

Presence of Residual Venous Thrombus at Warfarin Withdrawal: a Predictor for Recurrence after a First Episode of Symptomatic Provoked Proximal Deep Venous Thrombosis in Thai Population?

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ABSTRACT

Objective: To assess the risk for venous thromboembolism (VTE) recurrence by presence of residual venous thrombus (RVT) at warfarin withdrawal following symptomatic first provoked proximal DVT.

Methods: Medical records of 45 consecutive patients with symptomatic first provoked proximal DVTs who had undergone warfarin surveillance for ≥ 3 months were reviewed retrospectively. Altogether, 22 patients discontinued anticoagulation after ≥ 3 months regardless of duplex ultrasonography results of RVT diagnosed by compression ultrasonography. Another 23 patients discontinued anticoagulation after the RVT disappeared. Primary outcome was recurrent VTE.

Results: Four of the 45 patients experienced recurrent VTE (8.89%), including 2 (9.00%) of 22 patients who had discontinued anticoagulant regardless of duplex ultrasonography results and 2 (8.70%) of 23 patients who discontinued anticoagulation after RVT disappearance ($p = 0.963$). All of the recurrent VTE were recurrent DVT.

Conclusion: RVT at warfarin withdrawal was not a predictor for recurrence VTE following a first symptomatic provoked proximal DVT.

Keywords: Deep vein thrombosis; duplex ultrasound; VTE management (Siriraj Med J 2019; 71: 486-490)

INTRODUCTION

Because the recurrent rate of a proximal deep venous thrombosis (DVT) of the leg that had been provoked by surgery or by nonsurgical transient risk factors is high during the first 3 months, the American College of Chest Physicians recommends treatment with anticoagulation for 3 months after the diagnosis.¹ In patients with provoked proximal DVTs, the estimated 5-year cumulative risk

of recurrent venous thromboembolism (VTE) after discontinuing anticoagulant treatment was reported to be 3% for surgery-provoked VTEs and 15% for VTEs provoked by nonsurgical, reversible risk factors.² The risk of recurrence of a provoked DVT is considered low enough not to warrant prolonged anticoagulation, although the risk of recurrence is not negligible in the long term. In addition, the risk of recurrence associated

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with provoked VTE varies among reports. Patients with VTE due to reversible risk factors have a 10-year cumulative recurrence rate of 22.5%: surgically provoked VTE 11.4%, patients with medical illness 31.8%, women with pregnancy-related or hormonal therapy 20.3%.³

The presence of residual venous thrombus (RVT) has been associated with an increased risk of thrombotic recurrence in patients with provoked venous thrombosis. Recurrent DVT occurs not only in previously thrombosed veins but also at other sites.⁴ RVT may indicate an underlying prothrombotic state for the initial DVT.⁴

The role of RVT as a predictor for a recurrent proximal provoked DVT remains unclear. The DACUS study showed that RVT was predictive of recurrence of a provoked DVT. The AESOPUS study showed that the advantage of prolonging warfarin treatment on the basis of persistent RVT was more significant after unprovoked DVTs than provoked DVTs.⁵ Methods for measuring RVTs in the AESOPUS and DACUS studies differed, however, which might have affected the results of those studies.^{4,5}

There are no reported clinical studies on the relation between RVT and the risk of recurrent DVT after a first provoked proximal DVT in an Asian population. The specific objective of the study was to assess the risk for DVT recurrence conferred by RVT after anticoagulant withdrawal in a cohort of consecutive Asian patients with symptomatic provoked proximal DVT.

MATERIALS AND METHODS

This study is based on a retrospective review of cohort data. Consecutive patients attending a vascular surgery clinic because of a first episode of symptomatic proximal provoked DVT of a lower extremity who were on warfarin anticoagulation for at least 3 months between January 2011 and December 2013 were included. Patients with unprovoked DVT requiring indefinite anticoagulation, patients with antiphospholipid syndrome, and those with cancer were excluded.

Provoked DVT was defined as a DVT caused by reversible risk factors, including immobilization for > 30 min during surgery with general anesthesia, history of trauma during the previous 3 months, current use of oral contraception or hormonal therapy, recent fracture or plaster casting of a leg, confinement to bed for 3 days during the previous 3 months, pregnancy or puerperium, and/or prolonged travel (> 4 h) during the previous 4 weeks.

After at least 3 months of treatment, some of the vascular surgeons stopped warfarin following the American College of Chest Physicians Guideline, neither duplex

ultrasonography (DUS) nor the D-dimer test was performed in these patients. Although, some vascular surgeons prefer to evaluate the patients with compression ultrasonography and stopped warfarin after the patients were free of residual vein thrombus (RVT). The examination was performed with the patient in supine position and the affected leg externally rotated and slightly flexed at the knee. CUS images were obtained in transverse sections. Lumen compressibility was then evaluated by gentle pressure exerted using the ultrasound probe. The RVT diameter was determined by measuring the distance between the anterior and posterior walls of the vein before and after compression with the ultrasound probe.

Measurements of the common femoral vein diameter were obtained 1 cm below the inguinal ligament. Those of the popliteal vein were obtained at the most prominent crease in the mid-popliteal fossa.⁴ RVT was evaluated following the techniques described in the DACUS and AESOPUS studies.^{4,5} In the DACUS study, the percentage of the RVT was the ratio between the vein's diameter before and during compression.⁴ Patients were considered not to have an RVT when a persisting thrombus was $\leq 40\%$ of the venous measurement. Patients were considered to have an RVT when a persisting thrombus of $> 40\%$ was present in at least one of the two examined venous segments.⁴ In the AESOPUS study, RVT was defined as being present if the vein's transverse diameter was > 2 mm at maximum compression or absent if the transverse diameter was ≤ 2 mm.⁵

In this study, an RVT was considered present when the RVT measured by at least one technique was deemed positive. An RVT was considered absent when both techniques produced negative results.

In patients who performed to measure RVT, warfarin was stopped after no RVT was found. Patients in whom RVT was considered present continued to receive warfarin. These patients underwent CUS evaluation every 3 months until the RVT had disappeared. CUS was performed whenever a DVT was suspected to have recurred.

The study outcome was recurrent VTE. In cases of recurrence, CUS results were compared with those of the previous examination. Recurrent DVT was diagnosed if a previously fully compressible segment (contralateral or ipsilateral) was no longer compressible or there was a ≥ 4 mm increase in the diameter of the residual thrombus during compression. In difficult cases, CUS was repeated (after 5-7 days) or computed tomography venography was performed. The lower limb veins were evaluated using a GE LOGIC 9 system (GE Healthcare, Milwaukee, WI, USA) with 5- to 10-MHz linear transducers. Recurrent PE (pulmonary embolism) was diagnosed if clinical

suspicious, with confirmation by computed tomography pulmonary angiography.

The ethics committee of the Siriraj Institutional Review Board approved this study (Si 002/2019).

For the statistical analyses, continuous variables are described as the mean and standard deviation (SD) or the median and range, as appropriate. Categorical variables are described as the number and percentage. The t-test or Mann-Whitney U test was used to compare continuous variables, as appropriate. The χ^2 test or Fisher's exact test was used to compare categorical variables. The Kaplan-Meier method was used to estimate the recurrence-free survival curve and the recurrence rate. Cox regression analysis was used to investigate the association between RVT status (assessed by DUS) and recurrence of DVT. Those associations were evaluated using the hazard ratio and corresponding 95% confidence intervals. All p values were two-tailed with a significance level of 0.05. Data were recorded and analyzed using PASW Statistics 18.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

There were 45 patients with provoked DVT in this study. There were 35 (77.78%) women and 10 (22.22%) men. Twenty-two patients with provoked DVTs discontinued the anticoagulant after ≥ 3 months of treatment without DUS evaluation. The other 23 patients discontinued it after the RVT had disappeared. The mean age was 60.0 ± 18.9 years in patients who discontinued anticoagulant without DUS and 63.9 ± 19.4 years in patients who discontinued it after RVT disappearance. The mean follow-up time was 121.2 ± 40.2 weeks (range 50.0-207.0 weeks) for patients who discontinued the anticoagulant without DUS and 118.3 ± 38.8 weeks (range 52-243 weeks) for patients who discontinued it after RVT disappearance. Factors that provoked the DVT are shown in Table 1.

During the follow-up period, four recurrent DVTs (8.89%) were recorded from among 45 patients with a provoked DVT. Two of these patients (9.00%) had discontinued anticoagulant without DUS and two (8.70%) had discontinued anticoagulant after RVT disappearance ($p = 0.963$) (Fig 1). There was no recurrent PE in this study.

TABLE 1. Demographic data from Asian patients with their first symptomatic provoked DVT who discontinued anticoagulation.

| | Patients discontinued anticoagulant | | P-value |
|------------------------------|-------------------------------------|--------------------------|---------|
| | Without DUS (n = 22) | After no RVT (n = 23) | |
| Age | | | |
| Mean \pm SD, year | 60.0 \pm 18.9 | 63.9 \pm 19.4 | 0.502 |
| Sex | | | |
| Female, n (%) | 18 (81.8) | 17 (79.9) | 0.722 |
| Anticoagulant duration, week | | | |
| Median (range) | 30.5 (13.4-87.0) | 32.9 (13.0-75.7) | 0.901 |
| Mean \pm SD | 36.9 \pm 21.4 | 36.6 \pm 18.8 | |
| Provoked factors | | | |
| Surgery/Trauma | 11 (50) | 11 (47.8) | |
| Immobilization/Illness | 7 (31.8) | 9 (39.1) | |
| Hormonal used | 2 (9.1) | 2 (8.7) | 0.520 |
| Prolonged travel | 0 (0) | 1 (4.3) | |
| Pregnancy | 2 (9.1) | 0 (0) | |

Abbreviations: DVT = deep vein thrombosis; DUS = Duplex ultrasonography; RVT = residual vein thrombus

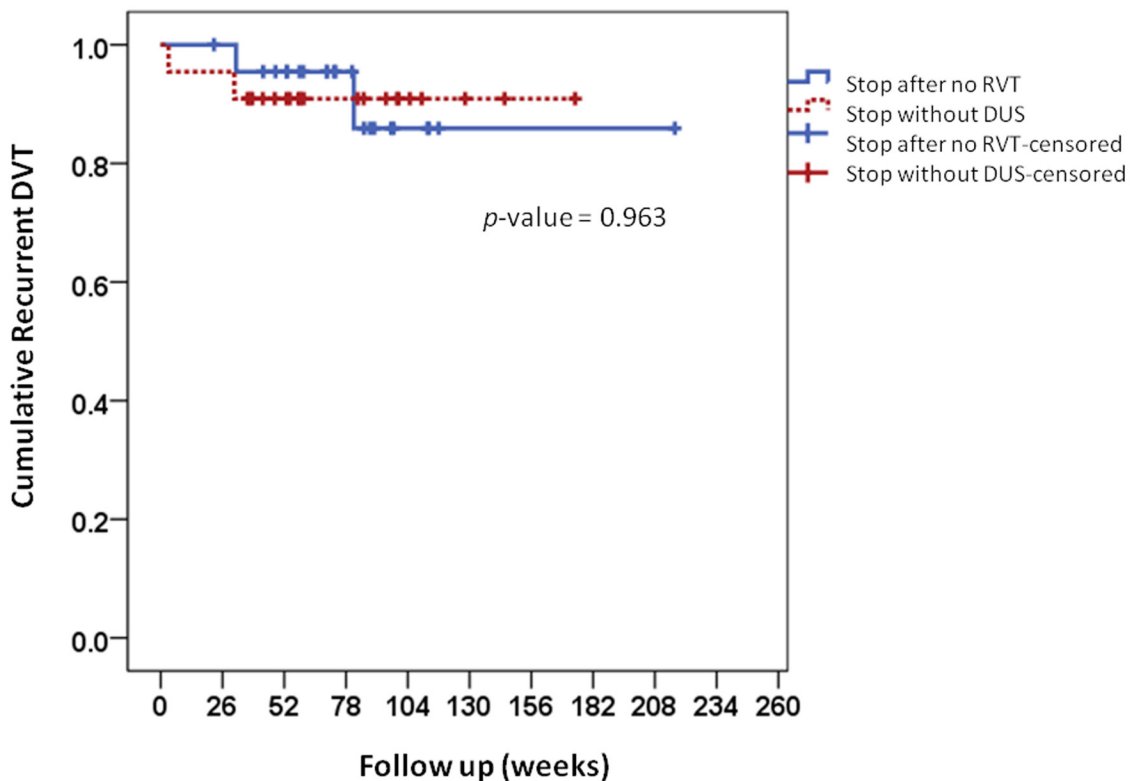


Fig 1. Kaplan-Meier curves for recurrent deep vein thrombosis (DVT) in patients who stopped taking an anticoagulant (warfarin) after no residual vein thrombosis (RVT) was detected and those who stopped the anticoagulant without duplex ultrasonography (DUS) confirmation.

DISCUSSION

Patients who develop a DVT associated with a transient surgical procedure (surgically provoked DVT) have a low rate of recurrence, estimated at 0.7% per year for the 2 years after stopping anticoagulation therapy.⁶ Patients who develop a non-surgically provoked DVT (e.g., due to immobilization, pregnancy, use of estrogen-containing contraception) have a slightly higher risk of recurrence, estimated at 4.2% per year for the same 2-year period after discontinuing anticoagulation therapy.⁶ The risk of recurrence after the appearance of a provoked DVT is considered low enough not to warrant prolonged anticoagulation, although the risk of recurrence is not negligible in Asian populations.²

In our study of Thai patients with provoked DVTs, the annual risk of recurrence after warfarin withdrawal was 6.77%. This risk was somewhat higher than the reported annual risk of recurrence in subjects with provoked DVTs in Caucasian populations.²

DVTs provoked by a major reversible risk factor, such as recent surgery, had a low risk of recurrence. Although the risk of recurrence in patients with DVTs provoked by a nonsurgical trigger was higher than that

for patients with DVTs provoked by surgery, the risk was still low.²

Provoked DVTs in a Thai population were at a sufficiently low risk of recurrence to recommend stopping anticoagulants at 3 months. If the provoking factor is incompletely resolved, however, it is appropriate to treat the patients longer than 3 months.⁹

Our results were in line with those of the AESOPUS study and a study by Cosmi et al. in which an RVT was not predictive for recurrence after provoked DVT.^{5,7} Our results, however, were different from those of the DACUS study in which RVT was predictive of recurrence following a provoked DVT.⁴

The reproducibility of RVT measurements could be an issue across studies because of the lack of widely accepted criteria for defining vein recanalization.⁸ For example, the AESOPUS study adopted the method of Prandoni et al.,^{3,5} whereas the RVT in the DACUS study was defined as a residual thrombus occupying more than 40% of the vein's area calculated in the absence of compression.^{4,5} Although measurements of RVT in the AESOPUS and DACUS studies were different, which could affect the results of the study, our center uses

both techniques to define the presence of an RVT, with a positive result from at least one of them indicating the need to continue anticoagulation.

Even though the presence of an RVT was not a risk factor for recurrence in Thai patients experiencing their first symptomatic provoked proximal DVT at the time of warfarin withdrawal, DUS should be performed to define the baseline characteristics of the vein's lumen for detecting a new thrombus in the future.

The small number of patients limits the statistical power of this study. Larger series are needed to clarify the relation between the presence of an RVT and recurrence of a DVT in Asian patients with a first episode of symptomatic provoked proximal DVT.

CONCLUSION

The presence of an RVT at the time of warfarin withdrawal was not a predictor for recurrence of the VTE in Thai patients with a first episode of symptomatic provoked proximal DVT.

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