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# Arterial thrombosis in Philadelphia-negative myeloproliferative neoplasms predicts second cancer. A case-control study.

**Running title:** Thrombosis heralding second cancer in MPN

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#### Key points

- In a case-control study, the frequency of thrombosis was higher in MPN patients with second cancer than in matched MPN cancer-free patients.
- The occurrence of arterial thrombosis was associated with a 2-fold increased risk of carcinoma.

## Abstract

Patients with Philadelphia-negative myeloproliferative neoplasms (MPN) are prone to the development of second cancers, but the factors associated with these events have been poorly explored. In an international nested case-control study, we recruited 647 patients with carcinoma (n=426), non-melanoma skin cancer (n=127), hematological second cancer (n=62) and melanoma (n=32) diagnosed concurrently or after the diagnosis of MPN. Up to 3 controls (n=1,234) without history of cancer matched with each case for center, sex, age at MPN diagnosis, date of diagnosis and MPN disease duration were included. Cases were comparable to controls for MPN type, exposure to driver mutations, and cardiovascular risk factors. The frequency of thrombosis preceding MPN diagnosis was similar for cases (19.8%) and controls (21.2%) ( $p=0.462$ ). Thrombotic events recorded after MPN diagnosis and before second cancer were higher in cases than in controls (75/647, 11.6%, vs. 100/1234, 8.1%,  $p=0.013$ ), because of a higher proportion of arterial thromboses (40/647, 6.2% vs. 46/1234, 3.7%,  $p=0.015$ ). After adjusting for many confounders, the occurrence of arterial thrombosis remained independently associated with the risk of carcinoma (odds ratio 1.97, 95% CI 1.14-3.41,  $p=0.015$ ), suggesting that MPN patients experiencing arterial events after MPN diagnosis deserve careful clinical surveillance to detect early carcinoma.

## Introduction

The clinical burden of the Philadelphia-negative myeloproliferative neoplasms (MPN) is marked by arterial and venous thrombosis, hemorrhagic complications, and a propensity to transform into myelofibrosis and acute myeloid leukemia.<sup>1</sup> In addition, recent cohort studies<sup>2-6</sup> and population-based results<sup>7-9</sup> highlighted that MPN patients are also prone to develop second cancer and lymphoproliferative disorders.<sup>7,8</sup>

It is well known that unprovoked venous thromboembolism (VTE) may precede a subsequent malignancy<sup>10</sup>, but the notion that malignancy can be heralded by arterial thrombosis has been reported only recently.<sup>11</sup> To date, this association has not been studied in MPN, in which arterial thrombosis is more frequent than venous thrombosis and solid tumors are reported with a higher frequency.

We recently published the results from a nested case-control study with 647 MPN cases with second cancer and 1,234 matched MPN cancer-free patients recruited from European Leukemia Net (ELN) centers, reporting the impact of the exposure to cytoreductive drugs on the occurrence of second cancer.<sup>12</sup> In the present study, we re-examined this large database with the following two purposes: (i) to evaluate the frequency and type of vascular complications in MPN patients with carcinoma, non-melanoma skin cancer, melanoma and hematological cancer excluding leukemia and (ii) to establish whether arterial and venous thrombosis registered during follow-up after diagnosis of MPN could predict the occurrence of a second cancer.

## Study design

Details of this multicenter international nested case-control study (MPN-K Study, *ClinicalTrials.gov*: NCT03745378) have been reported elsewhere.<sup>12</sup>

This project was approved by the Institutional Review Boards (IRBs) of each participating center. Cases were MPN patients with second cancer diagnosed concurrently or subsequent to MPN diagnosis. Date of second cancer diagnosis was defined as *index date*. Controls were MPN patients without second cancer. For each case, up to 3 cancer-free controls were matched for center, sex, age at MPN diagnosis, date of MPN diagnosis, and MPN disease duration.

The major thrombotic events of interest were ischemic stroke, transient ischemic attacks, acute myocardial infarction, unstable angina pectoris, peripheral arterial thrombosis, retinal artery or vein occlusion, deep venous thrombosis (including thrombosis of cerebral and splanchnic veins) and pulmonary embolism. All the events were objectively proven as previously described.<sup>13-15</sup>

Thrombosis had to be prior to or concurrent with MPN diagnosis or occurring in the period after MPN diagnosis and before index date.<sup>12</sup>

### *Statistical methods*

The Chi-square test or Fisher's Exact test (for categorical data), and t-test or Mann-Whitney U test (for continuous variables) were used when appropriate. The cumulative incidence of thrombosis from MPN diagnosis was estimated by the Kaplan-Meier method and was compared between cases and controls using the log-rank test. A multivariable conditional logistic regression model was fitted to estimate the Odds Ratio (OR) with 95% Confidence Interval (CI) of second cancer associated with the occurrence of thrombosis before/at MPN diagnosis and during follow-up. The estimates were adjusted for the effect of age at MPN diagnosis, cardiovascular risk factors (smoke, hypertension, dyslipidemia, diabetes), JAK2V617F mutation, and treatment during follow-up (primary antithrombotic prophylaxis with aspirin and/or cytoreduction). For all tested hypotheses, two-tailed p-values less than 0.05 were considered to be significant. Analyses were performed using STATA software, release 13 (StataCorp LP, College Station TX, USA).

### **Results and Discussion**

The most frequent category of cancer among the 647 cases was represented by carcinoma (65.8%) (Supplemental Table 1). Carcinoma involved mostly prostate (n=121), breast (n=88), lung (n=56), colorectal region (n=56); the complete details of cancer diagnoses have been reported elsewhere.<sup>12</sup> Cases were comparable with the 1,234 matched controls for demographics, type of MPN and potential confounders such as driver mutations, abnormal karyotype and cardiovascular risk factors (Supplemental Table 2).

Approximately 20% of either MPN cases or controls exhibited thrombosis before MPN or at diagnosis (19.8% vs. 21.1%, respectively, p=0.462) (Supplemental Table 3). In contrast, significant differences in the proportion of thrombosis were found after MPN diagnosis. After a median observation time from the diagnosis of MPN to the index date of 4.5 years (interquartile range 1.5-8.2) in cases and 3.7 years (interquartile range 1.5-7.5) in controls, a higher percentage of thrombosis was found in cases with respect to controls (75/647, 11.6% vs. 100/1234, 8.1%, respectively, p=0.013). Approximately one-third of thrombosis preceding cancer occurred in the 12 months before the diagnosis of second cancer (22/75, 29.3%). The excess of thrombosis in cases was due to a higher frequency of arterial thrombosis (40/647, 6.2% vs. 46/1234, 3.7%,

$p=0.015$ ), whereas no significant difference was found for venous thrombosis (35/647, 5.4% vs. 53/1234, 4.3%) (Supplemental Table 3). The distribution of thrombosis in the different MPNs is shown in Supplemental Table 4.

Among patients with thrombosis, no difference was found between cases and controls in the rate of arterial or venous thrombosis occurred during treatment with hydroxyurea; on the other hand, in cases with second cancer the proportion of arterial thrombosis in absence of hydroxyurea, was higher than in controls (1.5% vs. 0.4%,  $p=0.008$ ) (Supplemental Table 5).

Among the thrombotic events, 125 (71.4%) were new events and 50 (28.6%) were recurrences of a prior thrombosis. Compared to patients who had no thrombosis during follow-up, patients with recurrent thrombosis had a higher risk of second cancer (OR=2.13, 95% CI 1.19-3.81,  $p=0.011$ ) while patients with new thrombotic events during follow-up had a similar risk of develop a second cancer (OR=1.28, 95% CI 0.86-1.90).

While the cumulative incidence of venous thrombosis over time was similar among cases and controls ( $p=0.864$ ), the cumulative incidence of arterial thrombosis was higher in cases with second cancer ( $p=0.006$ ) (Figure 1).

The excess of arterial thrombosis after MPN diagnosis was limited to cases with carcinoma (Table 1). Moreover, cases with carcinoma experienced splanchnic vein thrombosis after MPN diagnosis more frequently than controls (Table 1). In the multivariable model, arterial thrombosis during the follow-up was confirmed to be an independent predictor of carcinoma, with an odds ratio of 1.97 (95% CI 1.14-3.41,  $p=0.015$ ) (Figure 1). Cardiovascular risk factors or *JAK2* mutational status had no impact on the risk of second carcinoma. Low dose aspirin, used as prophylaxis for incident thrombosis, showed a significant protective role on the occurrence of carcinoma, as discussed elsewhere.<sup>16</sup> Patients on cytoreduction during the follow-up received hydroxyurea in 91.1% of cases (952/1045); those latter had a similar risk of carcinoma and hematological second cancer, and a doubled risk of non melanoma-skin cancer with respect to the untreated patients (Figure 1). These findings reveal in MPN patients an association of arterial thrombosis with second cancer. Interestingly, in two recent large ELN surveys carried out in 387 MPN patients with VTE<sup>13,14</sup> and 597 MPN patients with cerebrovascular ischemic events<sup>15</sup>, the frequency of second cancer was 1.7-fold higher in the latter than in patients with VTE (8.5% versus 4.9%, respectively,  $p=0.036$ ).

The incidence of cancer following VTE in MPN patients was similar to that observed in the general population, where 5.2% of patients with unprovoked VTE develop cancer within 12 months from VTE.<sup>11</sup> In contrast, the frequency of second cancer after arterial thrombosis appears greater than

in the general population. In a series of 374,331 patients older than 67 years, 1.75% of cancer patients had an arterial thrombotic event within one year preceding diagnosis of cancer, with an increased risk of 69% versus the matched cancer-free controls.<sup>12</sup> In two other population-based studies, patients with lower limb arterial thrombosis or myocardial infarction had a cancer incidence 1.4 and 1.6-fold higher than subjects without thrombosis one to three years after the event.<sup>17,18</sup> Arterial thrombosis has been reported to be preferentially associated with lung and kidney cancer<sup>19</sup>; however, in our MPN series lung and kidney cancer accounted for only 13.1% and 1.1% of cases with carcinoma, respectively (Supplemental Table 1).

The procoagulant mechanisms underlying the cancer-associated thrombophilia are complex and multifactorial and have been specifically explored to explain the association with venous thrombosis.<sup>20</sup> Interestingly, there is evidence that patients with solid tumors have a higher prevalence of clonal hematopoiesis of undetermined significance (CHIP)<sup>21,22</sup>, and it is not surprising that MPN clonal diseases may further increase the carcinogenetic risk. A possible biological plausibility for the link between arterial thrombosis and carcinoma in MPN patients may be related to an underlying common pathogenic mechanism such as an aberrant inflammatory response consistently found in MPN.<sup>23</sup>

Our observations may have practical implications and suggest careful clinical surveillance for diagnosis of early cancer in MPN patients with arterial thrombosis during the follow-up. The *International Society on Thrombosis and Haemostasis* (ISTH) guidance for patients with unprovoked VTE could be adopted. This approach includes a careful medical history, physical examination, basic laboratory investigations, and chest X-ray, as well as age- and sex-specific cancer screening (i.e., breast, cervical, colon, and prostate).<sup>24</sup>

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### **Authorship contribution**

TB and VDS conceived and designed the study, collected the data, analyzed and interpreted the data, and wrote the manuscript; AG collected the data, performed the statistical analysis, interpreted the data, and wrote the manuscript; all the other authors collected the data,



interpreted the data, and revised the manuscript for important intellectual content. The final version of the manuscript was approved by all the authors.

### **Conflict of interest**

TB has been a speaker and consultant for Novartis and he has received research grant from AOP Orphan. VDS has received consulting and lecture fees from Amgen, Celgene, Novartis, and institutional research grants from Bayer and Novartis. MLF has been a member of advisory board for Novartis and she has received travel grants from the company. MFM has been a speaker and consultant for Novartis. MM has received honoraria for advisory boards and lectures at sponsored meetings from Celgene, Amgen, Janssen, Gilead, Novartis. AMV has been a speaker for Novartis, Celgene, and Shire and participated to advisory boards of Celgene, Incyte, Novartis. The remaining authors declare that they have no conflict of interest.

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**Table 1. Type of thrombosis before/at MPN diagnosis and during follow-up stratified by second cancer**

	CARCINOMA			NM-SKIN CANCER			HSC			MELANOMA		
	CONTROLS N=812	CASES N=426	p*	CONTROLS N=244	CASES N=127	p*	CONTROLS N=116	CASES N=62	p*	CONTROLS N=62	CASES N=32	p*
<b>Thrombosis before/at MPN diagnosis</b>	180 (22.2%)	84 (19.7%)	0.318	50 (20.5%)	27 (21.3%)	0.863	20 (17.2%)	12 (19.4%)	0.726	12 (19.4%)	5 (15.6%)	0.656
<b>Arterial thrombosis</b>	127 (15.6%)	57 (13.4%)	0.288	36 (14.8%)	21 (16.5%)	0.652	14 (12.1%)	8 (12.9%)	0.872	9 (14.5%)	3 (9.4%)	0.745
<i>Acute coronary syndrome</i>	54 (6.7%)	20 (4.7%)	0.168	20 (8.2%)	9 (7.1%)	0.705	4 (3.4%)	3 (4.8%)	0.696	2 (3.2%)	2 (6.3%)	0.603
<i>TIA</i>	32 (3.9%)	10 (2.3%)	0.141	7 (2.9%)	7 (5.5%)	0.205	5 (4.3%)	4 (6.5%)	0.721	4 (6.5%)	1 (3.1%)	0.658
<i>Ischemic stroke</i>	26 (3.2%)	20 (4.7%)	0.187	7 (2.9%)	4 (3.1%)	1.000	4 (3.4%)	0 (0.0%)	0.299	2 (3.2%)	0 (0.0%)	0.546
<i>Other arterial thrombosis</i>	15 (1.8%)	7 (1.6%)	0.796	2 (0.8%)	1 (0.8%)	1.000	1 (0.9%)	1 (1.6%)	1.000	1 (1.6%)	0 (0.0%)	1.000
<b>Venous thrombosis</b>	52 (6.4%)	27 (6.3%)	0.964	14 (5.7%)	6 (4.7%)	0.682	6 (5.2%)	4 (6.5%)	0.741	3 (4.8%)	2 (6.3%)	1.000
<i>DVT of the legs and/or pulmonary embolism</i>	23 (2.8%)	12 (2.8%)	0.987	6 (2.5%)	3 (2.4%)	1.000	3 (2.6%)	1 (1.6%)	1.000	1 (1.6%)	1 (3.1%)	1.000
<i>Splanchnic vein thrombosis</i>	12 (1.5%)	9 (2.1%)	0.411	5 (2.0%)	2 (1.6%)	1.000	2 (1.7%)	1 (1.6%)	1.000	1 (1.6%)	0 (0.0%)	1.000
<i>Cerebral vein thrombosis</i>	1 (0.1%)	2 (0.5%)	0.274	0 (0.0%)	0 (0.0%)	0.000	1 (0.9%)	1 (1.6%)	1.000	0 (0.0%)	0 (0.0%)	0.000
<i>Other venous thrombosis</i>	16 (2.0%)	4 (0.9%)	0.236	3 (1.2%)	1 (0.8%)	1.000	0 (0.0%)	1 (1.6%)	0.348	1 (1.6%)	1 (3.1%)	1.000
<b>Thrombosis during follow-up</b>	67 (8.3%)	51 (12.0%)	0.034	21 (8.6%)	15 (11.8%)	0.322	7 (6.0%)	5 (2.0%)	0.607	5 (8.1%)	4 (12.5%)	0.489
<b>Arterial thrombosis</b>	32 (3.9%)	29 (6.8%)	0.027	11 (4.5%)	6 (4.7%)	0.925	2 (1.7%)	2 (3.2%)	0.611	1 (1.6%)	3 (9.4%)	0.113
<i>Acute coronary syndrome</i>	8 (1.0%)	6 (1.4%)	0.503	4 (1.6%)	2 (1.6%)	1.000	0 (0.0%)	0 (0.0%)	-	1 (1.6%)	1 (3.1%)	1.000
<i>TIA</i>	14 (1.7%)	14 (3.3%)	0.079	1 (0.4%)	1 (0.8%)	1.000	1 (0.9%)	1 (1.6%)	1.000	0 (0.0%)	1 (3.1%)	0.340
<i>Ischemic stroke</i>	7 (0.9%)	6 (1.4%)	0.370	2 (0.8%)	1 (0.8%)	1.000	1 (0.9%)	1 (1.6%)	1.000	0 (0.0%)	1 (3.1%)	0.340
<i>Other arterial thrombosis</i>	3 (0.4%)	3 (0.7%)	0.420	4 (1.6%)	2 (1.6%)	1.000	0 (0.0%)	0 (0.0%)	-	0 (0.0%)	0 (0.0%)	-
<b>Venous thrombosis</b>	34 (4.2%)	22 (5.2%)	0.432	10 (4.1%)	9 (7.1%)	0.215	5 (4.3%)	3 (4.8%)	1.000	4 (6.5%)	1 (3.1%)	0.658
<i>DVT of the legs and/or pulmonary embolism</i>	21 (2.6%)	11 (2.6%)	0.997	6 (2.5%)	7 (5.5%)	0.129	2 (1.7%)	2 (3.2%)	0.611	2 (3.2%)	0 (0.0%)	0.546
<i>Splanchnic vein thrombosis</i>	3 (0.4%)	7 (1.6%)	0.038	1 (0.4%)	1 (0.8%)	1.000	0 (0.0%)	0 (0.0%)	-	1 (1.6%)	1 (3.1%)	1.000
<i>Cerebral vein thrombosis</i>	0 (0.0%)	1 (0.2%)	0.344	0 (0.0%)	0 (0.0%)	-	1 (0.9%)	0 (0.0%)	1.000	0 (0.0%)	0 (0.0%)	-
<i>Other venous thrombosis</i>	10 (1.2%)	3 (0.7%)	0.560	3 (1.2%)	1 (0.8%)	1.000	2 (1.7%)	1 (1.6%)	1.000	1 (1.6%)	0 (0.0%)	1.000

\*Chi-square test or Fisher's exact test (when appropriate) for categorical data. For 1 patient, type of thrombosis before/at MPN diagnosis and during follow-up was missing

## FIGURE LEGENDS

### **Figure 1. Kaplan-Meier curves and multivariable analysis**

- (A) Ten-year arterial and venous/splanchnic thrombosis-free curves from MPN diagnosis in cases and controls.
- (B) Effect of arterial and venous/splanchnic thrombosis on second cancer risk obtained by a multivariable conditional logistic regression model, adjusted for potential confounders (age, cardiovascular risk factors, JAK2 mutation, time of thrombosis - at diagnosis or during follow-up), and stratified by type of second cancer. Due to the low number of cases, no multivariable model was fitted for melanoma.

Figure 1



