Thrombophilia: grading the risk

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In this issue of Blood, Lijfering and colleagues provide data on the absolute risk for both initial and recurrent venous thrombosis in persons with thrombophilia. Based on these data, they subgroup thrombophilic defects into high- and low-risk disorders. They also conclude that some defects are not independent risk factors.

Ever since the first description of antithrombin deficiency as a cause of familial thrombophilia by Egeberg in 1965, the number of reported inherited risk factors for venous thrombosis has been increasing, especially in the past 15 years. Most previous studies have reported on relative rather than absolute risks and dealt with single defects. It is clear that thrombophilia is multi-factorial due to gene–gene and gene–environment interactions. While relative risk is useful in terms of learning about the pathophysiology of the disease, the clinician requires absolute risk information to help make decisions about patient management.

In this study involving 3 Dutch hospitals, Lijfering et al investigate 2479 relatives of 877 probands with thrombosis. To avoid bias, probands were excluded from the analysis. The risk for a first deep vein thrombosis (DVT) was 1.52% to 1.90% per year for those with deficiencies of antithrombin, protein C or protein S, and 0.34% to 0.49% per year for those with factor V Leiden, the prothrombin mutation or elevated FVIII. Within these 2 groups, the thrombotic risk was similar for each of the individual defects, and in the paper, the 2 groups were classified as high- and low-risk thrombophilias, respectively. The risk of recurrence was 55% at 10 years for defects in the first group, 25% for the second (see table). Although elevated levels of FIX, XI, TAFI, and homocysteine appeared to be associated with an increased thrombotic risk, all were closely linked to concomitant elevated FVIII and were not risk factors in isolation.

In analyzing the risk of venous thrombosis, the authors assume that the risk in persons with antithrombin, protein C, or protein S deficiency is the same, irrespective of the severity of the deficiency or mutation causing the defect. However, as they have recently shown in protein S deficiency, this may not be the case, and one would logically expect an inverse relationship between deficiency and risk.

Whether or not to test for thrombophilia is controversial because the clinical utility of doing so has not yet been proven. For FIX, XI, TAFI, and homocysteine, this study suggests the answer is a definitive no, since elevated levels are not associated with increased thrombotic risk independent of elevated levels of FVIII. In the case of heterozygosity for factor V Leiden, or the prothrombin mutation, or for elevated FVIII, the answer is also probably no because the risk of a first DVT at under 0.5% per year is not high enough to warrant primary warfarin prophylaxis and the recurrence risk is no different from that reported for patients with first DVT who have not been tested for thrombophilia.

More difficult is the issue of the higher risk thrombophilias represented by the deficiencies of the natural anticoagulants antithrombin, protein C, and protein S. The authors suggest that these are conditions with a much higher risk of first and recurrent thrombosis and should be managed differently from the commoner thrombophilias. Although based on these data alone

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**REFERENCES**


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**Thrombophilic defect** | **Annual risk of first DVT** | **Relative risk (compared to community controls)** | **Risk of recurrence**
---|---|---|---
Antithrombin deficiency | 1.52-1.90% | 18-19x | At 5 yrs – 40%, At 10 yrs – 50%
Protein C deficiency | 0.34-0.49% | 3-5x | At 5 yrs – 11%, At 10 yrs – 28%
Protein S deficiency | 1.90% | | |
Factor V Leiden | | | |
Prothrombin 20210A | | | |
High FVIII | | | |
High FIX | | | |
High FXI | | | |
High TAFI | | | |
Hyperhomocysteinemia | | | |

Based on the annual risk of first venous thrombosis and recurrence risk, thrombophilic defects can be subdivided into 3 groups.
there would be reluctance to advocate long-term primary prophylaxis, this should certainly be offered at times of additional high risk, such as after surgery, immobility, or pregnancy.

Clinically, the issue of thrombophilia testing and management is more relevant in the setting of patients who have experienced an event already. If testing has been performed and high-risk thrombophilia has been identified, this should certainly be taken into account when deciding on extended anticoagulation, especially for spontaneous events. The issue of whether all patients with a DVT should be screened for high-risk thrombophilia is unresolved but, for those with a spontaneous event at a young age and a positive family history, this should be considered. Definition of a positive family history is difficult, but the suggestion offered in this paper of more than 20% of relatives affected is not evidence-based and would be dependent on relatives being available for study.3

Any decision on whether to offer long-term anticoagulation will depend on the risk of bleeding while on anticoagulants as well as the thrombotic risk. This study reports a very low annual bleeding risk at 0.29% but with wide confidence intervals, because it is based on only 2 events. The authors speculate that this may be because the thrombophilic defect reduces the bleeding risk, and this observation certainly requires confirmation. Alternative explanations are the young age of the cohort, the fact that the patients are cared for by expert centers, and the small number of events.

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References


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ADAMTS13’s tail tale

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In mice, a long form and a short form of the VWF-cleaving protease ADAMTS13 have been identified, the latter lacking the 4 distal carboxyl-terminal domains. While these are not strictly required for regulating normal size distribution of VWF multimers, in this issue of Blood, Banno and colleagues reveal the role of these domains in down-regulating thrombogenesis in vivo.

Since the discovery of ADAMTS13 as a metalloprotease with a multi-domain structure, numerous studies have attempted to shed light on the specific roles of each of the ADAMTS13 domains in digesting large von Willebrand factor (VWF) multimers into smaller, less reactive ones. ADAMTS13 is composed of a signal peptide, propeptide, metalloprotease domain, central TSR (thrombospondin type 1 repeat), Cys-rich region, spacer domain, 7 additional TSRs, and 2 CUB domains. The active site of this enzyme is situated in the metalloprotease domain while the spacer domain plays a crucial role in substrate binding by interacting with a VWF exosite located at the C-terminus of the A2 domain. The exact physiologic significance of the carboxyl-terminal TSRs and the 2 CUB domains still remains unclear, in particular due to the use of different types of in vitro tests, often performed under nonphysiological conditions.

To unravel the in vivo role of the carboxyl-terminal domains of ADAMTS13, Banno and coworkers elegantly take advantage of the presence of 2 kinds of Adamts13 genes in laboratory mouse strains.1 The 129/Sv strain has the Adamts13 gene encoding full-length ADAMTS13 while several other strains, including C57BL/6, harbor an Adamts13 gene that expresses a truncated form of the enzyme, lacking the 2 C-terminal TSRs and CUB domains due to the insertion of an intracisternal A-particle retrotransposon. By introgressing the C57BL/6-Adamts13 gene onto the 129/Sv genetic background, the authors generate congenic mice that had the distal C-terminally truncated ADAMTS13 on a 129/Sv genetic background (Adamts13<sup>S/S</sup>) and use wild-type mice that have full-length ADAMTS13 (Adamts13<sup>L/L</sup>) and Adamts13<sup>S/S</sup> mice on the same 129/Sv genetic background for comparison.

The most obvious role of ADAMTS13 is to regulate VWF multimer size. Indeed, ADAMTS13 digests unusually large VWF multimers into smaller less thrombogenic forms,2 hence preventing the spontaneous intravascular platelet aggregation seen in patients with ADAMTS13 deficiency. Interestingly, Banno et al showed that both Adamts13<sup>S/S</sup> and Adamts13<sup>L/S</sup> mice do not have ultra large VWF multimers in their plasma, implying that the C-terminal domains are not strictly needed for maintaining normal VWF size. Consequently, the 2 C-terminal TSRs and CUB domains are not essential for the removal of ultralarge VWF multimers from the plasma.

Following VWF size regulation, a fascinating role of ADAMTS13 in attenuating thrombus growth has been described, possibly by cleaving VWF multimers that are peripheral to or incorporated in platelet rich thrombi.3 In this study, Banno et al used the congenic mice to demonstrate that the 2 C-terminal TSRs and CUB domains play a role in the down-regulation of thrombogenesis under high shear conditions. Both in vitro flow chamber experiments at high shear rates and in vivo thrombosis models show that blood from Adamts13<sup>S/S</sup> mice is more thrombogenic. This is evidenced by accelerated thrombus formation and decreased time to occlusion respectively when compared with blood from Adamts13<sup>L/L</sup> mice. Whether this would...
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