

Vascular and Neoplastic Risk in a Large Cohort of Patients With Polycythemia Vera

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The European Collaboration on Low-Dose Aspirin in Polycythemia Vera Investigators are listed in the Appendix.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

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A B S T R A C T

Purpose

The clinical course of polycythemia vera is often complicated by thrombosis as well as by the possible transition to myeloid metaplasia with myelofibrosis or acute myeloid leukemia. The aim of this study was to assess the rate of these complications in subjects receiving currently recommended treatments.

Patients and Methods

Overall, 1,638 patients from 12 countries were enrolled onto a large, prospective multicenter project aimed at describing the clinical history of polycythemia vera for the following outcomes: survival, the cumulative rate of cardiovascular death and thrombosis, the cumulative rate of leukemia, myelodysplasia, and myelofibrosis. The mean duration of the disease at entry and the duration of the follow-up were 4.9 and 2.7 years, respectively.

Results

The overall mortality rate of 3.7 deaths per 100 persons per year resulted from a moderate risk of cardiovascular death and a high risk of death from noncardiovascular causes (mainly hematologic transformations). Age older than 65 years and a positive history of thrombosis were the most important predictors of cardiovascular events. Antiplatelet therapy, but not cytoreductive treatment, was significantly associated with a lower risk of cardiovascular events. We found a consistent association between age and risk of leukemia, and between duration of the disease with risk of myelofibrosis.

Conclusion

The European Collaboration on Low-Dose Aspirin in Polycythemia Vera study documents that large international collaborative studies are feasible in this field, in which few epidemiologic data are available. The persistently high mortality rate from hematologic malignancies characterizes the unmet therapeutic need of polycythemic patients and suggests a priority for future studies in this disease.

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INTRODUCTION

Polycythemia vera (PV) is a chronic myeloproliferative disorder marked by a predisposition to arterial and venous thrombosis, myeloid metaplasia with myelofibrosis, and acute myeloid leukemia.^{1,2} Early studies in untreated patients found a high thrombosis incidence and a median survival of 18 months.³ Phlebotomy and cytoreductive treatment by chemotherapy have reduced

the number of thrombotic complications and have substantially improved survival. However, clinical studies have not provided adequate information for identifying an optimal treatment strategy for these patients. The Polycythemia Vera Study Group (PVSG) 01 trial found the use of chlorambucil and, to a lesser extent, ³²P, to be associated with a high leukemogenic risk, while, on the other hand, phlebotomy was less protective against thrombosis.⁴ Hydroxyurea,

alone or in association with phlebotomy, has never been tested in trials of adequate size and duration. Although the long-term safety of hydroxyurea has been questioned by some reports,^{5,6} its use increased during the last two decades and is currently the most used chemotherapeutic agent.⁷ More generally, while important progress has been made in the understanding of the basic biologic characteristics of the disease, resulting in innovative diagnostic criteria for PV,^{1,2,5} relatively little effort has been made in evaluating existing or new treatment options and in describing the clinical epidemiology and the mid- to long-term prognosis of this disease.

A cohort of 1,638 PV patients, who were screened for inclusion in the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) trial, was monitored prospectively to provide the profile of the disease as it is determined by the current clinical practice of a sample of specialized clinical centers across several European countries and to characterize the presently unmet therapeutic need of polycythemic patients.⁸⁻¹²

PATIENTS AND METHODS

Study Design

To assure a representative sample of the spectrum of the disease burden of the participating centers,¹⁰ all patients with new and old diagnoses of PV (made according to the criteria established by the PVSG¹ or by Pearson et al⁵) were included in a prospective study with no exclusion criteria with respect to age, therapy, or duration of disease. Treatment strategies had to comply with the recommendation of maintaining the hematocrit value at less than 0.45 and the platelet count at less than $400 \times 10^9/L$. Data regarding clinical outcomes, treatments, and laboratory values during the prospective follow-up were recorded at follow-up visits at 12, 24, 36, 48, and 60 months.

The study protocol conformed to good clinical practices and to the Declaration of Helsinki on medical research in humans.

At the time of study closure, the mean (\pm standard deviation) follow-up was 2.7 ± 1.3 years (4,393 person-years; maximum follow-up, 5.3 years).

Definition of Outcome Events

We examined survival, the cumulative rate of cardiovascular (CV) death and arterial and venous thrombosis, non-CV deaths, and the cumulative rate of hematologic transformation (leukemia, myelodysplasia, and myelofibrosis). The category of CV death included: documented diagnosis of myocardial infarction or stroke in the absence of any other evident cause, sudden death, death from heart failure, and all deaths classified as being CV in nature. Myocardial infarction was defined as at least two of the following: chest pain of typical intensity and duration; ST segment elevation or depression of 1 mm or more in any limb lead of the ECG, of 2 mm or more in any precordial lead, or both; or at least a doubling in cardiac enzymes. Diagnosis of stroke required unequivocal signs or symptoms of a neurologic deficit, with sudden onset and duration of more than 24 hours. Diagnosis had to be confirmed by computed tomography, magnetic resonance imaging, or other objective means, or by autopsy. A transient ischemic attack was defined as the abrupt onset of unilateral motor or sensory disturbance, speech defect, homonymous

hemianopsia, constructional apraxia, or transient monocular blindness that resolved completely in less than 24 hours. Pulmonary embolism was defined by a positive pulmonary angiogram, a high-probability ventilation-perfusion scan, or evidence of pulmonary embolism at necropsy. Deep vein thrombosis (DVT) was defined as a typical clinical picture with positive instrumental investigation (phlebography, ultrasonography, impedance plethysmography, and computed tomography at unusual sites). In the case of a suspected recurrence in a site of previous DVT, the diagnosis could be accepted if the instrumental test showed extension or recurrence of thrombosis as compared with previous testing.

Diagnosis and classification of leukemia and myelodysplasia were established using the French-American-British (FAB) Cooperative Group criteria.^{13,14} Myelofibrosis was defined as the development of a leukoerythroblastic blood picture, in the presence of splenomegaly, corroborated with a bone marrow biopsy showing diffuse bone marrow fibrosis.

The validation of causes of death, and thrombotic and hemorrhagic events was ensured by an ad hoc committee of expert clinicians. Each event was validated independently by two evaluators, and disagreement between the evaluators was assessed by the chairperson of the study. Events included in composite outcome measures were managed hierarchically (ie, we first looked at information on vital status, and if the patient was alive at the end of the study, we assessed whether a nonfatal event had occurred).

Statistical Methods

Survival and event-free survival were evaluated by fitting various Cox's regression models adjusted for the confounding effect of the following potential confounders: (1) baseline characteristics: age, sex, time from diagnosis to enrollment, previous arterial or venous thrombotic event, and previous bleeding episode; (2) indicators of risk factors and CV morbidity: left ventricular dysfunction (New York Heart Association class), angina pectoris (Canadian Angina Classification class), previous revascularization procedure (angioplasty or coronary artery bypass graft), smoking habits, history of diabetes mellitus, arterial hypertension, and total blood cholesterol; (3) hematologic parameters at 12 months: packed cell volume (PCV), and platelet and leukocyte count; (4) type of cytoreductive treatment at baseline: venesection,³²P, hydroxyurea, busulfan, chlorambucil, pipobroman, and interferon; and (5) antiplatelet or anticoagulant treatment.

Differences in proportions were ascertained by χ^2 tests. Survival and event-free survival were compared by Kaplan-Meier cumulative incidence plots. All *P* values are two-sided. All analyses were done using the SAS statistical package (SAS Institute Inc, Cary, NC).

RESULTS

Clinical Characteristics at Baseline

The study involved 94 hematologic centers from 12 countries that recruited 1,638 polycythemic patients. Approximately one third of these patients who had no clear indication or contraindication to aspirin treatment were entered onto a placebo-controlled randomized trial to assess the efficacy and safety of low-dose aspirin.⁸

The characteristics of the cohort recruited is presented in detail in Table 1 and reflects well the mix of epidemiologic and clinical features that are found in the routine

Table 1. Baseline Characteristics in 1,638 Patients With Polycythemia Vera

	Patients	
	No.	%
Demographics		
Age at recruitment, years		
Mean		65.4
SD		12.7
Males	942	57.5
Body mass index, kg/m ²		
Mean		25.4
SD		3.7
Age at diagnosis, years		
Mean		60.4
SD		13.2
Years from diagnosis to enrollment		
0-2	581	35.5
3-5	434	26.5
6-10	387	23.6
> 10	236	14.4
Prior cardiovascular events		
Prior thrombosis	633	38.6
Prior arterial thrombosis	470	28.7
AMI	146	8.9
Stroke	145	8.9
TIA	169	10.3
Peripheral	90	5.5
Prior venous thrombosis	225	13.7
Deep vein thrombosis	134	8.2
Pulmonary embolism	39	2.4
Superficial thrombophlebitis	100	6.1
Erythromelalgia	86	5.3
Intermittent claudication	77	4.7
Prior bleeding	133	8.1
Packed cell volume (L/L)		
Mean		0.47
SD		0.06
Packed cell volume (L/L)		
≤ 0.45	556	38.9
46-50	530	37.0
> 50	345	24.1
Platelet count (× 10 ⁹ /L)		
Mean		398
SD		208
WBC count (× 10 ⁹ /L)		
Mean		10.9
SD		8.6
Cardiovascular risk factors		
Hypertension	647	39.5
High blood cholesterol	58	3.5
Diabetes mellitus	116	7.1
Current smokers	209	12.8
Congestive heart failure	129	7.9
Angina pectoris	119	7.3
Myocardial revascularization procedures	40	2.4
Antiplatelet drugs	955	58.3
Anticoagulants	110	6.7

Table 1. Baseline Characteristics in 1,638 Patients With Polycythemia Vera (continued)

	Patients	
	No.	%
Cytoreductive treatments		
Phlebotomy	1,040	63.5
Any cytoreductive drug	1,009	61.6
Hydroxyurea	793	48.4
Pipobroman	106	6.5
Interferon	64	3.9
Busulphan	61	3.7
p ³²	44	2.7
Chlorambucil	5	0.3
Cardiovascular drugs		
ACE-inhibitors	315	19.2
Calcium antagonists	288	17.6
Diuretics	230	14.0
Beta-blockers	197	12.0
Nitrates	110	6.7
Digitalis	81	5.0
Cholesterol-lowering drugs	46	2.8

Abbreviations: SD, standard deviation; AMI, acute myocardial infarction; TIA, transient ischemic attack; ACE, angiotensin converting enzyme.

practice of care of PV. Against a mean age at recruitment of 65 years, the duration and the history of the disease before recruitment in the study and the start of the prospective follow-up were varied: up to 38% of the cases were diagnosed more than 5 years before inclusion in the study, and 633 patients (38.6%) had a positive history of thrombotic events. Arterial and venous thrombosis accounted for about three quarters and one quarter of previous thromboses, respectively. Ischemic stroke and transient ischemic attacks accounted for two thirds of arterial thromboses, while DVT and superficial phlebitis represented approximately 60% and 40% of vein thromboses. The temporal association of these thromboses with diagnosis of PV is shown in Figure 1. A positive history of bleeding was present in 8.1% of patients (gastrointestinal, 4.1%; intracranial, 0.7%; minor bleeding, 3.3%). The most prevalent CV risk factors were arterial hypertension (39.5%) and cigarette smoking (12.8%), while hypercholesterolemia was diagnosed in only 3.5% of subjects.

The proportion of patients within the target recommended value of hematocrit ≤ 0.45 L/L at baseline was approximately 40% (38.9% overall, 43.5% after excluding patients with diagnosis of PV in the year before recruitment to avoid the influence of pretreatment values). Correspondingly, at 12 months, considering this value as an indicator of the control of the disease during the course of the study, 47.9% of patients were maintained at the target PCV of less than 0.45 L/L, while 39.2% and 12.9% had values between 0.45 L/L and 0.50 L/L, and greater than 0.50 L/L, respectively. Platelet count was 398 × 10⁹/L at baseline, and 36.5% of patients had levels higher than 400 × 10⁹/L at 12 months.

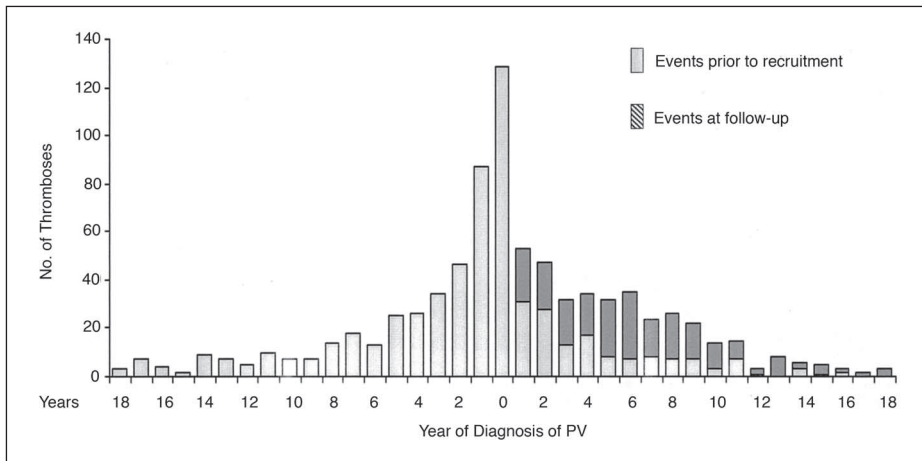


Fig 1. Temporal association of all thrombotic events registered in the entire cohort (prior thrombotoses and events at follow-up) with the time of diagnosis of polycythemia vera (PV).

At the time of recruitment, 28.4% of patients were managed by phlebotomy alone; 26.5%, by chemotherapeutic agents alone; and 35.1%, by phlebotomy plus chemotherapeutic agents. Antiplatelet therapy was being administered to 58% of PV patients. Among patients treated with cytoreductive drugs, hydroxyurea was by far the agent most frequently prescribed (Table 1).

The five national networks that recruited the most patients in the study were located in Italy (64%), Sweden (12%), Austria (8%), Spain (4%), and Israel (4%). A certain degree of variability in clinical characteristics was observed across countries (eg, lower age at recruitment in Italy and Austria, and a positive history of thrombosis was more frequent among Austrian patients). A large variability in treatment practices was apparent across the five countries. For instance, in Israel, 74.6% of patients were prescribed hydroxyurea, almost as the only cytoreductive drug, and only 47.5% were venesected, as compared with Austria, where the opposite approach was preferred, with 77.4% of patients using phlebotomy; 18.1%, interferon; and only 33.8%, hydroxyurea. As to control of the disease, the recommended PCV value of less than 0.45 L/L was recorded at baseline in 34.9% and 59.3% of patients from Italy and Sweden, respectively. Patients with PCV greater than 0.50 L/L at baseline varied from 9% in Austria to 43% in Spain.

Analysis of Survival

Table 2 provides the comprehensive descriptive profile of the outcomes of the study cohort throughout the 4,390 person-years of prospective observations (median, 2.8 years; 25th percentile, 1.9 years; 75th percentile, 3.8 years). A total of 164 deaths (10%) were recorded for an overall mortality rate of 3.7 deaths per 100 persons per year, with no major overall differences between men and women (the lower mortality rate of men in the younger than 65 years age group [1.7 v 2.3 per 100 persons per year] was paralleled by a lower rate for women in the older age group [6.1 v 7.3 per 100 persons per year]).

The incidence rates of CV and non-CV mortality were 1.7 and 1.8 deaths per 100 persons per year, respectively. CV mortality accounted for 45% of all deaths, while hematologic transformation and solid tumors were the cause of death in 13% and 19.5% of fatal cases, respectively.

Table 3 shows the results of the multivariate analysis adjusted for a number of potential confounders. Age older than 65 years (hazard ratio, 14.26; 95% CI, 4.48 to 45.33; *P* < .0001) and positive history of thrombotic events (hazard ratio, 1.93; 95% CI, 1.36 to 2.74; *P* = .0003), but not disease duration longer than 2 years (hazard ratio, 1.09; 95% CI, 0.74 to 1.60; *P* = .6544), were significantly associated with mortality.

Analysis of CV Event-Free Survival

The cumulative rate of CV events (CV death and non-fatal thrombotic events) was 5.5 events per 100 persons per year. As for nonfatal CV events, patients had similar rates of arterial and venous thrombotic events. The incidence of myocardial infarction was lower (0.3 events per 100 persons per year) than that of stroke (0.5 events per 100 persons per year). The cumulative rate of total thrombotic cerebrovascular events was remarkably high (1.4 events per 100 persons per year).

The results of the multivariate analysis adjusted for a number of potential confounders confirmed that age and history of thrombosis were the two most important prognostic indicators of CV events (Table 3). Thrombotic events before recruitment, regardless their occurrence before, at, or after the diagnosis of PV, were found to be a strong predictive factor for new thrombotic events during follow-up. Based on age and history of thrombosis, we could identify three groups at different risk of CV events, ranging from 2.5 (age < 65 years and no prior thrombosis) to 10.9 events per 100 persons per year (age ≥ 65 years and prior thrombosis). Patients younger than 65 years with positive history of thrombosis and those ≥ 65 years without prior

Table 2. Main Outcome Events During Follow-Up in 1,638 Patients With Polycythemia Vera

	Patients	
	No.	%
All causes of mortality	164	10.0
Cardiovascular death	74	4.5
Cardiac death	43	2.6
Coronary heart disease	25	1.5
Congestive heart failure	13	0.8
Other cardiac disease	5	0.3
Vascular death	31	1.9
Nonhemorrhagic stroke	13	0.8
Pulmonary embolism	6	0.4
Intracranial hemorrhage	2	0.1
Other hemorrhage	5	0.3
Other vascular death	5	0.3
Noncardiovascular death	79	4.8
Cancer	54	3.3
Hematologic transformation*	22	1.3
Solid tumors†	32	2.0
Other noncardiovascular causes	25	1.5
Unknown cause of death	11	0.7
Fatal + nonfatal cardiovascular events	226	13.8
Nonfatal thrombotic events	169	10.3
Arterial thrombosis	87	5.3
Myocardial infarction	14	0.9
Stroke	23	1.4
Transient ischemic attack	33	2.0
Peripheral arterial thrombosis	20	1.2
Venous thrombosis	88	5.4
Deep vein thrombosis	38	2.3
Pulmonary embolism	13	0.8
Superficial thrombophlebitis	46	2.8
Hematological transformation and cancer	130	7.9
Hematologic transformation	57	3.5
Acute leukemia	21	1.3
Myelodysplasia	1	0.1
Myelofibrosis	38	2.3
Other hematologic malignancy	3	0.2
Myeloma	1	0.1
Lymphoma	2	0.1
Solid tumors	71	4.3

NOTE. Patients with two or more events of different types can appear more than once in columns but only once in rows.
*Twenty-one cases of acute leukemia and one myelofibrosis.
†One case of myeloma.

thrombosis had similar, intermediate rates of CV events (4.9 and 5.0 events per 100 persons per year; Fig 2).

Antiplatelet therapy was significantly associated with a lower risk of CV events (hazard ratio, 0.72; 95% CI, 0.53 to 0.97; $P = .0315$), while no clear association was found between CV events and phlebotomy or pharmacologic cytoreductive treatments (Table 3).

The rates of total and major bleeding were 2.9 and 0.8 events per 100 persons per year, respectively. Age, disease duration, and history of bleeding, but not antiplatelet treatment at baseline, were associated with the risk of total

bleeding during follow-up. Only the history of previous bleeding was correlated with subsequent major bleeding (data not shown).

Analysis of Hematologic Transformation and Malignancy

The rates of total malignancy, hematologic transformation, and non-PV-related cancers were 3.0, 1.3, and 1.7 per 100 persons per year, respectively.

The results of the multivariate analyses showed different prognostic indicators for myelofibrosis and leukemia (Table 4). A long disease duration predicted the risk of developing myelofibrosis (for disease duration > 10 years: hazard ratio, 15.24; 95% CI, 4.22 to 55.06; $P < .0001$). For leukemia, although patients with long disease duration had a higher crude incidence rate (0.34 v 1.1 per 100 persons per year for patients with disease durations of < 5 years and > 10 years, respectively), when adjusting for all the potential confounders in the multivariate analysis, disease duration did not reach statistical significance. On the other side, age and some treatments seem to be stronger independent risk factors. Age ≥ 70 years was significantly associated with an increased risk of leukemia (hazard ratio, 4.99; 95% CI, 1.19 to 21.04; $P = .0283$), as was the use of cytoreductive drugs other than hydroxyurea and interferon at recruitment (hazard ratio, 10.99; 95% CI, 2.85 to 42.33; $P = .0005$). Acute leukemia constituted 8.2% and 34.5% of deaths among patients receiving hydroxyurea as the only cytoreductive agent and any other drug (excluding interferon alone), respectively.

DISCUSSION

As a large prospective cohort recruited and followed up in a qualified network of hematologic centers with the same criteria of a clinical trial, the ECLAP study provides an accurate description of the current clinical course of PV. Moreover, it demonstrates that large international collaborative studies are feasible in the field of rare diseases.

Few epidemiologic studies have been conducted in recent years to evaluate at which extent current therapeutic strategies influence the prognosis of the disease. According to the data obtained from such studies, the prognosis of PV patients is much better than that reported in the first descriptions of the disorder, when the median survival was less than 4 years in patients treated with nonaggressive venesection³ or after the introduction of P³² as the main treatment of the disease,¹⁵ but substantially stable survival has been achieved in the last 20 years after the introduction of the nonalkylating agents.^{11,16-18}

The overall mortality rate in our study was 3.7 deaths per 100 persons per year, and the age- and sex-standardized comparison of PV patients recruited in Italy with the Italian

Vascular/Neoplastic Risk in Polycythemia Vera

Table 3. Major Prognostic Indicators of Death and Cardiovascular Events in 1,638 Patients With Polycythemia Vera

	All Causes of Death		Cardiovascular Events	
	Relative Risk	95% CI	Relative Risk	95% CI
Age at recruitment, years				
< 55	1.00		1.00	
55-65	4.28	1.25 to 14.64	1.43	0.83 to 2.46
66-75	11.07	3.44 to 35.64	2.08	1.25 to 3.45
> 75	21.20	6.56 to 68.55	2.90	1.71 to 4.89
Disease duration, years				
0-2	1.00		1.00	
3-4	1.06	0.64 to 1.74	1.25	0.85 to 1.84
5-6	1.23	0.75 to 2.00	1.34	0.90 to 2.01
6-10	1.03	0.62 to 1.69	1.20	0.80 to 1.78
> 10	1.21	0.72 to 2.04	0.84	0.53 to 1.34
Previous thrombosis	1.93	1.36 to 2.74	2.09	1.55 to 2.81
Phlebotomy	0.75	0.53 to 1.04	0.89	0.67 to 1.18
Antiplatelet therapy	0.77	0.54 to 1.11	0.72	0.53 to 0.97
No cytoreductive drugs, or interferon alone	1.00		1.00	
Hydroxyurea alone	0.95	0.66 to 1.37	1.04	0.77 to 1.41
Other cytoreductive drugs	1.26	0.79 to 2.00	1.01	0.67 to 1.53

mortality rates in the year 2000 allowed us to calculate that the rates of total mortality and mortality from CV disease and leukemia of PV patients were 1.2, 1.4, and 36.1 times higher than those expected in the general population. These data support a representation of PV as a disease with an increased mortality, with an intermediate risk profile for CV deaths (< 65 and ≥ 65 years of age: 0.4 and 2.7 CV deaths per 100 persons per year, respectively), and with a significant contribution of acute leukemia to overall death.

Age older than 65 years and a previous history of thrombosis were the two most important prognostic factors and allowed identification of three groups of PV patients at progressively increasing risk of CV events, as depicted in Figure 2.

Antiplatelet drugs, anticoagulants, phlebotomy, and pharmacologic cytoreduction were used in 58%, 6.7%, 64%, and 62% of patients, respectively. In patients receiving antiplatelet treatment, there was a 32% lower rate of CV events. This observation in a cohort that included almost 40% of patients with prior history of thrombosis (Table 3) is highly consistent with the finding of the protective effects of aspirin in lower-risk patients randomly assigned to aspirin or placebo in the trial component of ECLAP⁸ and provides further support to the indication of aspirin as an effective antithrombotic agent in this disease.^{19,20}

On the other side, subjects with PV are patients at high risk of thrombosis, irrespective to the presence of the classical CV risk factors. Therefore, in this cohort, the high prevalence of these risk factors such as hypertension (40%) and cigarette smoking (13%) calls for increased attention of physicians to seriously consider as a supplement to pharmacologic treatment, the control of the classical CV comorbidities in these patients.

Clear and consistent associations of age with the risk of leukemia and of disease duration with the risk of myelofibrosis were observed. There was a higher incidence of leukemia in the heterogeneous subgroup of patients exposed to pharmacologic cytoreductive treatments other than hydroxyurea and interferon. This finding needs to be interpreted with caution, inasmuch as observational studies cannot provide unequivocal interpretation of the

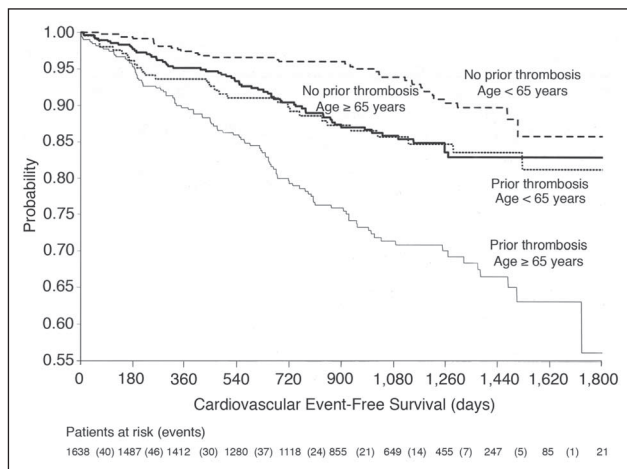


Fig 2. Cardiovascular event-free survival of 1,638 patients with polycythemia vera according to age and history of thrombosis. Age < 65 years without prior thrombosis: 2.5 events/100 persons/year; age ≥ 65 years without prior thrombosis: 4.9 events/100 persons/year (hazard ratio [HR], 1.96; 95% CI, 1.29 to 2.97; *P* = .0017); age < 65 years with prior thrombosis: 5.0 events/100 persons/year (HR, 2.00; 95% CI, 1.22 to 3.29; *P* = .0061); age ≥ 65 years with prior thrombosis: 10.9 events/100 persons/year (HR, 4.35; 95% CI, 2.95 to 6.41; *P* < .0001).

Table 4. Multivariate Analysis of Prognostic Indicators of Leukemia/Myelodysplasia, and Myelofibrosis in 1,638 Patients With Polycythemia Vera

	Leukemia/Myelodysplasia		Myelofibrosis	
	Relative Risk	95% CI	Relative Risk	95% CI
Age at recruitment, years				
< 60	1.00		1.00	
60-70	1.32	0.25 to 6.97	1.98	0.82 to 4.79
> 70	4.99	1.19 to 21.04	0.73	0.27 to 2.03
Disease duration, years				
0-2	1.00		1.00	
3-4	0.26	0.03 to 2.48	2.87	0.67 to 12.24
5-6	1.05	0.23 to 4.75	2.22	0.43 to 11.42
6-10	1.26	0.27 to 5.78	5.74	1.51 to 21.77
> 10	1.79	0.44 to 7.34	15.24	4.22 to 55.06
Phlebotomy	1.33	0.48 to 3.68	1.51	0.72 to 3.15
No cytoreductive drugs, or interferon alone	1.00		1.00	
Hydroxyurea alone	1.58	0.40 to 6.21	0.70	0.33 to 1.47
Other cytoreductive drugs	10.99	2.85 to 42.33	0.51	0.18 to 1.47

relationship between exposure to a particular treatment and outcomes, because of the confounding effect of indication bias.² The strong association between the duration of disease and long-term administration of cytoreductive therapy, as well as the tendency to adopt a more aggressive treatment in patients perceived to be at high risk, reflect the so-called work-up bias, and therefore do not allow easy discrimination between the risk of hematologic transformation due to the natural evolution of the disease, and that due to aggressive long-term pharmacologic cytoreduction. This problem was identified more than 50 years ago by W. Dameshek when he wrote that “it is difficult to state what the normal course of the disease would be without the various therapeutic methods which undoubtedly influence it.”²¹ The discrimination between the amount of risk of hematologic transformation intrinsic to the disease, and that due to the use of potentially leukemogenic cytoreductive drugs can be only obtained by large-scale clinical trials.¹²

The variability of the practices found in different countries confirms the results of a recent survey conducted by the American Society of Hematology and reflects possibly also the ongoing debate on the yield and the biologic background of a strict control of hematocrit values.^{22,23} Inadequate hematocrit reduction, the fear of hematologic transformation possibly associated with aggressive pharmacologic cytoreduction, and the lack of convincing evidence on the benefit of strict hematocrit control, are all possible explanations for such uncertainty.

While the results of the ECLAP trial⁸ indicate that aspirin is an effective and safe antithrombotic agent in patients with PV, the main findings of the observational study are (1) the unfavorable prognosis in terms of hematologic malignancies, (2) the clinical importance of therapeutic needs that can be adequately met in terms of efficacy

and safety with clinical trials, and (3) the feasibility of collaborative research in this disease.

Appendix

Principal ECLAP Investigators (recruiting 40 or more patients in the study)

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