Commentary

High Levels of Factor VIII and Venous Thrombosis

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The first families with a tendency to venous thrombosis were reported in the early 1900s (1) In 1965, Egeberg reported a family with thrombophilia and an identified hereditary defect (antithrombin deficiency) (2) In the early 1980s, deficiencies of other natural anticoagulants – protein C and protein S – were shown to be associated with venous thrombosis in families with familial thrombophilia (3, 4) Recently, several other blood abnormalities have been described that increase the risk of thrombosis resistance to activated protein C, usually the result of a mutation in factor V (factor V 1691A or factor V Leiden), a mutation in the prothrombin gene (PT20210A), and high levels of clotting factor VIII (5–8)

There are several major differences between the deficiencies of natural anticoagulants as risk factors for thrombosis, and these more recently described abnormalities First, biochemically, the deficiencies all lead to "loss of function" The mutated allele does not lead to any protein synthesis, or to a non-functional variant, with a resultant loss of anticoagulant activity, and an increased risk of thrombosis The variant protein that is the result of the 1691 G→A mutation (factor V Leiden), however, displays "gain of function" the molecule has become resistant to inactivation by activated protein C, its increased function leads to an increased thrombotic risk Similarly, although here the mechanism is less clear, the prothrombin mutation, at the 3'-untranslated end of the gene, is associated with elevated levels of prothrombin These, in turn, are associated with increased risk of thrombosis High levels of factor VIII are also likely to be expressions of gain in function A second characteristic that differentiates these "gain-of function" abnormalities from the deficiency defects is their high prevalence As is shown in the table, the prevalences in the general population of the Netherlands vary between 2 and 11 percent, while deficiencies of protein C, protein S and antithrombin are only found in a few per thousand or less (9-11) A third difference is that "gain-of-function"abnormalities tend to be less strong risk factors than "loss of-function"mutations while for the latter relative risks are around 10 for heterozygous carriers (relative to normal individuals), prothrombin 20210A and factor V Leiden increase the risk 3-8 fold For high levels of factor VIII such comparisons are less straightforward since they depend on the cut-off value that is used, but at the cut-off value of 150IU/dl the abnormality is also prevalent and of moderate strength Even though the risk increase may be less for the "gain-of-function" abnormalities, they are much more important than the deficiencies from a public health point of view (9) The proportion of thrombosis caused by a risk factor (attributable risk) depends on the relative risk and the number of people this risk applies to, i e , the prevalence As the table shows, a sizable proportion of all thrombotic events can be attributed to factor V Leiden, prothrombin 20210A and high levels of factor VIII – obviously, since these figures refer to the population, they are population-specific, and will differ between populations with different prevalences

High levels of factor VIII were associated with an increased risk of thrombosis in the Leiden Thrombophilia Study (LETS) (8) Individuals with levels of factor VIII C exceeding 150 IU/dl had a 3-fold increased risk compared to those with levels below 150IU/dl and a 6-fold increased risk compared to those with levels below 100IU/dl Arguments for this association to be causal were found in the "dose-response" relation between factor VIII levels and thrombosis, and in the finding that while blood group (non-O vs O), levels of von Willebrand factor and factor VIII levels each increased the risk of thrombosis in univariate analysis, only factor VIII levels remained as a strong risk factor when these three variables were mutually adjusted for (8) This study corroborated and explained findings of 25 years before, ie the report of Jick et al of the association between ABO blood group and the risk of thrombosis (12) Factor VIII levels which are to a large extent determined by blood group and von Willebrand factor levels appeared the effector of the thrombotic risk (8) While ABO blood group has been known as a determinant of factor VIII levels for many years (13, 14), this analysis indicated that there were other factors affecting the factor VIII levels Studies among women in whom factor VIII was measured to rule out hemophilia carriership (15), as well as among families with thrombophilia (16), showed that factor VIII levels are affected by familial factors other than blood group Until now, however, attempts to find genetic variants associated with factor VIII within the factor VIII gene have failed (17)

Two reports in this issue of Thrombosis and Haemostasis deal with factor VIII levels as a risk factor for venous thrombosis, and they contain several important findings (18, 19) First of all, the paper by Kraaijenhagen et al (18) confirms that high factor VIII levels increase the risk From their report it follows that levels exceeding 150 IU/dl increase the risk over 5-fold compared to levels below 100 IU/dl, which is in agreement with the results from the LETS study (8) By a family study they can also confirm that factor VIII levels within families correlate This paper, and the paper by O'Donnell et al (19) shows that high levels of factor VIII very often persist over time For factor VIII levels determined by blood group this is fully expected, but O'Donnell et al also show that these high levels were not secondary to high von Willebrand levels, ie, these data also suggest a persistent, probably genetic, origin of high levels of factor VIII beyond the vWF-mediated blood group effects O'Donnell et al have previously shown that high factor VIII levels are likely to be a cause of an increased thrombotic risk rather than a consequence, since adjustment for acute phase reactants (CRP, fibrinogen) did not lead to attenuation of the risk estimate (20) Similar results were obtained in the Leiden Thrombophilia Study (21)

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Table 1 Prevalence and populaton attributable risk of two types of prothrombotic abnormalities[1]

	population prevalence %	population attributable risk %
loss of function		
protein C deficiency	0 2	2
protein S deficiency	<1[2]	<1
antithrombin deficiency	0 02	<1
gain of function		
factor V Leiden	4	25
prothrombin 20210A	2	4
high levels of factor VIII[3]	11	16

[1] Figures may differ for various populations [2] Reliable population estimates for protein S deficiency are missing [3] Levels exceeding 150 IU/dl

and are again confirmed in the present studies Probably the strongest argument in this debate is the association between blood group and venous thrombosis, since blood group is invariant Nevertheless, none of these findings can completely rule out the possibility of post-hoc factor VIII elevation or an effect of blood group on venous thrombotic risk that is not mediated by factor VIII It will be important to see whether high levels of factor VIII are, as other types of thrombophilia, associated with increased thrombin generation Ongoing research will focus on the genotypes underlying high levels of factor VIII

Is there any clinical relevance to this, and should we screen for high levels of factor VIII in a thrombophilia work-up, or perhaps in all patients with thrombosis? This is a question we may in fact ask for all thrombophilia screening, since the therapeutical consequences of a diagnosis are unclear It is noteworthy that, contrary to factor V Leiden (22), high levels of factor VIII do not interact synergistically with the use of oral contraceptives (23), so that screening prior to subscribing oral contraceptives would not even offer a theoretical benefit The paper by Kraaijenhagen, as well as recent other data suggest that high levels of factor VIII increase the risk of recurrencies of thrombosis (24), which may point to the need for sustained anticoagulant treatment in these individuals A major research goal, which will assist us in setting rational clinical policies, is to find out the origin of elevated levels of factor VIII

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