Recurrence risk after anticoagulant treatment of limited duration for late, second venous thromboembolism

Tom van der Hulle, Melanie Tan, Paul L. den Exter, Mark J.G. van Roosmalen, Felix J.M. van der Meer, Jeroen Eikenboom, Menno V. Huisman, and Frederikus A. Klok

Department of Thrombosis and Hemostasis, Leiden University Medical Center, the Netherlands

ABSTRACT

Patients with a second venous thromboembolism generally receive anticoagulant treatment indefinitely, although it is known that the recurrence risk diminishes over time while the risk of hemorrhage persists with continued anticoagulation and increases with age. Based on these arguments and limited evidence for indefinitely prolonged treatment, the Dutch guidelines recommend considering treatment of a limited duration (i.e. 12 months) for a 'late' second venous thromboembolism, defined by a second venous thromboembolism diagnosed more than 1 year after discontinuing treatment for a first event. It is hypothesized that the risk of continued anticoagulation might outweigh the benefits in such circumstances. We evaluated this management in daily practice. Since 2003, limited duration of treatment was systematically considered at our hospital in consecutive patients, in whom we determined the recurrence risk. Of 131 patients with late second venous thromboembolism, 77 were treated for a limited duration, of whom 26 developed a symptomatic third venous thromboembolism thereafter during a cumulative follow-up of 277 years, resulting in an incidence rate of 9.4/100 patient-years (95% confidence interval: 6.1-14). The incidence rates in patients with unprovoked and provoked venous thromboembolism were 12/100 patient-years (95% confidence interval: 7.4-19) and 5.6/100 patient-years (95% confidence interval: 2.2-12), respectively [adjusted hazard ratio 2.8 (95% confidence interval: 1.1-7.2)]. The recurrence risk after treatment of limited duration for 'late' second venous thromboembolism exceeded the risk of hemorrhage associated with extended anticoagulation. Most patients may, therefore, be better served by treatment of indefinite duration, although the risk-benefit ratio of extended anticoagulation should be weighed for every patient.

Introduction

The optimal duration of treatment for a first episode of venous thromboembolism (VTE), whether deep vein thrombosis (DVT) or pulmonary embolism (PE), has been studied and debated extensively. In general, 3 months of anticoagulant treatment is recommended for patients with a provoked VTE. For those with an unprovoked VTE, it is recommended that treatment lasts at least 3 months, after which the patient should be evaluated for the risk-benefit ratio of extended therapy.[1] In contrast to the numerous studies evaluating the optimal duration of treatment for a first VTE, only one study has evaluated the optimal duration of treatment for a second VTE.[2] In that study, a cumulative VTE recurrence rate of 21% was reported during 4 years of follow-up in patients treated for 6 months, in contrast to a rate of 2.6% in patients in whom treatment was continued [relative risk 8.0; 95% confidence interval (CI): 2.5-26]. As expected, a limited duration of treatment resulted in a lower cumulative incidence of major hemorrhage (2.7% *versus* 8.6%; relative risk 0.3; 95% CI: 0.1-1.1).

Mainly based on this study, the Dutch multidisciplinary guidelines on the diagnosis and treatment of VTE suggests an indefinite duration of treatment for a second VTE, without making a distinction between provoked and unprovoked VTE [American College of Chest Physician (ACCP) level of evidence 2B].[3]

The guidelines also suggest considering a limited duration of treatment of 12 months for a 'late' second VTE in patients with a long interval between cessation of anticoagulant treatment for the first VTE and the second VTE (ACCP level of evidence 2C). A long interval was arbitrarily defined as a period of more than 12 months. The rationale for the latter recommendation is that patients with a late second VTE have a relatively limited risk of recurrent VTE, which is supported by indirect evidence that the risk of VTE recurrence is highest shortly after cessation of anticoagulant treatment for a first VTE and then rapidly decreases.[4,5] Taking into account that the anticoagulant-associated risk of hemorrhage persists while anticoagulant treatment is continued and considerably increases with age, it is argued that the risk of hemorrhage associated with long-term anticoagulant treatment may outweigh the reduction of risk of recurrent VTE associated with continued anticoagulant treatment in such circumstances.[6]

In accordance with the Dutch multidisciplinary guidelines, a limited duration of treatment of 12 months has been systematically considered in all patients diagnosed with a late second VTE since 2003 in the Department of Thrombosis and Hemostasis of our hospital. As this recommendation is supported by only limited evidence, its evaluation is essential. We, therefore, report the results of applying this recommendation in daily clinical practice.

Methods

We included all consecutive patients who were diagnosed with a late second VTE in the period 2003-2012 in the Department of

 doi:10.3324/haematol.2014.112896
Manuscript received on June 27, 2014. Manuscript accepted September 25, 2014.
Correspondence: t.van_der_hulle@lumc.nl

Thrombosis and Hemostasis of the Leiden University Medical Center (LUMC), Leiden, the Netherlands in a prospective registry. Specific inclusion criteria for the current analysis were: (i) a previously documented symptomatic first provoked or unprovoked VTE; (ii) a documented symptomatic second provoked or unprovoked VTE, and (iii) more than 1 year between cessation of anticoagulant treatment for the first VTE and the diagnosis of the second VTE.

In our hospital, suspected recurrent VTE is managed by using an algorithm starting with determination of pretest probability, followed by either D-dimer and or radiological imaging tests if indicated. The radiological criteria for diagnosing ipsilateral recurrent DVT are a compression ultrasonography that shows incompressibility of a different venous segment than at a reference examination or, in the case of a pronounced increase in vein diameter (≥4 mm), of a previous non-compressible venous segment.[7]

The treatment protocol recommended a limited duration of treatment for a late second VTE in the absence of another indication for anticoagulant treatment, but the final decision was made by the treating physician during the first visit of the included patients at our outpatient clinic, approximately 6 weeks after the diagnosis of the second VTE. Patients were rarely tested for hereditary thrombophilic factors, and no standardized model for predicting recurrence risk was used. Diagnostic procedures in the case of suspected recurrence were applied in a standard manner, in accordance with the national and international guidelines.[1,3] For all patients, follow-up was completed for at least 2 years or until March 2014, the patient's death or the primary endpoint was reached. The ethics committee of the LUMC approved this study and waived the requirement for informed consent since the study evaluated standard clinical practice.

The primary endpoint of the analysis was a symptomatic third DVT and/or PE during follow-up, demonstrated by objective diagnostic tests according to the guidelines.[1,3,7] The secondary outcome was the risk of major hemorrhage, defined according to the International Society of Thrombosis and Haemostasis criteria.[8]

Provoked VTE was defined as VTE occurring after major surgery or immobilization for at least 3 days within 4 weeks preceding the diagnosis, in a patient with active malignancy (a diagnosis of cancer within 6 months prior to enrolment, any treatment for cancer within the previous 6 months, or recurrent or metastatic cancer), after a recent long flight (>4 hours), during pregnancy or the peripartum period and in patients taking oral contraceptives or hormone replacement therapy. Unprovoked VTE was defined as VTE occurring without any of these provoking factors. Patients were classified according to whether they received treatment of a limited duration, defined as treatment for 12 months or less, or treatment of indefinite duration. Incidence rates of the primary and secondary endpoints were calculated and the Kaplan-Meier life table method was used to estimate the cumulative event rate.

A Cox proportional hazard model was used to calculate hazard ratios (HR) for clinical characteristics. We performed subpopulation analyses for: (i) patients with unprovoked and provoked second VTE; (ii) patients with unprovoked first and second VTE and those with provoked first and second VTE; (iii) DVT or PE as the second VTE; (iv) patients <65 years old and those ≥65 years old; (v) patients with an anticoagulant effect within the therapeutic range for <60% and ≥60% of the time, calculated by the Rosendaal method;[9,10] and (vi) a limited duration of treatment for the second VTE of 12 months and less than 12 months. Hazard ratios were adjusted for age, sex, type of the second VTE (DVT or PE±DVT) and whether the second VTE was provoked or unprovoked. Analyses were performed using SPSS version 20 (SPSS inc., Chicago, IL, USA).

Results

Between 2003 and 2012, 131 patients were diagnosed with a late second VTE. One patient was excluded from the analysis, because she died before the planned cessation of anticoagulant treatment after 12 months. The baseline characteristics of the whole cohort are shown in Table 1.

Limited duration of treatment

Overall, 77 patients were treated for a limited duration: five patients for a total of 3 months, 26 patients for 6 months and 46 patients for 12 months. All these patients were followed up for at least 2 years with a median duration of follow-up of 34 months after treatment cessation. The mean age at the time of diagnosis of the second VTE was 52 years, and 35 patients were male (46%).

In 50 patients (65%) the second VTE was a DVT, leaving 27 patients (35%) diagnosed with PE as the second VTE,

Table 1. Baseline characteristics.

Characteristic	Total cohort n=131 (%)	Limited treatment n=77 (%)	Indefinite treatment n=54 (%)
Mean age (SD)	53 (16)	52 (15)	54 (16)
Male sex	62 (47)	35 (46)	27 (50)
Known heart failure	3 (2.3)	2 (2.6)	1 (1.9)
Known COPD	4 (3.1)	2 (2.6)	2 (3.7)
Type of first VTE			
DVT	86 (66)	57 (74)	29 (54)
PE ± DVT	45 (34)	20 (26)	25 (46)
Unprovoked first VTE	58 (44)	33 (43)	25 (46)
Type of second VTE			
DVT	87 (66)	50 (65)	37 (69)
PE ± DVT	44 (34)	27 (35)	17 (31)
Unprovoked second VTE	80 (61)	47 (61)	33 (61)
Concordant *versus* discordant type (regarding the first and second VTE)			
2 times DVT, ipsilateral	45 (34)	29 (38)	16 (30)
2 times DVT, contralateral	27 (21)	17 (22)	10 (19)
2 times PE	30 (23)	16 (21)	14 (26)
1 DVT and 1 PE	29 (22)	15 (19)	14 (26)
Provoked second VTE	51 (39)	30 (39)	21 (39)
Surgery or immobilization	21 (16)	14 (18)	7 (13)
Oral contraceptive use	11 (8.4)	8 (10)	3 (5.6)
Long flight	8 (6.1)	5 (6.5)	3 (5.6)
Pregnancy	7 (5.3)	4 (5.2)	3 (5.6)
Active malignancy	11 (8.4)	1 (1.3)	10 (19)
Median time between first and second VTE in years (IQR)	6.2 (3.3-12)	7.2 (3.6-13)	5.8 (3.2-10)
1-5 years	55 (42)	31 (40)	24 (44)
5-10 years	35 (27)	18 (23)	17 (31)
>10 years	41 (31)	28 (36)	13 (24)
Treatment duration in months			
3	NA	5 (6.5)	NA
6	NA	26 (34)	NA
12	NA	46 (60)	NA
Time in therapeutic range*			
<60%	NA	6/67 (9.0)	NA
≥60%	NA	61/67 (91)	NA

*SD: standard deviation; COPD: chronic obstructive pulmonary disease; VTE: venous thromboembolism; DVT: deep vein thrombosis; PE: pulmonary embolism; IQR: interquartile range; *only available for 67 patients because ten patients were treated in a Thrombosis Service in another region; NA: not available.*

with or without symptomatic DVT. The type of the first VTE and second VTE was different in only 15 patients, while in the other 62 patients both events were of the same type. In 46 patients both the first and second VTE were DVT, in 29 (63%) cases the recurrent DVT was ipsilateral to the first, whereas in 17 (37%) cases the second DVT was contralateral to the first. The median time between the first and second VTE was 7.2 years (interquartile range, 3.6 – 13 years). A provoking risk factor for the second VTE was reported for 30 of 77 patients (39%): recent surgery and/or immobilization in 14 patients, oral contraceptive use in eight patients (one of whom also had a history of recent surgery and/or immobilization), a long flight in five patients (one of whom was also taking an oral contraceptive), pregnancy in four patients and malignancy in one patient, leaving 47 patients (61%) with unprovoked, late second VTE. The patient with cancer received the last dose of chemotherapy for testicular cancer at the moment of the second VTE, after which he was in complete remission, allowing treatment cessation according to the Dutch guidelines.

Five patients (6.5%) were treated for only 3 months based on the argument that the late recurrent event was caused by a transient provoking factor, 26 patients (34%) were treated for 6 months and the majority of the 46 patients (60%) were treated for 12 months after the diagnosis of late second VTE. Seven patients (9.1%) died during the follow-up after cessation of anticoagulation. Six of the deaths were not related to VTE: two patients had end-stage metastatic malignancy diagnosed during follow-up, one patient committed suicide, one patient developed non-anticoagulation-associated intracranial bleeding, one patient had end-stage heart failure and one patient died as a direct result of a traffic accident. The cause of death could not be retrieved for one patient, who died at the age of 91, 6 years after cessation of anticoagulant treatment for recurrent DVT.

Overall, 26 of the 77 patients were diagnosed with a third VTE during a cumulative follow-up of 277 patient-years. The third VTE was of the same type as the second VTE in 24 patients: of the 16 patients who developed DVT as the third VTE event, only one had PE as the second VTE and of the ten patients with PE as the third VTE only one had DVT as the second VTE. Of the 16 patients who developed DVT as the third VTE, 12 (75%) had been previously diagnosed with DVT on the same side (either as first or second VTE). Seven of the 26 patients had a provoked second VTE, of whom two patients (29%) experienced a provoked third VTE and five (71%) an unprovoked third VTE. The remaining 19 patients had an unprovoked second VTE: in four cases (21%) the third VTE was provoked, whereas in the other 15 (79%) the third VTE was also unprovoked.

The incidence rate of a third VTE after limited treatment was 9.4 per 100 patient-years (95% CI: 6.1 - 14), and 1-, 2-, 3- and 5-year cumulative VTE rates were 15% (95% CI: 3.1-34), 19% (95% CI: 6.1-38), 25% (95% CI: 10-42) and 33% (95% CI: 18-49), respectively. When the unexplained death was considered as attributable to recurrent VTE, the incidence rate was 9.7/100 patient-years (95% CI: 6.4-14).

Treatment of indefinite duration

For 39 of the 54 patients who were treated for an indefinite duration, the reason for this decision was documented: ten patients (19%) had an active malignancy, ten patients (19%) had known hereditary thrombophilia, nine patients (17%) had an additional indication for anticoagulant treatment, in four patients (7.4%) it was the patients' strong preference to continue treatment, in four patients (7.4%) antiphospholipid syndrome was diagnosed, one patient (1.9%) was persistently immobile, one patient (1.9%) had a strongly positive family history and in one patient (1.9%) the large thrombotic load of the second VTE was considered as a reason for continuing treatment. For the remaining 15 patients (28%), no specific reason was documented.

Among the patients on anticoagulant treatment for an indefinite period, 13 died during follow-up (24%): in 11 of these patients, VTE was ruled out as the cause of death, whereas the cause of death could not be retrieved for the other two patients.

Four patients developed a third VTE while being treated with anticoagulants during a cumulative follow-up of 332 patient-years, resulting in an incidence rate of 1.2/100 patient-years (95% CI: 0.33-3.1) (Figure 1). None of these events was fatal. When the unexplained deaths were considered as attributable to recurrent VTE, the incidence rate was 1.8/100 patient-years (95%CI 0.66-3.9). Major hemorrhage occurred in eight patients, resulting in an incidence rate of 2.4/100 patient-years (95% CI: 1.0-4.7). None of these hemorrhages was fatal.

Subgroup analyses in the patients treated for a limited duration

Cox-regression analysis demonstrated a higher risk of recurrence in patients with an unprovoked second VTE than in those with a provoked second VTE (adjusted HR 2.8; 95% CI: 1.1-7.2) (Figure 2). The incidence rate in patients with a provoked second VTE was 5.6/100 patient-years (95% CI: 2.2-12). The 1-, 2-, 3- and 5-year cumulative VTE rates were 10% (95% CI: 0.082-48), 10% (95% CI: 0.082-48), 14% (95% CI: 0.54-49) and 20% (95% CI: 1.8-53), respectively. The incidence rate in patients with an unprovoked second VTE was 12/100 patient-years (95% CI: 7.4-19). The 1-, 2-, 3- and 5-year cumulative VTE rates were 17% (95% CI: 3.0-42), 25% (95% CI: 7.8-46), 30% (95% CI: 13-51) and 41% (95% CI: 22-59), respectively. In patients with both an unprovoked first and second VTE the incidence rate of a third VTE was 8.7/100 patient-years (95% CI: 3.5-18) whereas in those with a provoked first and second VTE it was 4.6/100 patient-years (95% CI: 1.3-12).

In patients with DVT as the second VTE, the incidence rate of a third recurrence was 8.3/100 patient-years (95% CI: 4.8-14). In patients with PE as the second VTE, the incidence rate was 12/100 patient-years (95% CI: 5.6-21). This difference between the two groups was not statistically significant (adjusted HR 0.65; 95% CI: 0.29-1.5). The incidence rate of a third VTE in patients <65 years old was 9.9/100 patient-years (95% CI: 6.1-15) whereas in those ≥65 years old it was 7.8/100 patient-years (95% CI: 2.5-18), with an adjusted HR of 1.2 (95% CI: 0.43-3.4). Due to the low number of patients whose anticoagulation was in the therapeutic range for <60% of the time, we refrained from subgroup analyses based on this variable (Table 1). Finally, the VTE incidence rate in patients treated for 3 or 6 months was lower - although non-significantly - than that after a 12-month treatment period: 6.1/100 patient-years (95% CI: 2.8-12) *versus* 13/100 patient-years (95% CI: 7.7-21), with an adjusted HR of 0.6 (95% CI: 0.25-1.4).

Discussion

We evaluated the outcome in daily clinical practice of following the recommendation in the Dutch multidisciplinary guidelines to consider a limited duration of treatment in selected patients with a 'late' second VTE.[5] We found a VTE incidence rate of 9.4/100 patient-years after cessation treatment of a limited duration, with a cumulative VTE rate of 15% after 1 year follow-up which increased to 33% after 5 years of follow-up. In order to weigh these results, two issues should be discussed.

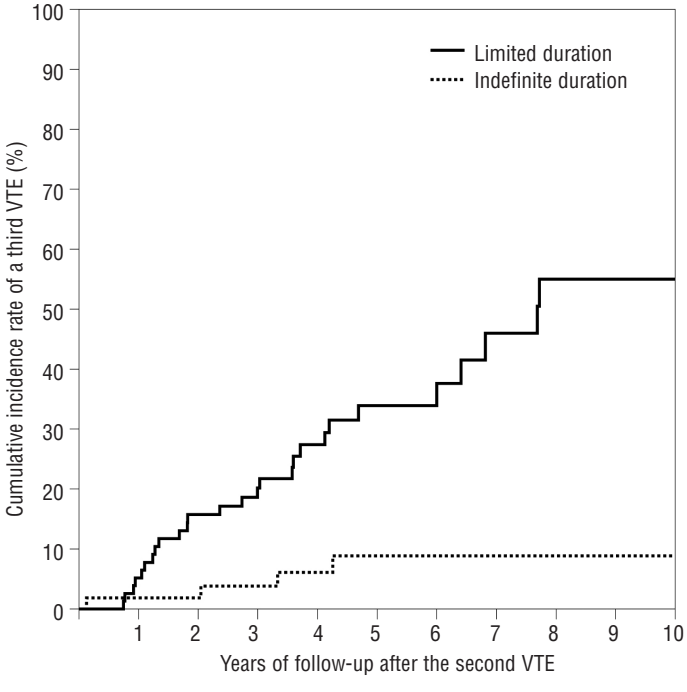
First, the VTE incidence rate of 9.4/100 patient-years largely exceeds the risk of major hemorrhage associated with long-term anticoagulant treatment, which was estimated to be 2.7/100 patient-years in a meta-analysis and was 2.4/100 patient-years in our cohort of patients who were treated for an indefinite period.[11] Notably, the clinical impacts of recurrent VTE and major hemorrhage are frequently considered as equivalent, which is supported by the more or less comparable case-fatality rate varying from 3.8 to 11% for recurrent VTE and 9.1% (95% CI: 2.5-22) for major hemorrhage.[11-13]

Second, we should compare our results to the 3-4% per year risk of recurrent VTE after a first VTE related to a transient provoking factor, since a limited duration of treatment is generally accepted for these patients.[1,14] The results of our subgroup analyses suggest that patients with a provoked second VTE have a much lower risk of recurrence than have patients with an unprovoked second VTE. Despite the wide confidence interval, the incidence rate of 5.6/100 patient-years (95% CI: 2.2-12) for a third VTE in patients with a provoked, late second VTE is relatively low and seems to approximate the risk of recurrent VTE after a first provoked VTE.

Based on these considerations, we argue that most patients with a late second VTE are generally better served by treatment of an indefinite duration. Furthermore, our results suggest that selecting patients with a relatively low VTE recurrence risk based on the interval between cessation of anticoagulant treatment and the second VTE is not an appropriate strategy. Nevertheless, it remains essential to weigh the risk-benefit ratio of extended anticoagulant treatment in every patient individually.

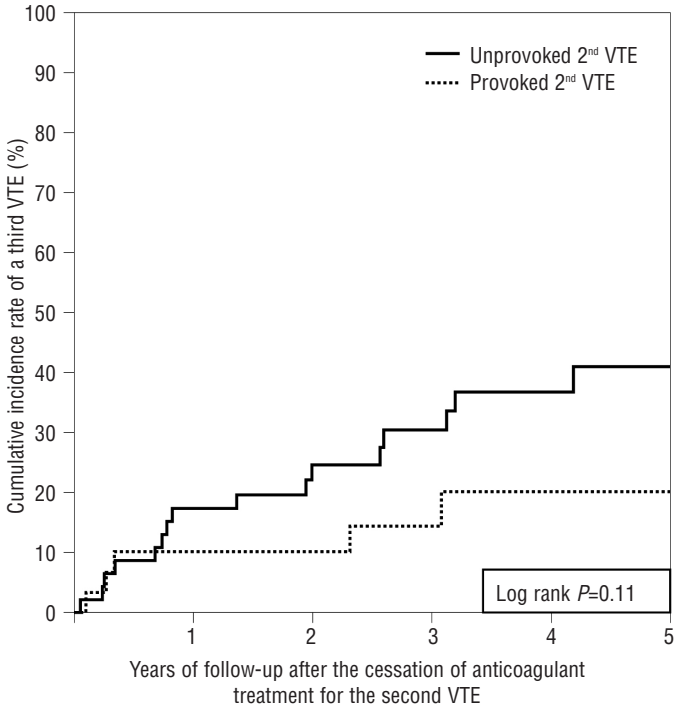
The introduction of new oral anticoagulants for the treatment of VTE must be considered in the context of our results, since these drugs are associated with a lower risk of bleeding complications than vitamin K antagonists, and yet have comparable efficacy.[15] The use of these drugs may, therefore, shift the risk-benefit ratio of long-term anticoagulant treatment in favor of indefinite duration of treatment for many patients.

The strengths of our study are the completeness of the data on recurrences, bleeding complications and follow-up. The large percentage of time that the patients spent in the therapeutic range of anticoagulation confirms the high quality of care they received. Moreover, we report previously undescribed outcomes in daily clinical practice of a unique treatment recommendation for patients with a second VTE. Finally, the recurrence risk in the group treated indefinitely as well as the observation that patients most



Treatment group	Follow-up in years	1	2	3	4	5	6	7	8	9	10
Limited duration	nrVTE	4	12	15	19	22	23	25	27	27	27
	PAR	73	63	51	38	27	17	12	12	7	4
Indefinite duration	nrVTE	1	1	2	3	4	4	4	4	4	4
	PAR	52	50	45	35	31	29	26	18	11	7

Figure 1. Cumulative incidence rate of a third venous thromboembolism in patients treated for a limited duration and patients treated for an indefinite duration. Follow-up started at the time of diagnosis of the second venous thromboembolism for both categories. nrVTE: number of recurrent VTE; PAR: patients at risk.



Subgroup	Follow-up in years	1	2	3	4	5
Provoked second VTE	nrVTE	3	3	4	5	5
	PAR	25	21	15	12	10
Unprovoked second VTE	nrVTE	8	11	13	15	16
	PAR	38	30	22	15	9

Figure 2. Cumulative incidence rate of a third venous thromboembolism in patients with a provoked second VTE or an unprovoked second VTE, treated for a maximum of 12 months. Follow-up started at the time of cessation of anticoagulant treatment. nrVTE: number of recurrent VTE; PAR: patients at risk.

frequently develop a recurrence of the same type, either DVT or PE, are in accordance with findings in previous large studies and therefore indicate that we studied a representative cohort of patients.[16]

Our analyses have limitations, of which the most important are related to the observational design of the study. As a result, the choice of patients who received treatment of a limited duration was not randomized, which may have resulted in a selection bias. As argued before, it is more likely that this would have resulted in an underestimation of the recurrence risk after a limited duration of treatment than in an overestimation. It is, therefore, very unlikely that our conclusions would have been different had a different study design been used. Also inherent to the design, is that 40% of the patients were treated for less than 12 months, despite the recommendation of a treatment duration of 12 months in the Dutch multidisciplinary guidelines. We did not, however, find a higher recurrence risk in patients treated for 3 or 6 months compared to that in patients treated for 12 months suggesting that this factor was of no or only little influence on our results. In addition, in a meta-analysis by Van Dongen and colleagues it was demonstrated that the recurrence risk after VTE did not depend on the duration of treatment, although this concerned a study of patients with a first VTE.[4] The lack of long-term follow-up data of the larger population from which our study subjects were derived, i.e. all patients with a diagnosis of first or recurrent VTE, did not allow us to compare the recurrence rate after a second VTE to that after a first VTE. Finally, due to the relatively small number of patients the confidence intervals for our primary and secondary endpoints were wide, especially for the subgroup analyses.

In conclusion, our study provides insight into the risk of recurrence after treatment of limited duration for a late second VTE, which exceeded the risk of hemorrhage associated with extended anticoagulant treatment in our cohort. We, therefore, argue that most patients with a late second VTE are generally better served by treatment of indefinite duration, although the risk-benefit ratio of extended anticoagulant treatment should be weighed for every individual patient in daily clinical practice.

Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

References

1. Kearon C, Akl EA, Comerota AJ, Prandoni P, 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(2 Suppl):e419S-e494S.
2. Schulman S, Granqvist S, Holmstrom M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. N Engl J Med. 1997;336(6):393-398.
3. Kwaliteitsinstituut voor de Gezondheidszorg CBO. Richtlijn Diagnostiek, Preventie en Behandeling van Veneuze Trombo-embolie en Secundaire Preventie Arteriële Trombose. 2009:111-116.
4. van Dongen CJ, Vink R, Hutten BA, Buller HR, Prins MH. The incidence of recurrent venous thromboembolism after treatment with vitamin K antagonists in relation to time since first event: a meta-analysis. Arch Intern Med. 2003;163(11):1285-1293.
5. Prandoni P, Noventa F, Ghirarduzzi A, 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(2):199-205.
6. Palareti G, Leali N, Coccheri S, et al. Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet. 1996;348(9025):423-428.
7. Huisman MV, Klok FA. Diagnostic management of acute deep vein thrombosis and pulmonary embolism. J Thromb Haemost. 2013;11(3):412-422.
8. Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost. 2005;3(4):692-694.
9. Palareti G, Legnani C, Cosmi B, Guazzaloca G, Cini M, Mattarozzi S. Poor anticoagulation quality in the first 3 months after unprovoked venous thromboembolism is a risk factor for long-term recurrence. J Thromb Haemost. 2005;3(5):955-961.
10. Rosendaal FR, Cannegieter SC, van der Meer FJ, Briet E. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost. 1993;69(3):236-239.
11. 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(11):893-900.
12. Carrier M, LE GG, 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(9):578-589.
13. Douketis JD, Gu CS, Schulman S, Ghirarduzzi A, Pengo V, Prandoni P. The risk for fatal pulmonary embolism after discontinuing anticoagulant therapy for venous thromboembolism. Ann Intern Med. 2007;147(11):766-774.
14. Iorio A, Kearon C, Filippucci E, 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(19):1710-1716.
15. van der Hulle T, Kooiman J, den Exter PL, Dekkers OM, Klok FA, Huisman MV. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2014;12(3):320-328.
16. Baglin T, Douketis J, Tosetto A, et al. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. J Thromb Haemost. 2010;8(11):2436-2442.