

Post-thrombotic syndrome in patients treated with rivaroxaban or enoxaparin/vitamin K antagonists for acute deep-vein thrombosis

A post-hoc analysis

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Summary

Post-thrombotic syndrome (PTS) is a common complication of deep-vein thrombosis (DVT). Poor quality treatment with vitamin K antagonists (VKA) is a risk factor for PTS. We hypothesised that treatment with the direct oral anticoagulant (DOAC) rivaroxaban may lower PTS incidence as compared to enoxaparin/VKA, as DOACs have a more stable pharmacologic profile than VKA. We performed a post-hoc subgroup analysis of the Einstein DVT trial (n=3449). Kaplan-Meier survival analysis was performed to compare the cumulative incidence of PTS between the rivaroxaban and enoxaparin/VKA groups. Hazard ratios (HR) and 95 % confidence intervals (CI) were calculated using Cox proportional hazards models. We included 336 patients with a mean age of 58 ± 16 years and a median follow-up after index DVT of 57 months (interquartile range 48–64). Of these, 162 (48 %) had been treated with rivaroxaban and 174 (52 %) with enoxaparin/VKA. The

cumulative PTS incidence at 60 months follow-up was 29 % in the rivaroxaban group and 40 % in the enoxaparin/VKA group. After adjusting for age, gender, body mass index, previous VTE, ipsilateral recurrent DVT, extent of DVT, idiopathic DVT, duration of anticoagulant treatment, compliance to assigned study medication, elastic compression stocking use and active malignancy, the HR of PTS development for rivaroxaban was 0.76 (95 % CI: 0.51–1.13). In conclusion, treatment of acute DVT with rivaroxaban was associated with a numerically lower but statistically non-significant risk of PTS compared to enoxaparin/VKA treatment. The potential effect on reducing PTS deserves evaluation in a large randomised trial.

Keywords

Post-thrombotic syndrome, rivaroxaban, vitamin K antagonists, deep-vein thrombosis

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Introduction

Post-thrombotic syndrome (PTS) is a common complication of deep-vein thrombosis (DVT) and occurs in 20–50 % of the patients after a DVT (1–4). Clinical presentation may vary from minor signs including skin discoloration, venous ectasia, discomfort and swelling, to severe manifestations such as chronic pain, intractable oedema or leg ulcers impairing. Due to its high prevalence, severity and chronicity, PTS has a significant impact on quality of life and is associated with considerable socioeconomic consequences for both the patient and the health care system (1, 5).

The pathogenesis of PTS is not fully understood. It has been thought that persistent venous obstruction, valve damage and an impaired microcirculation in the veins contribute to PTS development (6). Inadequate thrombus resolution might cause persistent venous obstruction and valve damage leading to venous hypertension (7). The regular treatment of DVT is unfractionated heparin or low-molecular-weight heparin (LMWH) followed by vitamin K antagonists (VKA). Several studies have shown that on average patients spend more than 20 % of their time below the therapeutic range during treatment with VKA (8–10). It is confirmed that the therapeutic intensity of VKA treatment is an essential determinant

for development of PTS since the time spent beneath the therapeutic range is associated with PTS development (9, 11). Furthermore, a systematic review found a significantly lower rate of PTS in patients treated with LMWH alone compared to patient treated with LMWH followed by VKA (12).

Rivaroxaban, one of the direct oral anticoagulants (DOACs) approved for treatment of venous thromboembolism (VTE), has a stable pharmacological profile and thereby could overcome the disadvantages of VKA. However, the risk of PTS in DVT patients treated with rivaroxaban is unknown. We hypothesised that treatment with rivaroxaban may lower the risk of PTS as compared with VKA treatment.

Methods

Study design and population

This investigator-initiated cohort study assessed the incidence of PTS in patients who participated in the Einstein DVT trial. The Einstein DVT trial was an open-label, randomised, event-driven, non-inferiority trial that compared the efficacy and safety of oral rivaroxaban alone (15 mg twice daily for 3 weeks, followed by 20 mg once daily) with subcutaneous enoxaparin followed by a VKA (either warfarin or acenocoumarol; target INR 2–3) in 3449 patients with acute, symptomatic DVT (for 3, 6, or 12 months). The Einstein DVT trial showed that rivaroxaban was as effective as enoxaparin followed by VKA in reducing the incidence of symptomatic recurrent VTE events (13).

All centres which were willing to collect assessments for PTS after the conclusion of the Einstein DVT study were invited to participate in this sub-study. Study centres were requested to complete a predefined questionnaire without enquiring the allocation to study treatment.

Patient data from the Einstein DVT trial were obtained after informed consent and independent review board approvals. Data from the Einstein DVT trial database had been entirely de-linked from personal health information when accessed for this study. This study is consistent with the principles of the Declaration of Helsinki. Bayer performed the analyses that the authors requested.

Definition of PTS

PTS was assessed with the Villalta score and performed by trained physicians or nurses (14). This score consists of five patient-rated symptoms (heaviness, pain, cramps, itching, and tingling) and six physician-rated signs (pretibial oedema, skin induration, hyperpigmentation, venous ectasia, redness, and pain on calf compression). For each item, a score of 0–3 was assigned using the contralateral unaffected leg as comparator. PTS was defined as a Villalta score of ≥ 5 persisting for at least three months. A total score of 5 to 14 points indicates moderate PTS, and ≥ 15 severe PTS. The presence of a venous ulcer of the lower limb indicates severe PTS, regardless of the Villalta score (14). The date of PTS development was reported by the patient. Use of elastic compression stockings (ECS) was scored by means of a questionnaire. Additional infor-

mation on the recurrence of symptomatic recurrent VTE and death during follow-up was collected at time of the PTS assessment. Only events that were objectively documented and/or led to hospitalisation were included.

Study outcomes

The primary outcome of this study was the cumulative incidence of PTS. Secondary outcomes were the severity of PTS, confirmed symptomatic recurrent VTE and death.

Statistical analyses

A Kaplan-Meier survival analysis was performed to compare the cumulative incidence of PTS between the two treatment groups. Differences between the curves were formally tested for significance with the log-rank test. Hazard ratios (HR) and 95% confidence intervals (CI) for the effect of rivaroxaban and enoxaparin/VKA were calculated by using Cox proportional hazards models. HRs were adjusted for age, gender, body mass index (BMI), previous VTE, ipsilateral recurrent DVT, extent of DVT (femoral vein or more proximal DVT vs popliteal or more distal DVT), idiopathic DVT, duration of anticoagulant treatment, compliance to assigned study medication, use of ECS and presence of an active malignancy (defined as a malignancy treated during the previous 6 months or presence of recurrent or metastatic malignancy).

Compliance in the rivaroxaban treatment group was calculated as follows. For the initial 21 days in which rivaroxaban 15 mg was given twice daily, the number of tablets taken was divided by 2 and then divided by the duration from randomisation up to the last intake of the twice daily regimen. For the subsequent period in which rivaroxaban 20 mg was given once daily, the number of tablets taken was divided by the duration from stop of twice-daily rivaroxaban up to the last intake of once-daily rivaroxaban. Compliance in the enoxaparin/VKA group was calculated as follows: for the initial treatment period with enoxaparin, subjects were considered compliant if they had at least four days of initial enoxaparin treatment, and if the INR was at least 2.0 on two consecutive measurements at least 24 hours apart before stop date of enoxaparin. For the subsequent VKA treatment period, subjects were considered compliant if the INR was measured at least monthly after the initial treatment period, regardless of the INR value. Compliance of $\geq 80\%$ was considered good.

Follow-up started at randomisation and ended for each individual at the date of estimated onset of PTS or at the date of the last PTS assessment.

Results

► Figure 1 shows the study profile: 25 centres participated with a total number of 492 randomised patients. The assessment of PTS was not performed in 156 (32%) patients, 81 in the rivaroxaban group and 75 in the enoxaparin/VKA group.

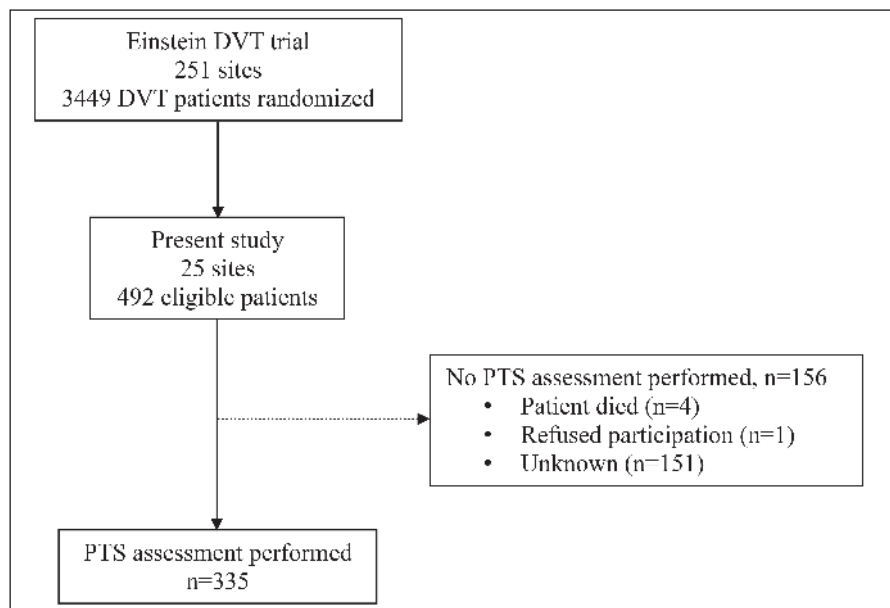


Figure 1: Study profile. DVT, deep-vein thrombosis; PTS, post-thrombotic syndrome.

The baseline characteristics of the 336 recruited patients are shown in ► Table 1. The mean age was 58 ± 16 years, mean body weight of 84 ± 18 kg and 197 (59%) subjects were male. Of the patients treated with rivaroxaban 101 (62%) had an idiopathic DVT compared to 114 (66%) in the enoxaparin/VKA group. In 92 (57%) rivaroxaban patients, the location of the index DVT was in the femoral vein or more proximal vs 117 (67%) in the enoxaparin/VKA patients. The median overall duration of anticoagulation was seven months (interquartile range [IQR] 6–26), six months (IQR 6–18) in the rivaroxaban and 12 months (IQR 6–51) in the enoxaparin/VKA group.

Assigned treatment and compliance

In total, 336 patients were included of whom 162 (48%) had been treated with rivaroxaban and 174 (52%) with enoxaparin/VKA. Compliance to assigned treatment was >80% in 153 (94%) rivaroxaban-treated patients vs 169 (97%) enoxaparin/VKA-treated patients. The INR was 21% of the time below 2 and 79% of the time 2 or higher in the enoxaparin/VKA group.

Follow-up

The median follow-up after index DVT was 57 months (IQR 48–64, ► Table 1). In 39 patients the follow-up was less than 24 months (► Figure 2). Eight patients with a follow-up less than 24 months developed PTS; four patients were treated with rivaroxaban and four were treated with enoxaparin/VKA. Twenty-three patients with a follow-up of less than 24 months had not developed PTS at the end of the follow-up; 13 were treated with rivaroxaban and 10 with enoxaparin/VKA. Another eight patients with a follow-up of less than 24 months died within the 24 months without developing PTS; four were treated with rivaroxaban and four were treated with enoxaparin/VKA.

PTS

The cumulative incidence of PTS at 60 months follow-up was 29% in the rivaroxaban group and 40% in the enoxaparin/VKA group (unadjusted HR 0.71, 95% CI: 0.48–1.03, $p=0.07$, ► Figure 3 and ► Table 2). The HR for PTS development in the rivaroxaban group was 0.76 (95% CI: 0.51–1.13, $p=0.18$, ► Figure 3) after adjustment for age, gender, BMI, previous VTE, ipsilateral recurrent DVT, extent of index DVT, idiopathic DVT, duration of anticoagulant treatment, compliance to assigned study medication, use of ECS and presence of active malignancy. Of the rivaroxaban-treated patients five (11%) developed severe PTS compared to six (9%) enoxaparin/VKA treated-patients (► Table 2).

Confirmed symptomatic recurrent VTE and death

The rates of symptomatic recurrent VTE and death during follow-up were similar in both groups (► Table 2). Recurrent VTE occurred in 34 (21%) patients treated with rivaroxaban and in 29 (17%) patients treated with enoxaparin/VKA. Death occurred in 10 (6%) patients treated with rivaroxaban vs 16 (9%) patients treated with enoxaparin/VKA.

Discussion

This is the first study that assessed the PTS incidence in patients treated with rivaroxaban vs enoxaparin/VKA. Our results showed that rivaroxaban-treated patients may have a lower risk of developing PTS as compared with enoxaparin/VKA-treated patient. The PTS risk reduction observed in the rivaroxaban group as compared to the enoxaparin/VKA group was not statistically significant but there was a trend towards a beneficial effect of rivaroxaban.

Characteristic	Rivaroxaban (n=162)	Enoxaparin/VKA (n=174)	Total (N=336)
Mean age, year – no. (± SD)	57 (± 16)	58 (± 16)	58 (± 16)
< 65 years	102 (63%)	99 (57%)	201 (60%)
Gender, male – no. (%)	91 (56%)	106 (61%)	197 (59%)
Weight, mean (± SD) kg	83 (± 19)	84 (± 17)	84 (± 18)
BMI, mean (± SD) kg/m	28(± 5)	28 (± 5)	28 (± 5)
Active malignancy at randomisation – no. (%)	8 (5%)	6 (3%)	14 (4%)
CrCL, mean (SD) ml/min	102 (± 39)	98 (± 37)	100 (± 38)
History of VTE	31 (19%)	36 (21%)	67 (20%)
Cause of DVT – no. (%)			
Idiopathic	101 (62%)	114 (66%)	215 (64%)
Provoked	61 (38%)	60 (35%)	121 (36%)
Location of index DVT – no. (%)			
Femoral vein or more proximal	92 (57%)	117 (67%)	209 (62%)
Popliteal vein or more distal	70 (43%)	57 (33%)	127 (38%)
Median duration of oral anticoagulant treatment – months (IQR)	6 (6–18)	12 (6–51)	7 (6–26)
The median duration of study medication – months (IQR)	6 (6–7)	6 (6–8)	6 (6–8)
≥80% compliance to assigned treatment – no. (%)	153 (94%)	169 (97%)	321 (96%)
Time INR <2	-	21%	-
Time INR 2–3		65%	
Confirmed ECS use – no. (%)	111 (69%)	134 (80%)	245 (73%)
Follow-up time – months (IQR)	58 (46–64)	57 (49–65)	57 (48–64)

Abbreviations: VKA, vitamin K antagonists; SD, standard deviation; BMI, body mass index; CrCL, Creatinin Clearance; VTE, venous thromboembolism; DVT, deep-vein thrombosis; IQR, interquartile range; INR, International Normalized Ratio. †femoral vein or more proximal vs popliteal vein or more distal.

Table 1: Baseline characteristics.

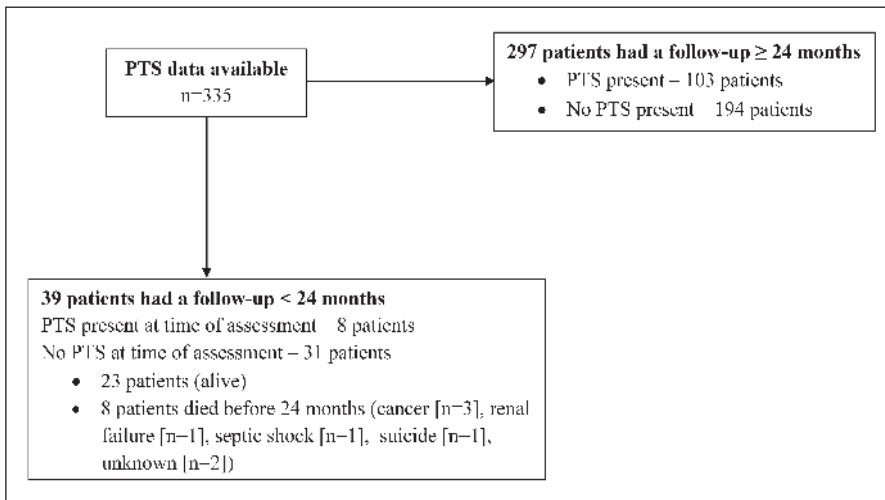


Figure 2: Follow-up less than 24 months vs more than 24 months. PTS, post-thrombotic syndrome.

Suboptimal quality of coagulation might cause inadequate clot resolution and consequently increase venous obstruction and valve damage leading to venous hypertension and ultimately PTS. During the Einstein DVT trial, enoxaparin/VKA patients were 21% of the time below the therapeutic range (INR 2–3) and more than 90% of the patients in both rivaroxaban and enoxaparin/VKA-treated patient had a compliance rate of $\geq 80\%$. This raises the question whether the TTR and compliance in the Einstein DVT trial can be translated to daily practice. It is known that patients treated with VKA and monitored in a community setting have a lower adherence than patients in a randomised control trial setting (10, 11). Considering that reduced treatment burden and regimen complexity are associated with better compliance, rivaroxaban patients might have a better adherence in clinical practice and thereby contributing to better long term clinical outcomes like PTS, especially in settings where INR control is suboptimal (15).

In our study, 31 (9%) patients had a follow-up of less than 24 months. Hypothetically, these patients could develop PTS if the follow-up was sufficient. However, it is unlikely that we underestimated the overall PTS incidence or the PTS incidence in one of the treatment arms, since the cumulative incidence of PTS in our study was similar to previous studies and the patients with a short follow-up were equally distributed between both treatment arms (4, 16, 17). In 156 patients we were not able to perform a PTS assessment, as the number of patients in the rivaroxaban and enoxaparin/VKA group were similar we deem it unlikely that this affected the PTS outcome in the two groups.

One of our study limitations is the open-label design of the Einstein DVT trial. Since the Villalta scale comprises five subjective symptoms recall bias cannot be ruled out. Patients' expectations could have affected the reporting of the symptoms. Observation bias could not be completely excluded. However, as the study investigators were instructed to proceed in a standardised way by using a predefined questionnaire without enquiring about the drugs received in the initial treatment of the DVT episode obser-

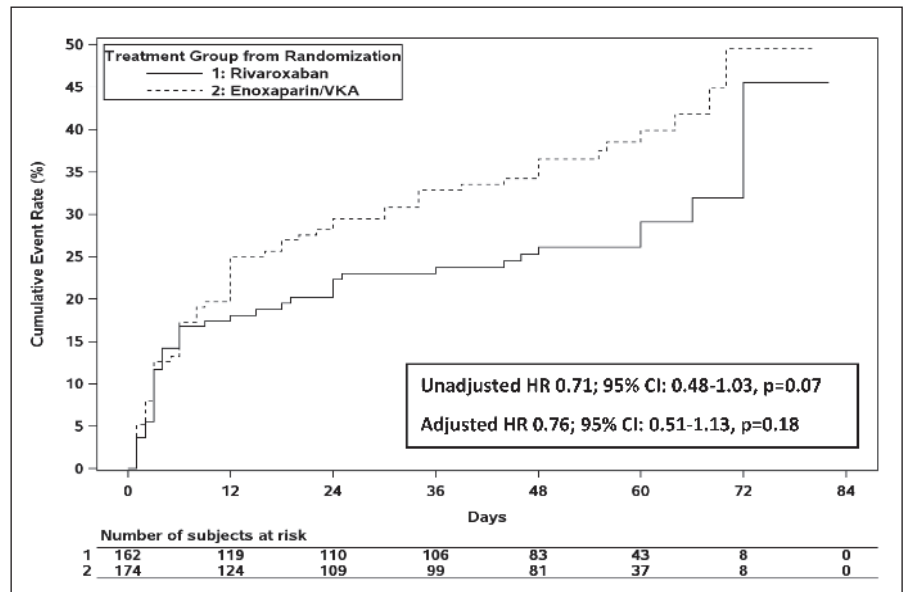
Table 2: Outcomes by treatment group.

	Rivaroxaban (n=162)	Enoxaparin/VKA (n=174)
Villalta severity category		
Mild and moderate	40 (89%)	60 (91%)
Severe	5 (11%)	6 (9%)
Ipsilateral leg ulcer	1 (2%)	4 (6%)
Recurrent VTE	34 (21%)	29 (17%)
Death	10 (6%)	16 (9%)

Abbreviations: VKA, vitamin K antagonists; ECS, elastic compression stocking; VTE, venous thromboembolism.

vation bias was minimized. Moreover, the development of PTS was defined according to the internationally recommended Villalta scale. Nonetheless, PTS diagnosis is based on the subjective symptoms reported by patients and the observation of the investigator, therefore observation bias could not be completely excluded. Moreover, recall bias could be present in this study since at a median follow-up time of 57 months patients were asked when the PTS complaints started. Another limitation is the inability to recruit all patients who were enrolled in the Einstein DVT trial. However, our subgroup is representative of the Einstein DVT population as the baseline characteristics were similar in the two cohorts. Furthermore, the risk of selection bias within the centres was reduced to a minimum as all Einstein DVT centres were invited to participate in this sub-study and all centres that could participate in this study tried to evaluate all Einstein DVT patients. On average, 75% of the Einstein DVT patients per centre were included in the current sub-study. Due to the small sample size sensitivity analyses with TTR stratification could not be performed. Nevertheless, regression analysis showed that compliance of less than 50% to assigned study medication is a risk factor for PTS development.

Figure 3: Cumulative incidence of the post-thrombotic syndrome in patients treated with rivaroxaban and patients treated with enoxaparin/VKA(Kaplan-Meier). VKA, vitamin K antagonists; HR, hazard ratio; CI, confidence interval.



What is known about this topic?

- PTS is a common complication of DVT
- DOACs are as effective as vitamin K antagonists in the treatment of DVT.
- No data are available on the effect of DOACs on the long-term outcome PTS.

What does this paper add?

- Treatment of acute DVT with rivaroxaban appeared to be associated with a lower risk of PTS compared to enoxaparin/VKA treatment.
- The potential effect on reducing PTS deserves evaluation in a large randomised trial.

Worse compliance exposes patients to inadequate treatment and thereby supporting the hypothesis that inadequate treatment is a risk factor for PTS development.

The median duration of treatment was longer in enoxaparin/VKA-treated patients than in rivaroxaban patients. This is likely due to the fact that continuation of treatment with rivaroxaban was not possible because the drug was not approved for the treatment of VTE at the time of the conduct of the Einstein study. However, this is a conservative bias. Furthermore, as post-randomisation variables could affect the outcome of PTS we deliberately chose to include these variables in our Cox proportional hazard model.

Conclusion

Treatment of acute DVT with rivaroxaban was associated with a numerically lower but statistically non-significant risk of PTS compared to enoxaparin/VKA treatment. The potential effect on reducing PTS deserves evaluation in a large randomized trial.

Author contributions

Y.W. Cheung: collecting data, analysis and interpretation of data, writing the manuscript. S. Middeldorp: interpretation of data, critically revising the manuscript. M.H. Prins: interpretation of data, critically revising the manuscript. A.F. Pap: analysis of data, critically revising the manuscript. A.W.A. Lensing: critically revising the manuscript. A.J. ten Cate-Hoek: providing clinical data, critically revising the manuscript. S. Villalta: critically revising the manuscript. M. Milan: critically revising the manuscript. J. Beyer-Westendorf: collecting data, critically revising the manuscript. P. Verhamme: collecting data, critically revising the manuscript. R.M. Bauersachs: collecting data, critically revising the manuscript. P. Prandoni: concept and study design, collecting data, interpretation of data, critically revising the manuscript

Conflicts of interest

P. Verhamme has received research support from Boehringer Ingelheim and Bayer Healthcare; and honoraria from Boehringer Ingelheim, Bayer Healthcare, BMS/Pfizer, Daiichi-Sankyo, Leo Phar-

ma, Portola. S. Middeldorp has received grants and speaker fees from GSK; received speaker fees and served on the advisory board of Bayer Healthcare; has received grants, and served on the advisory board of BMS/Pfizer, and Daiichi-Sankyo; has received speaker fees from Boehringer Ingelheim; grants from Sanquin and Aspen. A. W. A. Lensing and A. F. Pap are employees of Bayer Healthcare. R. M. Bauersachs has received honoraria from Bayer Healthcare, Boehringer Ingelheim, and BMS/Pfizer. J. Beyer-Westendorf has received honoraria from Bayer Healthcare, Boehringer Ingelheim, Daiichi-Sankyo, Leo Pharma, BMS/Pfizer; research support from Bayer Healthcare, Boehringer Ingelheim, and BMS/Pfizer. None of the other authors declares any conflicts of interest.

References

1. Prandoni P, Kahn SR. Post-thrombotic syndrome: prevalence, prognostication and need for progress. *Br J Haematol* 2009; 145: 286–295.
2. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the post-thrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med* 2008; 149: 698–707.
3. Prandoni P, Villalta S, Bagatella P, et al. The clinical course of deep-vein thrombosis. Prospective long-term follow-up of 528 symptomatic patients. *Haematologica* 1997; 82: 423–428.
4. Brandjes DP, Buller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997; 349: 759–762.
5. Pesavento R, Villalta S, Prandoni P. The postthrombotic syndrome. *Intern Emerg Med* 2010; 5: 185–192.
6. Strandness DE, Langlois Y, Cramer M, et al. Long-term sequelae of acute venous thrombosis. *J Am Med Assoc* 1983; 250: 1289–1292.
7. Prandoni P, Lensing AW, Prins MH, et al. The impact of residual thrombosis on the long-term outcome of patients with deep venous thrombosis treated with conventional anticoagulation. *Semin Thromb Hemost* 2015; 41: 133–140.
8. The Columbus Investigators. Low-molecular-weight heparin in the treatment of patients with venous thromboembolism. *N Engl J Med* 1997; 337: 657–662.
9. Chitsike RS, Rodger MA, Kovacs MJ, et al. Risk of post-thrombotic syndrome after subtherapeutic warfarin anticoagulation for a first unprovoked deep vein thrombosis: results from the REVERSE study. *J Thromb Haemost* 2012; 10: 2039–2044.
10. Mearns ES, Kohn CG, Song JS, et al. Meta-analysis to assess the quality of international normalized ratio control and associated outcomes in venous thromboembolism patients. *Thromb Res* 2014; 134: 310–319.
11. van Dongen CJ, Prandoni P, Frulla M, et al. Relation between quality of anticoagulant treatment and the development of the postthrombotic syndrome. *J Thromb Haemost* 2005; 3: 939–942.
12. Hull RD, Liang J, Townshend G. Long-term low-molecular-weight heparin and the post-thrombotic syndrome: a systematic review. *Am J Med* 2011; 124: 756–765.
13. The Einstein Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; 363: 2499–2510.
14. Kahn SR, Partsch H, Vedantham S, et al. Subcommittee on Control of Anticoagulation of the Scientific and Standardisation Committee of the International Society on Thrombosis and Haemostasis. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardisation. *J Thromb Haemost* 2009; 7: 879–883.
15. Barbosa CD, Balp MM, Kulich K, et al. A literature review to explore the link between treatment satisfaction and adherence, compliance, and persistence. *Patient preference and adherence* 2012; 6: 39–48.
16. Prandoni P, Lensing AW, Prins MH, et al. Below-knee elastic compression stockings to prevent the post-thrombotic syndrome: a randomized, controlled trial. *Ann Intern Med* 2004; 141: 249–256.
17. Kahn SR, Shapiro S, Wells PS, et al. Compression stockings to prevent post-thrombotic syndrome: a randomised placebo-controlled trial. *Lancet* 2014; 383: 880–888.