Secondary Prevention of Venous Thromboembolism: One Regimen May Not Fit All

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Abstract
Venous thromboembolism (VTE), which encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE), is now recognized as a chronic recurrent disease. The short-term anticoagulation after VTE includes the initiation phase and the early maintenance phase, for a usual duration of 3 months (Figure 1). Whether to consider an extended phase of anticoagulation in individual patients has become a major challenge for care providers, but logically depends on the risk of VTE recurrence and on that of bleeding. This decision can be further refined by patient preferences, a theoretically highly desirable criterion which however is often difficult to assess objectively, and by the efficacy/safety balance of available therapies.

Reference


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Secondary Prevention of Venous Thromboembolism
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Venous thromboembolism (VTE), which encompasses deep vein thrombosis and pulmonary embolism (PE), is now recognized as a chronic recurrent disease. Short-term anticoagulation after VTE includes the initiation phase and the early maintenance phase, usually for a duration of 3 months (Figure). Whether to consider an extended phase of anticoagulation in individual patients has become a major challenge for care providers but logically depends on the risks of VTE recurrence and bleeding.1 This decision can be further refined by patient preferences, a theoretically highly desirable criterion that, however, is often difficult to assess objectively, and by the efficacy/safety balance of available therapies.

Several factors modulate the risk of VTE recurrence. Most strikingly, the circumstances of the index event, whether provoked by a strong and transient condition or unprovoked (previously known as idiopathic), and male sex, associated with a doubling of VTE recurrence,2 help to guide the duration of anticoagulation. On the other hand, traditional VTE risk factors remain weak risk factors for recurrent VTE, if at all, due in part to an “index event bias.”3 Examples of such risk factors include thrombophilic factors (factor V Leiden and prothrombin G20210A mutations), age, and obesity. This may perhaps explain surprising contradictions in VTE recurrence prediction rules in current validation efforts with regard to the influence of age.4,6

Thus, patients with a deep vein thrombosis or a PE after surgery or trauma have a low risk (=1%/y) of a future recurrent event, and guidelines recommend stopping the anticoagulant treatment after 3 months in such patients.1 At the opposite of the clinical spectrum, a patient with a cancer-related VTE event should probably remain on anticoagulant therapy as long as the cancer is considered active, given the high risk of a recurrent event. In the middle of this spectrum, and specifically in patients with an unprovoked incident VTE event, there is uncertainty as to whether anticoagulant treatment should be extended or stopped. On one hand, VTE recurrence after treatment discontinuation in these patients has an annual incidence of ≈10% during the first 2 years, with a possible decline afterward.4 Interestingly, this incidence is not influenced by the duration of the initial anticoagulation (3–6 or 12 months). On the other hand, the cumulative bleeding risk induced by anticoagulation appears constant throughout time after the first 3 months. This complex situation is the heart of the dilemma of secondary prevention of unprovoked VTE.

Until recently, vitamin K antagonists were the only oral anticoagulant drugs suited for secondary prevention. Even in clinical trials, which potentially select individuals with lower bleeding risk than the general VTE population and with strict anticoagulation monitoring, the bleeding risk remains problematic. In the Secondary Prevention of Venous Thromboembolism (RE-MEDY) clinical trial, the annual incidence of major and “major or clinically relevant” bleeding events in the warfarin group (target international normalized ratio [INR], 2.0–3.0) was ≈1.6% and ≈9.2%, respectively, with a cumulative risk of any bleeding of ≈20% at 12 months.7 Previously, the Extended Low-Intensity Anticoagulation for Thromboembolism (ELATE) trial had suggested a better safety profile in patients on warfarin, with an annual incidence of any bleeding of only 3.7%.8 This observation is likely attributable to a selection of low-risk participants in ELATE, which may also explain the similar bleeding risks observed in participants with target INR of 2.0 to 3.0 and of 1.5 to 1.9. Current alternatives to warfarin (with a target INR of 2.0–3.0) may have different, and perhaps better, efficacy/safety profiles and have been evaluated in several trials in the past 15 years (Tables 1 and 2): warfarin with a target INR of 1.5–2.0,9 dabigatran 150 mg twice daily,7 rivaroxaban 20 mg daily,10 apixaban 2.5 or 5 mg twice daily,11 and aspirin 100 mg.12,13 New oral anticoagulants may perhaps cause less bleeding than warfarin with a target INR of 2.0 to 3.0, as demonstrated for dabigatran in the RE-MEDY trial (relative risk reduction, 29%) (Table 2), whereas their protection against recurrent VTE remains substantial (relative risk reduction, 80% to 92% for rivaroxaban, dabigatran, or apixaban compared with placebo). Aspirin offers less protection against recurrent VTE (relative risk reduction, 26% to 42%) than new oral anticoagulants, likely with a better bleeding profile, as indicated by indirect comparisons. Warfarin with a target INR of 1.5 to 2.0 remains a viable option in our opinion, with a thrombotic protection likely between those of aspirin and the other agents.

In this issue of Circulation, Andreozzi et al14 report the results of the Sulodexide for the Prevention of Recurrent Venous Thromboembolism (SURVET) study and add an alternative to the regimens listed above. Sulodexide is a purified glycosaminoglycan containing heparin sulfate and dermatan sulfate with affinities for antithrombin and heparin cofactor II, respectively.
It has also been ascribed profibrinolytic and antiaggregatory platelet activities. Since the early 1990s, sulodexide has been evaluated for various vascular and thrombotic conditions, mainly for prevention purposes, and in small-scale studies. The SURVET study is a manufacturer-funded, double-blind, randomized trial designed to test the superiority of sulodexide over placebo for the extended prevention after an incident unprovoked VTE. In brief, 615 participants were randomly allocated to sulodexide 500 lipasemic units (LSU) twice daily (50 mg twice daily) or a matching placebo 1 to 12 weeks after the end of an early maintenance anticoagulation course of anticoagulant treatment.

| Regimens Tested for Secondary Prevention of VTE Recurrence in Randomized, Placebo-Controlled Trials After an Initial Course of Anticoagulant Treatment |
|---|---|---|---|---|---|
| **Anticoagulant drugs** | **VTE Recurrence** | **Major or Clinically Relevant Bleeding** |
| | Intervention Arm | Placebo Arm | Relative Risk (95% CI) | Intervention Arm | Placebo Arm | Relative Risk (95% CI) |
| *Warfarin* (INR 1.5-2.0) (PREVENT)* | 2.6/100 p-y (14/555) | 7.25/100 p-y (37/523) | 0.36 (0.19–0.67) | 0.9/100 p-y* (5/525) | 0.4/100 p-y* (2/253) | 2.53 (0.49–13.0) |
| Rivaroxaban 20 mg (EINSTEIN Extension)* | =2.2/100 p-y† (8/360) | =12.2/100 p-y† (42/349) | 0.18 (0.09–0.39) | =10.1/100 p-y† (36/360) | =2.0/100 p-y† (7/359) | 5.19 (2.3–11.7) |
| Dabigatran 150 mg twice daily (AMPLIFY Extension)* | =3.8/100 p-y† (28/748) | =5.1/100 p-y† (35/683) | 0.19 (0.11–0.48) | =3.3/100 p-y† (22/682) | =1.20 (0.69–2.10) | 1.62 (0.96 to 2.73) |
| Aspirin 100 mg (WARFASA)* | 6.6/100 p-y (28/205) | 11.2/100 p-y (43/397) | 0.58 (0.36–0.93) | 1.0/100 p-y* (4/405) | 1.0/100 p-y* (4/417) | 0.98 (0.24–3.96) |
| Sulodexide 500 LSU twice daily (SURVET) | =2.7/100 p-y† (15/537) | =5.6/100 p-y† (30/538) | 0.49 (0.27–0.92) | =0.4/100 p-y* (2/307) | =0.4/100 p-y* (2/308) | 0.97 (0.14–6.88) |

*AMPLIFY Extension indicates Efficacy and Safety Study of Apixaban for Extended Treatment of Deep Vein Thrombosis or Pulmonary Embolism; ASPIRE, Aspirin to Prevent Recurrent Venous Thromboembolism; CI, confidence interval; EINSTEIN Extension, Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism; INR, international normalized ratio; LSU, lipasemic units; p-y, patient-years; PREVENT, Prevention of Recurrent Venous Thromboembolism; RE-SONATE, Twice-Daily Oral Direct Thrombin Inhibitor Dabigatran Exetilate in the Long Term Prevention of Recurrent Symptomatic VTE; SURVET, Sulodexide for the Prevention of Recurrent Venous Thromboembolism; VTE, venous thromboembolism; and WARFASA, Warfarin and Aspirin trial. *Only major bleeding. †Estimated from the available data.
answer is “not at this time” because of the limitations of the data from the SURVET study.

First, the generalizability of the sample remains unclear. Information on the 43 recruiting centers and on the medical history of participants is scarce, especially about risk factors for recurrent VTE or bleeding such as obesity or chronic renal failure. Widely different absolute risks of recurrent VTE at 2 years between countries, ranging from 0% up to 28%, may underline sampling heterogeneity across research centers. Globally, the risks of both bleeding and thrombotic outcomes in the placebo group compare favorably with those in the placebo groups from all other VTE extension treatment studies in the placebo group compare favorably with those in the placebo group. However, the lack of preplanned subgroup analyses and of a data monitoring and adjudicating committee independent of the principal investigators may perhaps reflect subpar methodology.

Second, the SURVET study suffers from methodological imperfections. The authors do not report on adherence to the study medication and to the surveillance protocol. Although they do not consider the 5% loss to follow-up critical on the basis of several sensitivity analyses, missing data remain unpredictable. Participants with inadequately short durations of anticoagulation (<3 months) after their incident VTE were included, accounting for some of the 6% of major protocol violations. In addition, the lack of preplanned subgroup analyses and of a data monitoring and adjudicating committee independent of the principal investigators may perhaps reflect subpar methodology.

Third, the low rate of recurrent VTE in this study resulted in imprecise findings, compatible with both a very appealing and a not-so-relevant reduction in recurrent VTE (95% confidence interval, −73% to −8%). Refinement of the actual risk reduction associated with sulodexide is needed.

Despite these limitations, the SURVET trial provides evidence that a novel actor, sulodexide, at the oral dose of 500 LSU twice daily could be added to the regimens that play a role after the initial course of anticoagulant treatment. Confirmatory data in methodologically sound clinical studies are mandatory, however, before firm recommendations can be made for that particular new regimen.

Further developments may also bring new alternatives to the drugs listed in the Figure and the Tables. In particular, the ongoing Reduced-Dosed Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic VTE (Venous Thromboembolism; EINSTEIN CHOICE) superiority trial compares daily rivaroxaban 10 mg with rivaroxaban 20 mg and with aspirin 100 mg, hypothesizing a bleeding safety advantage of halving the dose used in the Once-Daily Oral Direct Factor Xa Inhibitor Rivaroxaban in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-Vein Thrombosis or Pulmonary Embolism (EINSTEIN Extension) study. This will be the first study to directly compare a new oral anticoagulant with aspirin in this setting. In addition, statins may be of potential interest for the secondary prevention of VTE. In the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism (JUPITER), daily rosuvastatin 20 mg reduced the risk of incident VTE by 43%, including idiopathic VTE (absolute risk reduction, 0.14%/y). For secondary prevention of VTE, several pharmacoepidemiological studies have demonstrated an association between statin use and a reduction in the risk of recurrent VTE of ≈30%. Further observational data and clinical trials are warranted to better characterize this association and to evaluate its causality.

This already long list and the perspective of upcoming new regimens raise a new question for extended anticoagulation after incident VTE: Which regimen for which patients? At first glance, we can differentiate 2 groups of regimens: drugs with high antithrombotic efficacy but also an important incremental risk of bleeding, and drugs with less effective thrombotic protection but a better bleeding safety profile. This would offer a triple choice to patients with incident VTE and their care providers: no extension of anticoagulation or an extension with a drug from 1 of these 2 categories. This choice depends, once again, on the risks of recurrence (high or low) and the risk of bleeding. Given the high incidence of VTE in the general population with possible substantial risk of recurrence, this clinical dilemma of critical importance underlines the need for risk stratification tools and further research on secondary prevention of VTE.

One single regimen may indeed not fit all patients and clinical situations.

### Table 2. Regimens Tested for Secondary Prevention of VTE Recurrence in Randomized, Warfarin (INR 2.0–3.0)-Controlled Trials After an Initial Course of Anticoagulant Treatment

<table>
<thead>
<tr>
<th>Intervention Arm</th>
<th>Warfarin Arm (INR 2.0–3.0)</th>
<th>Relative Risk (95% CI)</th>
<th>Major or Clinically Relevant Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n events/N)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin Arm (INR 1.5–1.9 (ELATE)†</td>
<td>1.9/100 p-y (16/369)</td>
<td>0.7/100 p-y (6/369)</td>
<td>2.8 (1.1–7.0)</td>
</tr>
<tr>
<td>Dabigatran 150 mg twice daily (RE-MEDY)†</td>
<td>≈1.3/100 p-y†</td>
<td>≈0.9/100 p-y†</td>
<td>1.44 (0.78–2.64)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; ELATE, Extended Low-Intensity Anticoagulation for Thrombo-Embolism; INR, international normalized ratio; p-y, patient-years; RE-MEDY, Secondary Prevention of Venous Thrombo-Embolism; and VTE, venous thromboembolism.

*Only major bleeding.
†Estimated from the available data.
Disclosures
Dr Bounameaux has received a research grant, speaker’s fees, and honoraria for studies with edoxaban from Daiichi-Sankyo; a research grant, speaker’s fees, and honoraria for studies with rivaroxaban from Bayer Healthcare; and honoraria from Sanofi-Aventis. Dr Blondon reports no conflicts.

References

Key Words: Editorials • anticoagulation • antiplatelet therapy • venous thromboembolism
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