completed 6–12 months of anticoagulation therapy and for whom there was clinical equipoise regarding the continuation or cessation of anticoagulation therapy.[7] The study drugs were administered for 12 months.

Symptomatic recurrent VTE or death from VTE occurred in 8.8% of patients in the placebo group, compared with 1.7% of patients in the 2.5 mg of apixaban group (a difference of 7.2% points; 95% CI, 5.0–9.3) and 1.7% of patients in the 5 mg of the apixaban group (a difference of 7.0% points; 95% CI, 4.9–9.1) ($P < 0.001$ for both comparisons). The rates of major bleeding were 0.5% in the placebo group, 0.2% in the 2.5 mg apixaban group, and 0.1% in the 5 mg apixaban group. The rates of clinically relevant nonmajor bleeding were 2.3% in the placebo group, 3.0% in the 2.5 mg apixaban group (HR 1.20, 95% CI 0.69–2.10; P = NS), and 4.2% in

the 5 mg apixaban group (HR 1.62, 95% CI 0.96–2.73; *P* = NS). The rate of death from any cause was 1.7% in the placebo group, compared with 0.8% in the 2.5 mg apixaban group, and 0.5% in the 5 mg apixaban group.

It was concluded that extended anticoagulation with apixaban at either a treatment dose (5 mg) or a thromboprophylactic dose (2.5 mg) reduced the risk of recurrent VTE without increasing the rate of major bleeding.

Sulodexide

In a multicenter, double-blind study, 615 patients with first-ever unprovoked VTE who had completed 3–12 months of oral anticoagulant treatment were randomly assigned to sulodexide 500 lipasemic units twice daily or placebo for 2 years in addition to elastic stockings.[8]

VTE recurred in 15 of the 307 patients who received sulodexide and in 30 of the 308 patients who received placebo (HR, 0.49; 95% CI 0.27–0.92; *P* = 0.02). The analysis in which patients lost to follow-up was assigned to failure yielded a risk ratio among treated versus controls of 0.54 (95% CI, 0.35–0.85; *P* = 0.009). No major bleeding episodes occurred; two patients in each treatment group had clinically relevant bleeding episodes. Adverse events were similar in the two groups.

It was concluded that sulodexide given after discontinuation of anticoagulant treatment reduced the risk of recurrence in patients with unprovoked VTE, with no apparent increase of bleeding risk.

Strategies to Identify Patients at Increased Risk of Recurrence

Residual thrombus and recurrence of deep-vein thrombosis

In the DACUS study, ultrasound was used to determine the presence of residual thrombus. Residual venous thrombus was considered present (RVT+) if on compression organized thrombus occupied > 40% of the vein diameter. It was considered absent (RVT−) if thrombus occupied <40% of the vein diameter.[9]

Patients with the first episode of DVT treated with oral anticoagulant therapy for 3 months were managed according to residual thrombus findings. Those who were RVT+ were randomized to either stop or continue anticoagulants for nine additional months, whereas in those who were RVT−, anticoagulant therapy was stopped. Outcomes were recurrent VTE and/or major bleeding. Residual thrombosis was detected in 180 (69.8%) of 258 patients; recurrent events occurred in 27.2% of those who discontinued (25/92; 15.2% person-years), and 19.3% of those who continued with anticoagulant therapy (17/88; 10.1% person-years). The relative adjusted HR was 1.58 (95% CI, 0.85–2.93; *P* = 0.145). Of 78 (30.2%) patients with RVT−, only 1 (1.3%; 0.63% person-years) had a recurrence. The adjusted HR of patients with RVT + versus those with RVT − was 24.9 (95% CI, 3.4–183.6; *P* = 0.002). One major bleeding event (1.1%; 0.53% person-years) occurred in patients who stopped and two occurred (2.3%; 1.1% person-years) in those who continued anticoagulant therapy. It was concluded that the absence of residual venous thrombus (RVT−) identified a group of patients at very low risk for recurrent thrombosis who could safely stop anticoagulant therapy.

The extended DACUS study was a prospective study to assess the optimal duration of VKA therapy considering the risk of recurrence of thrombosis according to residual vein thrombosis.[10] Patients with a first unprovoked DVT were evaluated for the presence of residual vein thrombosis after 3 months of VKA administration; those who were RVT- suspended VKA, while those who were RVT+ continued oral anticoagulation for up to 2 years. Recurrent thrombosis and/or bleeding events were recorded during treatment (RVT+ group) and 1 year after VKA withdrawal (both groups). Among 409 patients evaluated for unprovoked DVT, 33.2% (136 of 409 patients) were RVT-, and VKA was stopped. The remaining 273 (66.8%) patients who were RVT+ received anticoagulants for an additional 21 months; during this period of treatment, recurrent VTE and major bleeding occurred in 4.7% and 1.1% of patients, respectively. After VKA suspension, the rates of recurrent thrombotic events were 1.4% and 10.4% in the RVT − and RVT + groups, respectively (relative risk = 7.4; 95% CI = 4.9–9.9). These results indicate that in patients who are RVT−, a short period of treatment with a VKA is sufficient; in those who are RVT+, treatment extended to 2 years substantially reduces but does not eliminate the risk of recurrent thrombosis.

D-dimer and recurrence of deep-vein thrombosis

D-dimer testing 1 month after the discontinuation of anticoagulation in patients with a first unprovoked proximal deep-vein thrombosis or PE who had received a VKA for at least 3 months was performed in the study.[11] Patients with a normal D-dimer level did not resume anticoagulation, whereas those with an abnormal D-dimer level were randomly assigned either to resume or to discontinue treatment. The study outcome was the composite of recurrent VTE and major bleeding during an average follow-up of 1.4 years.

The D-dimer assay was abnormal in 223 of 608 patients (36.7%). A total of 18 events occurred among the

120 patients who had elevated D-dimer and stopped anticoagulation (15.0%) as compared with three events among the 103 patients who had elevated D-dimer and resumed anticoagulation (2.9%) for an adjusted HR of 4.26 (95% CI, 1.23–14.6; P = 0.02). Thromboembolism recurred in 24 of 385 patients with a normal D-dimer level (6.2%). Among patients who stopped anticoagulation, the adjusted HR for recurrent thromboembolism among those with an abnormal D-dimer level, compared with those with a normal D-dimer level, was 2.27 (95% CI, 1.15–4.46; P = 0.02).

It was concluded that patients with an abnormal D-dimer level 1 month after the discontinuation of anticoagulation have a significant incidence of recurrent VTE, which is reduced by the resumption of anticoagulation.

Strategy combining residual thrombus and D-dimer testing

In 620 consecutive outpatients with a first proximal DVT who had completed at least 3 months of anticoagulation (unprovoked in 483 and associated with minor risk factors in 137), the ultrasound presence of residual vein thrombosis (RVT+) was assessed and defined as incompressibility of at least 4 mm.[12] In 517 patients who were RVT – and with negative D-dimer, anticoagulation was stopped and D-dimer was repeated after 1 and 3 months. Anticoagulation was resumed in 63 of the 72 patients in whom D-dimer reverted to positivity.

During a mean follow-up of 3 years, recurrent VTE developed in 40 (7.7%) of the 517 patients, leading to an annual rate of 3.6% (95% CI, 2.6–4.9): 4.1% (95% CI, 2.9–5.7) in individuals with unprovoked DVT, and 2.2% (95% CI, 1.1–4.5) in those with DVT associated with minor risk factors. Of the 233 patients with unprovoked DVT, 17 (7.3%) developed events in the 1st year of follow-up. Major bleeding complications occurred in eight patients, while on anticoagulation, leading to an annual rate of 1.2% (95% CI, 0.6–2.4).

It was concluded that discontinuing anticoagulation in patients with a first episode of proximal DVT based on the assessment of RVT and serial D-dimer led to an overall annual rate of recurrent VTE lower than 5.0%, which is the rate deemed as acceptable by the Subcommittee on Control of Anticoagulation of the International Society of Thrombosis and Hemostasis.

Assessment of risk of recurrence versus risk of bleeding with adjustment of anticoagulation

It is now established that the risk of recurrence of VTE and risk of bleeding are not the same in every patient. Methods that can assess these risks which have met with moderate success are now available.[13] In addition, as indicated in this review, secondary effective prophylactic anticoagulation therapy is now available with very low risk of bleeding (apixaban and sulodexide). Thus, recommendations for secondary prophylaxis should be based on calculations for the risk of recurrence versus the risk of bleeding with appropriate drug selection.

The risk of recurrence can be assessed empirically as high, moderate, or low using established risk factors [Table 1], calculated using the Vienna nomogram[14,15] or using the disabilities of the arm, shoulder, and hand (DASH) score.[16] The Vienna nomogram is based on a prospective cohort study involving 929 patients and risk factors of gender, type of VTE (PE, proximal DVT, and distal DVT) and elevated D-dimer after stopping anticoagulants. It has been validated externally[17] in a separate cohort with an area under the curve of 0.63. The DASH score is based on a patient-level metaanalysis involving 1818 patients and the following risk factors: D-dimer after cessation of anticoagulation, age, gender, and use of hormones at the onset of VTE.

The risk of bleeding can also be assessed empirically as high, moderate, or low using the criteria as shown in Table 2 or using a prediction model such as the RIETE score.[18] The latter has been derived from a large cohort of patients with VTE and is based on the following risk factors: age, recent bleeding, creatinine level, anemia, malignancy, and symptomatic PE. It can identify patients at low, intermediate, or high risk for major bleeding during the first 3 months of anticoagulation, but it has not yet been externally validated.

Based on the available medications and knowledge of the risk of recurrence versus the risk of bleeding, a health-care provider can make up a plan or algorithm for

Table 1: Risk of deep-vein thrombosis recurrence after the first episode

High (one or more risk factors)
Unprovoked two or more VTE episodes
Iliofemoral DVT
Residual thrombus (>40%)
Active cancer
Serious thrombophilia
D-dimer >500 1-3 months after stopping anticoagulation
Life-threatening PE
Inflammatory bowel disease
Moderate (one risk factor)
Unprovoked isolated calf DVT
Male
Obesity
Low (one transient risk factor)
Postmajor surgery or bed rest for >4 days
Post-POP or postmajor trauma
Postestrogen therapy or pregnancy

DVT: Deep-vein thrombosis, VTE: Venous thromboembolism, POP: Plaster of paris

Table 2: Risk of bleeding during anticoagulation therapy

High
History of major bleeding
Platelet count: <50,000
Need for double antiplatelet therapy
Portal hypertension (bleeding esophageal varices)
History of stroke or cerebral changes
Metastatic carcinoma
Renal insufficiency liver failure
Diabetes
Age: >75
Moderate
History of clinically relevant nonmajor bleeding
One antiplatelet drug
Platelet count: 50,000-100,000
Age: 65-75
Low
No history of bleeding
No bleeding during previous antigen therapy
No associated prohemorrhagic drugs
Age: <65

extended prophylaxis in patients with moderate-or-high risk of DVT. An example is given below.

Patients at high risk of recurrence

a. Low risk of bleeding: any anticoagulant can be given (VKA, rivaroxaban, and apixaban)
b. Intermediate risk of bleeding: apixaban
c. High risk of bleeding: Low-dose apixaban and sulodexide.

Patients at intermediate risk of recurrence

a. Low risk of bleeding: any anticoagulant can be given (VKA, rivaroxaban, and apixaban)
b. Intermediate risk of bleeding: apixaban
c. High risk of bleeding: Low-dose apixaban, sulodexide, and aspirin.

Patients at low risk of recurrence

Anticoagulants can be omitted, but if the patient insists, then aspirin or sulodexide would be the author's choice.

The efficacy of such plans needs to be validated in prospective studies.

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Conflicts of interest

There are no conflicts of interest.

References

1. Prandoni P, Lensing AW, Prins MR. Long-term outcomes after deep venous thrombosis of the lower extremities. Vasc Med 1998;3:57-60.
2. Kahn SR, Shrier I, Julian JA, Ducruet T, Arsenault L, Miron MJ, *et al.* Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. Ann Intern Med 2008;149:698-707.
3. 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.
4. Brighton TA, Eikelboom JW, Mann K, Mister R, Gallus A, Ockelford P, *et al.* Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med 2012;367:1979-87.
5. 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;368:709-18.
6. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, *et al.* Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.
7. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, *et al.* Apixaban for extended treatment of venous thromboembolism. N Engl J Med 2013;368:699-708.
8. Andreozzi GM, Bignamini AA, Davì G, Palareti G, Matuška J, Holý M, *et al.* Sulodexide for the prevention of recurrent venous thromboembolism: The sulodexide in secondary prevention of recurrent deep vein thrombosis (SURVET) study: A multicenter, randomized, double-blind, placebo-controlled trial. Circulation 2015;132:1891-7.
9. Siragusa S, Malato A, Anastasio R, Cigna V, Milio G, Amato C, *et al.* Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: The Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. Blood 2008;112:511-5.
10. Siragusa S, Malato A, Saccullo G, Iorio A, Di Ianni M, Caracciolo C, *et al.* Residual vein thrombosis for assessing duration of anticoagulation after unprovoked deep vein thrombosis of the lower limbs: The extended DACUS study. Am J Hematol 2011;86:914-7.
11. Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, *et al.* D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med 2006;355:1780-9.
12. Prandoni P, Vedovetto V, Ciammaichella M, Bucherini E, Corradini S, Enea I, *et al.* Residual vein thrombosis and serial D-dimer for the long-term management of patients with deep venous thrombosis. Thromb Res 2017;154:35-41.
13. Fahrni J, Husmann M, Gretener SB, Keo HH. Assessing the risk of recurrent venous thromboembolism – A practical approach. Vasc Health Risk Manag 2015;11:451-9.
14. Eichinger S, Heinze G, Jandeck LM, Kyrle PA. Risk assessment of recurrence in patients with unprovoked deep vein thrombosis or pulmonary embolism: The Vienna prediction model. Circulation 2010;121:1630-6.
15. Eichinger S, Heinze G, Kyrle PA. D-dimer levels over time and the risk of recurrent venous thromboembolism: An update of the Vienna prediction model. J Am Heart Assoc 2014;3:e000467.
16. Tosetto A, Iorio A, Marcucci M, Baglin T, Cushman M, Eichinger S, *et al.* Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: A proposed prediction score (DASH). J Thromb Haemost 2012;10:1019-25.
17. Marcucci M, Iorio A, Douketis JD, Eichinger S, Tosetto A, Baglin T, *et al.* Risk of recurrence after a first unprovoked venous thromboembolism: External validation of the Vienna prediction model with pooled individual patient data. J Thromb Haemost 2015;13:775-81.
18. Nieto JA, Solano R, Ruiz-Ribó 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.