Recent Advances in Molecular Diagnostics of Thrombophilia

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We live in "polymorphic times" as one of our invited authors, *Elena Faioni,* recently indicated our epoch [1]. The common factor V Leiden mutation and the prothrombin G20210A polymorphism were just the beginning of the molecular age of thrombophilia. Genetic abnormalities probably predisposing to thrombosis currently spring up like mushrooms. More and more, we understand the mechanisms of familial thrombophilia. In this issue of *Laboratoriums Medizin,* upcoming molecular aberrations are presented. We are dealing with encouraging findings which, however, have to overcome future studies to finally settle in the thrombophilia program. Furthermore, the reviews focus on genetic alterations which may play a role in venous thromboembolism, thereby keeping in mind the possible significance of these molecular defects for arterial thromboembolism. It is the complex pathogenesis of arterial thrombosis that often veils the true nature of genetic abnormalities. In the latter field, we are confronted with a variety of polymorphisms of which the relevance for the development of arterial thrombosis has been very controversially discussed in the last years. Of the presented molecular defects, the mutant C677T methylenetetrahydrofolat reductase already found its way into the clinical laboratories. However, *Ralf Junker* et al. emphasize in their review that this variant could not yet be considered as an established marker of thrombophilia [2]. It is a good example for a genetic alteration of which the clinical relevance is probably more puzzled than clarified by case-control studies with their own characteristic biases. Moreover, this is an example for a genetic factor that – besides environmental factors – only partially contributes to the phenotype. The factor XIII Val34Leu polymorphism as discussed by *Silke Ehrenforth* and coauthor has not turned out to be a new hereditary risk for but has evolved as a protective polymorphism against thrombosis [3]. Interestingly, there are alterations that do not represent independent risk factors of their own. They seem to be only involved if hereditary thrombophilia, e.g. the factor V Leiden mutation, preexists. Presented by *Elena Faioni,* the factor V HR2 haplotype might be such an alteration [4]. The interaction of inherited defects can be also quite different. At least in some families with protein C gene mutations, the prothrombin G20210A polymorphism, an originally independent risk factor, does not contribute to the thrombotic risk of the carriers [5]. Like antithrombin, the tissue factor pathway inhibitor (TFPI) is an inhibitor outside the protein C pathway, but its role in the pathogenesis of thrombotic disease is not well understood. *Brinkmann* et al. present new insights in the molecular background of TFPI [6]. Finally, *Mario von Depka* and coauthor show us candidates for which only very few studies indicated a possible role for venous thromboembolism, among them the well-known lipoprotein (a) [7].

In these polymorphic times, has screening for inherited thrombophilia already an impact on the management of patients? *Greaves* and *Baglin* argued last year that, "in the current state of knowledge, identification of a particular genetic predisposition should rarely influence management" [8]. Indeed, after a first episode of previous thromboembolism the intensity of oral anticoagulation would not currently change if a preexisting hereditary risk factor is known. Contrary to patients with an antiphospholipid antibody syndrome, patients with a previous thrombotic event and protein S or C deficiency would not be anticoagulated longer than six months. This is also true for patients with a heterozygote factor V Leiden mutation, although the two methodologically best studies on the recurrence probability demonstrated an increased recurrence rate [9]. In any case, a long-term prophylaxis is recommended to patients with recurrent events. Family screening was questioned at least in the case of symptomatic factor V Leiden carriers [10]. The prophylactic approach in asymptomatic carriers would not be different from common practice. Even in pregnancy, the incidence of thrombotic events would be too low to recommend antepartum prophylaxis. Screening before prescription of oral contraceptives is also not indicated since the advice against the use of the pill could have unpredictable family planning consequences. Hence, is thrombophilia screening worthless? I do not think so. At the moment, patients with a high recurrence risk like antithrombin deficiency, homocygote factor V Leiden mutation or combined inheritance of genetic alterations are already anticoagulated more than six months after a first thrombotic event. Pro-

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longed anticoagulation of heterozygous factor V Leiden carriers seems to be cost-effective at least for patients after idiopathic deep vein thrombosis [11]. Thrombophilia screening can support the compliance for further thromboprophylaxis after an episode of oral anticoagulation. Patients have usually a strong need for causality. With the awareness of a permanent risk factor, an affected patient will easier follow the physician's advice to administrate heparin in risk situations, e.g. during long distance air travels. Furthermore, there is evidence that only pregnant women with a history of venous thromboembolism whose previous episode has been idiopathic or who had inherited thrombophilia would benefit from an antepartum thromboprophylaxis with heparin [12]. Testing family members of affected patients is another issue of thrombophilia screening. Yet asymptomatic family members with an inhibitor deficiency developed less thrombotic events if they received an anticoagulant prophylaxis in risk periods like pregnancy or prolonged immobilization. This was the result of a prospective, but non-randomised study with different regimes of risk-period related anticoagulant prophylaxis [13]. Even family screening for factor V Leiden could be warranted despite the low incidence of pregnancy-related thrombosis of 1 %. The knowledge of factor V Leiden probably alters the policy in pregnant women with additional hazards since usually heparin is not administered to women with immature labour and required immobilization. Elder women may also benefit from family screening. In the last years, postmenopausal hormone replacement therapy established a risk for venous thromboembolism [14–17]. Oral but not transdermal administration seems to promote prothrombin activation [18]. Hence, it might be wise to recommend transdermal estradiol to yet asymptomatic women with inherited thrombophilia.

Nowadays, physicians "can rely only on their perception of the problem" as *Elena Faioni* summarized [4]. Solid data that showed a clear benefit for patients with inherited thrombophilia by a modified thrombosis prophylaxis are lacking. However, the first trials are in progress. PREVENT is a randomised double-blind, placebo-controlled trial of long-term low-dose warfarin (INR 1,5–2,0) among patients with a previous history of idiopathic venous thrombosis who have completed a standard course of 3–6 months of oral anticoagulation. The use of low-dose warfarin should prevent major hemorrhagic events that have to be faced with full-dose warfarin. This trial specifically addresses risks and benefit of long-term anticoagulation of factor V Leiden carriers [19].

Thrombophilia screening could give us the key for an individual thromboprophylaxis. Competent counselling on thrombophilia is already now an essential task for clinicians and laboratorians as well. We must not leave patients with their inherited thrombophilia alone.

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