OBJECTIVES:

- To review the frequency, clinical relevance and diagnostic testing of Factor V Leiden and prothrombin gene mutation G20210A.
- To indicate the role of these factors in patients with thrombotic diseases, in family members, and in the general population.
- To review recommendations for management of affected individuals.

BACKGROUND:

Thrombophilias are a group of inherited conditions associated with an increased risk of developing venous thromboembolism (VTE). A point mutation (G1691A) of the gene that codes for clotting Factor V produces an abnormal Factor V molecule known as Factor V Leiden (FVL). FVL is the most common thrombophilia with an approximate incidence of 5% to 8% in Caucasians. The functional consequence of this mutation is impaired inactivation of Factor V (also known as “activated protein C resistance”), resulting in increased thrombin generation.

The second most frequent thrombophilia is a single nucleotide substitution (G20210A) in the promoter region of the gene for the clotting Factor II (prothrombin). This prothrombin gene mutation (PGM) results in an increase in the concentration of prothrombin.

In their heterozygous forms, FVL or PGM are associated with a modest increase in VTE risk. Rare homozygous or compound heterozygous individuals (being heterozygous for both) have a greater VTE risk. There is no association between the presence of these mutations and arterial cardiovascular disease (stroke, acute coronary syndrome, peripheral arterial disease) in the general population. There is a weak association between these mutations and late pregnancy loss; however, the clinical significance is unknown. Despite the thrombotic risk associated with these mutations, affected individuals have a normal life-expectancy.

RISK OF THROMBOSIS WITH FVL AND PGM:

FVL is present in approximately 20% of unselected, symptomatic VTE patients, and in up to 40% of patients with a strong family history of VTE. While most individuals who are heterozygous for FVL or PGM will not develop VTE over their lifetime, the overall VTE risk is mildly elevated, and this risk is compounded by increasing age, oral contraceptive (OCP) use, menopausal hormone therapy (MHT), pregnancy, and other VTE risk factors. Heterozygous patients are not considered to be at increased risk of VTE recurrence compared with patients who have an unprovoked episode of VTE without one of these mutations. As both FVL and PGM are autosomal dominant conditions, first degree relatives of carriers have a 50% chance of also being carriers of the mutation.

DIAGNOSIS AND SCREENING:
The presence of FVL or PGM can be detected by DNA testing using a routine blood sample. Additionally, the presence of FVL can be screened for by Activated Protein C Resistance, a functional screening test. No functional test exists to detect the presence of PGM. **The practice of widespread thrombophilia testing is not effective at reducing adverse outcomes and rarely influences clinical decision-making; thus it is not recommended.** The advantages and disadvantages of testing should be discussed with the patient and testing should be reserved for those in whom results will influence clinical decision-making. A positive test result may produce unnecessary anxiety for the patient and their family and may affect their eligibility for insurance. The role of FVL and PGM in pregnancy loss and other pregnancy complications is not clearly established, so screening in such women is not recommended.

**TREATMENT OF VTE:**

The therapeutic options and duration of VTE treatment are generally not affected if FVL or PGM are present. There is little, if any, difference in the risk of VTE recurrence, when anticoagulation is stopped, between those with or without FVL or PGM in the heterozygous form.

**PREVENTION OF VTE:**

Individuals with FVL or PGM should receive appropriate thromboprophylaxis during periods of increased VTE risk including the immediate post-partum period. Women who are heterozygous for FVL or PGM do not warrant routine thromboprophylaxis during pregnancy unless they have previously experienced VTE in pregnancy or associated with OCP use, or an unprovoked VTE OCP and MHT use in carriers of FVL or PGM are associated with a further increase in VTE risk; therefore, the risk-benefit of OCP or MHT use should be carefully discussed. In asymptomatic women carriers of FVL or PTG with no other risk factors (such as a personal or family history of venous thrombosis) who cannot tolerate reliable, alternative non-estrogen forms of contraception (including progesterone alone), combined oral contraceptives containing estrogen can be considered on a case by case basis. It would require a careful discussion of risks and benefits and a consideration of the values and preferences of the patient.

**OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:**

- Deep Vein Thrombosis (DVT): Treatment
- Pediatric Thrombosis
- Pregnancy: Thromboprophylaxis
- Pulmonary Embolism (PE): Management

**REFERENCES:**


**Date of Version:** 2017Jan13

*Please note that the information contained herein is not to be interpreted as an alternative to medical advice from your doctor or other professional healthcare provider. If you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare providers, and as such you should never delay seeking medical advice, disregard medical advice or discontinue medical treatment because of the information contained herein.*