

## Brief report

## Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients

\*Alessandra Carobbio,<sup>1</sup> \*Juergen Thiele,<sup>2</sup> \*Francesco Passamonti,<sup>3</sup> Elisa Rumi,<sup>3</sup> Marco Ruggeri,<sup>4</sup> Francesco Rodeghiero,<sup>4</sup> Maria Luigia Randi,<sup>5</sup> Irene Bertozzi,<sup>5</sup> Alessandro M. Vannucchi,<sup>6</sup> Elisabetta Antonioli,<sup>6</sup> Heinz Gisslinger,<sup>7</sup> Veronika Buxhofer-Ausch,<sup>7</sup> Guido Finazzi,<sup>1</sup> Naseema Gangat,<sup>8</sup> \*Ayalew Tefferi,<sup>8</sup> and \*Tiziano Barbui<sup>1</sup>

<sup>1</sup>Ospedali Riuniti di Bergamo, Bergamo, Italy; <sup>2</sup>University of Cologne, Cologne, Germany; <sup>3</sup>University of Pavia, Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia, Italy; <sup>4</sup>S. Bortolo Hospital, Vicenza, Italy; <sup>5</sup>University of Padua, Padua, Italy; <sup>6</sup>University of Florence, Florence, Italy; <sup>7</sup>Medical University of Vienna, Vienna, Austria; and <sup>8</sup>Mayo Clinic, Rochester, MN

In an international collaborative study, a central histologic review identified 891 patients with essential thrombocythemia, strictly defined by World Health Organization criteria. After a median follow-up of 6.2 years, 109 (12%) patients experienced arterial (n = 79) or venous (n = 37) thrombosis. In multivariable analysis, predictors of arterial thrombosis included age more than 60 years (P = .03; hazard ratio

[HR] = 1.7), thrombosis history (P = .003; HR = 2.1), cardiovascular risk factors including tobacco use, hypertension, or diabetes mellitus (P = .007; HR = 1.9), leukocytosis ( $> 11 \times 10^9/L$ ; P = .04; HR = 1.7), and presence of *JAK2V617F* (P = .009; HR = 2.6). In contrast, only male gender predicted venous thrombosis. Platelet count more than  $1000 \times 10^9/L$  was associated with a lower risk of arterial thrombo-

sis (P = .007; HR = 0.4). These associations, except the one with leukocytosis, remained significant (or near significant) when analysis was restricted to *JAK2V617F*-positive cases. The current study clarifies the contribution of specific disease and host characteristics to the risk of arterial versus venous thrombosis in essential thrombocythemia. (*Blood*. 2011;117(22):5857-5859)

## Introduction

Essential thrombocythemia (ET) is a myeloproliferative neoplasm characterized by specific bone marrow morphology, increased risk of thrombohemorrhagic complications, and a natural propensity toward leukemic or fibrotic transformation. Until 2001, diagnostic criteria that were adopted for use in clinical trials, observational studies, and routine clinical practice were those of the Polycythemia Vera Study Group (PVSG). Since 2001, and particularly in 2008,<sup>1</sup> diagnostic criteria proposed by the World Health Organization (WHO) classification system for hematopoietic tumors have replaced the PVSG criteria and provided clear and concise guidelines for the diagnosis of ET and in its distinction from early/prefibrotic primary myelofibrosis.<sup>2</sup> In a recent paper, we showed that survival and disease progression in ET are significantly influenced by accurate morphologic diagnosis.<sup>3</sup>

In the current study, we examined the integrity of currently established or suspected risk factors for thrombosis, in the context of strict WHO diagnostic criteria for ET. Our large sample size allowed for separate analysis of arterial versus venous events as well as additional analysis restricted to *JAK2V617F*-positive cases.

## Methods

Clinicians and pathologists from 7 international centers of excellence for myeloproliferative neoplasm convened to create a clinicopathologic database of 1104 patients previously diagnosed and treated as ET. The study was approved by the institutional review board of each institution. Study

eligibility criteria included availability of treatment-naïve bone marrow specimens obtained within one year of diagnosis. All bone marrows subsequently underwent a central rereview by one of the authors (J.T.), of the WHO chapters on diagnostic criteria for ET, polycythemia vera, and primary myelofibrosis. The central histology review by J.T. was completely blinded to outcome data, which was analyzed after the completion of the histopathology review. Diagnosis was confirmed as ET in 891 patients (81%) and revised to early/prefibrotic primary myelofibrosis in 180 (16%); 33 cases were not evaluable. The current manuscript focuses on the 891 patients with WHO-defined ET, which included 438 (49%) patients with conventionally assigned low-risk disease (ie, age < 60 years and no history of thrombosis). Cytoreductive therapy was usually not given in low-risk patients at diagnosis. A proportion of them (37%) needed cytoreduction during follow-up because they met criteria of high risk. In contrast, the great majority (76%) of high-risk patients at diagnosis were treated with cytoreductive therapy. Aspirin therapy, usually at lower doses, was documented in 602 (68%) patients.

For the purposes of the current study, we considered only major vaso-occlusive events: ischemic stroke, cerebral transient ischemic attacks, acute myocardial infarction, peripheral arterial thrombosis, and venous thromboembolism. All statistical analyses considered parameters at the time of initial diagnosis. Outcomes of interest were reported as rates per 100 patient-years as well as cumulative incidences calculated at 5, 10, and 15 years from the date of diagnosis. The Cox proportional hazard regression model was used for multivariable analysis, adjusting for sex, age more than or equal to 60 years, previous thrombotic event, laboratory parameters measured at diagnosis (hemoglobin, platelet count, and white blood cell count), *JAK2V617F* mutational status and need for chemotherapy, and

Submitted February 24, 2011; accepted April 4, 2011. Prepublished online as *Blood* First Edition paper, April 13, 2011; DOI 10.1182/blood-2011-02-339002.

\*A.C., J.T., F.P., A.T., and T.B. contributed equally to this study.

The online version of this article contains a data supplement.

The publication costs of this article were defrayed in part by page charge payment. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

© 2011 by The American Society of Hematology

**Table 1. Main outcome events during follow-up in 891 WHO-ET patients**

	No.	%	Rate, % patient-years (95% CI)
Patients with nonfatal thrombotic events	109	12	1.7 (1.4-2.1)
<b>Arterial</b>	79	9	1.2 (1.0-1.5)
AMI	17	2	0.26 (0.16-0.42)
Stroke-TIA	47	5	0.73 (0.54-0.97)
PAT	15	2	0.23 (0.14-0.38)
Venous (VTE)	37	4	0.6 (0.4-0.8)
Patients with fatal and nonfatal thrombotic events	119	13	1.9 (1.6-2.3)

AMI indicates acute myocardial infarction; TIA, cerebral transient ischemic attack; PAT, peripheral arterial thrombosis; and VTE, venous thromboembolism.

antiplatelet drugs during follow-up. *P* values < .05 were considered significant.

## Results and discussion

As shown in Table 1, after a median follow-up of 6.2 years (range, 0-27 years), the rate of fatal and nonfatal thrombotic events, among the 891 patients with WHO-defined ET, was 1.9% patient-years (95% confidence interval, 1.6-2.3 patient-years). The incidence of nonfatal arterial events (1.2% patient-years) was higher than that of venous events (0.6% patient-years). These results are similar to previous values reported on patient cohorts defined by PVSG criteria. For example, in the PT1 randomized hydroxyurea versus anagrelide clinical trial in high-risk ET,<sup>4</sup> the rate of major thrombosis among the hydroxyurea-treated group of patients was approximately 2% patient-years; in other observational studies that included patients diagnosed according to PVSG criteria, the corresponding rate ranged from 1.5% to 2.5% patient-years.<sup>5-7</sup> Therefore, in strictly WHO-defined ET, the incidence and type of major vascular events appear to be similar to what has been described for PVSG-defined ET. This particular observation is consistent with our previously reported findings that showed no significant difference in the incidence of thrombotic complications between ET and early/prefibrotic primary myelofibrosis.<sup>3</sup>

Table 2 shows the results of multivariable analysis of risk factors for all thrombotic events as well as arterial versus venous thrombosis. The most remarkable and relatively novel finding is the fact that only male sex (*P* = .04; hazard ratio [HR] = 2) predicted venous thrombosis. Although it is possible that sex differences in vascular anatomy and response to inflammation explain the increased risk of venous events in males,<sup>8</sup> additional studies are

needed to confirm the association between male sex and venous thrombosis in ET. Furthermore, because data extraction regarding history of thrombosis did not distinguish between arterial and venous thrombosis, we cannot conclude on the absence of a correlation between previous history of venous thrombosis and recurrence of the same. In addition, the therapeutic implication of this observation is unclear because it is unknown whether the same results would have been noted in the absence of specific therapy. Regardless, the observed paucity of clinical risk factors for venous thrombosis in ET warrants examination of novel laboratory markers instead; the latter might include cytokines and other markers of inflammation.<sup>9,10</sup>

In contrast to the findings regarding venous thrombosis, several factors were found to be independently predictive of arterial thrombosis (Table 2): age > 60 years (*P* = .03; HR = 1.7), history of thrombosis (*P* = .003; HR = 2.1), presence of cardiovascular risk factors in the form of tobacco use, hypertension, or diabetes mellitus (*P* = .007; HR = 1.9), leukocytosis (> 11 × 10<sup>9</sup>/L; *P* = .04; HR = 1.7), and presence of *JAK2V617F* (*P* = .009; HR = 2.6). The difference of risk factors between arterial and venous thrombosis may be related to a more specific pathogenetic role of leukocytosis and related inflammatory markers to induce a chronic endothelial dysfunction in arteries. These findings support the current use of a more aggressive treatment approach in older patients and in those with previous vascular events and suggest the need for prospective studies that examine the value of cytoreductive (and aspirin) therapy in the presence of cardiovascular risk factors, leukocytosis, or *JAK2V617F*. In the latter regard, it is important to note that a recent study suggested that aspirin therapy in low-risk ET was valuable in preventing venous thrombosis in *JAK2V617F*-positive patients and arterial thrombosis in those with cardiovascular factors.<sup>11</sup> This communication suggested a different risk factor profile for *JAK2V617F*-positive ET. We examined this possibility in the current study by restricting our analysis to *JAK2V617F*-positive patients; the results showed that leukocytosis was no longer a risk factor for thrombosis, whereas older age, thrombosis history, and cardiovascular risk factors retained borderline significance (supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). Regardless, taken together, these observations mandate that future studies involving cytoreductive drugs must be controlled for aspirin use and study patients should be stratified according to their *JAK2V617F* mutational status, leukocyte count, and presence or absence of cardiovascular risk factors.

Finally and somewhat unexpectedly, the presence of extreme thrombocytosis (platelet count > 1000 × 10<sup>9</sup>/L) independently associated with a lower risk of arterial thrombosis, in both the entire

**Table 2. Multivariate analysis for risk factors predicting fatal and nonfatal thrombotic events in the follow-up of 891 WHO-ET patients**

Parameters at diagnosis	Major thrombosis (n = 109)		Arterial thrombosis (n = 79)		Venous thrombosis (n = 37)	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age > 60 y	1.50 (1.00-2.25)	0.049	1.69 (1.05-2.73)	0.031	1.26 (0.63-2.52)	.506
Previous thrombosis	1.93 (1.27-2.91)	0.002	2.07 (1.28-3.34)	0.003	1.78 (0.86-3.66)	.119
Male sex	1.34 (0.91-1.95)	0.135	0.98 (0.62-1.54)	0.919	1.99 (1.03-3.83)	.039
CV risk factors*	1.56 (1.03-2.36)	0.038	1.91 (1.19-3.07)	0.007	0.77 (0.33-1.83)	.556
WBC > 11 × 10 <sup>9</sup> /L	1.14 (0.72-1.79)	0.583	1.66 (1.01-2.72)	0.044	0.52 (0.19-1.38)	.516
Hemoglobin < 12 g/dL	1.36 (0.58-3.18)	0.479	1.53 (0.60-3.93)	0.376	0.48 (0.06-3.72)	.479
Platelet count > 1000 × 10 <sup>9</sup> /L	0.50 (0.30-0.84)	0.009	0.42 (0.22-0.78)	0.007	0.97 (0.44-2.15)	.943
<i>JAK2V617F</i>	2.04 (1.19-3.48)	0.009	2.57 (1.27-5.19)	0.009	1.43 (0.65-3.11)	.372

Analysis adjusted also for chemotherapy and antiplatelet needs during follow-up.

CV indicates cardiovascular; and WBC, white blood cell count.

\*Smoking, arterial hypertension, and diabetes (at least one).

study population ( $n = 891$ ;  $P = .007$ ;  $HR = 0.4$ ) and the group of patients who were *JAK2V617F*-positive ( $n = 422$ ;  $P = .01$ ;  $HR = 0.2$ ). This observation, which can be explained by the occurrence of acquired von Willebrand syndrome in ET patients with extreme thrombocytosis,<sup>12</sup> is consistent with previous reports<sup>5</sup> and questions the wisdom of aggressive platelet-lowering therapy in low-risk patients with ET. However, we failed to demonstrate a correlation between extreme thrombocytosis and major bleeding.

## Acknowledgment

A.M.V. was supported by Associazione Italiana per la Ricerca sul Cancro (Milano) "Special Program Molecular Clinical Oncology  $5 \times 1000$ " to Associazione Italiana per la Ricerca sul Cancro-Gruppo Italiano Malattie Mieloproliferative.

## References

- Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood*. 2009;114(5):937-951.
- Tefferi A, Thiele J, Orazi A, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. *Blood*. 2007;110(4):1092-1097.
- Barbui T, Thiele J, Passamonti F, et al. Survival and risk of leukemic transformation in essential thrombocythemia are significantly influenced by accurate morphologic diagnosis: an international study on 1104 patients [abstract]. *ASH Annual Meeting Abstracts*. 2010;116:457.
- Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. *N Engl J Med*. 2005;353(1):33-45.
- Carobbio A, Finazzi G, Antonioli E, et al. Thrombocytosis and leukocytosis interaction in vascular complications of essential thrombocythemia. *Blood*. 2008;112(8):3135-3137.
- Passamonti F, Rumi E, Arcaini L, et al. Prognostic factors for thrombosis, myelofibrosis, and leukemia in essential thrombocythemia: a study of 605 patients. *Haematologica*. 2008;93(11):1645-1651.
- Tefferi A, Gangat N, Wolanskyj A. The interaction between leukocytosis and other risk factors for thrombosis in essential thrombocythemia. *Blood*. 2007;109(9):4105.
- Alvarado CM, Diaz JA, Hawley AE, Wroblewski SK, Sigler RE, Myers DD Jr. Male mice have increased thrombotic potential: sex differences in a mouse model of venous thrombosis. *Thromb Res*. 2011;127(5):478-486.
- Barbui T, Carobbio A, Finazzi G, et al. Inflammation and thrombosis in essential thrombocythemia and polycythemia vera: different role of C-reactive protein and pentraxin 3. *Haematologica*. 2011;96(2):315-318.
- Tefferi A, Vaidya R, Caramazza D, Finke C, Lasho T, Pardanani A. Circulating interleukin (IL)-8, IL-2R, IL-12, and IL-15 levels are independently prognostic in primary myelofibrosis: a comprehensive cytokine profiling study. *J Clin Oncol*. 2011;29(10):1356-1363.
- Alvarez-Larran A, Cervantes F, Pereira A, et al. Observation versus antiplatelet therapy as primary prophylaxis for thrombosis in low-risk essential thrombocythemia. *Blood*. 2010;116(8):1205-1210; quiz 1387.
- Budde U, Dent JA, Berkowitz SD, Ruggeri ZM, Zimmerman TS. Subunit composition of plasma von Willebrand factor in patients with the myeloproliferative syndrome. *Blood*. 1986;68(6):1213-1217.

## Authorship

Contribution: A.T., T.B., J.T., G.F., and A.C. designed the research, contributed patients, participated in data analysis and interpretation, and wrote the paper; J.T. reviewed all bone marrow histopathology; and all other authors either contributed patients or participated in reviewing bone marrow histopathology and read and approved the final draft.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Tiziano Barbui, Ospedali Riuniti di Bergamo, Largo Barozzi 1, Bergamo, 24128 Italy; e-mail: tbarbui@ospedaliriuniti.bergamo.it; or Ayalew Tefferi, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: tefferi.ayalew@mayo.edu.



**blood**®

2011 117: 5857-5859

doi:10.1182/blood-2011-02-339002 originally published  
online April 13, 2011

## **Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients**

Alessandra Carobbio, Juergen Thiele, Francesco Passamonti, Elisa Rumi, Marco Ruggeri, Francesco Rodeghiero, Maria Luigia Randi, Irene Bertozzi, Alessandro M. Vannucchi, Elisabetta Antonioli, Heinz Gisslinger, Veronika Buxhofer-Ausch, Guido Finazzi, Naseema Gangat, Ayalew Tefferi and Tiziano Barbui

---

Updated information and services can be found at:

<http://www.bloodjournal.org/content/117/22/5857.full.html>

Articles on similar topics can be found in the following Blood collections

[Brief Reports](#) (1941 articles)

[Clinical Trials and Observations](#) (4581 articles)

[Free Research Articles](#) (4596 articles)

[Myeloid Neoplasia](#) (1704 articles)

[Platelets and Thrombopoiesis](#) (739 articles)

[Thrombosis and Hemostasis](#) (1083 articles)

---

Information about reproducing this article in parts or in its entirety may be found online at:

[http://www.bloodjournal.org/site/misc/rights.xhtml#repub\\_requests](http://www.bloodjournal.org/site/misc/rights.xhtml#repub_requests)

Information about ordering reprints may be found online at:

<http://www.bloodjournal.org/site/misc/rights.xhtml#reprints>

Information about subscriptions and ASH membership may be found online at:

<http://www.bloodjournal.org/site/subscriptions/index.xhtml>