

The Rate of Progression to Polycythemia Vera or Essential Thrombocythemia in Patients with Erythrocytosis or Thrombocytosis

Marco Ruggeri, MD; Alberto Tositto, MD; Maurizio Frezzato, MD; and Francesco Rodeghiero, MD

Background: The clinical relevance of mild erythrocytosis (hematocrit > 0.48 in women or > 0.51 in men) or thrombocytosis (platelet count > 400×10^9 cells/L) in asymptomatic persons is uncertain.

Objective: To estimate the frequency of polycythemia vera or essential thrombocythemia in persons with erythrocytosis or thrombocytosis in a general population.

Design: Cohort study.

Setting: Vicenza, Italy.

Participants: 10 000 community dwellers age 18 to 65 years and enrolled in the Vicenza Thrombophilia and Atherosclerosis project.

Measurements: Platelet count and hematocrit at baseline in all participants and at second follow-up if baseline results were abnormal. Measurement of erythrocyte sedimentation rate, peripheral arterial saturation, serum erythropoietin level, and leukocyte alkaline phosphatase level; chest radiography; abdominal ultrasonography; and occult fecal blood testing were done in persons with confirmed high hematocrit or platelet counts. Polycythemia

vera and essential thrombocythemia were diagnosed according to the Polycythemia Study Group criteria.

Results: At baseline examination, 1 person had polycythemia vera, 1 had essential thrombocythemia, 88 had erythrocytosis, and 99 had thrombocytosis. Second examination confirmed erythrocytosis in 40% (95% CI, 29% to 51%) and thrombocytosis in 8% (CI, 4% to 15%) of those with abnormal baseline results. Among persons with confirmed abnormalities, further evaluation revealed 11 with idiopathic erythrocytosis, 2 with polycythemia vera (3/10 000 [CI, 0.6 to 8.7/10 000]), and 3 with essential thrombocythemia (4/10 000 [CI, 1.09 to 10.2/10 000]). After 5 years of follow-up, 1 additional person with a high platelet count developed essential thrombocythemia, and no persons developed hemorrhagic or thrombotic complications.

Conclusions: The prevalences of polycythemia vera and essential thrombocythemia were higher than expected in this general population. However, the risks for developing polycythemia vera, essential thrombocythemia, or associated vascular complications in persons with erythrocytosis or thrombocytosis were low.

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For author affiliations, see end of text.

An elevated hematocrit or platelet count in an otherwise healthy person has become an increasingly common finding since the introduction of the automated blood cell count. However, the optimal clinical approach for these patients remains elusive. According to discharge diagnoses from hospitals or cancer registries, polycythemia vera and essential thrombocythemia are considered two rare disorders, with a prevalence of approximately 1 to 5 cases per million persons (1–12). However, population-based estimates of the prevalences of these conditions are not available. Furthermore, the risks for developing overt polycythemia vera, overt essential thrombocythemia, or associated complications in persons with erythrocytosis or thrombocytosis is unknown. As a result, it is unknown whether persons with erythrocytosis or thrombocytosis need immediate evaluation or close follow-up or whether a more conservative approach is reasonable.

We sought to estimate the prevalences of polycythemia vera and essential thrombocythemia in a cohort of healthy persons from the general population. We also prospectively evaluated the outcomes over 5 years of persons with isolated, persistently high hematocrit or platelet counts.

METHODS

Study Sample

We evaluated the first 10 000 persons enrolled in the Vicenza Thrombophilia and Atherosclerosis (VITA) project. In this cross-sectional study, eligible persons were

white, lived in the township of Vicenza in northern Italy, were between 18 and 65 years of age on 1 January 1993, and were born on an even date. Details of the recruitment of the cohort have been published elsewhere (13). Blood sampling was delayed in persons with a history of fever, surgery, or trauma in the preceding 2 weeks or after delivery in pregnant participants. Data on life habits, personal and familial history of venous and arterial thrombosis, and a previous diagnosis of hematologic disease (including myeloproliferative disorders) were collected by direct interview using standardized questionnaires (14). Medical records were obtained in persons with a personal history suggestive of polycythemia vera or essential thrombocythemia. The local Ethical Committee approved the study protocol, and all participants gave informed consent.

Measurements

Blood was collected in EDTA-containing Vacutainer tubes (Becton, Dickinson and Co., Franklin Lakes, New Jersey) in fasting persons before 10:00 a.m. An automated blood count was performed within 2 hours by using the impedance particle counting method in a Coulter T-890 cell counter (Beckman Coulter, Miami, Florida). The instrument performance was checked daily; the between-day coefficient of variation for hematocrit and platelet count was 2.1% and 3.3%, respectively. A peripheral blood smear was examined when the leukocyte or platelet count was abnormal. Fibrinogen levels were measured on citrated

plasma with the prothrombin time–derived method on an IL-800 automated coagulometer (Instrumentation Laboratory, Milan, Italy).

Screening Strategy

In a pilot study, we evaluated the hematocrit at presentation in 100 consecutive patients with polycythemia vera who received a diagnosis at our department and who had increased erythrocyte mass, as determined by ^{51}Cr -labeled erythrocytes (defined according to the Polycythemia Vera Study Group criteria as 36 mL/kg of body weight in men and 32 mL/kg in women). Measurements were taken with the same cell counter subsequently used for the present study. The hematocrit in all male and female patients with polycythemia vera was greater than 0.51 or greater than 0.48, respectively. These hematocrit values were chosen as sex-specific cutoff values before the study was started. The cutoff value for high platelet count was arbitrarily set at 400×10^9 cells/L. In the VITA project, all persons with a hematocrit or platelet count greater than the previously defined values had new clinical examinations at least 6 months (median, 8 months) later. In all persons with confirmed high hematocrit or platelet count, we also obtained erythrocyte sedimentation rate, peripheral arterial oxygen saturation (SpO_2 capillary-blood oximeter NC20, Nellcore, Milan, Italy), and serum erythropoietin and leukocyte alkaline phosphatase levels; chest radiography; abdominal ultrasonography; and a fecal occult blood test.

Diagnostic Criteria for Polycythemia Vera

A diagnosis of polycythemia vera was considered in persons with a confirmed high hematocrit and a normal arterial oxygen saturation in association with splenomegaly, normal or reduced serum erythropoietin level (<30 U/L), or increased leukocyte alkaline phosphatase activity. In these patients, a definitive diagnosis was made by invasive evaluation (increased erythrocyte volume with ^{51}Cr -labeled cells; diagnostic bone marrow biopsy; analysis of the t(9;22) translocation (Philadelphia chromosome) with karyotype and *bcr/abl* fusion gene analysis; and karyotype abnormalities on bone marrow cultures).

Diagnostic Criteria for Essential Thrombocythemia

A diagnosis of essential thrombocythemia was considered in persons with a platelet count greater than 600×10^9 cells/L at the second examination. This finding had to be associated with normal erythrocyte sedimentation rate and serum iron, transferrin, and ferritin concentrations; a negative result on fecal occult blood testing; and normal chest radiograph and abdominal ultrasonogram. In these persons, the diagnosis was confirmed by invasive evaluation (diagnostic bone marrow biopsy or lack of Philadelphia chromosome on bone marrow cultures and lack of *bcr/abl* fusion gene).

All cases of idiopathic erythrocytosis (defined as high hematocrit with no secondary causes and no features of polycythemia vera) or polycythemia vera were followed for 5 years. All persons with a confirmed diagnosis of throm-

Context

According to data from hospitalized patients and cancer registries, the estimated prevalences of polycythemia vera and essential thrombocythemia are 1 to 5 cases per million persons. Population-based estimates have not been available.

Contribution

In this study of 10 000 residents of Vicenza, Italy, the prevalence of polycythemia vera and essential thrombocythemia are 300 and 400 cases per million persons, respectively. No thrombotic or vascular complications occurred over 5 years of follow-up in these otherwise healthy 18- to 65-year-old adults.

Implications

Polycythemia vera and essential thrombocythemia are more common than previously thought, but complications are rare. Complications may be higher in older and sicker patients.

–The Editors

bocytosis or essential thrombocythemia were prospectively followed for 5 years. Thus, all patients with a definitive diagnosis of polycythemia vera and essential thrombocythemia had a clear picture of polycythemia vera or essential thrombocythemia according to the Polycythemia Vera Study Group criteria. Moreover, all persons with an increased hematocrit or platelet count at enrollment in the VITA project were followed for at least 5 years.

Statistical Analysis

Data were analyzed by using Stata software, version 8.0 (Stata Corp., College Station, Texas). Differences between groups were computed by using the Mann–Whitney test and the Fisher exact test, as appropriate; a two-sided *P* value less than 0.05 was considered statistically significant. Exact confidence intervals for the prevalence data were computed by assuming a Poisson distribution of polycythemia vera and essential thrombocythemia cases in the general population (15).

Role of the Funding Source

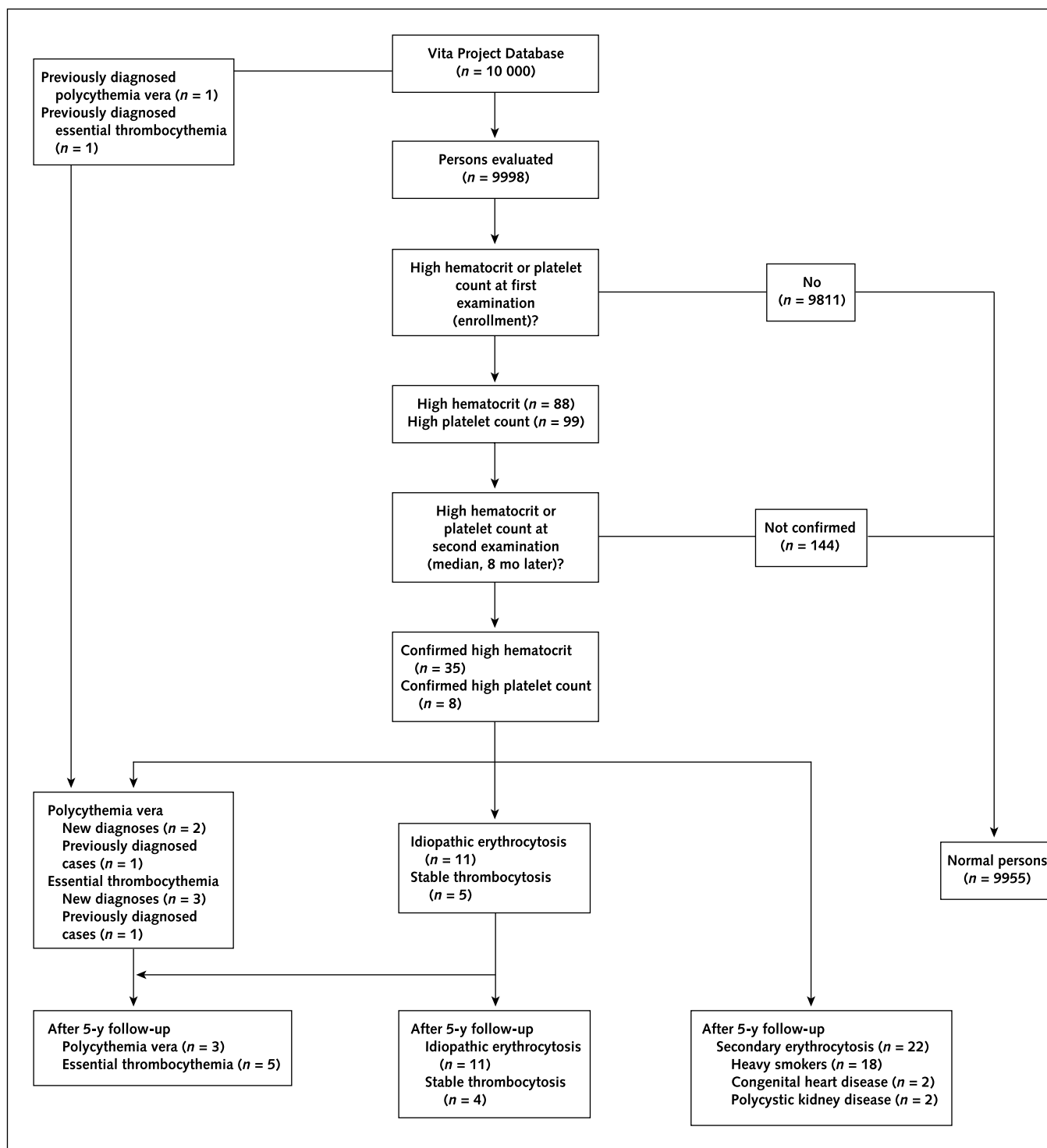
The funding sources had no role in the design, conduct, analysis, and reporting of the study or in the decision to submit the manuscript for publication.

RESULTS

From June 1993 to September 1996, 13 780 eligible persons were contacted, and 10 059 were enrolled in the VITA project; the total accrual rate was 73%. The sample composition was almost identical to that of the original eligible sample. There were more women (53.4%) than men (46.6%) in the study group; the average age of men and women (43 years) was similar.

We analyzed the data from the first 10 000 consecu-

Figure. Flow chart of study participants and results.



tively enrolled persons. Within this cohort, 1 person had a 2-year history of polycythemia vera, and 1 had a 1-year history of essential thrombocythemia. These 2 persons were excluded from subsequent studies but were included in the prevalence estimate. In the remaining 9998 persons, the mean hematocrit value was 0.41 (0.44 in men vs. 0.39 in women) ($P < 0.001$); the 99th percentile was 0.46 for

women and 0.50 for men. Therefore, our a priori cutoff for hematocrit values (0.48 for women and 0.51 for men) was greater than the 99th percentile of the studied sample. Women had higher mean platelet counts than did men (244 vs. 226×10^9 cells/L) ($P < 0.001$); the 99th percentile was similar (409 and 381×10^9 cells/L for women and men, respectively). Therefore, our a priori cutoff ($400 \times$

Table 1. Patient Characteristics at Second Examination*

Characteristic	Normal on First Examination (n = 9811)	Erythrocytosis Confirmed (n = 35)	P Value vs. Normal	Thrombocytosis Confirmed (n = 8)	P Value vs. Normal
Men, n (%)	5262 (46)	31 (88.5)	0.001	3 (37)	>0.2
Mean age ± SD, y	43.4 (13)	48.1 (14)	0.03	51 (8)	0.09
BMI > 25 kg/m ² , n (%)	3662 (37)	21 (60)	0.005	4 (50)	>0.2
Smoker, n (%)	2545 (25.9)	18 (51)	0.001	3 (37)	>0.2
Leukocyte count > 10 × 10 ⁹ cells/L, n (%)	399 (4)	5 (14.2)	0.013	3 (37)	0.003
Fibrinogen level > 3.0 g/L, n (%)	3299 (33.6)	14 (40)	>0.2	4 (50)	>0.2

* BMI = body mass index.

10⁹ cells/L) was greater than the 99th percentile for men and around this limit for women.

Among the 9998 persons, we identified 88 with high hematocrit values (71 men and 17 women) and 99 with high platelet counts (29 men and 70 women) in the first examination. At a second examination, performed a median of 8 months later (range, 6 to 14 months) in only these persons, a high hematocrit value was confirmed in 35 of 88 (40% [CI, 29% to 51%]) persons. An abnormally high platelet count was confirmed in 8 of 99 persons (8% [CI, 4% to 15%]). Confirmation of a high platelet count was strongly dependent on the platelet count at first examination. Thrombocytosis greater than 600 × 10⁹ cells/L was confirmed in 3 of 6 persons (50%), and thrombocytosis between 400 and 600 × 10⁹ cells/L was confirmed in 5 of 93 (5.3%) persons. The observed lack of reproducibility of the abnormal results is probably related to a preanalytical variability (16) or the presence of a concomitant, transient clinical condition, such as stress or smoking (17).

After thorough investigation of the 35 persons with confirmed high hematocrit values, 2 patients fulfilled the criteria for polycythemia vera, secondary erythrocytosis was diagnosed in 22 patients (18 heavy smokers, 2 persons with polycystic kidney disease, and 2 persons with congenital heart disease), and idiopathic erythrocytosis was diagnosed in 11 patients. After a 5-year follow-up of all 33 persons not immediately fulfilling a diagnosis of polycythemia vera, 2 from the group with idiopathic erythrocytosis were treated with phlebotomy because their hematocrit values increased to greater than 0.55; in the remaining 9 patients, the hematocrit value remained stable (0.51 to 0.53) (Figure).

After thorough investigation, 3 of the 8 persons with confirmed thrombocytosis fulfilled the diagnostic criteria for essential thrombocythemia. After 5-year follow-up of the remaining 5 persons with mild thrombocytosis (between 400 and 600 × 10⁹ cells/L), 1 met the full criteria for essential thrombocythemia and 4 had a stable platelet count (range, 450 to 547 × 10⁹ cells/L) (Figure). A comparison of patients with a diagnosis of polycythemia vera with normal persons showed significant differences in mean age, body mass index, smoking status, and leukocyte count, whereas persons with essential thrombocythemia differed only in leukocyte count (Table 1).

Thus, a complete hematologic evaluation of this co-

hort of 10 000 patients led to the identification of 3 cases of polycythemia vera (prevalence, 3/10 000 [CI, 0.6 to 8.7/10 000]) and of 4 cases of essential thrombocythemia (prevalence, 4/10 000 [CI, 1.09 to 10.2/10 000]). Table 2 presents the clinical characteristic of these patients at diagnosis and after 5-year follow-up.

DISCUSSION

We undertook this study to evaluate the clinical significance of high hematocrit or platelet count in a large, population-based cohort. Asymptomatic polycythemia vera and essential thrombocythemia were more prevalent in this general population than anticipated. From a cohort of 10 000 persons, we observed 3 cases of polycythemia vera and 4 cases of essential thrombocythemia, with an estimated prevalence of 300 and 400 cases per million persons, respectively. Previous studies of patients followed in hematology clinics suggested that the prevalence of polycythemia vera ranged from 0.8 to 4.9 cases per million persons (1), whereas no data are available in the literature about the prevalence of essential thrombocythemia. The observed 100-fold increased prevalence of polycythemia vera found in our study is probably related to incomplete determination of asymptomatic cases in the previous hospital-based studies. However, our prevalence estimates are similar to estimates extrapolated from the incidence of new polycythemia vera and essential thrombocythemia cases diagnosed in the population of Olmsted County, Minnesota (8, 11). We suspect that our estimates are conservative because persons older than 65 years were not included: Polycythemia vera and essential thrombocythemia primarily affect middle-age persons, and the average age at diagnosis is 60 years (18).

The second main finding of the study comes from the prospective observation of persons with a high hematocrit or platelet count at baseline. Of the persons with high hematocrit values, only 42% had a high hematocrit value confirmed on second examination, and polycythemia vera was subsequently diagnosed in only 3.4% (3 of 87). In persons with high platelet counts at baseline, essential thrombocythemia was diagnosed in 50% of those with an initial platelet count greater than 600 × 10⁹ cells/L but was uncommon in persons with platelet counts of 400 to

Table 2. Clinical Data at Baseline, 6 Months, and 5 Years*

Patient	Diagnosis	Sex	Age	Baseline						
				Platelet Count <i>y</i> $\times 10^9$ cells/L	Hematocrit	Presence of Palpable Spleen	LAP Score > 140	Leukocyte count > 10×10^9 cells/L	Erythropoietin Level < 10 U/L	Karyotype Abnormal
1	ET	F	56	900	0.35	Yes	No	No	No	No
2	ET	M	61	867	0.38	No	No	No	No	No
3	ET	F	38	734	0.36	No	No	No	No	No
4	ET	F	42	624	0.36	No	No	No	No	No
5	ET	F	27	485	0.41	No	No	Yes	No	No
6	PV	M	55	612	0.45†	Yes	Yes	Yes	Yes	No
7	PV	M	48	350	0.53	No	Yes	No	Yes	Yes‡
8	PV	M	52	235	0.53	Yes	Yes	Yes	Yes	No

* ET = essential thrombocythemia; F = female; LAP = leukocyte alkaline phosphatase; M = male; PV = polycythemia vera.

† Patient was receiving phlebotomy therapy.

‡ 46, xy, del(19).

600×10^9 cells/L. Prospective evaluation of 93 persons with platelet counts between 400 and 600×10^9 cells/L at baseline showed that at 5 years, 4 persons had persistent, asymptomatic thrombocytosis and 1 developed essential thrombocythemia. The probability of developing essential thrombocythemia at 5 years was about 1% for persons with an initial platelet count greater than 400×10^9 cells/L. Although we observed some slight differences in clinical and laboratory characteristics between persons with a diagnosis of polycythemia vera and essential thrombocythemia and normal persons, the number of identified patients with polycythemia vera and essential thrombocythemia was too limited to evaluate the diagnostic utility of these factors.

Among persons with confirmed high hematocrit or high platelet count at the second examination, we observed no vascular disturbances during the entire follow-up. At baseline, none of these persons had a history of previous vascular events. It seems that the risk for venous or arterial thromboembolism is low in persons who are 18 to 65 years of age, are asymptomatic, and have a confirmed high hematocrit or high platelet count.

Our findings in a geographically limited population of relatively young persons without comorbid disease who were followed for only 5 years may not apply to older, sicker patients. However, they suggest that the risk for thrombotic complications in polycythemia vera or essential thrombocythemia may be lower than previously estimated. Thrombotic complications in patients with polycythemia vera or essential thrombocythemia, which range from 10% to 20% (19–21), have been estimated in hospital-based cohorts. The overall thrombotic risk should be noticeably lower after inclusion of asymptomatic patients with polycythemia vera or essential thrombocythemia, thus raising important questions about the need for primary prophylaxis or cytoreductive treatment in asymptomatic patients.

Moreover, our data help suggest a reasonable clinical approach to patients with an incidental finding of a high hematocrit or platelet count. A complete blood count after 6 to 12 months could exclude from further investigation

about 60% and 90% of cases with an incidentally discovered, mildly increased hematocrit or platelet count, respectively. Exclusion of secondary causes of thrombocytosis or erythrocytosis by physical examination and laboratory testing is always warranted. Patients with a platelet count persistently between 400 and 600×10^9 cells/L could be re-evaluated every 2 years without need for immediate specialized and invasive procedures; however, a more stringent diagnostic approach is advisable in patients with a platelet count greater than 600×10^9 cells/L. In patients with a confirmed high hematocrit count and no obvious cause of secondary erythrocytosis, a complete hematologic evaluation should be performed to differentiate polycythemia vera from primary erythrocytosis.

The efficiency of the diagnostic work-up is the most crucial validity issue in our study. The diagnostic criteria introduced by the Polycythemia Vera Study Group for the diagnosis of polycythemia vera (22, 23) include the use of a radioactive tracer for erythrocyte mass measurement. This procedure was introduced to increase the specificity of the diagnosis by ruling out so-called apparent polycythemia; it is the most frequently used test for the diagnosis of polycythemia, as reported in a recent U.S. survey (24). However, the clinical utility of erythrocyte mass measurement has been recently challenged, especially after the introduction of the serum erythropoietin assay (25). Our study demonstrates that clinical follow-up, with careful exclusion of secondary causes of erythrocytosis, may be safe and possibly could avoid an expensive evaluation in most asymptomatic patients with a presumptive diagnosis of polycythemia vera. However, erythrocyte mass measurement may be recommended in symptomatic patients needing prompt diagnosis and treatment or in patients who cannot be followed regularly. Regarding the diagnosis in persons with mild thrombocytosis, a possible evolution into essential thrombocythemia was excluded by a 5-year follow-up (26).

In conclusion, in this population-based epidemiologic study, we identified 8 cases of chronic myeloproliferative disease in 10 000 persons. Although these patients had no

Table 2—Continued

6 Months		5 Years		Therapy Received during the 5-Year Follow-Up
Platelet Count	Hematocrit	Platelet Count	Hematocrit	
$\times 10^9$ cells/L		$\times 10^9$ cells/L		
2096	0.36	540	35	Hydroxyurea
1130	0.38	435	37	Busulfan
1000	0.37	980	38	None
654	0.38	865	37	None
490	0.41	1227	42	None
620	0.46	680	44	Phlebotomy
360	0.53	650	46	Phlebotomy, aspirin
210	0.54	367	45	Phlebotomy

clinical symptoms before diagnosis and did not develop major vascular disturbances during 5-year follow-up, our results should be considered with caution. The thrombotic risk may be noticeably different in persons with other risk factors, such as advanced age, hypertension, smoking, or diabetes. Furthermore, an occurrence of thrombosis or transformation into myelofibrosis or acute myeloid leukemia has been observed in up to 30% of the patients followed for a more prolonged period (12, 20, 21). Specific therapy was initiated in 5 of the identified patients (Table 2), but the cost–benefit ratio of the treatment of asymptomatic persons with polycythemia vera or essential thrombocythemia is still uncertain. With the ever-increasing availability of routine blood cell counts and the high prevalence of chronic myeloproliferative disorders observed in this study, prospective evaluation of cohorts of asymptomatic patients is required to establish the need for treatment of asymptomatic patients who are discovered incidentally.

From S. Bortolo Hospital, Vicenza, Italy.

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Requests for Single Reprints: Francesco Rodeghiero, MD, Department of Hematology, S. Bortolo Hospital, 36100 Vicenza, Italy; e-mail, rodeghiero@hemato.ven.it

Current author addresses and author contributions are available at www.annals.org.

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Current Author Addresses: Drs. Ruggeri, Tosetto, Frezzato, and Rodeghiero: Department of Hematology, S. Bortolo Hospital, via Rodolfi, 37, 36100 Vicenza, Italy.

Author Contributions: Conception and design: M. Ruggeri, A. Tosetto. Analysis and interpretation of the data: M. Ruggeri, A. Tosetto. Drafting of the article: M. Ruggeri, A. Tosetto, F. Rodeghiero. Critical revision of the article for important intellectual content: M. Ruggeri, A. Tosetto, F. Rodeghiero.

Final approval of the article: M. Ruggeri, A. Tosetto, F. Rodeghiero. Provision of study materials or patients: M. Frezzato. Statistical expertise: A. Tosetto. Obtaining of funding: F. Rodeghiero. Administrative, technical, or logistic support: M. Frezzato. Collection and assembly of the data: M. Frezzato.