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TRANSLATIONAL PERSPECTIVE

Von Willebrand Factor Activity in Thrombosis

An Overlooked Target for Intervention?

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Von Willebrand disease (VWD) is the most common heritable bleeding disorder. Low von Willebrand factor (VWF) activity occurs in as much as 1% of the general population. The clinical phenotype of VWD is, however, markedly lower. VWD can be caused by mutations within the *VWF* (von Willebrand factor) gene located on Chromosome 12 or by variants occurring outside the *VWF* locus, which either reduce the total amount of translated protein (types 1 and 3 disease) or the functional activity of the protein (type 2 disease). Acquired VWD based on development of autoantibodies against the protein also exists, albeit very rarely. VWF is a central component in the primary hemostasis, where it binds platelets to the injured vessel wall (**Figure 1**). This generates a primary platelet-rich clot that acts as a scaffold for the secondary hemostasis. In addition, VWF serves as a carrier of coagulation factor VIII in circulation. Binding of factor VIII to VWF protects the former against rapid degradation. As a central component in hemostasis, it is worth highlighting that the regulation of VWF has not been considered a target for medical therapy to prevent cardiovascular thrombosis.

In vivo, VWF is synthesized by the vascular endothelium and megakaryocytes. During biosynthesis, the protein is assembled into larger multimeric forms that range between 2 and 40 subunits, the largest of which are referred to as ultramultimers. There is a direct proportionality between the number of subunits in a multimeric molecule of VWF and its ability to facilitate hemostasis, due to larger multimers having more collagen and glycoprotein Ibα (GPIbα) binding sites. Because of this, a high proportion of ultramultimeric VWF is a potent risk factor for developing thrombosis. In some cases, a high proportion of ultramultimeric VWF can even lead to the disease thrombotic thrombocytopenic purpura, which is characterized by multiple thromboses within the smaller blood vessels.

The diagnosis of VWD can be a cumbersome matter. First and foremost, VWF is not measured by routine coagulation screening tests, for example prothrombin time (international normalized ratio) and activated partial thromboplastin time, which often is the cause of a lack of diagnosis before a major bleeding event in the cardiovascular setting. Generally, a diagnosis of VWD requires a repeated activity measurement of <30% of normal activity in steady state, for example in individuals without concurrent inflammation (the protein expression is regulated as an acute phase reactant). Nevertheless, the relationship between the blood type system and the activity of VWF still presents a challenge for the clinical diagnosis of VWD. Individuals with blood type O generally have a 25% lower activity of VWF in plasma when compared with those with type A, B, or AB. Of relevance, people with blood type O have also been reported to experience a lower frequency of thrombosis, whereas individuals with blood type A, B, or AB have a nearly 3-fold increased risk of venous thrombosis compared with individuals with blood type O.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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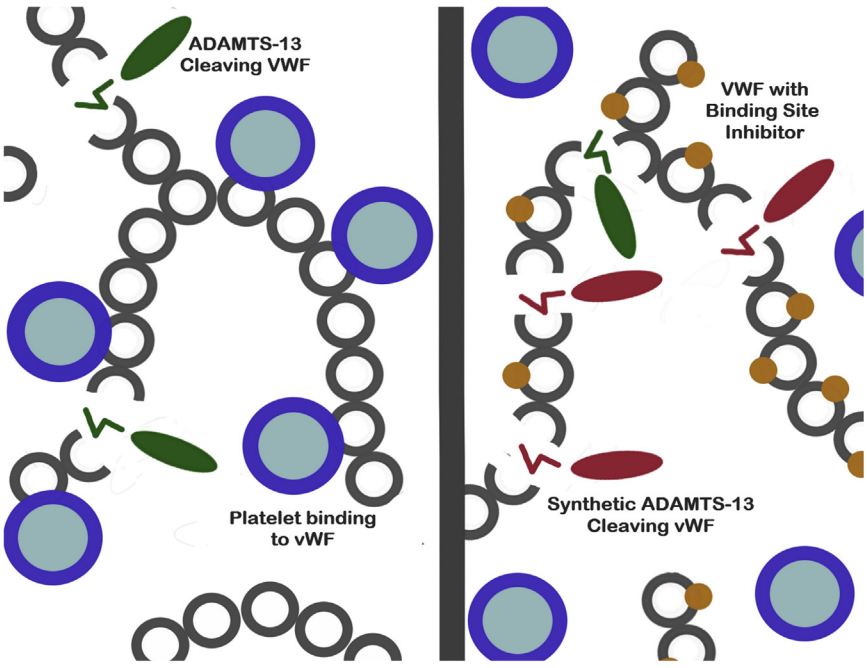
FIGURE 1 Interaction of Von Willebrand Factor, Platelets, and ADAMTS-13



(Left) The normal binding of von Willebrand factor (VWF) and platelets, and the function of ADAMTS-13. **(Right)** A hypothetical drug blocking the binding of platelets to VWF, and an effect of an exogenous ADAMTS-13 on VWF.

Though it is unclear whether reduced activity of VWF is the sole cause of the lower risk of thrombosis in people with blood type O, a partial relationship between the variables seems relevant to consider. In support of such an argument, higher VWF levels in plasma have been found to be an independent predictor of thrombosis. An effect of blood type and platelet function may, however, also play a role in the cardiovascular phenotype of individuals with blood type O (1). Finally, a few reports have suggested that a reduced level of ADAMTS-13, the key enzyme involved in cleaving/inactivating the ultralarge VWF forms, represents an independent risk factor for coronary thrombosis (2).

Following the current data on blood type, VWF, and risk of thrombosis, it seems reasonable to hypothesize that a lower activity of VWF will reduce the risk of thrombosis. A largescale Dutch study analyzed the relationship between VWD and the risk of arterial thrombosis. The study found that between 635 Dutch individuals with VWD and 2 reference groups adjusted for age, sex, and body weight, the group with VWD experienced 39% fewer cases of arterial thrombotic events compared with the first reference group, and 67% fewer cases compared with the second. Similar values were found for cardiovascular disease and ischemic stroke (3). Another largescale study analyzed a group of 355 VWD patients from a 25-year period and found a notable decrease in the risk of arterial thrombosis (4). Several smaller studies suggest that both venous and arterial thromboses occur less frequently in patients with VWD compared with healthy control subjects (5,6). However, the possibility that the variable and generally underdiagnosed nature of VWD in the general population means that its relationship to thrombosis can only be fully understood in larger-scale studies, is important to consider in regard to the conclusions of small-scale studies. Furthermore, some individuals have acquired or inherited prothrombotic factors that cause a considerably increased risk of thrombosis. An inherent thrombophilia could, in theory, be offset if the individual also had VWD. This raises the question of whether lowering the activity VWF could be the basis for future medicine designed to prevent thrombosis.

Thrombosis in the coronary arteries is the most common cause of sudden cardiac death. Although there are many modalities for preventing thrombosis,

anticoagulation therapy still comes with an increased risk of bleeding, including cerebral hemorrhage. As such, there is still a need for new drugs to prevent thrombosis without increasing bleeding tendency. Lowering the concentration of VWF in circulation would be such a possibility. This could be achieved with a drug targeted to either inhibit the secretory pathway of VWF or to activate the general degradation of the protein. In this context, the safest way here would probably be to target clearance rather than total protein expression, as the risk of bleeding could rapidly outweigh the antithrombotic consequences. Given that VWF also has a role as carrier protein for coagulation factor VIII, this could also be a potential target by mimicking some aspects of hemophilia A. Finally, the binding capacity of VWF to either fibrinogen or collagen could represent a molecular target for intervention.

Reducing the amount of large VWF multimers in plasma by increasing the circulating levels of ADAMTS-13 may be another option. Though the total amount of VWF would go unchanged, a reduction in large VWF multimers would lower platelet aggregation. This reduction could be achieved either through the administration of recombinant ADAMTS-13, or by interrupting the clearance pathway of the protein. Though the process in which ADAMTS-13 is cleared in vivo has not been fully mapped, it is suspected to be in relation to the asialoglycoprotein receptor in the liver. Selective inhibition of the VWF pathway in animal models has also been found to prevent platelet aggregation for both venous and arterial thrombosis.

In conclusion, there is now evidence to suggest that a decrease in the activity of VWF, as seen in patients with VWD type 1 or people with blood type O, is associated with a reduction of the risk of thrombosis. The potential of VWF to be a new antithrombotic target in the future prevention of arterial thrombosis deserves more attention in translational science. For now, we urge for clinical studies on the VWF phenotype and the risk of arterial thrombosis, particularly in cardiological settings where both venous and arterial thromboses are still far from conditions with a safe and efficient therapy option.

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