Von Willebrand Factor and ADAMTS13
Too Much or Too Little of a Good Thing?

Brian T. Emmer, David Ginsburg, Karl C. Desch

On Willebrand factor (VWF) promotes platelet adhesion and aggregation at sites of vascular injury and serves as a carrier for coagulation factor VIII. The activity of VWF is modulated by ADAMTS13 (a disintegrin and metalloprotease with thrombospondin motif repeats 13), a metalloprotease that cleaves highly procoagulant, ultralarge VWF multimers into smaller, less procoagulant forms. Deficiency for VWF quantity or activity results in the bleeding disorder von Willebrand disease, whereas severe deficiency in ADAMTS13 results in the clotting disorder thrombotic thrombocytopenic purpura.

Since the identification of ADAMTS13 as the VWF cleaving protease in 2001 and the recognition that severe ADAMTS13 deficiency is associated with thrombotic thrombocytopenic purpura, several case control studies have looked for connections between specific disease risk and partial ADAMTS13 deficiency. Likewise, reduced levels of ADAMTS13 have been associated prospectively with an increased risk of coronary artery disease and ischemic stroke. Prospective studies of elevated plasma VWF antigen levels (not associated with ADAMTS13 deficiency) have found a positive correlation between high VWF levels and coronary artery disease, ischemic stroke, and cardiovascular mortality. For both VWF and ADAMTS13, an association with all-cause mortality has not been reported.

In this issue of ATVB, Sonneveld et al. expand on the previous investigation of the Rotterdam cohort, which included 6130 individuals aged >55 years followed up for a median of 11.3 years. The authors measured VWF and ADAMTS13 levels in this cohort and risk-adjusted outcomes for age, sex, smoking status, body mass index, blood pressure, serum cholesterol, comorbid diabetes mellitus, and the use of antiplatelet, lipid lowering, or antihypertensive medications. Consistent with previous studies, they found an association of high VWF levels with cardiovascular mortality (hazard ratio [HR], 1.29). In addition, they also found that individuals with ADAMTS13 levels in the lowest quartile had an increased risk of cardiovascular mortality (HR, 1.46). The association with cardiovascular mortality was even stronger for individuals with both elevated VWF and low ADAMTS13 (HR, 1.73). This is the first prospective report to link low ADAMTS13 levels, either with or without concurrent high VWF levels, to cardiovascular mortality.

Unlike previous studies, the authors here also find an association of VWF and ADAMTS13 levels with all-cause mortality. In this cohort, 76.4% (1423/1862) of all deaths were deemed because of causes other than cardiovascular disease. The authors found that high VWF (HR, 1.21), low ADAMTS13 (HR, 1.46), and the combination of both (HR, 1.58) were each associated with increased rates of all-cause mortality. The cause of death for the majority of these cases was not reported; no significant association was found for deaths from cancer or chronic obstructive pulmonary disease, but the incidence of these events was too low to conclusively exclude a relationship.

Strengths of this study include its prospective nature, the size of the cohort, the duration of follow-up, and the risk adjustment for several potential confounding variables. However, it remains possible that unrecognized confounding variables may be driving the association. For example, markers of systemic inflammation including erythrocyte sedimentation rate, C-reactive protein, and white blood cell count have all been linked with increased all-cause mortality, and both VWF and ADAMTS13 are dysregulated in inflammatory states.

Although this study provides robust evidence of an association of abnormal VWF/ADAMTS13 and all-cause mortality, it does not demonstrate causality. However, the authors promote the reasonable hypothesis that lower ADAMTS13 leads to increased amounts of more procoagulant VWF multimers, which in turn leads to a procoagulant state increasing the risk of death. However, dysregulated VWF and ADAMTS13 may simply be a marker for disease rather than a pathogenic factor. It is worth noting that several other components of the hemostatic system outside of the VWF–ADAMTS13–platelet axis, including fibrinogen, D-dimer, coagulation factor VIII, and plasmin–antiplasmin complexes, have similarly been correlated with increased risk of mortality. A recent systematic review found that abnormal levels of 20 of 51 measured biomarkers were associated with increased mortality. The relative predictive value of abnormal VWF/ADAMTS13 in this context has not been determined. Nevertheless, the study reported here provides new and important evidence of an association between dysregulated VWF/ADAMTS13 and all-cause mortality. Further investigation is warranted to clarify the prognostic value and mechanism of this association.
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References

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