Elevated Factor VIII Levels and the Risk of Thrombosis

Pieter W. Kamphuisen, Jeroen C.J. Eikenboom, Rogier M. Bertina

In vivo, a delicate balance exists between fibrin formation and fibrinolysis. Reduced blood flow, changes in the vessel wall, and changes in blood composition (hypercoagulability) may all result in a disturbance of this balance, which favors fibrin formation and ultimately may lead to the formation of occlusive thrombi. Venous thromboembolism is the result of clot formation in a vein at sites of reduced blood flow. Arterial thrombosis involves the formation of platelet aggregates at high shear rates at sites of vessel-wall injury.

Classic acquired risk factors for venous thrombosis include trauma, immobilization, pregnancy, surgery, malignancy, and infection. These are all factors that may cause tissue damage, stasis of the blood, or changes in blood composition. Inherited risk factors for venous thrombosis,2-5 most of which concern defects in the procoagulant and anticoagulant pathways, account for a substantial proportion of all thrombotic events. Table 1 summarizes prevalences and relative risks of inherited risk factors for venous thrombosis,2-5 most of which concern defects in the procoagulant and anticoagulant pathways, account for a substantial proportion of all thrombotic events. Table 1 summarizes prevalences and relative risks of

In the present review, we will summarize the present knowledge on the relation between factor VIII and thrombosis and discuss the possible determinants of elevated factor VIII levels in plasma.

Determinants of Plasma Factor VIII Levels

Genetic Determinants of Plasma Factor VIII Levels

In healthy individuals, family studies have indicated a genetic influence on the level of factor VIII:C.24,43 Factor VIII levels varied less among twins than among unrelated individuals. Filippi et al44 have suggested a primary role of X-linked genetic determinants on the basis of the observation of a positive correlation of factor VIII:C levels within groups of male pairs who had identical X alleles. Ørstavik et al39 found that the variance of factor VIII and vWF:Ag levels was smaller within twin pairs than between these pairs. They estimated that 57% of the total variation in plasma factor VIII levels and 66% of the variation in vWF levels were genetically determined. Most recently, Souto et al45 reported a heritability of 0.4 for factor VIII levels in the families of the Genetic Analysis of Idiopathic Thrombosis (GAIT) study.

vWF and blood group are important determinants of the factor VIII level in plasma. The blood group non-O is associated with higher vWF and factor VIII levels than is blood group O,37-39 with a mean difference of 31.5 IU/dL for vWF:Ag and 22.4 IU/dL for factor VIII:C.46 Individuals with blood group AB have the highest vWF levels, whereas AA, AO, BB, and BO genotypes have intermediate levels.37,47,48 Most of the effect of blood group on the factor VIII level is mediated through vWF.38,46 Blood group A, B, and H(O) oligosaccharide structures have been identified on vWF,49,50 which may affect the clearance of vWF and, thus, of the vWF/factor VIII complex.51,52 Indeed, in patients with hemophilia A, the half-life of infused factor VIII was shorter in patients with blood group O (15.3 hours) than in patients with blood group A (19.7 hours).53 Both are much longer than the half-life of uncomplexed factor VIII as determined in patients with severe von Willebrand disease (2.8 hours).54 Interestingly, ABO blood group and plasma vWF level are independent predictors of factor VIII half-life.53

The high levels of factor VIII in patients with thrombosis persist over time31,55 and are, in general, not caused by
TABLE 1. Genetic Risk Factors for Venous Thrombosis: Prevalence and Relative Risk

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Healthy Control Subjects, n (%)</th>
<th>Thrombosis Patients, n (%)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor V Leiden</td>
<td>14 (3)</td>
<td>92 (20)</td>
<td>8</td>
</tr>
<tr>
<td>Prothrombin 20210A</td>
<td>11 (2.3)</td>
<td>29 (6.2)</td>
<td>2.8</td>
</tr>
<tr>
<td>Protein C deficiency</td>
<td>4 (0.8)</td>
<td>15 (3.1)</td>
<td>6.5</td>
</tr>
<tr>
<td>Protein S deficiency</td>
<td>6 (1.3)</td>
<td>5 (1.1)</td>
<td>0.7</td>
</tr>
<tr>
<td>Antithrombin deficiency</td>
<td>1 (0.2)</td>
<td>5 (1.1)</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Data are from the Leiden Thrombophilia Study which involved 474 consecutive patients with a first deep vein thrombosis and 474 healthy control subjects.6–8 Protein S deficiency was not associated with increased thrombotic risk in this case-control study, which contrasts with previous findings in family studies.10,11

acute-phase reactions.30,31,56 In addition, O’Donnell et al55 showed that only 50% of these persistently high factor VIII levels were associated with high vWF:Ag levels, indicating that vWF is not always responsible for high factor VIII plasma levels.

Factor VIII:C levels show a familial clustering, which remains after adjustment for the influence of vWF and blood group.40 Analysis of familial aggregation of factor VIII levels ≥150 IU/dL in 12 large thrombophilic families57 identified blood group as the main determinant: 86% of the subjects with factor VIII levels ≥150 IU/dL had blood group non-O. However, after adjustment for blood group and age, factor VIII levels ≥150 IU/dL still aggregated in these families. Others have also observed a high concordance of factor VIII levels between first-degree relatives of patients with thrombosis with high factor VIII levels.31,58

So far, no variations in the factor VIII or vWF gene that are associated with high factor VIII levels have been identified. No sequence variations were found in the promoter and 3′ terminus of the factor VIII gene in 62 patients with thrombosis with high factor VIII levels.59 Furthermore, we found no clear association between vWF or factor VIII:Ag levels and polymorphisms in the promoter (−1793 C/G, −1234 C/T, −1185 A/G, and −1051 G/A) and factor VIII binding region (2615 A/G and 2805 G/A) of the vWF gene.60 However, Kightley et al61 reported a significant association between vWF levels and the −1234 C/−1185 A/−1051G allele in group O blood donors aged >40 years. No association was found between 2 highly informative CA repeats in the factor VIII gene (intron 13 and 22) and plasma levels of factor VIII:Ag.62 Therefore, other genes may be implicated in the regulation of plasma vWF and factor VIII levels. Finally, factor VIII levels are influenced by sex (higher in women than men) and race (higher in blacks than whites).61,62

Other Determinants of Plasma Factor VIII Levels

Body mass index (positively correlated with factor VIII levels) and higher levels of glucose (diabetes mellitus), insulin, fibrinogen, and triglycerides are also associated with increased factor VIII levels.33,63,64 Factor VIII levels increase with age, with an average rise of 5 to 6 IU/dL per decade.46,63 Oral contraceptives seem to have no effect on factor VIII levels.65,66

Several stimuli can cause a transient or sustained increase in factor VIII levels. Exercise transiently induces a rise of factor VIII that is probably a result of adrenalin and β2-adrenoreceptor stimulation.66–71 Also, 8-arginine vasopressin and its analogue 1-deamino-8-arginine vasopressin enhance plasma vWF and factor VIII levels indirectly or directly via signaling via the V2 receptor.72 Sustained rises in factor VIII are seen during pregnancy, surgery, chronic inflammation, malignancy, liver disease, hyperthyroidism, intravascular hemolysis, and renal disease.73,74 In most conditions, there is a concordant increase of factor VIII and vWF:Ag levels.

Determinants of High Factor VIII Levels

Apart from the ABO blood group, no genetic components have been identified that are associated with high plasma factor VIII levels.

Possible determinants of elevated factor VIII levels are summarized in Table 2. The main determinant is an elevated vWF level, which is under the control of autosomal genes. The ABO blood group, which is the best-characterized modifier of the plasma vWF level, explains ≈30% of the genetically determined variation in vWF levels.30 In humans, the majority of genetic factors regulating vWF remain to be determined. Candidate genes include a variety of genes coding for proteins involved in the biosynthesis and clearance of vWF.75 In mice, 2 modifier loci of vWF have been identified, 1 of which concerns an N-acetylgalactosaminyltransferase gene.76,77 Other important determinants of vWF level are age, acute phase, stress, and endothelial dysfunction.

Twenty-six percent of the subjects with factor VIII:Ag levels ≥150 IU/dL have vWF levels <150 IU/dL,46 and only 50% of patients with thrombosis with sustained factor VIII:C levels ≥150 IU/dL also have persistent high vWF:Ag levels.55 This illustrates that there are determinants of elevated factor VIII levels that do not act via vWF. Differences in genetically defined binding affinities of vWF and factor VIII may result in variations of plasma factor VIII levels that are not explained by variations in the vWF level. Differences in the stability of unbound factor VIII, which normally has a very short half-life, may also play a role.54

Factors V and VIII are related proteins and share common biosynthetic pathways, as reflected by recent studies of Nichols and colleagues78,79 and Neerman-Arbez et al80 in combined factor V and VIII deficiencies. The gene coding for the ER-Golgi Intermediate Compartment protein ERGIC-53
was shown to have quantitative effects on factor VIII levels. Factor V:Ag levels are correlated to some extent with plasma factor VIII:Ag levels,\textsuperscript{81} suggesting that common posttranslational modifications may explain part of the large variation in plasma factor V and VIII levels.

In all studies investigating the effect of high factor VIII on thrombosis, subjects with malignancy or chronic diseases were excluded, which makes the contribution of inflammation to high factor VIII levels in these groups small. Most likely, high factor VIII levels are the result of a combination of genetic and acquired factors.

**Elevated Factor VIII Levels and Thrombosis**

**Arterial Thrombosis**

**Low Factor VIII Levels**

In 1989, a study by Rosendaal et al\textsuperscript{82} reported that low factor VIII levels protect against ischemic heart disease. Mortality due to ischemic heart disease is much lower in patients with hemophilia A than in the general male population,\textsuperscript{82,83} which may suggest that factor VIII is involved in the pathogenesis of arterial thrombosis. Also vWF, the main determinant of the factor VIII level in plasma, may play a role in the pathogenesis of atherothrombosis. Autopsy findings from patients with severe von Willebrand disease have shown extensive atherosclerosis,\textsuperscript{86} suggesting that vWF supports the progression of microthrombi into occlusive thrombus.

**High Factor VIII Levels**

The first reports on a possible association between factor VIII and coronary artery disease date from the early 1960s.\textsuperscript{87} In the same period, blood group non-O and high factor VIII-related antigen (vWF) were identified as candidate risk factors for the same period, blood group non-O and high factor VIII–related antigen (vWF) were identified as candidate risk factors for severe von Willebrand disease have shown extensive atherosclerosis but no occlusive arterial thrombi,\textsuperscript{84,85} which suggests that even very low vWF levels may not fully protect against the development of atherosclerotic lesions. Similarly, dogs with severe von Willebrand disease and undetectable vWF levels did not develop acute occlusive thrombi in atherosclerotic arteries,\textsuperscript{86} suggesting that vWF supports the progression of microthrombi into occlusive thrombus.

**Potential Mechanisms for the Relation of High Factor VIII Levels to Arterial Thrombosis**

Several studies have addressed whether vWF or factor VIII is the causative factor in arterial thrombogenesis and whether the risk of high vWF and factor VIII is blood group dependent. Meade et al\textsuperscript{82} found that factor VIII remained associated with ischemic heart disease after adjustment for blood group, without taking vWF into account. Also in the Hoorn study (Jager et al\textsuperscript{97}), high vWF levels were associated with cardiovascular mortality independent of blood group in diabetic and nondiabetic subjects. When vWF and factor VIII are mutually adjusted for, neither of the 2 remained associated with coronary disease.\textsuperscript{95} Therefore, it is likely that factor VIII and vWF increase the risk of arterial thrombosis, independent of blood group.

The ARIC Study demonstrated strong associations of factor VIII and vWF with risk factors for atherosclerosis,\textsuperscript{63} such as hypertension, diabetes, body mass index, and triglycerides. Some of these factors are known to be associated with perturbed endothelial and vascular inflammation.\textsuperscript{98,99} High shear forces, such as those that occur in stenosed vessels, increase vWF secretion by vascular endothelium\textsuperscript{41} and, thus, will stimulate platelet adhesion and aggregation at the site of damaged arterial walls, which may lead to thrombus formation.\textsuperscript{100} This may explain why elevated factor VIII and vWF levels are associated with stroke in subjects with presumed large-vessel disease,\textsuperscript{97} which is mainly the result of atherothromboembolism.\textsuperscript{101} At the same time, high factor VIII levels may stimulate the formation of thrombin and, thus,
result in increased platelet activation and fibrin formation, processes that may contribute to the development of large occlusive thrombi from the microthrombi initially formed on the damaged endothelium.

Is there a causal relationship between high factor VIII and vWF levels and arterial thrombosis? Atherosclerosis itself could have affected the clotting factor levels by chronic inflammatory responses and elevated factor VIII, or vWF levels may reflect the inflammation and progression of atherosclerosis. However, such a model cannot explain the association between blood group (which is genetically determined) and cardiovascular disease, unless blood group does not act via vWF. Furthermore, the effect of factor VIII and vWF on arterial thrombosis was not attenuated after adjustment for age and other classical risk factors, such as hypertension, body mass index, cholesterol, and baseline ischemic heart disease. Even C-reactive protein, a strong marker of inflammation, did not clearly affect the risk associated with high vWF levels. The lack of association between factor VIII and vWF levels with carotid intima-media thickness among subjects with prevalent cardiovascular disease is another argument against elevated factor VIII/vWF being simply the consequence of atherosclerosis. In conclusion, it seems likely that high factor VIII and vWF levels have independent roles in increasing the risk of arterial thrombosis. The latter hypothesis is supported by the low cardiovascular mortality in patients with hemophilia A.

### Venous Thrombosis

#### High Factor VIII Levels

In 1969, Jick et al found that blood group non-O is associated with an increased risk of venous thrombosis. Today, we know that individuals with blood group non-O have higher levels of vWF and factor VIII than do those with blood group O. In a large population-based case-control study on venous thrombosis (the Leiden Thrombophilia Study), blood group non-O, vWF:Ag, and factor VIII:C levels were all associated with an increased risk for venous thrombosis by univariate analysis. In multivariate analysis, levels were all associated with an increased risk for venous blood group O. In a large population-based case-series, subjects with levels ≥150 IU/dL have a 3-fold increased risk. Furthermore, each increase in the factor VIII:C level of 10 IU/dL is associated with a 10% increase in the risk of a first thrombotic event.

The association between high factor VIII:C levels and venous thrombosis has been confirmed in several independent studies. Also, high factor VIII antigen (factor VIII:Ag) levels are associated with venous thrombosis in the Leiden Thrombophilia Study. The relative risk for venous thrombosis of factor VIII:Ag levels ≥150 IU/dL is 5.3 (95% CI 2.7 to 10.1) compared with levels <100 IU/dL, which is very similar to the risk previously reported for factor VIII activity levels ≥150 IU/dL. After excluding all subjects with factor V Leiden, prothrombin 20210A mutation, and a deficiency of protein C, protein S, or antithrombin (defined as previously described) or of lupus anticoagulant, the thrombosis risk for factor VIII:Ag levels ≥150 IU/dL is still increased (odds ratio 4.7, 95% CI 2.3 to 9.3).

The prevalence of elevated factor VIII levels is high: 25% of patients with a first episode of deep-vein thrombosis and 11% of healthy control subjects have factor VIII levels ≥150 IU/dL. After excluding all subjects with factor V Leiden, prothrombin 20210A mutation, and a deficiency of protein C, protein S, or antithrombin (defined as previously described) or of lupus anticoagulant, the thrombosis risk for factor VIII:Ag levels ≥150 IU/dL is still increased (odds ratio 4.7, 95% CI 2.3 to 9.3).

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There are several studies reporting that high levels of factor VIII are associated with an increased risk of recurrences of thrombosis. Kraaijenhagen et al found factor VIII levels ≥150 IU/dL in 57% of patients with recurrent venous thrombosis. Kyrel et al followed 360 patients with venous thromboembolism and found a recurrence in 27% of patients with factor VIII levels >234% (90th percentile in the patient group!) and in 9% of patients without elevated factor VIII levels.

#### Interaction of Factor VIII and Other Risk Factors for Thrombosis

In thrombophilic families in which protein C deficiency and factor V Leiden were both present, a history of thrombosis was present in 31% of individuals with protein C deficiency, in 13% of individuals with factor V Leiden, and in 73% of subjects with the combined defects. In addition, selected patients from thrombophilic families with factor V Leiden have, on average, a lower median age at the first thrombotic event (29 years) than “unselected” consecutive thrombotic patients with factor V Leiden (43 years). These observations suggested that venous thromboembolism is a multi-causal disease and that several risk factors for thrombosis need to accumulate in the individual before a threshold is passed and a thrombotic event will occur.

Recently, the influence of high factor VIII levels on the occurrence of venous thrombosis was investigated among the relatives of symptomatic factor V Leiden carriers. Compared with their relatives with either high factor VIII or factor V Leiden, first-degree relatives with the combination of a factor VIII level ≥150 IU/dL and factor V Leiden had an increased rate of venous thrombosis. This means that factor...
VIII levels \( \geq 150 \text{ IU/dL} \) will contribute to the risk of venous thrombosis of factor V Leiden carriers.

Factor VIII levels >150 IU/dL also affected the thrombotic risk of oral contraceptive users. In women with factor VIII:C \( \geq 150 \text{ IU/dL} \), the risk associated with oral contraceptive use was 10.3 (95% CI 3.7 to 28.9), which is 2-fold higher than the risk among nonusers with factor VIII:C <150 IU/dL (odds ratio 5.3, 95% CI 1.8 to 15.5). There is no indication that the simultaneous presence of high factor VIII and oral contraceptive use will result in an excess of thrombotic events (interaction).

### Relationship Between High Factor VIII and Venous Thrombosis

The precise role of high factor VIII levels in defining venous thrombotic risk is still unknown. After its activation by thrombin, factor VIIIa dissociates from vWF to form a complex with factor IXa, which will result in marked acceleration of the activation of factor X. Activated factor X then converts prothrombin into thrombin, which in turn converts soluble fibrinogen into insoluble fibrin. It is possible that high factor VIII levels just increase the rate of thrombin and fibrin formation (in plasma, there is a large molar excess of factor IX over factor VIII).

Another possibility is that high factor VIII levels influence thrombotic risk via an effect on the APC sensitivity ratio (APCR). It has been shown that (in the absence of factor V Leiden) the thrombosis risk for the lowest quartile of normalized APCR (<0.92) is 4.4-fold higher than that for the highest quartile (\( \geq 1.05 \)). For these measurements, “first-generation” APC-resistant tests were used (no dilution of the sample with factor V–deficient plasma). This explains the finding that high factor VIII levels are associated with a reduced sensitivity for APC in the absence of factor V Leiden (see Figure). After adjustment for factor VIII levels, the thrombosis risk associated with a normalized APCR <0.92 fell from 4.4- to 2.5-fold, indicating that factor VIII has a strong confounding effect on the thrombosis risk of a low APCR ratio. Vice versa, it is also possible that high factor VIII exerts a thrombotic risk through the associated decreased responsiveness to APC. In all subjects of the Leiden Thrombophilia Study who do not have the factor V Leiden mutation, the thrombosis risk associated with factor VIII levels \( \geq 150 \text{ IU/dL} \) is 4.8 (95% CI 3.1 to 7.5) compared with the risk associated with levels <100 IU/dL (Table 5). Entering normalized APCR as a continuous variable lowered the thrombosis risk of factor VIII levels \( \geq 150 \text{ IU/dL} \) by 50%, to 2.7 (95% CI 1.6 to 4.7). Adjustment for age, blood group, and vWF did not change this risk estimate (odds ratio 2.4, 95% CI 1.2 to 5.2). Although high factor VIII remained an independent risk factor for thrombosis, these data show that adjustment for the APCR leads to attenuation of the risk of thrombosis. Therefore, it is possible that the risk of high factor VIII is at least partly mediated through an acquired APC resistance via a pathway that is independent of vWF and blood group.

### Should We Screen Patients With Thrombosis for High Factor VIII Levels?

An important question is whether we should screen patients with thrombosis for high factor VIII levels. High levels of factor VIII are a risk factor for a first thrombotic event, but high levels also seem to increase the risk of recurrences, which may indicate that sustained anticoagulant treatment is needed in these patients. When high factor VIII is included in a thrombophilia workup, we must make sure that testing for high factor VIII is reliable and that the individual’s risk of thrombosis is estimated correctly.

First, the assay of factor VIII itself may lead to considerable variation. Together with vWF:Ag, factor VIII:C showed the highest between-duplicate (5.6%) and between-day (15%) coefficients of variation. Most often, factor VIII is measured as factor VIII:C by using modifications of the activated partial thromboplastin time (1-stage assay). This 1-stage assay has the advantage of simplicity but can give falsely high results that are due to activation of the coagulation system during blood collection procedures and/or storage. Factor VIII:Ag can be measured by ELISA. The advantage of an ELISA (if properly designed) over the 1-stage assay is that it is not susceptible to activation of the coagulation system. The disadvantage of the ELISA is that it is more complicated to perform.

Furthermore, there is a large intrapatient variation in factor VIII levels, and finally, there is the important question of how we should interpret the result of a factor VIII measurement in terms of risk of a first thrombotic event and risk of recurrences. Should we use cutoff values? How should we handle in this context information on the presence of disease(s) that have been reported to be associated with high factor VIII levels (eg, malignancies)? Should we combine the result of the factor VIII measurement with information on

![Factor VIII:C and normalized APCR in 337 patients and 455 control subjects who do not have the factor V Leiden mutation.](image)

### TABLE 5. ORs for Factor VIII:C Levels, Unadjusted and Adjusted for APCR (Without Factor V Leiden)

<table>
<thead>
<tr>
<th>Factor VIII:C</th>
<th>Univariate OR (95% CI)</th>
<th>Multivariate OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 IU/dL</td>
<td>1†</td>
<td>1*</td>
</tr>
<tr>
<td>100–125 IU/dL</td>
<td>2.4 (1.6–3.5)</td>
<td>1.9 (1.3–2.9)</td>
</tr>
<tr>
<td>125–150 IU/dL</td>
<td>3.2 (2.1–4.8)</td>
<td>2.1 (1.3–3.3)</td>
</tr>
<tr>
<td>≥150 IU/dL</td>
<td>4.8 (3.1–7.5)</td>
<td>2.7 (1.6–4.7)</td>
</tr>
</tbody>
</table>

*Adjusted for activated partial thromboplastin time–based normalized APCR.
†Reference category.
vWF levels and blood group? Should we restrict the analysis to carriers of other risk factors of thrombosis? Still another problem is the timing of factor VIII measurement: during the acute thrombotic event, factor VIII levels may be elevated because of an acute phase reaction, and a reliable baseline value might not be obtained before several months. Taken together, there are still too many questions to be answered to recommend factor VIII measurement in routine thrombophilia screening.

Conclusions

High levels of factor VIII are a risk factor for thrombosis, with a greater impact on venous than on arterial thrombosis. This risk is dose dependent for venous thrombosis, and factor VIII levels ≥150 IU/dL account for 16% of all venous thrombotic events, whereas factor VIII levels >123 IU/dL explain 4% of all arterial events. High factor VIII levels may increase the risk of venous thrombosis via enhanced thrombin formation and/or through the induction of acquired APC resistance. The relationship between factor VIII and arterial thrombosis may be based on the combination of increased thrombin formation and increased platelet adhesion/aggregation, induced by vWF, at sites of arterial wall damage.

The molecular basis of high factor VIII levels is only partially known and consists of genetic and acquired factors. Blood group, acting through vWF levels, is an important genetic factor that explains ∼30% of the variation in factor VIII levels. Attempts to find other genetic loci associated with high vWF and factor VIII levels have failed until now. It is likely that the largest part of high factor VIII levels is caused by a rise in vWF levels, which points to an increased synthesis or decreased clearance of the vWF–factor VIII complex. However, a substantial percentage of high factor VIII levels is not completely vWF-mediated and may point to genetically defined differences in the affinity of factor VIII for vWF.

Acknowledgments

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