

ORIGINAL ARTICLE

Cardiovascular Events and Intensity of Treatment in Polycythemia Vera

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ABSTRACT

BACKGROUND

Current treatment recommendations for patients with polycythemia vera call for maintaining a hematocrit of less than 45%, but this therapeutic strategy has not been tested in a randomized clinical trial.

METHODS

We randomly assigned 365 adults with JAK2-positive polycythemia vera who were being treated with phlebotomy, hydroxyurea, or both to receive either more intensive treatment (target hematocrit, <45%) (low-hematocrit group) or less intensive treatment (target hematocrit, 45 to 50%) (high-hematocrit group). The primary composite end point was the time until death from cardiovascular causes or major thrombotic events. The secondary end points were cardiovascular events, cardiovascular hospitalizations, incidence of cancer, progression to myelofibrosis, myelodysplasia or leukemic transformation, and hemorrhage. An intention-to-treat analysis was performed.

RESULTS

After a median follow-up of 31 months, the primary end point was recorded in 5 of 182 patients in the low-hematocrit group (2.7%) and 18 of 183 patients in the high-hematocrit group (9.8%) (hazard ratio in the high-hematocrit group, 3.91; 95% confidence interval [CI], 1.45 to 10.53; $P=0.007$). The primary end point plus superficial-vein thrombosis occurred in 4.4% of patients in the low-hematocrit group, as compared with 10.9% in the high-hematocrit group (hazard ratio, 2.69; 95% CI, 1.19 to 6.12; $P=0.02$). Progression to myelofibrosis, myelodysplasia or leukemic transformation, and bleeding were observed in 6, 2, and 2 patients, respectively, in the low-hematocrit group, as compared with 2, 1, and 5 patients, respectively, in the high-hematocrit group. There was no significant between-group difference in the rate of adverse events.

CONCLUSIONS

In patients with polycythemia vera, those with a hematocrit target of less than 45% had a significantly lower rate of cardiovascular death and major thrombosis than did those with a hematocrit target of 45 to 50%. (Funded by the Italian Medicines Agency and others; ClinicalTrials.gov number, NCT01645124, and EudraCT number, 2007-006694-91.)

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POLYCYTHEMIA VERA IS A RARE HEMATOLOGIC neoplasm characterized by clonal proliferation of multipotent bone marrow progenitors, leading to abnormal production of erythroid cells and an increased red-cell mass.¹⁻⁴ Acquired mutations in *JAK2* (*JAK2* V617F and exon 12 mutations) are found in almost all patients with polycythemia vera.^{5,6} Major causes of death and complications include thrombosis, bleeding, and hematologic transformation into overt myelofibrosis or acute leukemia.

Recommendations for the management of polycythemia vera are based on thrombotic risk and a limited number of randomized clinical trials and observational studies that described the clinical course of the disease and indirectly evaluated the role of different treatments. Thus, evidence from prospective clinical trials is limited, and clinical expertise still plays a major role in guiding therapy in patients with this disease. It is recommended that the hematocrit be kept below 45% and the platelet count below 400,000 per cubic millimeter on the basis of studies^{1,4} that showed a proportional increase in the rate of thrombotic events with increased hematocrits and platelet counts. Intensive management of these hematologic variables is widely practiced, despite the lack of solid data in support of this recommendation.⁴ Indeed, a post hoc analysis of two large, randomized clinical trials⁷⁻⁹ did not show a significant increase in the incidence of major thrombosis when a hematocrit of 45 to 50% was maintained. Thus, the usefulness of tight hematocrit control in reducing thrombosis is uncertain, and an aggressive treatment to reach that hematocrit target could result in toxic effects.

In a large-scale, multicenter, prospective, randomized clinical trial, called the Cyto-reductive Therapy in Polycythemia Vera (CYTO-PV) study, we compared the efficacy of conventional treatment (phlebotomy, hydroxyurea, or both) aimed at maintaining the recommended hematocrit target of less than 45%, as compared with a level of 45 to 50%, for the prevention of thrombotic events in patients with polycythemia vera.

METHODS

ELIGIBILITY CRITERIA

The study design has been described in detail previously.¹⁰ Adults with a diagnosis of polycythemia vera according to World Health Organi-

zation (WHO) 2008 diagnostic criteria, including the presence of cells carrying a *JAK2* V617F or exon 12 mutation, were eligible to participate in the study. Patients with the following characteristics were not eligible: substantial liver disease (alanine aminotransferase or aspartate aminotransferase level, >2.5 times the upper limit of the normal range) or renal disease (creatinine level, >2 mg per deciliter [177 μ mol per liter]); a history of active substance or alcohol abuse within the past year; pregnancy, lactation, or lack of an accepted method of contraception for women of childbearing age; the presence of any life-threatening condition or any disease that is likely to substantially shorten life expectancy; previous side effects while receiving hydroxyurea; or any condition that in the opinion of the investigator could result in poor adherence to the protocol. All patients provided written informed consent.

STUDY DESIGN

From May 2008 to February 2012, we enrolled 365 patients at 26 centers in Italy. At enrollment, the patients were stratified according to the presence or absence of a history of thrombosis, age group (<65 years or \geq 65 years), and referring medical center. We randomly assigned the patients in a 1:1 ratio to undergo phlebotomy, receive hydroxyurea, or both, with one group receiving more aggressive therapy for a hematocrit target of less than 45% (low-hematocrit group) and the other group receiving less aggressive therapy for a hematocrit target of 45 to 50% (high-hematocrit group). The protocol dictated that the hematocrit target to which the patient was assigned had to be maintained during the course of the study. The choice of the best therapeutic approach was left to the investigator (phlebotomy, cyto-reductive drugs, or both), although a recommendation was made to use hydroxyurea as the drug of choice in patients at high risk for thrombosis (age, >65 years; or previous thrombosis) or in those with progressive thrombocytosis or splenomegaly. Other drugs were permitted according to the physician's judgment.

Phlebotomy was initially performed by removing 250 to 500 ml of blood every other day or twice a week until the hematocrit target was reached. Hydroxyurea was initially administered at a dose of 0.5 to 1.0 g daily. In the first 6 months of the study, patients receiving hydroxyurea were followed with weekly blood counts to adjust the dose to achieve a platelet count of less than

400,000 per cubic millimeter. The hydroxyurea dose was reduced in cases of a leukocyte count of less than 3500 per cubic millimeter. Low-dose aspirin was to be administered to all patients who had no contraindications. Any other treatment for controlling additional cardiovascular risk factors (e.g., diabetes, hypertension, and hyperlipidemia) was encouraged. If the medication was discontinued or changed, the reason was recorded in case-report forms. All patients were followed until study completion. A permanent discontinuation or change in the randomized hematocrit target was considered only in the best interest of the patient, but the schedule of planned follow-up visits according to study protocol did not change.

Information recorded at each visit included the occurrence of thrombotic or hemorrhagic events, hematologic transformation, or onset of solid tumors. Follow-up forms requesting details of diagnoses of the primary end point were completed every 6 months.

The trial was approved by the ethics committees at each participating hospital, and standard operating procedures compliant with international guidelines¹¹ were adopted. The protocol, including the statistical analysis plan, is available with the full text of this article at NEJM.org.

STUDY END POINTS

The primary composite end point was the time until death from cardiovascular causes or throm-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Low Hematocrit (N=182)	High Hematocrit (N=183)	All Patients (N=365)
Age at recruitment — yr	64.8±12.1	64.3±12.2	64.5±12.2
Male sex — no. (%)	116 (63.7)	111 (60.7)	227 (62.2)
Time from diagnosis to enrollment			
Mean — yr	4.5±5.6	4.0±5.3	4.3±5.4
0–2 yr — no. (%)	88 (48.4)	92 (50.3)	180 (49.3)
Hematologic values			
Hemoglobin — g/dl	15.2±1.7	15.4±1.7	15.3±1.7
Hematocrit — %	47.2±5.1	47.5±4.4	47.4±4.7
Platelet count — per mm ³	390,000	421,000	406,000
Red-cell count — per mm ³	5,800,000	5,700,000	5,700,000
White-cell count — per mm ³	9000	9700	9300
Previous thrombotic events — no. (%)	52 (28.6)	53 (29.0)	105 (28.8)
Arterial	29 (15.9)	34 (18.6)	63 (17.3)
Venous	25 (13.7)	20 (10.9)	45 (12.3)
Previous hemorrhagic events — no. (%)	6 (3.3)	12 (6.6)	18 (4.9)
Mutational status — no. (%) [†]			
JAK2 V617F	177 (97.3)	178 (97.3)	355 (97.3)
JAK2 exon 12	3 (1.6)	3 (1.6)	6 (1.6)
Treatments for cardiovascular risk factors — no. (%)			
Hypocholesterolemic medication	23 (12.6)	24 (13.1)	47 (12.9)
Antidiabetic medication	9 (4.9)	8 (4.4)	17 (4.7)
Antihypertensive medication	93 (51.1)	83 (45.4)	176 (48.2)
Antithrombotic treatment — no. (%)			
Antiplatelet agent	151 (83.0)	157 (85.8)	308 (84.4)
Aspirin	139 (76.4)	140 (76.5)	279 (76.4)
Anti-vitamin K agent	25 (13.7)	24 (13.1)	49 (13.4)

Table 1. (Continued.)			
Characteristic	Low Hematocrit (N=182)	High Hematocrit (N=183)	All Patients (N=365)
Cytoreductive treatment			
Use of phlebotomy			
Patients — no. (%)	127 (69.8)	121 (66.1)	248 (68.0)
Procedures in past 6 mo — no.			
Median	2.0	2.0	2.0
Interquartile range	1.0–3.0	1.0–2.5	1.0–2.5
Use of hydroxyurea			
Patients — no. (%)	98 (53.8)	94 (51.4)	192 (52.6)
Dose — mg/day			
Median	732	750	750
Interquartile range	500–1000	500–1000	500–1000
Use of other drugs — no. of patients (%)			
Pipobroman	9 (4.9)	8 (4.4)	17 (4.7)
Interferon	6 (3.3)	1 (0.5)	7 (1.9)
Busulfan	1 (0.5)	1 (0.5)	2 (0.5)

* Plus–minus values are means \pm SD. There was no significant difference between the two groups.

† One patient in the low-hematocrit group had both *JAK2* V617F and exon 12 mutations.

botic events (stroke, acute coronary syndrome, transient ischemic attack, pulmonary embolism, abdominal thrombosis, deep-vein thrombosis, or peripheral arterial thrombosis), as defined by the *International Classification of Diseases, 9th Revision, Clinical Modification*. An end-point committee adjudicated causes of death and events that were included in the primary end point on the basis of prespecified definitions and procedures. (The definitions are provided in the table in the Supplementary Appendix, available at [NEJM.org](http://nejm.org).)

The secondary end point was the total rate of cardiovascular events, defined as the primary end point plus superficial-vein thrombosis. Additional end points were incidence of cancer, progression to myelofibrosis, myelodysplasia or leukemic transformation, total and nonfatal major hemorrhage (any hemorrhage requiring transfusion, hospitalization, or both), and minor bleeding.

SAFETY

Serious and relevant adverse events were recorded according to the classification code of the *Medical Dictionary for Regulatory Activities* and were graded according to the National Cancer Institute Common Toxicity Criteria (<http://ctep.cancer.gov/>

protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

STUDY OVERSIGHT

This investigator-initiated clinical trial was sponsored mainly by the Italian Medicines Agency (AIFA). Medical therapy was provided as part of the standard care of the National Health System.

The steering committee was solely responsible for the planning and coordination of the study, the analysis and interpretation of the data, the preparation of the manuscript, and making the decision to submit the manuscript for publication. No agreements concerning confidentiality of the data were stipulated between the funder and the authors. The study was designed by the lead and senior authors. Data collection was performed at Consorzio Mario Negri Sud through a Web-based database-management system and supervised by the study coordinator. Study investigators recruited and followed the patients during the course of the study. The analyses were performed by the lead author and the statisticians at Consorzio Mario Negri Sud. The manuscript was drafted by the lead author, reviewed by the members of the steering committee, and cir-

culated for comments among the main authors. No one who is not an author contributed to the manuscript. The authors vouch for the accuracy and completeness of the data and the fidelity of study conduct and analysis to the study protocol.¹⁰

STATISTICAL ANALYSIS

We determined that 1000 patients would need to be enrolled and followed for 5 years in order to provide a power of 80% to detect a relative risk reduction of 30% in the low-hematocrit group on the basis of an event rate in the high-hematocrit group of 5% per year^{7,12,13} and an alpha level of 0.05. After 4 years of recruitment, 365 patients had been enrolled in the study. Because of a progressive decline in the rate of recruitment as well as competition with trials testing the efficacy of new JAK2-inhibiting drugs, the steering committee decided to close the study in 2012 and to analyze the study results, since the planned recruitment target was unlikely to be reached.

Baseline characteristics of the study patients were compared with the use of the chi-square test or Fisher's exact test for categorical variables and the t-test or nonparametric test for continuous variables. We used the Kaplan–Meier method to analyze survival and used the log-rank test to assess differences between survival curves. Unadjusted hazard ratios and 95% confidence intervals were calculated by fitting Cox proportional-hazards models. The assumption of proportional hazards for the two study groups was checked by means of log-minus-log survival plots and the time-dependent covariate test. Interaction of the experimental treatments with the prespecified subgroups was assessed by fitting a Cox model with one term representing the treatment group, one representing the covariate of interest, and an interaction term. The following subgroups were considered: pharmacologic versus nonpharmacologic cytoreductive therapy; sex; median age; previous thrombosis versus no previous thrombosis; low-risk disease versus high-risk disease; baseline platelet and white-cell counts (above or below the median value); the presence or absence of splenomegaly, diabetes, or hypertension; and the use versus nonuse of aspirin or other anticoagulant drugs.

All reported P values are two-sided. All analyses were performed with the use of SAS software, version 9.2.

Figure 1 (facing page). Hematocrit (HCT) and White-Cell and Platelet Counts during the Study.

Patients in the low-HCT group were assigned to receive more intensive therapy, in which the goal was to reach and maintain an HCT target of less than 45%. Patients in the high-hematocrit group were assigned to receive less intensive therapy, in which the goal was to reach and maintain an HCT target of 45 to 50%. Shown are the 25th, 50th (median), and 75th percentiles for hematocrit (Panel A), white-cell count (Panel B), and platelet count (Panel C) at various time points in the two study groups.

RESULTS

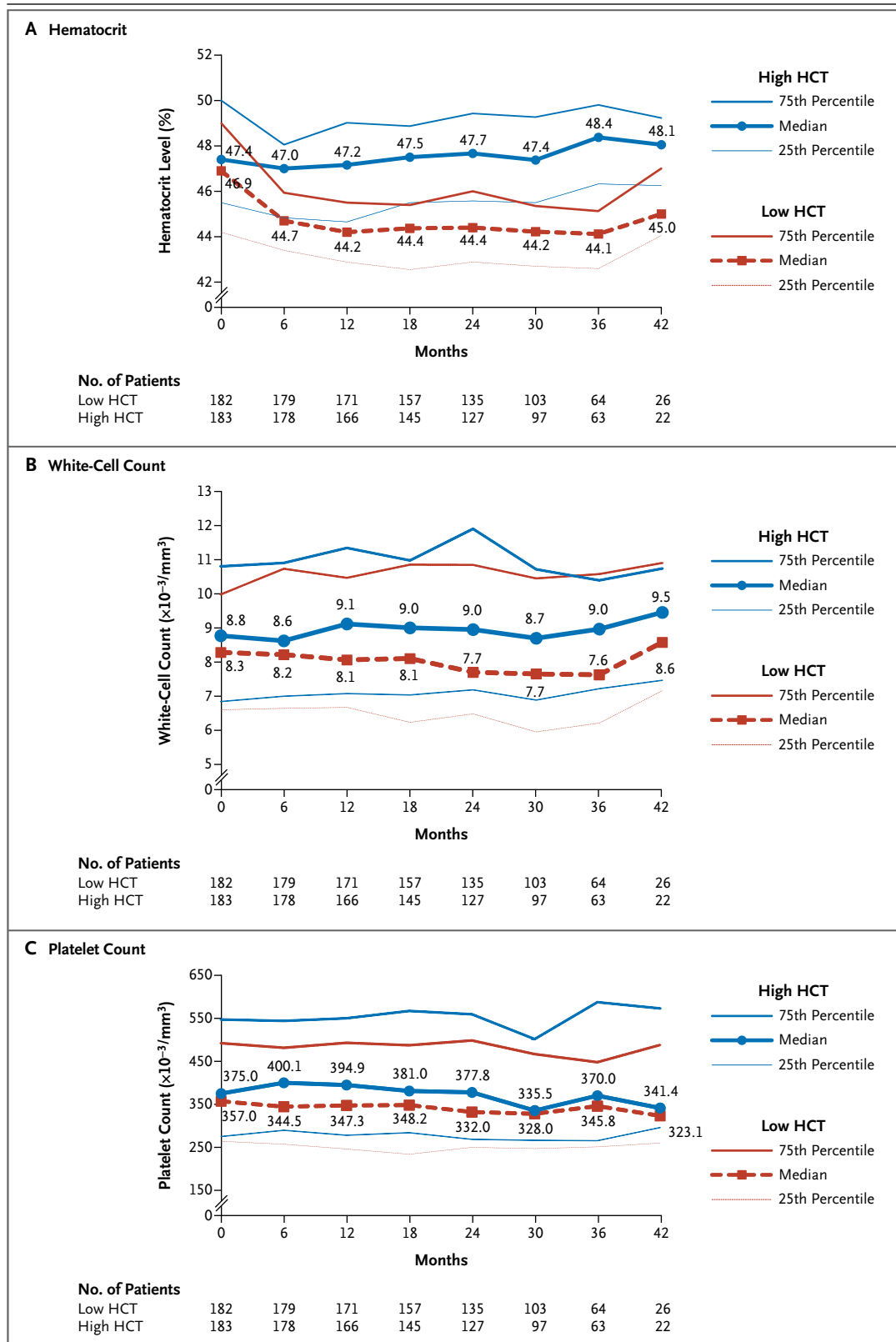
PATIENTS

Of the 365 patients in the study, 182 were randomly assigned to the low-hematocrit group and 183 to the high-hematocrit group. The intention-to-treat analysis included all 365 patients (Fig. S1 in the Supplementary Appendix). Baseline characteristics were well balanced between the two groups (Table 1). Approximately half the patients had received an initial diagnosis within 2 years before randomization. All patients carried the JAK2 V617F mutation except for 10, of whom 5 carried a JAK2 exon 12 mutation and 5 had an unknown mutation status; enrollment of the latter 5 patients constituted a deviation from the protocol.

Of the 365 patients, 245 (67.1%) were at high risk because of an age of 65 years or older or previous thrombosis; 91 patients (24.9%) had had thrombotic events more than 12 months before undergoing randomization, and 63 of these events (60.0%) were arterial thromboses. Fifty-five percent of the patients had hypertension and 17% had hypercholesterolemia. The most common therapies at enrollment were antiplatelet agents (84.4%) — most frequently aspirin (76.4%) — phlebotomy (68.0%), hydroxyurea (52.6%), and antihypertensive medication (48.2%).

CHANGES IN TYPE OF THERAPY

Patients were followed for a mean (\pm SD) of 28.9 \pm 10.9 months (range, 1.5 to 48.1). We assessed the change of therapy from baseline to the 6-month follow-up visit in the two study groups. In the low-hematocrit group, phlebotomy was initiated in 14 patients (7.7%) and hydroxyurea treatment in 10 patients (5.5%); in previously



treated patients, the mean dose of hydroxyurea increased by 5.5% (from 763 to 806 mg daily) and the number of phlebotomies increased by 36.4% (average per patient, 2.2 to 3.0 during a 6-month period). In the high-hematocrit group, 52 patients (28.4%) stopped phlebotomy and 8 (4.4%) stopped hydroxyurea treatment; in patients treated in both visits, the mean dose of hydroxyurea decreased by 9.8% (from 783 to 706 mg daily) and the number of phlebotomies increased by 15.8% (average per patient, 1.9 to 2.2 during a 6-month period).

HEMATOCRIT, WHITE-CELL COUNT, AND PLATELET COUNT

The mean (\pm SD) hematocrit at baseline was similar in the low-hematocrit group and high-hematocrit group ($47.2\pm 5.1\%$ vs. $47.5\pm 4.4\%$). During the study period, the median hematocrit level that was maintained in the low-hematocrit group was 44.4%, as compared with 47.5% in the high-hematocrit group (Fig. 1A). Approximately three of four patients in each group were correctly maintained in the randomly assigned hematocrit target range during the study. The white-cell count remained significantly higher in the high-hematocrit group than in the low-hematocrit group ($P<0.001$) (Fig. 1B). No significant between-group difference was noted in the platelet count (Fig. 1C).

PRIMARY AND SECONDARY END POINTS

After a median of 31 months of follow-up, the primary end point was recorded in 5 of 182 patients in the low-hematocrit group (2.7%) and 18 of 183 patients in the high-hematocrit group (9.8%) (hazard ratio in the high-hematocrit group, 3.91; 95% confidence interval [CI], 1.45 to 10.53; $P=0.007$) (Fig. 2A). The incidence of death from cardiovascular causes or major thrombosis was 1.1 per 100 person-years in the low-hematocrit group and 4.4 per 100 person-years in the high-hematocrit group. Total cardiovascular events occurred in 4.4% of patients in the low-hematocrit group and 10.9% of those in the high-hematocrit group (hazard ratio, 2.69; 95% CI, 1.19 to 6.12; $P=0.02$) (Fig. 2B). No significant interaction was found for the effect of study-group assignment in the subgroup analyses (Fig. 3).

Progression to myelofibrosis, myelodysplasia or leukemic transformation, and bleeding were observed in six, two, and two patients respec-

tively, in the low-hematocrit group, as compared with two, one, and five patients, respectively, in the high-hematocrit group (Table 2). Twelve solid tumors were observed during the study: seven in the low-hematocrit group and five in the high-hematocrit group. Two other hematologic cancers occurred, one in each study group.

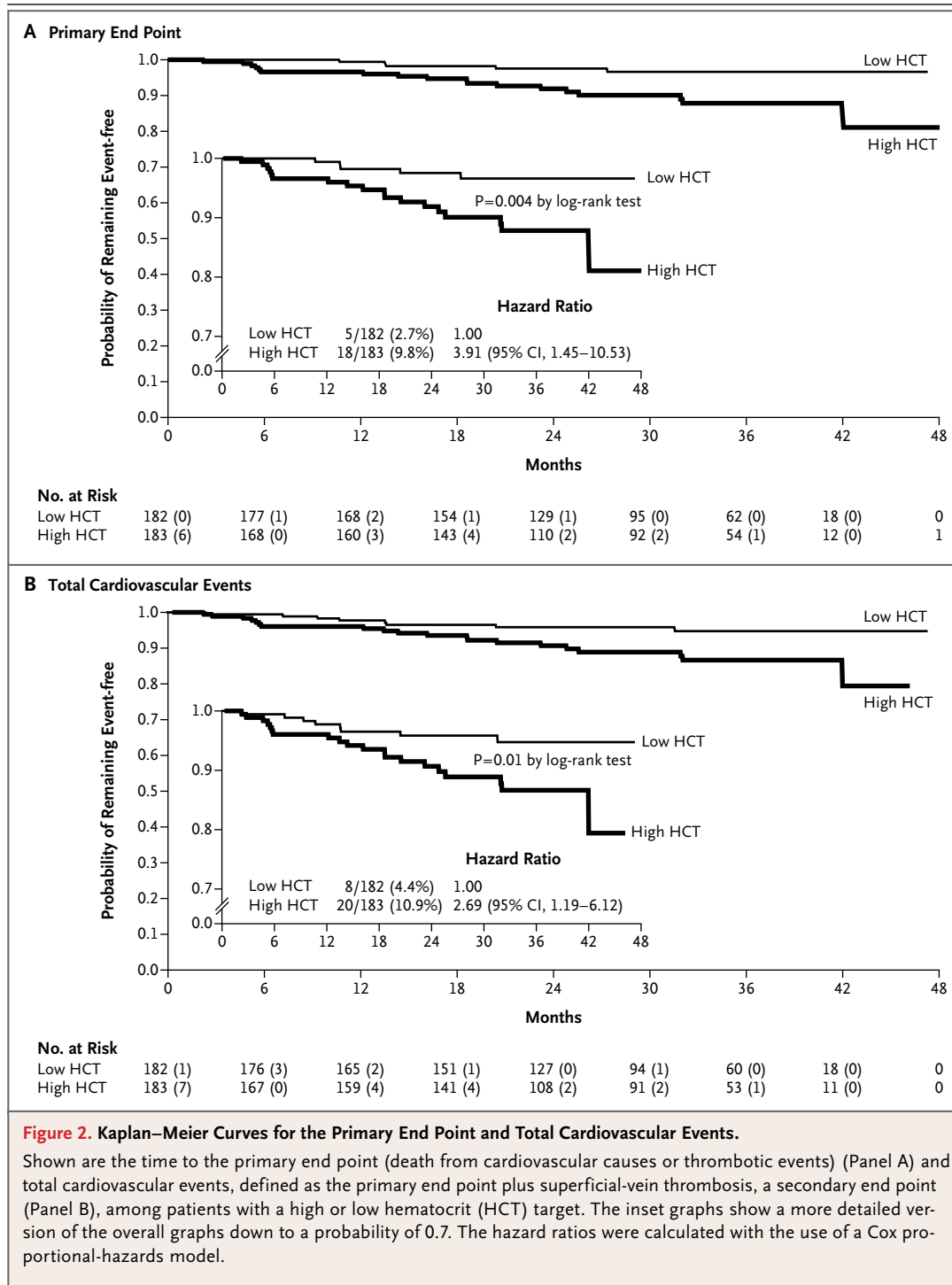
ADVERSE EVENTS

By the end of the study, 4 patients (2.2%) in the low-hematocrit group and 5 (2.7%) in the high-hematocrit group had stopped or changed their assigned treatment, mainly because of progression of disease. Thirty-nine adverse events were reported in 35 patients, 25 of which occurred in the low-hematocrit group and 14 in the high-hematocrit group (see the Materials section in the Supplementary Appendix). One serious adverse event occurred during the study in the low-hematocrit group (one bone fracture) and three in the high-hematocrit group (one case of diarrhea, one case of dizziness, and one case of bronchitis).

DISCUSSION

The results of this study in patients with polycythemia vera who were receiving conventional treatment (including phlebotomy, hydroxyurea, or both) show that maintaining a hematocrit target of 45 to 50% was associated with four times the rate of death from cardiovascular causes or major thrombosis, as was maintaining a hematocrit target of less than 45%. The incidence of the primary end point was 1.1 events per 100 patient-years in the low-hematocrit group, as compared with 4.4 events per 100 patient-years in the high-hematocrit group. Rates of deep-vein thrombosis and cerebral vascular events including strokes and transient ischemic attacks were increased in the high-hematocrit group, confirming the higher incidence of thrombosis observed in the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) study.^{7,14} On the other hand, slight, nonsignificant increases in rates of hematologic progression and solid cancer were observed in the low-hematocrit group. However, the follow-up period was too short to make inference about transformation rates into myelofibrosis, myelodysplasia, or leukemia in the two study groups.

This significant benefit in the low-hematocrit group was largely unanticipated on the basis of



previous reports and contrasts with findings of the post hoc, hypothesis-generating analyses of the ECLAP study and the Polycythemia Vera Study Group (PVSG-01).⁷⁻⁹ However, post hoc multivariate analyses can adjust only for con-

founding, do not fully adjust results in case of measurement error, are usually not powered to test for interaction, cannot account for unmeasured factors, and can be influenced by the indication bias. Conversely, our findings are in

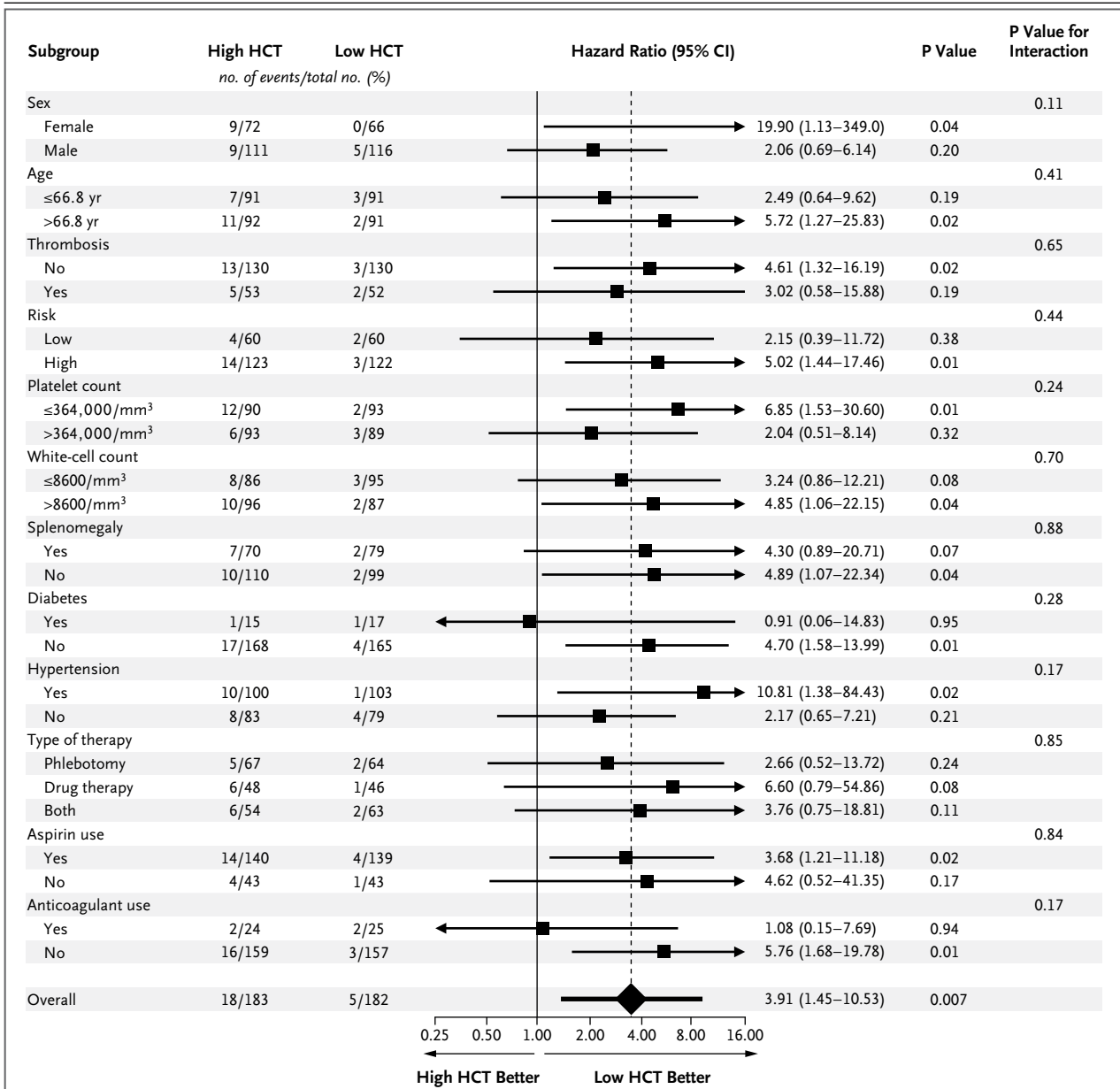


Figure 3. Risk of the Primary End Point in Prespecified Subgroups.

Among prespecified subgroups of patients with a high or low hematocrit (HCT), hazard ratios are indicated by solid squares. Horizontal lines represent the 95% confidence intervals as calculated by a Cox proportional-hazards model, with arrows indicating that the upper or lower limit is not shown. P values for hazard ratios were calculated with the use of Cox proportional-hazards models. Interaction of the study treatments with the prespecified subgroups was assessed by fitting a Cox model with one term representing the treatment group, one representing the covariate of interest, and an interaction term; P values for the interaction term are shown. A double-logarithmic scale is shown on the x axis. One patient in the low-HCT group had missing values for laboratory measures at baseline. For some subgroups, values do not sum to totals because categories with very low frequencies were excluded from the analysis.

agreement with the original retrospective observation published more than 30 years ago by Pearson and Wetherley-Mein,¹⁵ which led to the adoption of current guidelines (though in the absence of randomized clinical trials).¹

Notably, our results do not address whether even lower hematocrit thresholds would be even better. The benefit of intensive hematocrit reduction was consistent in the examined subgroups, and no significant heterogeneity of results was

Table 2. Primary and Secondary End Points.*

End Point	Low Hematocrit (N=182)	High Hematocrit (N=183)	All Patients (N=365)	Hazard Ratio (95% CI)	P Value
	<i>number (percent)</i>				
Primary end point†	5 (2.7)	18 (9.8)	23 (6.3)	3.91 (1.45–10.53)	0.007
Total cardiovascular events‡	8 (4.4)	20 (10.9)	28 (7.7)	2.69 (1.19–6.12)	0.02
Death					
All patients	3 (1.6)	6 (3.3)	9 (2.5)	2.15 (0.54–8.62)	0.28
Cardiovascular causes	0	4 (2.2)	4 (1.1)	NA	
Myocardial infarction	0	1 (0.5)	1 (0.3)	NA	
Stroke	0	2 (1.1)	2 (0.5)	NA	
Pulmonary embolism	0	1 (0.5)	1 (0.3)	NA	
Cancer	2 (1.1)	1 (0.5)	3 (0.8)	0.55 (0.05–6.02)	0.62
Nonfatal events					
Myocardial infarction	3 (1.6)	0	3 (0.8)	NA	
Stroke	0	4 (2.2)	4 (1.1)	NA	
Peripheral arterial thrombosis	0	3 (1.6)	3 (0.8)	NA	
Deep-vein thrombosis	1 (0.5)	4 (2.2)	5 (1.4)	4.11 (0.46–36.74)	0.21
Pulmonary embolism	0	1 (0.5)	1 (0.3)	NA	
Transient ischemic attack	1 (0.5)	4 (2.2)	5 (1.4)	4.24 (0.47–37.97)	0.20
Superficial thrombophlebitis	4 (2.2)	2 (1.1)	6 (1.6)	0.51 (0.09–2.79)	0.44
Bleeding	2 (1.1)	5 (2.7)	7 (1.9)	2.53 (0.49–13.06)	0.27
Hematologic progression or cancer					
Myelofibrosis	6 (3.3)	2 (1.1)	8 (2.2)	0.34 (0.07–1.67)	0.18
Myelodysplasia or acute leukemia	2 (1.1)	1 (0.5)	3 (0.8)	0.52 (0.05–5.71)	0.59
Other hematologic cancer	1 (0.5)	1 (0.5)	2 (0.5)	1.02 (0.06–16.23)	0.99
Solid cancer	7 (3.8)	5 (2.7)	12 (3.3)	0.74 (0.23–2.33)	0.60

* NA denotes not applicable.

† The primary end point was death from cardiovascular causes or thrombotic events (stroke, acute coronary syndrome, transient ischemic attack, pulmonary embolism, abdominal thrombosis, deep-vein thrombosis, or peripheral arterial thrombosis). The incidence of the primary end point was 1.1 per 100 person-years in the low-hematocrit group, as compared with 4.4 per 100 person-years in the high-hematocrit group.

‡ Total cardiovascular events consisted of the primary end point plus superficial-vein thrombosis. The incidence of total cardiovascular events was 1.9 per 100 person-years in the low-hematocrit group, as compared with 5.0 per 100 person-years in the high-hematocrit group.

found according to age, previous thrombosis, platelet or white-cell counts, splenomegaly, previous cytoreductive treatment, or antiplatelet or anticoagulant medication. Similar results were found in men and women. An association be-

tween increased blood viscosity and both arterial and venous thrombosis has been reported in various epidemiologic studies in general populations and in patients with nonclonal erythrocytosis, such as polycythemia of high altitude,

erythropoietin receptor mutations, Chuvash polycythemia, hemoglobin mutants with high oxygen affinity, and 2,3-bisphosphoglycerate deficiency. In these conditions, which are all characterized by an elevated hematocrit with normal leukocyte and platelet counts, rates of thrombotic complications are higher than in controls but far below those seen in patients with polycythemia vera.^{16,17} Among patients with polycythemia vera, in addition to the hematocrit levels, other components of the myeloproliferative process may be associated with thrombosis, including quantitative and qualitative defects of platelets and leukocytes, as shown also in essential thrombocythemia.¹⁸⁻²⁰

The hematocrit is not a perfect therapeutic guide in patients with polycythemia vera because it cannot be used as an accurate surrogate for the red-cell mass (e.g., increases in plasma volume could mask the degree of increase in red-cell mass).¹ In our study, patients in the high-hematocrit group had significantly higher leukocyte counts than did those in the low-hematocrit group, but platelet counts were similar in the two groups. Thus, in the high-hematocrit group, in which the use of hydroxyurea was less frequent than in the low-hematocrit group, the persistence of leukocytosis could have contributed to an excess of thrombosis. This finding cannot be generalized to cytoreductive drugs other than hydroxyurea. The issue of the potential long-term leukemogenesis from hydroxyurea has been raised as a potential limitation to its wider use. However, hydroxyurea is a standard therapy in high-risk patients with polycythemia vera, and the leukemogenic risk of hydroxyurea in the long term is low, though the issue is controversial.^{12,21}

Some limitations of our study should be acknowledged. A significant result was obtained even though the study was closed before its planned end. Nevertheless, a higher-than-expected benefit was noted in the low-hematocrit group. The main study findings were consistent with those obtained in the prespecified subgroups. Not unexpectedly for a pragmatic trial in clinical practice that tested the efficacy of different therapeutic targets,^{22,23} not all patients were maintained at the assigned hematocrit target. However, the intention-to-treat analysis showed positive results despite the variability.

In conclusion, among patients with polycythemia vera, maintaining a hematocrit target of less than 45%, as compared with a target of 45 to 50%, was associated with a significantly lower rate of thrombotic complications without an increase in serious treatment complications.

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APPENDIX

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