Arterial and Venous Thromboembolic Complications in 832 Patients with *BCR-ABL*-Negative Myeloproliferative Neoplasms

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Abstract

Arterial (ATE) and venous (VTE) thromboembolic complications are common causes of morbidity and mortality in *BCR-ABL*-negative myeloproliferative neoplasms (MPNs). However, there are few studies that include all MPN subtypes and focus on both MPN-associated ATE and VTE. In our single-center retrospective study of 832 MPN patients, a total of 180 first thromboembolic events occurred during a median follow-up of 6.6 years (range: 0–37.6 years), of which 105 were VTE and 75 were ATE. The probability of a vascular event at the end of the follow-up period was 36.2%, and the incidence rate for all first ATE/VTE was 2.43% patient/year. The most frequent VTE localizations were deep vein thrombosis with or without pulmonary embolism (incidence rate: 0.59% patient/year), while strokes were the most frequent ATE with an incidence rate of 0.32% patient/year. When comparing the group of patients with ATE/VTE ($n = 180$) and the group without such an event ($n = 652$) using multivariate Cox regression analyses, patients with polycythemia vera (hazard ratio [HR]: 1.660; [95% confidence interval [CI] 1.206, 2.286]) had a significantly higher risk of a thromboembolic event than the other MPN subtypes. In contrast, patients with a *CALR* mutation had a significantly lower risk of thromboembolism compared with *JAK2*-mutated MPN patients (HR: 0.346; [95% CI: 0.172, 0.699]). In summary, a high incidence of MPN-associated VTE and ATE was observed in our retrospective study. While PV patients or generally *JAK2*-mutated MPN patients had a significantly increased risk of such vascular events, this risk was reduced in *CALR*-mutated MPN patients.

Keywords

- arterial thrombosis
- deep vein thrombosis
- management of disease
- venous thrombosis

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Introduction

BCR-ABL-negative myeloproliferative neoplasms (MPNs), with the three common subtypes polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF), are clonal disorders of the hematopoietic stem cell. They are associated with an increased risk of arterial (ATE) and venous (VTE) thromboembolic complications, which are a major contributor to the higher morbidity and mortality in MPNs.[1–3] Several studies reported a 10-fold increased incidence of MPN-associated ATE/VTE compared with the healthy population.[4–6] This risk seems to be particularly increased in *JAK2*-mutated MPNs,[7] while a lower risk of VTE is reported in *CALR*-mutated patients with myelofibrosis.[8]

Incidence rates for VTE have been reported to range from 0.5 to 3.7% per patient/year,[5,9–12] which is significantly higher than the corresponding incidence for the healthy population with 0.1 to 0.2%.[13–15] In addition, the risk of VTE at "unusual" sites such as splanchnic or cerebral venous thrombosis is increased in MPN patients.[16,17] MPN-associated ATE appears to be less common than VTE, with a reported incidence of ~0.2 to 1.5% patient/year.[5,9,18] However, in younger MPN patients younger than 50 years, the incidence of ATE appears to be sixfold higher compared with the healthy population.[19]

To obtain more detailed information on the frequency, risk factors, and localizations of MPN-associated ATE/VTE, we conducted a retrospective single-center study including 832 patients with all MPN subtypes.

Patients and Methods

The clinical data of all MPN patients presenting regularly at our institution were collected from June 2007 to December 2020 (time of the last data cut on December 31, 2020). All MPN patients were diagnosed according to the currently valid WHO criteria. The study was approved by the ethics committee of our institution. Patients gave their consent for data collection within the German Registry Trial (GSG-MPN). The main objective of this study was to determine the incidence rates, risk factors, and localizations of MPN-associated arterial (ATE) and venous (VTE) thromboembolic events.

In line with previous studies,[20,21] we defined an ATE or VTE associated with an MPN, if it occurred within 2 years prior to MPN diagnosis or afterward. Therefore, the follow-up time started 2 years before MPN diagnosis and ended at the time of the first thromboembolic event (ATE or VTE) or the last visit to our center (whichever came first). Data were collected retrospectively from medical records. If necessary, further information was requested from the patients and/or the attending physicians. For each MPN patient, the following data were collected: demographic data, mutation profile, and method of objective diagnosis of ATE/VTE. In addition, further details on ATE/VTE such as location, total number, and time of diagnosis were recorded. The included MPN patients were diagnosed between 1983 and 2020, and the ATE/VTE occurred from 1992 to 2020. The following localizations were defined as VTE: deep venous thrombosis (DVT) of the legs or arms with or without pulmonary artery embolism (PE), venous thrombosis of the cerebral and splanchnic veins (hepatic, portal, mesenteric, and splenic veins), superficial vein thrombosis, and retinal vein thrombosis. ATE was defined as transient ischemic attack (TIA), myocardial infarction (MI), angina pectoris (AP), stroke, lower limb arterial embolism, intermittent claudication, renal infarction, splenic infarction, and arterial embolism elsewhere. Objective diagnostic procedures such as ultrasound, computed tomography, angiography, or scintigraphy were required for the diagnosis of ATE or VTE.

Statistical Methods

The incidence of ATE/VTE was calculated by dividing the number of events by the total number of patient-years. For continuous variables, the median and the range were provided. A Cox regression model was used to model the effect of different variables on ATE/VTE. A significance level of $\alpha = 0.05$ was used for all analyses.

Results

A total of 832 MPN patients (507 females [60.9%] and 325 males [39.1%]) were enrolled in the study. The median age at MPN diagnosis was 50.7 years (range: 11.0–88.9 years) and the median follow-up time was 6.6 years per patient (0–37.6 years). The different MPN subtypes were essential thrombocythemia (ET) with 264 (31.7%) patients, polycythemia vera (PV) with 284 (34.1%) patients, myelofibrosis (MF) with 259 (31.1%), and MPN unclassifiable with 25 (3.0%) patients. Of the 259 myelofibrosis patients, 93 (11.2%) patients were diagnosed with prefibrotic myelofibrosis and 166 (20.0%) with primary or secondary MF.

The driver mutations were distributed as follows: *JAK2* mutation, 581 (69.8%); *CALR* mutation, 120 (14.4%); *MPL* mutation, 21 (2.5%); and triple negative, 43 (5.2%). In 67 (8.1%) patients, only an incomplete mutation test was available.

Of the 832 patients, 180 (21.6%) had first ATE/VTE (105 VTE [58.3%] and 75 ATE [41.6%]). Of the 180 first events, 58 (32.2%) occurred within 2 years prior to MPN diagnosis, with a median time between event and MPN diagnosis of 8 months (range: 1–24 months). The other 122/180 (67.8%) events were diagnosed at the time of MPN diagnosis ($n = 39$, 21.6%) or after ($n = 83$, 46.1%). The median time between MPN diagnosis and the ATE/VTE occurring at or after MPN diagnosis was 1.3 years (range: 0–69.1 years).

The demographic data and clinical characteristics of all 832 MPN patients with 180 first thromboembolic complications are summarized in ►**Table 1**.

A Kaplan–Meier curve of the 180 first thromboembolic events (ATE and VTE) in 832 patients during the follow-up period is presented in ►**Fig. 1**. The probability of "thromboembolic-free" survival at the end of the follow-up time was 63.8%.

Regarding anticoagulation at the time of first ATE/VTE, 44/180 patients (24.44%) received primary prophylactic

Table 1 Overview of demographic data and clinical characteristics of 832 MPN patients with 180 first arterial (ATE) and venous (VTE) thromboembolic complications

Male/female; n (%)	**325/507 (39.1/60.9)**
Median age at MPN diagnosis; years (range)	50.7 (11.0–88.9)
Median follow-up time; years (range)	6.6 (0–37.6)
MPN diagnosis	
Essential thrombocythemia (ET); n (%)	264 (31.7)
Polycythemia vera (PV); n (%)	284 (34.1)
Myelofibrosis (MF); n (%) Prefibrotic myelofibrosis; n (%) Primary and secondary myelofibrosis; n (%)	259 (31.1) 93 (11.2) 166 (20.0)
MPN unclassified; n (%)	25 (3.0)
Driver mutations**	
JAK2;* n (%)	581 (69.8)
CALR; n (%)	120 (14.4)
MPL; n (%)	21 (2.5)
Triple negative; n (%)	43 (5.2)
Incomplete;** n (%)	67 (8.1)
Thromboembolic complications; n	180
Thromboembolic complications diagnosed before MPN diagnosis;* n (%)	58 (32.2)
Thromboembolic complications diagnosed at the time of MPN diagnosis; n (%)	31 (17.2)
Thromboembolic complications diagnosed after MPN diagnosis	91 (50.6)
VTE; n (%)	105 (58.3)
ATE; n (%)	75 (41.6)

*In a period of 2 years before MPN diagnosis.
**In 67/832 (8.1%) patients, only an incomplete mutational profile was available.

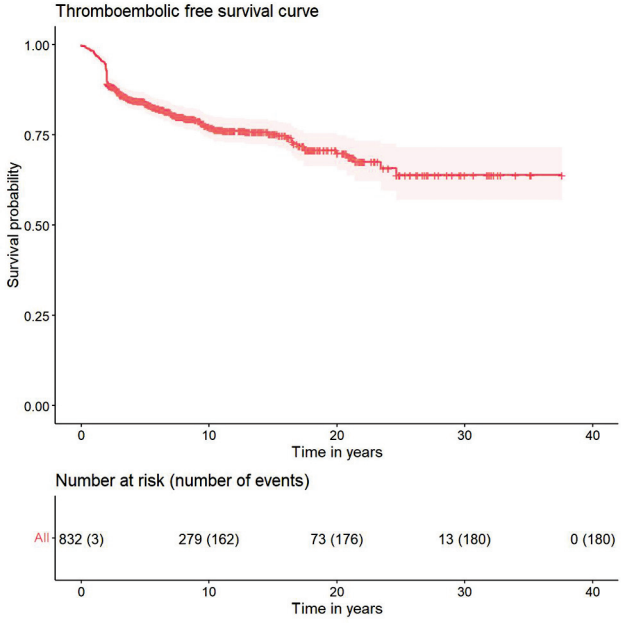

Fig. 1 Kaplan–Meier curve presenting the probability of "thromboembolic-free" survival of the 832 MPN patients with 180 first thromboembolic events (arterial/venous) during the follow-up time.

antiplatelet aggregation therapy with aspirin (ASS). Another three patients (1.67%) were treated with oral vitamin K antagonists (VKAs). Remarkably, no patient with ATE/VTE that occurred in the period of 2 years before or at the same time as the MPN diagnosis ($n = 97$, or 53.89%) received any anticoagulation or antiplatelet aggregation therapy at the time of event. In 21.11% of the patients (38/180), a cytoreductive MPN therapy was used at the time of the first vascular event, in most cases (20/180, or 11.11%) hydroxyurea (HU). The most common used anticoagulation treatment after the first ATE was ASS in 53.33% (40/75) of the cases. After VTE, most patients (45/105, or 42.86%) were treated with VKA.

The incidence rate for the 180 first thromboembolic events was 2.43% patient/year. Specifically, the incidence rate for the first VTE ($n = 105$) was 1.42%, and for the 75 first ATE it was 1.01% patient/year. The localizations and the corresponding incidence rates for the first 180 ATE/VTE are shown in ►**Table 2**.

The most common VTE localization was DVT with or without pulmonary embolism (PE; $n = 44$, incidence rate: 0.59% patient/year). VTE at "unusual" sites as splanchnic thrombosis ($n = 38$, 0.51% patient/year) or sinus vein

Table 2 Localization and incidence rates of the first 180 arterial and venous thromboembolic complications (ATE/VTE) in 832 MPN patients

	First ATE/VTE ($n = 180$)	Incidence rate for first ATE/VTE (% patient/year)
Localization		
ATE, *n* (%)	**75** (41.7)	**1.01**
Stroke, *n* (%)	24 (13.3)	0.32
Transient ischemic attack (TIA), *n* (%)	22 (12.2)	0.30
Splenic infarction, *n* (%)	8 (4.4)	0.11
Myocardial infarction, *n* (%)	9 (5.0)	0.12
Angina pectoris, *n* (%)	2 (1.1)	0.03
Renal infarction, *n* (%)	1 (0.6)	0.01
Other ATE, *n* (%)	9 (5.0)	0.12
VTE, *n* (%)	**105** (58.3)	**1.42**
Deep vein thrombosis with or without pulmonary embolism, *n* (%)	44 (24.4)	0.59
Splanchnic vein thrombosis, *n* (%)	38 (21.1)	0.51
Superficial vein thrombosis, *n* (%)	10 (5.6)	0.14
Sinus vein thrombosis, *n* (%)	8 (4.4)	0.11
Other VTE, *n* (%)	5 (2.8)	0.07

thrombosis ($n = 8$, 4.4%) were also frequently observed. The two most common ATE localizations were strokes ($n = 24$) and TIA ($n = 22$) with incidence rates of 0.32 and 0.30% patient/year, respectively. Cumulative incidence functions were used to compare the incidence of ATE ($n = 75$) with the incidence of VTE ($n = 105$) during the follow-up period (►**Fig. 2**). The cumulative risk of VTE (red curve) seems to be increased compared with the risk of ATE (blue curve).

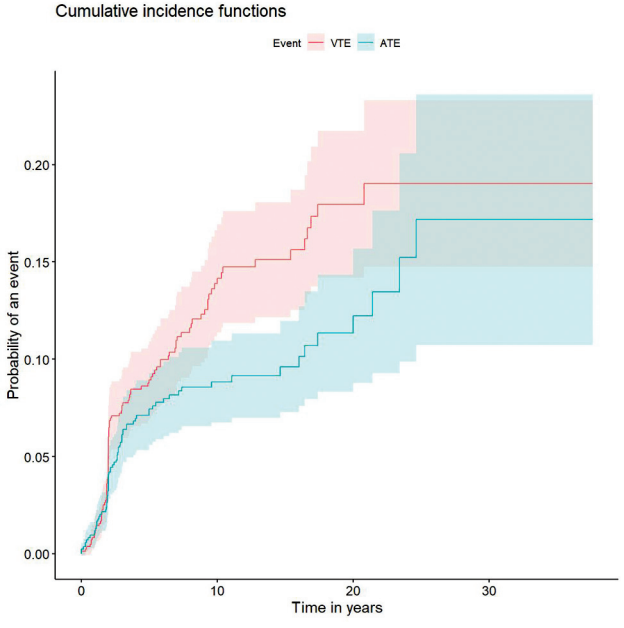

Fig. 2 Cumulative incidence functions comparing the probability of "thromboembolic-free" survival of a venous thromboembolic event (red curve) with the risk of an arterial thromboembolic event (blue curve). ATE, arterial thromboembolic; VTE, venous thromboembolic.

However, when considering the entire follow-up period, the 95% confidence intervals overlapped almost over the entire observation period.

In a next step, different time points (1, 3, 5, 10, and 20 years after the start of the follow-up time) were defined to compare the cumulative incidence estimates (with confidence intervals) for ATE/VTE (►**Table 3**). Only at the time point "10 years," a larger numerical difference could be found.

In a next step, a multivariate Cox regression was performed with the variables "age at MPN diagnosis," "gender," "mutation status," and "MPN diagnosis" to analyze their influence on the risk of the 180 first thromboembolic complications. The likelihood ratio test for this Cox regression was significant ($p < 0.001$) indicating that the model provides a significantly better fit than a model without any covariates. For the covariate "mutation status," the *JAK2* mutation was set as the reference mutation. For the covariate "MPN diagnosis," the PV diagnosis was compared with the other MPN subtypes (ET, MF, and MPN unclassified). The estimators for the covariates are shown in ►**Table 4**.

According to this analysis, the *CALR* mutation (0.346; 95% confidence interval [CI]: 0.172, 0.699) significantly reduced the risk of ATE/VTE by a factor of 0.35 compared with the *JAK2* mutation. Furthermore, an "incomplete mutation status," which occurred in 8.1% ($n = 67$) of the patients, was associated with a significantly lower risk of a thromboembolic event (hazard ratio [HR]: 0.461; [95% CI: 0.224, 0.949]). Regarding MPN subtypes, PV diagnosis significantly increased the risk of a thromboembolic event by a factor of 1.660 (HR: 1.660; [95% CI: 1.206, 2.286]) compared with the other MPN subtypes. Gender and age at MPN diagnosis did not significantly influence the risk of thromboembolism.

Table 3 The cumulative incidences for ATE and VTE at specific time points

Time point (after begin of the follow-up time)	Cumulative incidence for VTE [95% CI]	Cumulative incidence for ATE [95% CI]
1 y	0.011 [0.004, 1.018]	0.012 [0.005, 0.019]
3 y	0.075 [0.057, 0.093]	0.060 [0.044, 0.076]
5 y	0.089 [0.070, 0.109]	0.074 [0.056, 0.093]
10 y	0.142 [0.114, 0.169]	0.088 [0.068, 0.109]
20 y	0.180 [0.142, 0.217]	0.122 [0.088, 0.157]

Abbreviations: ATE, arterial thromboembolic; VTE, venous thromboembolic.
Note: Different time points after the start of the follow-up time were defined and the cumulative incidence estimates (and their respective confidence intervals) at these specific time points were calculated.

Discussion

About 30% of all MPN patients are diagnosed with thromboembolism within 15 years of initial diagnosis.[22] Therefore, one of the most important goals of MPN therapy is the prevention of thromboembolic events, as these have a major impact on morbidity and mortality. However, there is only limited data on the most common sites, incidences, and risk factors of MPN-associated ATE/VTE.

An evaluation of the German SAL-MPN registry[18] including 454 MPN patients of all subtypes showed that 33.6% of the patients had a vascular event (ATE or VTE). A total of 31.5% of the 68 MPN-associated VTEs observed were located in the deep veins of the leg and 15.2% in the splanchnic veins.

Table 4 Multivariate Cox regression of the 832 MPN patients with 180 first thromboembolic events (ATE/VTE) with the variables "age at MPN diagnosis," "gender," "mutation status," and "MPN diagnosis"

Multivariate COX regression	
Variable	**HR [95% CI]**
Age at MPN diagnosis	1.010 [1.000, 1.020]
Gender	0.903 [0.663, 1.229]
Mutational status[a]	
CALR	0.346 [0.172, 0.699][b]
MPL	1.409 [0.607, 3.266]
"Triple negative"	1.024 [0.491, 2.134]
Incomplete mutational status	0.461 [0.224, 0.949][b]
Polycythemia vera[c]	1.660 [1.206, 2.286][b]

Abbreviations: ATE, arterial thromboembolic; ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasms; VTE, venous thromboembolic.
Notes: The 95% confidence intervals for the estimators are given in parentheses. The *CALR*-mutation (HR: 0.346 [95% CI: 0.172, 0.699]), an "incomplete mutation status" (HR: 0.461 [95% CI: 0.224, 0.949]), and PV diagnosis (HR: 1.660 [95% CI: 1.206, 2.286]) were statistically significant.
[a]Compared with the *JAK2* mutation.
[b]Statistically significant.
[c]Compared with the other MPN subtypes (ET, MF, and MPN unclassified).

Of the 69 ATEs in the same study, 27.7% of the patients had a MI and stroke was observed in 19.3% of cases. A multivariate regression model was conducted to predict ATE/VTE, but neither MPN subtype nor *JAK2* mutation had a significant effect. However, data on the frequency of *CALR* and *MPL* mutation in the study cohort were not published.

In our study, 21.6% (180/832) of patients developed a thromboembolic complication with a 36.2% probability of being diagnosed with ATE/VTE at the end of the follow-up period (median: 6.6 years). Comparable to the study of the German SAL-MPN registry,[17] the most common VTE localizations were DVT with or without PE (incidence rate: 0.59% patient/year) and splanchnic thrombosis (0.51% patient/year). The two most frequent ATE localizations were strokes ($n = 24$) and TIA ($n = 22$). Although the incidence rate of VTE (1.42% of patient/year) was higher than the incidence of ATE (1.01% of patient/year), no clear statistical difference between the VTE- and the ATE-incidence during the complete follow-up period (►Fig. 2; ►Table 3) was found.

However, cumulative incidence functions using Kaplan–Meier estimates (►Fig. 2) for nonfatal events (e.g., ATE/VTE) could be overestimated in populations at high mortality risk. Of note, in our study cohort, only 10.0% (83/180) of patients died during the follow-up period (median: 6.6 years), which appears to be lower compared with a Swedish population-based registry study[2] including 9,285 MPN patients, of whom 52.1% died within the first 10 years after MPN diagnosis.

Remarkably, more than half of the thromboembolic complications (53.89%) occurred before or at the time of MPN diagnosis. As shown in ►Figs. 1 and 2, the incidence of ATE/VTE was highest at the beginning of the follow-up period. Furthermore, the median time to first event was only 1.3 years for the 67.8% of ATE/VTE that occurred at or after MPN diagnosis. Thus, therapeutically uncontrolled MPN appears to be an important risk factor for thromboembolic events. Recently published data from a Danish population-based registry,[15] which includes nearly 500,000 patients with newly diagnosed solid cancer, also showed an increased incidence of VTE in the first 12 months after diagnosis. Another risk factor, according to the results of the multivariate Cox regression model in our study, was a PV diagnosis (compared with all other MPN diagnoses). If a

patient was diagnosed with PV, the ATE/VTE risk was increased by a factor of 1.66. In contrast, *CALR*-mutated patients had a significantly lower ATE/VTE risk than patients with a *JAK2* mutation (HR: 0.346; [95% CI: 0.172, 0.699]).

As mentioned earlier, none of the patients with an ATE/VTE before or at the time of MPN diagnosis received any primary prophylactic anticoagulation (or cytoreductive) therapy at the time of the event. However, most events (53.89%) occurred in this group of patients. This fact could influence further MPN studies as well as recommendations for the prophylaxis (primary and secondary) of MPN-associated vascular events.

Regarding limitations of the analysis, the retrospective design of the single-center study and the number of vascular events recorded in our cohort (180 ATE/VTE in 832 patients) should be considered. This could also explain the different results compared with the study of the German SAL-MPN registry,[17] which investigated 147 ATE/VTE in 454 patients.

In summary, our study shows a significantly increased risk of VTE and ATE (often at "unusual" sites) in MPN patients compared with the healthy population,[13,14,22] and this risk seems to be particularly increased in newly diagnosed and/or uncontrolled MPN. While patients diagnosed with PV or generally JAK2 mutated MPN patients had a significantly increased risk of thromboembolic complications compared with the other MPN subtypes, this risk was significantly reduced in *CALR*-mutated patients.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The questionnaire and study protocol for this retrospective study were approved by the Ethics Committee of the Ruhr-Universität Bochum, based in Bad Oeynhausen.

Consent to Participate

Written consent was obtained from all individual participants included in the study.

Code Availability

Not applicable.

Funding

No funding was committed for this study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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