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Current practice of testing for Factor V Leiden and Prothrombin G20210A mutation in a university hospital

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Abstract

Background, current state of research
Heritable thrombophilia and venous thromboembolism
The first specific cause of thrombophilia (the propensity to develop thrombosis because of abnormalities in coagulation) was described in 1965 by Egeberg. He reported that thrombophilia could be caused by a deficiency of antithrombin III, a natural anticoagulant. Since then, many other causes of thrombophilia, both heritable and acquired, have been described. Factor V Leiden (FV Leiden), prothrombin G20210A mutation, and deficiencies of the natural anticoagulants (antithrombin III, protein C, and protein S) are recognized as heritable causes of thrombophilia and evidence suggests that they are associated with a first venous thromboembolism (VTE).

For this project we will focus on the two most common heritable thrombophilia, which are FV Leiden and prothrombin G20210A mutations. In fact, their prevalence within Caucasian European ranges between 3-7% and 1-2%, for FV Leiden and prothrombin G20210A mutation respectively. Within patients with a first unprovoked VTE event, approximately 20% are heterozygous carriers of FV Leiden and prothrombin G20210A mutation is present in about 5%.

While the association between FV Leiden and prothrombin G20210A mutation and a first **VTE** is well accepted, their association with recurrent **VTE** is more controversial. A meta-analysis including patients with a first **VTE** demonstrated a slightly increased risk of recurrent **VTE** for heterozygous FV Leiden (relative risk **[RR]** 1.4,

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95% CI 1.1-1.8) or prothrombin G20210A mutation (RR 1.7, 95% CI 1.3-2.3). In a prospective study conducted among young patients with a first VTE, testing for FV Leiden and prothrombin G20210A mutation did not reduce the incidence of recurrent **VTE**. In another prospective cohort of patients with a first VTE, Christiansen et **al.** concluded that "".extensive, if any, thrombophilic work-up after a first thrombotic event is not likely to confer a clinical benefit on the patient".

Thrombophilia testing
According to current guidelines, duration of anticoagulant therapy in patients with **VTE** should not be based on the results of thrombophilia testing. Indeed, no randomized trialm has ever assessed the benefit of testing for thrombophilic risk factors to prevent a recurrent **VTE**. A recent survey reported that in 77% of patients for whom heritable thrombophilia testing was performed, the test results did not influence medical management. Moreover, in a large registry of consecutive patients with VTE, a substantial proportion of thrombophilia testing did not comply with national guidelines, raising the question whether patients really benefit from thrombophilia testing.

In fact, positive testing for heritable causes of thrombophilia (namely genetic testing for FV Leiden and prothrombin G20210A mutation) could generate anxiety in patients and their family, while patients tested negative may be falsely reassured that they are not at an increased risk of recurrent **VTE**. Screening for thrombophilia can also have social consequences, such as difficulty in obtaining life or private health insurance.

Further, FV Leiden and prothrombin G20210A mutation are costly lab tests, ranging around 160 CHF each. Moreover, non-genetic heritable thrombophilia assays (deficiencies in antithrombin III, protein C, and protein S) might be ordered together with FV Leiden and prothrombin G20210A mutation by doctors. Besides the additional costs, those non-genetic heritable thrombophilia are influenced by the presence of acute thrombosis or ongoing anticoagulation, so that strict conditions for testing have to be met. Thus, non-genetic heritable thrombophilia testing should be performed neither in patients receiving anticoagulation, nor shortly after an acute VTE, in order to avoid inadequate results and interpretation.

In conclusion, the predictive value of the most common types of heritable thrombophilia (factor V Leiden and the G2021 OA prothrombin mutation) regarding recurrent VTE is limited and does not influence subsequent patient management. Thus, systematic testing for heritable thrombophilia should be avoided, but to which extent such testing is practiced in Switzerland is currently unknown.