

Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments

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Supplemental material for De Stefano et al., Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments.

Appendix

Investigators and institutions of the Chronic Myeloproliferative Disorders - Working Party of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) that participated in this research.

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Table S1. Baseline characteristics of the patients stratified according to diagnosis.

	PV (n= 235)	ET (n= 259)	P value
Sex (M / F) - no. (% of male sex)	138/97 (58.7)	101 / 158 (38.9)	< 0.001
Median age at diagnosis - yrs (range)	63 (18-87)	61 (19-88)	
Median age at thrombosis - yrs (range)	64 (20-90)	63 (21-89)	
First arterial index thrombosis - no. (%)	155 (65.9)*	186 (71.8) *	0.17
First venous index thrombosis - no. (%)	85 (36.1) *	75 (28.9) *	0.10
Presence of at least one vascular risk factor - no. (%)	142 (60.4)	147 (56.7)	0.41
- smoke - no. (%)	32 (13.6)	39 (15.0)	0.70
- hypertension - no. (%)	119 (50.6)	111 (42.8)	0.08
- hypercholesterolemia - no. (%)	24 (10.2)	38 (14.6)	0.17
- diabetes mellitus - no. (%)	23 (9.8)	18 (6.9)	0.25
- chronic atrial fibrillation - no. (%)	12 (5.1)	18 (6.9)	0.45
Presence of inherited or acquired thrombophilia no./no. tested (%)	20/69 (28.9)	22/73 (30.1)	1.00
History of remote thrombosis - no. (%)	30 (12.7)	21 (8.1)	0.10
Thrombosis at diagnosis of PV and ET or during the 2 years before - no. (%)	129 (54.8)	152 (58.6)	0.41
First thrombosis after diagnosis (index thrombotic event) - no. (%)	106 (45.2)	107 (41.4)	0.41
Patients receiving one treatment or more than one treatment after the index thrombosis:			
- antiplatelet agents - no. (%)	168 (71.4)	194 (74.9)	0.41
- long-term oral anticoagulation - no. (%)	42 (17.8)	48 (18.5)	0.90
- phlebotomy - no. (%)	155 (65.9)	0	<0.0001
- any pharmacological cytoreductive treatment - no. (%) #	156 (66.3)	195 (75.2)	0.03

PV, polycythemia vera; ET, essential thrombocythemia; * in five patients with PV and two with ET the first event involved both arterial and venous vessels. # cytoreductive treatment included hydroxyurea, pipobroman, busulphan, interferon, and anagrelide.

Table S2. Details of the first thrombotic events in the patient cohort stratified according to diagnosis.

	PV (n=235)	ET (n=259)	p value	Total (n=494)
First arterial index thrombosis - no. (%)	155 (65.9)*	186 (71.8)*	0.17	341 (69.0)*
- total acute coronary syndromes - no (%)	52 (22.1)	54 (20.8)	0.74	106 (21.4)
- myocardial infarction - no. (%)	41 (17.4)	40 (15.4)	0.62	81 (16.4)
- unstable angina - no. (%)	11 (4.7)	14 (5.4)	0.83	25 (5.0)
- total cerebrovascular disease - no. (%)	88 (37.4)	103 (39.7)	0.64	191 (38.6)
- ischemic stroke - no. (%)	38 (16.2)	35 (13.5)	0.44	73 (14.7)
- transient ischemic attack - no. (%)	50 (21.2)	68 (26.2)	0.20	118 (23.9)
- peripheral arterial occlusion - no. (%)	8 (3.4)	20 (7.7)	0.05	28 (5.6)
- mesenteric arterial thrombosis - no (%)	3 (1.3)	5 (1.9)	0.72	8 (1.6)
- splenic infarction - no (%)	2 (0.8)	2 (0.7)	1.00	4 (0.8)
- retinal artery thrombosis - no. (%)	2 (0.8)	2 (0.7)	1.00	4 (0.8)
First venous index thrombosis - no. (%)	85 (36.1)*	75 (28.9)*	0.10	160 (32.3)*
- total venous thromboembolism at usual sites -no. (%)	67 (28.5)	47 (18.1)	0.007	114 (23.0)
- deep vein thrombosis of the limbs and / or pulmonary embolism - no. (%)	52 (22.1)	35 (13.5)	0.01	87 (17.6)
- superficial vein thrombosis - no. (%)	15 (6.4)	12 (4.6)	0.43	27 (5.4)
- total venous thrombosis at unusual sites - no (%)	16 (6.8)	26 (10.0)	0.25	42 (8.5)
- hepatic venous thrombosis - no. (%)	1 (0.4)	6 (2.3)	0.12	7 (1.4)
- portal-mesenteric venous thrombosis - no (%)	12 (5.1)	18 (6.9)	0.45	30 (6.1)
- cerebral venous thrombosis - no. (%)	3 (1.3)	2 (0.7)	0.67	5 (1.0)
- retinal venous thrombosis - no. (%)	2 (0.8)	2 (0.7)	1.00	4 (0.8)

PV, polycythemia vera; ET, essential thrombocythemia; *in 5 patients with PV and 2 with ET the first event involved both arterial and venous vessels.

Table S3. Treatment of patients and recurrences in different treatment groups.

	<i>PV</i> (<i>n</i> = 235)	<i>ET</i> (<i>n</i> = 259)	<i>Total</i>	<i>Recurrences</i> (% of patients)
Different treatment groups – no. patients				
cytoreduction only [#]	20	20	40	20 (50.0)
antiplatelet agents only	53	38	91	32 (35.2)
antiplatelet agents + cytoreduction [#]	112	148	260	78 (30.0)
long-term oral anticoagulation only	16	18	34	15 (44.1)
long-term oral anticoagulation + cytoreduction [#]	23	22	45	8 (17.8)
antiplatelet agents + oral anticoagulation	2	3	5	2 (40.0)
antiplatelet agents + oral anticoagulation + cytoreduction [#]	1	5	6	0
no pharmacological treatment	8	5	13	11 (84.6)

PV, polycythemia vera; *ET*, essential thrombocythemia; [#]cytoreductive treatment includes hydroxyurea, pipobroman, busulphan, interferon, and anagrelide.

Table S4. Recurrences after the index thrombotic event in the patients stratified according to diagnosis.

	<i>PV</i> (<i>n</i> =235)	<i>ET</i> (<i>n</i> =259)	<i>p</i> <i>value</i>
Total observation time – yrs	1,419	1,533	
Median observation time – yrs (range)	5.4 (0.1-26.2)	5.2 (0.1-22)	
Overall first recurrences – no. (% of patients)	85 (36.1)	81 (31.2)	0.25
Incidence of first recurrences (% patient-years)	6.0	5.3	
Recurrent arterial thrombosis – no. (% of recurrences)	50 (58.8)*	51 (62.9)	0.63
- total acute coronary syndromes	6 (7.0)	13 (16.0)	0.08
- myocardial infarction	4 (4.7)	6 (7.4)	0.52
- unstable angina	2 (2.3)	7 (8.6)	0.09
- total cerebrovascular disease	36 (42.3)	29 (35.8)	0.42
- ischemic stroke	14 (16.4)	7 (8.6)	0.16
- transient ischemic attack	22 (25.9)	22 (27.2)	0.86
- peripheral arterial occlusion	5 (5.9)	6 (7.4)	0.76
- mesenteric arterial thrombosis	1 (1.2)	0	1.00
- splenic infarction	0	2 (2.5)	0.23
- retinal artery thrombosis	2 (2.4)	0	0.49
Recurrent venous thrombosis – no. (% of recurrences)	36 (42.3)*	30 (37.0)	0.52
- total venous thromboembolism at usual sites	33 (38.8)	26 (32.1)	0.41
- deep venous thrombosis of the limbs and/or pulmonary embolism	27 (31.8)	19 (23.5)	0.29
- superficial vein thrombosis	6 (7.0)	7 (8.6)	0.77
- total venous thrombosis at unusual sites	3 (3.6)	4 (4.9)	0.71
- hepatic venous thrombosis	1 (1.2)	0	1.00
- portal-mesenteric venous thrombosis	2 (2.4)	3 (3.7)	0.67
- cerebral venous thrombosis	0	1 (1.2)	0.48
Major bleeding after the index thrombosis – no (% of patients)	13 (5.5)	14 (5.4)	1.00
Incidence of major bleeds after the index thrombosis (% patient-years)	0.9	0.9	

PV, polycythemia vera; *ET*, essential thrombocythemia; *in one patient with *PV* recurrence involved both arterial and venous vessels.

Table S5. Risk factors for first recurrent thrombosis according to the baseline characteristics of the patients.

	<i>Hazard ratio (95% CI)</i>	<i>P (univariable analysis)</i>	<i>Hazard ratio (95% CI)</i>	<i>P (multivariable analysis)</i>
Sex (male vs. female)	1.08 (0.79-1.46)	0.62	1.05 (0.76-1.44)	0.76
Diagnosis (PV vs ET)	1.16 (0.85-1.57)	0.32	1.23 (0.82-1.82)	0.29
Age at thrombosis (>60 yrs vs < 60 yrs)	1.52 (1.10-2.09)	0.01	1.67 (1.19-2.32)	0.002
One or more vascular risk factors (presence vs absence)*	1.00 (0.81-1.22)	0.96	1.00 (0.98-1.02)	0.98
History of remote thrombosis (presence vs absence)§	1.18 (0.73-1.90)	0.48	1.05 (0.64-1.70)	0.82
Type of index thrombosis PV or ET-related (arterial vs venous)	0.80 (0.58-1.10)	0.18	0.92 (0.64-1.31)	0.65
Treatment after the index thrombotic event				
antiplatelet agents	<i>0.67 (0.48-0.92)</i>	<i>0.02</i>	0.72 (0.50-1.02)	0.07
long-term oral anticoagulation	1.00 (0.95-1.05)	0.71	1.00 (0.94-1.05)	0.84
phlebotomy	0.91 (0.65-1.25)	0.60	0.72 (0.47-1.09)	0.13
any pharmacological cytoreductive treatment#	<i>0.57 (0.41-0.78)</i>	<i>0.0007</i>	<i>0.53 (0.38-0.73)</i>	<i>0.0002</i>

*PV, polycythemia vera; ET, essential thrombocythemia; *smoking, hypertension, hypercholesterolemia, diabetes mellitus, chronic atrial fibrillation; §history of thrombosis prior to 2 years before diagnosis of PV or ET; #cytoreductive treatment includes hydroxyurea, pipobroman, busulphan, interferon, and anagrelide.*