(MMPs) that contribute to plaque destabilization. A recent study showed that combined treatment with hepatocyte growth factor and VEGF leads to down-regulation of the NFκB pathway and thus inhibition of VCAM expression.[4]

More studies like the one by Lucerna and colleagues are needed to finally devise successful treatment strategies for ischemic vascular disease in order to avoid the excessive vascular inflammation that may accompany VEGF treatment.

*The authors declare no competing financial interests.* ■


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HEMOSTASIS

Comment on Goodeve et al, page 112, and James et al, page 145

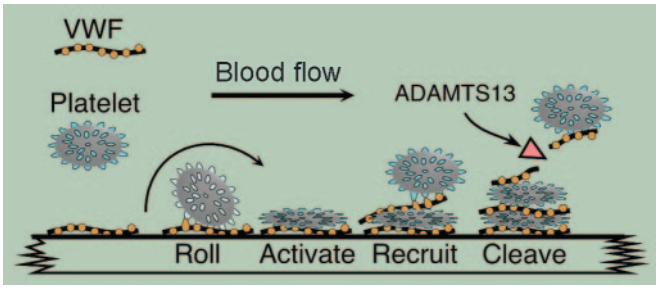
# VWD data worth 10 000 words

**J. Evan Sadler** WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

At last, 2 studies on VWD type 1 reported in this issue of *Blood* by Goodeve and colleagues and James and colleagues provide a first look at the spectrum of VWF mutations in large cohorts of patients diagnosed with VWD type 1 across Europe and Canada.

Von Willebrand disease (VWD) type 1 may be the most common inherited bleeding disorder, but until now we've had little information about its molecular pathogenesis. The results should accelerate progress toward optimizing the management of patients with all types of VWD.

James and colleagues recruited 123 families for which the index case had bleeding symptoms and von Willebrand factor (VWF) levels between 5 and 50 IU/dL. Subjects with abnormal VWF multimer patterns or other evidence of qualitative defects were excluded. Although a family history of VWD was not required, the mean number of affected persons per family was 1.9.[1] The entry criteria for the study of Goodeve and colleagues were less stringent with respect to VWF level. A total of 150 patients were accepted based on a historical diagnosis of VWD type 1 at their treatment centers, but at least 25% of them proved to have VWF:Ag or VWF:RCo levels greater than 50 IU/dL on retesting. On the other hand, Goodeve and colleagues required at least 2 subjects with VWD for each family, and the mean number of affected persons per family was 2.9.[2] In addition, 57 subjects with subtle abnormalities of VWF multimer structure were retained in Goodeve and colleagues' study population, though analyzed separately. Mutations were identified by sequencing the VWF gene promoter region, exons, and flanking intron segments.




**VWF mediates platelet adhesion at sites of vascular injury, and the metalloprotease ADAMTS13 limits thrombus growth cleaving VWF. Defects in VWF secretion or clearance are common causes of VWD type 1.**

The major conclusions from both studies are interesting and remarkable. First of all, despite the selection of patients based on their retention in hemostasis clinics, candidate VWF mutations were not found for 27% (James et al) and 36% (Goodeve el al) of index cases diagnosed with VWD type 1. When subjects with abnormal VWF multimers were excluded, 45% of European index cases did not have mutations. For these patients, bleeding cannot be attributed to VWF defects but instead may be caused by other genetic or environmental factors. The likelihood of finding a potential mutation was inversely related to the VWF level. For example, in the study of Goodeve and colleagues, 50% of patients with VWF:Ag levels greater than 45 IU/dL had mutations, whereas 96% of patients with VWF:Ag levels less than 15 IU/dL had mutations. These results are consistent with the conclusion that many patients diagnosed with VWD type 1 have mild bleeding symptoms and modestly low VWF by coincidence.[3]

In addition, the spectrum of VWD type 1 mutations was quite distinctive: approximately 90% of patients in whom mutations were found had at least 1 missense mutation, often associated with the loss or creation of cysteine residues. For comparison, more than 80% of mutations in VWD type 3 are nonsense mutations, frameshifts, or large deletions. Such null mutations are fairly common in the population, but the heterozygous state does not often cause medically significant bleeding. Therefore, VWD type 1 is not at all like heterozygous VWD type 3. Instead, the quantitative VWF deficiency that occurs in VWD type 1 usually is caused by dominant, qualitative VWF abnormalities that affect VWF secretion or clearance without substantially altering multimer assembly or platelet binding (see figure). These findings provide a foundation for prospective studies of VWD type 1 to evaluate the relationship between mutations, mechanisms of disease, risk of future bleeding, and response to treatment.

*J.E.S. is also affiliated with the Howard Hughes Medical Institute.*

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