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Antibody-Based Protection of von Willebrand Factor Degradation

Recently, Bartoli et al. (1) reported on the use of doxycycline to reduce ADAMTS-13-mediated von Willebrand factor degradation during supraphysiological shear stress. We have read their article with interest, noticing reference in their discussion to one of our recent publications that appeared in *Thrombosis and Haemostasis* (2). However, we would like to correct some significant misinterpretations of our data as cited by the investigators. Indeed, our antibody is referred to as a monoclonal antihuman ADAMTS-13 antibody. This is incorrect. In fact, we have reported on the discovery and characterization of a monoclonal antihuman von Willebrand factor antibody, designated Mab508. This is not only clearly written in the abstract, but our article also describes in detail the epitope within von Willebrand factor that is recognized by this antibody. Describing our antibody as being antihuman ADAMTS-13 is therefore an important oversight.

Second, the investigators suggest that our antibody blocks ADAMTS-13 activity by 83% and that such widespread inhibition may inadvertently provoke a hypercoagulable, thrombotic thrombocytopenic purpura-like state and thrombosis. The investigators seem to confuse 2 types of experiments reported in our article. First, we clearly show that the anti-von Willebrand factor antibody blocks binding and degradation of von Willebrand factor by ADAMTS-13 by a maximum of 50%. The figure 83% actually refers to the inhibition of the high-molecular weight multimers, not of von Willebrand factor as a whole. This is an essential difference, as it actually prevents (rather than induces) Mab508 from provoking the occurrence of ultralarge von Willebrand factor multimers that could potentially induce thrombotic thrombocytopenic purpura-like symptoms. This specificity is an important strength of our antibody, particularly when compared with the nonspecific inhibition of ADAMTS-13 and other proteases that is achieved when using doxycycline.

We hope that this letter clarifies the scope of our article (identification of an anti-Von Willebrand factor antibody that partially interferes with ADAMTS-13-mediated degradation).

*Peter J. Lenting, PhD
Cécile V. Denis, PhD
Sophie Susen, MD, PhD
Eric van Belle, MD, PhD

*Inserm U1176
Université Paris-Sud
Université Paris-Saclay
80 rue du General Leclerc
Le Kremlin-Bicetre 94276
France
E-mail: peter.lenting@inserm.fr

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Please note: Drs. Lenting, Denis, and Susen are inventors on a patent related to Mab508 that is owned by Inserm-Transfert SA. Dr. van Belle has reported that he has no relationships relevant to the contents of this paper to disclose.

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REPLY: Antibody-Based Protection of von Willebrand Factor Degradation

Thank you for the opportunity to respond to Dr. Lenting and colleagues. In our paper that examined doxycycline to reduce ADAMTS-13-mediated von Willebrand factor (vWF) degradation during left ventricular assist device (LVAD)-like shear stress (1), we referenced a recent paper by Rauch et al. (2).

In their study, Rauch et al. (2) used a monoclonal antibody (mAb508) to block ADAMTS-13/vWF interactions in order to preserve high-molecular-weight vWF multimers. We acknowledge that “anti-ADAMTS-13” antibody was incorrect terminology and that their antibody is in fact an anti-vWF antibody that blocks the ADAMTS-13/vWF interaction. We congratulate Dr. Lenting and colleagues for this important mechanistic work with potential therapeutic implications. However, we disagree with statements made in their recent Letter to the Editor. Other than correcting the terminology, our concern that mAb508 therapy may lead to hypercoagulability and thrombosis remains unchanged.

Continuous-flow LVADs accelerate vWF degradation by ADAMTS-13 (the vWF protease) and cause an acquired vWF deficiency that predisposes patients to episodic bleeding (3). Within this pathophysiologic mechanism, supraphysiologic shear stress from the LVAD triggers high-molecular-weight vWF multimers to undergo quaternary shape-change activation that exposes vWF-binding sites for collagen and platelets as an initial step in primary hemostasis. In parallel, ADAMTS-13 binding sites are exposed, and ADAMTS-13 cleaves vWF into small, nonfunctional degradation fragments. In their study, Rauch et al. (2) demonstrated that mAb508 inhibited vWF by 83% and ADAMTS-13 degradation of vWF by 50%. As a result in the setting of mechanical circulatory support, high-molecular-weight vWF multimers were protected from shear stress-induced metabolism. Importantly, mAb508 not only reduced degradation of vWF under flow conditions but also did not affect the hemostatic potential of vWF multimers to which it bound. As a result, high-molecular-weight vWF multimers were activated but not degraded.

We are concerned that a therapeutic approach in which activated vWF is protected against degradation by ADAMTS-13 may lead to an overabundance of hemostatically active (prothrombotic) high-molecular-weight vWF multimers. Indeed, we can infer from the study by Rauch et al. (2) that mAb508 therapy in patients may lead to the accumulation of prothrombotic vWF multimers that cannot be metabolized (inactivated) by ADAMTS-13. Prothrombotic vWF multimers that encounter the thrombogenic, blood-contacting artificial interior surface of an LVAD may promote LVAD thrombosis. As such, we raise caution if this line of investigation is translated into clinical practice.

We hope that our response has clarified our work. Again, we congratulate Dr. Lenting and colleagues for their novel and important contribution. We are hopeful that these types of investigations may lead to targeted therapy to reduce LVAD-associated bleeding without precipitating LVAD thrombosis.

*Carlo Bartoli, MD, PhD

*Resident, Division of Cardiovascular Surgery
Hospital of the University of Pennsylvania
Stemmler Hall, Room 351
Philadelphia, Pennsylvania 19104
E-mail: carlo.bartoli@uphs.upenn.edu

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Prognosis in Patients With Takotsubo Cardiomyopathy

Recently, increasing research efforts have been directed to the prognosis of patients with Takotsubo cardiomyopathy (TTC). Several study groups have published outcome data during the last year. A Swedish registry study found a 30-day mortality of 4.1% in 302 patients with TTC (1). The large International Takotsubo Registry included 1,750 patients, and it reported 5.9% mortality after 30 days (2). The rate of death during long-term follow-up was 5.6% per patient-year. Furthermore, our bicentric study in 286 prospectively identified TTC patients revealed 28-day, 1-year, and long-term mortality rates of 5.5%, 12.5%, and 24.7%, respectively (3). Of note, all these trials compared mortality in TTC with matched cohorts of patients with acute myocardial infarction or acute coronary syndrome, and found a similar risk of death (1–3). Long-term mortality in TTC even exceeded that of patients presenting with ST-segment elevation myocardial infarction in 1 study (3). These findings challenge the initial opinion of a favorable prognosis in TTC patients due to complete recovery of left ventricular dysfunction within days to weeks. Murugiah et al. (4) examined the United States Medicare database and reported 30-day and 1-year mortality rates of 2.5% and 6.9% for patients with principal TTC and 4.7% and 11.4% for patients with secondary TTC, respectively. These results illustrate the indisputable prognostic difference between principal and secondary TTC, which has also been demonstrated previously (5). However, the observed mortality in the overall TTC population is comparable to the aforementioned trials in unselected TTC patients, albeit at the lower end of the reported rates.

Considering these novel insights, we think that the prognosis of TTC should no longer be referred to as favorable for patients with principal TTC. During the acute and subacute phases of the disease, patients are prone to severe complications, including heart failure, cardiogenic shock, or life-threatening