Serial 2-Point Ultrasonography Plus D-Dimer vs Whole-Leg Color-Coded Doppler Ultrasonography for Diagnosing Suspected Symptomatic Deep Vein Thrombosis
A Randomized Controlled Trial

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Context Patients with suspected deep vein thrombosis (DVT) of the lower extremities are usually investigated with ultrasonography either by the proximal veins (2-point ultrasonography) or the entire deep vein system (whole-leg ultrasonography). The latter approach is thought to be better based on its ability to detect isolated calf vein thrombosis; however, it requires skilled operators and is mainly available only during working hours. No randomized comparisons are yet available evaluating the relative values of these 2 strategies.

Objective To assess if the 2 diagnostic strategies are equivalent for the management of symptomatic outpatients with suspected DVT of the lower extremities.

Design, Setting, and Patients A prospective, randomized, multicenter study of consecutive symptomatic outpatients (n=2465) with a first episode of suspected DVT of the lower extremities who were randomized to undergo 2-point or whole-leg ultrasonography. Data were taken from ultrasound laboratories of 14 Italian universities or civic hospitals between January 1, 2003, and December 21, 2006. Patients with normal ultrasound findings were followed up for 3 months, with study completion on March 20, 2007.

Main Outcome Measure Objectively confirmed 3-month incidence of symptomatic venous thromboembolism in patients with an initially normal diagnostic workup.

Results Of 2465 eligible patients, 345 met 1 or more exclusion criteria and 22 refused to participate; therefore, 2098 patients were randomized to either 2-point (n=1045) or whole-leg (n=1053) ultrasonography. Symptomatic venous thromboembolism occurred in 7 of 801 patients (incidence, 0.9%; 95% confidence interval [CI], 0.3%-1.8%) in the 2-point strategy group and in 9 of 763 patients (incidence, 1.2%; 95% CI, 0.5%-2.2%) in the whole-leg strategy group. This met the established equivalence criterion (observed difference, 0.3%; 95% CI, −1.4% to 0.8%).

Conclusion The 2 diagnostic strategies are equivalent when used for the management of symptomatic outpatients with suspected DVT of the lower extremities.

Trial Registration clinicaltrials.gov Identifier: NCT00353093

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at presentation to detect calf DVT extending to the proximal veins (serial 2-point ultrasonography). Repeat testing may be safely avoided in patients with a normal D-dimer test result at presentation.

The newer color-coded Doppler ultrasound scanners allow the evaluation of the entire deep venous system, from the groin to the ankle (whole-leg ultrasonography). With this strategy, color flow artifacts are exploited to enhance small vessel visualization, although vein compressibility still constitutes the main diagnostic criterion. The advantage of this approach is the ability to exclude isolated calf DVT, allowing for 1-day treatment of all patients, without additional testing. Conversely, it needs top-quality ultrasound equipment and experienced operators; therefore, it is often unobtainable after hours and during the weekends.

Despite the lack of definite evidence, whole-leg ultrasonography is thought to be better than serial 2-point ultrasonography, especially in the everyday practice of ultrasound laboratories, based on the assumption that detecting isolated calf DVT is a clinically relevant issue. As a consequence, many patients with suspected DVT need to wait hours or even days before whole-leg ultrasonography is obtained and are frequently (unnecessarily) administered anticoagulants in the meantime.

Recent observations challenge this view and claim that prompt detection of calf DVT may not be as relevant as previously believed. Conversely, the systematic evaluation of the calf vein system may bring about a definite risk of overtreating thrombosis that may otherwise heal spontaneously.

To test the hypothesis that the 2 diagnostic strategies are equivalent for the exclusion of a first episode of suspected DVT in symptomatic outpatients, we undertook a prospective, randomized, multicenter study assessing the incidence of symptomatic venous thromboembolism (VTE) during a 3-month follow-up period in patients spared anticoagulation on the basis of a normal initial workup with either serial 2-point ultrasonography plus D-dimer (2-point strategy) or whole-leg color-coded Doppler ultrasonography (whole-leg strategy).

**METHODS**

**Patients**

All consecutive outpatients who were referred by the emergency department or a primary care physician to 1 of the 14 study centers (all ultrasound laboratories located in Italy) with a first episode of suspected symptomatic DVT of the lower extremities were eligible for inclusion. Exclusion criteria included pregnancy, age younger than 18 years, history of VTE, suspected pulmonary embolism, life expectancy of less than 3 months, ongoing anticoagulation (>48 hours), mandatory indication for anticoagulation (eg, atrial fibrillation), and geographic inaccessibility to follow-up. Patients were enrolled between January 1, 2003, and December 21, 2006, with study completion on March 20, 2007. The study was conducted according to the ethical principles stated in the Declaration of Helsinki, and the protocol was approved by the institutional review board of each participating center.

**Randomization**

Eligible patients, after signing a written informed consent form, were assigned to either the 2-point or the whole-leg strategy. The investigators had to contact the coordinating center by telephone to obtain the patient's group allocation. A randomization list was available for each center, arranged by blocks of 10 patients to ensure balancing (generated by nQuery Advisor; Statistical Solutions Ltd, Cork, Ireland)).

**Study Outline**

**Two-Point Strategy.** Patients with normal ultrasound findings at presentation underwent D-dimer testing. Patients with normal D-dimer levels were spared further investigation and were not anticoagulated. Patients with abnormal D-dimer levels were scheduled for a repeat ultrasonography at 1 week, or earlier if clinically indicated. Those patients with normal repeat ultrasound findings were spared further investigation and were not anticoagulated.

**Whole-Leg Strategy.** Patients with normal ultrasound results at presentation were spared further investigation and were not anticoagulated.

**Follow-up.** Patients with normal findings at the initial diagnostic workup were scheduled for an end of follow-up visit after 3 months, which consisted of (1) a standardized interview to assess their general health status, chest or leg complaints, and history of hospital admission for any cause; (2) a physical examination; and (3) an ultrasonographic evaluation. Patients were instructed to refer to the study centers immediately if they experienced syncope, shortness of breath, chest pain, palpitations, and either new or worsening leg symptoms. Patients who did not attend the scheduled visit were contacted by telephone by the investigators and interviewed using a standardized questionnaire to assess their general health status, chest or leg complaints, and history of hospital admission for any cause.

**Interventions**

All diagnostic evaluations were performed by certified physicians with long-standing experience in vascular ultrasonography.

**Two-Point Strategy.** Two-point ultrasonography was performed and interpreted as described elsewhere. Briefly, the common femoral at the groin and the popliteal vein down to its branching into the calf deep veins at the popliteal fossa were examined in the transverse plane with a linear probe (5-10 MHz). Vein incompressibility was the only diagnostic criterion applied. Test results were categorized as normal (compressible veins) or abnormal (noncompressible veins).

D-dimer testing was evaluated by using a rapid whole-blood bedside D-dimer assay (SimpliRED D-Dimer; AGEN Biomedical Ltd, Brisbane, Australia), which was based on red blood
cells agglutination. Results were categorized as normal (no visible agglutination) or abnormal (visible agglutination or noninterpretable findings).

Whole-Leg Strategy. Lacking a widely accepted protocol for whole-leg ultrasonography, the standard procedure for the study purposes was agreed a priori by all investigators during a consensus meeting held before the beginning of the study. All veins were imaged continuously along their length, in the transverse plane, with a linear probe (5-10 MHz). The proximal deep veins were examined first, including the femoral veins (common, superficial, and deep) and the popliteal vein down to its trifurcation. Then, only in patients with normal proximal findings, the calf veins were evaluated, including the axial (peroneal and posterior tibial) and the muscular veins. Vein incompressibility was the sole diagnostic criterion adopted for abnormal testing of the proximal and axial calf veins. Adjunctive criteria for abnormal testing of the muscular veins only included lack of spontaneous or reverse-flow intraluminal color-filling after augmentation maneuvers (ie, manual squeezing of the calf).

Main Outcome Measure
We assessed the incidence of objectively proven symptomatic VTE occurring during a 3-month follow-up period in patients with normal findings at the initial diagnostic workup, with either of the 2 diagnostic strategies.

End Point Adjudication
All suspected symptomatic events were to be evaluated as follows. Deep vein thrombosis was confirmed by abnormal findings on compression ultrasonography or venography, and pulmonary embolism was confirmed by abnormal computed tomography, high probability ventilation-perfusion lung scanning, or abnormal pulmonary angiography. Fatal pulmonary embolism was adjudicated by autopsy, or on clinical grounds in case of sudden and otherwise inexplicable death, according to the opinion of an independent physician. An independent and blind committee adjudicated the suspected thromboembolic events based on all relevant documents and footage.

Sample Size Calculation and Statistical Analysis
As specified in the study protocol, the investigation was designed to determine whether the 2 strategies would have similar safety (ie, as an equivalence study). The observed cumulative incidence of symptomatic VTE events during follow-up after a normal workup with either the 2-point or whole-leg strategy is around 1%. To be conservative, we assumed that both strategies would be equally accurate, however, as only whole-leg ultrasonography is able to detect calf DVT, a lower incidence of VTE events would be expected during follow-up in this group. We specified that the 2 strategies would be clinically equivalent if the upper boundary of the 95% confidence interval (CI) around the difference between the proportion of events in the 2 groups at the end of follow-up was within 1.5%. We calculated that a sample size of 796 patients in each group would satisfy these requirements, with an 80% power if the proportion of events during the 3-month follow-up was 1% in both groups. Assuming an initial prevalence of DVT of up to 25%, we calculated that we needed to enroll at least 1050 patients in each group.

Sample size was estimated by nQuery Advisor version 5.0 (Statistical Solutions Ltd). The binomial distribution was used to determine 95% CI for proportions. To account for patients who were lost and/or died during follow-up, we performed a sensitivity analysis. Statistical analyses were performed by using SPSS statistical software version 15.0 (SPSS Inc, Chicago, Illinois).

RESULTS
Patients
Of 2465 eligible patients with suspected DVT, 345 were excluded because the patients did not meet inclusion criteria and 22 refused to participate (FIGURE). Consequently, 2098 patients were randomized to either the 2-point strategy (n=1045) or the whole-leg strategy (n=1053). Table 1 shows the demographic and clinical characteristics of the study patients at entry.

Initial Prevalence of DVT
Of 1045 patients randomized to the 2-point strategy, 231 (22.1%; 95% CI, 19.6%-24.6%) had abnormal findings at the initial diagnostic workup; by definition, all events were proximal DVT. A total of 217 patients (20.8%) had abnormal ultrasound findings at presentation, and 828 had normal test results and underwent D-dimer testing. D-dimer testing results were abnormal in 256 of 828 patients (30.9%) who were scheduled for repeat ultrasonography within 1 week. During the week, none of these 256 patients received antithrombotic drugs and none developed signs or symptoms of pulmonary embolism; however, 17 patients presented for retesting during the week because of worsening leg symptoms (of these, 2 patients had abnormal ultrasound test results). Of the 239 patients with improved or unchanged leg symptoms who presented for repeat ultrasonography at the 1-week visit, 12 had abnormal findings. Thus, 14 of the 256 patients (5.5%) with abnormal D-dimer testing had abnormal repeat ultrasonography. The remaining 814 patients, which included 572 patients with normal D-dimer and 242 patients with abnormal D-dimer and normal serial ultrasonography, were not anticoagulated and were followed up for 3 months.

Of the 1053 patients randomized to the whole-leg strategy, 278 (26.4%; 95% CI, 23.7%-29.1%) had abnormal ultrasound findings at presentation. Of these, 213 patients (76.6%) had proximal DVT, 36 patients (13.0%) had isolated axial (posterior tibial or peroneal) DVT, and 29 patients (10.4%) had isolated muscular vein thrombosis. The remaining 775 patients with normal ultrasound findings were not anticoagulated and were followed up for 3 months.

Three-Month Follow-up
Table 2 shows the type, timing, diagnostic method used, and location of the...
outcome events that occurred during the 3 months of follow-up. Of 814 patients allocated to the 2-point strategy, 9 (1.1%) died during follow-up, because of cancer (n=5), brain hemorrhage (n=1), ischemic stroke (n=1), myocardial infarction (n=1), and heart failure (n=1); and 4 patients (0.5%) were lost to follow-up (unknown whereabouts). Sixteen patients had suspected symptomatic VTE during the follow-up period, which was objectively confirmed in 7 patients and not found in 9 patients. Therefore, in this group, the incidence of confirmed symptomatic VTE during the 3-month follow-up period was 0.9% (95% CI, 0.3%-1.8%). Of 785 patients eligible for the clinical and instrumental end of follow-up visit, 189 (24%) regularly presented to the clinics and 596 (76%) were interviewed by telephone.

Of 775 patients randomized to the whole-leg strategy, 7 (0.9%) died during follow-up, because of cancer (n=5), massive trauma (n=1), and myocardial infarction (n=1); and 5 patients (0.6%) were lost to follow-up (unknown whereabouts). Twenty-one patients had suspected symptomatic VTE during the follow-up period, which was objectively confirmed in 9 patients and not found in 12 patients. Therefore, the incidence of confirmed symptomatic VTE during the 3-month follow-up period was 1.2% (95% CI, 0.5%-2.2%). Of 742 patients eligible for the clinical and instrumental end of follow-up visit, 172 (23%) regularly presented to the clinics and 570 (77%) were interviewed by telephone.

The observed difference between the 2 groups in terms of symptomatic VTE at the end of the 3-month follow-up period was 0.3% (95% CI, −1.4% to 0.8%), which is within the chosen equivalence limit. The sensitivity analysis, including patients who died during the study and/or were lost to follow-up, did not yield different results from the main analysis.

**COMMENT**

Our study shows that the 2-point and whole-leg strategies are equivalent for the management of symptomatic patients with suspected DVT. The 3-month incidence of objectively confirmed VTE in patients with an initial normal diagnostic ultrasound was similar in the 2 study groups. Furthermore, the observed data are consistent with those reported in previous large cohort studies.3-8,11,14

Two specific issues deserve further discussion. First, despite a significantly higher initial prevalence of DVT in the whole-leg group compared with the 2-point group (absolute difference, 4.3%; 95% CI, 0.5%-8.1%), the long-term outcome of the patients was quite similar. Interestingly, that difference was entirely accounted for by 65

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**Figure. Flow of Study Patients**

- 2465 Patients assessed for eligibility
  - 345 Excluded
    - 103 Had previous venous thromboembolism
    - 66 Had suspected pulmonary embolism
    - 59 Had short life expectancy
    - 44 Were unavailable for follow-up
    - 40 Had indication for anticoagulation
    - 19 Aged <18 y
    - 14 Were pregnant
    - 22 Refused to participate

- 2088 Randomized
  - 1045 Randomized to receive 2-point strategy
    - 1045 Had first diagnostic ultrasound
    - 217 Excluded (abnormal ultrasound [proximal DVT])
    - 828 Had normal ultrasound and underwent D-dimer testing
    - 572 Had normal D-dimer test
    - 256 Had abnormal D-dimer test and underwent second ultrasound
    - 14 Excluded (abnormal ultrasound [proximal DVT])
    - 242 Had normal second ultrasound
    - 814 Eligible for 3-mo follow-up
    - 4 Lost to follow-up
    - 9 Died
  - 1053 Randomized to receive whole-leg strategy
    - 1053 Had diagnostic ultrasound as randomized
    - 278 Excluded (abnormal ultrasound)
    - 213 Had proximal DVT
    - 36 Had isolated axial DVT
    - 29 Had isolated muscular vein thrombosis
    - 775 Eligible for 3-mo follow-up
    - 5 Lost to follow-up
    - 7 Died
  - 2098 Randomized
    - 828 Had normal ultrasound and underwent D-dimer testing
    - 217 Excluded (abnormal ultrasound [proximal DVT])
    - 278 Excluded (abnormal ultrasound)
    - 213 Had proximal DVT
    - 36 Had isolated axial DVT
    - 29 Had isolated muscular vein thrombosis
    - 801 Completed 3-mo end-of-follow-up visit
    - 13 Excluded from analysis (did not complete 3-mo follow-up)
    - 763 Completed 3-mo end-of-follow-up visit
    - 60 Included in analysis
    - 12 Excluded from analysis (did not complete 3-mo follow-up)

DVT, deep vein thrombosis. Two-point strategy indicates serial 2-point ultrasonography plus D-dimer; whole-leg strategy indicates whole-leg color-coded Doppler ultrasonography.
cases of isolated calf DVT identified by whole-leg ultrasonography; thus, one might speculate that detecting isolated calf DVT may not be as relevant as previously believed.11-14,25 However, because objectively diagnosed symptomatic calf DVT requires full anticoagulation,25,30 the quest for distal DVT might even expose patients to the harm of unnecessary treatment.15,21 This interesting hypothesis, previously suggested15,21-24 and still awaiting confirmation, is indirectly supported by the findings of a recent randomized trial11 and of several cohort studies.12-14 In these studies, which routinely investigated the calf veins, the reported incidence of thromboembolic events after 3 to 6 months of follow-up in patients spared anticoagulants on the basis of a normal ultrasound is fully comparable with that observed in studies which did not investigate the calf veins.31 A properly designed randomized study is necessary to address this issue in a formally and scientifically correct fashion.

Second, the thorough evaluation of the femoral veins (common, superficial, or deep) and of the popliteal vein did not increase the overall diagnostic yield of the whole-leg strategy. The initial prevalence of proximal DVT was similar in both groups (22.1% in the 2-point strategy group vs 20.2% in the whole-leg strategy group). This finding confirms that, in symptomatic outpatients, proximal DVT always involves the common femoral vein, the popliteal vein, or both; and therefore the superficial and deep femoral veins are usually not worth investigating.2,4,32

Our results were obtained using adequate methods. All consecutive symptomatic patients referred to the participating centers were eligible for inclusion in the study. Confounding

| Table 1. Demographic and Clinical Characteristics of the Study Patients at Presentation
<table>
<thead>
<tr>
<th></th>
<th>Two-Point Strategy (n = 1045)</th>
<th>Whole-Leg Strategy (n = 1053)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>63.7 (16.3)</td>
<td>62.5 (16.2)</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>439 (42.0)</td>
<td>430 (40.8)</td>
</tr>
<tr>
<td>Obesity (BMI ≥30), No. (%)</td>
<td>157 (15.0)</td>
<td>165 (15.7)</td>
</tr>
<tr>
<td>Current smoker, No. (%)</td>
<td>93 (8.9)</td>
<td>74 (7.0)</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient-physician delay, mean (SD), d</td>
<td>7.14 (5.3)</td>
<td>7.14 (6.1)</td>
</tr>
<tr>
<td>Risk factors of thrombosis, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>292 (27.9)</td>
<td>315 (29.9)</td>
</tr>
<tr>
<td>Prolonged immobilization (≥7 d)</td>
<td>156 (14.9)</td>
<td>147 (14.0)</td>
</tr>
<tr>
<td>Surgery (≥4 wk)</td>
<td>154 (14.7)</td>
<td>126 (11.9)</td>
</tr>
<tr>
<td>Leg trauma or fracture, plaster cast</td>
<td>256 (24.5)</td>
<td>262 (24.9)</td>
</tr>
<tr>
<td>Paralysis or paresis</td>
<td>30 (2.9)</td>
<td>28 (2.6)</td>
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<tr>
<td>No. of women in pregnancy or puerperium</td>
<td>8 (1.3)</td>
<td>11 (1.8)</td>
</tr>
<tr>
<td>No. of women receiving hormone therapy</td>
<td>38 (6.3)</td>
<td>40 (6.4)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>51 (4.9)</td>
<td>42 (4.0)</td>
</tr>
<tr>
<td>Long-distance travel (≥8 h)</td>
<td>17 (1.6)</td>
<td>11 (1.0)</td>
</tr>
</tbody>
</table>

Table 2. Distribution and Timing of Venous Thromboembolic Events

<table>
<thead>
<tr>
<th>Allocation Group End Points</th>
<th>Two-point strategy</th>
<th>Whole-leg strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral DVT</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Ipsilateral DVT</td>
<td>12</td>
<td>V/Q lung scan and computed tomography</td>
</tr>
<tr>
<td>Ipsilateral DVT</td>
<td>12</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ipsilateral DVT</td>
<td>21</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ipsilateral DVT</td>
<td>66</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ipsilateral DVT</td>
<td>68</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ipsilateral DVT</td>
<td>81</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ipsilateral DVT</td>
<td>2</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ipsilateral DVT</td>
<td>18</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ipsilateral DVT</td>
<td>42</td>
<td>Pulmonary embolism</td>
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<td>Ipsilateral DVT</td>
<td>48</td>
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<td>Ipsilateral DVT</td>
<td>54</td>
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<td>Ipsilateral DVT</td>
<td>68</td>
<td>Pulmonary embolism</td>
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<tr>
<td>Ipsilateral DVT</td>
<td>88</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ipsilateral DVT</td>
<td>88</td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Ipsilateral DVT</td>
<td>92</td>
<td>Pulmonary embolism</td>
</tr>
</tbody>
</table>

Abbreviations: DVT, deep vein thrombosis; NA, not applicable; V/Q, ventilation-perfusion.

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factors were minimized by excluding patients with a history of previous VTE. Demographic characteristics and risk factors for DVT were evenly distributed in the 2 study groups. Patients randomized to the 2-point strategy were treated according to a highly standardized method.14-17 The D-dimer assay we used has a high reproducibility and negative predictive value in clinically symptomatic patients.10,20,55 Lacking a widely accepted protocol for whole-leg ultrasonography, all investigators agreed a priori the evaluation technique and the diagnostic criteria to be used. Only experienced physicians did ultrasonography. Follow-up was performed prospectively, and predefined criteria were applied to diagnose symptomatic VTE. Only a minority (0.6%) of the patients with a normal initial workup were lost to follow-up; although among the patients who completed the 3-month period of observation, approximately 75% were contacted by telephone and approximately 25% presented to the clinics for a clinical and instrumental evaluation. The latter finding may be regarded as a potential limitation, although telephone interviews quite commonly substitute for end-of-follow-up visits, especially when patients’ samples are large.11,13,14 However, patients often fail to present for repeat testing, for various reasons.14 Given that the characteristics of the study patients and the rate of both initial and long-term DVT were consistent with those reported by previous similar studies,3-8,11-14 our results are likely to be valid and generalizable.

In conclusion, both serial 2-point ultrasonography plus D-dimer and whole-leg color-coded Doppler ultrasonography represent reliable diagnostic options for the management of symptomatic patients with suspected DVT of the lower extremities. Either strategy may be chosen based on the clinical context, on the patients’ needs, and on the available resources. The former is simple, convenient, and widely available but requires repeat testing in one-fourth of the patients. The latter offers a 1-day answer, desirable for patients with severe call complaints, for travelers, and for those living far from the diagnostic service, but is cumbersome, possibly more expensive, and may expose patients to the risk of (unnecessary) anticoagulation.

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Author Contributions: Drs Bernardi and Camporese had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Bernardi, Piccoli, Prandoni. Acquisition of data: Bernardi, Camporese, Siragusa, Imperati, Berchi, Gherarduzzi, Verlato, Anastasio, Prati, Pesavento, Bova, Maltempi, Zanatta, Cogo, Cappelli, Bucherini, Cuppini. Analysis and interpretation of data: Bernardi, Camporese, Bülles, Imperati, Prati, Novventa, Prandoni. Drafting of the manuscript: Bernardi, Camporese, Bülles, Berchi, Novventa, Prandoni. Administrative, technical, or material support: Bernardi, Camporese, Piccoli, Prandoni. Critical revision of the manuscript for important intellectual content: Bernardi, Camporese, Bülles, Piccoli, Prandoni. Statistical analysis: Bernardi, Novventa.

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REFERENCES


