A large-scale trial testing the intensity of cytoreductive therapy to prevent cardiovascular events

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In the first randomized clinical trial assessing the proper target hematocrit level, or percentage of red blood cells that should be maintained in patients with polycythemia vera (PV), researchers have concluded that the current recommendation to maintain a hematocrit level of less than 45 percent is associated with a lower risk of thrombosis compared with a less aggressive treatment strategy of maintaining a hematocrit level between 45 and 50 percent.

PV is a rare blood disorder that causes the bone marrow to produce too many red blood cells, making the blood much thicker.This can dramatically increase the risk of blood clots such as deep-vein thrombosis (DVT, a blood clot that forms in a vein deep in the legs) or pulmonary embolism (PE, a blood clot in the lung) and cardiovascular events such as heart attack or stroke. Because thrombosis is the most common cause of death in patients with PV, prompt diagnosis and treatment to reduce the thickness of the blood is critical.

Patients with PV usually have elevated hematocrit levels (approximately 50 to 70%, compared with less than 50% in the general population), which puts them at a higher risk of suffering heart attacks, strokes, and DVT/PE than the general population. In order to reduce this risk, a hematocrit level of less than 45 percent is recommended and initially maintained through phlebotomies. If the hematocrit level cannot be reduced through multiple phlebotomies or disease progression is

documented, patients receive hydroxyurea or chemotherapy to eliminate the excess red blood cells. While these two treatment strategies have become widely accepted for PV, until recently no prospective randomized clinical trial has confirmed whether tight control of hematocrit levels below 45 percent successfully prevents or reduces blood clots in patients with PV.

In order to assess the efficacy and safety of maintaining a hematocrit level of lower than 45 percent versus a more liberal approach (keeping hematocrit levels between 45 and 50%), investigators from Italy conducted a study comparing the two strategies among 365 patients with newly diagnosed PV. Patients in Arm A were treated aggressively to maintain hematocrit levels at less than 45 percent, while the patients in Arm B were treated to maintain levels between 45 and 50 percent. The primary composite endpoint was major clots, including stroke, heart attack, transient ischemic attacks ("mini strokes"), clots in the veins in the abdomen, DVT or PE, and cardiovascular death.

The investigators observed that the risk of developing major clots was four times higher in those patients whose hematocrit levels were kept between 45 and 50 percent than in patients whose levels were kept below 45 percent. With the more intensive regimen in Arm A, 1.1 percent of the patients had a major clot versus 4.4 percent in the less aggressive regimen in Arm B. The median hematocrit levels during follow-up were 44 percent and 48 percent, respectively. Treatment with phlebotomy, anti-clotting drugs, and hydroxyurea were comparable.

There was no difference in the safety profile between the regimens. Six patients in Arm A and one patient in Arm B developed myelofibrosis, a blood disorder that causes the bone marrow to be replaced by scar tissue. Researchers observed no statistical difference in the frequency of acute leukemias that occurred in three patients in Arm A and one patient in Arm B.

"These data validate the notion that it is important to keep hematocrit levels below 45 percent for this population of patients who are at a high risk of developing clotting complications," said Tiziano Barbui, MD, lead author and Professor of Hematology and Scientific Director of the Research Foundation at Ospedali Riuniti di Bergamo in Italy. "The results from our study will be especially important in the development of new drugs for polycythemia vera, as we look to maintain these levels more effectively and with minimal complications."

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