

## Screening for the Risk for Bleeding or Thrombosis

Mark H. Eckman, MD; John K. Erban, MD; Sushil K. Singh, MD; and Grace S. Kao, MD

**Background:** Numerous tests are available to assess patient risk for bleeding or thrombosis. Appropriate use of these tests must involve consideration of the clinical setting, disease prevalence, performance characteristics of the tests, cost, and consequences of false-positive and false-negative results.

**Purpose:** To summarize information about coagulation testing in three common clinical settings: nonsurgical hospitalized patients, surgical patients, and patients having a first venous thromboembolic event.

**Data Sources:** All English-language studies identified in searches of MEDLINE (1966 to April 2002) and reference lists of key articles.

**Study Selection:** All published studies of blood coagulation testing as routine diagnostic tests or in the preoperative care of patients reporting postoperative bleeding complications, and all published studies of patients with the factor V Leiden mutation reporting venous thromboembolic outcomes.

**Data Extraction:** 5 observational studies of routine coagulation testing in nonsurgical hospitalized patients and 12 observational studies of preoperative coagulation testing, from which both sensitivity and specificity could be calculated.

**Data Synthesis:** Test performance characteristics for the partial thromboplastin time in predicting postoperative hemorrhage were pooled by type of surgery. Likelihood ratios for positive and negative results were calculated for each group; 95% confidence intervals were calculated. Patients with prolonged partial thromboplastin times did not have a statistically significantly increased risk for postoperative complications.

**Conclusion:** For nonsurgical and surgical patients without synthetic liver dysfunction or a history of oral anticoagulant use, routine testing has no benefit in assessment of bleeding risk. Routine testing after a first episode of venous thromboembolism is not recommended for most patients.

*Ann Intern Med.* 2003;138:W15-W24.

[www.annals.org](http://www.annals.org)

For author affiliations, see end of text.

In this article, we review the laboratory tests used to screen patients for bleeding or thrombosis, their sensitivity and specificity, prevalence of bleeding disorders or thrombophilia in several clinical settings, and studies evaluating the clinical utility and economic effects of such testing. We add to past reviews on this topic by updating the literature review and by examining the utility of testing from a Bayesian perspective, using concepts of pretest probabilities, likelihood ratios, and post-test probabilities (for example, positive predictive value and negative predictive value).

### SCREENING FOR THE RISK FOR BLEEDING

Screening tests include the readily available prothrombin time (PT), partial thromboplastin time (PTT), platelet estimate or count, and template bleeding time. All but the template bleeding time are highly reproducible, automated, and inexpensive on an individual basis but are expensive in the aggregate when routinely used to screen an unselected population (1). Obtaining a detailed history is the most important first step in determining whether testing is warranted (2).

#### Nonsurgical Hospitalized Patients

##### PT and PTT

Patients hospitalized for nonsurgical diagnoses do not benefit from routine admission testing of PT or PTT when no evidence of synthetic liver dysfunction or history of oral anticoagulant use exists (3–6). Although randomized trials have not been done to assess the outcomes of hospitalized nonsurgical patients for whom coagulation testing was withheld, observational studies investigating the utility of

these tests have failed to show improvement in clinical outcomes (5, 7, 8). Routine admission testing increases both expense and likelihood of false-positive results, leading to unnecessary additional testing. In 1979, Robbins and Rose (6) retrospectively analyzed abnormal results obtained from more than 1000 PTT measurements. Approximately 14% (143 patients) of the values were prolonged; however, 82% of the patients had known risk factors for bleeding (for example, known history of hemophilia, oral anticoagulant use, or history of liver disease). More important, the test did not alter clinical management for any of the patients.

In a study of patients admitted to a Veterans Administration medical service for liver disease and bleeding disorders, Eisenberg and Goldfarb (4) found that PT contributed little to information already obtained from the history and physical examination. Only 2 of 107 patients who had a PT screening test had abnormal results, whereas 41 of 121 patients who had a pertinent history or physical examination had prolonged PTs.

Erban and colleagues (9) evaluated ordering patterns and clinical indications for PT and PTT in 375 patients admitted to the medical service at the University of Pennsylvania, Philadelphia, Pennsylvania. Eighty-one percent of patients had PT and PTT ordered. When the appropriateness of test ordering compared with guidelines developed by the Medical Necessity Project of the Blue Cross and Blue Shield Associations of America (5) was evaluated, at least 70% of testing was not clinically indicated. They also found that test results had little impact on clinical care. Using 1988 U.S. dollars, they estimated that the direct cost per year attributable to inappropriate ordering of PTs and

**Table 1. Preoperative Assessment of Bleeding Risk\***

History
Excessive bruising, bleeding more than 3 minutes after brushing teeth, nosebleeds, prolonged bleeding after cuts, severe or prolonged menstrual periods
History of blood loss through the gastrointestinal or genitourinary tract
Severe bleeding after dental extraction, surgical operation, or childbirth
History of hemophilia or inherited familial hemorrhagic disorder
Personal history of liver disease, renal failure, hypersplenism, and hematologic or collagen vascular disease
Current or recent use of medication that may interfere with hemostasis
Physical examination
Purpura, hematoma, jaundice, and signs of cirrhosis

\* Data from reference 28.

PTTs was more than \$60 000 at their institution alone. Although many physicians consider these tests to be inexpensive, small-ticket items, overuse in the aggregate can generate substantial unnecessary medical costs.

### Platelet Count

The performance of routine platelet counts in asymptomatic nonsurgical patients also is not indicated and proves to be expensive. As shown by Robbins and Mushlin in 1979 (3), costs were more than \$50 000 per patient found to have asymptomatic thrombocytopenia. However, platelet counts may be useful to follow treatment involving certain medications. In a prospective study of more than 1100 consecutive patients with venous thromboembolism, Monreal and coworkers (10) demonstrated that patients who had heparin-induced bleeding had lower platelet counts before treatment (mean [ $\pm$  SD],  $227 \pm 112 \times 10^9/L$  vs.  $262 \pm 110 \times 10^9/L$ ;  $P = 0.01$ ).

Monitoring platelet counts during heparin therapy is also appropriate because of the possibility of heparin-induced thrombocytopenia, which has an incidence of approximately 1% to 3% (11). In type I, thrombocytopenia occurs during the first few days of heparin therapy. The platelet count seldom decreases below  $100 \times 10^9/L$  and often returns to normal despite continued heparin therapy. In contrast, type II causes severe thrombocytopenia starting approximately 5 to 15 days after initiation of heparin therapy (12–14). Early detection of thrombocytopenia and immediate discontinuation of heparin therapy are critical in preventing or reducing the risk for potentially life-threatening complications (15–18).

### Surgical Patients

#### PT and PTT

The PT and PTT were originally designed and optimized to detect deficiencies of coagulation factors, not to assess clinical risk for hemorrhage (1). Normal ranges are based on the general population and do not reflect values of postsurgical patients without significant bleeding. Equally important, the likelihood of a significant hereditary deficiency of a coagulation factor in an unselected patient population is small—approximately 17 per 100 000 men (factor VIII and factor IX deficiencies and von Wille-

brand disease) and 5 per 100 000 women (von Willebrand disease) (5, 8, 19). The prevalence of an isolated congenital deficiency of factor VII is even lower: 2 to 3 per 1 million persons (20, 21). Acquired deficiencies of factor VII are generally suspected in the presence of advanced hepatic disease, malabsorption, or malnutrition.

One population that bears special mention, however, are Ashkenazic Jews. These persons originate from eastern Europe and make up about 80% of North American Jews. The prevalence of heterozygous factor XI deficiency (an autosomal dominant trait with incomplete penetrance) is between 5.5% and 11%, whereas the prevalence of the homozygous deficiency is between 0.1% and 0.3% in this population (22–24). Three percent of Ashkenazic Jews have sufficiently low factor levels to have abnormal hemostasis, and about 1% actually do have excessive postoperative bleeding (25). Unlike other inherited coagulation disorders, factor XI deficiency often remains occult until surgery, at which time bleeding can be severe (24, 25). Furthermore, hemorrhage can be prevented by administering fresh frozen plasma before surgery. Nearly all factor XI-deficient patients have prolonged PTTs (22). If a cut-off point at the 80th percentile of the normal range of PTT is used to identify patients at risk for bleeding (factor XI level  $< 0.3$  U/mL), only 4.4% of these cases will be missed (confidence limits, 0.1% to 21%—that is, sensitivity of 95.6%) (22). Therefore, it may be reasonable to screen Ashkenazic Jewish patients by using PTT. If results are abnormal, the test should be repeated; if the results are still abnormal, factor XI level should be measured.

When which patients to screen is being considered, it is useful to stratify patient risk on the basis of known clinical factors associated with perioperative bleeding. In 1983, Rapaport (26) published a simple questionnaire to estimate the risk for perioperative hemorrhage. In another study that used data from all surgical patients admitted in 1981 to Strong Memorial Hospital in Rochester, New York, Suchman and Mushlin (27) found the probability of postoperative hemorrhage to be 0.22% in low-risk patients and 1.7% in high-risk patients. Patients were assigned to the high-risk group if they had any of the following criteria: known coagulopathy, potential factor deficiency (for exam-

**Table 2. Risk for Bleeding Complications on the Basis of Clinical History and Physical Examination**

Study, Year (Reference)	Low-Risk Patients	High-Risk Patients
Suchman and Mushlin, 1986 (27)		
Total patients, <i>n</i>	11 334	1004
Postoperative hemorrhage, %	0.22	1.7
Houry et al., 1995 (28)		
Total patients, <i>n</i>	2291	951
Death related to hemorrhage, %	0.13	0.21
Bruises, %	4.8	8.7
Hematomas, %	3.0	4.0
Reoperation to control hemorrhage, %	0.48	1.2

Table 3. Test Characteristics of Partial Thromboplastin Time for Postoperative Hemorrhage\*

Characteristic	Definite Hemorrhage			
	Low-Risk Patients		High-Risk Patients	
	Present	Absent	Present	Absent
Partial thromboplastin time elevated, <i>n</i>	2	241	10	94
Partial thromboplastin time not elevated, <i>n</i>	23	1561	7	196
	25	1802	17	290
Sensitivity, %	8.0		58.8	
Specificity, %	86.6		67.6	
Likelihood ratio for a positive test result (95% CI)	0.60 (0.16–2.3)		1.81 (1.2–2.8)	
Likelihood ratio for a negative test result (95% CI)	1.06 (0.95–1.2)		0.61 (0.34–1.1)	

\* Data from reference (27); 95% CIs were calculated (30).

ple, history of liver disease, malabsorption, or malnutrition), trauma, or hemorrhage. In a prospective multicenter study, Houry and colleagues (28) followed 3242 patients scheduled for general surgical procedures in 17 centers in France between 1988 and 1992. A questionnaire was used to determine whether patients had any historical risk factors or physical examination findings for bleeding (Table 1). In 2291 patients without clinical findings suggestive of an increased risk for bleeding (Table 2), 3 deaths were related to hemorrhage (0.13%), while 109 patients had bruises (4.8%) and 68 had hematomas (3.0%); 11 patients required another operation to control hemorrhage (0.48%). In 951 patients with at least 1 clinical risk factor, 2 deaths were related to hemorrhage (0.21%), 83 patients had bruises (8.7%), and 38 had hematomas (4.0%); 11 patients required another procedure for hemorrhage control (1.2%).

After pretest probabilities of bleeding complications have been established on the basis of clinical risk factors, the next step is to note the post-test or posterior probability of hemorrhage in patients with both normal and abnormal test results. In their study of more than 2000 patients who had preoperative coagulation testing, Suchman and Mushlin (27) found that PTT had a sensitivity of 33% and a specificity of 84% in predicting postoperative hemorrhage. As shown in Table 3, they next calculated sensitivity and specificity in patients with and without prolonged PTT. The likelihood ratio of a positive test result (true-positive rate/false-positive rate) can be used to determine the probability of disease given a positive test result (29). A test result with a likelihood ratio of 1.0 provides no additional information to the pretest probability. Therefore, a patient with a positive result is no more likely to have disease than before the test was performed. In Suchman and Mushlin's study (30), the likelihood ratio among low-risk patients was actually less than 1.0 (0.6 [95% CI, 0.16 to 2.3]). However, the 95% CI crosses 1.0, meaning that elevated PTT does not reliably predict increased or decreased risk for hemorrhage. Coagulation studies in patients with a low clinical risk for postoperative hemorrhage at best may be misleading and result in confusion and

further unnecessary testing. Among patients at high risk for hemorrhage, the likelihood ratio is 1.8 (CI, 1.2 to 2.8). The odds-likelihood formulation of Bayes rule (post-test odds = prior odds  $\times$  likelihood ratio) shows that the post-test odds of hemorrhage in high-risk patients with elevated PTT are still low (31:1000 [17:1000  $\times$  1.81]). Among patients at high risk for hemorrhage, the likelihood ratio of a negative test result (false-negative rate/true-negative rate) is 0.61 (CI, 0.34 to 1.1). If Bayes rule is applied, the post-test odds of hemorrhage in a high-risk patient with a normal PTT are 10:1000 (17:1000  $\times$  0.61). As shown in this example, PTT is not very useful as a screening test for postoperative hemorrhage, even in "high-risk" patients, because of low sensitivity, high false-positive rate, wide confidence intervals around the likelihood ratios, and the low pretest odds of postoperative hemorrhage.

Clinical studies confirm that PTT should not be used as a screening test in asymptomatic patients (3, 4, 6). In the study by Houry and coworkers (28), bleeding complications were similar in low-risk patients regardless of PTT; 0.15% (CI, 0% to 0.32%) of 1951 low-risk patients with normal test results died of bleeding complications, whereas none of the 340 low-risk patients with abnormal test results died of hemorrhagic complications. Along these lines, among low-risk patients with normal test results, 4.6% had bruises, 3.0% had hematomas, and 0.46% required another operation to control hemorrhage. The corresponding figures for low-risk patients with abnormal test results were 5.9%, 2.9%, and 0.59%. In a study of 101 patients requiring abdominal or thyroid surgery, Eika and colleagues (31) observed no correlation between preoperative screening and postoperative bleeding. Rohrer and colleagues (32) studied 514 screening tests in 282 patients before elective general and vascular surgical procedures. Although 4.1% of results were abnormal, no clinically significant coagulopathies were identified. We compiled the test characteristics of various combinations of coagulation studies stratified by the type of procedure or surgery (7, 27, 28, 33–42). As shown in Table 4, many of these studies had likelihood ratios for positive results that were less than 1.0 and like-

Table 4. Test Performance Characteristics for "Coagulation Studies" in Predicting Postoperative Hemorrhage\*

Study, Year (Reference)	Type of Coagulation Study	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio
		% (n/n)			
General surgery or unspecified					
Clark and Eisenberg, 1981 (8)	PT and PTT	100 (1/1)	97 (467/479)	33	0
Turnbull and Buck, 1987 (35)	PTT	0 (0/13)	99 (196/197)	0	1.01
Suchman and Mushlin, 1986 (27)	PTT	33 (9/27)	84 (1769/2107)	2.08	0.79
Macpherson et al., 1993 (33)	PTT	0 (0/0)	93 (103/111)	0	1.08
Houry et al., 1995 (28)	PT, PTT, platelet count, and bleeding time	18 (2/11)	85 (1942/2280)	1.20	0.96
Kussmann et al., 1997 (34)	PT, PTT, and platelet count	24 (11/46)	97 (974/1008)	8	0.78
Pooled (PTT only)		23 (9/40)	86 (2068/2415)	1.64 (95% CI, 0.92–2.9)	0.90 (95% CI, 0.76–1.1)
Adenotonsillectomy					
Thomas and Arbon, 1976 (41)	PTT	0 (0/3)	100 (203/203)	0	1.00
Tami et al., 1987 (42)	PTT	19 (5/26)	91 (742/811)	2.10	0.89
Close et al., 1994 (39)	PTT	0 (0/2)	84 (79/94)	0	1.19
Howells et al., 1997 (40)	PT and PTT	14 (1/7)	85 (216/254)	0.93	1.01
Pooled (PTT only)		16 (5/31)	92 (1024/1108)	2.00 (95% CI, 0.87–4.6)	0.91 (95% CI, 0.78–1.1)
Angiography					
Darcy et al., 1996 (43)	PT and PTT	11 (10/95)	88 (792/905)	0.92	1.01
Gynecologic surgery					
Myers et al., 1994 (45)	PT and PTT	0 (0/0)	97 (339/351)	0	1.03

\* PT = prothrombin time; PTT = partial thromboplastin time.

likelihood ratios for negative results that were greater than 1.0. In addition, each of the studies examined different combinations of tests, including PT, PTT, bleeding time, and platelet count. We show pooled results for the studies that examined PTT for each category of surgery. These results should be interpreted cautiously because of heterogeneity in study characteristics, testing panels, and definitions of outcomes (that is, abnormal test results or hemorrhage).

In a study of coagulation testing as a predictor of angiographic bleeding complications in adults, Darcy and colleagues (43) concluded that abnormal PT and PTT did not correlate with an increased risk for hematoma at the arterial access site. Burns and colleagues (44) found no correlation between bleeding time and blood loss in 43 patients having coronary bypass graft surgery ( $r^2 = 0.04$ ). In the setting of a gynecologic oncology service, Myers and colleagues (45) found that preoperative coagulation testing provided little clinically useful information. Finally, in a study of 153 adult dental school patients, Redding and Olive (46) found that the medical history identified most patients at risk for bleeding, whereas PT, PTT, and bleeding time had little predictive power.

Therefore, because of the low pretest probability and the low likelihood ratio for predicting postoperative bleeding complications, PT and PTT are poor screening tests for patients at low risk for postoperative hemorrhage. With the exception of Ashkenazic Jews, patients without historical risk factors or physical findings suggestive of an increased bleeding risk are unlikely to have congenital or acquired coagulopathies that will result in increased postoperative bleeding and do not require testing.

#### Platelet Count and Bleeding Time

The platelet count is highly reproducible but does not assess platelet function; therefore, it presents the clinician with incomplete and possibly misleading information. The bleeding time provides additional information; however, this test is highly dependent on the skill of the technician, and the results can be altered by certain medications and are difficult to reproduce. Investigators have found bleeding time to be a poor screening test for perioperative hemorrhage (47–50). In a study of 167 consecutive surgical patients, Gewirtz and colleagues (48) found that patients with an abnormal bleeding time (5%) were no more likely to have significant bleeding than those with a normal bleeding time. In 1990, Rodgers and Levin (51) reviewed 862 studies that examined the use of bleeding time. In a linear regression analysis that used data from 23 of these studies, they found a poor correlation between bleeding time and platelet count.

Receiver-operating characteristic (ROC) curves can be used to describe how well a test discriminates between patients with and without disease, in this case perioperative bleeding. Areas under the ROC curve range from 0.5 for a test with no discriminatory power (that is, a likelihood ratio of 1.0) to 1.0 for a highly discriminating test. Areas under the curve for bleeding time from two surgical studies were approximately 0.5 (that is, a 45-degree line), indicating poor discriminatory power in predicting perioperative bleeding (50, 52). Using ROC curves constructed from data in 27 studies, Rodgers and Levin found that bleeding time failed to discriminate between patients who were taking aspirin and those who were not. Finally, in 5 studies of patients with uremia, bleeding time, hematocrit, and plate-

let count had similar performance in predicting bleeding complications (51). In light of these findings, the American Society of Clinical Pathologists published a position paper in 1998 concluding that in the absence of a history of a bleeding disorder, bleeding time is not a useful predictor of risk for hemorrhage associated with surgical procedures. They also stated that a normal bleeding time does not exclude the possibility of excessive hemorrhage and, finally, that bleeding time cannot be used to reliably identify patients who may have recently ingested aspirin or nonsteroidal anti-inflammatory agents or those who may have platelet defects attributable to these drugs (47).

A new tool, a platelet function analyzer, has been developed as a quantitative, rapid, *in vitro* test of platelet function at high shear rates (53–56). Preliminary studies have demonstrated that “closure times” measured with this system are sensitive to impairment of von Willebrand factor, inhibition of platelet glycoprotein Ib or IIb/IIIa receptors with monoclonal antibodies or peptides, and aspirin-related platelet dysfunction (57–60). Although some studies have shown good sensitivity in the detection of aspirin-induced defects in patients taking 325-mg doses (54, 61), others have noted equivocal results at lower doses (100 mg) (62). With the increased use of platelet receptor-blocking agents in cardiovascular diseases, several centers are investigating the utility of the platelet function analyzer in monitoring the adequacy of glycoprotein IIb/IIIa inhibition during percutaneous coronary intervention (63, 64).

### TESTING FOR THE RISK FOR THROMBOSIS

Patients face an increased risk for thrombosis in several clinical settings. Important questions are whether, when, and how to screen for these hypercoagulable states. Acquired causes of thrombophilia include cancer, antiphospholipid antibodies, the nephrotic syndrome, and hyperhomocystinemia. The most frequent cause of heritable thrombophilia is the factor V Leiden mutation (65). Defects in protein C, protein S, antithrombin III, and the newly identified prothrombin gene mutation account for most of the remaining cases (66, 67).

A common clinical dilemma is whether to test for the factor V Leiden mutation in patients who have had a first venous thromboembolic event. Data conflict on the risk for recurrent thrombosis in patients who have positive results on testing for the factor V Leiden mutation (68). Studies by Simioni, Baglin, and Ridker and their colleagues (69–71) have shown an increased risk for recurrence. Other investigators have not corroborated these findings (72, 73); however, some of the studies may not have been large enough to detect a clinically significant difference.

#### Prevalence

On the basis of a study of 4047 men and women participating in the Physicians' Health Study or the Women's Health Study, the factor V Leiden mutation is present in 1.25% to 6% of the U.S. population (74). Prevalence

**Table 5. Summary and Recommendations**

#### Nonsurgical Hospitalized Patients

Testing should be performed only when there are specific clinical indications on the basis of the history or physical examination (Grade 1C).

Measurement of the platelet count is recommended before heparin therapy is initiated; monitoring of platelet counts during treatment is also recommended because of the possibility of heparin-induced thrombocytopenia (Grade 1C+).

#### Surgical Patients

Patients without evidence of historical risk factors or physical findings suggestive of a bleeding disorder have a low risk for peri- and postoperative hemorrhage. Abnormal test results for hemostasis occur infrequently in patients without these risk factors. When test results are abnormal in these patients, they perform poorly in predicting postoperative hemorrhage. Therefore, routine preoperative coagulation testing is not recommended (Grade 1C+).

Preoperative testing with the partial thromboplastin time, prothrombin time, and platelet count is warranted for patients with clinical evidence to suggest a bleeding disorder (Grade 2C).

It is reasonable to obtain routine preoperative partial thromboplastin time on Ashkenazic Jewish persons because of the increased prevalence of occult factor XI deficiency (Grade 2C).

#### Testing after the First Episode of Venous Thromboembolism

After a first episode of venous thromboembolism, patients with the factor V Leiden mutation may have an increased risk for recurrence. However, the magnitude and duration of risk remain unclear at this time. Patients with the factor V Leiden mutation who do not have a clear precipitating factor (for example, idiopathic venous thromboembolism) may have an even greater risk for recurrence. The prevalence of factor V Leiden varies substantially across ethnic groups. The cost-effectiveness of testing patients for factor V Leiden mutation and treating affected persons with prolonged oral anticoagulant therapy depends on the risk for recurrence, the prevalence of factor V Leiden mutation, the risk for major hemorrhage while receiving anticoagulant therapy, and patient age.

Therefore, routine testing after a first episode of venous thromboembolism is not recommended for most patients (Grade 2C).

Testing may be reasonable for patients with no obvious precipitating factor who are at low risk for bleeding complications from oral anticoagulant therapy, for patients age 50 years or younger, or for patients with a first-degree relative with a history of venous thromboembolism before 50 years of age (Grade 2C).

varied significantly between different ethnic groups. Carrier frequency was 5.27% (CI, 4.42% to 6.22%) in whites, 2.21% in 407 Hispanic Americans, 1.23% in 650 African Americans, 0.45% in 442 Asian Americans, and 1.25% in 80 Native Americans.

The prevalence of the factor V Leiden mutation may be as much as sevenfold higher in patients who have had a first episode of venous thrombosis (not related to cancer) than in healthy controls (75). As was shown in a population-based case-control study of 301 patients younger than 70 years of age (the Leiden Thrombophilia study), resistance to activated protein C was present in 21% of patients with venous thrombosis compared with 5% of age- and sex-matched controls (76). In a pooled analysis of 2456 white patients, the factor V Leiden mutation was detected in an average of 18.4% of patients with venous thromboembolic disease (77).

#### Tests and Test Characteristics

Testing is first done by checking for resistance to activated protein C (APC) (78–82). The most common plasma-based test involves measuring the activated PTT in

the presence and absence of APC; results are expressed as a ratio of these values. A reduced ratio is predictive of the factor V Leiden mutation, although false-positive results may occur for many reasons, including elevated levels of factor VIII coagulant activity and oral contraceptive use (83). In one of the largest series, the sensitivity and specificity of the activated PTT ratio were 84% and 72%, respectively (84). Testing is performed either before anticoagulation is started or while patients are still receiving warfarin, before a decision has been made about continuing anticoagulant therapy (85). In the latter case, a modified APC resistance test is used. The modified test involves diluting the patient's plasma in factor V–deficient plasma (80), which makes the test insensitive to the administration of anticoagulants (86–88). Patients with APC resistance undergo genetic testing for the factor V Leiden mutation by using polymerase chain reaction (89, 90).

### Rationale for Testing

The rationale for testing rests on the assumption that affected individuals would receive anticoagulant therapy that was more effective than the usual regimen. Standard therapy after a first episode of venous thromboembolism in patients with reversible or time-limited risk factors consists of 3 to 6 months of oral anticoagulant therapy within an international normalized ratio target range of 2 to 3 (91, 92). Although studies have demonstrated lower rates of recurrence in patients receiving longer anticoagulant therapy, the price has been a higher rate of hemorrhagic events (93–95). The most recent guidelines of the American College of Chest Physicians recommend at least 6 months of anticoagulant therapy after an idiopathic venous thromboembolic event (91). However, for patients at increased risk for recurrence due to inherited defects in anticoagulation, such as the factor V Leiden mutation, no satisfactory evidence can help decide the optimal duration or intensity of anticoagulant therapy.

Despite this lack of clear evidence, many clinicians have already integrated testing for the factor V Leiden mutation and other hypercoagulable disorders into their routine approach. Two recent reviews on the thrombophilias (83, 96) recommend that testing be pursued only in patients with one or more features strongly suggestive of thrombophilia, such as age at onset younger than 50 years, a history of recurrent thrombosis, or a first-degree family member who had onset of thrombosis before 50 years of

age. Several decision and cost-effectiveness analyses have been done to address this question (97–99).

Using different methods, Sarasin and Eckman and their coworkers (97, 99) came to similar conclusions: Testing followed by life-long anticoagulation is not “cost-effective.” The only patients for whom this protocol may be reasonable are those who have idiopathic venous thromboembolism and are at low risk for bleeding complications from oral anticoagulant therapy (99). The analysis by Marchetti and colleagues (98) yielded similar results from which they drew different conclusions. Although screening had an incremental cost-effectiveness ratio of \$12 833 per quality-adjusted life-year, it resulted in only a 2-day average gain in quality-adjusted life expectancy. These researchers concluded that screening was cost-effective; however, they added that it was not cost-effective in patients at high risk for fatal bleeding (>0.34% per year) or at low risk for recurrent deep venous thrombosis (<9% in the first 2 years). In addition, they found that screening was cost saving if restricted to patients with idiopathic thrombosis.

Studies suggest that patients who are homozygous for the factor V Leiden mutation (75, 81) are at somewhat greater risk for recurrent venous thromboembolism. Furthermore, since the inheritance of congenital thrombophilias is independent, co-inheritance of the factor V Leiden mutation with other “common” thrombophilias, such as the G20210A mutation in the prothrombin gene, does occur. Patients who are heterozygous for both mutations have an even greater risk for recurrence (100). By using data pooled from two small studies with a total of 39 patients having both the factor V Leiden and prothrombin gene mutations (100, 101), Marchetti and colleagues calculated an odds ratio of 5.9 (CI, 2.65 to 13.12) for recurrence. On the basis of these preliminary data, they extended their previous cost-effectiveness analysis and found that screening for both mutations followed by 2 years of oral anticoagulant therapy resulted in a 1-day average gain in quality-adjusted life expectancy and an incremental cost-effectiveness ratio of \$13 624 per quality-adjusted life-year (102). Future cost-effectiveness analyses of more complicated strategies that include a battery of tests for the more common thrombophilias and that reserve treatment only for patients with multiple predispositions—particularly

**Table 6. Statements and Medical Subject Heading Terms for the Search Process**

Nonsurgical Patients	Surgical Patients	Factor V Leiden
<i>blood coagulation disorders AND blood coagulation tests AND diagnostic tests, routine AND human AND English language</i>	<i>blood coagulation disorders AND blood coagulation tests AND human AND English language AND [preoperative care OR postoperative complications]</i>	<i>factor V Leiden AND [follow-up studies OR recurrence]</i>
	<i>blood coagulation tests AND evaluation studies AND [preoperative care OR postoperative complications]</i>	<i>factor V Leiden AND [cost-benefit analysis OR costs and cost analysis OR decision trees]</i>

Table 7. Grading System Developed by the American College of Chest Physicians

Grade of Recommendation	Clarity of Risk/Benefit	Methodologic Strength of Supporting Evidence	Implications
1A	Clear	Randomized, controlled trials without important limitations	Strong recommendation; can apply to most patients in most circumstances without reservation
1B	Clear	Randomized, controlled trials with important limitations (inconsistent results, methodologic flaws)	Strong recommendations, likely to apply to most patients
1C+	Clear	No randomized, controlled trials, but randomized, controlled trial results can be unequivocally extrapolated; or overwhelming evidence from observational studies	Strong recommendation; can apply to most patients in most circumstances
1C	Clear	Observational studies	Intermediate-strength recommendation; may change when stronger evidence available
2A	Unclear	Randomized trials without important limitations	Intermediate-strength recommendation; best action may differ depending on circumstances or patients' or societal values
2B	Unclear	Randomized, controlled trials with important limitations (inconsistent results, methodologic flaws)	Weak recommendation; alternative approaches likely to be better for some patients under some circumstances
2C	Unclear	Observational studies	Very weak recommendations; other alternatives may be equally reasonable

those with idiopathic thromboembolism—will be of great interest once additional clinical data are available.

### LIMITATIONS AND CONCLUSIONS

All of the studies in this investigation of screening for the risk for bleeding in hospitalized surgical or nonsurgical patients were observational. Although it is unlikely that selection bias affected the results since such a large proportion of patients had routine testing, randomized trials investigating the effect of withholding routine admission and preoperative testing on patient outcomes would have provided methodologically stronger results. We could not pool results for many studies because of the diversity in study characteristics, testing panels, and definitions of outcomes. Nevertheless, most of the evidence from these observational studies shows that 1) routine screening of unselected patients has little power to discriminate between those who will have bleeding complications and those who will not and 2) withholding such testing is unlikely to cause harm and will certainly reduce costs. Table 5 summarizes the conclusions and recommendations.

The issue of testing for the factor V Leiden mutation, the most common cause of thrombophilia in patients with a history of venous thromboembolism, is plagued by the uncertainty about the risk for recurrent thrombosis. The observational studies we reviewed had vastly different designs, durations of anticoagulant therapy, and end points, making them difficult to combine into a summary analysis. Furthermore, most did not address the question of whether prolonged anticoagulant therapy in persons with the mutation decreases the risk for recurrence. Final recommendations await confirmation from ongoing clinical trials, such as the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial, which will evaluate the efficacy of prolonged treatment with low-dose warfarin in the secondary prevention of venous thromboembolism and will perform subgroup analyses of trial end points in patients with the factor V Leiden mutation (103).

### APPENDIX

#### Search Process

Data sources included all English-language studies identified in MEDLINE (1966 to April 2002) and reference lists of key articles. Searches were performed for three major topics: routine coagulation testing for nonsurgical hospitalized patients, routine coagulation testing for surgical patients, and the risk for recurrent venous thromboembolism in patients with the factor V Leiden mutation. Search statements for these areas were as shown in Table 6 (Medical Subject Heading terms are italicized).

Articles included in the summary analysis of test characteristics in the prediction of postsurgical bleeding had to include coagulation test results in patients with bleeding (to calculate sensitivity) and those without bleeding (to calculate specificity). Many studies did not include patients without bleeding and were excluded from the summary analysis in Table 4. The 95% CIs for likelihood ratios of pooled studies were calculated by using the method of Obuchowski and coworkers (30).

#### Grades of Recommendations

Final recommendations were graded (Table 5) on the basis of the methodologic quality of the underlying evidence and the trade-off between benefits of testing on the one hand and risks, harms, or costs on the other. We use the systematic grading system developed by the Consensus Conference on Antithrombotic Therapy of the American College of Chest Physicians, summarized in Table 7 (104).

From University of Cincinnati, Cincinnati, Ohio; and New England Medical Center, Boston, Massachusetts.

**Grant Support:** In part by grant LM 07092-08 from the National Library of Medicine, Bethesda, Maryland.

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

**Current Author Addresses:** Dr. Eckman: Division of General Internal Medicine, University of Cincinnati Medical Center, PO Box 670535, 231 Albert Sabin Way, Cincinnati, OH 45267-0535.

Dr. Erban: Division of Hematology/Oncology, New England Medical Center, Box 542, 750 Washington Street, Boston, MA 02111.

Dr. Singh: Division of Cardiology, New England Medical Center, Box 079, 750 Washington Street, Boston, MA 02111.

Dr. Kao: Division of Transfusion Medicine, Harvard Joint Program in Transfusion Medicine, Dana-Farber Cancer Institute, 44 Binney Street, D 530, Boston, MA 02115.

## References

- Owen CA Jr. Historical account of tests of hemostasis. *Am J Clin Pathol.* 1990;93:S3-8. [PMID: 2180278]
- Borzotta AP, Keeling MM. Value of the preoperative history as an indicator of hemostatic disorders. *Ann Surg.* 1984;200:648-52. [PMID: 6486913]
- Robbins JA, Mushlin AI. Preoperative evaluation of the healthy patient. *Med Clin North Am.* 1979;63:1145-56. [PMID: 529881]
- Eisenberg JM, Goldfarb S. Clinical usefulness of measuring prothrombin time as a routine admission test. *Clin Chem.* 1976;22:1644-7. [PMID: 975511]
- Suchman AL, Griner PF. Diagnostic uses of the activated partial thromboplastin time and prothrombin time. *Ann Intern Med.* 1986;104:810-6. [PMID: 3706933]
- Robbins JA, Rose SD. Partial thromboplastin time as a screening test. *Ann Intern Med.* 1979;90:796-7. [PMID: 434687]
- Eisenberg JM, Clarke JR, Sussman SA. Prothrombin and partial thromboplastin times as preoperative screening tests. *Arch Surg.* 1982;117:48-51. [PMID: 7055424]
- Clarke JR, Eisenberg JM. A theoretical assessment of the value of the PTT as a preoperative screening test in adults. *Med Decis Making.* 1981;1:40-3. [PMID: 7052404]
- Erban SB, Kinman JL, Schwartz JS. Routine use of the prothrombin and partial thromboplastin times. *JAMA.* 1989;262:2428-32. [PMID: 2795828]
- Monreal M, Urrutia A, Marti S, Cuxart A, Roncales J. Platelet count and the risk for bleeding in hospitalized patients with venous thromboembolism starting anticoagulant therapy. *Haemostasis.* 1997;27:91-8. [PMID: 9212357]
- Schmitt BP, Adelman B. Heparin-associated thrombocytopenia: a critical review and pooled analysis. *Am J Med Sci.* 1993;305:208-15. [PMID: 8475945]
- Chong BH. Heparin-induced thrombocytopenia. *Aust N Z J Med.* 1992;22:145-52. [PMID: 1530537]
- King DJ, Kelton JG. Heparin-associated thrombocytopenia. *Ann Intern Med.* 1984;100:535-40. [PMID: 6367579]
- Samama MM. Laboratory monitoring of unfractionated heparin treatment. *Clin Lab Med.* 1995;15:109-17. [PMID: 7781273]
- Samama MM, Poller L. Contemporary laboratory monitoring of low molecular weight heparins. *Clin Lab Med.* 1995;15:119-23. [PMID: 7781274]
- Lecompte T, Luo SK, Stieltjes N. Thrombocytopenia associated with low-molecular-weight heparin [Letter]. *Lancet.* 1991;338:1217.
- Warkentin TE. Clinical presentation of heparin-induced thrombocytopenia. *Semin Hematol.* 1998;35(4 Suppl 5):9-16; discussion 35-6. [PMID: 9855179]
- Warkentin TE, Chong BH, Greinacher A. Heparin-induced thrombocytopenia: towards consensus. *Thromb Haemost.* 1998;79:1-7. [PMID: 9459312]
- Biron C, Mahieu B, Rochette A, Capdevila X, Castex A, Amiral J, et al. Preoperative screening for von Willebrand disease type 1: low yield and limited ability to predict bleeding. *J Lab Clin Med.* 1999;134:605-9. [PMID: 10595788]
- Bachmann F. Diagnostic approach to mild bleeding disorders. *Semin Hematol.* 1980;17:292-305. [PMID: 7003721]
- Hoffman R. *Hematology—Basic Principles & Practice.* New York: Churchill Livingstone; 1995:1795.
- Seligsohn U, Modan M. Definition of the population at risk for bleeding due to factor XI deficiency in Ashkenazic Jews and the value of activated partial thromboplastin time in its detection. *Isr J Med Sci.* 1981;17:413-5. [PMID: 7263201]
- Seligsohn U. High gene frequency of factor XI (PTA) deficiency in Ashkenazi Jews. *Blood.* 1978;51:1223-8. [PMID: 647126]
- Sidi A, Seligsohn U, Jonas P, Many M. Factor XI deficiency: detection and management during urological surgery. *J Urol.* 1978;119:528-30. [PMID:

650760]

- Bashevkin ML, Nawabi IU. Factor XI deficiency in surgical patients. *N Y State J Med.* 1979;79:1360-2. [PMID: 291793]
- Rapaport SI. Preoperative hemostatic evaluation: which tests, if any? *Blood.* 1983;61:229-31. [PMID: 6821695]
- Suchman AL, Mushlin AI. How well does the activated partial thromboplastin time predict postoperative hemorrhage? *JAMA.* 1986;256:750-3. [PMID: 3723774]
- Houry S, Georgeac C, Hay JM, Fingerhut A, Boudet MJ. A prospective multicenter evaluation of preoperative hemostatic screening tests. The French Associations for Surgical Research. *Am J Surg.* 1995;170:19-23. [PMID: 7793487]
- Pauker S, Eckman M. Principles of diagnostic testing. In: WN Kelly, ed. *Textbook of Internal Medicine.* 2nd ed. Philadelphia: JB Lippincott; 1992:13-6.
- Obuchowski NA. Sample size calculations in studies of test accuracy. *Stat Methods Med Res.* 1998;7:371-92. [PMID: 9871953]
- Eika C, Havig O, Godal HC. The value of preoperative haemostatic screening. *Scand J Haematol.* 1978;21:349-54. [PMID: 725532]
- Rohrer MJ, Michelotti MC, Nahrwold DL. A prospective evaluation of the efficacy of preoperative coagulation testing. *Ann Surg.* 1988;208:554-7. [PMID: 3190281]
- Macpherson CR, Jacobs P, Dent DM. Abnormal peri-operative haemorrhage in asymptomatic patients is not predicted by laboratory testing. *S Afr Med J.* 1993;83:106-8. [PMID: 8451684]
- Kussmann I, Koller M, Heinke T, Rothmund M. [Value of preoperative blood coagulation analysis for assessment of hemorrhage risk in general surgery]. *Chirurg.* 1997;68:684-8. [PMID: 9340232]
- Turnbull JM, Buck C. The value of preoperative screening investigations in otherwise healthy individuals. *Arch Intern Med.* 1987;147:1101-5. [PMID: 3592875]
- Zwack GC, Derkay CS. The utility of preoperative hemostatic assessment in adenotonsillectomy. *Int J Pediatr Otorhinolaryngol.* 1997;39:67-76. [PMID: 9051441]
- Manning SC, Beste D, McBride T, Goldberg A. An assessment of preoperative coagulation screening for tonsillectomy and adenoidectomy. *Int J Pediatr Otorhinolaryngol.* 1987;13:237-44. [PMID: 3679679]
- Burk CD, Miller L, Handler SD, Cohen AR. Preoperative history and coagulation screening in children undergoing tonsillectomy. *Pediatrics.* 1992;89(4 Pt 2):691-5. [PMID: 1557263]
- Close HL, Kryzer TC, Nowlin JH, Alving BM. Hemostatic assessment of patients before tonsillectomy: a prospective study. *Otolaryngol Head Neck Surg.* 1994;111:733-8. [PMID: 7991252]
- Howells RC 2nd, Wax MK, Ramadan HH. Value of preoperative prothrombin time/partial thromboplastin time as a predictor of postoperative hemorrhage in pediatric patients undergoing tonsillectomy. *Otolaryngol Head Neck Surg.* 1997;117:628-32. [PMID: 9419090]
- Thomas GK, Arbon RA. Preoperative screening for potential T&A bleeding. *Arch Otolaryngol.* 1970;91:453-6. [PMID: 5445322]
- Tami TA, Parker GS, Taylor RE. Post-tonsillectomy bleeding: an evaluation of risk factors. *Laryngoscope.* 1987;97:1307-11. [PMID: 3669843]
- Darcy MD, Kanterman RY, Kleinhoffer MA, Vesely TM, Picus D, Hicks ME, et al. Evaluation of coagulation tests as predictors of angiographic bleeding complications. *Radiology.* 1996;198:741-4. [PMID: 8628863]
- Burns ER, Billett HH, Frater RW, Sisto DA. The preoperative bleeding time as a predictor of postoperative hemorrhage after cardiopulmonary bypass. *J Thorac Cardiovasc Surg.* 1986;92:310-2. [PMID: 3736089]
- Myers ER, Clarke-Pearson DL, Olt GJ, Soper JT, Berchuck A. Preoperative coagulation testing on a gynecologic oncology service. *Obstet Gynecol.* 1994;83:438-44. [PMID: 8127539]
- Redding SW, Olive JA. Relative value of screening tests of hemostasis prior to dental treatment. *Oral Surg Oral Med Oral Pathol.* 1985;59:34-6. [PMID: 3856205]
- Peterson P, Hayes TE, Arkin CF, Bovill EG, Fairweather RB, Rock WA Jr, et al. The preoperative bleeding time test lacks clinical benefit: College of American Pathologists' and American Society of Clinical Pathologists' position article. *Arch Surg.* 1998;133:134-9. [PMID: 9484723]

48. Gewirtz AS, Miller ML, Keys TF. The clinical usefulness of the preoperative bleeding time. *Arch Pathol Lab Med.* 1996;120:353-6. [PMID: 8619746]
49. Burns ER, Lawrence C. Bleeding time. A guide to its diagnostic and clinical utility. *Arch Pathol Lab Med.* 1989;113:1219-24. [PMID: 2535679]
50. Barber A, Green D, Galluzzo T, Ts'ao CH. The bleeding time as a preoperative screening test. *Am J Med.* 1985;78:761-4. [PMID: 3993657]
51. Rodgers RP, Levin J. A critical reappraisal of the bleeding time. *Semin Thromb Hemost.* 1990;16:1-20. [PMID: 2406907]
52. Simon TL, Akl BF, Murphy W. Controlled trial of routine administration of platelet concentrates in cardiopulmonary bypass surgery. *Ann Thorac Surg.* 1984;37:359-64. [PMID: 6370157]
53. Mammen EF, Alshameeri RS, Comp PC. Preliminary data from a field trial of the PFA-100 system. *Semin Thromb Hemost.* 1995;21(Suppl 2):113-21. [PMID: 7660152]
54. Mammen EF, Comp PC, Gosselin R, Greenberg C, Hoots WK, Kessler CM, et al. PFA-100 system: a new method for assessment of platelet dysfunction. *Semin Thromb Hemost.* 1998;24:195-202. [PMID: 9579642]
55. Carcao MD, Blanchette VS, Stephens D, He L, Wakefield CD, Butchart S, et al. Assessment of thrombocytopenic disorders using the Platelet Function Analyzer (PFA-100). *Br J Haematol.* 2002;117:961-4. [PMID: 12060138]
56. Kundu SK, Heilmann EJ, Sio R, Garcia C, Davidson RM, Ostgaard RA. Description of an in vitro platelet function analyzer—PFA-100. *Semin Thromb Hemost.* 1995;21(Suppl 2):106-12. [PMID: 7660150]
57. Rand ML, Carcao MD, Blanchette VS. Use of the PFA-100 in the assessment of primary, platelet-related hemostasis in a pediatric setting. *Semin Thromb Hemost.* 1998;24:523-9. [PMID: 10066147]
58. Sestito A, Sciahbasi A, Landolfi R, Maseri A, Lanza GA, Andreotti F. A simple assay for platelet-mediated hemostasis in flowing whole blood (PFA-100): reproducibility and effects of sex and age. *Cardiologia.* 1999;44:661-5. [PMID: 10476592]
59. McKenzie ME, Gurbel PA, Levine DJ, Serebruany VL. Clinical utility of available methods for determining platelet function. *Cardiology.* 1999;92:240-7. [PMID: 10844384]
60. Ortel TL, James AH, Thames EH, Moore KD, Greenberg CS. Assessment of primary hemostasis by PFA-100 analysis in a tertiary care center. *Thromb Haemost.* 2000;84:93-7. [PMID: 10928477]
61. Homoncik M, Jilma B, Hergovich N, Stohlawetz P, Panzer S, Speiser W. Monitoring of aspirin (ASA) pharmacodynamics with the platelet function analyzer PFA-100. *Thromb Haemost.* 2000;83:316-21. [PMID: 10739392]
62. Feuring M, Haseroth K, Janson CP, Falkenstein E, Schmidt BM, Wehling M. Inhibition of platelet aggregation after intake of acetylsalicylic acid detected by a platelet function analyzer (PFA-100). *Int J Clin Pharmacol Ther.* 1999;37:584-8. [PMID: 10599950]
63. Madan M, Berkowitz SD, Christie DJ, Smit AC, Sigmon KN, Tchong JE. Determination of platelet aggregation inhibition during percutaneous coronary intervention with the platelet function analyzer PFA-100. *Am Heart J.* 2002;144:151-8. [PMID: 12094202]
64. Madan M, Berkowitz SD, Christie DJ, Jennings LK, Smit AC, Sigmon KN, et al. Rapid assessment of glycoprotein IIb/IIIa blockade with the platelet function analyzer (PFA-100) during percutaneous coronary intervention. *Am Heart J.* 2001;141:226-33. [PMID: 11174336]
65. Middeldorp S, Henkens CM, Koopman MM, van Pampus EC, Hamulyak K, van der Meer J, et al. The incidence of venous thromboembolism in family members of patients with factor V Leiden mutation and venous thrombosis. *Ann Intern Med.* 1998;128:15-20. [PMID: 9424976]
66. Mateo J, Oliver A, Borrell M, Sala N, Fontcuberta J. Laboratory evaluation and clinical characteristics of 2,132 consecutive unselected patients with venous thromboembolism—results of the Spanish Multicentric Study on Thrombophilia (EMET-Study). *Thromb Haemost.* 1997;77:444-51. [PMID: 9065991]
67. Margaglione M, Brancaccio V, Giuliani N, D'Andrea G, Cappucci G, Iannaccone L, et al. Increased risk for venous thrombosis in carriers of the prothrombin G→A20210 gene variant. *Ann Intern Med.* 1998;129:89-93. [PMID: 9669991]
68. Svensson P, Dahlback B. Resistance to activated protein C as a basis for venous thrombosis. *N Engl J Med.* 1994;330:517-522. [PMID: 8302317]
69. Simioni P, Prandoni P, Lensing AW, Scudeller A, Sardella C, Prins MH, et al. The risk for recurrent venous thromboembolism in patients with an Arg506→Gln mutation in the gene for factor V (factor V Leiden). *N Engl J Med.* 1997;336:399-403. [PMID: 9010145]
70. Baglin C, Brown K, Luddington R, Baglin T. Risk of recurrent venous thromboembolism in patients with the factor V Leiden (FVR506Q) mutation: effect of warfarin and prediction by precipitating factors. *East Anglian Thrombophilia Study Group.* *Br J Haematol.* 1998;100:764-8. [PMID: 9531346]
71. Ridker PM, Miletich JP, Stampfer MJ, Goldhaber SZ, Lindpaintner K, Hennekens CH. Factor V Leiden and risks of recurrent idiopathic venous thromboembolism. *Circulation.* 1995;92:2800-2. [PMID: 7586244]
72. Eichinger S, Pabinger I, Stumpflen A, Hirschl M, Bialonczyk C, Schneider B, et al. The risk for recurrent venous thromboembolism in patients with and without factor V Leiden. *Thromb Haemost.* 1997;77:624-8. [PMID: 9134632]
73. Rintelen C, Pabinger I, Knobl P, Lechner K, Mannhalter C. Probability of recurrence of thrombosis in patients with and without factor V Leiden. *Thromb Haemost.* 1996;75:229-32. [PMID: 8815565]
74. Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. *JAMA.* 1997;277:1305-7. [PMID: 9109469]
75. Rosendaal FR, Koster T, Vandenbroucke JP, Reitsma PH. High risk for thrombosis in patients homozygous for factor V Leiden (activated protein C resistance). *Blood.* 1995;85:1504-8. [PMID: 7888671]
76. Koster T, Rosendaal F, de Ronde H, Briet E, Vandenbroucke J, Bertina R. Venous thrombosis due to poor anticoagulant response to activate proteins C: Leiden Thrombophilia Study. *Lancet.* 1993;342:1503-6. [PMID: 7902898]
77. De Stefano V, Chiusolo P, Paciaroni K, Leone G. Epidemiology of factor V Leiden: clinical implications. *Semin Thromb Hemost.* 1998;24:367-79. [PMID: 9763354]
78. Dahlback B, Carlsson M, Svensson P. Familial thrombophilia due to a previously unrecognized mechanism characterized by poor anticoagulant response to activated protein C: prediction of a co-factor to activated protein C. *Proc Natl Acad Sci U S A.* 1993;90:1004-8. [PMID: 8430067]
79. De Ronde H, Bertina R. Laboratory diagnosis of APC-resistance: a critical evaluation of the test and the development of diagnostic criteria. *Thromb Haemost.* 1994;72:880-6. [PMID: 7740458]
80. Dahlback B. Are we ready for factor V Leiden screening? *Lancet.* 1996;347:1346-7. [PMID: 8637335]
81. Zoller B, Svensson P, He X, Dahlback B. Identification of the same factor V Leiden mutation in 47 out of 50 thrombosis-prone families with inherited resistance to activated proteins C. *J Clin Invest.* 1994;94:2521-4. [PMID: 7989612]
82. Bertina RM, Koeleman BP, Koster T, Rosendaal FR, Dirven RJ, de Ronde H, et al. Mutation in blood coagulation factor V associated with resistance to activated protein C. *Nature.* 1994;369:64-7. [PMID: 8164741]
83. Bauer KA. The thrombophilias: well-defined risk factors with uncertain therapeutic implications. *Ann Intern Med.* 2001;135:367-73. [PMID: 11529700]
84. Bontempo FA, Hassett AC, Faruki H, Steed DL, Webster MW, Makaroun MS. The factor V Leiden mutation: spectrum of thrombotic events and laboratory evaluation. *J Vasc Surg.* 1997;25:271-5; discussion 276. [PMID: 9052561]
85. Seligsohn U, Lubetsky A. Review articles: medical progress: genetic susceptibility to venous thrombosis. *N Engl J Med.* 2001;344:1222-31. [PMID: 11309638]
86. Arkel YS, Ku D, Kamiyama M, Pajaro R, Alder H, Marchand A. A highly specific functional test for factor V Leiden: a modified tissue factor assay for activated protein C resistance. *Haemostasis.* 1998;27:290-304. [PMID: 9731110]
87. Cadroy Y, Sie P, Alhenc-Gelas M, Aiach M. Evaluation of APC resistance in the plasma of patients with Q506 mutation of factor V (factor V Leiden) and treated by oral anticoagulants. *Thromb Haemost.* 1995;73:734-5. [PMID: 7495093]
88. Tosoet A, Rodeghiero F. Diagnosis of APC resistance in patients on oral anticoagulant therapy. *Thromb Haemost.* 1995;73:732-3. [PMID: 7495092]
89. Zoller B, Dahlback B. Linkage between inherited resistance to activated protein C and factor V gene mutation in venous thrombosis. *Lancet.* 1994;343:1536-1538. [PMID: 7911873]
90. Voorberg J, Roelse J, Koopman R, Buller H, Berends F, ten Cate J, et al. Association of idiopathic venous thromboembolism with single point mutation at Arg506 of factor V. *Lancet.* 1994;343:1535-6. [PMID: 7911872]
91. Hyers TM, Agnelli G, Hull RD, Morris TA, Samama M, Tapson V, et al.

- Antithrombotic therapy for venous thromboembolic disease. *Chest*. 2001;119(1 Suppl):176S-93S. [PMID: 11157648]
92. Hirsh J. The optimal duration of anticoagulant therapy for venous thrombosis. *N Engl J Med*. 1995;332:1710-1. [PMID: 7760874]
93. Schulman S, Rhedin AS, Lindmarker P, Carlsson A, Larfars G, Nicol 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;332:1661-5. [PMID: 7760866]
94. Levine MN, Hirsh J, Gent M, Turpie AG, Weitz J, Ginsberg J, et al. Optimal duration of oral anticoagulant therapy: a randomized trial comparing four weeks with three months of warfarin in patients with proximal deep vein thrombosis. *Thromb Haemost*. 1995;74:606-11. [PMID: 8584992]
95. Holmgren K, Andersson G, Fagrell B, Johnsson H, Ljungberg B, Nilsson E, et al. One-month versus six-month therapy with oral anticoagulants after symptomatic deep vein thrombosis. *Acta Med Scand*. 1985;218:279-84. [PMID: 3907286]
96. Federman DG, Kirsner RS. An update on hypercoagulable disorders. *Arch Intern Med*. 2001;161:1051-6. [PMID: 11322838]
97. Sarasin FP, Bounameaux H. Decision analysis model of prolonged oral anticoagulant treatment in factor V Leiden carriers with first episode of deep vein thrombosis. *BMJ*. 1998;316:95-9. [PMID: 9462312]
98. Marchetti M, Pistorio A, Barosi G. Extended anticoagulation for prevention of recurrent venous thromboembolism in carriers of factor V Leiden—cost-effectiveness analysis. *Thromb Haemost*. 2000;84:752-7. [PMID: 11127850]
99. Eckman MH, Singh SK, Erban JK, Kao G. Testing for factor V Leiden in patients with pulmonary or venous thromboembolism: A cost-effectiveness analysis. *Medical Decision Making*. 2002;22:108-24. [PMID: 11958494]
100. De Stefano V, Martinelli I, Mannucci PM, Paciaroni K, Chiusolo P, Casorelli I, et al. The risk for recurrent deep venous thrombosis among heterozygous carriers of both factor V Leiden and the G20210A prothrombin mutation. *N Engl J Med*. 1999;341:801-6. [PMID: 10477778]
101. Margaglione M, D'Andrea G, Colaizzo D, Cappucci G, del Popolo A, Brancaccio V, et al. Coexistence of factor V Leiden and Factor II A20210 mutations and recurrent venous thromboembolism. *Thromb Haemost*. 1999;82:1583-7. [PMID: 10613638]
102. Marchetti M, Quaglini S, Barosi G. Cost-effectiveness of screening and extended anticoagulation for carriers of both factor V Leiden and prothrombin G20210A. *QJM*. 2001;94:365-72. [PMID: 11435632]
103. Ridker PM. Long-term, low-dose warfarin among venous thrombosis patients with and without factor V Leiden mutation: rationale and design for the Prevention of Recurrent Venous Thromboembolism (PREVENT) trial. *Vasc Med*. 1998;3:67-73. [PMID: 9666536]
104. Guyatt G, Schunemann H, Cook D, Jaeschke R, Pauker S, Bucher H. Grades of recommendation for antithrombotic agents. *Chest*. 2001;119(1 Suppl):3S-7S. [PMID: 11157639]