RESEARCH ARTICLE

Cerebral vein thrombosis in patients with Philadelphia-negative myeloproliferative neoplasms
An European Leukemia Net study

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To investigate the characteristics and clinical course of cerebral vein thrombosis (CVT) in patients with myeloproliferative neoplasms (MPN) we compared 48 patients with MPN and CVT (group MPN-CVT) to 87 with MPN and other venous thrombosis (group MPN-VT) and 178 with MPN and no thrombosis (group MPN-NoT) matched by sex, age at diagnosis of MPN ($\pm$5 years) and type of MPN. The study population was identified among 5,500 patients with MPN, from January 1982 to June 2013. Thrombophilia abnormalities were significantly more prevalent in the MPN-CVT and MPN-VT than in MPN-NoT group ($P = 0.015$), as well as the *JAK2* V617F mutation in patients with essential thrombocythemia ($P = 0.059$). Compared to MPN-VT, MPN-CVT patients had a higher rate of recurrent thrombosis (42% vs. 25%, $P = 0.049$) despite a shorter median follow-up period (6.1 vs. 10.3 years, $P = 0.019$), a higher long-term antithrombotic (94% vs. 84%, $P = 0.099$) and a similar cytoreductive treatment (79% vs. 70%, $P = 0.311$). The incidence of recurrent thrombosis was double in MPN-CVT than in MPN-VT group (8.8% and 4.2% patient-years, $P = 0.022$), and CVT and unprovoked event were the only predictive variables in a multivariate model including also sex, blood count, thrombophilia, cytoreductive, and antithrombotic treatment (HR 1.97, 95%CI 1.05–3.72 and 2.09, 1.09–4.00, respectively).
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■ Introduction

Essential thrombocythemia, polycythemia vera and myelofibrosis are Philadelphia chromosome-negative chronic myeloproliferative neoplasms (MPN) characterized by a clonal proliferation of an abnormal hematopoietic stem cell [1,2]. MPN can transform into MF and acute leukemia [3,4] and their natural history is distinguished by a tendency towards thrombotic and hemorrhagic complications, that are major causes of patients morbidity and mortality [5–7]. Thrombosis can involve arteries (acute myocardial infarction, ischemic cerebrovascular, or peripheral disease) or veins (deep vein thrombosis at various sites and pulmonary embolism), the former likely more frequent [5–7]. Venous thrombosis (VT) can occur in common sites as the deep circulation of the lower limbs but also in unusual sites. Indeed, typical manifestations of VT in patients with MPN are those of the splanchnic circulation (hepatic, portal, mesenteric, and splenic veins), particular in young women and, to a lesser extent, of the cerebral circulation [7,8]. Cerebral vein thrombosis (CVT) is a life-threatening disease that in the general population is rare, accounting for 3–4 cases every million adults, affects mainly women in fertile age because is strongly associated with the use of oral contraceptives or pregnancy [9]. In patients with MPN the prevalence of CVT is 1% or less [10–12] and among patients with CVT, MPN is concomitantly diagnosed in 3–7% of cases [12–14]. In the general population the natural history of CVT is characterized by a relatively good prognosis (80% of patients who survived the acute phase recover completely) [15] and low recurrence rate of VT, estimated 2–3% for CVT and 4–7% for other more common VTs [13,16]. No data are available on the natural history of CVT in patients with MPN. This multicenter, observational, retrospective study was aimed to evaluate the prevalence, characteristics, risk factors and clinical course of CVT in a large population of patients with MPN and to compare patients with CVT to those with VT at other sites and those without VT.

TABLE I. General Characteristics of the Study Population and Comparison of MPN-CVT Patients with MPN-VT or MPN-NoT Patients

	MPN-CVT patients	MPN-VT patients	p	MPN-NoT patients	p
N	48	87	–	178	–
Median age (range) at diagnosis of MPN	47 (17–84)	46 (15–86)	0.871	52 (18–82)	0.508
Median age (range) at thrombosis	48 (16–83)	52 (18-91)	0.764	–	
Female/Male (n)	27/21	48/39	0.904	105/73	0.733
Type of MPN (n) (%)					
Essential thrombocythemia (ET)	30 (63)	53 (61)	0.898	105 (59)	0.589
Polycythemia vera (PV)	11 (23)	24 (28)		51 (28)	
Primary myelofibrosis (MF)	6 (12)	7 (8)		21 (12)	
Post-ET or post-PV myelofibrosis	1 (2)	3 (3)		1 (1)	
$JAK2V617F$, n (%)[a]	35 (81)	58 (83)	0.843	110 (76)	0.103
$JAK2V617F$, n (%) in ET[b]	19 (76)	32 (78)	0.847	53 (55)	0.059
$JAK2V617F$ allelic burden, median (range)	21 (4–91)	31 (3–100)	0.455	30 (2–100)	0.520
MPL mutations, n (%)	1 (2)	0	NA	1 (0.5)	NA
EEC, n (%)	6 (13)	8 (9)	0.632	10 (6)	0.406
Abnormal karyotype, n (%)	3 (6)	3 (3)	0.559	4 (2)	0.092
Thrombophilia screening, n (%)	17/42 (40)	19/55 (35)	0.549	22/105 (21)	0.015
Antithrombin deficiency	–	–		1	
Protein C deficiency	2	4		2	
Protein S deficiency	2	4		6	
Heterozygous factor V Leiden	2	4		2	
Heterozygous prothrombin G20210A	3	1		3	
Hyperhomocysteinemia	10	6		9	
High factor VIII levels	–	–		–	
Antiphospholipid antibodies	6	7		7	
No thrombophilia abnormalities	25	36		83	
Combined thrombophilia abnormalities	11	12		15	
Hematological evolution, n (%)	4 (8)	10 (11)	0.564	10 (6)	0.331
From PV to MF	–	1		1	
From ET to MF	3	7		7	
AML/MDS	1	2		2	
Deaths, n (%)	4 (8)	17 (20)	0.135	15 (8)	0.995
Pulmonary thromboembolism	–	3		–	
Budd-Chiari syndrome	2	–		–	
Arterial thrombosis	–	1		–	
Major bleeding	1	–		1	
AML/MDS	1	2		2	
Solid tumor	–	2		1	
Infection	–	–		3	
Organ failure	–	1		2	
Transplant related mortality	–	1		1	
Other/Unknown	–	7		5	

MPN myeloproliferative neoplasms; EEC endogenous erythroid colonies; AML acute myeloid leukemia; MDS myelodisplastic syndrome.
[a] JAK2 status available in 273 patients.
[b] JAK2 status available in 162 patients.

■ Methods

The patient cohort was recruited in 11 Hematology Units, 10 in Italy and one in Spain, in the frame of the European Leukemia Network. Centers were asked to provide information on their regularly followed patients with MPN who developed CVT (group MPN-CVT) with no exclusion criteria but the lack of objective documentation of the thrombotic event. For each MPN-CVT patient, information on 1–2 patients with MPN who developed objectively documented VT other than CVT (group MPN-VT) and on 3–4 patients with MPN who never had venous or arterial thrombosis (group MPN-NoT) were requested. The index CVT or VT was the first thrombotic event occurred during the follow-up period or within the year preceding the diagnosis of MPN. MPN-VT and MPN-NoT patients should match as much as possible MPN-CVT patients by sex, age at diagnosis of MPN (±5 years) and type of MPN. Demographic data, location of thrombosis, type of presenting symptoms, results of thrombophilia screening, full blood count at thrombosis, medical history focusing on potential risk factors for thrombosis (infections, trauma, oral contraceptive use, pregnancy, puerperium) and treatment of thrombosis and MPN were recorded in a dedicated data base. In the absence of the aforementioned circumstabtial risk factors for thrombosis the event was considered "unprovoked". Only patients with objectively confirmed diagnosis of CVT (digital angiography, computed tomography angiography, magnetic resonance, or magnetic resonance angiography) or other VT (the same as above but in other body districts, B-mode ultrasound, ventilation/perfusion lung scan) were included. Major bleeding was defined according to the Scientific and Standardization Committee of the International Society on thrombosis and hemostasis [17]. The institutional review boards

of the Hospitals approved the study that was carried out and is reported according to the STROBE guidelines for observational studies [18].

Statistical analysis. Summary statistics are presented by groups of interest. For continuous variables, median and 5th–95th percentiles or range are provided. Comparisons were estimated by *t*-test or analogs nonparametric test. For categorical variables, the number and percentage in each category are displayed. Comparison were estimated by Chi-square or Fisher exact test for frequency less than 5. The relative risk with 95% confidence interval (CI) was calculated as odds ratio using a 2×2 contingency table. The annual incidence of recurrent thrombosis was calculated by dividing the number of events by the total number of patient-years. Thrombosis recurrence free-survival was calculated from the date of first thrombotic event to the date of the first recurrence, or to the last follow-up for censored observations. Kaplan–Meier method was used to estimate survival curves. Cox multivariable model including sex, CVT, blood counts, thrombophilia, unprovoked event, cytoreductive, and antithrombotic treatment was performed in order to find significant predictors of recurrence. Starting with all candidate variables, backward selection was used testing whether the deletion or not of each variable improves the model, and repeating this process until no further improvement is possible.

■ Results

Characteristics of MPN patients with thrombosis

Forty-eight patients formed the MPN-CVT group. Diagnosis of CVT was concomitant to that of MPN in 22 patients (46%) and was

TABLE II. Comparison Between MPN-CVT and MPN-VT Patients

	MPN-CVT patients	MPN-VT patients	P
Data at CVT/VT			
Hemoglobin g/dl, median (range)	14.0 (8.1–20.7)	13.4 (8.5–17.6)	0.662
Hematocrit %, median (range)	41.5 (24.5–62.2)	42.1 (26.0–53.3)	0.762
White blood cells × 10^9/L, median (range)	10.0 (2.3–16.6)	8.5 (3.7–44.5)	0.179
Platelets × 10^9/L, median (range)	452 (10–1059)	484 (7.85–1500)	0.685
Splenomegaly, n (%)	11 (23)	34 (39)	0.076
Risk factors for CVT/VT, n (%)	15 (31)	23 (26)	0.612
Oral contraceptives	5	4	
Hormone replacement therapy	1	1	
Infection	2	2	
Pregnancy/puerperium	2	–	
Trauma	–	3	
Solid cancer	–	5	
Surgery	6	14	
Autoimmune disease	1	2	
Fracture, prolonged immobilization	1	3	
Liver disease	1	–	
Thrombosis before diagnosis of MPN, n (%)[a]	9 (19)	22 (25)	0.367
Venous thrombosis	2	10	
Splanchnic vein thrombosis	3	4	
Arterial thrombosis	4	8	
Bleeding before diagnosis of MPN, n (%)	1 (2)	9 (10)	0.073
Data during follow-up			
Median follow-up, years (range)	6.09 (0–34)	10.3 (0–31)	0.019
Cytoreductive treatment, n (%)	38 (79)	61 (70)	0.311
Phlebotomy	6	9	
Hydroxyurea	26	49	
Anagrelide	4	4	
Interferon	6	5	
Pipobroman	–	–	
Busulphan	–	2	
Other[b]	2	1	
Antithrombotic treatment, n (%)	45 (94)	73 (84)	0.099
Subcutaneous heparin	4	9	
Vitamin K antagonists	25	39	
Antiplatelet agents	13	19	
Vitamin K antagonists + antiplatelet agents	3	6	
Cytoreductive+Antithrombotic treatment, n (%)	35 (73)	57 (66)	0.377
Recurrent thrombosis, n (%)[c]	20 (42)	22 (25)	0.049
Venous thrombosis	10	11	
Splanchnic vein thrombosis	6	6	
Arterial thrombosis	4	5	
Major bleeding, n (%)	7 (15)	9 (10)	0.412
Central nervous system	3	2	
Gastrointestinal	1	5	
Muscle	1	–	
Menorrhagia	–	1	
Epistaxis	1	1	
Hematuria	1	–	

[a] Types of thrombosis before index event were 3 superficial, 2 portal, 1 splenic vein thrombosis, 1 acute myocardial infarction, 1 transient ischemic attack, 1 stroke, 1 peripheral artery thrombosis among MPN-CVT patients and 4 superficial, 3 upper limb, 1 lower limb, 1 caval, 1 retinal, vein thrombosis, 3 acute myocardial infarction, 4 transient ischemic attacks, 1 peripheral artery thrombosis among MPN-VT patients.

[b] n = 2 Ruxolitinib, 32P; n = 1 Vercyte.

[c] Types of recurrent thrombosis were 9 lower limb deep vein thrombosis and/or pulmonary embolism, 3 portal, 2 hepatic, 1 splenic vein thrombosis, 1 acute myocardial infarction, 2 transient ischemic attacks, 1 peripheral artery thrombosis among MPN-CVT patients and 6 lower limb deep vein thrombosis and/or pulmonary embolism, 4 superficial, 1 upper limb, 3 portal, 1 hepatic, 1 splenic, 1 mesenteric vein thrombosis, 2 transient ischemic attack, 1 stroke, 2 peripheral artery thrombosis among MPN-VT patients.

made within the year before or after diagnosis of MPN in 8 (17%) and 18 (38%) patients, respectively, by mean of angio-RM scan in 29 (60%), angio-CT scan in 20 (42%), or angiography in 4 (8%). The most frequently involved cerebral sinuses were the superior sagittal in 24 patients (50%) and the lateral sinus in 21 (44%). Two or more sinuses were involved in 22 patients (46%) and intracranial hemorrhage was present in 11 (23%). The most common presenting symptom of CVT was headache (85% of patients), followed by focal neurological defects (50% of patients had sensory symptoms, visual loss, aphasia, dysarthria, paresis, and vertigo). Only 5 patients (10%) had impaired consciousness (coma in 2 of them) and 3 (6%) had seizures. In the acute phase 29 patients (60%) were treated with intra-

venous or subcutaneous heparin. Forty-five patients (94%) received long-term antithrombotic treatment that included vitamin K antagonists in 28 (58%) or antiplatelet agents in 13 (27%) of them. Four patients (9%) remained in subcutaneous low-molecular weight or unfractionated heparin.

Eighty-seven patients formed the MPN-VT group. Diagnosis of VT was concomitant to that of MPN in 25 patients (29%). Types of VT were deep vein thrombosis of the lower extremities and/or pulmonary embolism in 66 patients (76%), of the splanchnic veins in 19 (22%) and of the upper extremities in 2 (2%). Treatment of acute VT consisted of intravenous or subcutaneous heparin, that was followed by long-term antithrombotic treatment in 73 patients (84%) and

TABLE III. Type of Cytoreductive and Antithrombotic Treatment at the Time of Recurrence

Index event	Type of recurrent thrombosis	Cytoreductive treatment	Antithrombotic treatment
CVT	CVT	Anagrelide	None
CVT	DVT + PE	Hydroxyurea	Antiplatelet agents
CVT	DVT	None	Subcutaneous heparin
CVT	DVT	Hydroxyurea	VKA
CVT	DVT	None	VKA
CVT	DVT	None	VKA
CVT	DVT	None	Subcutaneous heparin
CVT	DVT	None	Subcutaneous heparin
CVT	PE	Hydroxyurea	VKA + antiplatelet agents
CVT	PE	Hydroxyurea	Not known
CVT	Splanchnic VT	Hydroxyurea	Antiplatelet + subcutaneous heparin
CVT	Splanchnic VT	Hydroxyurea	VKA + antiplatelet agents
CVT	Splanchnic VT	Hydroxyurea	VKA + antiplatelet agents
CVT	Splanchnic VT	None	None
CVT	Splanchnic VT	None	None
CVT	Splanchnic VT	None	Antiplatelet agents
CVT	Transient ischemic attack	Hydroxyurea	VKA
CVT	Acute myocardial infarction	None	VKA
CVT	Peripheral artery thrombosis	None	VKA
CVT	Transient ischemic attack	None	VKA
OTHER VT	DVT	Interferon	Antiplatelet agents
OTHER VT	DVT	None	VKA
OTHER VT	DVT	Hydroxyurea	Subcutaneous heparin
OTHER VT	DVT	Hydroxyurea	Subcutaneous heparin
OTHER VT	PE	None	Subcutaneous heparin
OTHER VT	PE	not known	VKA
OTHER VT	PE	Hydroxyurea	Antiplatelet agents
OTHER VT	Superficial VT	Hydroxyurea	Antiplatelet agents
OTHER VT	Superficial VT	Hydroxyurea	None
OTHER VT	Superficial VT	Hydroxyurea	Antiplatelet agents
OTHER VT	Superficial VT	Pipobroman	Antiplatelet agents
OTHER VT	Splanchnic VT	None	VKA
OTHER VT	Splanchnic VT	Hydroxyurea	VKA
OTHER VT	Splanchnic VT	None	None
OTHER VT	Splanchnic VT	None	Antiplatelet agents
OTHER VT	Splanchnic VT	None	None
OTHER VT	Splanchnic VT	None	Not known
OTHER VT	Ischemic stroke	Interferon	VKA + antiplatelet agents
OTHER VT	Transient ischemic attack	Anagrelide	VKA + antiplatelet agents
OTHER VT	Peripheral artery thrombosis	None	None
OTHER VT	Peripheral artery thrombosis	Hydroxyurea	Antiplatelet agents
OTHER VT	Transient ischemic attack	None	Not known

CVT, cerebral vein thrombosis; VT, venous thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism; VKA, vitamin K antagonists.

consisted of vitamin K antagonists in 45 (52%) or antiplatelet agents in 19 (22%) of them. Nine patients (10%) remained in subcutaneous low-molecular weight or unfractionated heparin.

Comparison of patients with and without thrombosis

Patients were selected from a total population of ~5,500 patients with MPN followed in the 11 participating Centers until June 2013 (administrative censoring) from the longest period of 31 years (January 1982). Table I shows the characteristics of MPN and the distribution of thrombophilia abnormalities in the study population. Types of MPN were equally distributed in the three groups of patients, being essential thrombocythemia the most represented. At the time of thrombosis MPN-CVT patients were slightly younger than MPN-VT. Median age at recruitment of the MPN-NoT patients was 55 years (range 18–87). Compared to MPN-NoT, MPN-CVT, and MPN-VT patients had a higher prevalence of thrombophilia abnormalities (21% vs. 40% and 35% $P = 0.015$) and, among those with essential thrombocythemia, of the *JAK2* V617F mutation (76% and 78% vs. 55%, $P = 0.059$). The development of CVT or VT did not influence the evolution on MPN nor the expectancy of life. Only one death related to VT was recorded in patients who died for pulmonary embolism.

Comparison of MPN-CVT and MPN-VT patients

Thrombophilia abnormalities (Table I) and other risk factors for thrombosis (Table II) were similarly distributed in MPN-CVT and MPN-VT patients. No differences were seen in the full blood count at the time of thrombosis. MPN-CVT patients had a shorter median follow-up than MPN-VT patients (6.1 vs. 10.3 years, $P = 0.019$) and received long-term antithrombotic treatment in a higher proportion (94% vs. 84%, $P = 0.099$). The majority of patients in the MPN-CVT and MPN-VT groups received a cytoreductive (79% and 70%) or an anticoagulant treatment (94% and 84%), mainly hydroxyurea and vitamin K antagonists (Table II). Nine (19%) MPN-CVT and 22 (25%) MPN-VT patients had had venous or arterial thrombosis before diagnosis of MPN. Compared to MPN-VT, MPN-CVT patients had a higher rate of recurrent thrombosis (42% vs. 25%, $P = 0.049$) that in two-thirds of patients in both groups was venous, with a similar site distribution apart from a slightly higher rate of splanchnic vein thrombosis in MPN-CVT patients (Table II). Also the overall distribution of thrombotic events before or after diagnosis of MPN was similar in the two groups, apart from a slightly higher rate of splanchnic vein thrombosis in MPN-CVT than in MPN-VT patients (19% vs. 11%, OR 1.77, 95%CI 0.66–4.73).
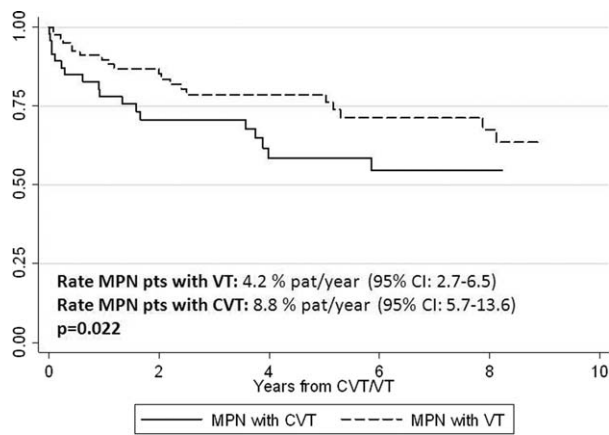
Figure 1. Thrombosis recurrence-free survival in MPN patients with previous CVT or VT.

Details of anticoagulant and cytoreductive treatments at the time of recurrence are shown in Table III. At the time of recurrence, 16 MPN-CVT (80% of recurrent patients) and 16 MPN-VT patients (73% of recurrent patients) were on antithrombotic treatment; recurrent thrombosis in patients receiving vitamin K antagonists (with or without antiplatelet agents), occurred in 10 of 28 (36%) in the MPN-CVT and in 6 of 45 (13%) in the MPN-VT group ($P = 0.04$). On the other hand, recurrent thrombosis in patients receiving antiplatelet agents only occurred in 2 of 13 (15%) in the MPN-CVT and in 7 of 19 (37%) in the MPN-VT group ($P = 0.24$). Finally, recurrent thrombosis in patients receiving hydroxyurea (with or without antithrombotic treatment) occurred in 8 of 26 (31%) in the MPN-CVT and in 8 of 49 (16%) in the MPN-VT group ($P = 0.23$). A combined cytoreductive and antithrombotic treatment was ongoing in 7 of 35 MPN-CVT (20%) and in 11 of 57 MPN-VT patients (19%) ($P = 1.00$).

CVT recurred in only one patient, who was receiving cytoreductive treatment only. The incidence of recurrent thrombosis was 8.8% patient-years (95% CI 5.7–13.6) in MPN-CVT and 4.2% patient-years (95% CI 2.7–6.5) in MPN-VT patients (log-rank test, $P = 0.022$) (Fig. 1). After stepwise selection, a multivariate model including sex, CVT, blood count, thrombophilia, unprovoked event, cytoreductive, and antithrombotic treatments, retained only CVT and unprovoked event as variables predictive of recurrent thrombosis (HR 1.97, 95%CI 1.05–3.72 and 2.09, 1.09–4.00, respectively). No difference was seen in the incidence of major bleeding (Table II).

■ Discussion

This study shows that CVT complicated MPN in ∼1% of cases and nearly 50% of patients have a concomitant diagnosis of the two diseases. The most frequently associated risk factors for CVT, as well as for VT, were thrombophilia abnormalities and, in patients with essential thrombocythemia, the *JAK2* V617F mutation. The distribution of thrombophilia abnormalities in patients without thrombosis reflects those observed in the general population, being for the three most common abnormalities factor V Leiden, prothrombin G20210A, and hyperhomocysteinemia 2%, 3%, and 10%, respectively. These figures were higher in patients with CVT (7%, 5%, and 24%) or VT (7%, 2%, and 11%), but much lower than those observed in thrombosis patients without MPN [19]. In the latter, CVT was strongly associated with prothrombin mutation, detected in up to 20% of cases, approximately as twice as much than factor V Leiden [9]. Our interpretation of this finding is that MPN are *per se* a strong risk factor for thrombosis and the risk associated with other risk factors appears diluted. Similarly to genetic risk factors, also transient ones such as

oral contraceptive or postmenopausal hormone use were less frequent (approximately half the prevalence) either in women with CVT (22%) or VT (10%) than in thrombosis patients without MPN, but the reason of this finding is likely attributable to the relative contraindication to use such hormones in women with an already increased baseline thrombotic risk due to MPN itself. Another interesting finding was a small trend to develop splanchnic vein thrombosis in patients with CVT, but this requires further confirmation.

Treatment of CVT consisted of long-term antithrombotic drugs, mainly vitamin K antagonists, in almost the totality of patients. Despite of this, MPN-CVT patients had a higher rate of recurrent thrombosis in a shorter follow-up median period of 6 years than MPN-VT patients, with a similar cytoreductive and antithrombotic treatment in the two groups. We noticed that neither cytoreductive therapy with hydroxyurea nor anticoagulant therapy with vitamin K antagonists was able to prevent recurrent VT in at least one-third of the patients with CVT. Accordingly, at the multivariate analysis neither cytoreductive nor antithrombotic treatment was independently associated with a reduction of recurrent thrombosis.

This finding is partially in contrast with a previous retrospective observation of patients with MPN and previous thrombosis that showed a benefit of either vitamin K antagonists or antiplatelet agents on the risk of recurrence in patients with a first venous thrombotic event, and a benefit of cytoreductive treatment only in patients with a first arterial thrombosis [20]. Finally, as observed in patients without MPN, also in those with MPN the probability of recurrent CVT is low, occurring in only one patient with essential thrombocythemia and the *JAK2* V617F mutation.

Strengths of this study are the relatively large sample of patients with MPN and CVT and the long duration of follow-up that allowed the estimation of the risk of recurrent thrombosis. Among the limitations there is the retrospective design of the study, that impose caution on the interpretation of results on antithrombotic therapy, because some information that are important in the evaluation of the risk of recurrent thrombosis, such as the international normalized ratio of the prothrombin time at the time of recurrence or the median time of patients in therapeutic range are lacking. In addition, the aforementioned interpretation is complicated further by the heterogeneity of antithrombotic treatments, although their distribution was similar in patients with MPN and CVT or VT and there is no reason to think that patients on vitamin K antagonists for CVT or VT had a different adherence to therapy. Finally, it remains to stratify the patients according to the presence or absence of the recently described calreticulin gene mutations that were not systematically searched in patients without the *JAK2* V617F mutation.

In conclusion, among patients MPN those who had a CVT have a higher probability to develop recurrent thrombosis than patients who had VT at other sites than cerebral veins, as well as those who had an unprovoked than a provoked event. Specifically designed studies are needed to assess the optimal prevention of recurrent thrombosis in patients with MPN, in terms of cytoreductive and/or antithrombotic treatments.

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■ Author Contributions

IM designed the study, conceived the data base, wrote the article; VDS designed the study, conceived the data base, included patients and gave a substantial contribution drafting the article; AC performed statistical analyses and critically revised and approved the article;

MLR, CS, AR, MCF, FC, EAR, SR, LC, AT, LF, SB AMV, LP, RC, EC, AC, AI, EMP, EME, and AS included patients and critically

revised and approved the article; TB conceived, designed and coordinated the study, critically revised and approved the article.

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