Editorial

On Target
Optimum International Normalized Ratio for Left Ventricular Assist Device Patients

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he use of mechanical circulatory support for patients with advanced heart failure has increased exponentially within the past 10 years. Durable left ventricular assist devices (LVADs) in particular have changed the treatment paradigm for medically refractory heart failure, with an evolution in patient selection from those tethered to the hospital bed with inotrope support as a bridge to transplant, to those with earlier stage disease, and for use as destination devices for those not eligible for heart transplant. Interagency Registry for Mechanically Assisted Circulatory Support has registered more than 15,000 patients implanted with Food and Drug Administration–approved devices since the creation of the program in 2006.1 LVADs not only prolong life but have been shown to improve the quality of life and the functional capacity of patients.2 Many factors are responsible for the explosion in use and improved outcomes. Remarkable improvements in device design and technology, including smaller device size and better power supply, have lead to easier placement and improved patient acceptance. The engineered changes in pump flow mechanisms and component materials, however, with the shift from pulsatile to continuous-flow pumps, represent the most dramatic change.

Despite the technological advances in LVADs and the overall improvement in life expectancy, serious complications persist. The 2 major complications—thrombosis and bleeding—are the result of the inherent prothrombotic nature of the artificial surfaces in contact with the blood and the requirement for mandatory anticoagulation to prevent thrombosis. Bleeding events comprise the highest adverse events. Interagency Registry for Mechanically Assisted Circulatory Support reports a bleeding rate of 9.41 events per 100 patient-months in the first year after implantation during the time period 2008 to 2011, with a subsequent decrease to 7.79 events per 100 patient-months during 2012 to 2014.2 During these 2 time periods, as the bleeding rate declined, reports of the most severe adverse event—pump thrombosis—increased.3 This increase appeared abruptly in 2011, with a 6-fold increase reported by Interagency Registry for Mechanically Assisted Circulatory Support.4 These 2 trends may be related, with changes in approach to anticoagulation over time possibly contributing to both decreased bleeding and increased pump thrombosis, although other factors may also play a role in pump thrombosis.

In this issue of Circulation: Heart Failure, Nassif et al retrospectively review the association between outpatient intensity of anticoagulation, as measured by INR, and major event rates of bleeding and thrombosis in their single-center continuous-flow LVAD population. Their analysis included 249 patients implanted with either Heartmate II or HVAD devices during an 8-year period between 2005 and 2013. The goal was to identify the ideal target INR for warfarin management in patients with continuous-flow LVADs. Previously published studies designed to identify optimal anticoagulation strategies for continuous-flow LVADs are few, with small numbers of patients, and many are from the time period before the observed increase in pump thrombosis.4 Understandably, prospective randomized controlled trials are not practical or ethical in this patient population.

The results of their weighted analysis indicate that a target INR of 2.6 is optimal for avoiding both bleeding and thrombotic complications and therefore minimizing mortality. This INR value was derived by stratifying events based on the INR range and using models with weighting of bleeding and thrombotic events based on expected 30-day mortality rates. Pump thrombosis and intracranial hemorrhage were assigned higher per month mortality rates (0.16–0.49), gastrointestinal bleeding the lowest (0.01), and ischemic stroke in the middle (0.11). These weighted mortality rates were derived from an average of their internal data set of 455 patients and published mortality rates. Event rates were evaluated for 3 different time periods, from LVAD implantation to 3 months, 3 to 6 months, and >6 months, with 6 discrete INR ranges, starting at 0, with increments of 0.49, up to >3.5. INR values at the time of the event or just preceding the event were used in calculations.

The strengths of this study include the number of INRs evaluated, the use of the Rosendaal method to determine days in therapeutic range, the frequency of INR testing in the outpatient setting with INRs drawn on average every 11 days, and
stratification using small INR range increments. The use of the method of weighting adverse events, however, is not entirely clear, nor is it clear how these weights were derived. It is not obvious that the cohort of 249 in this study is separate from their internal population of 455 and that the 455 do not include patients from which published mortality rates were obtained as they reference one of their own studies.9 Counting patients more than once could skew their weighted event rates. The number of patients with Heartmate II versus HVAD could be informative for many reasons, particularly whether their findings are device specific, but analysis by LVAD type is not noted. Differences in events stratified by time over the 8-year time span would also be of interest given the significant difference in pump thrombosis rates before and after 2011. Although they do note that the target INR ranges for the Heartmate II changed over time at their institution, from 2.0 to 2.5, to 1.5 to 2.0, and back to 2.0 to 3.0 during the past 5 years, it would be useful in interpreting their results to see event rates as a function of year of implant, as well as INR strata. As they discuss, the greater rate of suspected pump thrombosis in the later years may have affected their findings and conclusions. The authors’ goal was to assess outpatient warfarin management, but censoring patients with events immediately post implantation but before discharge may make their conclusion that INR is not correlated with thrombotic events in the time period of 0 to 3 months inaccurate. Despite these limitations, the study results are compelling. Using a model with no weighting of adverse events, the optimal target INR was determined to be 2.4.

Warfarin is known to have a narrow therapeutic window, with steep nonlinear dose response curves for thrombosis or hemorrhage on either side of the therapeutic window. It is not at all surprising that Nassif et al7 found a high correlation with hemorrhagic and thrombotic events and INR values. Results from many studies have previously determined that the ideal INR target range is 2.0 to 3.0 for patients with atrial fibrillation, with similar findings of increased stroke for INR <1.8 and increased risk of hemorrhage for INR ≥3.5.10–12 An attempt to tailor the target INR based on increased risk factors for thromboembolic stroke or intracranial hemorrhage in atrial fibrillation, including age, history of previous stroke, or CHADS2 score, found no utility in doing so. This nested case–control study confirmed that 2.0 to 3.0 should be the standard INR range for atrial fibrillation to minimize bleeding and thrombosis, with little gain in safety or efficacy by adjusting the INR range up or down.13 Results depicted by Nassif et al7 in their Figure 3 are strikingly similar, if not identical, to the plots of odds ratios versus INR generated in the risk–adjusted INR range study for atrial fibrillation. Patients with LVADs, however, have different complications than those with atrial fibrillation. Although data generated by Nassif et al demonstrate a sharp decrease in thrombotic rates once the INR is ≥2.5, similar to that seen in atrial fibrillation, the bleeding rates in LVAD patients are much higher at any given INR, even in the range of 1.5 to 1.99, primarily driven by gastrointestinal bleeding rates, a phenomenon not seen in patients with atrial fibrillation.

We can push the intensity of warfarin anticoagulation no further. Both efficacy and safety are maximized within the INR range of 2.0 to 3.0, even with the artificial surfaces of LVADs, based on the data presented by Nassif et al.7 Although most centers have reverted to using a target INR range of 2.0 to 3.0 in the past few years, pump thrombosis rates have not declined significantly. At best, the rates of pump thrombosis have plateaued.14

New approaches to anticoagulation are required to prevent device thrombosis and minimize bleeding, especially gastrointestinal bleeding, the most frequent complication of LVAD use. Although direct oral anticoagulants result in a significant decrease in intracranial hemorrhage in patients with atrial fibrillation,15 dabigatran as a single-agent anticoagulant therapy was found to be inferior to warfarin in a randomized controlled trial of prevention of thromboembolic stroke in patients with mechanical heart valves.16 The trial was halted early after the first interim analysis; the results are concerning for possible similar lack of efficacy of the direct oral anticoagulants in LVAD patients. Intriguing new approaches to anticoagulation, and to uncoupling pathological thrombosis from physiological hemostasis, are in the early stages of development. These approaches involve targeting components of the classical intrinsic pathway of coagulation, particularly factor XI and factor XII. Factor XII is activated by the prekallikrein–kinin system, which is activated when blood is exposed to artificial surfaces. Active FXII then activates factor XI, although FXI can be activated through other mechanisms. Preclinical studies in pri-

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a lower target INR has been shown not to improve safety in atrial fibrillation patients over time\(^7\) and doing so in LVAD patients may possibly contribute to pump thrombosis, clinical parameters may demand these measures to stop significant or even life-threatening bleeding.

Although burdensome, current LVADs extend life and improve its quality. Continued vigilant assessment and management of warfarin in these patients is required, until new approaches to inhibiting thrombosis mature, and device design and technology evolve to improve compatibility at the blood–VAD interface—hopefully rendering traditional anticoagulants unnecessary.

**Disclosures**

Dr Connors is a consultant for St Jude’s Thoratec.

**References**


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