ORIGINAL ARTICLE

Hydroxyurea Compared with Anagrelide in High-Risk Essential Thrombocythemia

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ABSTRACT

BACKGROUND

We conducted a randomized comparison of hydroxyurea with anagrelide in the treatment of essential thrombocythemia.

METHODS

A total of 809 patients with essential thrombocythemia who were at high risk for vascular events received low-dose aspirin plus either anagrelide or hydroxyurea. The composite primary end point was the actuarial risk of arterial thrombosis (myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic attack, or peripheral arterial thrombosis), venous thrombosis (deep-vein thrombosis, splanchnic-vein thrombosis, or pulmonary embolism), serious hemorrhage, or death from thrombotic or hemorrhagic causes.

RESULTS

After a median follow-up of 39 months, patients in the anagrelide group were significantly more likely than those in the hydroxyurea group to have reached the primary end point (odds ratio, 1.57; 95 percent confidence interval, 1.04 to 2.37; P=0.03). As compared with hydroxyurea plus aspirin, anagrelide plus aspirin was associated with increased rates of arterial thrombosis (P=0.004), serious hemorrhage (P=0.008), and transformation to myelofibrosis (P=0.01) but with a decreased rate of venous thromboembolism (P=0.006). Patients receiving anagrelide were more likely to withdraw from their assigned treatment (P<0.001). Equivalent long-term control of the platelet count was achieved in both groups.

CONCLUSIONS

Hydroxyurea plus low-dose aspirin is superior to anagrelide plus low-dose aspirin for patients with essential thrombocythemia at high risk for vascular events.

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THE PRINCIPAL FEATURE OF ESSENTIAL thrombocythemia, a clonal hematologic stem-cell disorder,[1-4] is thrombosis, with arterial events being more common than venous events. Hemorrhage also occurs, particularly if the platelet count is very high. In the long term, some cases transform to myelofibrosis, myelodysplasia, or acute myeloid leukemia. Factors that increase the risk of thrombosis are an age of more than 60 years, prior thrombosis, and, to a lesser extent, cardiovascular risk factors.[5-7] The importance of the platelet count as a risk factor is unclear, but a reduction in platelet count reduces the frequency of thrombosis, and aspirin relieves the microvascular symptoms of essential thrombocythemia.

Hydroxyurea is widely used as first-line therapy for high-risk patients, often in combination with low-dose aspirin. A previous randomized study demonstrated that hydroxyurea controlled the platelet count and reduced the incidence of thrombotic events in patients with a high risk of thrombosis.[8] Patients treated with hydroxyurea alone have a low incidence of leukemic transformation (3 to 4 percent),[9,10] whereas those given more than one cytotoxic agent are at increased risk for acute myeloid leukemia. It is not clear whether this increased risk is an effect of the treatment or a consequence of aggressive disease.

Anagrelide was developed as an inhibitor of platelet aggregation but was later found to reduce the platelet count at doses lower than the amount required to inhibit platelet aggregation.[11,12] The drug blocks megakaryocyte differentiation[13,14] and proliferation[15] and inhibits the action of cyclic AMP phosphodiesterase.[16] Despite the lack of evidence of efficacy reported in a randomized trial, anagrelide is commonly used as first-line therapy for high-risk patients with essential thrombocythemia, even though it is substantially more expensive than hydroxyurea. Here we report the results of the United Kingdom Medical Research Council Primary Thrombocythemia 1 study, which compared hydroxyurea plus aspirin with anagrelide plus aspirin in patients with essential thrombocythemia at high risk for thrombosis.

METHODS

STUDY POPULATION

We conducted an open-label, randomized trial comparing hydroxyurea plus aspirin with anagrelide plus aspirin in patients with essential thrombocythemia at high risk for vascular events. Patients were eligible if they met diagnostic criteria for essential thrombocythemia and were at high risk for thrombotic or hemorrhagic events. Both patients with newly diagnosed disease and previously treated patients who were at least 18 years old were eligible.

We used the diagnostic criteria of the Polycythemia Vera Study Group for essential thrombocythemia.[17] The Supplementary Appendix (available with the full text of this article at www.nejm.org) lists reasons for exclusion of patients from the study. Patients were classified as at high risk if they met one or more of the following criteria: an age of at least 60 years; current or previous platelet counts of 1 million per cubic millimeter or more; a history of ischemia, thrombosis, or embolism; hemorrhage caused by essential thrombocythemia; hypertension requiring therapy; and diabetes requiring the administration of a hypoglycemic agent.

In the United Kingdom, Ireland, and Australia, 815 patients were randomly assigned to receive one of the study drugs in 138 centers between August 20, 1997, and August 15, 2002. Six patients, three in each group, were misdiagnosed as having essential thrombocythemia (two patients with chronic myeloid leukemia, two with reactive thrombocytosis, one with idiopathic myelofibrosis, and one with polycythemia vera); these patients were excluded from the analysis. Of the remaining 809 patients, 404 were randomly assigned to receive hydroxyurea plus aspirin and 405 to receive anagrelide plus aspirin; patients in both groups were followed for a median of 39 months (range, 12 to 72). Only six patients were lost to follow-up, including four as a result of emigration. Complete follow-up information was available until the last visit of these six patients. The institutional research ethics committees in each center approved the study protocol, and written informed consent was obtained from all patients.

Patients who were assigned to receive hydroxyurea were started on 0.5 to 1 g daily; those assigned to receive anagrelide were started on 0.5 mg twice daily. Doses were subsequently adjusted to maintain the platelet count at less than 400,000 per cubic millimeter. Treatment was considered to have failed in patients whose platelet count was not less than 600,000 per cubic millimeter after having received the assigned therapy for at least three months; these patients left the study. All patients received aspirin at a daily dose of 75 mg (100 mg in

Australia). If aspirin was contraindicated, alternative agents were used: dipyridamole in 13 patients and clopidogrel in 4 patients. The protocol recommended delaying the introduction of aspirin in patients with very high platelet counts.

Information that was recorded at each visit included thrombotic or hemorrhagic events or transformation to neoplasm, other adverse events, a full blood count, measurement of the spleen, and a list of all other medications the patient was receiving. Follow-up forms requesting details of principal endpoint diagnoses were completed annually.

END POINTS

The composite primary end point was the time from randomization until the patient died from thrombosis or hemorrhage or had an arterial or a venous thrombotic event or a serious hemorrhage (see the Supplementary Appendix). Secondary end points were the time to the first arterial or venous thrombotic event or to the first serious hemorrhage; the time to death; the incidence of transformation to myelofibrosis, acute myeloid leukemia, myelodysplasia, or polycythemia vera; and control of the platelet count.

In the Supplementary Appendix, we list definitions of myocardial infarction, stroke, transient ischemic attack, deep-vein thrombosis, pulmonary embolism, serious hemorrhage, and transformation to acute myeloid leukemia, myelodysplasia, and polycythemia vera; also described is how transformation to myelofibrosis was determined.[18-24] All primary and secondary end points that were reported before July 31, 2004, were validated by a committee of clinicians who were blinded to the patients' treatment assignments. Two clinicians evaluated each event independently, and the study chairman resolved any disagreements. A committee of three hematopathologists who were blinded to the treatment assignments reviewed the results of the bone marrow biopsies of all patients with myelofibrotic or other transformations. Two hematologists who were blinded to treatment assignments independently reviewed all bone marrow aspirates and peripheral-blood smears from patients with transformations, and the study chairman resolved any disagreements.

STATISTICAL ANALYSIS

To detect a doubling in the rate of the primary end point (from 2 percent to 4 percent per year)[6,8] in either group over a median of four years of follow-up, with 80 percent power and a significance level of 0.05, we estimated that the trial would require that 560 patients be randomly assigned to a study group. Randomizations were undertaken and conveyed by telephone or fax to the Clinical Trial Service Unit in Oxford, United Kingdom. Minimization[25] was used to ensure that equal numbers of patients were assigned to each group, both overall and within subgroups defined by previous treatment (no treatment vs. aspirin or cytoreductive therapy or both) and previous treatment assignment (for patients who were initially in groups at low and intermediate risk).

Annual interim analyses were assessed by the data monitoring committee of the Medical Research Council, which uses the Haybittle–Peto stopping guideline, a difference of at least 3 SE between the two groups.[26] In 2002, this committee noted an excess of vascular events and deaths close to the boundary of 3 SE, together with an excess of myelofibrosis, other adverse events, and withdrawal from treatment. In 2003, the difference in vascular events and deaths exceeded the boundary of 3 SE, and the differences in myelofibrosis, other adverse events, and withdrawal from treatment were maintained. On September 1, 2003, the trial was closed and a letter sent to investigators recommending that they consider changing the treatment of participating patients from anagrelide to hydroxyurea. Because the Haybittle–Peto guideline is a conservative stopping rule, P values do not require adjustment for the interim analyses.[27]

Differences in baseline characteristics according to treatment assignment were assessed with the use of the chi-square test (two-by-two tables), the Mantel–Haenszel test for trend (with a grouped timing of trial entry), or the Mann–Whitney U test (for continuous data). Wilcoxon rank-sum tests were used to compare platelet counts between the two groups at three monthly time points for the first two years after randomization. Kaplan–Meier analysis and the log-rank test[28] were used to compare time to event from randomization on an intention-to-treat basis, with data of surviving patients censored on August 31, 2003, or (for those lost to follow-up) on the date of the last follow-up. The observed number of events (O) minus the expected number of events (E) in the anagrelide group and its variance (V) were calculated from the log-rank survival analysis and used to calculate the odds ratio[28] (as the exponent of $[(O-E) \div V]$). Tests for interaction were used to assess whether the

Table 1. Baseline Characteristics of the Patients.*

Feature	Hydroxyurea plus Aspirin (N=404)	Anagrelide plus Aspirin (N=405)
Demographic characteristics		
Male sex — no. (%)	180 (45)	162 (40)
Median age at entry — yr (range)	62 (21–88)	61 (23–88)
Laboratory and clinical features at diagnosis		
Platelet count — $\times 10^{-3}$/mm^3		
Mean	1011±320	1004 ±344
Median (range)	947 (425–2250)	930 (208–2320)
Hemoglobin — g/liter		
Mean†	139±15	140±14
Median (range)	140 (82–174)	140 (99–174)
White-cell count — $\times 10^{-3}$/mm^3		
Mean	10.4±3.3	10.0±3.3
Median (range)	9.9 (4.2–27.4)	9.4 (3.1–32.2)
Neutrophil count — $\times 10^{-3}$/mm^3		
Mean	7.1±2.8	7.0±2.9
Median (range)	6.6 (1.9–18.7)	6.4 (1.4–27.2)
Splenomegaly — no./total no. (%)	27/362 (7)	36/351 (10)
Laboratory and clinical features at trial entry		
Platelet count — $\times 10^{-3}$/mm^3		
Mean	853±383	839±359
Median (range)	837 (212–2860)	812 (211–2372)
Hemoglobin — g/liter		
Mean	136±15	138±14
Median (range)	136 (86–181)	138 (93–174)
White-cell count — $\times 10^{-3}$/mm^3		
Mean	9.1±3.5	8.8±3.2
Median (range)	8.8 (2.0–24.0)	8.6 (1.7–25.6)
Neutrophil count — $\times 10^{-3}$/mm^3		
Mean	6.0±2.9	5.9±2.7
Median (range)	5.7 (0.6–19.4)	5.6 (0.9–19.8)
Splenomegaly — no./total no. (%)	22/345 (6)	26/335 (8)

treatment effect differed among subgroups of patients.[29]

In the Supplementary Appendix, we describe how the trial was conceived, conducted, and analyzed. Shire, the manufacturer of anagrelide, provided the drug at a reduced price but was otherwise not involved in the trial.

RESULTS

BASELINE CHARACTERISTICS

There were no significant differences between the two groups with respect to laboratory and clinical features at diagnosis or trial entry (Table 1). The groups were well matched with respect to risk fac-

Table 1. (Continued.)

Feature	Hydroxyurea plus Aspirin (N=404)	Anagrelide plus Aspirin (N=405)
Time between diagnosis and enrollment — no. (%)		
<3 mo	250 (62)	240 (59)
3 mo to 5 yr	109 (27)	114 (28)
>5 yr	45 (11)	51 (13)
Prior treatment — no. (%)		
None	77 (19)	68 (17)
Aspirin or other antiplatelet agent alone	194 (48)	199 (49)
Any cytoreductive agent	133 (33)	138 (34)
Hydroxyurea	118 (29)	123 (30)
Anagrelide	0 (0)	1 (<1)
Interferon alfa	7 (2)	7 (2)
Busulfan	13 (3)	23 (6)
Other (phosphorus-32, mitobronitol, or unknown agent)	12 (3)	10 (2)
Thrombotic and hemorrhagic risk factors — no./total no. (%)		
Previous arterial thrombosis	72/400 (18)	74/402 (18)
Previous venous thromboembolism	29/400 (7)	20/402 (5)
Previous peripheral vascular disease	152/400 (38)	131/402 (33)
Previous angina	22/400 (6)	21/402 (5)
Regular daily cigarette smoking at enrollment	62/331 (19)	48/342 (14)
Diabetes	17/400 (4)	12/402 (3)
Hypertension	94/400 (24)	90/402 (22)
Previous hemorrhage	26/400 (6)	23/402 (6)

* Plus–minus values are means ±SD.
† No male patient had a hemoglobin level of more than 175 g per liter, and one female patient had a hemoglobin level of more than 165 g per liter.

tors for thrombosis and hemorrhage and to hematologic transformation. Approximately one third of patients in each group had previously received hydroxyurea.

CONTROL OF THE PLATELET COUNT

Control of the platelet count was similar in the two groups by nine months after trial entry and subsequently (Fig. 1). At three and six months after trial entry, platelet counts in the anagrelide group were significantly higher than those in the hydroxyurea group (P<0.001 for both time points). The difference remained significant when the analysis was restricted to patients with newly diagnosed disease at trial entry (data not shown) and therefore did not reflect a need for patients who had previously received a diagnosis of essential thrombocythemia to change from hydroxyurea to anagrelide after randomization to the anagrelide group. The median white-cell count in the hydroxyurea group was significantly and persistently lower than that in the anagrelide group (P<0.001), starting at three months after trial entry (data not shown).

VASCULAR END POINTS

As compared with the hydroxyurea group, the anagrelide group had a significantly higher rate of the composite primary end point of arterial or venous

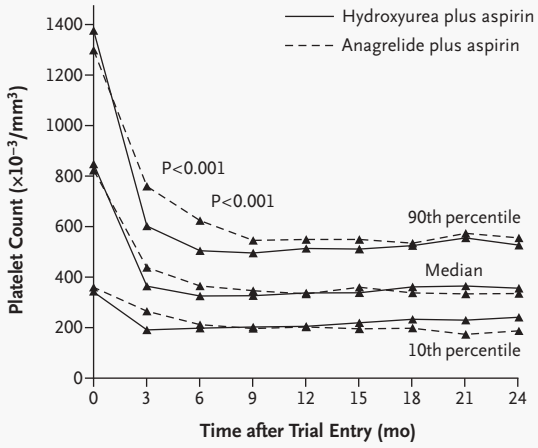


Figure 1. The Median and 10th and 90th Percentiles of the Platelet Count, According to Month after Trial Entry.

Data points are based on patients with a platelet count recorded within one month of each time point and remaining on their assigned treatment. Platelet counts were significantly different between the two groups at three and six months after trial entry but not at other time points.

thrombosis, serious hemorrhage, or death from vascular causes (odds ratio, 1.57; 95 percent confidence interval, 1.04 to 2.37; P=0.03) (Table 2). The estimated risk of the primary end point at five years was 16 percent in the anagrelide group (95 percent confidence interval, 12 to 21) and 11 percent in the hydroxyurea group (95 percent confidence interval, 7 to 14), with a median follow-up of 39 months (Fig. 2). The rates of the primary end point were also compared in prespecified subgroups of patients (newly diagnosed vs. previously diagnosed disease; previous cytoreductive therapy vs. no previous cytoreductive therapy; and previous hydroxyurea therapy vs. no previous hydroxyurea therapy). There was no evidence of heterogeneity of treatment effect between these subgroups.

Analyses of prespecified secondary vascular end points revealed statistically significant differences between the two groups (Table 2 and Fig. 3). Arterial thrombosis developed in more than twice as many patients in the anagrelide group as in the hydroxyurea group (odds ratio, 2.16; 95 percent confidence interval, 1.27 to 3.69; P=0.004). There were significantly more transient ischemic attacks in the anagrelide group than in the hydroxyurea group (14 vs. 1; odds ratio, 5.72; 95 percent confidence interval, 2.08 to 15.73; P<0.001). The rates of myocardial infarction, unstable angina, and thrombotic stroke were higher in the anagrelide group but not significantly different from the rates in the hydroxyurea group. There was also a significant increase in the rate of serious hemorrhage in the anagrelide group (odds ratio, 2.61; 95 percent confidence interval, 1.27 to 5.33; P=0.008), with gastrointestinal hemorrhage being particularly common (odds ratio, 3.54; 95 percent confidence interval, 1.33 to 9.44; P=0.01).

By contrast, the rate of venous thromboembolism in the anagrelide group was approximately one fourth that in the hydroxyurea group (odds ratio, 0.27; 95 percent confidence interval, 0.11 to 0.71; P=0.006), and there was a significantly lower rate of deep-vein thrombosis in the anagrelide group (odds ratio, 0.20; 95 percent confidence interval, 0.06 to 0.71; P=0.009). Pulmonary emboli developed in only seven patients, but five of the seven were in the hydroxyurea group. The rates of death from any cause and death from thrombotic or hemorrhagic causes were not significantly different between the two groups, although the study was not powered to detect any difference in mortality.

Since patients who received anagrelide were more likely to withdraw from their assigned treatment than were patients who received hydroxyurea (Table 3), survival analyses were repeated with data that were censored on the date of the patients' withdrawal from treatment. The various rates of arterial or venous thrombosis, serious hemorrhage, and reaching the composite primary end point all remained statistically significant, with minimal changes in the P values (data not shown).

The rates of the primary end point in the two groups were compared for various periods after trial entry. There was no significant heterogeneity between the odds ratio for events in the first nine months and the odds ratio for subsequent events (data not shown). The differences in platelet count in the first nine months are therefore unlikely to be of clinical significance.

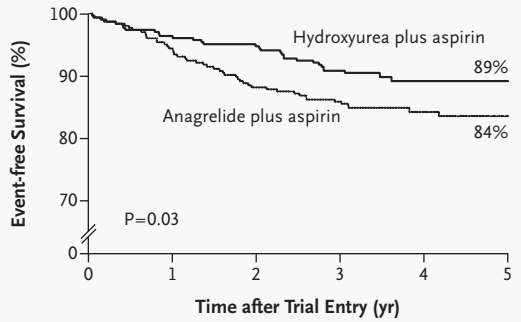
DISEASE TRANSFORMATION

As compared with the hydroxyurea group, the anagrelide group had a significantly increased rate

Table 2. Number of Patients Reaching Principal Study End Points.*

Feature	Hydroxyurea plus Aspirin (N=404)	Anagrelide plus Aspirin (N=405)	Odds Ratio (95% CI)	P Value†
	no. of patients			
Primary end point				
Arterial or venous thrombosis, serious hemorrhage, or death from thrombosis or hemorrhage	36	55	1.57 (1.04–2.37)	0.03
Secondary end point				
Arterial thrombosis	17	37	2.16 (1.27–3.69)	0.004
Myocardial infarction	7	13	1.84 (0.76–4.41)	NS
Unstable angina	2	4	1.94 (0.39–9.63)	NS
Stroke	7	9	1.30 (0.49–3.47)	NS
Transient ischemic attack	1	14	5.72 (2.08–15.73)	<0.001
Other‡	2	0		NE
Venous thromboembolism	14	3	0.27 (0.11–0.71)	0.006
Deep-vein thrombosis	9	1	0.20 (0.06–0.71)	0.009
Pulmonary embolism	5	2	0.43 (0.01–1.87)	NS
Hepatic-vein thrombosis	1	0		NE
Serious hemorrhage	8	22	2.61 (1.27–5.33)	0.008
Gastrointestinal bleeding	3	13	3.54 (1.33–9.44)	0.01
Intracranial bleeding	4	1	0.30 (0.05–1.75)	NS
Nasal bleeding	1	4	3.34 (0.58–19.25)	NS
Other bleeding§	0	4		NE
Death	27	31	1.15 (0.69–1.93)	NS
Thrombotic cause¶	9	11	1.23 (0.51–2.94)	NS
Hemorrhagic cause	4	4	1.01 (0.25–4.02)	NS
Hematologic cause (transformation)	4	3	0.77 (0.18–3.39)	NS
Other cause	12	14	1.17 (0.54–2.53)	NS
Hematologic transformation				
Myelofibrosis	5	16	2.92 (1.24–6.86)	0.01
Mo after trial entry — median (range)	30 (7–54)	28 (10–52)		
Mo after diagnosis — median (range)‖	34 (27–107)	45 (12–182)		
Acute myeloid leukemia or myelodysplasia	6	4	0.67 (0.20–2.33)	NS
Mo after trial entry — median (range)	26 (7–46)	43 (8–55)		
Mo after diagnosis — median (range)¶	36 (26–58)	83 (9–150)		
Polycythemia vera	1	1	1.00 (0.06–1.60)	NS

* CI denotes confidence interval, NS not significant, and NE not able to be evaluated (since one group had no events).
† P values were obtained with the use of log-rank analysis.
‡ This category includes arterial embolus of either the lower or upper limbs.
§ This category includes retroperitoneal, pericardial, urinary, and obstetrical hemorrhage.
¶ This category includes three patients who died suddenly of presumed cardiac causes (one in the hydroxyurea group and two in the anagrelide group).
‖ There was no significant difference in the duration of disease before transformation with use of the Wilcoxon rank-sum test.



No. at Risk						
Hydroxyurea plus aspirin	404	388	298	204	129	57
Anagrelide plus aspirin	405	379	272	190	119	52

Figure 2. Kaplan–Meier Estimates of Survival Free of the Primary End Point of Arterial or Venous Thrombosis, Serious Hemorrhage, or Death from Any of These Causes.

of transformation to myelofibrosis (odds ratio, 2.92; 95 percent confidence interval, 1.24 to 6.86; P=0.01) (Table 2). The estimated actuarial risk of myelofibrosis five years after trial entry was 2 percent for the hydroxyurea group (95 percent confidence interval, 0 to 5) and 7 percent for the anagrelide group (95 percent confidence interval, 3 to 10) (Fig. 3D). Of the 21 patients with myelofibrotic transformation, 3 had died by September 2003, all in the anagrelide group.

The increased rate of myelofibrosis in the anagrelide group remained evident after patients who had previously received busulfan were excluded from the analysis (P=0.04). None of the 21 patients had anemia, leukoerythroblastic findings on peripheral-blood smears, or systemic symptoms at trial entry, and only 1 (5 percent) had splenomegaly (as compared with 7 percent for the trial as a whole). Furthermore, the higher rate of myelofibrotic transformation was not an artifact of the precise definition that was used, since making the diagnostic criteria more stringent by requiring the inclusion of three clinical or laboratory features instead of two, or by the exclusion of any one of the five criteria from the set, did not affect the statistical significance.

Myelodysplasia or acute myeloid leukemia developed in 10 patients, 4 in the anagrelide group and 6 in the hydroxyurea group (Table 2). Median survival was 14 months from transformation, and seven patients had died by September 2003. Polycythemia vera developed in two patients (one in each group), at 3 and 49 months after trial entry.

SAFETY AND SIDE EFFECTS

The number of patients who withdrew from the assigned treatment before closure of the trial was higher in the anagrelide group than in the hydroxyurea group (148 vs. 79, P<0.001) (Table 3). Significantly more patients withdrew from the anagrelide group because of side effects (88 vs. 43, P<0.001) or because either an end point (particularly myocardial infarction or hematologic transformation) or a serious adverse event had developed (most commonly, cardiac failure, serious arrhythmia, or pancytopenia). The lower rate of withdrawal from treatment with hydroxyurea was still evident even when analysis was restricted to patients who had not previously received hydroxyurea (P<0.001).

The rates of nonthrombotic cardiovascular events (particularly palpitations), gastrointestinal events (especially diarrhea and abdominal pain), noncardiac edema, headache, and constitutional symptoms were all significantly higher in the anagrelide group (Table 3). The rate of dermatologic side effects, including mouth ulcers, was significantly increased in the hydroxyurea group.

DISCUSSION

This study of more than 800 patients with essential thrombocythemia who were at high risk for thrombosis shows that, as compared with hydroxyurea plus aspirin, anagrelide plus aspirin was associated with higher rates of arterial thrombosis, serious hemorrhage, transformation to myelofibrosis, and treatment withdrawal but a lower rate of venous thromboembolism. The participation of many secondary and tertiary hematology centers and the involvement of three countries suggest that these conclusions can be generalized.

The rates of major arterial and venous thrombosis in the hydroxyurea group in this trial were similar to those in the hydroxyurea group in the study of Cortelazzo and colleagues[8] (actuarial rate of first thrombosis, 4 percent at two years in both trials), which suggests that the study populations in the two trials were broadly similar. However, the rate of major arterial and venous thrombosis in the anagrelide group in our trial was less than that ob-

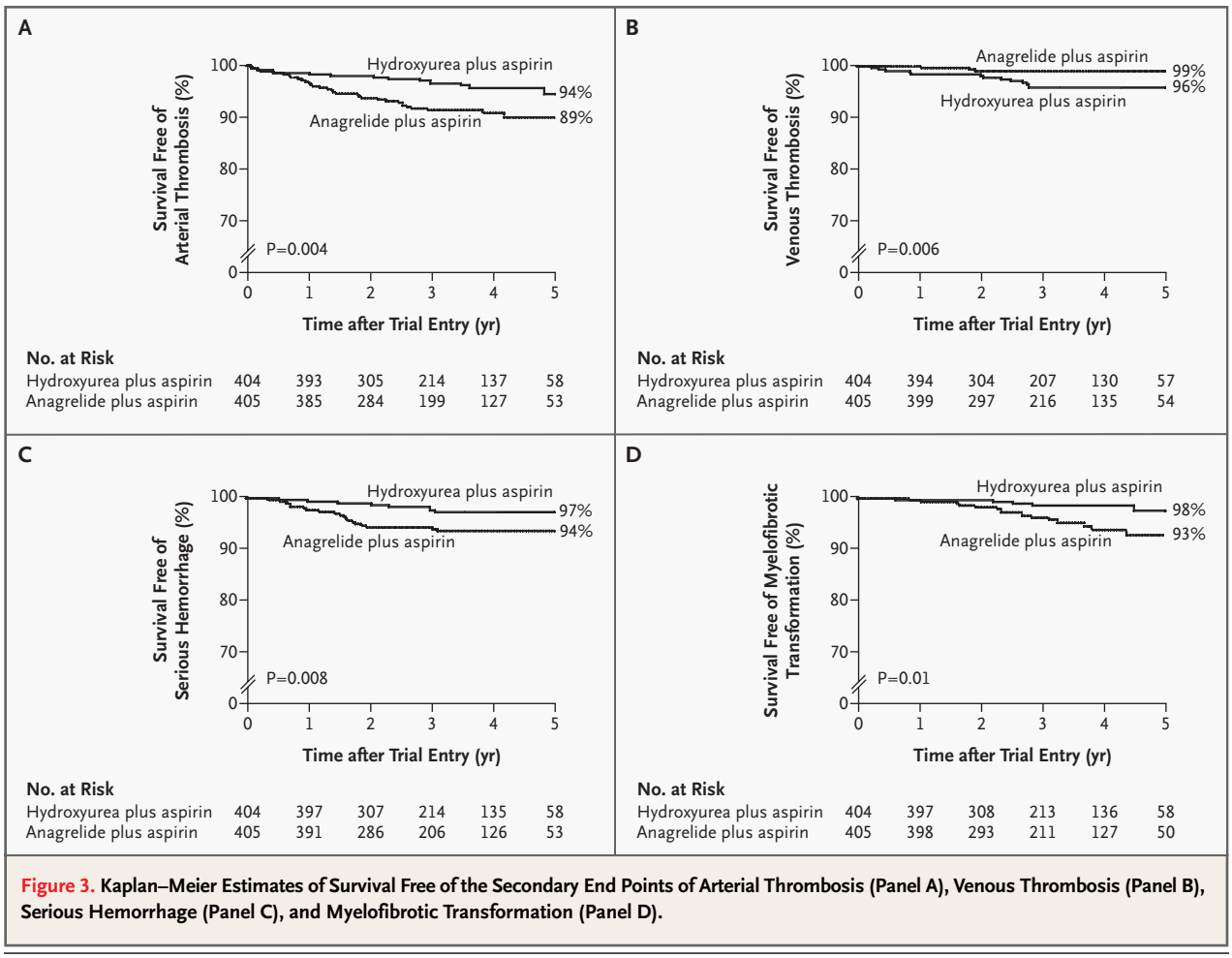


Figure 3. Kaplan–Meier Estimates of Survival Free of the Secondary End Points of Arterial Thrombosis (Panel A), Venous Thrombosis (Panel B), Serious Hemorrhage (Panel C), and Myelofibrotic Transformation (Panel D).

served in the control group (which did not receive hydroxyurea) in the Italian study (actuarial rate of first thrombosis, 8 percent vs. 26 percent at two years, respectively). Since more than 80 percent of the thrombotic events in the Italian trial were arterial, these comparisons suggest that anagrelide partially protects against arterial thrombosis. It is interesting to note that both trials reported a marked effect of hydroxyurea on rates of transient ischemic attack, which suggests a particular role for hydroxyurea in the prevention of this complication.

In contrast to the rate of arterial thrombosis, the rate of venous thrombosis was significantly lower in the anagrelide group. Since the incidence of venous thrombosis in untreated patients with high-risk essential thrombocythemia is unknown, it is unclear whether this rate is increased by hydroxyurea or decreased by anagrelide. The optimal treatment of a patient with prior venous thrombosis will depend not only on individual circumstances but also on the fact that arterial thrombosis is more than three times more common than venous thrombosis in essential thrombocythemia.

The equivalent long-term control of the platelet count in both groups implies that, in addition to lowering the platelet count, either hydroxyurea or anagrelide may modulate thrombosis by other mechanisms. The lower white-cell count in patients receiving hydroxyurea may be relevant, since white cells contribute to the procoagulant response at sites of vascular injury.[30] Moreover, neutrophil activation occurs in essential thrombocythemia and correlates with activation of both endothelial cells and the coagulation cascade.[31] Hydroxyurea also has direct effects on endothelial function[32] and acts as a nitric oxide donor.[33]

Table 3. Treatment Withdrawal and Adverse Events.

Feature	Hydroxyurea plus Aspirin (N=404)	Anagrelide plus Aspirin (N=405)	P Value*
Withdrawal from treatment			
No. of patients who withdrew from assigned treatment	79	148	<0.001
Reason for withdrawal			
Side effect	43	88	<0.001
Serious adverse or end-point event	4	22	<0.001
Lack of platelet control	15	19	NS
Pregnancy or other contraindication	2	8	0.03
Choice of patient	10	5	NS
Other reason	5	6	NS
Adverse events			
Nonthrombotic cardiovascular events	27	92	<0.001
Cardiac failure (including acute ventricular failure)	7	14	NS
Arrhythmia (atrial flutter, atrial fibrillation, need for pacemaker)	4	8	NS
Palpitations (including irregular pulse)	7	63	<0.001
Other nonthrombotic cardiovascular event†	12	22	NS
Gastroenterologic events	36	59	0.01
Diarrhea	6	18	0.01
Nausea and vomiting	12	16	NS
Peptic ulcer, esophagitis, and gastritis	18	18	NS
Abdominal pain	1	9	0.008
Irritable-bowel symptoms	0	5	NE
Inflammatory bowel disease	2	2	NS
Other gastroenterologic event‡	8	18	0.04

The increased risk of serious hemorrhage in the anagrelide plus aspirin group may reflect interference of anagrelide with platelet function in a way that synergizes with low-dose aspirin. Anagrelide blocks platelet phosphodiesterase activity[16] and at high doses (0.5 to 10.0 mg per kilogram of body weight) inhibits thrombus formation in animal models.[34] Although the results of most assays of platelet function are normal in patients with essential thrombocythemia who receive anagrelide, some subtle effects on platelet function have been reported.[35,36] The results presented here suggest that if anagrelide is used, the decision whether to use concurrent aspirin therapy should depend on the relative risk of arterial thrombosis and hemorrhage in each patient.

The incidence of transformation to myelofibrosis was higher in the anagrelide group than in the hydroxyurea group. The reason for this difference is unknown. Hydroxyurea reduces reticulin fibrosis in a variety of myeloproliferative disorders, including essential thrombocythemia.[37,38] By contrast, the many immature forms that arise when anagrelide blocks differentiation of megakaryo-

Table 3. (Continued.)

Feature	Hydroxyurea plus Aspirin (N=404)	Anagrelide plus Aspirin (N=405)	P Value*
Dermatologic event	45	29	0.05
Rash	10	15	NS
Leg ulcer	20	9	0.04
Mouth ulcers	8	1	0.02
Other dermatologic event	16	7	NS
Hematologic event (excluding transformation)	24	35	NS
Iron-deficiency anemia	4	10	NS
Other anemia	13	22	NS
Thrombocytopenia, neutropenia, or both	8	5	NS
Other hematologic event	1	4	NS
Event involving other systems			
Noncardiac edema	5	25	<0.001
Headache	8	51	<0.001
Constitutional symptoms§	12	41	<0.001
Diabetes	10	3	0.05
Peripheral vascular disease	11	11	NS
Minor hemorrhage	42	50	NS
Nonhematologic cancer	14	11	NS

* P values were obtained with the use of log-rank analysis. NS denotes not significant, and NE not able to be evaluated (since one group had no events).
† Other nonthrombotic cardiovascular events include hypertension, 5 patients in the hydroxyurea group and 9 patients in the anagrelide group (NS); chest pain, 4 patients and 8 patients, respectively (NS); aortic aneurysm, 2 patients and 2 patients, respectively (NS); and multiorgan failure, 1 patient and 3 patients, respectively (NS).
‡ Other gastroenterologic events included gallstones, no patients in the hydroxyurea group and 1 patient in the anagrelide group (NE); abnormal liver-function tests, no patients and 4 patients, respectively (NE); diverticular disease, 1 patient and 4 patients, respectively (NS); ascites, no patients and 1 patient, respectively (NE); celiac disease, no patients and 1 patient, respectively (NE); colonic polyp, no patients and 1 patient, respectively (NE); volvulus, 1 patient and no patients, respectively (NE); constipation, 2 patients and 5 patients, respectively (NS); and hemorrhoids, 4 patients and 3 patients, respectively (NS).
§ Constitutional symptoms included fatigue, weight change, fevers, flushing, sleep disturbance, and loss of appetite.

cytes may produce relatively high levels of profibrotic cytokines.

In summary, the results of this trial suggest that hydroxyurea plus aspirin should remain first-line therapy for patients with essential thrombocythemia at high risk for vascular events.

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