Editorial

The investigation of biomarkers in cardiovascular disease: time for a coordinated, international effort

Richard C. Becker*

Duke Thrombosis Center, Duke University Medical Center, Duke Clinical Research Institute, 2400 Pratt Street, Durham, NC 27715, USA

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Biomarkers may be defined as measurable cells, proteins, and/or metabolic by-products that represent, either directly or indirectly, one or more biological or pathologic processes active within a defined system or disease state. In a majority of cases, biomarkers delineate variances from normal biology and either appear for the first time (newly expressed) or, more commonly according to traditional thinking, elevate beyond a normal range in response to one or more stimuli or pathologic events [e.g. cardiac specific troponin in acute myocardial infarction (MI)], rendering a clinical diagnosis; however, biomarkers may themselves participate actively in the subsequent evolution and expression of disease (e.g. C-reactive protein in atherothrombosis). Thus, biomarkers, considered collectively and functionally, serve as diagnostic aids (type I), prognostic indicators (type II) and, perhaps more often than previously realized, fundamental contributors to the pathobiological basis of disease (type III) (types I–III are examples of a biomarker classification or categorization scale).

In the article by Ray et al.,1 von Willebrand factor (vWF) is considered as a biomarker of the type II and III categories.1 The ENTIRE-TIMI 23 Investigators1 evaluated enoxaparin, a low molecular weight heparin preparation, and unfractionated heparin (UFH) with full-dose tenecteplase (TNK) and half-dose TNK plus abciximab in 483 patients with ST segment elevation MI. A total of 314 patients had serial measurement of vWF (baseline and 48–72 h) and coronary angiography 60 min from treatment initiation. TIMI flow grade < 3 or a corrected TIMI frame count > 40 was associated with greater increases of vWF than normal (physiologic) coronary blood flow. Patients with CK-MB of 75th percentile or above had greater increases as well and those with vWF changes of 75th percentile or above were at greater risk for death or recurrent MI at 30 days. Although there was no significant difference in coronary flow between anticoagulant strategies, randomization to enoxaparin independently reduced vWF and the composite endpoint of death or MI compared with UFH treatment (odds ratio 0.33; CI 0.12–0.91; P = 0.03) in this Phase II study.

vWF, a glycoprotein ranging in size from 600 000 to 20 million Daltons, which participates actively in both platelet adhesion to damaged or disrupted vascular surfaces and high-shear state platelet aggregation, can follow several distinct pathways of secretion from vascular endothelial cells. The first represents a constitutive pathway linked directly to synthesis. The second is a regulated pathway involving storage of mature molecules for release following stimulation by one or more mediators, including histamine; leukotriene D4; platelet activating factor; vascular permeability factor; the terminal component of complement, adrenaline, fluid mechanical forces, factor Vila, thrombin, and fibrin. Weibel–Palade bodies (containing vWF) are rapidly translocated to the cell surface after agonist stimulation. The association of vWF with the external surface of endothelial cells may be mediated by vitronectin receptors, GP Ib, or a constituent of the Weibel–Palade body itself. The nature (or stimulus) of release carries important functional ramifications. Thrombin, for example, which is actively generated among patients with ACS, particularly those receiving fibrinolytic therapy, provokes the appearance of high molecular weight vWF multimers (not present in the circulation under normal
citations). In addition to stimulating endothelial cell vWF release, thrombin proteolytically inactivates the plasma metalloproteinase ADAMTS 13: a major regulator of vWF multimer size and function. The largest VWF multimers have the greatest overall functional activity (thrombogenic potential) and are best measured using the ristocetin cofactor activity (vWF R:Co) assay (4) as used in the present study. Polymerizing fibrin interacts with vWF in a manner that influences the rate of formation and stability of platelet thrombi. Large VWF multimers bind preferentially to fibrin. In addition to stabilizing the developing thrombus, vWF participates in the subsequent incorporation of platelets into polymerizing fibrin, as well as adhesion of platelets to newly formed fibrin strands.5

The natural history and clinical expression of atherothrombotic coronary artery disease have several distinct pathobiological underpinnings. The most compelling is a relationship between endothelial cell injury, inflammation, atherogenesis, and thrombogenesis. Because VWF participates in site-specific thrombus formation and its functional activity has been correlated with both platelet aggregation under high shear stress and infarct size,6 it may well represent a multidimensional biomarker in patients with acute coronary syndrome,7 including those with ST segment elevation MI as suggested by the TIMI Investigators.5

A fundamental question raised by the observations reported by Ray et al.5 is, 'Why should enoxaparin be associated with the suppression of vWF?' In particular, are the biological effects direct (at the cellular/translational level) or indirect (mediated by alterations in one or more biochemical mediators of endothelial cell vWF release)? There is no evidence that heparin provokes the release of endothelium-associated vWF into blood.8 In contrast, incubation of cultured endothelial cells with heparin (either UFH or enoxaparin) reduces vWF release: a relationship which is inversely proportional to the duration of exposure.9 In the ENTIRE-TIMI 23 study, the median duration of antithrombin treatment was 44 h with UFH and 76 h with enoxaparin. The direct thrombin inhibitor, hirudin, attenuates vWF–platelet interactions through the surface GPIb/IX complex, platelet–endothelial cell binding (via vWF),10 proteolytic inactivation of ADAMTS 13,3 and vWF levels in patients with ACS.11 Accordingly, direct effects, by mechanisms not yet fully characterized, and pharmacologically attenuated thrombin generation (and/or activity) represent somewhat simplified but biologically plausible explanations for the studies’ findings. This hypothesis, as well as the potential impact of treatment duration, should be investigated carefully in a larger patient cohort, EXTRACT-TIMI 25, as should the overall functional significance (thrombotic capacity) of vWF levels, given a recognized heparin binding functional domain (A1) (on vWF) that has been shown to participate in attenuated platelet function both in vitro and in vivo following heparin administration.2 Monoclonal antibodies of vWF and recombinant vWF fragment 10 may also warrant consideration and study in clinical trials as targeted pharmacological modalities guided by measured levels of a functional (type III) biomarker.

The investigation of biomarkers (and molecular markers) as diagnostic, prognostic, and functional (ergo potentially modifiable) contributors to cardiovascular disease requires a large-scale, coordinated, and collaborative effort to define their role better in clinical practice. The development of national/international core laboratories and repositories (biomarker networks), working groups to establish definitions, classifications, measurement standards and priorities for study, as well as prospective incorporation of plasma, cellular, and tissue biomarker programs in both industry- and government-supported research efforts, is an absolute prerequisite for meaningful progress in the field and ultimately patient benefit.

References