



**EDUCATIONAL OBJECTIVE:** Readers will prescribe anticoagulation for the appropriate length of time after venous thromboembolic events

**SCOTT KAATZ, DO, MSc, FACP<sup>a</sup>**

Clinical Associate Professor of Medicine, Associate Residency Program Director, Department of Medicine, and Director, Anticoagulation Clinics, Henry Ford Hospital, Detroit, MI

**WAQAS QURESHI, MD**

Henry Ford Hospital, Detroit, MI

**ROBERT C. LAVENDER, MD, FACP<sup>b</sup>**

Professor of Medicine, Division of General Internal Medicine, University of Arkansas for Medical Sciences, Little Rock

# Venous thromboembolism: What to do after anticoagulation is started

## ABSTRACT

After anticoagulation has been started in patients with venous thromboembolism (VTE), three issues need to be addressed: the length of therapy, measures to help prevent postthrombotic syndrome, and a basic workup for malignancy in patients with idiopathic VTE.

## KEY POINTS

A low-molecular-weight heparin for at least 6 months is the treatment of choice for cancer-related VTE.

We recommend 3 months of anticoagulation for VTE caused by a reversible risk factor and indefinite treatment for idiopathic VTE in patients without risk factors for bleeding who can get anticoagulation monitoring.

Clinical factors are more important in deciding the duration of anticoagulation therapy than evidence of an inherited thrombophilic state.

Elastic compression stockings reduce the risk of postthrombotic syndrome substantially.

Patients with idiopathic VTE should have a basic screening for malignancy.

<sup>a</sup> Dr. Kaatz has disclosed consulting, teaching and speaking, independent contracting (including contracted research), and membership on advisory committees or review panels for the Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Ortho-McNeil, and Johnson and Johnson corporations.

<sup>b</sup> Dr. Lavender has disclosed receiving research support for clinical trials from the Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Daiichi Sankyo corporations.

doi:10.3949/ccjm.78a.10175

**D**EEP VEIN THROMBOSIS and pulmonary embolism are collectively referred to as venous thromboembolic (VTE) disease. They affect approximately 100,000 to 300,000 patients per year in the United States.<sup>1</sup> Although patients with deep vein thrombosis can be treated as outpatients, many are admitted for the initiation of anticoagulation. Initial anticoagulation usually requires the overlap of a parenteral anticoagulant (unfractionated heparin, low-molecular-weight heparin [LMWH] or fondaparinux) with warfarin for a minimum of 5 days and until the international normalized ratio (INR) of the prothrombin time is above 2.0 for at least 24 hours.<sup>2</sup>

Three clinical issues need to be addressed after the initiation of anticoagulation for VTE:

- Determination of the length of anticoagulation with the correct anticoagulant
- Prevention of postthrombotic syndrome
- Appropriate screening for occult malignancy.

## HOW LONG SHOULD VTE BE TREATED?

The duration of anticoagulation has been a matter of debate.

The risk of recurrent VTE appears related to clinical risk factors that a patient has at the time of the initial thrombotic event. An epidemiologic study<sup>3</sup> found that patients with VTE treated for approximately 6 months had a low rate of recurrence (0% at 2 years of follow-up) if surgery was the risk factor. The risk climbed to 9% if the risk factor was nonsurgical and to 19% if there were no provoking risk factors.

TABLE 1

## Annual event rates of recurrent venous thromboembolism

| DURATION OF FOLLOW-UP | PROVOKED BY SURGERY | PROVOKED BY NONSURGICAL FACTOR | UNPROVOKED (IDIOPATHIC) |
|-----------------------|---------------------|--------------------------------|-------------------------|
| 12 months             | 1%                  | 5.8%                           | 7.9%                    |
| 24 months             | 0.7%                | 4.2%                           | 7.4%                    |

DATA FROM IORIO A, KEARON C, FILIPPUCCI E, ET AL. RISK OF RECURRENCE AFTER A FIRST EPISODE OF SYMPTOMATIC VENOUS THROMBOEMBOLISM PROVOKED BY A TRANSIENT RISK FACTOR: A SYSTEMATIC REVIEW. ARCH INTERN MED 2010; 170:1710-1716.

The likelihood of VTE recurrence and therefore the recommended duration of treatment depend on whether the VTE event was provoked, cancer-related, recurrent, thrombophilia-related, or idiopathic. We address each of these scenarios below.

### HOW LONG TO TREAT PROVOKED VTE

A VTE event is considered provoked if the patient had a clear inciting risk factor. As defined in various clinical trials, these risk factors include:

- Hospitalization with confinement to bed for 3 or more consecutive days in the last 3 months
- Surgery or general anesthesia in the last 3 months
- Immobilization for more than 7 days, regardless of the cause
- Trauma in the last 3 months
- Pregnancy
- Use of an oral contraceptive, regardless of which estrogen or progesterone analogue it contains
- Travel for more than 4 hours
- Recent childbirth.

However, the trials that tested different lengths of anticoagulation have varied markedly in how they defined provoked deep vein thrombosis.<sup>4-7</sup>

A systematic review<sup>8</sup> showed that patients who developed VTE after surgery had a lower rate of recurrent VTE at 12 and 24 months than patients with a nonsurgical provoking risk factor, and patients with nonprovoked (idiopathic) VTE had the highest risk of recurrence (TABLE 1).

### Recommendation:

#### Warfarin or equivalent for 3 months

The American College of Chest Physicians (ACCP) recommends 3 months of anticoagulation with warfarin or another vitamin K antagonist for patients with VTE secondary to a transient (reversible) risk factor,<sup>2</sup> and we agree.

### HOW LONG TO TREAT CANCER-RELATED VTE

Patients with cancer are at higher risk of developing VTE. Furthermore, in one study,<sup>9</sup> compared with other patients with VTE, patients with cancer were three times more likely to have another episode of VTE, with a cumulative rate of recurrence at 1 year of 21% vs 7%. Cancer patients were also twice as likely to suffer major bleeding complications while on anticoagulation.<sup>9</sup>

Warfarin is a difficult drug to manage because it has many interactions with foods, diseases, and other drugs. These difficulties are amplified in many cancer patients during chemotherapy.

Warfarin was compared with a LMWH in four randomized trials in cancer patients, and a meta-analysis<sup>10</sup> found a 50% relative reduction in the rates of recurrent deep vein thrombosis and pulmonary embolism with LMWH treatment. These results were driven primarily by the CLOT trial (Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients With Cancer),<sup>11</sup> which showed an 8% absolute risk reduction (number needed to treat 13) without an increase in major bleeding when cancer-related VTE was treated with an LMWH—ie, dalteparin (Fragmin)—for 6 months compared with warfarin.

Current thinking suggests that VTE should be treated until the cancer is resolved. However, this hypothesis has not been adequately tested, and consequently, the ACCP gives it only a level 1C recommendation.<sup>2</sup> The largest of the four trials comparing warfarin and an LMWH lasted only 6 months. The safety of extending LMWH treatment beyond 6 months is currently unknown but is under investigation (clinicaltrials.gov identifier NCT00942968).

The duration of anticoagulation treatment has been a matter of debate

**Recommendation:****LMWH therapy for at least 6 months**

The ACCP guidelines recommend LMWH therapy for 3 to 6 months, followed by warfarin or another vitamin K antagonist or continued LMWH treatment until the cancer is resolved.<sup>2</sup>

The National Comprehensive Cancer Network guidelines recommend an LMWH for 6 months as monotherapy and indefinite anticoagulation if the cancer is still active.<sup>12</sup>

The American Society of Clinical Oncology guidelines recommend an LMWH for at least 6 months and indefinite anticoagulant therapy for selected patients with active cancer.<sup>13</sup>

We agree that patients with active cancer should receive an LMWH for at least 6 months and indefinite anticoagulation until the cancer is resolved.

In our experience, many patients are reluctant to give themselves the daily injections that LMWH therapy requires, and so they need to be well-informed about the marked decrease in VTE recurrence with this less-convenient and more-expensive therapy. Many patients face insurance barriers to cover the cost of LMWH therapy; however, careful attention to preauthorization can usually overcome this obstacle.

■ **HOW LONG TO TREAT RECURRENT VTE**

It makes clinical sense that patients who have a second VTE event should be treated indefinitely. This theory was tested in a randomized clinical trial<sup>14</sup> in which patients with provoked or unprovoked VTE were randomized after their second event to receive anticoagulation for 6 months vs indefinitely.

After 4 years of follow-up, the recurrence rate was 21% in patients assigned to 6 months of treatment and only 3% in patients who continued anticoagulation throughout the trial. On the other hand, major hemorrhage occurred in 3% of patients treated for 6 months and in 9% in patients who continued anticoagulation indefinitely.

Of note, most of the patients in this trial had unprovoked (idiopathic) VTE, so the results should not be extrapolated to patients with provoked VTE, who accounted for only 20% of the study population.<sup>14</sup>

**Recommendation:****Long-term anticoagulation**

We agree with the ACCP recommendation<sup>2</sup> that patients who have had a second episode of unprovoked VTE should receive long-term anticoagulation. Because of a lack of data, the duration of therapy for patients with a second episode of provoked VTE should be individualized.

■ **HOW LONG TO TREAT THROMBOPHILIA-RELATED VTE****Inherited thrombophilias**

Patients with VTE that is not related to a clear provoking risk factor or cancer frequently have testing to evaluate for a hypercoagulable state. This workup traditionally includes the most common inherited thrombophilias for gene mutations for factor V and prothrombin as well as for deficiencies in protein C, protein S, antithrombin and the acquired antiphospholipid syndrome.

The key questions that should be asked prior to embarking on this workup are:

- Will the results change the length of therapy for the patient?
- Will testing the patient help with genetic counseling and possible testing of family members?
- Will the results change the targeted INR range for warfarin or other vitamin K antagonist therapy?

Patients with inherited thrombophilia have a greater risk of developing an initial VTE event; however, these tests do not help predict the recurrence of VTE in patients with established disease more than clinical risk factors do. A prospective study demonstrated this by looking at the effect of thrombophilia and clinical factors on the recurrence of venous thrombosis and found that inherited prothrombotic abnormalities do not appear to play an important role in the risk of a recurrent event.<sup>15</sup> On the other hand, clinical factors, such as whether the first event was idiopathic or provoked, appear more important in determining the duration of anticoagulation therapy.<sup>15</sup> A systematic review of the common inherited thrombophilias showed the VTE recurrence rate of patients with factor V Leiden was higher than in patients without the muta-

**Cancer-related VTE poses a higher risk of recurrence than other forms of VTE**

**Patients who have a second episode of unprovoked proximal VTE should receive long-term anticoagulation**

tion; however, the absolute rates of recurrence were not much different than what would be expected in patients with idiopathic VTE.<sup>16</sup>

A retrospective study involving a large cohort of families of patients who already had experienced a first episode of either idiopathic or provoked VTE showed high annual risks of recurrent VTE associated with hereditary deficiencies of protein S (8.4%), protein C (6.0%), and antithrombin (10%).<sup>17</sup> However, for the more commonly occurring genetic thrombophilias, the factor V Leiden and prothrombin G20210A mutations, family members with either gene abnormality had low rates of VTE, suggesting that testing of relatives of probands is not clinically useful.<sup>16</sup>

## Antiphospholipid syndrome

Antiphospholipid syndrome is an acquired thrombophilia. A patient has thrombotic antiphospholipid syndrome when there is a history of vascular thrombosis in the presence of persistently positive tests (at least 12 weeks apart) for lupus anticoagulants, anticardiolipin antibodies, or anti-beta-2 glycoprotein I. A prospective study of 412 patients with a first episode of VTE found that 15% were positive for anticardiolipin antibody at the end of 6 months of anticoagulation. The risk of recurrent VTE after 4 years was 29% in patients with antibodies and 14% in those without antibodies (relative risk 2.1; 95% confidence interval [CI] 1.3–3.3;  $P = .0013$ ).<sup>18</sup>

Recent reviews advise indefinite warfarin anticoagulation in patients with VTE and persistence of antiphospholipid antibodies.<sup>19</sup> However, the optimal duration of anticoagulation is uncertain. Until well-designed clinical trials are done, the current general consensus is to anticoagulate these patients indefinitely.<sup>20,21</sup> Retrospective studies had suggested that patients with antiphospholipid antibodies required a higher therapeutic INR range; however, this observation was tested in two trials that found no difference in thromboembolic rates when patients were randomized to an INR of 2.0–3.0 vs 3.1–4.0,<sup>22</sup> or 2.0–3.0 vs 3.0–4.5.<sup>23</sup>

## No formal recommendations

In the absence of strong evidence, the ACCP guidelines do not include a recommendation

on the duration of anticoagulation treatment specific to inherited thrombophilias. We believe that clinical factors are more important than inherited thrombophilias for deciding the duration of anticoagulation, and that testing is almost never indicated or useful. However, patients with antiphospholipid syndrome are at high risk of recurrence, and it is our practice to anticoagulate these patients indefinitely.

## ■ HOW LONG TO TREAT UNPROVOKED (IDIOPATHIC) VTE

A VTE event is thought to be idiopathic if it occurs without a clearly identified provoking factor.

Commonly accepted risk factors for VTE are recent surgery, hospitalization for an acute medical illness, active cancer, and some inherited thrombophilias. Less clear is whether immobilization, pregnancy, use of female hormones, and long-distance travel should also be considered as provoking conditions. Various trials have used different combinations of risk factors as exclusion criteria to define idiopathic (unprovoked) VTE when assessing the length or intensity of anticoagulation (TABLE 2).<sup>24–29</sup> The ACCP guidelines<sup>2</sup> cite estrogen therapy, pregnancy, and travel longer than 8 hours as minor risk factors for VTE.

In an observational study,<sup>3</sup> patients with oral contraceptive use, transient illness, immobilization, or a history of travel had an 8.8% risk of recurrence vs 19.4% in patients with unprovoked VTE. The meta-analysis discussed above (TABLE 1)<sup>8</sup> also shows that patients with these nonsurgical risk factors have a lower rate of recurrence than patients with idiopathic VTE.

The high rate of recurrence of idiopathic VTE (4% to 27% after 3 months of anticoagulation<sup>24–26</sup>) suggests that a longer duration of treatment is reasonable. However, increasing the length of therapy from 3 to 12 months delays but does not prevent recurrence, the risk of which begins to accumulate once anticoagulation is stopped.<sup>24,25</sup>

Three promising strategies to identify subgroups of patients with idiopathic VTE who are at highest risk of recurrence and who would benefit the most from prolonged anticoagulation are D-dimer testing, evaluation for residual vein thrombosis in patients who present with a deep vein thrombosis, and clinical prediction rules.

TABLE 2

**Risk factors excluded in trials of treatment of idiopathic venous thromboembolism**

| RISK FACTORS EXCLUDED                                                               | KEARON ET AL, <sup>26</sup> 1999 | AGNELLI ET AL, <sup>25</sup> 2001 | AGNELLI ET AL, <sup>24</sup> 2003 | RIDKER ET AL, <sup>29</sup> 2003 | KEARON ET AL, <sup>27</sup> 2003 | PALARETI ET AL, <sup>28</sup> 2006 |
|-------------------------------------------------------------------------------------|----------------------------------|-----------------------------------|-----------------------------------|----------------------------------|----------------------------------|------------------------------------|
| Hospitalization with confinement to bed for 3 consecutive days in previous 3 months | X                                |                                   |                                   |                                  | X                                | X                                  |
| Surgery or general anesthesia in previous 3 months                                  | X                                | X                                 | X                                 | X                                | X                                | X                                  |
| Cancer                                                                              | X                                | X                                 | X                                 | X                                | X                                | X                                  |
| Thrombophilia                                                                       | X                                | X                                 | X                                 |                                  | X                                | X                                  |
| Immobilization more than 7 days from any cause                                      |                                  | X                                 | X                                 |                                  |                                  |                                    |
| Trauma in the previous 3 months                                                     | X                                | X                                 | X                                 |                                  |                                  |                                    |
| Pregnancy                                                                           |                                  | X                                 | X                                 |                                  |                                  | X                                  |
| Recent childbirth                                                                   |                                  | X                                 | X                                 |                                  |                                  | X                                  |
| Taking oral contraceptives                                                          |                                  | X                                 | X                                 |                                  |                                  |                                    |

ADAPTED FROM KAATZ S, QURESHI W, FAIN C, PAJE D. DURATION OF ANTICOAGULATION TREATMENT IN PATIENTS WITH VENOUS THROMBOEMBOLISM. J AM OSTEOPATH ASSOC 2010; 110:638–644. COPYRIGHT 2010 AMERICAN OSTEOPATHIC ASSOCIATION. REPRINTED WITH THE CONSENT OF THE AMERICAN OSTEOPATHIC ASSOCIATION.

**D-dimer testing**

D-dimer is a degradation product of fibrin and is an indirect marker of residual thrombosis.<sup>30</sup>

In a systematic review of patients with a first episode of unprovoked VTE,<sup>31</sup> a normal D-dimer concentration at the end of at least 3 months of anticoagulation was associated with a 3.5% annual risk of recurrence, whereas an elevated D-dimer level at that time was associated with an annual risk of 8.9%. These results were confirmed in a systematic review of individual patient data.<sup>32</sup>

In a randomized trial,<sup>28</sup> patients with an idiopathic VTE event who received anticoagulation for at least 3 months had their D-dimer level measured 1 month after cessation of treatment. Those with an elevated level were randomized to either resume anticoagulation or not. Patients who resumed anticoagulation had an annual recurrence rate of 2%; however, those who were allocated not to restart anticoagulation had a recurrence rate of 10.9% per year. There was no difference in the rate of major bleeding between the two groups. Patients in this clinical trial who had a normal D-dimer level did not restart anticoagulation and had an annual recurrence rate of 4.4%.

**Evaluation for residual thrombosis**

Patients who have residual deep vein thrombosis after treatment have been shown to have higher rates of recurrent VTE.<sup>33</sup> Therefore, repeating Doppler ultrasonography is another clinical consideration that may help establish the optimal duration of anticoagulation.

A randomized trial<sup>34</sup> in patients with both provoked and idiopathic deep vein thrombosis showed a reduction in recurrence when those who had residual vein thrombosis were given extended anticoagulation. In the subset of patients whose deep vein thrombosis was idiopathic, the recurrence rate was 17% per year when treatment lasted only 3 months and 10% when it was extended for up to 1 year.

Another trial<sup>35</sup> randomized patients with provoked and idiopathic deep vein thrombosis to receive anticoagulation for the usual duration or to continue treatment until recanalization of the residual thrombus was demonstrated on follow-up Doppler ultrasonography. Patients who received this ultrasonography-tailored treatment had a lower rate of recurrence of VTE; however, the absolute reductions in recurrence rates cannot be calculated from this report for patients with idiopathic

**Inherited prothrombotic abnormalities do not appear to play an important role in the risk of a recurrent event**



**TABLE 3**  
**Suggested durations of anticoagulation for venous thromboembolism**

| CATEGORY OF VENOUS THROMBOEMBOLISM | LENGTH OF TREATMENT                                                                                                                  |
|------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Provoked                           | 3 months                                                                                                                             |
| Cancer-related                     | Until cancer is resolved                                                                                                             |
| Idiopathic                         | Probably indefinite                                                                                                                  |
| Recurrent                          | Indefinite                                                                                                                           |
| Thrombophilia-related              | Probably based on clinical factors, but patients with antiphospholipid antibody syndrome should receive anticoagulation indefinitely |

ADAPTED FROM KAATZ S, QURESHI W, FAIN C, PAJE D. DURATION OF ANTICOAGULATION TREATMENT IN PATIENTS WITH VENOUS THROMBOEMBOLISM. J AM OSTEOPATH ASSOC 2010; 110:638–644. COPYRIGHT 2010 AMERICAN OSTEOPATHIC ASSOCIATION. REPRINTED WITH THE CONSENT OF THE AMERICAN OSTEOPATHIC ASSOCIATION.

**We prefer using D-dimer levels over ultrasonography to detect residual vein thrombosis**

deep vein thrombosis.

A prospective observational study<sup>36</sup> of the predictive value of D-dimer status and residual vein thrombus found that only D-dimer was an independent risk factor for recurrent VTE after vitamin K antagonist withdrawal.

## A clinical prediction rule: 'Men and HERDOO<sub>2</sub>'

A promising tool for predicting if a patient is at low risk of recurrent VTE after the first episode of proximal deep vein thrombosis or pulmonary embolism is known by the mnemonic device "Men and HERDOO<sub>2</sub>." It is based on data prospectively derived by Rodger et al<sup>37</sup> to identify patients with less than a 3% annual risk of recurrent VTE after their first event of idiopathic proximal deep vein thrombosis or pulmonary embolism. Risk factors for recurrent VTE were male sex (the "men" of "Men and HERDOO<sub>2</sub>"), signs of postthrombotic syndrome, including hyperpigmentation of the lower extremities, edema or redness of either leg, a D-dimer level > 250 µg/L, obesity (body mass index > 30 kg/m<sup>2</sup>, and older age (> 65 years).

Overall, one-fourth of the population were women with no risk factors or one risk factor,

and their risk of recurrence was 1.6% per year. Men and women who had two or more risk factors for postthrombotic syndrome (hyperpigmentation, edema, or redness), elevated D-dimer, obesity, or older age were predicted to be at higher risk of recurrent VTE. Patients such as this should be considered for indefinite anticoagulation.

Ideally, clinical prediction rules should be validated in a separate group of patients before they are used routinely in practice,<sup>38</sup> and this clinical prediction rule is currently being tested in the REVERSE II study. If the results are consistent, this will be an easy-to-use tool to help identify patients who likely can safely stop anticoagulation therapy after 3 to 6 months (clinicaltrials.gov Identifier: NCT00967304).

The location of the thrombosis also influences the likelihood of recurrence. Patients with isolated distal (calf) deep vein thrombosis are less likely to suffer recurrent VTE than those who present with proximal deep vein thrombosis. However, trials focusing specifically on the precise subset of idiopathic isolated distal deep vein thrombosis are lacking. In a randomized trial<sup>39</sup> comparing 6 vs 12 weeks of anticoagulation for isolated distal deep vein thrombosis and 12 vs 24 weeks for proximal deep vein thrombosis, the annual rates of recurrence after 12 weeks of treatment were approximately 3.4% for isolated distal and 8.1% for proximal deep vein thrombosis.<sup>39</sup>

## Recommendation:

### At least 3 months of warfarin or equivalent

We agree with the ACCP recommendation<sup>2</sup> that patients with unprovoked VTE should receive at least 3 months of anticoagulation with a vitamin K antagonist.

If the patient has no risk factors for bleeding and good anticoagulant monitoring is achievable, we agree with long-term anticoagulation for proximal unprovoked deep vein thrombosis or pulmonary embolism, and 3 months of therapy for isolated distal unprovoked deep vein thrombosis.

Patient preferences and the risk of recurrence vs the risk of bleeding should be discussed with patients when contemplating indefinite anticoagulation.

If testing is being considered to assist in

the decision to prescribe indefinite anticoagulation, we prefer using D-dimer levels rather than ultrasonography to detect residual venous thrombosis because of its ease of use and the strength of the current evidence.

## ■ PREVENTING POSTTHROMBOTIC SYNDROME

The postthrombotic (postphlebotic) syndrome is a chronic and burdensome consequence of deep vein thrombosis that occurs despite anticoagulation therapy. It is estimated to affect 23% to 60% of patients and typically manifests in the first 2 years.<sup>40</sup> It is not only costly in clinical terms, with decreased quality of life for the patient, but health care expenditures have been estimated to range from \$400 per year in a Brazilian study to \$7,000 per year in a US study.<sup>40</sup>

Typical symptoms include leg pain, heaviness, swelling, and cramping. In severe cases, chronic venous ulcers can occur and are difficult to treat.<sup>41</sup>

The definition of postthrombotic syndrome has been unclear over the years, and six different scales that measure signs and symptoms have been reported.<sup>42</sup>

The Villalta scale has been proposed by the International Society of Thrombosis and Hemostasis as a diagnostic standard to define postthrombotic syndrome.<sup>42</sup> This validated scale is based on five clinical symptoms, six clinical signs, and the presence or absence of venous ulcers. Each clinical symptom and sign is scored as mild (1 point), moderate (2 points), or severe (3 points). Symptoms include pain, cramps, heaviness, paresthesia, and pruritus; the six clinical signs are pretibial edema, skin induration, hyperpigmentation, redness, venous ectasia, and pain on calf compression.

According to the International Society of Thrombosis and Hemostasis, postthrombotic syndrome is present if the Villalta score is 5 or greater or if a venous ulcer is present in a leg with previous deep vein thrombosis. Further, using the Villalta scale, postthrombotic syndrome can be categorized as mild (score 5–9), moderate (10–14), or severe ( $\geq 15$ ).

A limitation of the Villalta scale is that the presence or absence of a venous ulcer has not been assigned a score. Since a venous ulcer

requires more aggressive measures, the society defines postthrombotic syndrome as severe if venous ulcers are present.<sup>42</sup>

Acute symptoms of deep vein thrombosis may take months to resolve and, indeed, acute symptoms may transition to chronic symptoms without a symptom-free interval. It is recommended that postthrombotic syndrome not be diagnosed before 3 months to avoid inappropriately attributing acute symptoms and signs of deep vein thrombosis to the postthrombotic syndrome.<sup>42</sup>

## Studies of stockings

A systematic review of three randomized trials<sup>44</sup> concluded that elastic compression stockings reduce the risk of postthrombotic syndrome (any severity) from 43% to 20% and severe postthrombotic syndrome from 15% to 7%.<sup>43</sup>

The first of these trials<sup>44</sup> randomized patients soon after the diagnosis of deep vein thrombosis to receive made-to-order compression stockings that were rated at 30 to 40 mm Hg or to be in a control group that did not receive stockings. The second trial<sup>45</sup> randomized patients 1 year after the index event of deep vein thrombosis to receive 20- to 30-mm Hg stockings or stockings that were two sizes too large (the control group). The third study<sup>46</sup> randomly allocated patients to receive “off-the-shelf” stockings (30–40 mm Hg) or no stockings. Each study used its own definition of postthrombotic syndrome.

Although these studies strongly suggest compression stockings prevent postthrombotic syndrome, several methodologic issues remain:

- A standard definition of postthrombotic syndrome was not used
- The amount of compression varied between studies
- The studies were not blinded.

Lack of blinding becomes most significant when an outcome is based on subjective findings, like the symptoms that make up a large part of the diagnosis of postthrombotic syndrome.

The SOX trial, currently under way, is designed to address these methodologic issues and should be completed in 2012 ([clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00143598).

**After proximal deep vein thrombosis, use compression stockings for at least 2 years**

### Recommendation:

#### Stockings for at least 2 years

We agree with the ACCP recommendation that a patient who has had a symptomatic proximal deep vein thrombosis should wear an elastic compression stocking with an ankle pressure gradient of 30 to 40 mm Hg as soon as possible after starting anticoagulant therapy and continuing for a minimum of 2 years.<sup>2</sup>

### ■ SCREENING FOR OCCULT MALIGNANCY

VTE can be the first manifestation of cancer.

French physician Armand Trousseau, in the 1860s, was the first to describe disseminated intravascular coagulation closely associated with adenocarcinoma. Ironically, several years later, after suffering for weeks from abdominal pain, he declared to one of his students that he had developed thrombosis, and he died of gastric cancer shortly thereafter.<sup>47</sup>

Since cancer is a well-known risk factor for VTE, it is logical to screen for cancer as an explanation for an idiopathic VTE event.<sup>48</sup> To make an informed decision, one needs to understand the rate of occult cancer at the time VTE is diagnosed, the risk of future development of cancer, and the utility of extensive cancer screening.

The clinical efficacy, side effects, and cost-effectiveness of cancer screening in patients with idiopathic VTE are unknown. However, a systematic review<sup>47</sup> of 34 studies found that, in patients with idiopathic VTE, cancer was diagnosed within 1 month in 6.1%, within 6 months in 8.6%, and within 1 year in 10.0% (95% CI 8.6–11.3).

A subset of studies compared two strategies for screening soon after the diagnosis of idiopathic VTE: a strategy limited to the history, physical examination, basic blood work, and chest radiography vs an extensive screening strategy that also included serum tumor markers or abdominal ultrasonography or computed tomography. Limited screening detected 49% of the prevalent cancers; extensive screening increased this rate to 70%. Stated another way, the detection rate for prevalent cancers was 5% with limited screening and 7% with extensive screening soon after the diagnosis of idiopathic VTE.<sup>47</sup>

Patients with idiopathic VTE had higher

rates of cancer within 1 month of diagnosis than patients with provoked VTE (6.1% vs 1.9%), and this difference persisted at 1 year (10.0% vs 2.6%).<sup>47</sup>

### Recommendation:

#### Individualized cancer screening

Patients with idiopathic VTE have a significant risk of occult cancer within the first year after diagnosis, and cancer screening should be considered. Our practice for patients with idiopathic VTE is to perform a history and physical examination and ensure that the patient is up to date on age- and sex-specific cancer screening.

The use of additional imaging or biomarkers should be discussed with patients so they can balance the risks (radiation and potential false-positive results with their downstream consequences), costs, and potential benefits, given the lack of proven survival benefit or cost-effectiveness.

### ■ ORAL ANTICOAGULANT MANAGEMENT

Warfarin's multiple interactions, along with the need for INR monitoring, make it a difficult medication to manage.

The Joint Commission, the US organization for health service accreditation and certification, has defined National Patient Safety Goals and quality measures for the management of anticoagulation.<sup>49</sup> Organized anticoagulation management services, dosing algorithms, and patient self-testing using capillary INR meters or patient self-management of warfarin were recommended as tools to improve the time patients spend in the therapeutic INR range.<sup>50</sup>

#### Two new oral anticoagulants

The limitations of warfarin have stimulated the search for newer oral anticoagulants that do not require laboratory monitoring or have as many diet and drug interactions.

Two trials have been published with experimental oral anticoagulants that had similar efficacy and safety as warfarin in the treatment of VTE.

The study of dabigatran (Pradaxa) vs warfarin in the treatment of acute VTE (the RECOVER trial)<sup>51</sup> randomized 2,539 patients

**For patients with unprovoked (idiopathic) VTE, we assure they are up to date with routine guideline-based cancer screening**



with acute VTE to receive the oral direct thrombin inhibitor dabigatran or warfarin for approximately 6 months. Of note, each treatment group received a median of 6 days of heparin, LMWH, or fondaparinux at the beginning of blinded therapy. The rates of recurrent VTE and major bleeding were similar between the treatment arms, and overall bleeding was less with dabigatran. Dabigatran was approved in the United States in October 2010 for stroke prevention in atrial fibrillation but has yet to be approved for the treatment of VTE pending further study ([clinicaltrials.gov](http://clinicaltrials.gov) Identifier: NCT00680186).

A study of oral rivaroxaban (Xarelto) for symptomatic VTE (the EINSTEIN-DVT trial)<sup>52</sup> randomized 3,449 patients with acute deep vein thrombosis to rivaroxaban or enoxaparin (Lovenox) overlapped with warfarin or another vitamin K antagonist in the usual manner. No

difference was noted between the treatments in the rate of recurrence of VTE or of major bleeding. Of note, patients randomized to rivaroxaban received 15 mg twice a day for the first 3 weeks of treatment and then 20 mg per day for the remainder of their therapy and did not require parenteral anticoagulant overlap.

The long-awaited promise of easier-to-use oral anticoagulants for the treatment of VTE is drawing near and has the potential to revolutionize the treatment of this common disorder. In the meantime, close monitoring of warfarin and careful patient education regarding its use are essential. And even with the development of new drugs in the future, it is still imperative that patients with acute VTE receive the correct length of anticoagulation treatment, are prescribed stockings to prevent postthrombotic syndrome, and are updated on routine cancer screening. ■

## REFERENCES

1. Spencer FA, Emery C, Lessard D, et al. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. *J Gen Intern Med* 2006; 21:722–727.
2. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ; American College of Chest Physicians. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(suppl 6):454S–545S.
3. Baglin T, Luddington R, Brown K, Baglin C. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. *Lancet* 2003; 362:523–526.
4. Schulman S, Lockner D, Juhlin-Dannfelt A. The duration of oral anticoagulation after deep vein thrombosis. A randomized study. *Acta Med Scand* 1985; 217:547–552.
5. Optimum duration of anticoagulation for deep-vein thrombosis and pulmonary embolism. Research Committee of the British Thoracic Society. *Lancet* 1992; 340:873–876.
6. Schulman S, Rhedin AS, Lindmarker P, et al. A comparison of six weeks with six months of oral anticoagulant therapy after a first episode of venous thromboembolism. Duration of Anticoagulation Trial Study Group. *N Engl J Med* 1995; 332:1661–1665.
7. Kearon C, Ginsberg JS, Anderson DR, et al. Comparison of 1 month with 3 months of anticoagulation for a first episode of venous thromboembolism associated with a transient risk factor. *J Thromb Haemost* 2004; 2:743–749.
8. Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. *Arch Intern Med* 2010; 170:1710–1716.
9. Prandoni P, Lensing AW, Piccoli A, et al. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002; 100:3484–3488.
10. Hull RD, Pineo GF, Brant RF, et al; LITE Trial Investigators. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med* 2006; 119:1062–1072.
11. Lee AY, Levine MN, Baker RI, et al; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; 349:146–153.
12. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology, Venous Thromboembolic Disease. [http://www.nccn.org/professionals/physician\\_gls/pdf/vte.pdf](http://www.nccn.org/professionals/physician_gls/pdf/vte.pdf). Accessed August 3, 2011.
13. Lyman GH, Khorana AA, Falanga A, et al; American Society of Clinical Oncology. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol* 2007; 25:5490–5505.
14. Schulman S, Granqvist S, Holmström M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. *N Engl J Med* 1997; 336:393–398.
15. Christiansen SC, Cannegieter SC, Koster T, Vandenbroucke JP, Rosendaal FR. Thrombophilia, clinical factors, and recurrent venous thrombotic events. *JAMA* 2005; 293:2352–2361.
16. Segal JB, Brotman DJ, Necochea AJ, et al. Predictive value of factor V Leiden and prothrombin G20210A in adults with venous thromboembolism and in family members of those with a mutation: a systematic review. *JAMA* 2009; 301:2472–2485.
17. Brouwer JL, Lijfering WM, Ten Kate MK, Kluin-Nelemans HC, Veeger NJ, van der Meer J. High long-term absolute risk of recurrent venous thromboembolism in patients with hereditary deficiencies of protein S, protein C or antithrombin. *Thromb Haemost* 2009; 101:93–99.
18. Schulman S, Svenungsson E, Granqvist S. Anticardiolipin antibodies predict early recurrence of thromboembolism and death among patients with venous thromboembolism following anticoagulant therapy. Duration of Anticoagulation Study Group. *Am J Med* 1998; 104:332–338.
19. Derksen RH, de Groot PG. Towards evidence-based treatment of thrombotic antiphospholipid syndrome. *Lupus* 2010; 19:470–474.

20. Lim W, Crowther MA, Eikelboom JW. Management of antiphospholipid antibody syndrome: a systematic review. *JAMA* 2006; 295:1050–1057.
21. Fonseca AG, D'Cruz DP. Controversies in the antiphospholipid syndrome: can we ever stop warfarin? *J Autoimmune Dis* 2008; 5:6.
22. Crowther MA, Ginsberg JS, Julian J, et al. A comparison of two intensities of warfarin for the prevention of recurrent thrombosis in patients with the antiphospholipid antibody syndrome. *N Engl J Med* 2003; 349:1133–1138.
23. Finazzi G, Marchioli R, Brancaccio V, et al. A randomized clinical trial of high-intensity warfarin vs. conventional antithrombotic therapy for the prevention of recurrent thrombosis in patients with the antiphospholipid syndrome (WAPS). *J Thromb Haemost* 2005; 3:848–853.
24. Agnelli G, Prandoni P, Becattini C, et al; Warfarin Optimal Duration Italian Trial Investigators. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. *Ann Intern Med* 2003; 139:19–25.
25. Agnelli G, Prandoni P, Santamaria MG, et al; Warfarin Optimal Duration Italian Trial Investigators. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. *N Engl J Med* 2001; 345:165–169.
26. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med* 1999; 340:901–907.
27. Kearon C, Ginsberg JS, Kovacs MJ, et al; Extended Low-Intensity Anticoagulation for Thrombo-Embolism Investigators. Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; 349:631–639.
28. Palareti G, Cosmi B, Legnani C, et al; PROLONG Investigators. D-dimer testing to determine the duration of anticoagulation therapy. *N Engl J Med* 2006; 355:1780–1789.
29. Ridker PM, Goldhaber SZ, Glynn RJ. Low-intensity versus conventional-intensity warfarin for prevention of recurrent venous thromboembolism. *N Engl J Med* 2003; 349:2164–2167.
30. Bockenstedt P. D-dimer in venous thromboembolism. *N Engl J Med* 2003; 349:1203–1204.
31. Verhovsek M, Douketis JD, Yi Q, et al. Systematic review: D-dimer to predict recurrent disease after stopping anticoagulant therapy for unprovoked venous thromboembolism. *Ann Intern Med* 2008; 149:481–490, W94.
32. Douketis J, Tosetto A, Marcucci M, et al. Patient-level meta-analysis: effect of measurement timing, threshold, and patient age on ability of D-dimer testing to assess recurrence risk after unprovoked venous thromboembolism. *Ann Intern Med* 2010; 153:523–531.
33. Prandoni P, Lensing AW, Prins MH, et al. Residual venous thrombosis as a predictive factor of recurrent venous thromboembolism. *Ann Intern Med* 2002; 137:955–960.
34. Siragusa S, Malato A, Anastasio R, et al. Residual vein thrombosis to establish duration of anticoagulation after a first episode of deep vein thrombosis: the Duration of Anticoagulation based on Compression UltraSonography (DACUS) study. *Blood* 2008; 112:511–515.
35. Prandoni P, Prins MH, Lensing AW, et al; AESOPUS Investigators. Residual thrombosis on ultrasonography to guide the duration of anticoagulation in patients with deep venous thrombosis: a randomized trial. *Ann Intern Med* 2009; 150:577–585.
36. Cosmi B, Legnani C, Cini M, Guazzaloca G, Palareti G. D-dimer levels in combination with residual venous obstruction and the risk of recurrence after anticoagulation withdrawal for a first idiopathic deep vein thrombosis. *Thromb Haemost* 2005; 94:969–974.
37. Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. *CMAJ* 2008; 179:417–426.
38. McGinn TG, Guyatt GH, Wyer PC, Naylor CD, Stiell IG, Richardson WS. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. *JAMA* 2000; 284:79–84.
39. Pinede L, Ninet J, Duhaut P, et al; Investigators of the "Durée Optimale du Traitement AntiVitamines K" (DOTAVK) Study. Comparison of 3 and 6 months of oral anticoagulant therapy after a first episode of proximal deep vein thrombosis or pulmonary embolism and comparison of 6 and 12 weeks of therapy after isolated calf deep vein thrombosis. *Circulation* 2001; 103:2453–2460.
40. Ashrani AA, Heit JA. Incidence and cost burden of post-thrombotic syndrome. *J Thromb Thrombolysis* 2009; 28:465–476.
41. Kahn SR, Shrier I, Julian JA, et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. *Ann Intern Med* 2008; 149:698–707.
42. Kahn SR, Patsch H, Vedantham S, Prandoni P, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization 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 standardization. *J Thromb Haemost* 2009; 7:879–883.
43. Kolbach DN, Sandbrink MW, Hamulyak K, Neumann HA, Prins MH. Non-pharmaceutical measures for prevention of post-thrombotic syndrome. *Cochrane Database Syst Rev* 2004; CD004174.
44. Brandjes DP, Büller HR, Heijboer H, et al. Randomised trial of effect of compression stockings in patients with symptomatic proximal-vein thrombosis. *Lancet* 1997; 349:759–762.
45. Ginsberg JS, Hirsh J, Julian J, et al. Prevention and treatment of postphlebotic syndrome: results of a 3-part study. *Arch Intern Med* 2001; 161:2105–2109.
46. 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.
47. Carrier M, Le Gal G, Wells PS, Fergusson D, Ramsay T, Rodger MA. Systematic review: the Trousseau syndrome revisited: should we screen extensively for cancer in patients with venous thromboembolism? *Ann Intern Med* 2008; 149:323–333.
48. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. *JAMA* 2005; 293:715–722.
49. Kaatz S. Impact on patient care: patient case through the continuum of care. *J Thromb Thrombolysis* 2010; 29:167–170.
50. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G; American College of Chest Physicians. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133(suppl 6):1605–1985.
51. Schulman S, Kearon C, Kakkar AK, et al, for the RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; 361:2342–2452.
52. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; 363; 2499–2510.

ADDRESS: Scott Kaatz, DO, MSc, FACP, Department of Medicine, Henry Ford Hospital, 2799 W. Grand Boulevard, Detroit, MI 48202; e-mail skaatz1@hfhs.org.