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EDITORIAL COMMENT

# Gold Standard in Anticoagulation Assessment of Left Ventricular Assist Device Patients?

## How About Bronze*

Josef Stehlik, MD, MPH,† Stacy A. Johnson, MD,‡ Craig H. Selzman, MD§

Continuous-flow left ventricular assist devices (CF-LVADs) have become a standard therapeutic option in the management of eligible patients with advanced forms of heart failure. Although survival after LVAD implant has improved dramatically in the past decade, the cumulative incidence of LVAD-related adverse events is still high (1). Systemic anticoagulation is recommended in all CF-LVADs currently approved for clinical use. The balance of bleeding and thrombosis remains a constant and often perplexing challenge. Indeed, thrombotic and bleeding complications are a major source of morbidity and serve as a significant threat to the intended goals of LVAD therapy: improved quality of life and improved survival. Approaches that will decrease both bleeding and thrombotic complications are therefore needed.

In this issue of *JACC: Heart Failure*, Adatya et al. (2) thus set out to examine methods of ensuring adequacy of anticoagulation in LVAD patients treated with intravenous unfractionated heparin (UFH), either as a bridging anticoagulation approach in patients with a subtherapeutic international normalized ratio (INR) or as a treatment in suspected or confirmed pump thrombosis. The authors' institution used anti-factor Xa (anti-FXa) monitoring to adjust heparin dosing. They then evaluated concordance between anti-FXa and activated partial thromboplastin time (aPTT) assays, categorizing results into subtherapeutic, therapeutic, and supratherapeutic ranges.

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Even before we examine the results of the study (2), the following question will naturally arise: Is there a gold standard for laboratory monitoring of UFH? UFH is a glycosaminoglycan mixture that binds to antithrombin, and it consequently inactivates thrombin and a number of additional clotting factors, including factor Xa. Because UFH binds to other plasma proteins and the surfaces of platelets, macrophages, and endothelial cells, its pharmacokinetics can be unpredictable, and frequent monitoring is therefore recommended. The most widespread approach to heparin monitoring is the use of aPTT, an assay that measures the activity of the intrinsic and common pathways of coagulation. Typically, an aPTT of 1.5 to 2.5 times the control value is considered to be the therapeutic range. Interestingly, this goal was established by a retrospective study published in 1972 that found a lower rate of recurrence of venous thromboembolism in patients whose aPTT was in this range (3). In contrast to the many investigations that examined INR targets with warfarin therapy, no randomized trials were conducted to assess the efficacy of various aPTT goals. The randomized investigations focused on mode of administration and effect of heparin loading, and showed that

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From the †Division of Cardiovascular Medicine, University of Utah School of Medicine, Salt Lake City, Utah; ‡Department of Internal Medicine, Thrombosis Service, University of Utah School of Medicine, Salt Lake City, Utah; and the §Division of Cardiothoracic Surgery, University of Utah School of Medicine, Salt Lake City, Utah. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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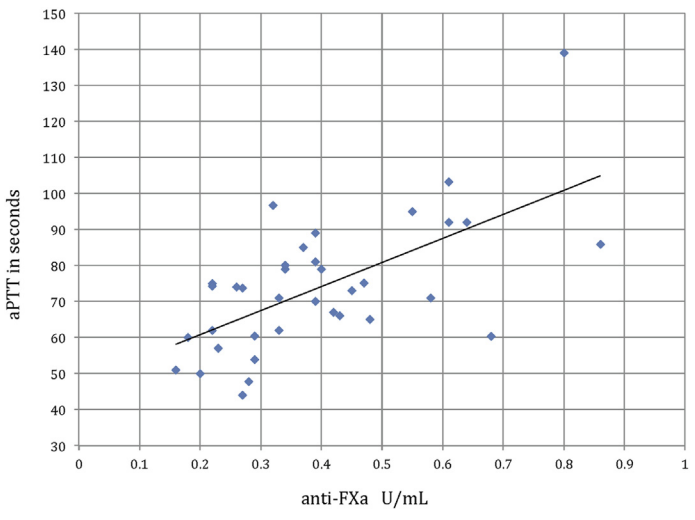
recurrence of venous thromboembolism was less likely when the target aPTT was achieved quickly (4). Due to the variability in responsiveness of aPTT assays to heparin, alternate methods of estimating plasma heparin concentration were examined, including protamine titration and anti-FXa activity level. To facilitate the clinical use of anti-FXa levels, an aPTT:anti-FXa correlation curve is constructed in the laboratory by detecting factor Xa activity after mixing known amounts of plasma, UFH, and factor Xa. Measurement of residual Xa activity in a patient's plasma is then extrapolated to the heparin concentration. Although it was originally expected that correlating aPTT to anti-FXa levels would improve agreement between laboratories and reproducibility of these measures, several studies failed to show this outcome. Instead, it was shown that anti-FXa assays, similar to aPTT assays, vary in their responsiveness to heparin, and possibly to an even greater extent (5,6). Anti-FXa assays may be more resistant to variability in the setting of stress and inflammation, but they also underestimate heparin concentrations in the presence of hemolysis and with acquired antithrombin deficiency; these clinical scenarios are often seen in LVAD patients after implantation or during pump thrombosis. Given the lack of an accepted gold standard for UFH monitoring, comparing simultaneous aPTT with anti-FXa measurements would be expected to confirm the known variability between these assays. To highlight this poor correlation, **Figure 1** displays our institution's aPTT:anti-FXa correlation curve as a representation of the expected assay variation.

**FIGURE 1** aPTT to Anti-FXa Correlation Curve




aPTT = activated partial thromboplastin time; anti-FXa = anti-factor Xa. Figure courtesy of ARUP Laboratories, Salt Lake City, Utah.

With this information in mind, what are the implications of the study by Adatya et al. (2)? The authors retrospectively evaluated result concordance in 340 paired anti-FXa levels and aPTT values ordered in 38 CF-LVAD patients and in 59 patients without CF-LVADs. The CF-LVAD patients received UFH for either subtherapeutic INRs or for treatment of suspected or confirmed CF-LVAD thrombus. The control patients were randomly selected from patients without CF-LVAD who were receiving UFH therapy, excluding those with advanced liver disease or a known hypercoagulable state. The assay concordance rate was remarkably poor in the CF-LVAD group (26%). In contrast, among 59 patients without CF-LVADs, the concordance rate was 67%. The most common reason for discordance was supratherapeutic aPTT (>100 s) despite a therapeutic anti-FXa level. In fact, of those patients with an aPTT >100 s, according to the anti-FXa assay only 9% were in the supratherapeutic range, whereas almost 90% were in the anti-FXa therapeutic range. Furthermore, there was a difference in concordance among the 2 CF-LVAD patient subgroups: among patients admitted for heparin bridging, the concordance rate was 36%, and in those admitted for suspected CF-LVAD thrombosis and/or hemolysis, the concordance rate was 16%. The authors noted that INR ≥1.5 and serum lactate dehydrogenase levels ≥2.5 times the upper limit of normal were associated with higher rates of discordance.

How should we interpret these findings? A closer look at the data may provide some additional insights and perhaps simplify the results. If we consider both UFH therapeutic strata the authors selected (i.e., the low and high therapeutic ranges) as 1 wider therapeutic range, we will find that among patients who had a therapeutic aPTT of 45 to 100 s, 74% also had therapeutic anti-FXa levels between 0.15 and 0.7 U/ml. This result does not seem dissimilar to patients without CF-LVADs and should probably not lead to a change in how we approach this clinical scenario. This leaves the group of patients in whom aPTT was supratherapeutic. Less than 10% of the supratherapeutic aPTT results, regardless of the CF-LVAD subgroup examined, corresponded to a supratherapeutic anti-FXa value, and most corresponded to an anti-FXa result in the therapeutic range. This finding was more likely in patients with higher INR and higher serum LDH values.

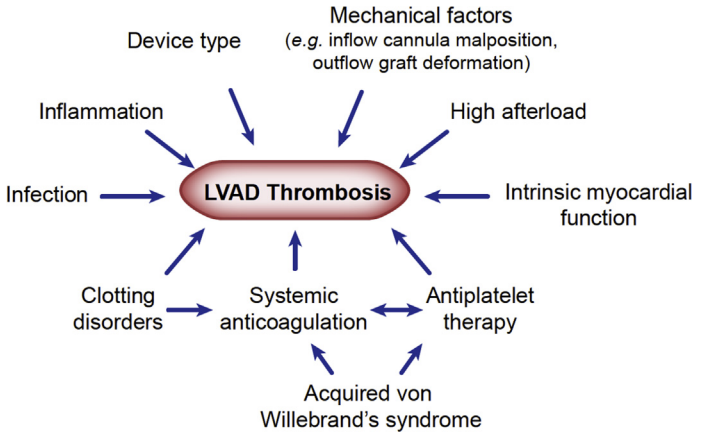
Should we be concerned about this discrepant finding? We propose that in the subgroup of patients being bridged to a therapeutic INR, without suspicion of pump thrombosis, we should not be concerned for the following reasons: 1) in studies of non-CF-LVAD patients, achieving the target aPTT range was effective in preventing thromboembolism despite poor correlation with the anti-FXa level; and 2) extrapolating from the results of this study, even reducing the heparin dose to achieve an aPTT target of 45 to 100 s should still result in a therapeutic anti-FXa level in >70% of the patients.

Therefore, we are now left with the subgroup of patients admitted for suspected CF-LVAD thrombus and/or hemolysis. Presumably, achieving consistent systemic anticoagulation in these patients would be of the highest importance, because anticoagulation serves as both a prophylactic and therapeutic modality. The high level of discordance in this subgroup is concerning, although it may be explained in part by hemolysis and the use of an anti-FXa-adjusted UFH protocol. Severe hemolysis and elevated free hemoglobin concentrations have been shown to lower anti-FXa activity levels relative to aPTT values in patients receiving UFH (7). Therefore, when UFH dosing is guided by using anti-FXa levels (as was done in the present study) in CF-LVAD patients with hemolysis, larger doses of UFH would be expected to be necessary to achieve the anti-FXa therapeutic range, resulting in supratherapeutic aPTT values.

The study by Adatya et al. (2) has methodological limitations. Selection bias might have influenced the composition of the bridging cohort, as patients treated with UFH may have differed from those treated with low-molecular-weight heparin or warfarin alone. Obtaining multiple measurements from a relatively small number of CF-LVAD patients could have magnified any patient-specific factors, affecting discordance between the anti-FXa and aPTT assays. In addition, all UFH dose adjustments were based solely on anti-FXa levels, without a comparator group, using aPTT-derived dose adjustments. In the absence of an accepted gold standard for UFH monitoring, this approach simply demonstrated the known variability between these assays. More data are therefore needed to elucidate whether aPTT-based or anti-FXa-based UFH dose adjustments may be attributed to differences in bleeding or thrombotic events. Such information would ultimately be necessary to inform changes in clinical practice. The size of the present study was not sufficient to assess the impact of anti-FXa and aPTT test results on these clinical outcomes. Of note, this study did not address the peri-implant period but focused mainly on admissions beyond the index CF-LVAD implant hospitalization. Inclusion of patients early after implant, when "seeding" of the CF-LVAD with thrombus may be more likely, could increase the likelihood of demonstrating differences in delayed pump thrombosis. Despite these limitations, this paper provides important information, and the topic should be investigated further. The fact that a subset of patients with CF-LVAD thrombosis may not be receiving adequate anticoagulation during a very critical period is troubling.

Furthermore, we need to keep in mind that the risk of thrombotic and bleeding complications in LVAD patients is not solely a result of keeping the level of anticoagulation within the desired limits (**Figure 2**). Multiple factors influence the hemostatic homeostasis in CF-LVAD recipients. A testimony to this complexity are patients who develop pump thrombosis on stable therapeutic INR or patients with recalcitrant gastrointestinal bleeding despite reduction or withholding of anticoagulation/antiplatelet therapy. Prospective investigations are therefore needed to determine the ideal approach to the monitoring of anticoagulation efficacy in this patient population.

**FIGURE 2 Clinical Factors Influencing the Risk of LVAD Thrombosis**




LVAD = left ventricular assist device.

**REPRINT REQUESTS AND CORRESPONDENCE:** Dr. Josef Stehlik, Division of Cardiovascular Medicine, University of Utah Health Sciences Center, 50 North Medical Drive, 4A100 SOM, Salt Lake City, Utah 84132. E-mail: josef.stehlik@hsc.utah.edu.

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**KEY WORDS** bleeding, heart failure, heparin, left ventricular assist device, systemic anticoagulation