von Willebrand Factor for Predicting Bleeding and Mortality
Real Deal or Another Failed Biomarker?*
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One of the largest controversies and unsolved mysteries of modern medicine is the uncertain relationship among the utility of laboratory biomarkers as reliable predictors of adverse clinical events. Unquestionably, adequate assessment of bleeding and death risks is the most desirable but hard to reach goal, especially in a cardiology clinic. A timely, elegant, well-designed study in >800 patients reported in this issue of the Journal is an important contribution to the field (1). A stable anticoagulated (international normalized ratio: 2.0 to 3.0) atrial fibrillation (AF) cohort was followed for at least 2 years, and adverse events were recorded and correlated with serum von Willebrand factor (vWF) levels. The obvious strengths of this study include the large sample size, excellent follow-up (median 828 days), single-center setting, precise classification of adverse events triaging all-cause death from cardiovascular mortality, and realistically assessed bleeding events. The paper concludes that serum vWF levels may serve as independent predictors of thrombotic and bleeding events and death during ≥2 years of follow-up. This biomarker may potentially be used to refine vascular events and bleeding risk stratification in AF.

Constantly expanding use of novel antithrombotic and antiplatelet agents increases affiliated bleeding rates, often overwhelming the potential anti-ischemic benefit. Importantly, conventional platelet activity biomarkers, such as p-selectin, glycoprotein IIb/IIIa, and inhibition of platelet aggregation (2), failed to predict both adverse vascular events and especially catastrophic bleeding. The well-done GRAVITAS (Gauging Responsiveness with A Verify Now Assay–Impact on Thrombosis And Safety) trial provides the first randomized evidence that patients with high residual platelet activity exhibited identical rates of death, myocardial infarction, and stent thrombosis despite double-dose clopidogrel compared with “good responders” treated with conventional 75 mg/day clopidogrel (3). The failure of platelet markers to predict mortality and/or severe bleeding events is clearly a disappointment; however, our expectations should not be excessive. Indeed, superficial mild to moderate hemorrhages, such as petechiae and ecchymosis, are well-established consequences of platelet dysfunction, and it makes sense that their occurrence correlates well with the inhibition of platelet aggregation (2). Most likely, the mechanism for development of severe, especially catastrophic, hemorrhages is much more complex and is probably not entirely dependent on platelet inhibition. It seems that unrecognized latent genetic defects (4) should be considered as the reason why certain patients experience massive bleeding events despite average and even low platelet inhibition after antithrombotic therapy (5,6).

AF is a growing epidemic, with the prevalence doubling after each decade of age from 0.55 at age 50 to 59 years to a woeful 9% at age 80 to 89 years. The lifetime risk of AF for patients older than 40 years of age is approximately 25%, indicating that 1 in 4 older individuals will experience AF (7). Because AF is overwhelmingly a disease of older people, increases in longevity, improved survival after myocardial infarction and congestive heart failure, and increasing prevalence of cardiac surgery are certain to lead to an increased prevalence of AF. Current estimates suggest that the prevalence of AF will reach 4 million by 2030 and climb to 5.6 million by 2050 (8). The main hazard of AF is a cardiogenic thromboembolism, increasing the risk of a stroke 4- to 5-fold. Approximately 15% of all ischemic strokes are attributable to AF, and at ages 80 to 89 years, approximately 24% of strokes are AF induced. Survival is also seriously reduced, with mortality rates doubled across a wide age range. These numbers are sobering in light of the substantial mortality and morbidity associated with AF. In 2001, AF was the primary and/or contributing cause of >70,000 deaths. The age-adjusted death rate (per 100,000) climbed substantially from 27.6 in 1980 to 69.8 in 1998 (7). The Framingham Heart Study showed that the presence of AF is independently associated with a 50% to 90% increase in the risk of death (9).

vWF is a large multimeric glycoprotein present in blood plasma and produced by Weibel-Palade bodies in endothelium, megakaryocytes, platelet α-granules, and subendothelial connective tissue (10). The basic vWF monomer is a 2,050-amino acid protein with various function-specific domains. Those include the D/D3 domain, which binds to factor VIII; the A1 domain, which binds to the platelet GPIIb-receptor, heparin, and possibly collagen; the A3 domain, which binds to collagen; and the C1 domain, in which the RGD domain binds to activated platelet integrin...
αHβ3. Functional multimers of vWF can be extremely large, >20,000 kDa, and consist of >80 subunits of 250 kDa each (9). These prothrombotic multimers are rapidly cleaved by the metallocproteinase ADAMTS-13 (A Disintegrin and Metalloproteinase with Thrombospondin motif) to smaller and much less active forms (11). The attractive hypothesis that assessing vWF and/or ADAMTS-13 may help in triaging patients with higher mortality or bleeding risks is not new. Some anecdotal observational evidence suggests that elevated plasma vWF level and lower ADAMTS-13 antigen activity may serve as significant and independent predictors of future secondary cardiovascular events in patients with coronary artery disease (12). Increased serum vWF levels were also strongly associated with late stent thrombosis (13). However, it seems that vWF/ADAMTS-13 may not be exclusive biomarkers for predicting cardiovascular events, but instead reflect the “acute phase” of various diseases such as acute pancreatitis (14), multiorgan failure in patients with alcoholic hepatitis (15), and metastatic colorectal carcinoma (16). There is no agreement on whether measuring vWF is indeed useful for predicting ischemic or hemorrhagic stroke, with some positive (17) but also negative (18) evidence. With regard to predicting bleeding, the data are extremely limited, although 1 study indicates that low vWF is associated with increased bleeding risk at the time of heart transplantation (19).

The convincing data yielded from the index study by Roldán et al. (1) have few important practical implications. First, serial assessment of vWF in AF patients is urgently needed to better validate this promising biomarker, linking its immediate changes to the timing of adverse events. Second, it is unclear to what degree the choice of an antithrombotic will affect the ability of soluble vWF to predict prognosis. This is especially true because warfarin is currently being aggressively substituted with novel thrombin inhibitors. Finally, these intriguing data (1) need to be confirmed in a properly designed and adequately powered randomized trial.

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REFERENCES


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