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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).

SEE PAGE 146

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