JAMA Insights

Factor V Leiden

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Factor V Leiden (FVL) is the most common inherited thrombophilia[1] and is caused by a missense variant in coagulation factor V that results in resistance to activated protein C (APC). As APC is an endogenous anticoagulant that inactivates factor V, FVL promotes a prothrombotic state. The prevalence of heterozygous FVL is 5% in the US population of European descent and 0.1% to 2.2% in those with non-European ancestry.[2,3] The homozygous state is rare (<1% of the US population).

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FVL Association With Venous and Arterial Thrombosis

The incident lifetime venous thromboembolism (VTE) risk for individuals heterozygous for FVL and older than 45 years was 17% in a study using prospective data from the Cardiovascular Health Study (N = 5414) and the Atherosclerosis Risk in Communities study (N = 14 185).[4] In a pooled analysis of case-control and cohort studies (11 239 cases and 21 521 controls), heterozygous FVL was associated with an increased risk of VTE (odds ratio [OR], 4.22 [95% CI, 3.35-5.32]) compared with noncarriers of FVL, and homozygous FVL was associated with a VTE OR of 11.45 (95% CI, 6.79-19.29; absolute rates not provided).[5] A pooled analysis of 24 observational studies (N = 13 571) that prospectively assessed patients with prior VTE reported that the relative risk of recurrent VTE in those heterozygous for FVL was 1.4, with an absolute risk of 7% to 14% per year.[1,6] A meta-analysis of 56 case-control or cohort studies that included 10 229 adults with arterial ischemic stroke and 31 816 controls reported that patients with arterial stroke were more likely to have FVL (irrespective of zygosity status) than controls (pooled OR, 1.25 [95% CI, 1.08-1.44]).[7]

FVL and Pregnancy Outcomes

A study of 2034 healthy nulliparous women who underwent screening for thrombophilia polymorphisms reported no association between FVL (homozygous or heterozygous) and a composite outcome of pregnancy complications, including severe preeclampsia, fetal growth restriction, placental abruption, stillbirth, or neonatal death.[8] A trial of 326 women with an inherited thrombophilia (58% heterozygous for FVL) and 2 or more unexplained miscarriages reported no improvement in live birth rate with prophylactic low-molecular-weight heparin vs no treatment.[9]

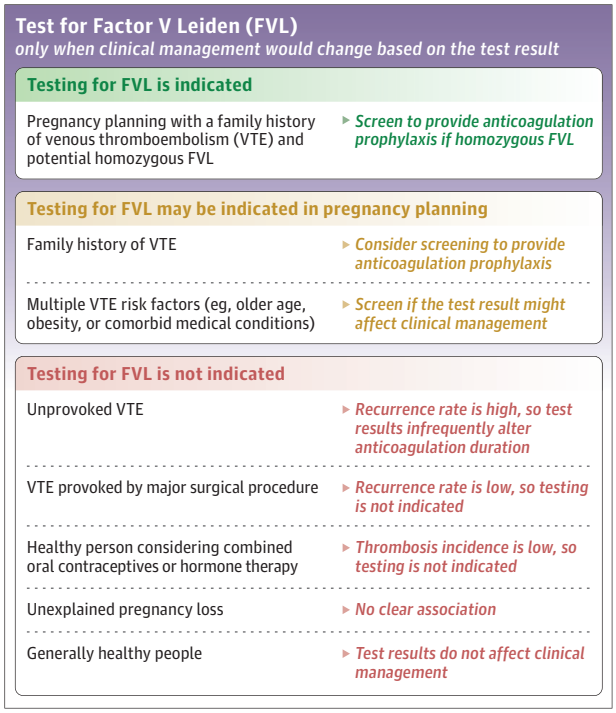
FVL Testing

FVL testing is performed by DNA analysis of peripheral blood using polymerase chain reaction testing or by a functional coagulation test that assesses plasma APC resistance. Individuals with APC resistance should undergo genetic testing to confirm the FVL genetic variant and determine if 1 or 2 copies of FVL are present. FVL genotyping is not covered by all health insurers, so cost should be discussed prior to testing (**Figure**).

Testing in Patients With Symptomatic VTE

Testing for FVL is not recommended unless it affects clinical management (eg, length of anticoagulation), and most VTE anticoagulation management decisions are not affected by FVL test results.[6] Unnecessary testing for FVL increases health care costs and can result in overdiagnosis, unnecessary worry, or false reassurance.[2]

Figure. Approach to Testing



The 2023 American Society of Hematology (ASH) guidelines[6] provided conditional recommendations against testing for FVL and other tests for thrombophilia (eg, prothrombin 20210A sequence variation; deficiencies of antithrombin, protein C, or protein S; and antiphospholipid antibodies) to guide anticoagulation duration in patients with unprovoked VTE (defined as VTE events not associated with a major transient risk factor). The ASH guidelines also conditionally recommended against thrombophilia testing to determine duration of anticoagulant treatment in patients with VTE provoked by a surgical procedure who have completed a short-term course (typically 3 months) of therapeutic anticoagulation.[6]

Controversy exists about the role of FVL testing after VTE in patients with nonsurgical major transient risk factors (eg, confinement to a hospital bed for ≥3 days with an acute illness) and/or hormonal risk factors (eg, pregnancy, post partum, use of combined oral contraceptives [COCs]). While the 2023 ASH guidelines provided a conditional recommendation for thrombophilia testing in patients with VTE provoked by nonsurgical major transient risk factors,[6] some professional societies, such as the British Society for Haematology, do not recommend such testing, as the risk of recurrent VTE is low.

For patients with unprovoked VTE involving unusual sites, such as cerebral and splanchnic veins, thrombophilia testing (including FVL) is recommended only if the information would inform decisions about duration of anticoagulation.[6] If indefinite anticoagulation is already planned, thrombophilia testing is not recommended.[6] However, if discontinuation of anticoagulation is being considered after primary short-term treatment, the ASH guidelines conditionally recommended thrombophilia testing, with consideration of extended anticoagulation if thrombophilia is identified.[6]

Testing in Asymptomatic Individuals

Among people without a prior VTE who have a first-degree relative with FVL, FVL testing is not recommended.

Testing in Individuals Planning Pregnancy or Who Are Pregnant

Testing for FVL is recommended for individuals with a family history of VTE and known homozygous FVL or compound heterozygosity (ie, concurrent heterozygous FVL and heterozygous prothrombin 20210A).[6] If a person is homozygous for FVL or compound heterozygous, thromboprophylaxis antepartum and postpartum is recommended.[7] In contrast, for individuals who are heterozygous for FVL, the ASH guidelines suggest no antepartum or postpartum thromboprophylaxis. However, some thrombosis experts recommend postpartum prophylaxis in this situation if other thrombosis risk factors, such as cesarean delivery or obesity, are present. Although FVL testing of individuals with a family history of VTE and heterozygous FVL is not recommended, it may be useful in patients with other thrombosis risk factors.

Testing Prior to Use of COCs or Hormone Therapy

Routine FVL testing of individuals without family history of VTE prior to starting COCs or hormone therapy is not recommended because the absolute VTE risk in these populations is low.[6] VTE rarely occurs in individuals using COCs (~0.01% per year), and the absolute risk of VTE remains low for FVL heterozygotes (1/345 [0.3%] annually) and for FVL homozygotes (1/116 [0.86%] annually).

The baseline risk of VTE with hormone therapy is 0.1% to 0.2% per year and varies with the hormone therapy formulation.[10] In a study reporting data from the Women's Health Initiative estrogen plus progestin clinical trial, the absolute risk of VTE among women taking estrogen plus progestin with heterozygous or homozygous FVL was 0.8% per year, with a cumulative VTE incidence of 3.3% to 6.7% over 5 years of hormone therapy.[10]

Asymptomatic Individuals With FVL

Asymptomatic individuals should not routinely be tested for FVL. However, if an asymptomatic individual is tested (eg, using commercially available genetic testing to learn about ancestry and genetic health risks) and found to have FVL, they should be counseled about signs and symptoms of VTE. Although they should not routinely be treated with prophylactic anticoagulation, in high-risk settings, such as an operation, extending typical thromboprophylaxis (eg, prophylactic dose of a low-molecular-weight heparin) for a longer than standard duration (typically for as long as the person remains hospitalized) may be considered, especially in those with other VTE risk factors (eg, obesity, cancer, and aged ≥65 years).

Conclusions

Testing for FVL in patients with VTE should only be performed when the results may affect management decisions about anticoagulation, such as duration of anticoagulation in splanchnic vein thrombosis or use of prophylactic anticoagulation in pregnant individuals with a family history of VTE and known homozygous FVL or compound heterozygosity. Testing for FVL is not routinely recommended for asymptomatic individuals, those with unprovoked VTE, or VTE provoked by a surgical procedure.

ARTICLE INFORMATION

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Note: Source references are available through embedded hyperlinks in the article text online.

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