

# Residual Venous Thrombosis as a Predictive Factor of Recurrent Venous Thromboembolism

Paolo Prandoni, MD, PhD; Anthonie W.A. Lensing, MD, PhD; Martin H. Prins, MD, PhD; Enrico Bernardi, MD; Antonio Marchiori, MD; Paola Bagatella, MD; Michela Frulla, MD; Laura Mosenza, MD; Daniela Tormene, MD; Andrea Piccioli, MD; Paolo Simioni, MD, PhD; and Antonio Girolami, MD

**Background:** The optimum duration of anticoagulant therapy after an episode of deep venous thrombosis (DVT) is controversial. Contributing to the controversy is uncertainty about whether residual venous thrombosis, as assessed by repeated ultrasonography over time, increases the risk for recurrent thromboembolism.

**Objective:** To determine the risk for recurrent thromboembolism in patients who have persistent residual thrombosis compared with patients who have early vein recanalization.

**Design:** Prospective cohort study.

**Setting:** A university hospital in Padua, Italy.

**Patients:** 313 consecutive symptomatic outpatients with proximal DVT who received conventional short-term anticoagulation.

**Measurements:** Ultrasonographic assessment of the common femoral and popliteal veins was performed 3 months after acute DVT in all patients and at 6, 12, 24, and 36 months in patients

found to have residual venous thrombosis. Veins were considered recanalized if they were 2.0 mm or less in diameter on a single test or 3.0 mm or less in diameter on two consecutive tests. Recurrent thromboembolism was assessed during a 6-year period.

**Results:** The cumulative incidence of normal results on ultrasonography was 38.8% at 6 months, 58.1% at 12 months, 69.3% at 24 months, and 73.8% at 36 months. Of 58 recurrent episodes, 41 occurred while the patient had residual thrombosis. The hazard ratio for recurrent thromboembolism was 2.4 (95% CI, 1.3 to 4.4;  $P = 0.004$ ) for patients with persistent residual thrombosis versus those with early vein recanalization.

**Conclusions:** Residual venous thrombosis is an important risk factor for recurrent thromboembolism. Ultrasonographic assessment of residual venous thrombosis may help clinicians modify the duration of anticoagulation in patients with DVT.

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For author affiliations, see end of text.

Patients with deep venous thrombosis (DVT) of the lower extremities are usually treated with an initial course of unfractionated or low-molecular-weight heparin followed by at least 3 months of oral anticoagulant therapy. This treatment regimen reduces the risk for short-term thromboembolic complications to approximately 5% (1, 2). Although the short-term outcome of this disease has been extensively documented, only a few studies have addressed the risk for late recurrent venous thromboembolism. These studies suggest that this risk persists for years and is related to patient characteristics at initial presentation (1, 2). It has been documented that patients with continuous risk factors, such as cancer or the antiphospholipid antibody syndrome, and those with idiopathic thrombosis have a two- to threefold increased risk for recurrence compared with patients who developed a thrombotic event in association with a transient risk factor (3–5). As a consequence, longer anticoagulant treatment (up to several years) has been evaluated in patients with idiopathic DVT, with the aim of decreasing recurrences in patients with idiopathic DVT (6, 7). Although long-term anticoagulant therapy is effective in preventing recurrences, it is inconvenient and carries a risk for bleeding (8–11). It would be beneficial to further improve our ability to identify patients who are at higher risk for recurrent events.

The absolute incidence of recurrent venous thromboembolism decreases over time (3, 5). Residual thrombus mass also decreases over time in patients with proximal venous thrombosis, according to recent studies that used

repeated ultrasonographic imaging (12, 13). If vein recanalization indicates a lower risk for recurrent disease, ultrasonographic imaging might help clinicians adjust the duration of oral anticoagulant therapy on an individual basis in patients who have had an episode of DVT. To estimate whether the risk for recurrent venous thromboembolism is higher in the presence of residual thrombosis, we performed repeated ultrasonography in a large number of patients with proximal venous thrombosis who were followed prospectively for up to 6 years.

## METHODS

### Study Design

We performed a prospective cohort follow-up study to assess the potential effect of residual venous thrombosis on the risk for recurrent venous thromboembolism in patients with a first episode of symptomatic DVT. The institutional review board of Padua University, Padua, Italy, approved the study.

### Inception Cohort

All consecutive outpatients who were referred to the Department of Medical and Surgical Sciences of the University of Padua between 1993 and 1996 for clinical suspicion of a first episode of DVT and who met inclusion criteria were eligible. Inclusion criteria were proximal venous thrombosis on compression ultrasonography, absence of diseases requiring indefinite anticoagulation (such as atrial fibrillation, active cancer, chronic medical illnesses,

**Context**

Doctors typically treat deep venous thrombosis with anticoagulants for 3 to 6 months to prevent recurrence. Patients at high risk for recurrence may benefit from longer treatment. Can we identify them with ultrasonography that detects persistent thrombosis?

**Contribution**

Three hundred thirteen patients with deep venous thrombosis had ultrasonography every 6 to 12 months for 3 years. Recurrent thromboembolism, assessed over 6 years, was more frequent among those showing persistent residual thrombosis rather than early vein recanalization.

**Implications**

We now need trials that evaluate prolonged anticoagulation in patients with and without residual thrombosis to see whether tailoring treatment on the basis of serial ultrasonography is beneficial.

—The Editors

or other permanent risk factors for venous thrombosis), life expectancy of more than 6 months, and ability to return to the study center for follow-up visits. Eligible patients received conventional anticoagulation (full doses of unfractionated or low-molecular-weight heparin followed by 3 months of oral anticoagulant therapy). Patients who completed the initial 3 months of treatment without a recurrent thrombotic episode and who gave informed consent were recruited for the current study.

On the basis of laboratory results and clinical characteristics, patients were divided into three categories: those who had thrombophilia, those who had secondary DVT, and those who had idiopathic DVT. Tests for thrombophilia (antithrombin, protein C or S defect, factor V Leiden mutation, prothrombin G20210 gene mutation, and lupus-like anticoagulants) were performed before anticoagulation was started or at least 2 weeks after its conclusion. On the basis of test results, patients were categorized as being with or without thrombophilia. Patients without thrombophilia were further classified as having idiopathic DVT or DVT secondary to transient risk factors, according to a standardized form for clinical data collection completed at referral. Secondary thrombosis was defined as that occurring during pregnancy or childbirth; during estrogen use for contraception or hormone replacement therapy (ongoing or interrupted for <1 month); or after recent trauma, fracture, or surgery (within <3 months). If thrombophilia screening could not be performed, patients were classified as having idiopathic or secondary DVT on the basis of clinical presentation.

**Ultrasonographic Assessments**

The first ultrasonographic assessment was performed 3 months after the initial event. Patients found to have re-

sidual thrombosis were scheduled for repeated assessment 6, 12, 24, and 36 months after the initial event. Independent experts who were unaware of patients' clinical details or of previous ultrasonographic findings performed assessments according to a standardized procedure. Only the common femoral vein at the saphenofemoral junction and the popliteal vein in the midpopliteal fossa were scanned for residual venous thrombosis. Vein compression was performed in the transverse plane; vein diameter was measured during maximal compression and was expressed in millimeters. Veins were considered recanalized if they were 2.0 mm or less in diameter on a single test or 3.0 mm or less in diameter on two consecutive tests. This definition was based on ultrasonographic findings from a separate group of 145 patients with proven proximal DVT who were followed prospectively at our institution in the early 1990s; fewer than 2.0% of these patients developed recurrent thromboembolism in the 2 years after vein recanalization (12).

**Follow-up and Recurrent Venous Thromboembolism**

All recruited patients were instructed to interrupt oral anticoagulant therapy when they were included in the current study. Patients were followed to document the incidence of symptomatic recurrent DVT or pulmonary embolism. Patients were educated about the main signs and symptoms of recurrent venous thromboembolism and received a card with the telephone numbers of the thrombosis clinic. They were instructed to return to the study center if they noted clinical manifestations suggestive of recurrent venous thrombosis (edema, redness, tenderness, pain, or swelling) in either leg or suggestive of pulmonary embolism (dyspnea, chest pain, or tachycardia). Patients were also seen at the time of ultrasonographic assessments and were contacted at least twice yearly to ascertain whether signs and symptoms had occurred. If they had, patients were invited to come to the study center for additional diagnostic procedures.

Recurrent DVT was diagnosed by compression ultrasonography, followed by ascending phlebography in case of indeterminate findings, or a strong discrepancy between clinical suspicion and negative results on ultrasonography (14). Patients with suspected pulmonary embolism had ventilation-perfusion lung scanning, which was followed by pulmonary angiography if findings were inconclusive (15). Fatal pulmonary embolism was diagnosed on the basis of autopsy findings or the opinion of an independent physician.

**Statistical Analysis**

The first 3 months of initial anticoagulant treatment were not included in any of our analyses. For the remaining months, Kaplan-Meier estimates and 95% CIs were calculated to assess the risk for recurrent venous thromboembolism. Time-dependent multivariate Cox proportional hazards models were then used to calculate hazard ratios for recurrent venous thromboembolism in patients with

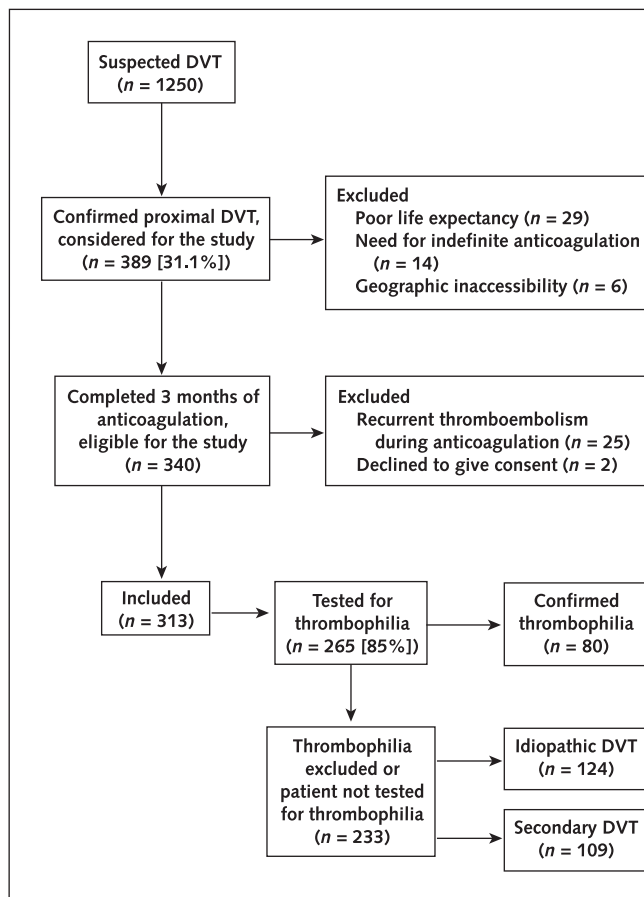
residual thrombosis versus those without. For this analysis, patients who did not have a recurrence were censored at the end of the available follow-up or at death. In addition, the clinical categorization of patients was evaluated by using two dummy variables to indicate the presence of idiopathic DVT or thrombophilia. Secondary thrombosis was therefore used as the reference group, and in each case, the duration of oral anticoagulant treatment was used as a time-dependent covariate. Finally, all of these variables, as well as age and sex, were introduced in a stepwise hierarchical Cox model (16, 17). The results of these analyses were expressed as risk ratios and 95% CIs. In addition, incidence density of recurrent venous thromboembolism (events per observation-year) was calculated for the various combinations of clinical characteristics. All calculations were performed by using SAS software, version 6.10 (SAS Institute, Inc., Cary, North Carolina).

## RESULTS

### Patients

Of 1250 patients who were referred for clinical suspicion of first DVT, 389 (31.1%) received a diagnosis of proximal venous thrombosis on compression ultrasonogra-

Figure 1. Flow diagram for inclusion of patients in the study.



DVT = deep venous thrombosis.

Table 1. Characteristics of the 313 Study Patients

Variable	Value
Men, n (%)	146 (46.6)
Mean age $\pm$ SD, y	59.5 $\pm$ 17.6
Screened for thrombophilia, n (%)	265 (84.6)
Thrombophilia, n	80
Factor V gene mutation	34
Prothrombin gene mutation	19
Protein S deficiency	6
Protein C deficiency	4
Lupus-like anticoagulants	6
Antithrombin deficiency	5
Combination of two abnormalities	6
Idiopathic thrombosis, n (%)	124 (39.6)
Secondary thrombosis, n (%)	109 (34.8)
Duration of anticoagulation, n (%)	
3 mo	248 (79.2)
6–12 mo	65 (20.8)*

\* In 19 of 80 patients with thrombophilia (23.7%), 26 of 124 patients with idiopathic thrombosis (21.0%), and 20 of 109 patients with secondary thrombosis (18.3%).

phy (Figure 1). Forty-nine of these 389 patients were excluded because of poor life expectancy ( $n = 29$ ), diseases requiring permanent anticoagulation ( $n = 14$ ), or inability to attend follow-up visits ( $n = 6$ ). Of the remaining 340 eligible patients, 25 developed a recurrent thromboembolic event during initial anticoagulation. Therefore, 315 patients completed an uneventful 3-month period of anticoagulation. Of these, 313 agreed to participate and were enrolled in the study.

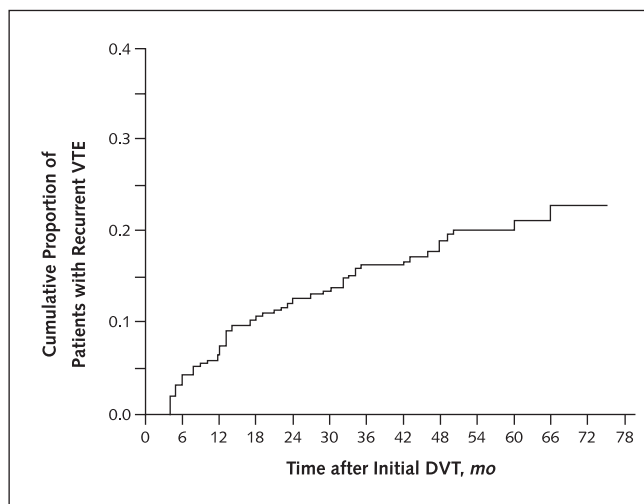
The main demographic and clinical characteristics of the study patients are presented in Table 1. Tests for thrombophilia were performed in 265 patients (85%), and 80 (30.2%) had positive results. One hundred nine patients had a thrombotic event associated with one or more triggering risk factors, and 124 had an idiopathic thrombotic event.

Although all patients had been instructed to stop anticoagulation after the initial 3-month period, 65 (20.8%) continued warfarin treatment for an additional 3 months ( $n = 27$ ) or an additional 6 months ( $n = 38$ ). Attending physicians decided to continue therapy on an individual basis, regardless of thrombophilia status or the results of ultrasonographic tests. As shown in Table 1, anticoagulation was continued for a few additional months in similar proportions of the three study groups (thrombophilic patients, patients with idiopathic thrombosis, and patients with thrombosis secondary to transient risk factors).

### Cumulative Incidence of Normal Results on Ultrasonography

The first ultrasonographic assessment, performed 3 months after the initial event, yielded normal results in 61 patients (19.5%). The cumulative incidence of normal ultrasonographic results was 38.8% at 6 months, 58.1% at 12 months, 69.3% at 24 months, and 73.8% at 36 months. This rate did not differ significantly between patients with and those without thrombophilia (risk ratio,

**Figure 2. Cumulative incidence of recurrent venous thromboembolism (VTE), excluding events that occurred during the initial 3-month period.**



DVT = deep venous thrombosis.

0.91 [95% CI, 0.64 to 1.29]) or between patients with idiopathic thrombosis and those with secondary thrombosis (risk ratio, 0.89 [CI, 0.65 to 1.22]).

### Recurrent Venous Thromboembolism

Of the 313 included patients, 110 presented during follow-up with clinically suspected recurrent venous thromboembolism; recurrent venous thromboembolism was confirmed in 58 (53%). In 44 patients, recurrences were thromboses involving a previously affected extremity ( $n = 19$ ) or the contralateral leg ( $n = 25$ ); the remaining 14 patients had pulmonary embolisms. Forty-one patients who experienced recurrences developed them while residual thrombosis was present. The cumulative incidence of recurrent thromboembolism was 4.2% of 296 patients at 6 months, 7.4% of 280 patients at 12 months, 12.7% of 258 patients at 24 months, 16.2% of 199 patients at 36 months, and 21.1% of 71 patients at 5 years (Figure 2). None of the 65 patients who continued warfarin treatment beyond the first 3 months developed thromboembolic recurrences while receiving anticoagulation.

Of the 58 patients who had recurrent events, 29 were in the thrombophilia group (29 of 80 patients [36.2%]), 20 were in the idiopathic DVT group (20 of 124 patients [16.1%]), and 9 were in the secondary thrombosis group (9 of 109 patients [8.3%]). Based on the Cox proportional hazards model, the hazard ratio for recurrent venous thromboembolism was 2.8 (CI, 1.5 to 5.0;  $P = 0.001$ ) in patients with idiopathic thrombosis and 3.3 (CI, 2.0 to 5.5;  $P = 0.001$ ) in patients with thrombophilia compared with patients who had secondary thrombosis.

Of the 58 recurrent episodes, 41 occurred while patients had residual thrombosis and 17 occurred after normalization of the affected veins. Using a time-dependent univariate Cox proportional hazards model, we found that

the hazard ratio for a recurrent event was 2.9 (CI, 1.6 to 5.2;  $P = 0.001$ ) when residual thrombosis was present. In a multivariate stepwise Cox proportional hazards model in which persistent residual thrombosis was used as a time-dependent variable, we determined that the hazard ratio for a recurrent event was 2.4 (CI, 1.3 to 4.4;  $P = 0.004$ ) in patients with residual thrombosis, 2.5 (CI, 1.4 to 4.4;  $P = 0.003$ ) in patients with idiopathic thrombosis, and 3.1 (CI, 1.8 to 5.2;  $P < 0.001$ ) in patients with thrombophilia versus patients with secondary thrombosis. Age and sex did not appear in the final model. Table 2 shows the related annual incidence density of recurrent venous thromboembolism in relation to type of initial thrombosis, presence of thrombophilia, recanalization of the thrombosed vein, and time elapsed since initial event.

### DISCUSSION

In the past, patients with a first episode of DVT were usually treated for a fixed period of 3 months regardless of the underlying cause (18). Currently, there is a trend toward adjusting the duration of anticoagulation according to patients' clinical characteristics at baseline. Selected patients with permanent risk factors, such as active cancer, prolonged immobilization due to chronic medical illnesses, the antiphospholipid antibody syndrome, and other thrombophilic conditions, generally receive long (and sometimes lifelong) courses of oral anticoagulant therapy (1, 2, 19). In most patients without permanent risk factors, anticoagulation is usually withdrawn after a shorter period, ranging from 6 months to 2 years in patients with idiopathic thrombosis (4, 6, 7, 19, 20) and from 6 to 12 weeks in those with transient risk factors (4, 19, 20). However, in all patients, the risk for recurrence after a short, fixed period of anticoagulation varies greatly. Approximately 70%

**Table 2. Incidence Density of Recurrent Venous Thromboembolism\***

Variable	Recurrent Venous Thromboembolism	
	3–24 Months since First DVT	≥24 Months since First DVT
<b>Patients with thrombophilia</b>		
Normal results on ultrasonography, %	10.3 (3.3–24)	7.1 (2.8–14.5)
Events per observation-years, $n/n$	5/48.5	7/99.1
Residual venous thrombosis, %	23.2 (13.3–37.7)	2.6 (0.1–14.5)
Events per observation years, $n/n$	16/68.9	1/38.3
<b>Patients with secondary DVT</b>		
Normal results on ultrasonography, %	0.0 (0.0–3.9)	0.0 (0.0–3.0)
Events per observation years, $n/n$	0/94.1	0/121.5
Residual venous thrombosis, %	7.1 (2.6–15.5)	4.9 (1.0–4.4)
Events per observation years, $n/n$	6/84.2	3/60.8
<b>Patients with idiopathic DVT</b>		
Normal results on ultrasonography, %	4.4 (1.2–11.2)	0.6 (0.0–3.4)
Events per observation years, $n/n$	4/91.4	1/166.2
Residual venous thrombosis, %	7.5 (3.2–14.7)	10.1 (4.1–20.9)
Events per observation years, $n/n$	8/107.3	7/69.0

\* Values in parentheses are 95% CIs. DVT = deep venous thrombosis.

of patients with unexplained thrombosis do not develop a recurrence (3–7, 20), and 10% of patients with transient risk factors do (3–5, 20). Therefore, improving our ability to identify patients who are more likely to develop a recurrence might help clinicians individually tailor the duration of anticoagulation. This, in turn, would allow a more favorable risk–benefit ratio in the use of anticoagulant treatment.

Our results confirm that the lack of an identifiable cause and the presence of thrombophilic conditions in patients with a first episode of symptomatic DVT are both associated with increased risk for recurrent venous thromboembolism (3–7, 20–27). Our results also strongly suggest that the risk for recurrence is considerably higher in patients with residual venous thrombosis on repeated ultrasonography than in patients with early vein recanalization (hazard ratio, 2.4 [CI, 1.3 to 4.4]). Therefore, persistent residual venous thrombosis should be considered a powerful and independent risk factor for recurrent thromboembolism. In this respect, ultrasonographic testing performed at fixed intervals to monitor for thrombus evolution may help clinicians individually modify the duration of anticoagulant therapy, especially in persons with idiopathic DVT and those with transient risk factors for thrombosis.

On the basis of patient characteristics alone, risk estimates for recurrence in the first 2 years after an acute episode of DVT ranged from 4% per year (in patients with secondary thrombosis) to 15% per year (in patients with thrombophilia). Ultrasonographic testing widened this range from 0% (in patients with secondary DVT who had vein recanalization) to 23% (in patients with thrombophilia and residual vein thrombosis). In patients with idiopathic thrombosis and normal results on ultrasonography, the risk for recurrence (4% per year) was low enough to allow consideration of interrupting anticoagulation. Conversely, the incidence of recurrence in patients with secondary thrombosis and residual venous thrombosis, more than 7% per year, might indicate continuation of anticoagulant treatment. Of interest, persistent residual thrombosis was associated with an increased risk for recurrence in patients with thrombophilia. However, this finding was observed only in the first 2 years of our study, when the recurrence rate in patients with normal results on ultrasonography (10%) was also high enough to justify continued treatment.

The concept of adjusting the duration of therapy for acute DVT on the basis of normal ultrasonographic results is appealing. However, the only available study exploring early interruption of anticoagulation (after 4 weeks) in patients with normal results on impedance plethysmography found a disappointingly high risk for recurrence (28). It should be noted, however, that impedance plethysmography can yield normal results in patients with DVT even in the presence of extensive residual venous thrombosis. For example, results of impedance plethysmography are normal

at 3 months in 90% of patients after acute proximal DVT (29, 30), while results of ultrasonography are normal in only 25%, as shown in this and in other investigations (12, 31). Moreover, 4 weeks of anticoagulant treatment is not considered sufficient according to current standards and might have contributed to the high recurrence rate (19). Our results, which are consistent with those of Piovello and colleagues (32), suggest that ultrasonography, unlike impedance plethysmography, can accurately quantify the persistence of residual thrombosis in proximal venous segments, thus enabling better stratification of recurrence risk.

What potential underlying mechanism leads to the relationship between persistent residual thrombosis and increased risk for recurrent thrombosis? Residual thrombosis could impair venous outflow, resulting in blood stasis with consequent clot formation. However, this seems unlikely. One third of our patients developed recurrent thrombosis in the initially unaffected leg, and an additional third developed isolated pulmonary embolism. Therefore, residual thrombosis probably reflects an underlying hypercoagulable state that puts patients at higher risk for recurrent events.

We believe our results are widely generalizable. Consecutive patients with clinically suspected and objectively confirmed DVT were prospectively followed for up to 6 years. All suspected recurrent events were objectively confirmed. The ultrasonographic method used to evaluate vein recanalization was based on findings obtained in a separate cohort of patients with proximal DVT. This method is highly reproducible, fast, and easy to perform because it involves examining only the midpopliteal and inguinal regions with a real-time B-mode scanner (12).

Our results suggest that patients with proximal venous thrombosis whose veins do not recanalize are likely to develop recurrent thrombotic events after withdrawal of oral anticoagulant therapy. These conclusions apply to patients with idiopathic venous thrombosis, patients with thrombosis secondary to transient risk factors, and patients with thrombophilic abnormalities. Assessment of the thrombotic burden, therefore, allows new opportunities for individual management of patients with venous thrombosis rather than management based on broad guidelines alone (33). In the future, randomized studies should assess the risks and benefits of adjusting the duration of oral anticoagulant therapy according to the presence or absence of residual venous thrombosis.

From University Hospital of Padua, Padua, Italy; and University of Amsterdam, Amsterdam, and Maastricht University, Maastricht, the Netherlands.

**Potential Financial Conflicts of Interest:** None disclosed.

**Requests for Single Reprints:** Paolo Prandoni, MD, PhD, Department of Medical and Surgical Sciences, University of Padua, Via Ospedale Civile 105, 35128 Padua, Italy; e-mail, paoprandoni@tin.it.

Current author addresses and author contributions are available at [www.annals.org](http://www.annals.org).

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**Current Author Addresses:** Drs. Prandoni, Bernardi, Marchiori, Bagatella, Frulla, Mosena, Tormene, Piccioli, Simioni, and Girolami: Department of Medical and Surgical Sciences, University of Padua, Via Ospedale Civile 105, 35128 Padua, Italy.

Dr. Lensing: Center for Vascular Medicine, Academic Medical Center, University of Amsterdam, Meibergdreef 9, Box 22660, Amsterdam, the Netherlands.

Dr. Prins: Department of Epidemiology, Maastricht University, PO Box 5800, Maastricht, the Netherlands.

**Author Contributions:** Conception and design: P. Prandoni, A.W.A. Lensing.

Analysis and interpretation of the data: A.W.A. Lensing, M.H. Prins, E. Bernardi, A. Marchiori, P. Simioni.

Drafting of the article: P. Prandoni, A.W.A. Lensing, E. Bernardi, A. Marchiori, M. Frulla.

Critical revision of the article for important intellectual content: M.H. Prins, M. Frulla, D. Tormene, A. Piccioli, P. Simioni, A. Girolami.

Final approval of the article: P. Prandoni, A.W.A. Lensing, M.H. Prins, E. Bernardi, A. Marchiori, P. Bagatella, M. Frulla, L. Mosena, D. Tormene, A. Piccioli, P. Simioni, A. Girolami.

Provision of study materials or patients: P. Prandoni, P. Bagatella, M. Frulla, L. Mosena, D. Tormene, P. Simioni, A. Girolami.

Statistical expertise: A.W.A. Lensing, M.H. Prins, E. Bernardi, A. Marchiori.

Administrative, technical, or logistic support: D. Tormene, P. Simioni, A. Girolami.

Collection and assembly of data: P. Prandoni, P. Bagatella, L. Mosena, D. Tormene, A. Piccioli, P. Simioni.