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ORIGINAL ARTICLE

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Highly reduced survival in essential thrombocythemia and polycythemia vera patients with vascular complications during follow-up

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Abstract

Objective: To explore the relative importance of risk factors, treatments, and blood counts for the occurrence of vascular complications and their impact on life expectancy in essential thrombocythemia (ET) and polycythemia vera (PV).

Methods: Nested case-control study within the Swedish MPN registry. From a cohort of 922 ET patients and 763 PV patients, 71 ET and 81 PV cases with vascular complications were compared with matched controls.

Results: Incidence of vascular complications was 2.0 and 3.4 events per 100 patient-years in ET and PV, respectively. At diagnosis, no significant risk factor differences were observed between cases and controls in neither of the diseases. At the time of vascular event, ET complication cases did not differ significantly from controls but in PV, cases had significantly higher WBCs and were to a lesser extent treated with anti-thrombotic and cytoreductive therapy. Life expectancy was significantly decreased in both ET and PV cases compared with controls.

Conclusions: The risk of vascular complications is high in both ET and PV, and these complications have a considerable impact on life expectancy. The protective effect of anti-thrombotic and cytoreductive therapy for vascular complications in PV underscores the importance of avoiding undertreatment.

KEYWORDS

essential thrombocythemia, myeloproliferative neoplasms, polycythemia vera

1 | INTRODUCTION

Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs) are characterized by expansion of blood cells, constitutional symptoms, vascular complications and a potential to transform to myelofibrosis (MF) and acute myeloid leukemia (AML). These disorders are stem cell–derived myeloid neoplasms that typically carry mutually exclusive *JAK2*, *CALR* or *MPL* mutations. The most common MPNs are essential thrombocythemia (ET) and polycythemia vera (PV).

Compared with the general population, survival is reduced in both ET and PV[1] and risk factors for inferior survival include age, leucocytosis and thrombotic history.[2,3] Since thrombotic and cardiovascular events are the leading causes of mortality among PV and ET patients[3,4] and established therapies cannot prevent transformation

to MF and AML, the goal of treatment is primarily focused on reducing the risk of vascular complications.[5] Risk factors for MPN-associated vascular complications include age, thrombosis and bleeding history, sex, cardiovascular risk, mutation type and burden, inflammatory stress[6] and for bleeding also marked thrombocytosis.[7]

Therapy against vascular risk is guided by risk classification of the disease. In PV, high-risk disease is defined by age >60 years and/or history of thrombosis.[5] In ET, the IPSET-thrombosis system, including age, previous thrombosis, cardiovascular risk factors and *JAK2*V617F mutation, defines patients into four risk categories.[8] In the current Nordic care program,[9] a simpler risk assessment is applied defining high-risk by age >60 years and/or history of thrombosis and/or platelets >1500, and the latter being a risk factor for bleeding.

Low-dose aspirin[10] and phlebotomy with a hematocrit target of <45%[11] reduce vascular complications in PV and should be given to all patients. Cytoreductive therapy is recommended to high-risk PV patients[5] based on observational studies and extrapolating data from ET studies.[12,13] In ET, no randomized trials have confirmed the benefit of low-dose aspirin although aspirin has widely been recommended in high-risk disease.[5] However, in low-risk CALR mutated disease, aspirin may increase the risk of bleeding without reducing the risk of thrombosis.[14] In high-risk ET, hydroxyurea treatment guided by platelet count has proven beneficial to reduce the incidence of vascular complications.[15,16] On the contrary, in non–high-risk ET, hydroxyurea treatment has not proven beneficial.[17]

Previous reports in MPNs have confirmed a high incidence of vascular complications.[4,18-20] The underlying factors predisposing for vascular complications are often multifactorial involving disease-specific factors, treatment-related protective factors and comorbid classical vascular risk factors.[21] Importantly, one smaller study from the Hamilton region in Canada has demonstrated an inferior prognosis for patients not treated in accordance with guidelines.[22]

The Swedish MPN registry was opened in 2008 and is a truly population-based registry with a reporting coverage over 95%. Real-world data have previously been published from the registry, presenting incidence of vascular complications prior to MPN diagnosis.[23]

In this study, we conducted a nested case-control study within the Swedish MPN registry to explore the relative importance of risk factors, treatments, and blood counts for vascular complications during follow-up in ET and PV as well as the impact of vascular complications on life expectancy.

2 | METHODS

2.1 | Study population

The Swedish MPN registry, which is a part of the Swedish Blood Cancer Registry, was founded in 2008. It is mandatory by Swedish law to report newly diagnosed MPN patients to the registry. From January 2010, newly diagnosed MPN patients were also followed prospectively, with planned follow-up every third year.

Patients in the registry diagnosed with ET or PV, defined by 2008 WHO criteria, from January 2010 through September 2015, with a 3-year or 6-year follow-up were included in the study. From this study base, cases were identified as having a thromboembolic or hemorrhagic reported vascular complication after diagnosis. Vascular complications were defined as vascular events that required medical intervention or observation. Each case was assigned a matched control from the study base matched by MPN sub-entity, sex, and age at diagnosis. From the registry reports, age, gender, blood counts, erythropoietin (EPO), and *JAK2* V617F mutation status at diagnosis were obtained for cases and controls. Hospital records were reviewed for co-morbidity, smoking habits, and vascular complications prior to diagnosis as well as concomitant cytoreductive and anti-thrombotic treatments and blood counts at the time of vascular complication. For controls, these parameters were registered at the time from diagnosis corresponding to the time from diagnosis to the vascular event in the matched case.

2.2 | Ethics

The Regional Ethics Committee of Gothenburg, Sweden, approved the study.

2.3 | Statistical analysis

Differences in the distribution of variables among the categories were analyzed using Mann-Whitney test. Chi-square test was used for comparison between groups. Overall survival estimations were calculated by Kaplan-Meier analysis and compared using Log-rank test. For multivariate analysis, IBM SPPS statistics 25 was used. Unconditional logistic regression[24] was conducted including matching parameters in the analysis (age and sex) to avoid a potential bias from missing data in one of the two matched patients. When applicable, $P < .05$ was considered statistical significant and 95% confidence intervals (CI) were used.

3 | RESULTS

A total of 922 ET patients and 763 PV patients fulfilled the inclusion criteria. The mean follow-up times were 46 months for ET patients and 37 months for PV patients, corresponding to 3533 and 2382 patient-years, respectively.

3.1 | ET patients, general

Seventy-one ET patients (8%) experienced at least one vascular complication during the follow-up time, which corresponds to 2.0

events per 100 patient-years. Of these, 49 were thromboembolic and 22 were hemorrhagic, corresponding to 1.4 and 0.6 events per 100 patient-years, respectively. Patients with vascular complications were significantly older at the time of diagnosis compared with the whole ET group, and the mean ages were 73 and 65 years, respectively ($P < .001$). The patients' characteristics at the time of diagnosis are shown in Table 1.

The median time from diagnosis to the time of vascular complication was 24 months (range 0-71 months). The most common thromboembolic events were cardiac, deep vein thrombosis (DVT)/pulmonary embolism (PE), and cerebral. Among the hemorrhagic complications gastro-intestinal and cerebral were the most common (Table 2).

3.2 | ET patients, case-control analysis

At the time of diagnosis, there were no significant differences, in blood counts, *JAK2* V617F mutation status, EPO levels or vascular events prior to diagnosis between the 71 ET patients with complications and the matched controls (Table 1). Cardiovascular risk factors and smoking habits did not differ significantly between cases and controls. Of the total 142 patients included in the case-control analysis, 126 (89%) fulfilled high-risk criteria by the Nordic MPN guidelines.

At the time of vascular event, there were no significant differences in mean hemoglobin concentration (Hb), hematocrit or platelet counts. The mean white blood cell (WBC) count was 9.1 × 10^9/L in cases compared with 7.1 × 10^9/L in controls, a non-significant statistical difference ($P = .063$, Table 3). Seventy-five % of the ET cases were treated with cytoreductive therapy by the time of the vascular event compared with 82% in controls ($P = .416$). The majority of cytoreductive treated patients were treated with hydroxyurea, 83% in cases and 93% in controls. In both groups, 93% had prophylactic treatment with an anti-thrombotic agent (Table 3), and aspirin/clopidrogrel constituted 77% in cases and 92% in controls.

In multivariate analysis, there were no significant differences in risk factors between cases and controls at the time of vascular complication (Table 5) and results were similar analyzing only high-risk matched patient pairs (data not shown).

The estimated 5-year survival was significantly impaired in cases compared with matched controls, 65% and 81%, respectively ($P = .020$, Figure 1).

3.3 | PV patients, general

During follow-up, 81 (11%) of the PV patients experienced at least one vascular event, which corresponds to 3.4 events per 100 patient-years. Fifty-nine of these were thromboembolic and 22 were

TABLE 1 Characteristics of ET patients at the time of diagnosis

	All ET n = 922	ET with vascular comp n = 71 [A]	Matched ET controls n = 71 [B]	*P* A vs B
Age				
Median (range)	68 (16-94)	77 (36-91)	76 (38-94)	.814
Mean ± SD	65 ± 16	73 ± 13	73 ± 13	
Sex				
Female/male	537/385	47/24	44/27	.726
Hemoglobin				
Mean ± SD	138 ± 15	136 ± 15	136 ± 17	.915
Hematocrit				
Mean ± SD	42 ± 4	42 ± 5	42 ± 5	.637
WBC				
Mean ± SD	9.1 ± 5.5	9.8 ± 3.1	10.4 ± 3.1	.193
Platelets				
Mean ± SD	817 ± 312	845 ± 279	815 ± 291	.306
EPO				
Mean ± SD	8.5 ± 21.5	8.4 ± 7.7	6.7 ± 5.0	.394
JAK2				
V617F/wt.	568/314	50/20	46/22	.776
Vascular comp prior to diag.				
Yes/no	332/575	36/35	28/41	.302

Note: Sex, *JAK2* mutational status; numbers of patients. Hemoglobin; g/L, Hematocrit; %, WBC and Platelets; ×10^9/L and EPO; U/L.

Abbreviation: SD; standard deviation.

TABLE 2 Vascular complications in ET and PV patients

	Thromboembolic complications						Hemorrhagic compl.		
	Cardiac	DVT/PE	Cerebral	Splanchnic	Arterial	Other	G-I	Cerebral	Other
ET n = 71	15	15	13	2	3	1	11	5	6
PV n = 81	14	18	21	1	5	0	7	6	9

Note: Number of patients with different vascular complications during follow-up.

TABLE 3 Blood counts, IPSET risk score and concomitant treatment in ET and PV patients at the time of vascular complication

	ET			PV		
	Vascular comp n = 71 [A]	Matched controls n = 71 [B]	*P* A vs B	Vascular comp n = 81 [C]	Matched controls n = 81[D]	*P* C vs D
Hemoglobin						
Mean ± SD	124 ± 21	131 ± 17	.168	129 ± 16	134 ± 12	.077
Hematocrit						
Mean ± SD	39 ± 6	40 ± 5	.419	42 ± 5	43 ± 4	.212
WBC						
Mean ± SD	9.1 ± 5.0	7.6 ± 3.4	.063	13.5 ± 9.6	9.6 ± 4.9	<.001*
Platelets						
Mean ± SD	539 ± 329	478 ± 226	.647	414 ± 283	349 ± 146	.360
IPSETthromb	3.7 ± 1.6	3.6 ± 1.8	.757			
Cytoreductive therapy						
Yes/no	53/18	58/13	.416	41/40	64/17	<.001*
Anti-thrombotic therapy						
Yes/no	66/5	66/5	1.000	70/11	80/1	.007*

Note: Cytoreductive therapy and anti-thrombotic therapy; numbers of patients. Hemoglobin; g/L, Hematocrit; %, WBC and Platelets; $\times 10^9$/L. IPSET-thrombosis risk score[8] at diagnosis.

Abbreviation: SD; standard deviation.

*$P < .05$.

hemorrhagic, corresponding to 2.5 and 0.9 events per 100 patient-years, respectively. Patients with vascular complications were significantly older compared with the whole PV cohort with mean ages of 73 and 68 years, respectively ($P < .001$). The patients' characteristics are shown in Table 4.

The median time from diagnosis to complication was identical to ET patients, that is, 24 months (range 0-89 months). Cerebral ischemic events were the most frequent, followed by DVT/PE and cardiac events. Gastro-intestinal and cerebral bleedings were the most frequent hemorrhagic complications (Table 2).

3.4 | PV patients, case-control analysis

No significant differences in blood counts, EPO, *JAK2* V617F allele burden, vascular events prior to diagnosis, co-morbidity or smoking habits, were found between the 81 cases and their matched controls at the time of diagnosis (Table 4).

All but four patients (two matched pairs) fulfilled high-risk criteria.

At the time of the vascular event, cases had a mean WBCs of 13.5×10^9/L compared with 9.6×10^9/L among controls ($P < .001$). No significant differences were found between the groups regarding Hb, hematocrit, and platelets. Significant differences were found in the use of concomitant cytoreductive therapy with only 51% of cases receiving treatment compared to 79% of controls ($P < .001$). In both groups, 88% of treated patients received hydroxyurea. Regarding anti-thrombotic treatment, 86% of the cases received treatment compared with 99% of the controls ($P = .007$, Table 3).

In multivariate analysis, cytoreductive therapy (odds ratio 0.22, CI 0.096-0.50, $P = <.001$) and anti-thrombotic therapy (odds ratio 0.085, CI 0.009-0.79, $P = .03$) were both identified as significant protective factors for vascular complications (Table 5). There was no effect of WBCs on the odds ratio for vascular complication in multivariate analysis, indicating that the risk effect of WBCs in univariate analysis was confounded by a protective effect of cytoreductive therapy. The risk effect of elevated WBCs was calculated both with WBCs as a continuous variable and a categorical variable with different cutoffs (>10, >11, >15) with similar results, WBCs > 11 is shown in Table 5. Cytoreductive therapy was a significant protective factor

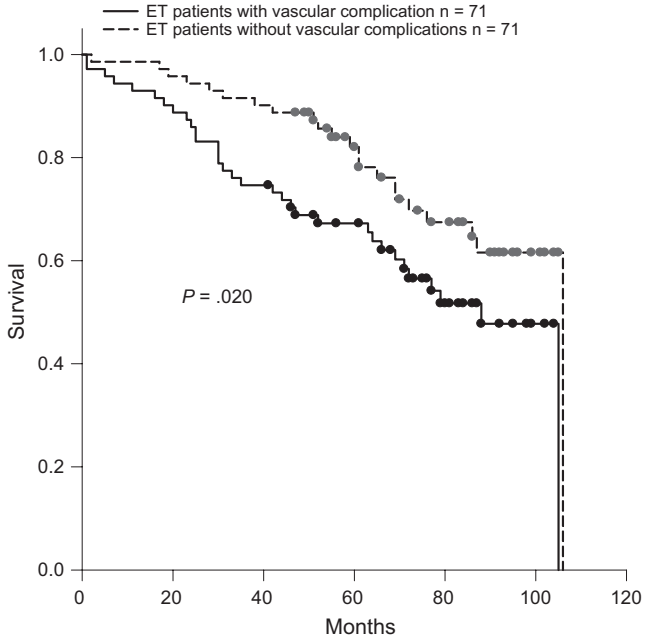

FIGURE 1 Estimated survival, Kaplan-Meier Log rank, for 71 ET patients with vascular complications during follow-up and 71 matched controls with ET without vascular complications

both for bleeding events (odds ratio 0.046, CI 0.05-0.46, $P = .046$) and thrombotic events (odds ratio 0.30, CI 0.12-0.75, $P = .011$). When analyzing the data according to risk group, cytoreductive therapy was identified as a protective factor for vascular complications for high-risk patients (odds ratio 0.21, CI 0.09-0.48, $P < .001$) whereas numbers of patients were too small for multivariate analysis in low-risk PV patients.

The estimated 5-year survival was 60% in cases compared with 85% in matched controls. This difference was highly statistically significant ($P < .001$, Figure 2).

4 | DISCUSSION

To the best of our knowledge, this is the first countrywide population-based study of vascular complications in ET and PV, including 922 ET patients and 763 PV patients prospectively followed for at least 3 years. The vast majority of patients fulfilled high-risk criteria, and we demonstrate a high incidence of both thrombotic and bleeding vascular complications.

Eight percent of the ET patients experienced at least one vascular complication during the follow-up time corresponding to 1.4 thromboembolic and 0.6 hemorrhagic events per 100 patient-years, respectively. The incidence of thromboembolic events is identical to the report from the Austrian MPN registry.[18]

In PV, 11% experienced vascular events during follow-up, which corresponds to 2.5 thromboembolic, and 0.9 hemorrhagic events per 100 patient-years, which is in accordance with findings from other groups.[19] The types of thromboembolic events were similar in

TABLE 4 Characteristics of PV patients at the time of diagnosis

	All PV n = 763	PV with vascular comp n = 81 [A]	Matched PV controls n = 81 [B]	*P* A vs B
Age				
Median (range)	69 (17-98)	75 (31-98)	75 (31-95)	.940
Mean ± SD	68 ± 13	73 ± 11	73 ± 11	
Sex				
Female/male	371/392	36/45	40/41	.637
Hemoglobin				
Mean ± SD	173 ± 22	172 ± 23	175 ± 24	.301
Hematocrit				
Mean ± SD	53 ± 7	54 ± 6	55 ± 7	.380
WBC				
Mean ± SD	12.7 ± 11.5	12.6 ± 4.9	12.2 ± 4.9	.454
Platelets				
Mean ± SD	554 ± 277	530 ± 285	517 ± 241	.944
EPO				
Mean ± SD	2.8 ± 7.3	2.7 ± 2.3	5.6 ± 18.9	.369
JAK2 V617fF%				
Mean ± SD	nd	49 ± 28	46 ± 28	.446
Vascular comp prior to diag.				
Yes/no	268/491	35/46	27/53	.248

Note: Sex and vascular complications prior to diagnosis; numbers of patients. Hemoglobin; g/L, Hematocrit; %, WBC and Platelets; $\times 10^9$/L, EPO; U/L, *JAK2* allele burden; %.

Abbreviation: SD; standard deviation.

TABLE 5 Multivariate analysis comparing cases and controls regarding blood counts and concomitant treatment at the time of vascular complications

	ET		PV	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Age	1.01 (0.97-1.04)	.596	1.00 (0.97-1.04)	.898
Sex	1.06 (0.51-2.2)	.881	1.28 (0.62-2.66)	.509
Hematocrit ≥ 45	–[a]	–	1.01 (0.98-1.03)	.610
WBC > 11	1.48 (0.54-4.05)	.446	1.44 (0.64-3.2)	.374
Platelets > 400	1.08 (0.51-2.3)	.842	0.57 (0.25-1.3)	.571
Anti-thrombotic therapy	0.88 (0.22-3.6)	.866	0.085 (0.009-0.79)	.03*
Cytoreductive therapy	0.53 (0.20-1.5)	.220	0.22 (0.096-0.50)	<.001*

Note: Sex; male/female, Hematocrit; %, WBC and Platelets; $\times 10^9$/L.

Abbreviation: CI, confidence interval.

[a]Too few cases for analysis.

*$P < .05$.

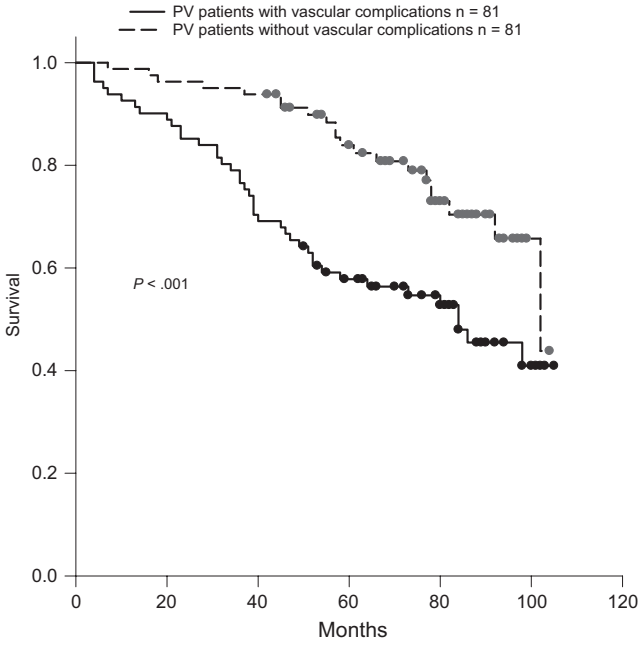

FIGURE 2 Estimated survival, Kaplan-Meier Log rank, for 81 PV patients with vascular complications during follow-up and 81 matched controls with PV without vascular complications

ET and PV, and we found that cardiac, DVT/PE, and cerebral complications dominated in both groups. The incidence of hemorrhagic events was consistent with previous epidemiological studies in ET[20] and PV.[4] Hemorrhagic events were mainly gastro-intestinal and cerebral in both diagnoses.

When comparing the 71 ET patients and 81 PV patients with vascular complications with matched controls, no significant differences were found in blood values, EPO, *JAK2* V617F allele burden or vascular complications prior to diagnosis (Tables 1 and 4). Neither did co-morbidities nor smoking habits differ significantly between the groups. This finding might seem contradictory to the previously published data from the Swedish national MPN registry[23] demonstrating that an elevated WBC is a risk factor for vascular complications in ET. However, the former study addressed vascular complications prior to diagnosis whereas we now only focus on events during follow-up. It is therefore possible that cytoreductive therapy in ET patients with previous vascular events diminished the risk of an elevated WBC count during follow-up. However, the mechanism behind such possible protective effect of therapy cannot be identified by our current analysis but are of considerable interest to be investigated in future studies. The proportion of patients who experienced a vascular complication prior to diagnosis was higher in our real-world data (36%) compared with ET and PV patients in a cohort from four European centers (26%).[25]

At the time of vascular complication, PV cases had significantly higher mean WBC compared with controls, that is 13.5 × 10^9/L and 9.6 × 10^9/L, respectively ($P < .001$), whereas Hb, hematocrit, and platelets did not differ significantly (Table 3). The same comparisons were performed in ET but here the difference in mean WBCs between cases and controls did not quite reach statistical significance ($P = .063$, Table 3). The smaller difference in WBCs in ET may be a result of the proportionally higher cytoreductive treatment frequency among ET patients compared with PV patients, which were 79% and 51%, respectively ($P < .001$). Moreover, compared with PV, there was a smaller difference in the proportion of patients receiving cytoreductive therapy between cases and controls in ET, (75% and 82%, respectively, $P = .416$). Even if the differences in WBC were only significant in univariate analysis in PV and borderline in ET, it might be worth discussing if the goal of cytoreductive treatment in these diseases should be normalization of WBCs rather than focusing on platelet levels, which were not different between cases and controls in neither disease (Table 3).

In this study, with a predominance of high-risk PV patients, we demonstrate a strong protective effect of cytoreductive therapy for both thrombotic and bleeding vascular events. In multivariate analysis, the odds ratio for vascular complications in PV patients treated with cytoreductive therapy was 0.22 (CI 0.096-0.50, $P < .001$). In the absolute majority of patients in the study, hydroxyurea was used as cytoreductive agent. This finding is in accordance with previously published observations showing a strong protective effect

of hydroxyurea on vascular complications in PV.[12] Cytoreductive therapy has been established in high-risk ET, but the indication for use of cytoreduction in high-risk PV with normal platelet and leukocyte counts has obviously not been adapted to all hematology centers in Sweden. Similar treatment practices have been described in Canada[22] and the Netherlands.[26]

Since the ECLAP study was published in 2004,[10] the benefit of low-dose aspirin in PV in preventing thromboembolic complications has been established. Despite of this knowledge and recommendations given by the Nordic MPN guidelines for many years, 14% of PV cases were not treated with anti-thrombotic therapy. This is compared with only 1% in the control group ($P = .007$), and the difference was confirmed in multivariate analysis ($P = .03$).

In contrast, 93% of both ET cases and controls were on anti-thrombotic therapy. Given that the majority of all ET patients (89%) was classified as high-risk, this indicates that guidelines were followed more consequently in this group, which might be due to a broader perception among physicians of a causal relationship between platelets and thrombosis.

Established therapies for ET and PV cannot prevent transformation to MF or AML,[1,27] and therefore, cytoreductive and anti-thrombotic therapies are mainly aimed to reduce the risk of vascular complications. The present study confirms that vascular complications have a considerable impact on life expectancy in both PV and ET as previously shown by other groups.[3,4] Accordingly, PV patients with vascular events had an expected 5-year survival of about only 60% compared with 83% in controls ($P < .001$). Corresponding 5-year survival rates for ET in our study were 67% and 83% ($P = .020$).

The major strengths of this study are the use of population-based registers in Sweden that have a long tradition of cancer reporting and a high overall coverage. We could also validate good data quality in the registry when comparisons were made to the original data in the patient charts. Despite this, we cannot totally exclude that some vascular complications may not reported to the registry. However, it is unlikely that this have had a significant influence of our results and conclusions.

We therefore conclude that the risk of vascular complications is high in both ET and PV and that these complications have a considerable impact on life expectancy. We were able to show that cytoreductive and anti-thrombotic therapies have significant protective roles in PV. We were not able to demonstrate a similar protective effect of cytoreductive and anti-thrombotic therapies in ET, which may be due to a higher treatment frequency in ET impeding a comparison between treated and untreated patients. These findings have clinical implications for high-risk PV patients for which a stronger recommendation to follow current guidelines for cytoreductive and anti-thrombotic treatment is warranted.

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