Hydroxycarbamide Plus Aspirin Versus Aspirin Alone in Patients With Essential Thrombocythemia Age 40 to 59 Years Without High-Risk Features

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ABSTRACT

Purpose
Cytoreductive therapy is beneficial in patients with essential thrombocythemia (ET) at high risk of thrombosis. However, its value in those lacking high-risk features remains unknown. This open-label, randomized trial compared hydroxycarbamide plus aspirin with aspirin alone in patients with ET age 40 to 59 years and without high-risk factors or extreme thrombocytosis.

Patients and Methods
Patients were age 40 to 59 years and lacked a history of ischemia, thrombosis, embolism, hemorrhage, extreme thrombocytosis (platelet count $\geq 1,500 \times 10^9/L$), hypertension, or diabetes requiring therapy. In all, 382 patients were randomly assigned 1:1 to hydroxycarbamide plus aspirin or aspirin alone. The composite primary end point was time to arterial or venous thrombosis, serious hemorrhage, or death from vascular causes. Secondary end points were time to first arterial or venous thrombosis, first serious hemorrhage, death, incidence of transformation, and patient-reported quality of life.

Results
After a median follow-up of 73 months and a total follow-up of 2,373 patient-years, there was no significant difference between the arms in the likelihood of patients reaching the primary end point (hazard ratio, 0.98; 95% CI, 0.42 to 2.25; $P = 1.0$). The incidence of significant vascular events was low, at 0.93 per 100 patient-years (95% CI, 0.61 to 1.41). There were also no differences in overall survival; in the composite end point of transformation to myelofibrosis, acute myeloid leukemia, or myelodysplasia; in adverse events; or in patient-reported quality of life.

Conclusion
In patients with ET age 40 to 59 years and lacking high-risk factors for thrombosis or extreme thrombocytosis, preemptive addition of hydroxycarbamide to aspirin did not reduce vascular events, myelofibrotic transformation, or leukemic transformation. Patients age 40 to 59 years without other clinical indications for treatment (such as previous thrombosis or hemorrhage) who have a platelet count $< 1,500 \times 10^9/L$ should not receive cytoreductive therapy.

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INTRODUCTION

Essential thrombocythemia (ET) is a chronic myeloid malignancy characterized by thrombocytosis and, in most patients, a somatic mutation affecting JAK2 (50% to 60%), CALR (25% to 35%), or MPL (5% to 10%). A major complication is thrombosis, most frequently arterial. High risk of thrombosis is associated with age older than 60 years or history of prior thrombosis; other factors may include the JAK2 V617F mutation, cardiovascular risk factors, or increased white cell count. Patients have increased risk of hemorrhage, especially with marked thrombocytosis, whereas platelet count is not associated with thrombotic risk. A minority of patients transform to myelofibrosis...
(MF), acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), or polycythemia vera (PV).\(^8\)

Patients with ET at high risk of thrombosis developed fewer thrombotic events when treated with the cytoreductive agent hydroxycarbamide.\(^9\) In the Primary Thrombocythemia-1 (PT-1) high-risk study, the composite vascular end point of arterial thrombosis, venous thrombosis, serious hemorrhage, or death from vascular events was reduced in patients randomly assigned to hydroxycarbamide compared with those who received anagrelide.\(^8\)

Hydroxycarbamide therapy was associated with lower risks of thrombotic events when treated with the cytoreductive agent hydroxycarbamide compared with those who received anagrelide.\(^8\) Hydroxycarbamide therapy was associated with lower risks of arterial thrombosis, venous thrombosis, serious hemorrhage, or death from vascular events was reduced in patients randomly assigned to hydroxycarbamide compared with those who received anagrelide.\(^8\)

Moreover, the chronic disease course of these patients, with complications that occur at a low rate but have major clinical consequences, means that clinical studies should follow a substantial cohort of patients over a prolonged time period. We report the results of the PT-1 intermediate-risk prospective, randomized trial comparing hydroxycarbamide plus aspirin with aspirin alone in patients with ET age 40 to 59 years and lacking high-risk factors.

**Patients and Methods**

**Patients**

Patients were recruited from 140 hospitals in the United Kingdom, Ireland, Australia, France, and New Zealand between July 21, 1997, and July 31, 2012. Research ethics committees in each country approved the study protocol, and all participants gave written informed consent.

Eligible patients met Polycythemia Vera Study Group diagnostic criteria for ET (listed in the Data Supplement) and were either newly diagnosed or previously treated. Patients were classified as intermediate risk if they were age 40 to 59 years and did not meet any high-risk criteria: a history of ischemia, thrombosis, or embolism; hemorrhage caused by ET; hypertension or diabetes requiring pharmacologic therapy; current or previous platelet counts ≥ 1,000 \(× 10^{9}/L\). The exclusion for extreme thrombocytosis reflects the increased risk of hemorrhage associated with acquired von Willebrand syndrome, such that cytoreduction is warranted in these patients.\(^5,12,19\) During the study (on May 6, 2004), the upper limit of the platelet count for eligibility was increased to 1,500 \(× 10^{9}/L\). Exclusion criteria are listed in the Data Supplement.

**Fig 1.** CONSORT diagram. Details of patients randomly assigned, treated, and followed up in the study. Data were not collected regarding eligibility screening before randomization. Changes to cyto-reductive treatment are shown. In the aspirin-alone arm, 71 patients started hydroxycarbamide (HC) and 11 started anagrelide; 23 patients subsequently received one or more additional agents (hydroxycarbamide [14], anagrelide [1], interferon-alfa [1], thalidomide [1]). In the hydroxycarbamide-plus-aspirin arm, nine patients were randomly assigned to hydroxycarbamide but never started it; 13 patients stopped hydroxycarbamide without simultaneously starting a second-line agent; 14 patients switched to an alternative cytoreductive agent (anagrelide [12], interferon-alfa [1], busulphan [1]), and 3 started anagrelide without stopping hydroxycarbamide. PV, polycythemia vera.
Hydroxycarbamide in Intermediate-Risk Essential Thrombocythemia

Randomization

Eligible patients were randomly assigned in a 1:1 ratio to receive aspirin alone or hydroxycarbamide plus aspirin. Patients were entered into the trial by fax or by telephoning the Clinical Trial Service Unit (CTSU), Oxford, United Kingdom, until June 23, 2010, and subsequently at the Cambridge Clinical Trials Unit (CCTU), Cambridge, United Kingdom. Random assignment was accomplished by the central computer at CTSU and CCTU, using a minimization algorithm to ensure that equal numbers of patients were allocated to each arm, overall and within subgroups of previous treatment (none, aspirin only, cytoreductive therapy only, or both). A random number generator was used to assign the initial patients, then by minimization with a random component. At CCTU, treatment allocations were assigned by the randomization program and communicated by staff to the enrolling doctor or nurse by fax or telephone, followed by a confirmation letter to the responsible clinician. At CCTU random assignments and treatment allocations were handled by fax to the treating clinician.

Procedures

The study was open label. Patients assigned to hydroxycarbamide plus aspirin were treated with 0.5 to 2 g oral hydroxycarbamide once per day, adjusted to maintain platelet counts within the range of 200 to 400 × 10^9/L. All patients were advised to take aspirin 75 mg once per day (100 mg in Australia) or an alternative antiplatelet agent if aspirin was contraindicated. Visit frequency, which was at the physician’s discretion, was recommended to be at a minimum of every 3 months. Details of principal end point diagnoses and adverse events were recorded annually in both arms, and quality-of-life data were recorded annually for the first 5 years (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 [EORTC QLQ-C30], version 2).

Peripheral blood samples for central molecular analysis were collected at trial entry from 259 patients for DNA extraction (Strangeways Research Laboratory, Cambridge, United Kingdom) and screened for JAK2 V617F, CALR, and MPL mutations at the Department of Haematology, University of Cambridge (described in the Data Supplement). For 177 patients, a bone marrow trephine biopsy performed at trial entry was reviewed centrally by two hematopathologists for diagnostic accuracy (123 patients had a peripheral blood smear provided).

Outcomes

The composite primary end point was time from random assignment until the patient died as a result of thrombosis or hemorrhage or had a serious hemorrhage or thrombotic event (see the Data Supplement). Secondary end points were time to the first arterial or venous thrombotic event or to the first serious hemorrhage; time to death; incidence of transformation to MF, AML, MDS, or PV; and patient-reported quality of life. Full end point definitions are listed in the Data Supplement. End points that occurred before May 31, 2013, and were reported before October 31, 2013, were validated after independent evaluation by two clinicians who were blinded to the patients’ treatment assignments; this included review of peripheral blood smears and/or bone marrow samples for transformations to MF, AML, and MDS. The study chairman resolved any disagreements.

Trial Oversight

Annual interim analyses, including details of primary and secondary end points and unexpected or serious toxicities, were assessed by an independent data monitoring committee. Stopping guidelines stated that a difference of at least three standard deviations in an interim analysis of a major end point might be needed to justify halting or modifying the trial prematurely (the Haybittle-Peto rule). The study was funded by the Medical Research Council, United Kingdom, and Cancer Research UK. The funders had no role in study design, data collection, analysis, or interpretation, or writing the report. The corresponding author had full access to all study data and had final responsibility for the decision to submit the report for publication.

Table 1. Baseline Characteristics of the Analysis Populations

<table>
<thead>
<tr>
<th>Feature</th>
<th>Aspirin Alone (n = 176)</th>
<th>Hydroxycarbamide Plus Aspirin (n = 182)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>83/176 47%</td>
<td>63/35 35%</td>
</tr>
<tr>
<td>Age at entry, years</td>
<td>51 41-58</td>
<td>52 42-58</td>
</tr>
<tr>
<td>Disease duration, months</td>
<td>4.2 0.69-60</td>
<td>3.2 0.66-61</td>
</tr>
<tr>
<td>Newly diagnosed patients</td>
<td>76/143 56%</td>
<td>87/48 46%</td>
</tr>
<tr>
<td>Characteristics at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count × 10^9/L</td>
<td>764 599-1,010</td>
<td>750 594-1,070</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>143 126-162</td>
<td>140 125-159</td>
</tr>
<tr>
<td>White cell count × 10^9/L</td>
<td>8.6 5.9-12.0</td>
<td>8.8 6.1-13.0</td>
</tr>
<tr>
<td>Neutrophil count × 10^9/L</td>
<td>5.6 3.4-8.6</td>
<td>5.7 3.6-8.7</td>
</tr>
<tr>
<td>Palpable splenomegaly</td>
<td>7/161 4%</td>
<td>5/171 3%</td>
</tr>
<tr>
<td>Blood counts at trial entry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count × 10^9/L</td>
<td>726 587-1,050</td>
<td>744 570-1,080</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>140 125-160</td>
<td>138 124-159</td>
</tr>
<tr>
<td>White cell count × 10^9/L</td>
<td>8.5 5.6-12.2</td>
<td>8.2 5.9-11.8</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxycarbamide</td>
<td>19 10</td>
<td>19 10</td>
</tr>
<tr>
<td>Anagrelide</td>
<td>2 1</td>
<td>1 1</td>
</tr>
<tr>
<td>Busulphan</td>
<td>2 1</td>
<td>3 2</td>
</tr>
<tr>
<td>Interferon</td>
<td>1 1</td>
<td>4 2</td>
</tr>
<tr>
<td>Key driver mutations</td>
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</tr>
<tr>
<td>JAK2</td>
<td>73/124 59%</td>
<td>68/135 50%</td>
</tr>
<tr>
<td>MPL</td>
<td>5/124 4%</td>
<td>8/135 6%</td>
</tr>
<tr>
<td>CALR</td>
<td>32/124 26%</td>
<td>36/135 27%</td>
</tr>
<tr>
<td>Triple negative</td>
<td>14/124 11%</td>
<td>23/135 17%</td>
</tr>
</tbody>
</table>

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Statistical Analysis

Sample size was originally calculated based on the following: if the primary end point were in the order of 4% per annum,26 detection of a 50% reduction in complication rate (at 2P = .05, with 80% power) in the hydroxycarbamide-plus-aspirin arm compared with the aspirin-alone arm, the trial was estimated to require a sample size of 280 in each arm observed for a median of 4 years. Based on the possibility of a low event rate, a decision was made in November 2006 that a number-needed-to-treat (NNT) calculation was more appropriate and to continue recruitment until 2012. This duration of follow-up would be the maximum period of time required to generate either a significantly different treatment effect or a point estimate for the NNT to prevent one primary end point per year of > 100, with 95% confidence that NNT is greater than 50.

Rates of the primary and secondary end points and treatment changes were compared between arms on an intention-to-treat basis using Kaplan-Meier curves and log-rank tests, with censoring at the time of death, withdrawal from the study, or last visit for patients lost to follow-up. For the quality-of-life analysis, EORTC QLQ-C30 summary scores21 were calculated for each patient questionnaire and compared between the arms using linear mixed effects models. Hemoglobin, white cell, and platelet counts were analyzed for patients with at least four blood count recordings available in the first 120 months on the study by using linear mixed effects models. Additional details are provided in the Data Supplement.

Patients and Treatment

The PT-1 intermediate-risk trial randomly assigned 382 patients to receive aspirin alone (190 patients) or hydroxycarbamide plus aspirin (192 patients) between July 21, 1997, and July 31, 2012 (Fig 1). Twenty-four patients who were identified after random assignment to be ineligible for trial entry (incorrect diagnosis or risk group) were excluded from the analysis (Fig 1). Median duration of follow-up was 73 months (range, 0 to 187 months): 73 months in the aspirin-alone arm (range, 3 to 183 months) and 73 months in the hydroxycarbamide-plus-aspirin arm (range, 1 to 187 months). Total follow-up was 2,373 patient-years.

The two arms were well matched with respect to laboratory and clinical features at diagnosis and trial entry (Table 1). Of the 259 patients with molecular information, 141 (54%) had a JAK2 V617F mutation, 68 (26%) a CALR mutation, 13 (5%) an MPL mutation, and 37 (14%) none of these mutations. Of 177 patients for whom a trephine biopsy at trial entry was reviewed centrally, 167 (94%) met British Committee for Standards in Haematology diagnostic criteria for ET,23 other diagnoses being myeloproliferative neoplasm, unclassifiable (5 patients) and primary MF (5 patients). One hundred forty-three (81%) met WHO diagnostic criteria for ET.

Changes in cytoreductive treatment were permitted at the discretion of the treating physician and are shown, with reasons, in Figure 1. In the aspirin-alone arm, 82 (47%) of 176 patients in the analysis population started a cytoreductive agent; the median time without cytoreduction from trial entry (ie, time until treatment change, death, consent withdrawal, loss to follow-up, or end of trial) was 36 months. In the hydroxycarbamide-plus-aspirin arm, 39 (21%) of 182 patients in the analysis population had a change in treatment, defined as stopping hydroxycarbamide and/or starting an alternative cytoreductive agent; the median time on trial hydroxycarbamide from trial entry (ie, time until treatment change, death, consent withdrawal, loss to follow-up, or end of trial) was 55 months.

Vascular End Points and Death

Numbers of vascular events and deaths are provided in Table 2. There was no significant difference between the two arms in the composite primary end point of time from random assignment to arterial or venous thrombosis, serious hemorrhage, or death from vascular causes (11 events in each arm; odds ratio [OR] for hydroxycarbamide plus aspirin compared with aspirin alone was 0.98 [95% CI, 0.42 to 2.25; P = 1.0; Fig 2A, Table 2). The incidence of these vascular events during follow-up was 0.93 per 100 patient-years (95% CI, 0.61 to 1.41 per 100 patient-years). There remained no significant difference in this end point in a prespecified secondary analysis, in which patients were censored...
Fig 2. Kaplan-Meier curves for the (A) primary composite end point of arterial or venous thrombosis, serious hemorrhage, or death from vascular causes; (B) overall survival; (C) composite end point of rate of transformation to myelofibrosis (MF), acute myeloid leukemia (AML), or myelodysplastic syndrome (MDS); (D) transformation to polycythemia vera (PV); (E) composite end point of any major disease-related complication (arterial thrombosis, venous thromboembolism, major hemorrhage, transformation to AML, MDS, MF, or death from any of these causes). (F) Box plots showing summary scores for the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 questionnaire, performed at baseline and annually for 5 years after study entry; there were no significant differences between the study arms at any time point. Box and whisker plot showing median and vertical whisker showing 2nd and 98th percentile. HC, hydroxyurea.
on reaching the age of 60 years, because most would start
cytoreduction at this age if they were not already receiving it (OR,
0.54; 95% CI, 0.19 to 1.53; \( P = .3 \)). There were no significant
associations between the rate of the primary end point and the
presence of JAK2, CALR, or MPL mutations, age at trial entry, sex,
or blood counts at diagnosis (hemoglobin, white cell count, platelet
count; all \( P > .05 \); data not shown).

There were seven deaths during follow-up in the aspirin-alone
arm and 10 in the hydroxycarbamide-plus-aspirin arm (Table 2),
with no significant difference in overall survival between the arms
(OR, 1.4; 95% CI, 0.54 to 3.61; \( P = .5 \); Fig 2B).

**Disease Transformation and All Disease-Related
Complications**

The rate of disease transformation was low in both arms
(Table 2). In the aspirin-alone arm, five patients developed
transformation to MF, two to AML (one after MF), and none
transformed to MDS. In the hydroxycarbamide-plus-aspirin arm,
one patient developed transformation to MF, three to AML, and
one to MDS. There was no significant difference in the composite
end point of rate of transformation to MF, AML, or MDS (OR,
0.79; 95% CI, 0.24 to 2.58; \( P = .7 \); Fig 2C). In addition, six patients
in the aspirin-alone arm transformed to PV compared with none in
the hydroxycarbamide arm (\( P = .01 \); Fig 2D), in keeping with the
nonspecific effect of hydroxycarbamide in constraining
erythropoiesis. A prespecified analysis for any major disease-
related complication (ie, arteriole thrombosis, venous thrombo-
embolism, major hemorrhage, transformation to AML, MDS, or
MF, or death from any of these causes) did not show any
difference between the two arms (OR, 0.83; 95% CI, 0.41 to 1.7;
\( P = .6 \); Fig 2E).

**Adverse Events and Quality of Life**

There were no significant differences between the arms of the
study in the numbers of patients with specific adverse events, either
when symptoms were considered individually or when grouped by
system (eg, gastroenterologic, dermatologic). Selected adverse
events are listed in Table 3. There were no significant differences in
EORTC QLQ-C30 quality-of-life summary scores \(^{21} \) between the
arms at any year after study entry (Fig 2F).

**Impact of Treatment Changes**

Because patients in the aspirin-alone arm were more likely to
undergo a change in their allocation to cytoreductive therapy
(\( P < .001 \); Figs 1 and 3A), we considered the possibility that this
may have masked a difference between the arms. However the
primary end point continued to show no difference between the
arms in a post hoc analysis in which patients were censored at age
60 years or on the date of therapy initiation or change to their
cytoreductive treatment (OR, 0.72; 95% CI, 0.16 to 3.19; \( P = .7 \)).
Moreover, hemoglobin levels, white cell counts, and platelet
counts were all significantly lower in the hydroxycarbamide-plus-
aspirin arm from early in the study, and CIs started to overlap
only approximately 5 to 6 years after trial entry for platelet and
white cell counts and 3 to 4 years after trial entry for hemoglobin
(Fig 3B-D).

Previous studies have shown that, compared with no cytoreduction
or anagrelide, hydroxycarbamide reduces the risk of vascular events
in patients with high-risk ET.\(^ {8,9} \) We report the only (to the best of
our knowledge) prospective, randomized study to have compared
treatment with and without cytoreduction in ET patients who lack
high-risk factors. Patients were recruited over a 15-year period, and
the median duration of follow-up was more than 6 years, with a
total follow-up of 2,373 patient years, making this study unique
within the field.

This trial compared two treatment strategies in patients with
ET age 40 to 59 years who lacked high-risk factors and showed that
preemptive addition of hydroxycarbamide to aspirin did not re-
duce the risk of vascular events or myelofibrotic or leukemic
transformation. Our data indicate that the risk of significant
vascular events in this patient population is low and is not reduced
by preemptive hydroxycarbamide. There was also no association
between the primary end point and blood counts at diagnosis. This
specific group of patients should therefore be treated without
cytoreduction until another clinical indication arises.

It has been suggested that hydroxycarbamide may increase the
risk of leukemic transformation,\(^ {15} \) although this proposal remains
controversial.\(^ {14,17,18,23} \) Our results contribute the only data from a
prospective, randomized trial comparing hydroxycarbamide with
no cytoreduction in the myeloproliferative neoplasms in patients
who lack high-risk features. Rates of transformation to MF, AML,
and MDS were low, with no significant difference between the two arms over the course of the study. Hydroxycarbamide was also well tolerated; only 6% of patients allocated to the drug discontinued it as a result of adverse effects.

Limitations of this study reflect the fact that myeloproliferative neoplasms, most particularly ET, have a chronic course and so require long-term clinical trials. Such trials face inherent challenges, including predictable accumulation of changes to allocated treatment over time and the evolution of diagnostic criteria and risk stratification models. Long-term follow-up was important in this study because events can occur late in the disease, but long-term follow-up was reflected in changes in the risk profile of some patients during the study. Many patients in the aspirin-alone arm started cytoreduction during follow-up as a consequence of accepted clinical indications; similarly, some patients allocated to hydroxycarbamide plus aspirin changed or stopped cytoreduction during the study. Despite these changes, the primary end point showed no difference between the arms in a post hoc analysis with censoring at the time of treatment change, and blood counts remained significantly different between the arms for several years after trial entry. Treatment changes do, however, limit the conclusions that can be drawn about the long-term safety of hydroxycarbamide. A second limitation of the study is that a small number of patients were recruited at each center. We suspect that

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**Fig 3.** Treatment changes and blood counts during follow-up. (A) Kaplan-Meier curves showing changes from the allocated trial treatment (ie, patients in the aspirin-alone arm who started cytoreduction and patients in the hydroxycarbamide [HC]-plus-aspirin arm who stopped hydroxycarbamide and/or started an alternative cytoreductive agent). (B) Platelet counts, (C) white cell counts, and (D) hemoglobin levels during the study; mean and 95% CIs are shown. Baseline counts were not significantly different between the two arms (Table 1). The high density of early blood counts and the rapid change after starting hydroxycarbamide means that the spline curves of blood count data generate the false impression of a difference between the two arms at baseline, which is in fact not present. Treatment changes are shown as ticks below the x-axis. HC, hydroxycarbamide.
any selective recruitment was most likely to reflect the uncertain benefits and toxicities of hydroxycarbamide in this group of patients without previous disease complications, and we would not expect the generalizability of the results to be affected.

Diagnostic criteria for ET have been refined many times over the 15-year recruitment period of this study.11,22,24 Nonetheless, a high degree of concordance with current diagnostic criteria was observed on central review of diagnostic material. Concerning risk stratification, the plateletate threshold that defines high-risk disease has changed from $1,000 \times 10^3/L$ to $1,500 \times 10^3/L$,11,12 and the inclusion criteria of the study were modified accordingly. The recently proposed International Prognostic Score of Thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis) system suggests that patients with ET who are younger than age 60 years and who lack a prior thrombotic history could be subdivided into very-low-risk and low-risk groups according to the absence and presence, respectively, of a JAK2 mutation.25 It has been proposed that patients with a very low IPSET-thrombosis score might not require aspirin therapy,26 but this was not tested in our study. We did not identify a difference in vascular events between JAK2-mutated and -unmutated patients, in contrast to other studies,27,28 perhaps reflecting the low number of events and that molecular data were not available for all patients. Our data do not support preemptive cytoreduction, even in the subgroup of JAK2-mutated patients, in the absence of high-risk factors.

In conclusion, preemptive addition of hydroxycarbamide to aspirin did not reduce the risk of vascular events, myelofibrotic progression, or leukemic transformation in ET patients age 40 to 59 years who lacked high-risk factors for thrombosis or extreme thrombocytosis. Patients age 40 to 59 years without other clinical indications for treatment (such as previous thrombosis or hemorrhage) who have a platelet count < 1,500 $\times 10^3/L$ should not receive cytoreductive therapy.

REFERENCES


AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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