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

arrhythmias. Therefore, we suggest close monitoring in coronary care units, in a similar fashion as recommended for patients with acute coronary syndrome. Recovery of left ventricular function and electrocardiographic changes should be documented during regular follow-up visits after hospital discharge. Future research efforts should be directed to determining the detailed causes of death, and particularly, the impact of underlying noncardiovascular diseases in patients with secondary TTC. Furthermore, the development of evidence-based treatment approaches is desirable. It is necessary to enhance the awareness of the substantial mortality rates in TTC and to avoid trivializing the disease to ensure adequate management strategies and to achieve scientific progress.

Thomas Stiermaier, MD
Holger Thiele, MD
***Ingo Eitel, MD**

*Medical Clinic II
University of Lübeck
University Hospital Schleswig-Holstein
Ratzeburger Allee 160
Lübeck 23538
Germany
E-mail: ingo.eitel@uksh.de

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