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Editorial

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Thrombophilia testing. Useful or hype?

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Venous thromboembolism (VTE), which typically – although not exclusively – entails development of thrombosis into one or more veins of the (lower) limb(s) and possible embolization in one or both pulmonary arteries, is an important and growing public health concern. The global annual incidence of VTE is approximately 100 per 100,000 person-years among Whites, is slightly higher among Blacks and lower among Asian- and Native-Americans. The incidence of this pathology is also strongly influenced by ageing, increasing by approximately 90-fold from the time of childhood to the elderly. Although some studies described that male gender may be a predisposing factor, definitive data on this aspect are lacking [1].

In analogy with another frequent thrombotic disorder, cardiovascular disease [2], the pathogenesis of VTE is complex and substantially multifactorial. In brief, VTE is conventionally thought to develop in a patient with a genetic predisposition [3], in whom an acquired [4] or triggering factor [5] contributes to worsen the baseline impairment of the hemostatic balance towards a highly prothrombotic state [6], which ultimately culminates with onset of venous thrombi followed by potential propagation upward, throughout the venous system (Figure 1).

Due to relative high frequency, substantial genetic background and potentially preventable nature [3], this disease appears well suited for screening strategies that typically entail thrombophilia testing. Indeed, the coagulation laboratory has an enormous potential for investigation of patients with VTE [7], but all these weapons must be used with moderation and intelligence. In the general perspective of values-based reimbursement and accountability of laboratory performance, there is general consensus that a diagnostic test is only useful when it has an influence on clinical management, when it improves the outcome or, preferably, reverses an adverse outcome. Laboratory testing does not come for free. Irrespective of different reimbursement policies across various countries, laboratory testing still places a considerable economic burden on patients and healthcare system as a whole [8], and should hence be based on evidence of clinical efficacy (i.e., improving outcomes) rather than efficiency (i.e., diagnosing diseases). In this issue of the journal, we publish a double-edged sword debate about utility and futility of thrombophilia testing [9, 10]. In this editorial, I will not anticipate the contents of the pro and the counter, but I wish to express some general considerations about the potential benefits and the tangible risks of thrombophilia screening.

A necessary premise, shared with other areas of diagnostic testing, is that indiscriminate screening must be avoided, since this strategy carries a latent risk of identifying a large number of "prothrombotic subjects" by nature of a positive test result, who will never become "patients" (i.e., develop thrombosis throughout their lifetime) due to the low penetrance of most prothrombotic abnormalities. Using Factor V Leiden as an example, only 10% of heterozygous carriers of this polymorphism will develop VTE throughout their lifetime, with varying degrees of severity [11]. So, indiscriminate screening is clearly unacceptable, for a number of clinical (e.g., potential for inappropriate clinical management) and ethical (e.g., psychological distress) reasons. However, there are several elements that support focused testing in selected categories of individuals. It is an analysis of these aspects that are raised by Massimo Franchini, who takes the case in favor of testing [9], and Emmanuel Favaloro, who instead highlights areas of uncertainty and raises reasonable drawbacks against testing [10].

What should be clear to everybody is that thrombophilia testing is only effective in those patients who will benefit from targeted thromboprophylaxis or differential management (e.g., prolonged treatment) under specific clinical or environmental circumstances. Most of these conditions are clearly discussed by Franchini [9], as well as in a recent review of guidelines from Scientific Societies and Working Groups, authored by De Stefano and Rossi [12]. It is also noteworthy, however, that focused (or targeted) screening is nothing but foolproof, and there are additional actual risks of obtaining false-negative and false-positive results, as highlighted by Favaloro [10]. Beside obvious economic considerations in a world with limited resources, the consequences may be deleterious in

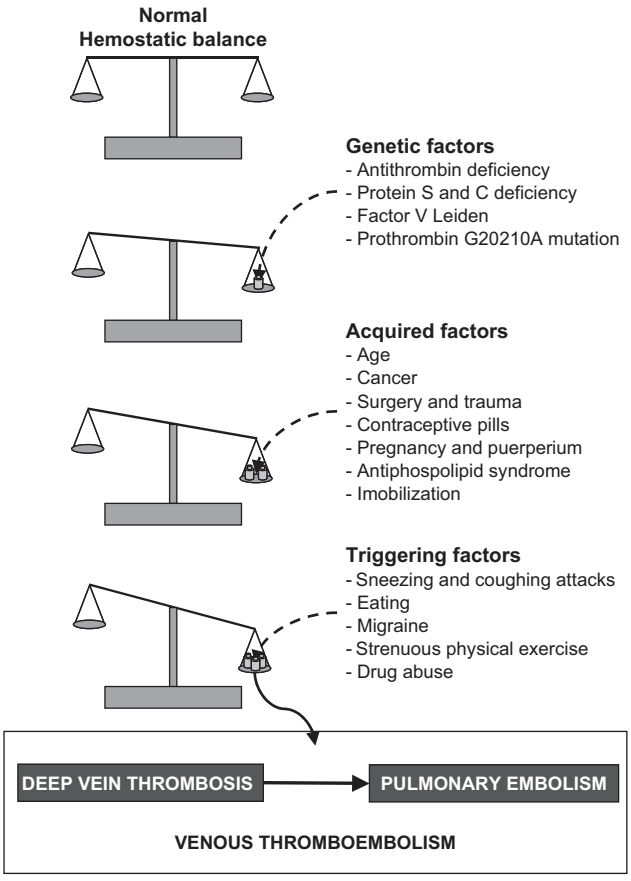

Figure 1 Pathogenesis of venous thromboembolism.

either circumstance. A false-negative result may encourage the misleading reassurance of a low thromboembolic risk, prevent the use of physical or chemical prophylaxis when otherwise needed, thus exposing the patient to an unethical risk of thrombosis. A false-positive result, which can be due to technical (i.e., "normal" outliers of reference ranges) [13] or clinical (i.e., laboratory testing in patients on anticoagulant therapy) [14] reasons, would instead jeopardize the clinical decision making, with the risk of establishing inappropriate prophylaxis or promoting unjustified lifestyle changes (e.g., avoidance of oral contraceptives in "false-positive" carriers of prothrombotic polymorphisms).

All this said and although it seems maybe pessimistic to conclude that thrombophilia testing generates outcomes that are even worse than not having investigated at all, the take-home message from this fervent debate is that we have not reached an univocal truth so far and – even in this field of diagnostic testing – specific counseling and "personalized" approaches are probably the most clinically efficacious and cost-effective solutions, wherein the various tests should be cautiously requested according to familiar and clinical history, the presence of inherited or acquired risk factors, the type, site and extension of thrombosis, and always weighted against the tangible threat of side effects of anticoagulant therapy.

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