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# Von Willebrand factor (VWF) as a risk factor for bleeding and thrombosis

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The von Willebrand factor (VWF) is analysed as a bleeding and thrombotic risk marker. When the VWF level is increased, it predicts a thrombotic phenotype and when VWF level is low in plasma, the phenotype varies to bleeding disorder. But it is quite challenging to define when the level is low, normal or high taking into account that these values are capricious and overlap. This matter should be solved by extensive epidemiologic studies. VWD is a hereditary disorder with several described mutations. VWF is a major acute-phase reactant, besides the physiological conditions such as blood group and pregnancy that affect plasmatic VWF levels. Subjects with O blood group have 25% less VWF than those of non O blood groups, and the latter show higher thrombus burden. VWF would be sensitive though not specific diagnostic marker of myocardial infarction. For the assessment of bleeding severity there are special surveys, scores and pictorial charts. The identification of VWF as a thrombotic risk marker has not been clearly established yet, but it has been involved in stroke and coronary disease. We only have the specific replacement therapy for the bleeding phenotype and we can speculate that enoxaparin and PEG-hirudin are able to blunt the VWF rise in patients with unstable angina pectoris and it is associated with a more favourable clinical outcome. Only two questions remain: does VWF as a bleeding risk marker have the same value as a thrombotic risk marker? Will successful treatments like those achieved for bleeding be also possible in the future for thrombosis?

**Keywords:** VWF, Risk marker, Bleeding phenotype, Thrombosis, Physiological variations

Bleeding, as well as thrombotic events, often occurs in subjects with weak multiple risk factors which interact to produce the symptoms.

Usually, a data-driven risk management strategy is used for cardiovascular disease and venous thromboembolism, an approach difficult to implement in bleeding cases given the limited availability of data on haemorrhagic risk factors. Finding a reliable risk marker for adverse events is one of the most desired but unattainable objectives in clinical medicine. We will analyse the characteristics of the chosen marker, von Willebrand factor (VWF).<sup>1</sup>

VWF is a huge protein of around 20 000 kD that has two fundamental roles: in primary haemostasis, it starts adhesion of platelets to sites of vascular damage and, in blood clotting, it protects factor VIII (FVIII) from attack by proteases, lengthening its survival. Besides, in recent years, it has been thoroughly studied as an

immune protective effect over FVIII to prevent the development of anti-FVIII inhibitors in Haemophilia A. VWF primary structure is formed by a signal peptide, a propeptide, and the mature VWF. Each VWF subunit has binding sites for FVIII, heparin, glycoprotein (GP) Ibalpha, collagen, GPIIb-IIIa, some of which depend on the shear-rate inducing conformational changes.

VWF, with its ultra large multimers (ULVWF), is synthesized in endothelial cells and megakaryocytes, but when released into circulation the ULVWF are lost due to ADAMTS13 action. This VWF-cleaving protease mediates thrombogenic regulation given that the size of the multimers is closely related to their activity over the platelets.

Therefore, when VWF level is increased, it predicts a thrombotic phenotype. However, when VWF level is low in plasma, the phenotype varies to bleeding disorder.<sup>1</sup> It is true that it is quite challenging to define when it is low, normal or high taking into account that these values are capricious and overlap, and this should be solved by extensive epidemiologic studies.

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Defects in VWF's quantity or quality may lead to a bleeding disorder, von Willebrand disease (VWD). Including all its types, it has a prevalence of 1% in general population. VWD is a hereditary disorder with several mutations described. Besides physiological conditions such as blood group and pregnancy that affect plasmatic VWF levels, it is a major acute-phase reactant. The different glycosylation patterns of the blood groups affect clearance rates. Subjects with O blood group have 25% less VWF than those of non O blood groups, and the latter show higher thrombus burden. VWF would be a sensitive though not specific late diagnostic marker of myocardial infarction.<sup>2</sup> It is related to the infarct size, to the inflammatory reaction and to the prothrombotic phase.

The VWF<sup>3</sup> and ADAMTS13<sup>4</sup> physiological variations that occur during pregnancy are the best way to control normal delivery bleeding, but they can turn prothrombotic in special situations.

For the assessment of bleeding there are special surveys, scores and pictorial charts, designed to evaluate the symptom severity. Also, it has been shown that when penetrance is incomplete VWF values prove more conflictive and an appropriate strategy is required to reach diagnosis. To predict major surgical bleeding in patients with VWD type 1 and possible type I the novel bleeding risk scores and a deep analysis of the patients' medical history are much more useful than checking the levels of VWF or FVIII.<sup>5</sup> The European VWD type 1 study suggests that past bleeding is a better guide to future bleeding than laboratory testing for VWF.

The identification of VWF as a thrombotic risk marker has not been clearly established yet, but it has been implicated in stroke and coronary disease. It is associated to endothelial damage with activation of VWF to offer an unfolded structure suitable for the interaction with GPIb alpha-V-IX and GP IV. For the time being, these findings have demographic but no individual value.

In a number of reports it has been established a relationship between VWF plasmatic levels and thrombotic cardiovascular events.<sup>6</sup> Increased levels of VWF, as found in the elderly, are difficult to isolate from other risk factors such as cholesterol, diabetes, hypertension, smoking. It has also been discussed if the said risk factors act through the increase in VWF. Recently, it has been identified a cluster of intronic VWF SNPs that is associated with plasma levels of VWF,<sup>7</sup> individually or additively, in a large cohort of healthy subjects. Although SNPs examined are distributed throughout the entire VWF gene without apparent cluster, all the positive SNPs are located in a 50-kb region. Exons in this region encode for VWF

D2, D', and D3 domains that are known to regulate VWF multimerization and storage.

Their independent predictive value disappears in a number of trials when it is associated to other risk markers or it is increased in the acute phase of other diseases such as pancreatitis, alcoholic hepatitis or metastatic colorectal carcinoma. In a recent study of atrial fibrillation (AF)<sup>8</sup> where the increased VWF level in plasma is associated to adverse prognosis of stroke, the fact that AF is a growing epidemic in patients over 40 years old, cannot be avoided.

It has been shown that an increase in VWF level is associated to an increased risk of first stroke although it cannot be said that there is an interaction with the VWF effect over stroke or coronary disease.<sup>9</sup> VWF level also correlates with thrombosis risk and inversely with bleeding risk within the apparently healthy population. This is how recently, while evaluating the adverse events marked by serum VWF in an anticoagulated population due to AF, Roldán *et al.*<sup>8</sup> concluded that VWF may be used to stratify patients with AF by thrombotic and haemorrhagic risk.

We must also consider products such as desmopressin or VWF-rich plasma, highly or partially purified, when their ability to increase protein goes beyond 200%. DDAVP may also induce the presence of ULVWF into circulation.

Currently, we only have the specific replacement therapy for the bleeding phenotype and we can speculate that enoxaparin and PEG-hirudin are able to blunt the VWF rise in patients with unstable angina pectoris and it is associated with a more favourable clinical outcome.<sup>10</sup>

It has been demonstrated that heparin inhibits VWF-GPIb binding, and some reports suggest that it overlaps the binding site within the VWF A1 domain. On the other hand, blocking recombinant peptide fragments, tricarboxylic acid, different monoclonal antibodies and pegylated aptamers are all able to interfere that binding. After checking [www.clinicaltrials.gov](http://www.clinicaltrials.gov), we found that in the future we will have rVWF (00816660) to replace VWF for VWD type 3 or ARC1779 (000507338) for acute myocardial infarction under percutaneous coronary intervention as VWF blocking agent.

Does VWF as a bleeding risk marker have the same value as a thrombotic risk marker?

Will successful therapeutic interventions be possible in the future for both bleeding and thrombosis?

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