

ORIGINAL ARTICLE

Efficacy and Safety of Low-Dose Aspirin in Polycythemia Vera

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ABSTRACT

BACKGROUND

The use of aspirin for the prevention of thrombotic complications in polycythemia vera is controversial.

METHODS

We enrolled 518 patients with polycythemia vera, no clear indication for aspirin treatment, and no contraindication to such treatment in a double-blind, placebo-controlled, randomized trial to assess the safety and efficacy of prophylaxis with low-dose aspirin (100 mg daily). The two primary end points were the cumulative rate of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes and the cumulative rate of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes. The mean duration of follow-up was about three years.

RESULTS

Treatment with aspirin, as compared with placebo, reduced the risk of the combined end point of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes (relative risk, 0.41; 95 percent confidence interval, 0.15 to 1.15; $P=0.09$) and the risk of the combined end point of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes (relative risk, 0.40; 95 percent confidence interval, 0.18 to 0.91; $P=0.03$). Overall mortality and cardiovascular mortality were not reduced significantly. The incidence of major bleeding episodes was not significantly increased in the aspirin group (relative risk, 1.62; 95 percent confidence interval, 0.27 to 9.71).

CONCLUSIONS

Low-dose aspirin can safely prevent thrombotic complications in patients with polycythemia vera who have no contraindications to such treatment.

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POLYCYTHEMIA VERA IS A CHRONIC disorder in which the clonal proliferation of hematopoietic precursors progressively increases the red-cell mass.¹ This expansion causes hyperviscosity of the blood, a major determinant of circulatory disturbances in patients with polycythemia vera.² Since thrombotic complications are a major cause of illness and death in untreated patients,^{3,4} chemotherapy and phlebotomy are often used in patients who are at high risk for thrombotic events.⁵

The efficacy and safety of antithrombotic drugs in patients with polycythemia vera are uncertain. Aspirin has long been avoided, because a trial conducted by the Polycythemia Vera Study Group reported a high incidence of gastrointestinal bleeding in patients who received a high dose of aspirin (900 mg daily).⁶ Recently, however, the use of aspirin in patients with polycythemia vera has been reconsidered, mainly because of its antithrombotic effects and evidence that the optimal benefit of aspirin can be achieved at doses considerably lower than the 900-mg daily dose that the study group tested.⁷

The increase in thromboxane synthesis that occurs in polycythemia vera⁸ suggests that thromboxane-dependent platelet activation is a major contributor to the increased risk of thrombosis among patients with the disease. In a pilot study, we found that low-dose aspirin effectively suppresses the production of thromboxane by platelets in patients with high platelet counts and is well tolerated.⁹ We now report the results of a multicenter trial of low-dose aspirin in patients with polycythemia, the European Collaboration on Low-Dose Aspirin in Polycythemia Vera (ECLAP) study.

METHODS

INTERNATIONAL NETWORK

A network of 94 hematologic centers in 12 countries was developed.¹⁰ The centers in each participating country were led by a national coordinator. The international coordinating center in Italy (Conorzio Mario Negri Sud) received all data forms and developed a centralized data base.

Of the 1638 patients included in the ECLAP project, 1120 were entered into a prospective, observational cohort study, and the other 518 (32 percent) were enrolled in our double-blind, placebo-controlled, randomized trial to assess the efficacy and safety of low-dose aspirin (100 mg daily in an enter-

ic-coated formulation [Bayer]). The main reasons for excluding patients in the ECLAP project from this aspirin trial were an indication for antithrombotic therapy (742 patients [66 percent]), a contraindication to aspirin therapy (271 patients [24 percent]), and the patient's unwillingness to participate (197 patients [18 percent]).

STUDY PATIENTS

Polycythemia vera was diagnosed on the basis of standard clinical and laboratory findings and criteria that have been described elsewhere.¹⁰ Patients were eligible if they had no clear indication for aspirin treatment and no clear contraindication to it, were able to provide written informed consent, and had no clinically significant coexisting conditions. There were no age limits.

A double-blind, placebo-controlled design was used. A total of 253 patients were randomly assigned to receive aspirin (100 mg daily), and 265 were randomly assigned to receive placebo. Randomization was centralized and was performed over the telephone. Patients were assigned to treatments with the use of a program based on the biased-coin algorithm, which allowed for stratification according to center. All patients who were recruited received other recommended treatments: phlebotomy, cytoreductive drugs, and standard cardiovascular drugs were given as required.

Data collection was recorded at follow-up visits at 12, 24, 36, 48, and 60 months. Compliance was monitored with the use of counts of aspirin or placebo pills and through attendance at follow-up visits.

STUDY END POINTS

The study had two primary combined efficacy end points: the cumulative rate of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes and the cumulative rate of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes. The secondary end points were fatal or nonfatal cerebrovascular events, fatal or nonfatal cardiac events, minor thrombotic complications (including atypical cerebral or visual symptoms of ischemia, erythromelalgia, and thrombophlebitis), and major and minor thrombotic complications as defined above. Additional analyses were performed for each component of the primary end points and for the main causes of death.

The safety of low-dose aspirin was assessed by

Table 1. Base-Line Characteristics of the Patients with Polycythemia Vera.*		
Characteristic	Aspirin Group (N=253)	Placebo Group (N=265)
Demographics		
Age at recruitment — yr	61.3±13.5	60.6±12.8
Male sex — no. (%)	154 (60.9)	154 (58.1)
Body-mass index†	25.5±3.5	25.7±3.6
Time between diagnosis and enrollment — no. (%)		
0–5 Yr	178 (70.4)	182 (68.7)
6–10 Yr	46 (18.2)	60 (22.6)
>10 Yr	29 (11.5)	23 (8.7)
Previous cardiovascular events — no. (%)		
Thrombosis	28 (11.1)	25 (9.4)
Arterial	12 (4.7)	11 (4.2)
Venous	20 (7.9)	16 (6.0)
Erythromelalgia	10 (4.0)	8 (3.0)
Hemorrhage	7 (2.8)	9 (3.4)
Hematologic values		
Hematocrit (%)	49±6	48±7
Median	48	47
Range (10th–90th percentile)	42–57	41–59
Red-cell count (×10 ³ mm ³)	5900±1300	5900±1300
Median	5900	6000
Range (10th–90th percentile)	4200–7500	4100–7700
White-cell count (per mm ³)	10,500±7300	11,000±10,600
Median	8800	8800
Range (10th–90th percentile)	5200–16,200	5600–16,200
Platelet count (per mm ³)	388,800±198,900	376,100±193,000
Median	339,000	329,000
Range (10th–90th percentile)	179,000–632,000	181,000–608,000
Cardiovascular risk factors — no. (%)		
Hypertension	86 (34.0)	94 (35.5)
High blood cholesterol level	5 (2.0)	7 (2.6)
Diabetes mellitus	12 (4.7)	23 (8.7)
Current smoking‡	30 (11.9)	51 (19.2)
Congestive heart failure	8 (3.2)	3 (1.1)
Cytoreductive therapy — no. (%)		
Phlebotomy	175 (69.2)	197 (74.3)
Any cytoreductive drug	149 (58.9)	145 (54.7)
³² P	7 (2.8)	9 (3.4)
Hydroxyurea	117 (46.2)	112 (42.3)
Busulfan	3 (1.2)	2 (0.8)
Chlorambucil	2 (0.8)	0
Pipobroman	15 (5.9)	13 (4.9)
Interferon alfa	10 (4.0)	15 (5.7)

Table 1. (Continued.)

Characteristic	Aspirin Group (N=253)	Placebo Group (N=265)
Cardiovascular drugs — no. (%)		
Calcium antagonists	31 (12.3)	36 (13.6)
Beta-blockers	20 (7.9)	26 (9.8)
Diuretics	30 (11.9)	30 (11.3)
ACE inhibitors	51 (20.2)	41 (15.5)
Digoxin‡	7 (2.8)	1 (0.4)
Nitrates	4 (1.6)	2 (0.8)
Cholesterol-lowering drugs	3 (1.2)	5 (1.9)

* Plus–minus values are means \pm SD. ACE denotes angiotensin-converting enzyme.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ P=0.03 for the comparison between groups.

analyzing rates of fatal and nonfatal major hemorrhage (any hemorrhage requiring transfusion, hospitalization, or both), minor hemorrhage, and any adverse event leading to the discontinuation of treatment.

DEFINITION OF EVENTS

Events were defined and classified according to the *International Classification of Diseases, Ninth Revision*. Death from cardiovascular causes included death after a documented diagnosis of myocardial infarction or stroke in the absence of any other evident cause, sudden death, death from heart failure, and any other death classified as having cardiovascular causes. Nonfatal acute myocardial infarction was defined by at least two of the following findings: chest pain of typical intensity and duration; ST-segment elevation or depression of 1 mm or more in any limb lead on electrocardiography, of 2 mm or more in any precordial lead, or both; and at least a doubling of the levels of cardiac enzymes.

A diagnosis of nonfatal stroke required unequivocal signs or symptoms of a neurologic deficit with sudden onset and a duration of more than 24 hours. The diagnosis had to be confirmed with the use of computed tomography (CT), magnetic resonance imaging, or other objective means or on autopsy. These criteria were also used for the diagnosis of fatal stroke. Alternatively, we used the diagnosis reported in the hospital records or on the death certificate. A transient ischemic attack was defined as the abrupt onset of unilateral motor or sensory disturbance, speech defect, homonymous hemianopia, constructional apraxia, or transient monocular

blindness (defined as the abrupt onset of a unilateral decrease in visual acuity involving a portion or the entirety of the visual field) that resolved completely in less than 24 hours.

Pulmonary embolism was defined by a positive pulmonary angiogram, a ventilation–perfusion scan or CT scan indicating a high probability of pulmonary embolism, or evidence of pulmonary embolism on autopsy. Deep venous thrombosis was defined by a typical clinical picture with positive results on investigation involving such techniques as phlebography, ultrasonography, impedance plethysmography, or CT.

The validation of the clinical events included in the primary end points was ensured by an ad hoc committee of expert clinicians who were unaware of the treatment-group assignments. Each event was validated independently by two evaluators, and disagreement between the evaluators was assessed by the chairman of the study.

The study protocol conformed to good clinical practice for trials and to the 2000 revision of the Declaration of Helsinki regarding medical research in humans. We obtained the approval of each local ethics committee before the start of the trial. All patients provided written informed consent. The study was conceived, conducted, and analyzed by the independent investigators under the aegis of the steering committee.

PLANNED SAMPLE SIZE AND EARLY TERMINATION

On the basis of the information that was available at the time the study was planned, the rate of events included in the first (more conservative) of the two

primary end points over a five-year follow-up period was estimated to be about 14 percent. To test for a beneficial effect of aspirin (a 30 percent rate reduction) at a convincing level of statistical significance (two-tailed $\alpha=0.05$, and $1-\beta=0.80$), we planned to recruit 940 patients per group.

After a planned interim safety analysis (in December 2000), the steering committee was informed that fewer centers than expected were recruiting effectively; that after the planned two years of recruitment, the rate of randomization was reduced to nearly zero; that an impractically long follow-up period would be required in order to accumulate the number of events needed to reach the predefined rate of end points; and that no additional support for the trial could be obtained. For these reasons, the study was stopped, and follow-up of the patients who had undergone randomization was completed during the next 12 months. These decisions were made with the advice and consent of the data and safety monitoring board and were communicated to the investigators, who were monitored to ensure that they conducted a final follow-up visit. We obtained updated follow-up information after September 1, 2001, for 92 percent of the patients who had undergone randomization, for a total duration of follow-up of 1478 person-years.

STATISTICAL ANALYSIS

Analyses were performed according to the intention-to-treat principle. We analyzed data with the use of Kaplan–Meier survival curves and the log-rank test. The efficacy of treatment was assessed by fitting base-line values for the risk-stratification variables into Cox regression models that were adjusted for the confounding effects of relevant prognostic indicators. Events included in the composite end points were analyzed hierarchically; that is, if the patient was alive at the end of the study, we determined whether a nonfatal event had occurred. We used the Kruskal–Wallis test for continuous variables. All reported P values are two-sided. All analyses were performed with the use of the SAS statistical software package (SAS Institute).

RESULTS

BASE-LINE CHARACTERISTICS OF THE PATIENTS

Table 1 summarizes the base-line demographic and clinical characteristics of the patients. A total of 26 percent of the patients were 70 years of age or older. There were significantly more current smokers in

the placebo group than in the aspirin group. The hematocrit was maintained at a median value of 46 percent during follow-up, with levels higher than 48 percent in 25 percent of patients. The platelet count was maintained at a median level of 321,000 per cubic millimeter during follow-up; 25 percent of patients had levels higher than 460,000 per cubic millimeter.

EFFICACY

Table 2 summarizes the thrombotic events in the two groups of patients. The 59 percent reduction in the risk of the combined primary end point of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes in the aspirin group, as compared with the placebo group, was not statistically significant, whereas the 60 percent decrease in the risk of the combined primary end point of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes was significant (95 percent confidence interval, 9 to 82 percent; $P=0.03$) (Fig. 1A and 1B).

Secondary analyses showed a significant reduction in the rate of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, deep venous thrombosis, or death from any cause (relative risk reduction, 53 percent; 95 percent confidence interval, 9 to 75; $P=0.02$) and reductions in the rates of minor thrombosis and any thrombosis, with relative risk reductions of 53 percent ($P=0.049$) and 58 percent ($P=0.003$), respectively (Table 2 and Fig. 2). The rates of major cerebrovascular events, nonhemorrhagic stroke, transient ischemic attack, peripheral thrombosis, deep venous thrombosis, and pulmonary embolism in the aspirin group were not significantly different from the rates of these complications in the placebo group.

The results of additional subgroup analyses confirmed the consistency of the effects of aspirin on the risk of death from cardiovascular causes and the risk of major arterial or venous thrombotic events among patients with various characteristics at base line (Fig. 3). All analyses were repeated with the use of multivariate models with adjustment for smoking status and the use or nonuse of digoxin or for major potential confounding factors (i.e., age, sex, duration of disease, smoking status, previous thrombotic and hemorrhagic events, digoxin use, hypertension, diabetes, congestive heart failure, angina pectoris, phlebotomy, and cytoreductive treatment). In the fully adjusted model, the rate of the combined

Table 2. Rates and Relative Risks of Major Study End Points in the Two Groups.*

End Point	Aspirin Group (N=253)	Placebo Group (N=265)	Relative Risk (95% CI)	P Value
	<i>no. (%)</i>			
Primary end points				
Nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes	5 (2.0)	13 (4.9)	0.41 (0.15–1.15)	0.09
Nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes	8 (3.2)	21 (7.9)	0.40 (0.18–0.91)	0.03
Secondary end points				
Nonfatal myocardial infarction, nonfatal stroke, or death from any cause	11 (4.3)	22 (8.3)	0.54 (0.26–1.11)	0.09
Nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, deep venous thrombosis, or death from any cause	13 (5.1)	29 (10.9)	0.47 (0.25–0.91)	0.02
Death from any cause	9 (3.6)	18 (6.8)	0.54 (0.24–1.20)	0.13
Death from cardiovascular causes	3 (1.2)	8 (3.0)	0.41 (0.11–1.53)	0.18
Cardiac	2 (0.8)	2 (0.8)	1.07 (0.15–7.58)	0.95
Acute myocardial infarction	1 (0.4)	1 (0.4)		
Other cardiac causes	1 (0.4)	1 (0.4)		
Vascular	1 (0.4)	6 (2.3)	0.18 (0.02–1.50)	0.11
Nonhemorrhagic stroke	0	4 (1.5)		
Intracranial hemorrhage	0	1 (0.4)		
Pulmonary embolism	0	1 (0.4)		
Other vascular causes	1 (0.4)	0		
Death from noncardiovascular causes	6 (2.4)	10 (3.8)	0.65 (0.24–1.79)	0.40
Major cerebrovascular events	3 (1.2)	10 (3.8)	0.32 (0.09–1.16)	0.08
Myocardial infarction	1 (0.4)	2 (0.8)	0.54 (0.09–23.57)	0.81
Major venous thrombosis	4 (1.6)	10 (3.8)	0.49 (0.13–1.78)	0.28
Deep venous thrombosis	2 (0.8)	6 (2.3)		
Pulmonary embolism	2 (0.8)	5 (1.9)		
Major or minor thrombosis	17 (6.7)	41 (15.5)	0.42 (0.24–0.74)	0.003
Minor thrombotic complications	10 (4.0)	22 (8.3)	0.47 (0.22–0.99)	0.049
Transient ischemic attack	4 (1.6)	9 (3.4)		
Peripheral arterial thrombosis	0	3 (1.1)		
Superficial venous thrombosis	2 (0.8)	6 (2.3)		
Erythromelalgia	4 (1.6)	5 (1.9)		

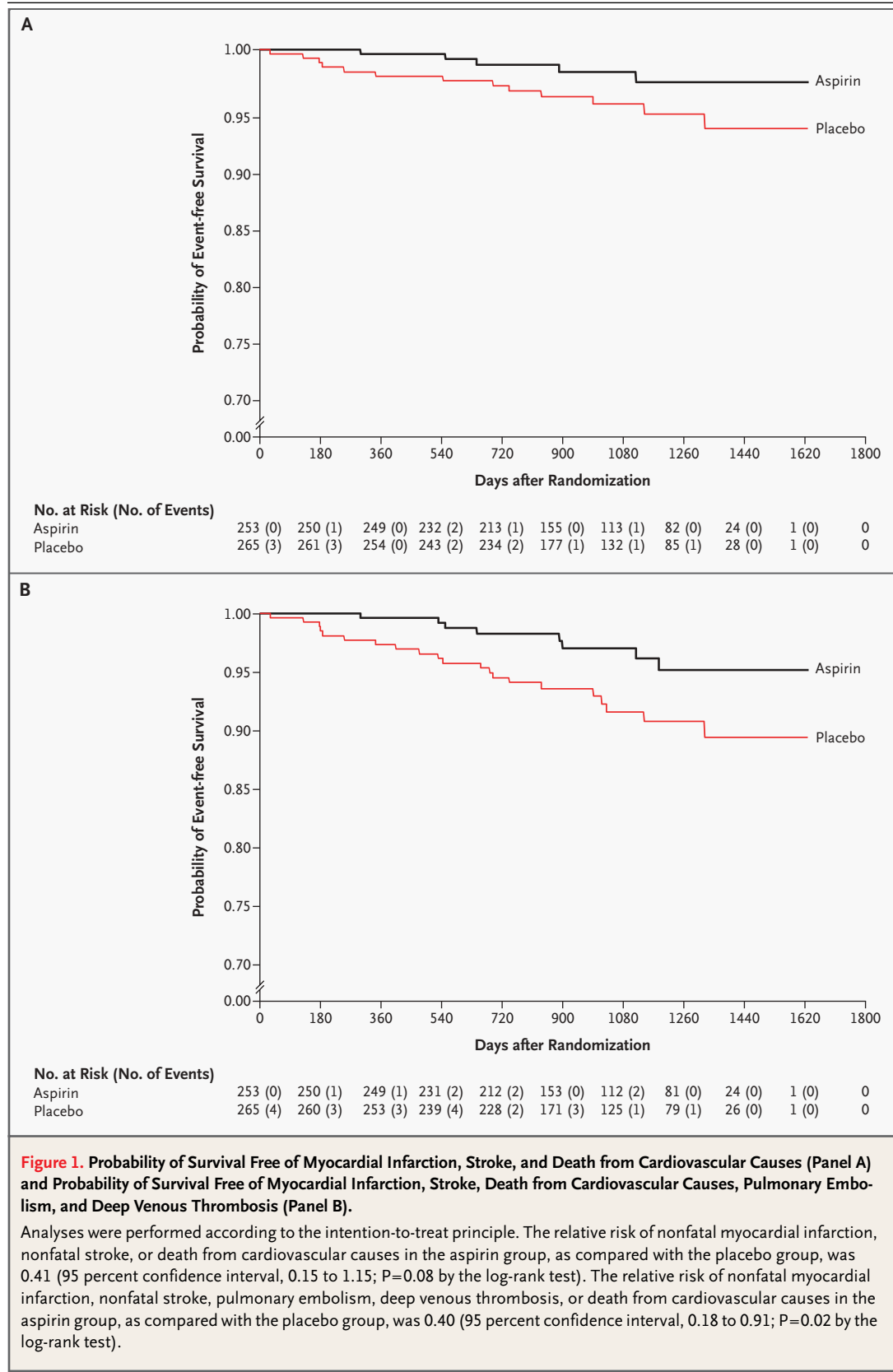
* Major cerebrovascular events include fatal and nonfatal stroke plus episodes of intracranial bleeding; minor thrombotic complications include transient ischemic attacks, superficial thrombophlebitis, peripheral arterial thrombosis, and erythromelalgia. Totals for categories may not equal the sum of the values for subcategories because some patients had more than one type of event. CI denotes confidence interval.

primary end point of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes was reduced by 77 percent ($P=0.02$) and the rate of the primary combined end point of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, deep venous thrombosis, or death from

cardiovascular causes was reduced by 71 percent ($P=0.008$).

SAFETY

Table 3 shows the rates and relative risks of episodes of bleeding in the two groups. In the aspirin



group, there were nonsignificant increases in the risks of any bleeding episode, a major bleeding episode, and a minor bleeding episode. Almost all the excess in the incidence of bleeding in the aspirin group was due to the 83 percent increase in the rate of minor bleeding episodes.

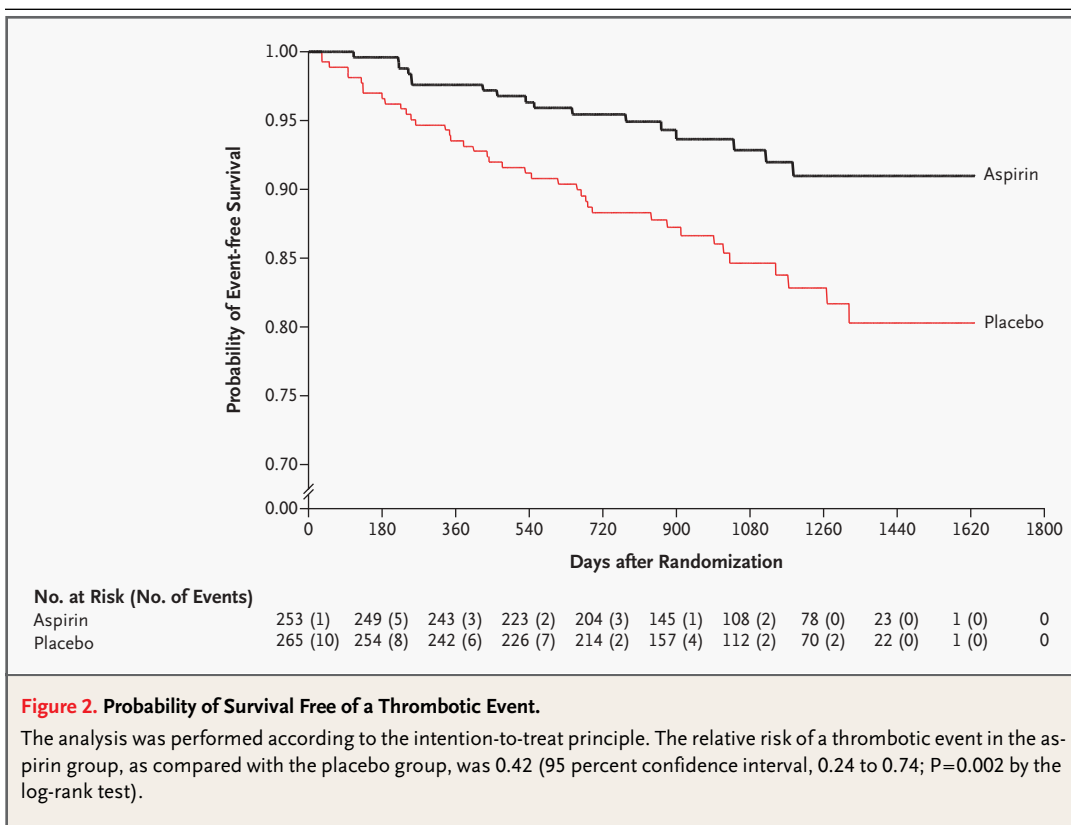
At the completion of the study, 24.5 percent of the patients in the aspirin group and 30.6 percent of those in the placebo group had stopped taking the study drug. Side effects were reported as the reason for the discontinuation of therapy in 7.1 percent of the patients in the aspirin group and 6.4 percent of those in the placebo group. Overall, gastrointestinal intolerance and bleeding were the most frequently reported side effects (reported in 2.8 percent and 4.4 percent, respectively, of the patients in the aspirin group and 4.5 percent and 1.5 percent, respectively, of the patients in the placebo group). Adverse events or side effects resulted in the discontinuation of use of the study drug in 28 patients in the aspirin group (11.1 percent) and in 27 patients in the placebo group (10.2 percent). There was no significant difference in the rate of any other adverse event.

DISCUSSION

The rationale for this trial was based on three considerations: the increased synthesis of platelet thromboxane in polycythemia,⁸ the fact that 100 mg of aspirin daily effectively suppresses this abnormality,⁸ and the finding in a preliminary trial involving patients with polycythemia that the prolonged administration of low-dose aspirin was well tolerated.⁹

The design of our study allowed us to exclude patients who were considered to have a clear indication for aspirin therapy. For this reason, we disqualified 45 percent of the potential enrollees, most of whom had a history of thrombosis. The patients who were enrolled had no contraindication to aspirin therapy, and most of them had no history of a thrombotic event. They account for about one third of the patients with polycythemia vera enrolled in our collaborative study of the disease. The present study can therefore be considered a primary prevention trial of aspirin in patients with polycythemia vera.

We had calculated that for such a study, a large sample or a very long duration of follow-up would



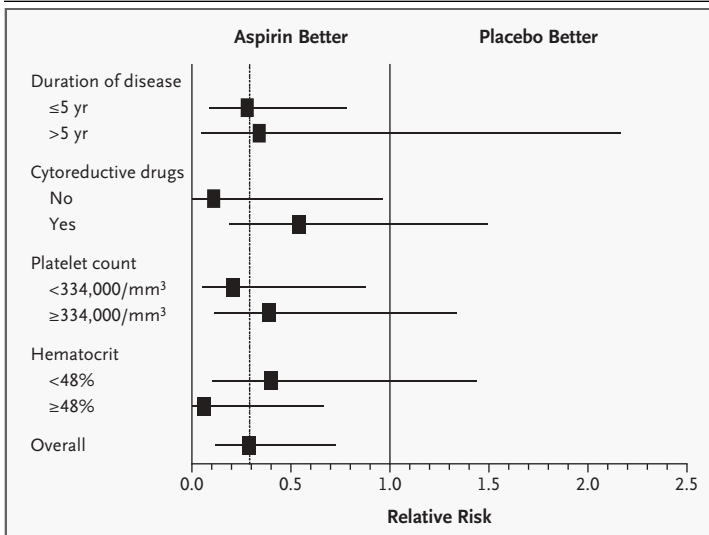


Figure 3. Effect of Aspirin on the Risk of a Major Arterial or Venous Event or Death from Cardiovascular Causes in Various Subgroups.

The analysis was performed according to the intention-to-treat principle, with adjustment for age, sex, the duration of disease, smoking status, the presence or absence of previous thrombotic or hemorrhagic events, the use or nonuse of digoxin, and the presence or absence of hypertension, diabetes, congestive heart failure, angina pectoris, phlebotomy, and cyto-reductive treatment. P=0.86 for the test of heterogeneity in the duration of disease, P=0.16 for the test of heterogeneity in the use of cyto-reductive drugs, P=0.53 for the test of heterogeneity in the platelet count, and P=0.07 for the test of heterogeneity in the hematocrit value.

be required to detect a 30 percent reduction in the risk of the defined end points with the use of aspirin.¹⁰ The ECLAP hematologic network recruited, in about two years, approximately one fourth of the number of patients that was originally projected. Despite this major limitation, the trial demonstrated a beneficial effect of aspirin; the risk reduction in the aspirin group (as great as 50 to 60 percent) was larger than that reported in any previous primary or secondary prevention trial involving subjects who did not have polycythemia vera.¹¹⁻¹⁷ Our results should be interpreted cautiously, however, because of the wide confidence intervals surrounding the point estimates. The relatively small number of events accounted for the fact that differences between the aspirin group and the placebo group reached statistical significance only for the second primary end point.

The overall strength of the results, however, is supported by their internal consistency. The effect of aspirin was detectable after approximately 180 days and appeared to be consistent for various arterial and venous vascular complications and in various subgroups.

In primary prevention trials that did not involve patients with polycythemia vera, aspirin had no statistically significant effects on the incidence of stroke or the rate of death, even though its use reduced by approximately 30 percent the risk of non-fatal myocardial infarction, the most frequent event in those studies.¹²⁻¹⁷ In our trial, there was a higher incidence of stroke than of myocardial infarction, and aspirin was effective in reducing the risk of all thrombotic events, including those affecting the cerebrovascular circulation.

Patients with polycythemia vera have an increase in the synthesis of thromboxane by a factor of approximately 10, as compared with age- and sex-matched controls.⁸ This abnormality can be largely suppressed with the use of low-dose aspirin.⁸ Aside from patients with polycythemia vera, only patients with acute coronary syndromes have increases in thromboxane synthesis of this magnitude^{18,19}; in such patients, low-dose aspirin therapy reduces the risk of major vascular events by 50 to 60 percent.²⁰ Thus, the apparently unusual size of the effect of aspirin in patients with polycythemia vera, as compared with its antithrombotic effect in other prevention trials,¹²⁻¹⁷ might reflect the increased synthesis of thromboxane, which we believe is the primary target of aspirin in platelets.⁷

Table 3. Rates and Relative Risks of Bleeding Episodes in the Two Groups.*

Type of Bleeding Episode	Aspirin Group (N=253)	Placebo Group (N=265)	Relative Risk (95% CI)	P Value
	no. (%)			
Any bleeding	23 (9.1)	14 (5.3)	1.82 (0.94-3.53)	0.08
Major bleeding	3 (1.2)	2 (0.8)	1.62 (0.27-9.71)	0.60
Gastrointestinal	2 (0.8)	0		
Intracranial	1 (0.4)	2 (0.8)		
Minor bleeding	20 (7.9)	12 (4.5)	1.83 (0.90-3.75)	0.10
Hematoma	2 (0.8)	2 (0.8)		
Gastrointestinal	7 (2.8)	3 (1.1)		
Hematuria	1 (0.4)	3 (1.1)		
Epistaxis	9 (3.6)	1 (0.4)		
Other	2 (0.8)	4 (1.5)		

* Major bleeding was defined as any bleeding episode that was fatal or necessitated transfusions or hospitalization. Totals for categories may not equal the sum of the values for subcategories because some patients had more than one type of bleeding episode. CI denotes confidence interval.

An important finding in our trial was the moderate increase in the risk of bleeding episodes associated with the long-term use of aspirin in polycythemia vera. The relative risk of major bleeding complications of 1.62 is consistent with the estimates from five primary prevention trials involving subjects who did not have polycythemia.¹²⁻¹⁷ The occurrence of a limited number of events precludes the precise estimation of the risk of bleeding, but the safety of prophylactic antiplatelet therapy in patients with polycythemia vera is corroborated by

the results of the epidemiologic cohort study of the ECLAP project (unpublished data). We believe that the risk of aspirin-induced bleeding in patients with this disease has been overemphasized.²¹ We recommend the use of aspirin to prevent thrombotic complications in patients with polycythemia vera who have no contraindication to this treatment.

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APPENDIX

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