# High risk of recurrent venous thromboembolism in *BCR-ABL*-negative myeloproliferative neoplasms after termination of anticoagulation

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## Abstract

Venous thromboembolism (VTE) is a major burden in patients with *BCR-ABL*-negative myeloproliferative neoplasms (MPN). In addition to cytoreductive treatment anticoagulation is mandatory, but optimal duration of anticoagulation is a matter of debate.

In our single center study, we retrospectively included 526 MPN patients. In total, 78 of 526 MPN patients (14.8%) had a MPN associated VTE. Median age at first VTE was 52.5 years (range 23-81). During study period of 3497 years a VTE event rate of 1.7% per patient/year was detected. 38.4% (38 of 99) of all VTEs appeared before or at MPN diagnosis and 55.6% (55 of 99) occurred at “uncommon” sites like splanchnic or cerebral veins. MPN patients with VTEs were significantly more frequent female (p=0.028), *JAK2* positive (p=0.018) or were diagnosed as polycythemia vera (p=0.009). MPN patients without VTEs had a higher rate of *CALR* positivity (p=0.023).

Total study period after first VTE was 336 years accounting for a recurrence rate of geändert per patient/year. In 36 of the 71 MPN patients with anticoagulation therapy after first VTE event (50.7%), prophylactic anticoagulation was terminated after a median time of 6 months (range 1-61) and 13 of those 36 patients (36.1%) had a VTE recurrence after a median of 13 months (range 4-168). In contrast, only three of 35 patients with ongoing anticoagulation had a VTE recurrence (p=0.0127).

Thus, termination of prophylactic anticoagulation was associated with a significant higher risk of VTE recurrence. Our data suggest that in MPN patients with VTEs a prolonged duration of anticoagulation may be beneficial.

Key words:

myeloproliferative neoplasms; recurrent venous thromboembolism; anticoagulation therapy

**Introduction**

Venous thromboembolism events (VTEs) represent common causes of morbidity and even mortality in patients with *BCR-ABL* negative myeloproliferative neoplasms (MPN) [1;2]. Prospective trials in MPN reported VTE incidence rates of 0.5% - 3.7% patient/year [3;4]. In non MPN-cohorts, annual incidence rates of VTEs are between 0.1% and 0.2% patient/year [5]. In MPN patients the distribution of VTE at uncommon sites like splanchnic or cerebral veins is over-represented in respect to the non-MPN patients [6,7]. There is now accumulating evidence that the risk for VTE is increased in *JAK2* positive MPN [8]. On the other hand, in MPN patients harboring a *CALR* mutation, the VTE risk seems to be reduced [9].

After VTE diagnosis in MPN patients there are often uncertainties about the optimal mode and duration of anticoagulation. A major concern is the potential higher risk for bleeding complications.

Hence, the risk for bleeding has to be balanced against the risk for a recurrent thrombosis.

In a recent retrospective trial in MPN patients, the rates of major bleedings were 2.4% patient/year on vitamin K antagonists in contrast to 0.7% patient/year off vitamin K antagonists, however, the difference was not statistically different [10]. In studies with non-MPN patients receiving vitamin K antagonists bleeding rates were reported between 1.2 - 2.2% [11,12,13,14]. A retrospective study from the Spanish GEFIM group [15] also found no significant differences regarding the risk for major bleedings in MPN patients on anticoagulation.

After initiation, the optimal duration of anticoagulation is a matter of debate. There are no controlled studies addressing this topic. A recent survey among hematologists in Europe and Israel reported a high heterogeneity in treatment practices regarding duration of anticoagulation and antiplatelet therapy in venous and arterial thrombosis in MPN patients [16]. In MPN patients, the frequency of recurrent thrombosis is reported with 4.7-8.9% patient-year [10,17]. In non-MPN patients after a first VTE, the recurrence rate of VTE seems to be lower with about 5% patient-year [18]. Consensus statements [19,20] suggested a prolongation of anticoagulation in MPN patients with a life-threatening VTE or after a VTE recurrence.

In our single center study, we retrospectively included 526 MPN patients in order to get information on the incidence, risk factors, recurrence rate of VTE and the optimal mode and duration of anticoagulation.

**Patients and methods**

We conducted a retrospective single center study evaluating the incidence, risk factors and recurrence rate, the optimal mode and duration of anticoagulation of venous thromboembolism (VTE) in MPN patients. We collected the data of all MPN patients in our institution diagnosed within our German MPN register trial (GSG-MPN) and the European

Leukemia Net Project. Patients gave their consent for data collection within the German register trial (GSG-MPN) and the European Leukemia Net project. All MPN patients had a diagnosis of MPN according to the WHO 2008 criteria. Overall, data of 526 patients were included in this study. The enrollment period started at 14/05/2013. The date of the last data acquisition ("data cut-off") was 01/03/2018.

In a next step, we identified those patients with MPN who had suffered from a VTE, including deep venous thrombosis (DVT) of the limbs, pulmonary embolism (PE), thrombosis of the cerebral and splanchnic veins (hepatic, portal, mesenteric, and splenic veins), superficial vein thrombosis and thrombosis of the retinal vein.

A diagnosis of VTE was accepted only if it was confirmed by objective methods according to current clinical practice, as previously reported ([17]), and was defined as a positive result using techniques such as angiography, ultrasonography, CT, or NMR. PE was defined as a positive pulmonary angiogram, a ventilation–perfusion scan or CT scan indicating a high probability of PE. Retinal vein thrombosis was defined by fluoroangiography or fundus examination.

We defined a VTE associated to MPN as a thrombosis, which occurred up to two years before MPN diagnosis or thereafter. The study period was defined as time from MPN diagnosis to last visit in our center. Additionally, we collected the VTE rate before MPN diagnosis and the VTE rate simultaneous to MPN diagnosis. The data were collected in an electronic system. The details of the survey procedure and the results obtained in the patients with DVT of the legs and/or PE have been previously published ([17]).

Briefly, for each patient, the following information was recorded: demographic data, mutational profile (if available), method of objective diagnosis, history of bleedings, and presence of cardiovascular (CV) risk factors or microvascular disturbances. Furthermore, VTE details like localizations, total number, and time of diagnosis, recurrences and treatments were collected. Finally, data regarding cytoreductive or antithrombotic treatment, the duration of the treatment, the reasons for discontinuation and the number of recurrences after termination of antithrombotic therapy were recorded.

The major aim of this study was to determine the rate of recurrent thrombosis in MPN patients with VTE after discontinuation of antithrombotic therapy.

The following manifestations of venous thrombotic events that occurred after the first VTE were defined as recurrences: DVT of the legs or arms, PE, thrombosis of the cerebral and splanchnic veins (hepatic, portal, mesenteric, and splenic veins), superficial vein thrombosis and thrombosis of the retinal vein.

The severity level of bleeding complications was defined according to the criteria of the International Society on Thrombosis and Hemostasis ([21]). According to these criteria, the severity of bleeding was defined as major or clinically relevant non-major bleeding.

Statistical methods:

For continuous variables, the median and range are provided. The annual incidence of VTEs and of recurrent thrombosis was calculated by dividing the number of events by the total number of patient-years. Differences in the proportions were estimated using Chi square test (statistical significance threshold set at $p<0.05$), t-test for two independent means or log-rank test.

## Results

Our analysis included 526 MPN patients with a higher rate of female MPN patients (59.9%). Clinical features of all 526 MPN patients at diagnosis are shown in **Table 1**. Most patients were ≤ 60 years (73.8%) and 68.4% were diagnosed as essential thrombocythemia (ET, 34.6%) or polycythemia vera (PV, 33.8%)

. A moleculargenetic testing for *JAK2*-, *CALR*- and *MPL*-mutations was available in 451 of the 526 MPN patients (85.7%). The *JAK2* mutation was the most frequent driver mutation (78.3%).

342/526 pts (65.0%) were diagnosed in the last decade.

**Table 1** Clinical features of all 526 MPN patients at diagnosis

| | |
|---|---|
| **Male/Female – N (%)** | **211/ 315 (40.1/ 59.9)** |
| **Age, years at MPN diagnosis, median (range)** | **50.9 (11.0-86.3)** |
| • < 40 years, n (%) | 143 pts.* (27.2) |
| • 40-60 years, n (%) | 245 pts. (46.6) |
| • > 60 years, n (%) | 138 pts. (26.2) |
| **Diagnosis – N (%)** | |
| • Essential thrombocythemia (ET) | 182 pts. (34.6) |
| • Polycythemia vera (PV) | 178 pts. (33.8) |
| • Myelofibrosis (MF) | 141 pts. (26.8) |
| • MPN unclassified | 25 pts. (4.8) |
| **Driver mutations**– N/N tested (%)** | |
| *JAK2* mutation | 353 / 451 pts. (78.3) |
| *CALR* mutation | 67 / 451 pts. (14.9) |
| *MPL* mutation | 11 / 451 pts. (2.4) |
| Triple negative | 20 / 451 pts. (4.4) |

* pts. = patients, ** available in 451/526 patients (85.7%)

The overall study period of all 526 patients was 3497.4 years (median time was 5.4 years, range 5-32.5 years). We identified 116 venous thromboembolism events (VTEs) in 88 MPN patients. Of these, 99 VTEs in 78 MPN patients were according to our definition MPN associated (= a thrombosis, which occurred up to 2 years before MPN diagnosis or thereafter), which results in an incidence rate for VTE diagnosed after MPN diagnosis (n=61)

of 1.7% per patient/year. 14 VTEs occurred in 13 pts during 2 years before MPN diagnosis and 24 VTE in 24 pts were detected simultaneous to MPN diagnosis.

The overall study period recorded after the first VTE was 336 years (median time 2 years, range 0.5-24.0). 20 VTE recurrences occurred in 16 of 78 patients (20.5%). The incidence rate for recurrent VTE was 6.0% per patient/year.

52/78 pts (66.7%) received their MPN diagnosis in the last decade (after 2007). In 66/78 pts (84.6%), the first VTE event was diagnosed in the last decade (2008-2018).

Overall, 99 MPN associated VTEs were found in 78 of 526 MPN patients (14.8%).

Clinical features of these 78 patients with 99 VTE events are listed in **Table 2**. There were more female than male MPN patients with VTEs (71.8% versus 28.2%). The majority had the first thrombotic event at ≤ 60 years (65.4%). Nearly half the VTEs occurred in PV (46.2%). Regarding localization, 44.4% VTEs were recorded in “common sites” like deep veins in lower limbs (DVT) or pulmonary embolisms (PE). However, 55.6% (55 of 99) of all VTEs occurred at “uncommon sites”, most of them (32 of 99, 32.3%) in splanchnic veins.

Interestingly, 38 of 99 (38.4%) VTEs were diagnosed before or simultaneous to MPN diagnosis. For the 14 VTEs diagnosed prior MPN, the median time between VTE event and MPN diagnosis was 9.5 months (range 1 – 24).

Concerning the mode of anticoagulation therapy after first VTEs, vitamin K antagonists (VKAs) were most commonly used (in 40 patients, 56.3%), followed by low molecular weight heparin (LMWH) in 17 patients (23.9%) and direct oral anticoagulants (DOACs) in 14 patients (19.7%). Seven of 78 patients with VTEs never received any anticoagulation treatment: central vein occlusion (1 patient), anal vein thrombosis (1 patient), cerebral vein thrombosis (1 patient), superficial thrombophlebitis (1 patient) and splanchnic vein thrombosis (3 patients), respectively. The patient with the cerebral vein thrombosis was not treated with anticoagulation, because this thrombosis was an incidental finding without any symptoms. One of the three MPN patients with splanchnic vein thrombosis that didn´t receive anticoagulation treatment was treated with acetylsalicylic acid alone. The other two refused to get any anticoagulation (“patient choice”). The anal vein thrombosis and the superficial thrombosis were only treated with local therapy.

In all 71 MPN patients with VTE and anticoagulation median time of anticoagulation after first VTE was 12 months (range 1-204). In 36 of 71 patients, anticoagulation has been stopped after a median time of 6 months (range 1-61). The reason for termination in 35 of 36 patients was that according to “doctor’s choice” a sufficient time of anticoagulation was reached. One patient had an allergic reaction to LMWH. In these 36 patients stopping anticoagulation after a median time of six months we recorded significantly more VTE recurrences (n=13) compared with 35 patients with ongoing anticoagulation (three recurrences; p=0.0127)

(**Table 2 and Figure 1**). After termination of anticoagulation the median time from first VTE to recurrence was 10 months (range 4-168).

**Table 2** Clinical features, localization and number of venous thromboembolism events (VTEs) mode of anticoagulation and VTE recurrences in 78 MPN patients with 99 MPN associated VTEs

| | |
|---|---|
| **Male/Female – N (%)** | **22/56 (28.2/71.8)** |
| **Age in years at first VTE diagnosis, median (range)** | **52.5 (23.0-81.0)** |
| • < 40 years, n (%) | 22 pts. (28.2) |
| • 40-60 years, n (%) | 29 pts. (37.2) |
| • > 60 years, n (%) | 27 pts. (34.6) |
| **Diagnosis in 78 MPN patients (pts.*) with VTE – N (%)** | |
| • Essential thrombocythemia (ET) | 25 pts. (32.1%) |
| • Polycythemia vera (PV) | 36 pts. (46.2%) |
| • Myelofibrosis (MF) | 17 pts. (21.8%) |
| **Localization of all 99 VTEs – N (%)** | |
| • Pulmonary embolism | 16 (16.2%) |
| *- Without detection of a deep vein thrombosis* | *9 (9.1%)* |
| • Deep vein thrombosis in a lower limb | 28 (28.3%) |
| • Other VTE regions („uncommon sites“) | 55 (55.6%) |
| • *Splanchnic veins* | *32 (32.3%)* |
| • *Cerebral veins* | *6 (6.1%)* |
| • Deep vein thrombosis *upper limb* | *2 (2.0%)* |
| • *Superficial vein thrombosis* | *12 (12.1%)* |
| • *Other sites*** | *3 (3.0%)* |
| **Number of VTEs in relation to MPN diagnosis – N (%) in n pts.** | |
| • Before MPN diagnosis | 14 (14.1%) in 13 pts. |
| • Simultaneous to MPN diagnosis | 24 (24.2%) in 24 pts. |
| • After MPN diagnosis | 61 (61.6%) in 50 pts. |
| **Mode of anticoagulation after first VTE in 71 pts. *** - N (%)** | |
| • VKAs (vitamin K antagonists) | 40 (56.3%) |
| • LMWH (Low molecular weight heparin) | 17 (23.9%) |
| • DOACs (direct oral anticoagulants) | 14 (19.7%) |
| **Pts. with termination of anticoagulation after first VTE – N (%)** | **36/71 (50.7%)** |
| **Pts. with ongoing anticoagulation after first VTE – N (%)** | **35/71 (49.3%)** |
| | |
| **Pts with VTE recurrences – N (%)** | **16/78 (20.5)** |
| Pts with a first VTE recurrence after termination of anticoagulation | 13/36 (36.1) |
| Pts with a first VTE recurrence and ongoing anticoagulation | 3/35 (8.6) |

*Pts. = patients, **anal venous thrombosis (n=1); thrombosis in the left atrial appendage (n=1); central retinal vein thrombosis (n=1), *** out of 78 pts. with a first VTE 71 received anticoagulation therapy with VKAs, DOACs or LMWH, one patient was treated with acetylsalicylic acid only and six patients had no anticoagulation.

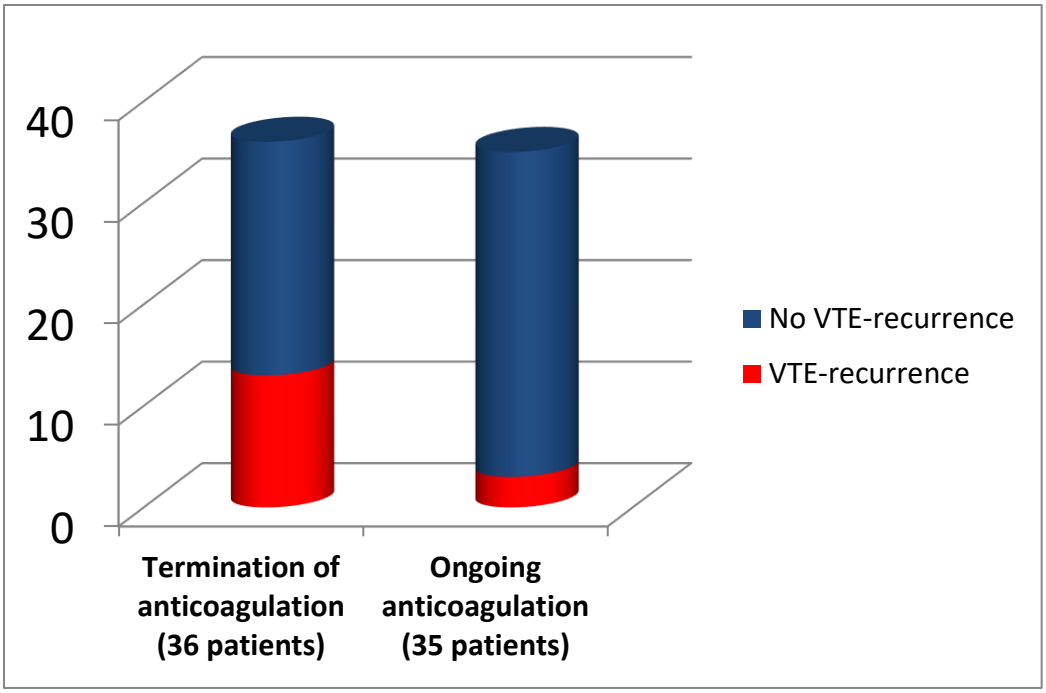


**Figure 1** Termination of anticoagulation and VTE recurrences: Regarding VTE recurrences, there were significantly (p=0.0127) more patients with a VTE-recurrence (n=13) after termination of anticoagulation in 36 patients compared with 3 recurrences in 35 patients with ongoing anticoagulation.

In a next step, we analyzed the data considering the thrombosis-free survival, meaning the interval between first VTE and the last visit in our center or the first VTE recurrence, whichever came first. Second or third VTE recurrences were not included in this analysis. The median thrombosis-free survival overall in our cohort was 1.95 years (range 0-23.6).

Comparing the thrombosis-free survial in the group of patients with ongoing versus the patients with termination of anticoagulation by log-rank test (Mantel-Haenszel test), there was no significant difference in this test (p=0.086) but a strong trend in favour of the patients with ongoing anticoagulation **(Figure 2)**

However, since there were only 16 relapses, the statistical power of this test is low, and a difference as suggested by the Kaplan-Meier plots may be unrevealed.

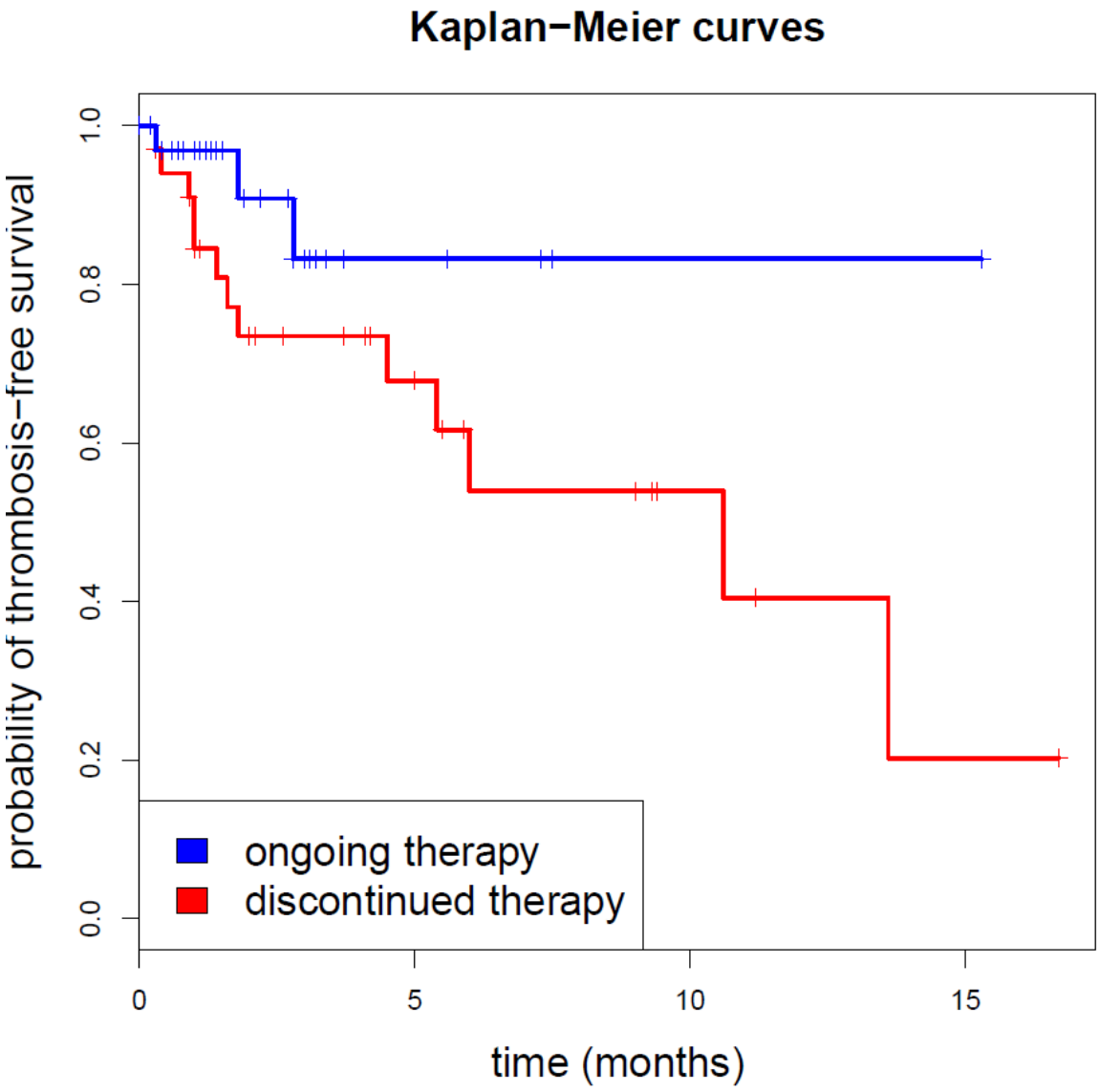


**Figure 2** Probability of thrombosis-free survival: Cumulativ probability of thrombosis-free survival in MPN patients with ongoing anticoagulation after first VTE (n=35, blue curve) or with discontinued anticoagulation therapy (n=36, red curve) (p=0.086)

In total, 20 VTE recurrences occurred in 16 of 78 patients. Two patients had more than one VTE recurrence. 3 of 20 VTE recurrences were before or at time of MPN diagnosis and 17 after MPN diagnosis. We found more VTE recurrences after termination of anticoagulation (n=16, 80.0%) than in patients with ongoing anticoagulation (n=4, 20%).

At the time of VTE recurrence 12 recurrences occurred in spite of cytoreductive therapy (hydroxyurea n=8, interferon alpha n=2, ruxolitinib n=2). As 3 VTE recurrences occurred before or at the time of MPN diagnosis and thus could not be treated with cytoreductive therapy (because MPN diagnosis was not known) only five recurrences occurred without

concomitant cytoreduction. In 14 of 20 VTE recurrences a blood count at time of VTE event was available (**Table 3**).

**Table 3** Timing of 20 VTE recurrences in 16 patients, anticoagulation, cytoreductive therapy and blood counts.

| **Number of VTE recurrences** | **20** |
|---|---|
| **VTE recurrences– N (%)** | |
| • Before or at time of MPN diagnosis | 3 (15.0) |
| • After MPN diagnosis | 17 (85.0) |
| • Under anticoagulation | 4 (20.0) |
| • After termination of anticoagulation | 16 (80.0) |
| • Under concomitant acetylsalicylic acid | 2 (10.0) |
| • No concomitant acetylsalicylic acid | 18 (80.0) |
| **MPN therapy at time of VTE recurrence* – N** | |
| • Hydroxyurea (HU) | 8 |
| • Interferon alpha (IFN) | 2 |
| • Ruxolitinib | 2 |
| • No MPN therapy | 5 |
| **Blood counts at time of VTE recurrence – median (range)** | |
| • Leucocytes (G/l) | 10.7 (4.3 – 37.8) |
| • Hemoglobin (g/dl) | 13.2 (8.1 – 17.1) |
| • Hematocrit (%) | 43.6 (25.1 – 56.0) |
| • Platelets (G/L) | 524.5 (176 – 1500) |

*3 VTE recurrences occurred before or at the time of MPN diagnosis

Overall, 448 of all 526 MPN patients (85.2%) included in our analysis never experienced any VTEs whereas 78 MPN patients (14.8%) had at least one MPN associated VTE. In **Table 4** we compared gender, age at diagnosis and age at time of VTE event, subtype of MPN, driver mutations and bleeding complications between these two groups (VTE and non-VTE group). Regarding gender we detected a significant higher rate of female MPN patients in the VTE group (56 of 78 patients, 71.8%) compared with the non-VTE group (259 of 448 patients, 57.8%) (p=0.028). There were no differences between the VTE group and the non-VTE group regarding age at diagnosis or age at the time of VTE event. MPN patients with VTE were significantly more frequent JAK2 positive (p=0.009; **Table 4**) or were diagnosed as polycythemia vera PV (p=0.018). On the other hand, more patients in the non-VTE cohort had a CALR-mutation (p=0.023). In the VTE group, clinical relevant major bleeding complications were not significantly increased, although there was a higher trend for hemorrhages in the VTE group (26.9% versus 19.2%, p=0.158). No fatal bleeding event occurred.

**Table 4** Clinical and molecular features of MPN patients with at least one MPN associated VTE (VTE group) compared with MPN patients without a MPN associated VTE (non-VTE group)

| | **VTE-group (n=78)** | **non-VTE group (n=448)** | **p** |
|---|---|---|---|
| **Male/Female – N (%)** | **22/ 56 (28.2/ 71.8)** | **189/ 259 (42.2/ 57.8)** | **0.028** |
| **Age, years at MPN diagnosis, median (range)** | **49.5 (22.6-82.2)** | **51.3 (11.0-86.3)** | 0.380 |
| **Diagnosis – N (%)** | | | |
| • Essential thrombocythemia (ET) | 25 (32.1) | 157 (35.0) | 0.701 |
| • Polycythemia vera (PV) | 36 (46.2) | 142 (31.7) | **0.018** |
| • Myelofibrosis (MF) | 17 (21.8) | 124 (27.7) | 0.345 |
| • MPN unclassified | 0 (0.0) | 25 (5.6) | 0.064 |
| **Driver mutations – N tested** | 74 | 377 | |
| • JAK2 mutation | 67/74 | 287/377 | **0.009** |
| • CALR mutation | 4/74 | 62/377 | **0.023** |
| • MPL mutation | 1/74 | 10/377 | 0.802 |
| • Triple negative | 2/74 | 18/377 | 0.629 |
| **Bleeding events – N (%)** | | | |
| • Major bleeding | 21 (26.9) | 86 (19.2) | 0.158 |

*n.e. not evaluable

Out of 526 MPN patients' 78 patients (14.8%) had a MPN associated VTE. After a median study period of two years, 16 of 78 patients had at least one VTE recurrence (20.5%). In **Table 5** we compared MPN patients with (16 patients) and without VTE recurrence (62 patients) according to gender, subtype of MPN, patients with first VTE before or simultaneous to MPN diagnosis and type of anticoagulation. The pts with VTE recurrence were significantly younger at first VTE event (p=0.020) than patients without recurrence.

**Table 5** Comparison of MPN patients without VTE recurrence with MPN pts with VTE recurrence:

| **78 pts.* with first VTE** | **Pts.* without VTE recurrence (n=62)** | **Pts.* with VTE recurrence (n=16)** | **p** |
|---|---|---|---|
| **Male/Female – N (%)** | **16 / 46 (25.8 / 74.2 )** | **6 / 10 (37.5 / 62.5 )** | 0.539 |
| **Diagnosis – N pts. (%)** | | | |
| • Essential thrombocythemia (ET) | 21 (33.8) | 4 (25.0) | 0.706 |
| • Polycythemia vera (PV) | 28 (45.2) | 8 (50.0) | 0.948 |
| • Myelofibrosis (MF) | 13 (21.0) | 4 (25.0) | 0.993 |
| **Age, years at first VTE diagnosis, median (range)** | 53.5 (24 – 81) | 42.0 (23 – 72) | **0.020** |
| **Pts.* with first VTE before or simultaneous to MPN diagnosis – N (%)** | 26 (41.9) | 8 (50.0) | 0.766 |
| **Anticoagulation therapy after first VTE – N (%)** | | | |
| • Vitamin K antagonists | 29 (46.8) | 11 (68.8) | 0.198 |
| • Low molecular weight heparin | 14 (22.6) | 3 (18.8) | 0.741 |
| • Direct oral anticoagulants | 12 (19.3) | 2 (12.4) | 0.786 |
| • No anticoagulation | 7 (11.3) | 0 (0) | 0.359 |

* pts. = patients, **n.e. not evaluable

**Discussion**

In our retrospective single center study, 78 of 526 myeloproliferative neoplasm (MPN) patients (14.8%) had a MPN associated VTE before (<2 years), at and after diagnosis. Most patients with VTE had a diagnosis of polycythemia vera (PV, n=36, 46.2%) followed by essential thrombocythemia (ET, n=25, 32.1%) and myelofibrosis (MF, n=17, 21.8%). During a study period of 3497 years, we recorded 99 VTE events leading to an incidence rate of 1.7% patient/year. In prospective trials, the rate for major VTE in PV was 0.7-1.3% patient/year ([3,22,23]) and 0.5%-1.2% patient/year in ET patients ([4,24,25]). In 707 patients with PMF the rate of VTE during follow up was 0.76% patient/year ([26]). Median age of our MPN patients at time of VTE diagnosis was 52.5 years (range 23-81) with only 34.6% patients older than 60 years. In a recent retrospective study of de Stefano et al. evaluating the role of warfarin in reducing recurrent VTE ([10]), the median age of 206 MPN patients at time of first VTE was 72 years with 82% older than 60 years. In a report of the Spanish GEMFIN in 150 ET and PV patients with arterial or venous thrombosis the median age was 66 years (range 51-75) ([15]). A possible explanation for the younger median age with a high venous thrombosis rate in our study is probably the fact that our center is a MPN reference center for more complicated cases. Accordingly, 55.6% of our VTE events occurred at “uncommon sites” with 32.3% splanchnic and 6.1% cerebral vein thrombosis. The corresponding rates of splanchnic and cerebral vein thrombosis in the above mentioned studies of de Stefano et al. and the Spanish GEMFIN were 49.5% and 35.3%, respectively ([10,15]). In the German SAL-MPN-registry, a non-interventional prospective study, the proportion of splanchnic vein thrombosis was 15% in all 455 MPN patients and was most frequent in MPN-U (60%), followed by post-PV MF (30.8%) ([27]). In a retrospective single institution survey, Cervantes et al. reported 155 PMF patients with 31 thrombotic events events, 6 (19%) had a splanchnic vein thrombosis and there was one cerebral venous thrombosis ([28]).

Interestingly, more than one third of all VTEs (38/99 or 38.4%) in our analysis appeared before (n=14) or simultaneous (n=24) to MPN diagnosis. This observation is in line with important retrospective studies on VTE in MPN. De Stefano et al. reported a MPN cohort with only splanchnic thrombosis, in which a high percentage (58%) of all thrombotic events was diagnosed before or simultaneous to MPN diagnosis ([29]). In 585 ET patients from the Mayo clinic, 81 patients had an arterial or venous thrombosis before or at diagnosis and 77 patients after diagnosis ([30]). In the German SAL-MPN-registry, the distribution for vascular occlusions peaked around diagnosis and was also similar in number before and after MPN diagnosis ([27]). This suggests that VTE events constitute a major indicator of MPN and typically trigger MPN diagnosis ([27]).

In our study, the incidence for a VTE recurrence was 6.0% patient/year and thus was comparable to VTE recurrence rates reported in the literature with 2.7-12% patient-year ([10,15,17]). Remarkably, the VTE recurrence rate in MPN is up to 3-times higher compared with non-MPN patients, where recurrence rates of VTE are reported in the range of 0.5-3.5% patient-year ([14,31]). One of our main findings was that stopping anticoagulation significantly increased the rate of re-thrombosis compared with ongoing anticoagulation (36.1% versus 8.6%; p=0.0127). The majority of our patients with VTE recurrence (81.3%) were without anticoagulation at the time of recurrence. These recurrences appeared in a relatively short period after discontinuation of anticoagulation with a median time of 10 months (range 4-168). At the time of VTE recurrence, 12 recurrences occurred in spite of cytoreductive therapy. As three VTE recurrences occurred before or at the time of MPN diagnosis and thus could not be treated with cytoreductive therapy (because MPN diagnosis was not known) only five recurrences occurred without concomitant cytoreduction suggesting that cytoreductive therapy alone may not be sufficient to prevent recurrent thrombosis. In spite of the fact that median blood counts were normal or quite close to normal values (Table 3), VTE recurrences occurred, also stressing the importance of an additional anticoagulation therapy. Importantly, despite a higher use of anticoagulation therapy in the “VTE-group” we did not observe a significantly increased rate of major clinical relevant bleeding complications.

In the Spanish GEMFIN study with 150 ET and PV patients with arterial or venous thrombosis the incidence of re-thrombosis was 4.5% and 12% patient-year under vitamin K antagonists (VKA) and after stopping it, respectively (p<0.0005). Treatment with VKA did also not result in a higher incidence of major bleeding ([15]). In the study of de Stefano et al. the incidence rate of recurrent thrombosis was 5.3% patient-year among VTE patients on long-term VKA and 12.8% patient-year after discontinuation of VKA (p=0.008). The rate of major bleeding was higher with 2.4% patient-year on VKA versus 0.7% patient-year off VKA, but not statistically significant ([10]).

In our VTE group there was a significantly higher proportion of PV diagnosis confirming that PV has the highest risk of VTE among MPN patients. Not surprisingly, *JAK2* mutated MPN patients had a higher risk of VTE compared to *CALR* mutated MPN, which is in line to reported data ([8,32,33]).

Regarding gender, we detected a significant higher rate of female MPN patients with a VTE event compared with the MPN pts without a thrombosis (p=0.028). To our best knowledge, there is no other study regarding this issue so far. Of course, larger trials are needed to clarify this issue.

Summarizing, our single center retrospective study shows a high ratio of VTE diagnosed before or simultaneous to MPN and VTEs at “uncommon” sites. Hence, we propose that an underlying MPN should be considered in cases of a first unprovoked VTE or a VTE at

“uncommon” site. Furthermore, our study suggests that early termination of prophylactic anticoagulation may be associated with a significant increased risk for VTE recurrence.

**The authors declare that they have no conflict of interest.**

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