CLINICAL UTILITY

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Question 35: What are the financial costs associated with testing?
Question 36: What are the economic benefits associated with actions resulting from testing?
Question 37: What facilities/personnel are available or easily put in place?
Question 38: What educational materials have been developed and validated, and which of these are available?
Question 39: Are there informed consent requirements?
Question 40: What methods exist for long term monitoring?
Question 41: What guidelines have been developed for evaluating program performance?

CLINICAL UTILITY

Question 26: What is the natural history of the disorder?

Summary

Major complications after an episode of recurrent deep venous thrombosis are:

- Death from pulmonary embolism, but the prevalence of factor V Leiden is higher in patients with deep venous thrombosis than in patients with pulmonary embolism, suggesting that factor V Leiden carries a lower risk for pulmonary embolism than thrombophilias from other causes.
- Post-thrombotic syndrome in approximately 25 percent.
- Recurrent episodes of deep venous thrombosis over the succeeding 10 years in about 20 percent.
- Risk of major bleeding due to treatment of 1-2.7 percent per year, of which 20 percent is fatal.

The following paragraphs describe major complications that can occur after a first episode of deep venous thrombosis, including death from a pulmonary embolism, the post-thrombotic syndrome, recurrent episodes of thrombosis, and side effects of treatment, such as major hemorrhage.

Pulmonary embolism

The International Cooperative Pulmonary Embolism Registry (Goldhaber *et al.,* 1999) found an overall three-month mortality of 17.4 percent for all patients with pulmonary embolism, with 45 percent of deaths ascribed directly to the embolic event. Simmoneau *et al.* (1997) and the

Columbus (1997) investigators found lower rates of 1.0 percent and 2.2 percent, respectively. However, neither article included individuals with massive pulmonary embolism requiring thrombolytic treatment.

It is now believed that the prevalence of the factor V Leiden mutation is higher in patients with uncomplicated deep venous thrombosis (i.e., without pulmonary embolism) than in patients with pulmonary embolism (with or without deep venous thrombosis) (Manten *et al* 1996; Martinelli *et al*., 1997). Bounameaux (2000) performed a meta-analysis that included the studies described above and came to the same conclusion as that reached in the separate studies. Several possible explanations are described for the difference in prevalence of the factor V Leiden mutation between patients with pulmonary embolism and patients with uncomplicated deep venous thrombosis. One explanation might be that all patients with pulmonary embolism are consecutive (unselected), while the patients with deep venous thrombosis come from specialized centers. However, this difference in prevalence was confirmed by several studies, making this explanation unlikely. Possibly, the clot in patients with factor V Leiden is more stable and more adherent to the vessel wall, thus leading less often to pulmonary embolism. *In vitro* observations show that, in factor V Leiden carriers, the thrombus occurs less often in the iliofemoral vein. Also, the thrombus is smaller in patients with factor V Leiden.

Margaglione *et al.* (2000) found that the frequency of the prothrombin 20210A mutation was the same among individuals with uncomplicated deep venous thrombosis and those with deep venous thrombosis and pulmonary embolism, whereas the frequency was lower for patients with pulmonary embolism only.

Post-thrombotic syndrome

The post-thrombotic syndrome occurs as a result of venous hypertension due to outflow obstruction and damage to the venous valves. Clinical characteristics are leg pain, skin changes and swelling. Leg ulcers are one of the most serious complications of post-thrombotic syndrome. Prandoni *et al.* (1996) found a cumulative incidence of the post-thrombotic syndrome of 22.8 percent after two years, 28 percent after five years, and 29.1 percent after eight years. Brandjes *et al.* (1996) found that, in patients with a first episode of proximal deep venous thrombosis, the cumulative incidence of mild-to-moderate post-thrombotic syndrome is about 50 percent, and of severe post-thrombotic syndrome 23 percent. The post-thrombotic syndrome is more likely to occur after recurrent episodes of deep venous thrombosis and can have great impact on quality of life. A study by Maessen-Visch *et al.* (1999) showed a significantly increased prevalence of the factor V Leiden mutation (23 percent) in patients with venous leg ulcers compared to a control group (7.5 percent). Ninety-one percent of the patients with the factor V Leiden mutation had a history of venous thromboembolism compared with 48 percent of the controls, suggesting that patients with venous thromboembolism and the factor V Leiden mutation have an increased risk of developing leg ulcers.

Recurrence risk

As shown in Question 21, few studies are available on the incidence of recurrence within five years after the first thrombosis. Rates vary around 20 percent for recurrent venous thrombosis within 10 years after the first event.

Bleeding risk

The risk of major bleeding due to anticoagulant treatment is 1-2.7 percent per year, of which one in five cases is fatal (Van der Meer *et al.,* 1993; Palareti *et al.,* 1996). The risk of bleeding complications rises significantly with age and the achieved International Normalized Ratio (Hirsh *et al*., 2002).

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CLINICAL UTILITY

Question 27: What is the impact of a positive (or negative) test on patient care?

SUMMARY

Impact of a positive test

A screening or diagnostic test is considered worthwhile, if a positive result leads to some clinical action, such as a change in treatment.

- Duration of anticoagulant treatment depends on the type of venous thrombotic event and whether it was caused by a temporary or consistent risk factor.
- There are no conclusive studies addressing the optimal duration of anticoagulation in homozygous individuals with the factor V Leiden mutation or individuals either homozygous or heterozygous for the prothrombin 20210A mutation.
- A decision analysis model showed benefit for extension of treatment for at least one year in patients heterozygous for the factor V Leiden mutation with deep venous thrombosis but not for those with pulmonary embolism.
- This report finds no significant increase in the incidence of recurrent thrombotic episodes among individuals hetero-or homozygous for the factor V Leiden or prothrombin 20210A mutation, in comparison to patients without the mutation.
- This implies that the outcome of these genetic tests (i.e. either a positive or a negative test) should not influence patient care.
- However, other studies are needed to confirm this.

Impact of a negative test

- A negative test result could lead to under-treatment and an increased prevalence of recurrent thrombotic episodes among individuals who are found not to have one of the mutations after an initial episode of venous thrombosis.

Recommendation regardless of outcome of screening test

- Use of elastic stocking(s) to prevent the post-thrombotic syndrome

Impact of a positive test

For a screening or diagnostic test to be worthwhile in the present context, the implication of a positive test result should be a change in treatment to prevent recurrence.

There are no conclusive studies addressing the question of the optimal duration of anticoagulation among homozygous individuals with the factor V Leiden mutation or among individuals either homozygous or heterozygous for the prothrombin 20210A mutation. Sarasin *et al.* (1998) developed a decision analysis model to determine the risks and benefits of stopping oral anticoagulation after three months, with re-initiation only after recurrent thrombosis, versus extending oral anticoagulation up to one to five years. The hypothetical cohort consisted of 1,000 carriers of factor V Leiden recovering from a first episode of deep vein thrombosis in the lower limbs. Even with using a best case scenario favoring prolonged anticoagulation (at least beyond one year), their analysis suggests that, among factor V Leiden carriers, the number of major hemorrhages induced by anticoagulants exceeds the number of clinical pulmonary emboli prevented over the entire range of duration of anticoagulation. However, the number of recurrent

deep vein thrombi prevented by prolonged treatment widely exceeds the number of iatrogenic induced hemorrhages.

A few studies provide reliable estimates on the risk of recurrent episodes of venous thrombosis in different treatment settings. They concluded that six weeks of oral anticoagulation is sufficient in isolated calf deep vein thrombosis (Pinede *et al.,* 2001), and that four weeks (Levine *et al.,* 1995), six weeks (Schulman *et al.,* 1995) and three months (Pinede *et al.,* 2001) of treatment is sufficient for patients with temporary risk factors. Patients with persisting risk factors may require six months of treatment (Schulman *et al.,* 1995), or at least more than three months of treatment (Levine *et al.,* 1995; Kearon *et al.,* 1999).

We find a mean incidence of recurrent venous thrombosis in factor V Leiden carriers of 4.8 percent per year in five studies, with three finding no significant increase over patients without the mutation. The mean incidence of recurrent venous thrombosis in prothrombin 20210A carriers per year is 4.1 percent with two out of the four eligible studies showing no significant difference in the recurrence risk between patients with and without the prothrombin 20210A mutation (Table 4, Questions 18 and 19). In one of the studies with a significant difference found, individuals with the factor V Leiden mutation were not excluded from the calculation (Miles *et al.,* 2001). Thus, from the results in this report, we can conclude that the risk of a recurrent venous thrombosis is not different among individuals who carry either the factor V Leiden or the prothrombin mutation, as opposed to individuals without these mutations. This implies that the outcome of these genetic tests (i.e. either a positive or a negative test) should not influence patient care. However, other studies are needed to confirm this.

Impact of a negative test
A negative test result could lead to under-treatment and an increased prevalence of recurrent thrombotic episodes among individuals who are found not to have one of the mutations after an initial episode of venous thrombosis.

Recommendations regardless the outcome of a screening or diagnostic test
Brandjes *et al.* (1997) studied the effect of elastic stockings on the risk of developing post-thrombotic syndrome after a first episode of venous thrombosis in a randomized trial. Patients with proximal vein thrombosis were randomized in a group with (n=96) and a group without elastic stockings (n=98). Wearing elastic stockings for at least two years after the first thrombotic event reduced the risk of post thrombotic syndrome by 50 percent. Venous ulceration was observed in four patients, one in the group wearing elastic stockings and three in the group without elastic stockings. In this study, none of the patients was tested for the factor V Leiden mutation. No difference in the rate of recurrent venous thrombosis was observed between the group wearing elastic stockings and the group that did not wear elastic stockings.

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CLINICAL UTILITY

Question 28: If applicable, are diagnostic tests available?

No diagnostic tests are available.

CLINICAL UTILITY

Question 29: Is there an effective remedy, acceptable action or other measurable benefit?

In patients receiving anticoagulant therapy, the likelihood of a recurrent episode of venous thrombosis is reduced, if the international normalized ratio (INR) is in the therapeutic range, although patients with advanced malignancy or anti-phospholipid antibody syndrome are at increased risk for recurrence despite having a therapeutic INR value (Hirsh *et al.,* 2002). However, as the risk of bleeding in general during therapy is high, lifelong treatment with anticoagulants is not generally recommended after a first episode of venous thrombosis.

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