S.S. FORMAZIONE PERMANENTE E AGGIORNAMENTO

Con il patrocinio dell'Università degli Studi di Torino

UNIVERSITÀ DEGLI STUDI DI TORINO

Evento Formativo Residenziale

PREVENZIONE E TRATTAMENTO DEGLI EVENTI TROMBOTICI NEI PAZIENTI ONCOLOGICI ED EMATOLOGICI: NUOVE SFIDE E AREE CRITICHE

Gestione e prevenzione delle complicanze trombotiche nelle malattie mieloproliferative PH-

Dott.ssa Antonella Vaccarino
SSD Ematologia
ASL Città di Torino, P.O. S. Giovanni Bosco

DATA

21 giugno 2022

dalle ore 9.00 alle ore 18.30

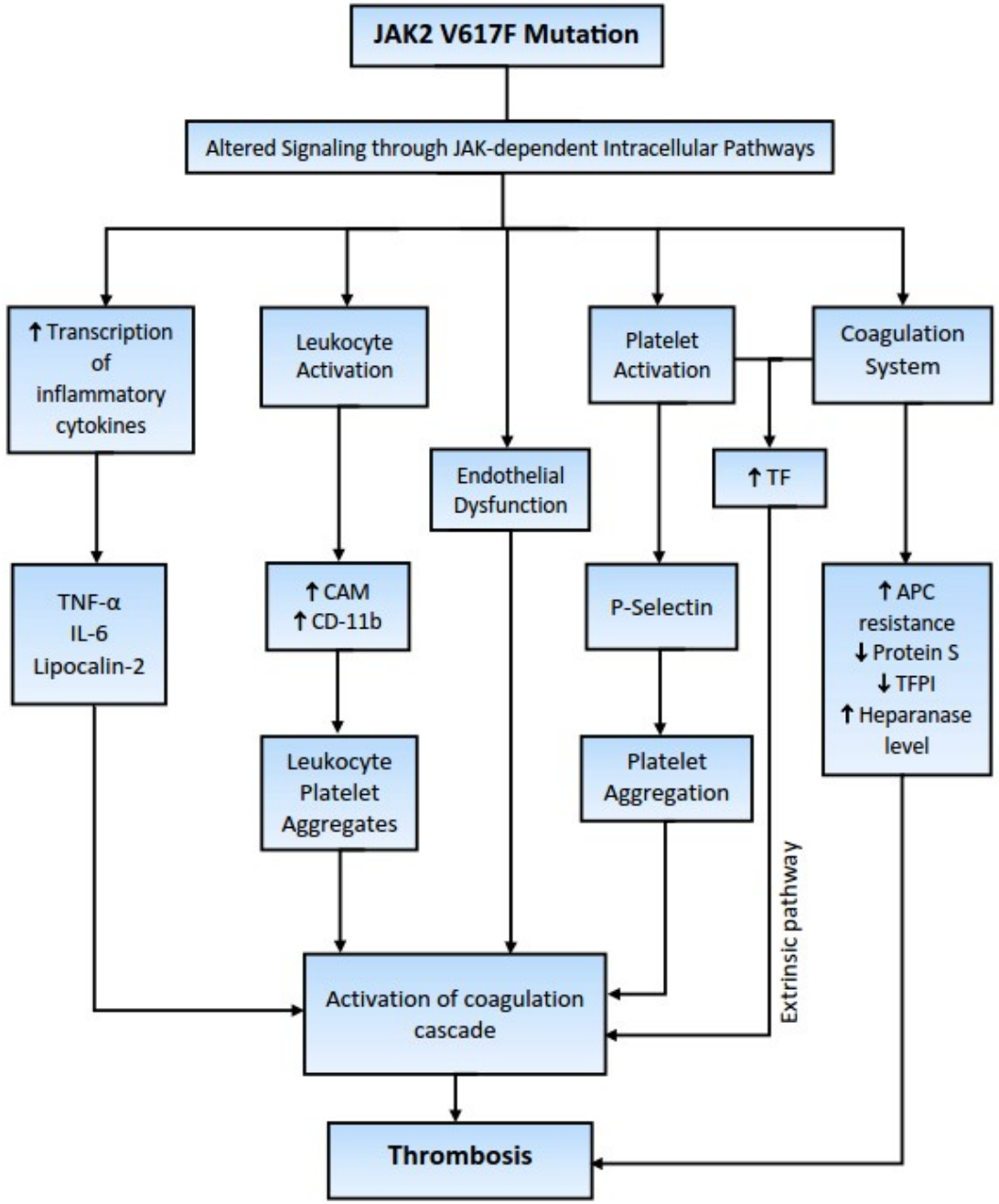
Pathophysiologic mechanisms of thrombosis in MPNs

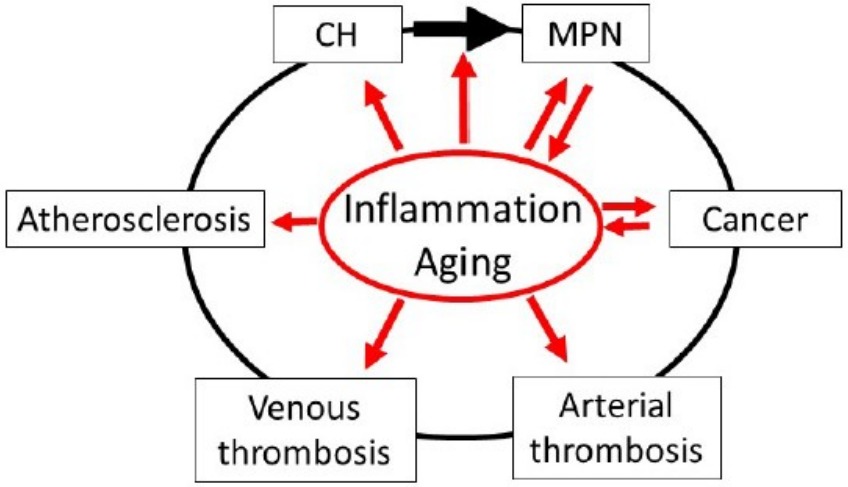
According to Virchow's triad of thrombosis, three factors contribute to its pathogenesis—an abnormality of the vessel wall, blood components, and the dynamics of blood flow. Similarly, various complex mechanisms work together in the pathogenesis of thrombosis in patients with MPN. Genetic aberrations (e.g., JAK2), quantitative and qualitative abnormalities of blood cells (leukocytes, platelets, etc.), and endothelial dysfunction all contribute to thrombogenesis in these patients. These pathophysiological mechanisms have been summarized in Table 5.

Thrombosis in Philadelphia negative classical myeloproliferative neoplasms: a narrative review on epidemiology, risk assessment, and pathophysiologic mechanisms

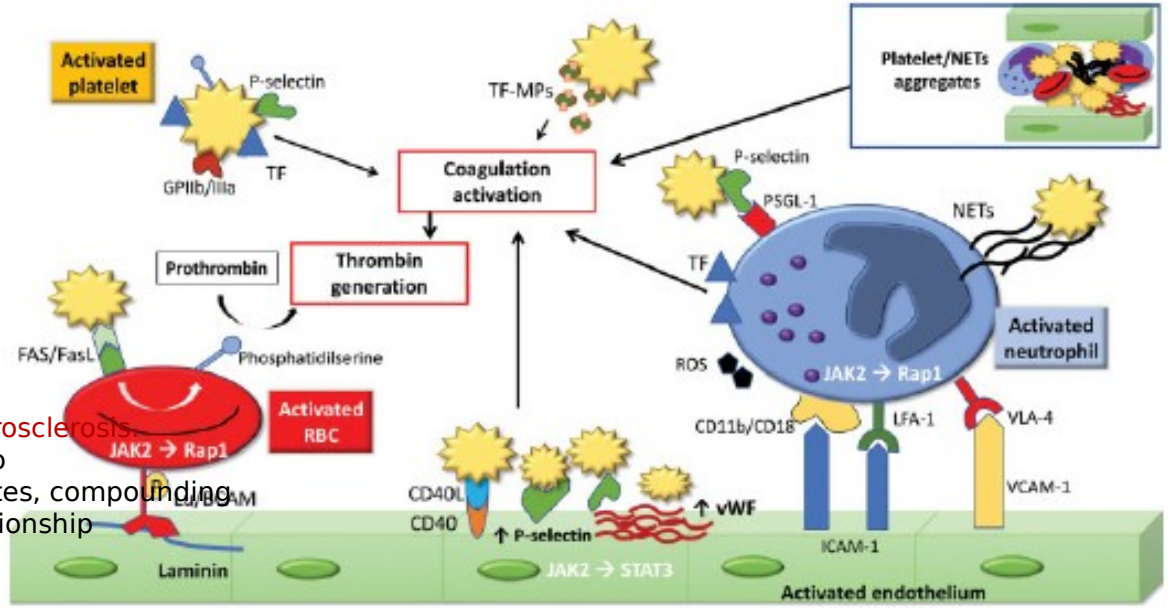
Somedeb Ball[1,3] · Kyaw Zin Thein[1] · Abhishek Maiti[2] · Kenneth Nugent[1]

Journal of Thrombosis and Thrombolysis (2018) 45:516–528
https://doi.org/10.1007/s11239-018-1623-4


JAK2 V617F Mutation
Altered Signaling through JAK-dependent Intracellular Pathways
↑ Transcription of inflammatory cytokines
Leukocyte Activation
Endothelial Dysfunction
Platelet Activation
Coagulation System
↑ TF
TNF-α
IL-6
Lipocalin-2
↑ CAM
↑ CD-11b
P-Selectin
↑ APC resistance
↓ Protein S
↓ TFPI
↑ Heparanase level
Leukocyte Platelet Aggregates
Platelet Aggregation
Extrinsic pathway
Activation of coagulation cascade
Thrombosis



The relationship between inflammation and aging as risk factors (red arrows) for the development of CH, MPN, cancer, thrombosis, and atherosclerosis. Inflammation is implicated in increasing the risk of evolution from CH to MPN (black arrow). In addition, MPN and cancer drive inflammatory states, compounding the effects of inflammation. Inflammation and aging confound the relationship between MPN and thrombosis due to their roles as independent risk factors for both arterial and venous thrombosis.



Clinical insights into the origins of thrombosis in myeloproliferative neoplasms

Alison R. Moliterno,[1] Yelena Z. Ginzburg,[2,3] and Ronald Hoffman[2,3]

Blood First Edition 25 November 2020. DOI 10.1182/blood.2020008043.

several reports indicate that a proinflammatory MPN milieu as well as excessive interactions between qualitatively abnormal vascular cells, including red blood cells (RBC), leukocytes, platelets,and endothelial cells (EC), are implicated in the generation of thrombotic events

Prevention and Management of Thrombosis in BCR/ABL-Negative Myeloproliferative Neoplasms

Anna Falanga[1,2] Marina Marchetti[1] Francesca Schieppati[1]

Hämostaseologie 2021;41:48–57.

INCIDENZA DEGLI EVENTI TROMBOTICI

- Incidenza degli eventi trombotici nettamente superiore rispetto alla popolazione generale da **3 a 10 volte**
- Gli **eventi arteriosi** sono 2/3 di tutti gli eventi (stroke, IMA, PAO)
- La frequenza degli eventi arteriosi prima o alla diagnosi di MPN è circa dal 16 al 27% in PV, 18% in ET e 4% in PMF
- Il tasso cumulativo di eventi trombotici nel follow-up è stato stimato in 5,5, da 1 a 3 e 1,75% di pazienti-anno in PV, ET e PMF, rispettivamente e la mortalità cardiovascolare è dell'1,7% paziente-anno nella PV
- In particolare nelle MPN sono frequenti le TV splacniche (SVT), cerebrali (CVT) e la sindrome di Budd-Chiari (BCS) (1-10% dei casi di malattia)

- **Obiettivo principale della terapia in pazienti con PV ET è ridurre il rischio di trombosi**
- **Stratificare i pazienti per il rischio trombotico**

- Algoritmi di trattamento adattati al rischio
- Evitare fattori di rischio che aumentano il rischio di VTE, adeguata profilassi..
- Correggere i fattori di rischio convenzionali per le trombosi arteriose (**ipertensione**, dislipidemia, diabete, fumo, obesità..).
- **Non indicato ricercare la trombofilia**
- Particolare attenzione al perichirurgico

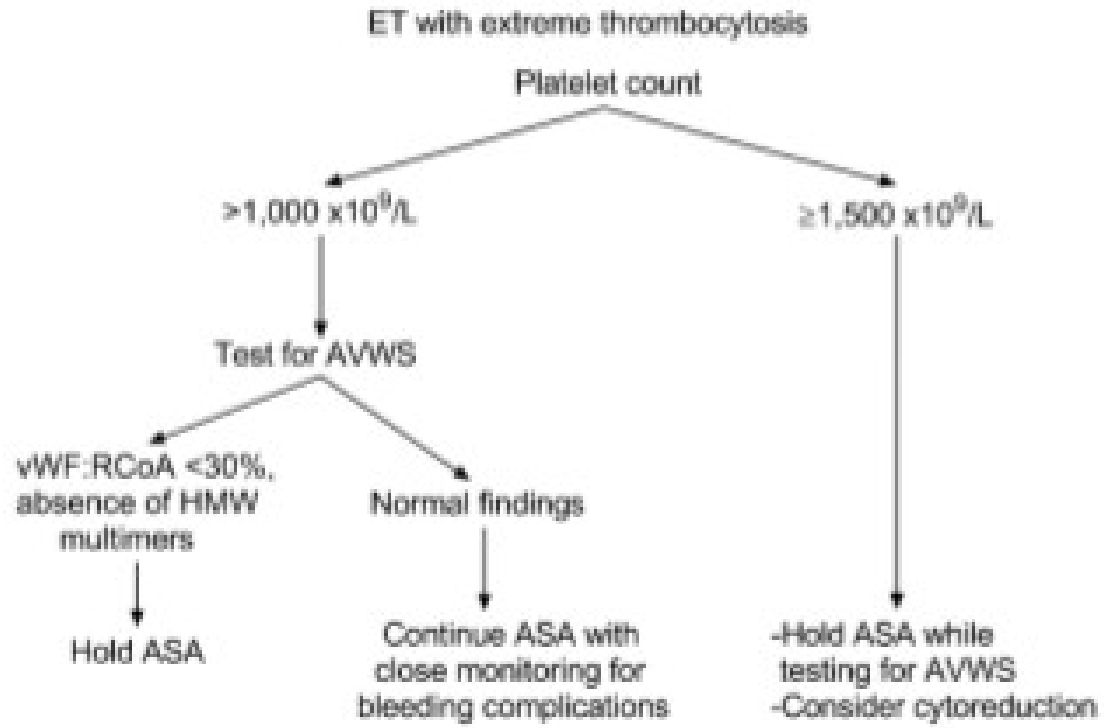
FATTORI DI RISCHIO

- **Età >60 anni**
- **Pregressa storia di Tromboembolismo (TE)**

- **FR** cardiovascolari convenzionali sono stati valutati con risultati non univoci (ma sicuramente impattano almeno quanto nella popolazione generale)
- **JAK2+** nella TE (IPSET score)
- **HCT>45%** nella PV (CYTO-PV)
- **Piastrinosi** nessuna correlazione con R trombotico, ma piastrinosi estrema e rischio di sanguinamento per AvWD (plts >1000000)

- Sempre più evidenze su **leucocitosi** (al momento non cut –off, non incluso negli score)

Gestione ASA e piastrinosi estrema



cancers
MDPI
Review

Essential Thrombocythemia and Acquired von Willebrand Syndrome: The Shadowlands between Thrombosis and Bleeding

Hassan Awada [1,*], Maria Teresa Voso [2,3], Paola Guglielmelli [4] and Carmelo Gurnari [1,2]

1 Department of Translational Hematology and Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH 44106, USA; carmelogurnari31@gmail.com
2 Department of Biomedicine and Prevention, University of Rome Tor Vergata, 00133 Rome, Italy; Voso@med.uniroma2.it
3 Fondazione Santa Lucia, Laboratorio di Neuro-Oncoematologia, 00143 Roma, Italy
4 CRIMM-Centro Ricerca e Innovazione delle Malattie Mieloproliferative, Department of Experimental and Clinical Medicine, Azienda ospedaliera-Universitaria Careggi, University of Florence, 50139 Florence, Italy; paola.guglielmelli@unifi.it
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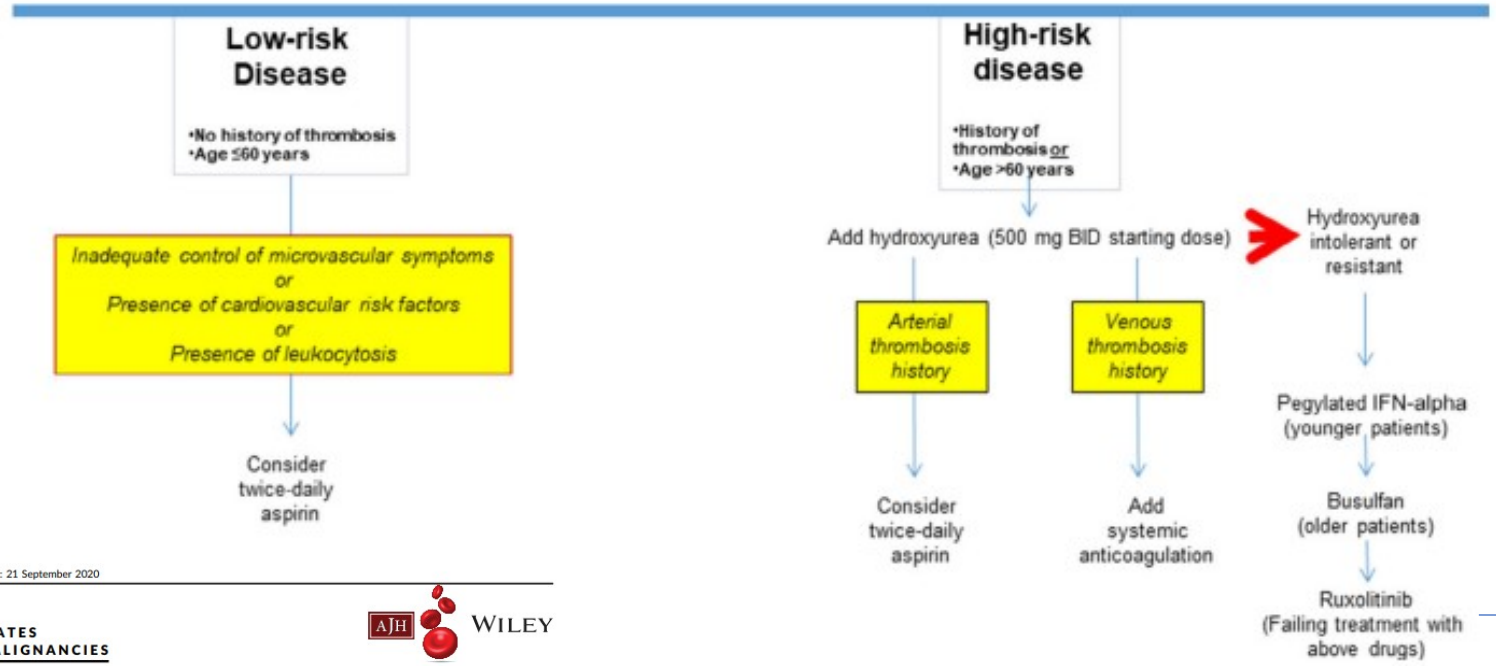
check for updates

Current Treatment Recommendations in Polycythemia Vera

Phlebotomy to hematocrit <45% in both males and females
+
Once-daily low-dose aspirin (40-100 mg)



Received: 18 September 2020 | Accepted: 21 September 2020
DOI: 10.1002/ajh.26008

ANNUAL CLINICAL UPDATES
IN HEMATOLOGICAL MALIGNANCIES

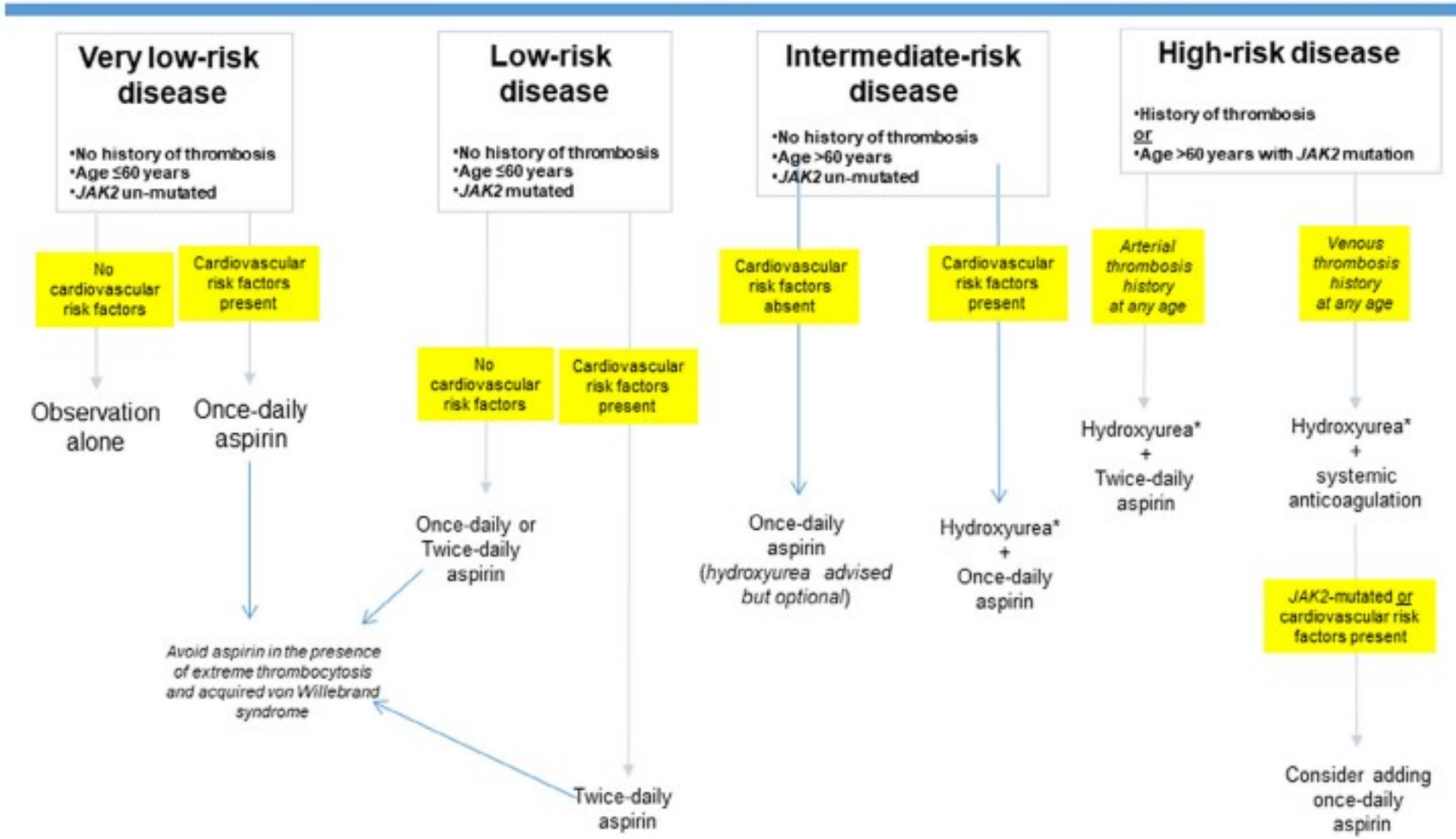
AJH WILEY

Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management

Ayalew Tefferi[1] | Tiziano Barbui[2]

Analisi di follow up a 5 anni dello studio RESPONSE evidenziano minor trombosi nel gruppo Ruxo

Current Treatment Recommendations in Essential Thrombocythemia



ASA BID più efficace nel ridurre l'attivazione piastrinica (misura trombossano B2)

Prefibrotic primary myelofibrosis

No previous thrombosis or bleeding, no thrombotic risk factors*	No previous thrombosis or bleeding, thrombotic risk factors*	Previous thrombosis	Previous bleeding
• Observation	• OD aspirin	• Arterial: OD aspirin • Venous: anticoagulation • If thrombocytosis or leukocytosis: cytoreduction with HU	• Avoid aspirin • If thrombocytosis or leukocytosis: cytoreduction with HU

In questi pz un aumentato R emorragico sembra evidente pre PMF: leucocitosi , pregressa emorragia, ASA, grado di fibrosi sembrano essere FR

Prevention and Management of Thrombosis in BCR/ABL-Negative Myeloproliferative Neoplasms

Anna Falanga[1,2] Marina Marchetti[1] Francesca Schieppati[1]

[1] Department of Immunohematology and Transfusion Medicine, Hospital Papa Giovanni XXIII, Bergamo, Italy
[2] University of Milano-Bicocca, Department of Medicine and Surgery, Monza, Italy

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Hämostaseologie 2021;41:48–57.

ARTICLE Open Access

Hydroxyurea prevents arterial and late venous thrombotic recurrences in patients with myeloproliferative neoplasms but fails in the splanchnic venous district. Pooled analysis of 1500 cases

Valerio De Stefano[1,2], Elena Rossi[1,2], Alessandra Carobbio[3], Arianna Ghirardi[3], Silvia Betti[1], Guido Finazzi[4], Alessandro M. Vannucchi[5] and Tiziano Barbui[3]

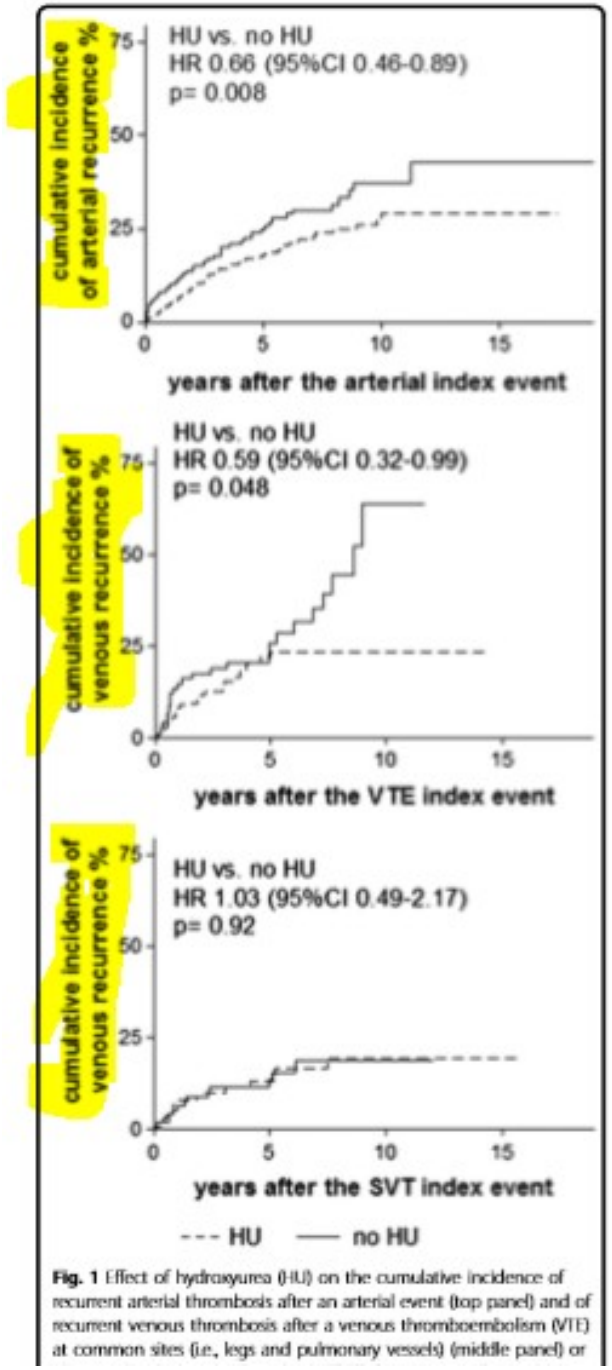


Fig. 1 Effect of hydroxyurea (HU) on the cumulative incidence of recurrent arterial thrombosis after an arterial event (top panel) and of recurrent venous thrombosis after a venous thromboembolism (VTE) at common sites (i.e., legs and pulmonary vessels) (middle panel) or

GESTIONE DELLE COMPLICANZE TROMBOTICHE ARTERIOSE

antiaggregante +citoriduzione

- Se i paz assumevano già ASA OD ---BD o clopidogrel
- Il trattamento in acuto delle trombosi arteriose organo specifiche (stroke, IMA, AOP) non è diverso dai pazienti che non sono affetti da MPD tranne che per l'inserimento della terapia citoriduttiva.
- **Si raccomanda la correzione ottimale dei fattori di rischio cardiovascolare**
- Citoriduzione ad ampio spettro --- HU

TRATTAMENTO DEL TROMBOEMBOLISMO VENOSO

- LMWH seguita da VKA con INR 2-3 /DOAC
- Rischio di recidiva dopo 1 anno da interruzione circa 8% e arriva fino al 42% a 5 anni
- Incidenza elevata di recidiva durante VKA 4-6%
- Incidenza di emorragia maggiore 2%
- Cautela nel sospendere il trattamento anticoagulante in particolare nei JAK-2+
- Se stop TAO riprendere ASA
- Cautela nel trattamento prolungato con LMWH per rischio di HIT

CURRENT OPINION
Management of venous thromboembolism in myeloproliferative neoplasms
Volume 24 • Number 2 • March 2017
Tiziano Barbui[a] and Valerio De Stefano[b]

PREVENZIONE DELLE RECIDIVE

Durata della terapia :

- si consiglia di proseguire la terapia anticoagulante a tempo indeterminato in caso di

- TVP idiopatica prossimale/TEP,
- TVP/TEP avvenute nonostante il miglior trattamento citoriduttivo/antiaggregante
- TVP/TEP ricorrenti

- Nelle TVP idiopatiche distali eseguire TAO per 3-6 mesi poi ASA
- Nelle TVP secondarie a chiara causa scatenante prossimali con o senza TEP eseguire TAO per 6-12 mesi poi ASA
- Nelle TVP secondarie distali eseguire TAO per 3 mesi
- **La citoriduzione** è raccomandata in tutte le TVP idiopatiche e deve essere valutata individualmente in caso di TVP secondaria


De Stefano et al. *Blood Cancer Journal* (2018)8:65
DOI 10.1038/s41408-018-0101-8

Blood Cancer Journal

CURRENT TREATMENT ALGORITHM Open Access

Antithrombotic therapy for venous thromboembolism in myeloproliferative neoplasms

Valerio De Stefano[1,2], Guido Finazzi[3] and Tiziano Barbui[4]

SICUREZZA DELLA TERAPIA ANTICOAGULANTE

- VKA (INR 2-3) riducono il R di recidiva in numerosi studi senza aumento del rischio emorragico

45. De Stefano V, Za T, Rossi E, Vannucchi AM, Ruggeri M, Elli E, et al. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. Haematologica. 2008;93(3):372–80.

- Hernández-Boluda JC, Arellano-Rodrigo E, Cervantes F, Alvarez-Larrán A, Gómez M, Barba P, et al. Oral anticoagulation to prevent thrombosis recurrence in polycythemia vera and essential thrombocythemia. Ann Hematol. 2015;94(6):911–8. **Demonstrated that vitamin K antagonists reduce recurrent thrombotic events in PV and ET without a significant increase in the rate of major bleeding.**

- Aumento del R emorragico con l'uso contemporaneo di anticoagulante e antiaggregante

TRATTAMENTO DELLE TROMBOSI CANCRO CORRELATE

- Edoxaban
- Rivaroxaban
- Apixaban
- Non inferiori vs LMWH nel trattamento del VTE nei paz con cancro

- In 2 studi si è evidenziato un aumento del sanguinamento maggiore nei paz con neoplasia gastrointestinale
- Pochi paz con MPD erano rappresentati negli studi

Are DOACs an alternative to vitamin K antagonists for treatment of venous thromboembolism in patients with MPN?

Francesca Schieppati[1] and Anna Falanga[1,2]

Table 1. Principal studies including MPN patients on VKA treatment for usual site VTE

Reference	Study population	N included in the study	N on VKAs	Overall thrombosis recurrence (A/V)	VTE recurrence	Major bleeding	Median follow-up (years)
De Stefano et al[14]	PV/ET with at least 1 episode of thrombosis (ATE and VTE)	494	90	33.6% (7.6% pt-y)*	13.1% (3% pt-y)*	5.4% (0.9% pt-y)* 7.7% (0.9% pt-y)† (2.8 pt-y)‡	5.3
Hernandez-Boluda et al[16]	PV/ET receiving VKA for a first VTE or ATE episode	150	150	28% (6.0% pt-y)†	24% (2.7% ON vs 9.0% OFF, p)†	11.3% (overall 1.7% pt-y, 1.8% ON vs 1.5% OFF)†	7.7
De Stefano et al[15]	PV/ET/PMF on systemic anticoagulation for a first VTE episode	206	155	21.8% (6.5% pt-y)* 12.2% (4.7% pt-y)†	17.4% (5.2% pt-y)* 9.6% (4.2% pt-y ON vs 9.6% pt-y OFF)†	6.4% (2.4% ON vs 0.7 OFF)†	3
Wille et al[17]	PV/ET/PMF with a first	78	40	—	20.5% (6.0% pt-y)*	26.9%	2

Table 2. Studies including at least 20 MPN patients on DOAC treatment for usual site VTE

Reference	Study population	N on DOAC	N on rivar	N on apix	N on edox	N on dabig	Overall thrombotic recurrence	VTE recurrence	Major bleeding	Median follow-up (years)
Ianotto et al[25]	PV/ET receiving DOAC for AF or VTE	25*	16	9	—	—	4% (1 stroke)	0	12%	2.1
Curto-Garcia et al[26]	PV/ET/PMF/ MDS-MPN receiving DOAC for VTE	32	17	14	1	0	3% (1 mesenteric ischemia)	0	0%	2.1
Serrao et al[27]	PV/ET/PMF receiving DOAC for AF or VTE	71†	26	21	14	10	0%	—	0%	1
Barbui et al[28]	PV/ET/PMF receiving DOAC for AF or VTE	442‡	187	157	48	50	4.9% (2.1% pt-y) (AF) 9.2% (4.5% pt-y) (VTE)	1.5% (0.6% pt-y) (AF) 7.1% (3.4% pt-y) (VTE)	6.9% (3.0 pt-y) (AF) 5.0% (2.3% pt-y) (VTE)	1.7

THROMBOSIS RECURRENCE AND BLEEDING

AVK

29%, respectively).[15] However, it is important to consider that the cumulative incidence of VTE recurrence in MPN patients receiving adequate VKA treatment still remains greater than that of the general population (7.8% vs 1.8%-3.5% at 1 year, respectively).[15]

tion with aspirin (compared to patients off VKAs). Nevertheless, bleeding complications with VKAs look higher in MPN compared to non-MPN patients (up to 2.8% vs 1.2%-2.2% in patient-years, respectively),[4] with disease-related factors contributing to the

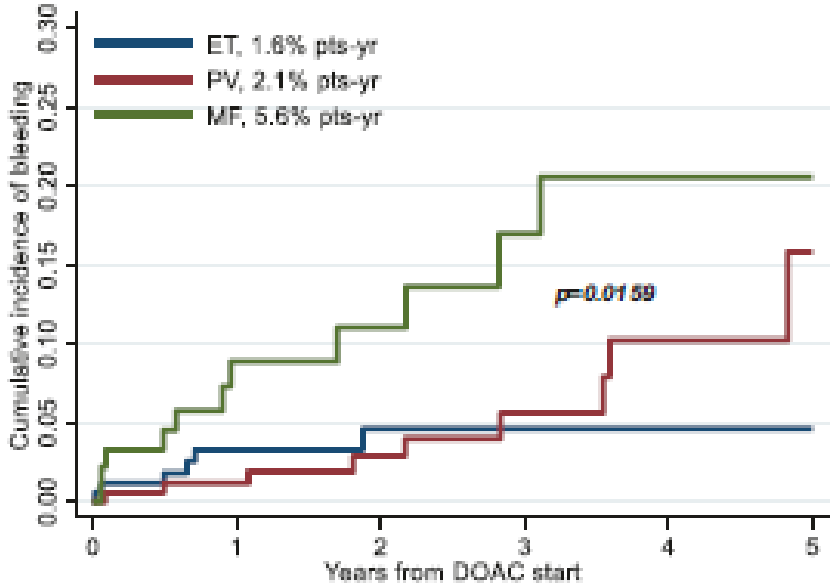
DOAC

rhagic complications in this setting.[28] Specifically, the incidence of a first VTE event in patients receiving a DOAC for AF was 0.6% in patient-years, while the incidence of recurrent VTE in patients receiving a DOAC for a prior VTE was 3.4% in patient-years, which was no different from the recurrence incidence observed in the VKA studies.[14-17] Moreover, annual rates of

dence observed in the VKA studies.[14-17] Moreover, annual rates of major bleeding ranged from 2.3% to 3% in patient-years,[28] also similar to VKAs. Therefore, on the basis of limited available evi-

similar to VKAs. Therefore, on the basis of limited available evidence, DOACs and VKAs seem to have a comparable risk/benefit profile in the treatment and secondary prevention of VTE in MPN patients. Finally, 2 recent small studies tried to retrospec-

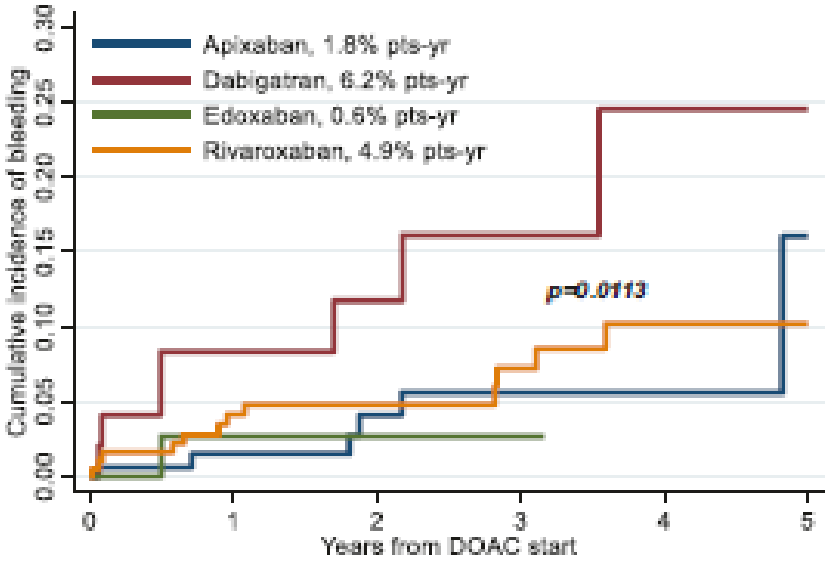
B



Number at risk

ET	172	(5)	119	(1)	69	(0)	39	(0)	26	(0)	10
PV	178	(2)	137	(2)	91	(2)	55	(2)	32	(1)	15
MF	32	(7)	57	(1)	37	(2)	24	(1)	14	(0)	10

C



CHRONIC MYELOPROLIFERATIVE NEOPLASMS

Direct oral anticoagulants for myeloproliferative neoplasms: results from an international study on 442 patients

Tiziano Barbui[1] · Valerio De Stefano[2] · Alessandra Carobbio[1] · Alessandra Iurlo[3] · Alberto Alvarez-Larran[4] · Beatriz Cuevas[5] · Francisca Ferrer Marín[6] · Alessandro M. Vannucchi[7] · Francesca Palandri[8] · Claire Harrison[9] · Hassan Sibai[10] · Martin Griesshammer[11] · Massimiliano Bonifacio[12] · Elena M. Elli[13] · Chiara Trotti[14] · Steffen Koschmieder[15] · Giuseppe Carli[16] · Giulia Benevolo[17] · Jean-Christophe Ianotto[18] · Swati Goel[19] · Anna Falanga[20,21] · Silvia Betti[2] · Daniele Cattaneo[3] · Eduardo Arellano-Rodrigo[4] · Lara Mannelli[7] · Nicola Vianelli[8] · Andrew Doyle[9] · Vikas Gupta[10] · Kai Wille[11] · Douglas Tremblay[22] · John Mascarenhas[22]

Received: 17 February 2021 / Revised: 14 April 2021 / Accepted: 29 April 2021 / Published online: 19 May 2021

Kaifie et al. Journal of Hematology & Oncology (2016) 9:18
DOI 10.1186/s13045-016-0242-9

Journal of Hematology & Oncology

RESEARCH Open Access

Bleeding, thrombosis, and anticoagulation in myeloproliferative neoplasms (MPN): analysis from the German SAL-MPN-registry

A. Kaifie[11], M. Kirschner[11], D. Wolf[2], C. Maintz[3], M. Hänel[4], N. Gattermann[5], E. Göldkurt[6], U. Platzbecker[7], W. Hollburg[8], J. R. Göthert[9], S. Parmentier[10], F. Lang[11], R. Hansen[12], S. Isfort[1], K. Schmitt[1], E. Jost[1], H. Serve[11], G. Ehninger[7], W. E. Berdel[13], T. H. Brümmendorf[1], S. Koschmieder[1*] and for the Study Alliance Leukemia (SAL)

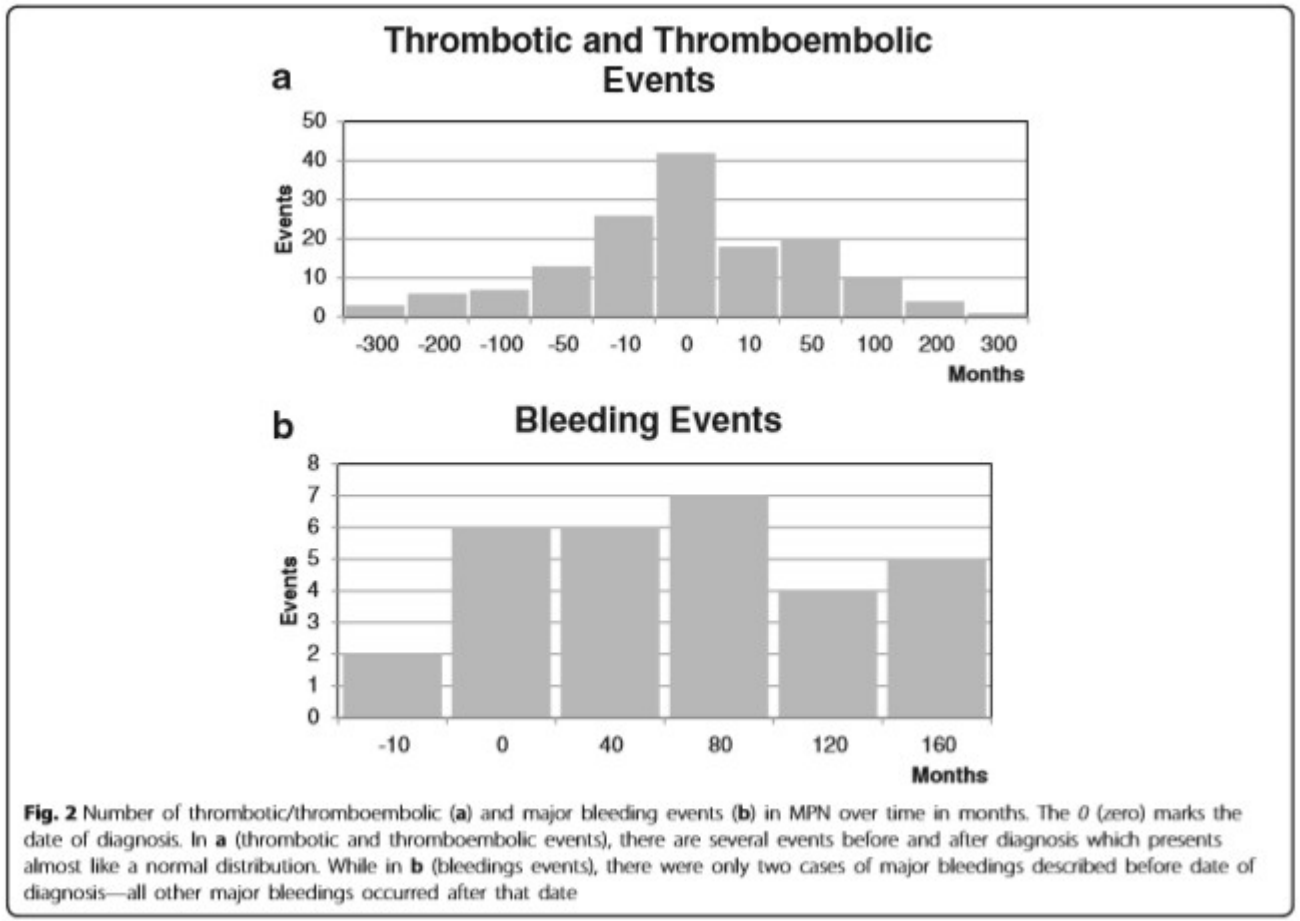


Fig. 2 Number of thrombotic/thromboembolic (**a**) and major bleeding events (**b**) in MPN over time in months. The *0* (zero) marks the date of diagnosis. In **a** (thrombotic and thromboembolic events), there are several events before and after diagnosis which presents almost like a normal distribution. While in **b** (bleedings events), there were only two cases of major bleedings described before date of diagnosis—all other major bleedings occurred after that date

Table 5 Odds ratios for major bleeding events

	Odds ratio (OR)	95 % CI
Diagnosis		
PV	1.2480	0.6123–2.5439
ET	*0.3440*	*0.1307–0.9053*
PMF	1.1892	0.5539–2.5531
Post-PV-MF	2.8235	0.8964–8.8935
Post-ET-MF	0.6079	0.0788–4.6904
MPN-U	2.5130	0.6872–9.1897
Thrombotic/thromboembolic event in medical history	*2.7083*	*1.3578–5.4021*
Splenomegaly (detected by palpation)	*2.2222*	*1.0095–4.8919*
Low platelets (<100/nl)	1.3120	0.5504–3.1275
High platelets (>1000/nl)	1.1874	0.4401–3.2035
ASS	1.1216	0.5539–2.2712
P2Y12 antagonist	2.8292	0.9979–8.0213
Double platelet inhibition	3.0500	0.9589–9.7016
Oral vitamin K antagonist	1.9739	0.7695–5.0634
Rivaroxaban	1.6092	0.1923–13.4665
Heparin	*5.6426*	*1.8360–17.3421*

Significant results are in italics

TAKE HOME MESSAGE

- La **trombosi** è la più frequente complicanza nei paz con MPN
- Maggiori studi sono necessari per capire se possa essere vantaggioso inserire la **conta dei leucociti** negli score di rischio trombotico
- I **DOAC** sembrano efficaci e sicuri nei paz con MPN anche sono auspicabili studi prospettici che confermino questi dati
- Attenzione al **rischio emorragico**
- Nuovi farmaci

- **Controllo ematocrito**: PTG-300 (agente epcidina mimetico) in corso trial di fase 2
- **Crizanlizumab** : ab anti P-slectina approvato per la prevenzione delle crisi vaso occlusive nella anemia falciforme trial in programmazione in paz con MPD
- **Dosi potenziate di ASA**:200 mg
- **Statine** azione antinfiammatoria… **inibitori di BET** riduce produzione di citochine pro –infiammatorie (test su MFI)