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EDITORIAL COMMENT

Left Ventricular Assist Device Thrombosis

Another Piece of the Puzzle?*

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The regulatory approval of continuous flow (CF) left ventricular assist devices (LVADs) created great enthusiasm, as these devices appeared to solve some of the major problems of pulsatile flow (PF) LVADs, including frequent mechanical failure within 12 to 18 months of implantation, the loud noise generated, and the inability to implant the larger PF pumps in smaller patients, most of whom were women (1,2). The CF LVADs also appeared to have superior rates of thrombosis and infection than PF LVADs (1,2). This enthusiasm persisted until January 2014, when Starling et al. (3,4) reported that the rate of thrombosis of 1 CF-LVAD (the HeartMate II [Thoratec Corp., Pleasanton, California]) at 3 months post-implantation had increased from 2.2% before March 2011 to 8.4% by January 1, 2013—a finding confirmed in the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry (3,4). LVAD thrombosis is a devastating complication, as it usually results either in the need for urgent transplantation or LVAD replacement or in death (3,5,6). A number of causes of LVAD thrombosis have been postulated, including underanticoagulation, inadequate antiplatelet therapy, platelet activation by device materials or shear stress, decreased flow rates with bearing heating and denaturation of coagulation proteins, abnormal angulation of the inflow cannula, new materials in the device, infection, overestimation of the level of anticoagulation using the activated partial thromboplastin time, and right ventricular failure (7–9). It is likely that many of these factors contribute to LVAD thrombosis, and in this issue of *JACC: Heart Failure*, yet another cause of LVAD thrombosis is described—erythropoiesis stimulating agents (ESAs). ESAs include several forms of erythropoietin—a glycoprotein produced in the kidney that acts on hematopoietic precursor cells to increase the production of red blood cells. The most commonly used human recombinant erythropoietins (epoetin alfa, epoetin beta, and darbepoetin alpha) differ primarily in glycosylation patterns and duration of action, but have similar effects on increasing red cell production and similar safety profiles (10).

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In this issue of *JACC: Heart Failure*, Nassif et al. (11) report a retrospective, single-center study of 212 HeartMate II LVAD recipients, demonstrating an increased risk of suspected LVAD thrombosis in those who received ESAs. ESAs were used in this study, as anemia is common in LVAD recipients, often in association with low erythropoietin levels (12). An increase in hemoglobin in LVAD recipients who are to be bridged to transplant is likely to reduce the need for blood products and, thus, reduce sensitization to human leukocyte antigens (HLA) (13). This is important, as anti-HLA antigens may prolong the time to an adequate donor match in patients listed for transplantation (14).

In this study, suspected LVAD thrombosis was defined as: 1) direct observation of obstructive thrombus in the pump or conduit; or 2) severe hemolysis, as defined by either a lactate dehydrogenase (LDH) level >4 times the upper limit of normal or a plasma-free hemoglobin >40 mg/dl, and symptoms of decompensated heart failure (HF). Using an inverse probability-weighted analysis, the authors found that the risk of suspected LVAD thrombosis in the cohort that received ESAs was nearly 2 times higher than in

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the cohort that did not receive ESAs (23% vs. 12%; p = 0.03). Survival free from LVAD thrombosis and stroke was 78.6% in the ESA group versus 94.5% in the non-ESA group (p < 0.001) when assessed at 180 days post-implantation. Using inverse weighting, all-cause mortality was significantly higher in the group receiving ESAs, with a hazard ratio of 1.62 (95% confidence interval [CI]: 1.12 to 2.33; p = 0.01). There was a dose-response relationship, with increasing doses of ESAs associated with increased thrombosis rates. Both the increased rate of thrombosis and the dose-response relationship are consistent with studies of ESAs in other clinical situations.

In 1986, a report by Winearls et al. (15) demonstrated erythropoietin to be effective in improving anemia in 10 chronic hemodialysis patients, but highlighted 2 important potential adverse effects of ESAs, with 2 of the 10 patients developing arteriovenous fistula clotting and 1 developing malignant hypertension. In 1989, Eschbach et al. (16) reported that the use of erythropoietin in 333 hemodialysis patients reduced the need for red blood cell transfusions and improved hematocrit and quality of life. However, 35% of patients had an increase in blood pressure, and 5.4% of treated patients had seizures postulated to be due to hypertensive encephalopathy (16). Nearly one-half of the patients developed iron deficiency and a modest increase in platelet count, although the significance of that finding was not immediately recognized.

Based on these and other studies, the U.S. Food and Drug administration (FDA) approved epoetin alpha for the treatment of anemia in dialysis patients in 1989. In 1993, 1,233 hemodialysis patients with HF or ischemic heart disease were enrolled in the Normal Hematocrit Trial to determine the risk and benefits of normalizing the hematocrit in this population. Epoetin alpha was titrated to raise the hematocrit to 30% or to a mean of 42% (17). The trial was stopped early due to a trend for an increase in the primary endpoint of time to death or first nonfatal myocardial infarction (hazard ratio: 1.3, 95% CI: 0.9 to 1.9).

In 2006, the results of 2 trials in patients with chronic kidney disease caused the FDA to add a black box warning for ESAs and to reduce the hemoglobin target to 10 to 12 g/dl due to an excess rate of thrombosis in the patients in higher hematocrit ranges. In the open-label CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial, patients with an estimated glomerular filtration rate (eGFR) of 15 to 50 ml/min/1.73 m^2 were treated with epoetin alpha to either a low (11.3 g/dl) or high (13.5 g/dl) target hemoglobin (18). There was a 34% increased risk of the composite cardiovascular endpoint of death, myocardial infarction, hospitalization for congestive HF (without renal replacement therapy), and stroke in the group treated to the higher hemoglobin target (18).

The CREATE (Cardiovascular Risk Reduction by Early Anemia Treatment with Epoetin Beta) used epoetin beta to treat patients with an eGFR of 15 to 35 ml/min/1.73 m^2 to hemoglobin concentrations of 11 to 12.5 g/dl or 13 to 15 g/dl (19). There were modest improvements in quality of life in the higher hemoglobin group but a higher rate of progression to end-stage renal disease. A 2007 meta-analysis of 9 randomized controlled trials that enrolled 5,143 patients with chronic kidney disease (CKD) and anemia demonstrated that, for patients randomized to ESAs to achieve a higher versus lower hemoglobin ranges, there was a significantly higher risk of all-cause mortality (risk ratio: 1.17, 95% CI: 1.01 to 1.35; p = 0.031), arteriovenous access thrombosis (risk ratio: 1.34, 95% CI: 1.16 to 1.54; p = 0.0001), and poorly controlled blood pressure (risk ratio: 1.27, 95% CI: 1.08 to 1.50; p = 0.004) in the higher hemoglobin target group than in the lower hemoglobin target group (20).

Subsequently, the TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) randomized 4,038 patients with CKD (eGFR 20 to 60 ml/min/1.73 m^2), diabetes, and anemia to receive darbepoetin to a target hemoglobin of 13 g/dl, with control patients receiving darbepoetin only if hemoglobin fell below 9 g/dl (21). Although quality of life improved in the high hemoglobin group, there was a doubling of the stroke rate and an increase in mortality due to cancer. Following the publication of the TREAT trial, the FDA recommended more conservative dosing guidelines, and the Kidney Disease: Improving Global Outcomes anemia guideline committee recommended that the target hemoglobin be <10 g/dl for anemic CKD patients not on dialysis (22,23).

Two randomized trials have evaluated the use of ESAs in HF—STAMINA-HeFT (Study of Anemia in Heart Failure Trial) and RED-HF (Reduction of Events with Darbepoetin alfa in Heart Failure) (24,25). In STAMINA-HeFT (N = 319), anemic patients with HF were randomized to placebo or darbepoetin alpha to raise the hematocrit to a target of 42% (24). There was a trend for an improvement in the primary endpoint of all-cause mortality and HF hospitalization and no excess of either myocardial infarction or hypertension in the darbepoetin group. However, in the much larger RED-HF trial (N = 2,278), the use of darbepoetin to raise the hematocrit to 13 g/dl did not result in an improvement in the primary endpoint of all-cause mortality or first HF hospitalization, and there was an increased rate of thromboembolic events

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(13.5% vs. 10%; p = 0.01) and an increased risk of stroke (5.4% vs. 3.9%) (25).

On the basis of the cumulative data, a clinical practice guideline from the American College of Physicians recommended against the use of ESAs in anemic patients with coronary disease unless the hemoglobin was ≤7 to 8 g/dl, and it recommended against the use of ESAs altogether in patients with coronary disease or HF with higher hemoglobin levels on the basis of the risks of hypertension, venous thromboembolic events, and ischemic cerebrovascular events at higher hematocrits (26). With this history of increased thrombosis with ESAs in other clinical situations, the results of the study by Nassif et al. (11) are not unexpected. However, a comparison of event rates in this report to those in previously published studies is somewhat limited by its retrospective nature and the criteria used to define thrombosis. Although higher doses of ESAs were associated with increased event rates, data regarding peak hemoglobin post-discharge were not provided; thus, we cannot compare hemoglobin targets in this study to prior reports. However, the dose response of increasing ESA dose and increasing thrombosis rate has been reported in several previous publications and in a recent meta-analysis (27).

It is also possible that this study underestimates the rate of LVAD thrombosis, as part of the definition of suspected LVAD thrombosis was an LDH target of >4 times the upper limit of normal. Previous studies have suggested a high sensitivity and specificity for LVAD thrombosis using an LDH of 2.5 times normal (5,6). Conversely, the rate of thrombosis may have been overestimated, as baseline and discharge hemoglobins were the same in both ESA and non-ESA groups, suggesting that something other than hemoglobin level might have stimulated physicians to choose ESAs in some patients and not others. It is quite possible that those who were more ill received ESAs or that other baseline factors not reported, such as a previous history of thrombosis, were important. A clear example of this potential bias is the higher rate of bacteremia in the ESA group (13% vs. 4%; p = 0.02). Further, it is known from previous reports that the rate of LVAD thrombosis rose nationwide during the course of this study, but the authors have done an excellent job of trying to account for this phenomenon.

Although the association of ESAs with thrombosis seems very likely, the underlying mechanism remains uncertain. A number of potential explanations have been have been proposed, including an increase in blood viscosity with increasing hemoglobin, enhanced thrombopoiesis due to either iron deficiency or direct stimulation of thrombopoiesis, increased oxidative stress with iron deficiency, and other direct effects of ESAs, such as hypertension. An increasing hemoglobin increases blood viscosity but is unlikely to affect blood coagulability in the normal range in healthy humans (28). Conversely, an increase in blood viscosity in the LVAD recipient might cause lower LVAD flow rates, leading to increased heat generation in the device, and resulting in denaturation of coagulation proteins and subsequent thrombosis. However, the hemoglobin in the patients with thrombosis was only about 10 g/dl, making excess viscosity an unlikely cause. Iron deficiency has been associated with increased platelet counts and platelet reactivity, and both are directly related to the severity of iron desaturation (29–31). Reports have shown that thrombopoiesis related to iron deficiency is associated with an excess mortality in dialysis patients (29,30).

In the study by Nassif et al. (11), baseline iron saturations were similar in the 2 groups, and previous clinical trials have considered the level in this study to be iron deficient for patients in an inflammatory milieu such as HF (32). We do not know if iron was routinely monitored and repleted in the study, and baseline, discharge, or follow-up platelet counts are not reported, so iron deficiency cannot be excluded as a potential cause. Iron deficiency has also been reported to be a cause of increased oxidative stress—another factor that might exacerbate thrombosis (28,31).

ESAs directly stimulate thrombopoiesis as well as erythropoiesis, and this effect may be another cause of thrombosis (16,28,33–35). Thrombocytosis has been associated with poor outcomes in patients with acute coronary syndromes even in the absence of ESAs, and this association was thought to be due to increased thrombosis (36). ESAs also may directly result in endothelial activation leading to thrombosis (34). There are a number of other direct but non-erythropoietic effects of ESAs demonstrated in animal models, including stimulation of endothelial and vascular cell growth, limitation of endothelial production of nitric oxide, stimulation of angiogenesis, and hypertension (28). A direct relationship between many of these effects and LVAD thrombosis is not obvious. However, hypertension caused by ESAs in CF LVAD recipients could decrease flow, causing excess heat, denaturation of coagulation proteins, and subsequent thrombosis. Unfortunately, we do not have follow-up blood pressures, a record of the need for additional antihypertensive therapy, or LVAD flow rates in these patients.

Given previous studies and the current study by Nassif et al. (11) it would be prudent to avoid the use of ESAs altogether in LVAD recipients until the

mechanism of this relationship is clarified and a solution is available. Because the mean hemoglobin was 10 g/dl in the patients with thrombosis, with or without the use of ESAs, it seems unlikely that simply using a lower hemoglobin target would prevent ESA-associated thrombosis. Although avoiding red cell transfusions is an important goal in CF LVAD recipients who will be bridged to transplant, the study does not report a reduced number of transfusions—indeed, at discharge, there was no difference between the ESA and non-ESA groups, and the risk-benefit ratio is quite high. In this study, only 3 of the 37 patients with suspected LVAD thrombosis survived 1 year without LVAD replacement or cardiac transplantation. In history and in medicine, "Those who cannot remember the past, are condemned to repeat it" (37).

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