Duration of Anticoagulation Therapy for Venous Thromboembolism

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Treatment of acute deep vein thrombosis and pulmonary embolism-often denominated together as venous thromboembolism (VTE)- consists of parenteral administration of heparin (usually low-molecular-weight heparin or alternatively unfractionated heparin or fondaparinux) overlapped and followed by oral vitamin K antagonists that are administered for a certain period (usually 3 to 12 months). Recommended or suggested durations differ according to guidelines. Practically, the clinical decision in an individual patient depends upon the estimated risks of VTE recurrence and treatment-induced bleeding. The risk of VTE recurrence is higher in idiopathic events (about 10% per year during the first two years and 3% per year thereafter) (odds ratio of 2.4, compared to secondary events); in male subjects (at least before the age of 60, with an odds ratio of 2-4); in patients with persistently elevated D-dimer level (odds ratio of 2.3, compared with normal level); and during the first two years after discontinuation of treatment. The annual risk of major bleeding on anticoagulant treatment vary largely in observational studies with figures of 2% to 29%, depending on the patient characteristics. The case-fatality rate is 8% (DVT), 12% (PE) for recurrent VTE, and about 10% for major bleed. These figures do not support long-term anticoagulant therapy, except in those patients exhibiting a very high risk of recurrence and/or a very low risk of bleeding.

New therapeutic aspects might impact on the duration of anticoagulant therapy after a venous thromboembolic event. They include the possibility of pursuing anticoagulant treatment at a reduced INR after an initial period with an INR 2-3, and the advent of new, more specific and orally active anticoagulants. These features might modify the risk-benefit balance of extending anticoagulant therapy beyond the usual, limited duration.

Introduction

Pulmonary embolism (PE), the source of which is predominantly a thrombosis of the deep veins of the legs (DVT), is a major health concern: it is the third cause of mortality by cardiovascular disease after coronary artery disease and stroke. In addition, late sequels of DVT may produce disabling leg symptoms in a substantial proportion of patients, including venous ulcers in few of them, resulting in a considerable economic burden. Moreover, chronic thromboembolic pulmonary hypertension may develop as a late complication of PE in a small subset of patients. For all these reasons, PE and DVT deserve to be diagnosed as early and appropriately as possible to initiate treatment without delay.

Treatment of acute venous thromboembolism (VTE) consists of initial therapy by parenteral subcutaneous administration of heparin (usually low-molecular-weight heparin, unfractionated heparin or fondaparinux) overlapped and secondary prevention by oral vitamin K antagonists that will be administered for a certain period (usually 3 to 12 months). Recommended or suggested durations differ according to guidelines, and clinical decision in an individual patient depends upon the estimated risks of VTE recurrence and bleeding.

New therapeutic aspects might impact on the duration of anticoagulant therapy after a venous thromboembolic event. They include the controversial possibility of pursuing anticoagulant treatment at a reduced INR after an initial period with an INR 2-3, and the advent of new, more specific and orally active anticoagulants. All these features might modify the risk-benefit balance of extending anticoagulant therapy beyond the usual, limited duration.

Evidence Regarding Duration of Anticoagulant Treatment after VTE

The duration of anticoagulant treatment following deep vein thrombosis (DVT) and pulmonary embolism (PE) remains controversial. Nevertheless, several facts have been highlighted in the past two decades that should help establish guidelines based on evidence rather than on variable opinions of leaders in the field. Obviously, the duration of anticoagulation should be dictated by the balance between two risks: the risk of recurrent VTE with and without treatment, and the risk of treatment-induced hemorrhage. In the present review, we used the terms idiopathic (or unprovoked) and secondary (provoked) to characterize thromboembolic events that occurred in the absence or in the

presence of obvious provoking factors, such as surgery or trauma. Admittedly, the definition of these terms may vary from study to study.

Evidence regarding this balance includes the following:

- According to a meta-analysis of 25 studies,[1] recurrent DVT or PE is rather rare during anticoagulant treatment (8.8%, 95% confidence interval [CI]: 5.0-14.1%) with a case-fatality rate of only 0.4% (95% CI : 0.2-0.6%).
- Recurrences occur preferentially during the initial 3 weeks after the start of treatment and concern mainly patients with cancer (odds ratio [OR] 2.7), chronic cardiovascular disease (OR 2.3), chronic respiratory disease (OR 1.9) and other clinically significant medical disease (OR 1.8).[2]
- Anticoagulant treatment is associated with a definite bleeding risk: heparin induces major bleeding at a rate of 0.8% per day (with a daily fatality rate of 0.05%),[3] and oral anticoagulants at a rate of 0.4% per month.[4]

Subsequently, well-conducted randomized clinical trials (some of which were combined in a recent meta-analysis[5]) provided the following conclusions:

- The risk of recurrent VTE is 40% lower in patients treated for 12 to 24 weeks compared with those treated for 3 to 6 weeks without significant difference in major bleeding risk;[5]
- The risk of recurrent VTE is lower following distal (DVT below the level of the popliteal vein) than proximal DVT, and a shorter (6 weeks) treatment duration might be indicated in the former.[6] Moreover, the need for treating distal DVT with anticoagulants remains controversial.[7]
- VTE related to transient risk factors (e.g., surgery, trauma) is associated with a definitely lower risk of recurrence.[8,9]
- After a follow-up of 2 years, the recurrence rate was 18.1% in patients with proximal DVT treated for 6 weeks compared with 9.5% in those treated for 6 months, thereby suggesting that 6 weeks are not enough for treating idiopathic proximal DVT.[9]
- In a small group of selected high-risk patients with idiopathic DVT,[10] the annual recurrence rate was 27.4% in patients given oral anticoagulants for 3 months compared with 1.3% in patients treated indefinitely; in the latter group, major hemorrhage occurred in 3.8% of patients, compared with none in the shorter treatment duration group; these results are consistent with the excellent efficacy of anticoagulant treatment while patients are on treatment but does not give information on what would happen following treatment discontinuation.
- In another study, after 2 years of follow-up, patients with DVT who were treated for 1 year had a recurrence rate of 15.7% compared with 15.8% in patients treated for 3 months,[11] suggesting that the clinical benefit associated with extending the duration of anticoagulant therapy beyond 3 months for proximal idiopathic DVT is not maintained after the therapy is discontinued ("catch-up phenomenon").
- In two studies comparing 3 months versus 6 months for proximal idiopathic DVT with or without PE,[6,12] the recurrence rate after 1 year was remarkably similar (about 8% in both groups in the two studies).
- One study showed that, after a second episode of VTE, the cumulative recurrence rate was 20.7% after 4 years in patients treated for 6 months compared with 2.6% in those treated indefinitely; the corresponding rates of major bleeding were 2.7% and 8.6%.[13]

Table 1 summarizes the results of the main studies comparing different durations of anticoagulant treatment following a first episode of idiopathic VTE. Most of these data were available in 2004 at the time the 7th ACCP Expert consensus conference[14] recommended the durations of anticoagulant treatment that are summarized in **Table 2**. Amazingly, the experts also suggested considering life-time anticoagulation in case of a first idiopathic thromboembolic event, a proposal that is unlikely to have a favorable benefit/risk ratio except in patients at very low risk of bleeding. These North-American recommendations are at variance with the guidelines of the British Thoracic Society,[8] which are also displayed in **Table 2**. Unfortunately, the 2008 8th ACCP Consensus conference recommendations[15] only partially reconciled these two viewpoints (**Table 2**).

Because patient characteristics and type of event differ from one case to the other, duration of anticoagulant therapy after VTE should be individualized as much as possible. This goal may be achieved by assessing individual risks of VTE recurrence and potential bleeding. Moreover, progress in anticoagulant treatments might positively impact on the benefit-risk balance of this therapy soon.

Individual Tailoring of the Duration of Anticoagulant Therapy after VTE

Evaluating the risk of thromboembolic recurrence

Rather than just following general guidelines, another interesting but more difficult approach to better tailor individually the duration of anticoagulant treatment would be to recognize which patients are at lower or, better, at higher risk to present a recurrent event. Some investigators tried to use D-dimer levels to predict the risk of recurrent event. In the PROLONG Study, Palareti et al[16] showed that following idiopathic DVT, D-dimer measured 1 month after discontinuation of oral anticoagulant treatment discriminates between patients at low- and higher-risk of recurrence. The risk of recurrent event in patients with a D-dimer level above the cut-off of 500 μg/L was 15% over 18 months, which

Table 1. Main randomized studies comparing different durations of anticoagulant therapy after acute unprovoked venous thromboembolism (VTE).

Study	Type of VTE	Duration of treatment	Number of patients (follow-up)	VTE recurrences and/or deaths, n (%, 95%CI)	Major bleeds, n (%)
Pinède[6]	Distal DVT	6 wk	105 (1 y)	3 (3.4)	1 (1.0)
		3 mo	92 (1 y)	2 (2.0)	3 (3.4)
Schulman[9]	DVT	6 wk	443 (2 y)	80 (18.1, 14.5-21.6)	1 (0.2)
		6 mo	454 (2 y)	43 (9.5, 6.8-12.2)	5 (1.1)
Agnelli[11]	DVT	3 mo	131 (37 mo)	21 (15.8)	0
		1 y	134 (38 mo)	21 (15.7)	4 (3.0)
Agnelli[37]	PE	6 mo	161 (33 mo)	18 (11.2)	0
		1 y	165 (35 mo)	15 (9.1)	3 (1.8)
Pinède[6]	Proximal DVT or PE	3 mo	270 (1 y)	21 (8.1)	5 (1.9)
		6 m	269 (1 y)	23 (8.7)	7 (2.6)
Campbell[12]	DVT and/or PE	3 mo	369 (1 y)	31 (8.5)	0
		6 mo	380 (1 y)	29 (7.8)	8 (2.1)
Kearon[10]	DVT*	3 mo	83 (10 mo)	17 (27.4% per y)	0
		continued	79 (10 mo)	1 (1.3% per y)	3 (3.8%)

* double-blind study (study was prematurely stopped); all other studies had an open study design

Abbreviations: DVT, deep vein thrombosis; PE, pulmonary embolism.

Table 2. Proposed durations of anticoagulant treatment following venous thromboembolism (VTE) according to widely used guidelines.*

Indication	7th ACCP guidelines[14]	8th ACCP guidelines[15]	BTS guidelines[8]
First episode of VTE secondary to a transient risk factor†	At least 3 months (Grade 1A).	3 months (Grade 1A).	4-6 weeks (Grade A).
First episode of idiopathic (unprovoked) VTE	At least 6-12 months (Grade 1A). Consider indefinite (Grade 2A).	At least 3 months (Grade 1A). After 3 months, evaluate risk-benefit ratio of long-term treatment (Grade 1C). In case of favorable risk-benefit ratio, long-term treatment (Grade 1A).	3 months (Grade A).
Other (recurrent, active cancer, ...)‡	12 months to lifetime (Grade 2A).	Long term (Grade 1A).	At least 6 months (Grade C).

* All recommendations are subject to modification by individual characteristics including patient preference, age, co-morbidity, bleeding risk, and likelihood of recurrence.

† Transient or time-limited risk factors include: surgery, trauma, immobilization, estrogen use.

‡ Proper duration of therapy is unclear in first event with homozygous factor V Leiden, homocystinemia, deficiency of protein C or S, or multiple thrombophilias; and in recurrent events with reversible risk factors. Long-term anticoagulation is suggested in high risk thrombophilias (e.g., antithrombin deficiency, antiphospholipid syndrome)

Abbreviations: ACCP, American College of Chest Physicians; BTS, British Thoracic Society

may not be considered sufficient to indicate lifelong anticoagulant treatment when considering the associated bleeding risk. On the other hand, the risk of recurrence was still 6.2% in the group with a D-dimer level below the cut-off (hazard ratio 2.27, 95%CI: 1.15–4.46). In a careful prospective study on 272 patients with a first episode of VTE (unprovoked or provoked by a non-surgical trigger), Baglin et al[17] recently confirmed that the positive predictive value of a D-dimer value of > 500 μg/L was only 16.5%, and the negative predictive value of a D-dimer below the cut-off was 86% for unprovoked recurrence. In fact, Baglin et al also convincingly showed that clinical risk factors confound the association between D-dimer and risk of recurrence, and that the clinical utility of D-dimer measurement in individual patients should be interpreted in conjunction with clinical risk factors, such as gender, age and pro-

voked or unprovoked type of the first event. Moreover, in this series, the recurrence rate was lower (5.5 per 100 patient-years, 95%CI: 3.7-7.8) than in the PROLONG study. In a similar attempt to better evaluate the risk of recurrence after a first DVT, Prandoni et al[18] showed that the presence of residual DVT is a risk factor for recurrent thromboembolism in patients with acute DVT. However, the exact instructions for use of either D-dimer or residual DVT remain to be established.

Male gender has also been consistently associated with an increased risk of recurrent VTE, with a relative risk of 3.6 (95%CI: 2.3 to 5.8),[19] 2.7 (95%CI: 1.5-4.8),[20] 3.3 (95%CI: 1.6-7.7, unadjusted)[17] and 2.9 (95%CI: 1.4-6.0, adjusted for type of first event, gender, and age at diagnosis).[17] However, in the REVERSE Study that was presented at the 2007 congress of the International Society on Thrombosis and Haemostasis (ISTH), Rodger et al suggested that this gender effect was age-dependent. Indeed, the increased risk in males was present only until the age of 60,[21] a finding that was not confirmed in the Cambridge study.[17] Nonetheless, the REVERSE collaborative group proposed a clinical rule that predicted a low recurrence risk (1.6% per year) in women with one or none of the following features: (1) hyperpigmentation, edema or redness on exam; (2) D-dimer plasma concentration with the Vidas D-dimer assay (bioMerieux, Marcy-l'Etoile, France) > 250 μg/L; (3) obesity (BMI > 30); or (4) age > 65 years. By comparison, women with 2 or more of these findings had a risk of recurrence of 14.1% per year. Clearly, this interesting clinical prediction rule must now be evaluated prospectively, which is presently occurring in the frame of the REVERSE II study.

At this stage, male gender, the unprovoked character of the event, and an increased D-dimer level 1 month after discontinuing anticoagulant treatment are the only criteria that have been consistently associated with an increased risk of thromboembolic recurrence. In addition, the first 2 years following the treatment discontinuation seem to represent a higher-risk period than the subsequent years.[22]

Evaluating the risk of bleeding

A common adverse effect of all anticoagulant drugs is bleeding, which occurs more frequently at the initiation of treatment ("demasking" of pre-existing lesions) and can have devastating consequences, particularly if there is an intracerebral or retroperitoneal bleeding. During that initial period, heparin is associated with a major bleeding risk of 0.8% per day.[3] In observational studies, major bleeding associated with VKA occurs at an age-dependent[23] monthly rate of about 0.4%.[4] Clinical scores have been prospectively validated and may guide the estimation of the hemorrhagic risk under oral anticoagulant treatment. The HEMORR2HAGES score (**Table 3**),[24] like many other scores, is derived from a cohort of patients given oral anticoagulants because of atrial fibrillation, not VTE. The recently proposed RIETE Registry score was constructed in a population of almost 20,000 consecutive patients with acute VTE to predict the risk of major bleeding within 3 months of anticoagulant therapy (**Table 4**).[25] Although this prediction is based on registry data, it has the great advantage of being based on patients with VTE, not atrial fibrillation. Overall, the risk of major bleeding was 2.4% within 3 months of anticoagulant therapy in this cohort, with 1 in every 3 cases being fatal. Twenty percent of the patients were at low risk of bleeding, 74% at intermediate risk, and 6% at high risk.

Balancing the risk of VTE recurrence and the risk of bleeding

Balancing the risk of thromboembolic recurrence and the risk of major bleeding has always been very difficult be-

Table 3. The HEMORR2HAGES Bleeding Risk Score.[24]

Risk factors	Score
Prior major bleed	2 points
Hepatic or renal disease	1 point
Alcohol abuse	1 point
Malignancy	1 point
Age > 75 years	1 point
Uncontrolled hypertension	1 point
Anemia	1 point
Excessive fall risk	1 point
Prior stroke	1 point
Reduced platelet count or function	1 point

Rate of major bleeding per 100 patient-years according to the score:

Score	0	1	2	3	4	≥ 5
Rate	1.9	2.5	5.3	8.4	10.4	12.3

Table 4. The RIETE Registry bleeding score.[25]

Risk factors	Score
Recent major bleeding	2 points
Creatinine level > 1.2 mg/dL (110 μmol/L)	1.5 points
Anemia (Hb < 13 (men) or 12 (women) g/dL)	1.5 points
Cancer	1 point
Clinically overt PE	1 point
Age > 75 years	1 point

Rate of major bleeding per 100 patient within 3 months of anticoagulant therapy according to the score:

Score	0	1-4	> 4
Rate (%, 95%CI)	0.3 (0.1-0.6)	2.6 (2.3-2.9)	7.3 (5.6-9.3)

cause these two events are of different natures. Moreover, thromboembolism is often considered a twist of fate while bleeding is usually seen as iatrogenic. The annual risk of recurrent VTE after a first idiopathic VTE is about 10% during the first 2 years, and then about 3%, which gives a cumulative recurrence rate of 20% at 3 years and 40% at 5 years.[18] Recently, a case-fatality rate for VTE after treatment discontinuation of 8% (idiopathic DVT) to 12% (idiopathic PE) could be established by Douketis et al[22] in a pooled analysis of the DURAC I study[9] and an Italian study[18] in more than 2000 patients who were followed for several years. On the other hand, annual risks of major bleeding have been reported in 2% to 12% in controlled studies,[24] or even 29%[25] in the RIETE Registry with a case-fatality rate of 10%[26] to 33%.[25]

Thus, assuming a hypothetical cohort of 1000 patients with idiopathic VTE, extending anticoagulant treatment beyond 6 months would result in the prevention of 80 PE recurrences (2 to 10 deaths, depending upon the assumptions chosen) at the cost of 20 to 60 (or even 150 according to the RIETE Registry) major bleeds (with 2 to 6, or even 15 deaths) after 1 year, which is certainly not an invitation for wide use of long-term anticoagulant therapy, except possibly in situations at very high risk of recurrence, such as antithrombin deficiency, recurrent VTE events or the antiphospholipid syndrome.[27]

Progress in Anticoagulant Regimens and Drugs that Might Impact on Treatment Duration

New anticoagulant regimens for long-term secondary prevention

Vitamin K antagonists (VKA) block a late step in the synthesis of four plasma coagulation factors (prothrombin or Factor II, FVII, FIX, and FX) by the liver. Because of the relatively long and different half-lives of circulating factors, a stable level of anticoagulation cannot be reached before 4 to 10 days. VKA include substances with a short (acenocoumarol, Sintrom®), intermediate (warfarin, Coumadin®, fluindione, Previscan®) or long (phenprocoumone, Marcoumar®) half-life. This feature, along with a genetically induced metabolic variability,[28,29] the influence of environmental variables such as vitamin K content of food, and a narrow therapeutic window require close monitoring of VKA treatment. Monitoring has been standardized, and the therapeutic level corresponds to an International Normalized Ratio (INR) between 2 and 3 (target 2.5). Below INR 2.0, the risk of thromboembolic recurrence increases, and above INR 3.0, the bleeding risk becomes definitely higher.

Efficacy of VKA treatment can be improved by supporting patients' compliance, avoiding concurrent drugs with potential interactions, or excessive ingestion of alcohol, and, in selected patients, by using self-testing or even self-dosing after careful teaching.[30] In addition, large loading doses should be avoided to overcome an initial paradoxical prothrombotic state due to the depletion of protein C, a naturally occurring vitamin K–dependent coagulation inhibitor with a very short half-life. Instead, VKA treatment should be initiated with doses likely to be close to the maintenance dose with INR check after two administrations, at least for VKA with a short half-life. Recently, response to warfarin in relation to genetic determinants (cytochrome P450 2C9, CYP2C9, and vitamin K epoxide reductase, VKORC1) was studied in clinical settings.[31,32] In one study,[32] a pharmacogenomic equation was able to explain about 50% of the variability in the warfarin dose, compared with only about 20% for a clinical equation.

An alternative to long-term oral anticoagulant therapy at a conventional INR of 2 to 3, low-intensity anticoagulant treatment with an INR 1.5 to 2.0 has been shown to be more effective than placebo in patients who were initially treated during at least 3 months with a classical INR of 2 to 3 after a venous thromboembolic event.[33] The possibility of reducing the intensity of anticoagulant treatment after an initial period of "full" anticoagulation has become a realistic option at least in some patients[34] to reduce the bleeding risk while maintaining some protection against thromboembolic recurrence. This option was, however, questioned by a Canadian trial that found a higher protection against recurrence in patients treated with full-intensity compared with low-intensity INR without an increase in bleeding risk.[35] However, the extremely low bleeding risk observed in this trial (less than 1% per year) is at variance with all previous trials on anticoagulant treatment,[34] which suggests that the study may not be representative of real life. Indeed, in a recently published study of an inception cohort of 472 patients beginning VKA treatment because of atrial fibrillation, the major hemorrhage rate was 4.7 per 100 patient-years in patients aged less than 80 and 13.1 per 100 patient-years in patients aged more than 80.[36] It was even greater in the RIETE Registry: in these patients with VTE, the overall rate of major bleeding was as high as 2.4% within 3 months of anticoagulant therapy. Moreover, the absolute VTE recurrence risk difference between full-intensity and low-intensity INR in the Canadian study was small. Nevertheless, the option of long-term secondary prophylaxis at a reduced INR has been strongly discouraged by the 7th ACCP consensus,[14] without convincing argumentation, however. The 8th ACCP Consensus conference did recently modify this viewpoint this by accepting low-intensity anticoagulation in patients "who have a strong preference for less frequent INR testing to monitor their therapy" (Grade 1A).

The upcoming oral anticoagulant drugs

Several new oral anticoagulants are presently under clinical development. These direct (i.e., antithrombin-indepen-

dent) inhibitors of Factor Xa (e.g., rivaroxaban, apixaban) or thrombin (e.g., dabigatran) avoid most of the drawbacks of heparin and do not require laboratory monitoring. Therefore, they have the potential to replace heparins, fondaparinux and VKA in the future in a substantial proportion of patients. The discussion of their advantages and potential disadvantages is beyond the scope of the present review. Great hope has been awakened with the advent of these novel anticoagulants, but large-scale, long-term experience is still lacking with all of them.

Conclusions and Perspectives

Anticoagulation is the treatment of choice in almost all patients with established DVT or PE. Treatment is usually initiated with low-molecular-weight heparin or fondaparinux, overlapped and followed by VKA. This treatment is highly efficacious in preventing recurrent VTE events but not devoid of bleeding risk. Treatment duration after VTE must therefore be individualized, e.g., with shorter duration in case of distal DVT, transient risk factor, or increased bleeding risk, and longer duration in case of a recurrent unprovoked event, especially if permanent risk factors are present.

Empirical recommendations on duration of anticoagulant treatment following acute VTE have been more and more replaced by sometimes contradictory, but more evidence-based guidelines. There are, however, still many situations in which treatment durations remain uncertain. All these therapeutic recommendations may change in the next years by improving safety of long-term anticoagulant treatment, which includes novel modalities of using warfarin (reduced INR of improved dosing by means of genetic determination) and the advent of novel oral anticoagulants.

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