LEUKEMIA2022
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AIL President: G. Toro
Coordinators: A.M. Carella, S. Amadori

ASSOCIAZIONE ITALIANA CONTRO LEUCEMIE LINFOMI E MIELOMA

Thrombosis and bleeding: rationale and therapeutic perspectives

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Pro.MI.SE
UniPA

UNDER THE AUSPICES OF:
fondazione GIMEMA onlus per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI
GITMO
SIES Società Italiana Emostasi Sperimentale
SIE - Società Italiana di Ematologia

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MPNs: thrombotic & hemorragic disorders?

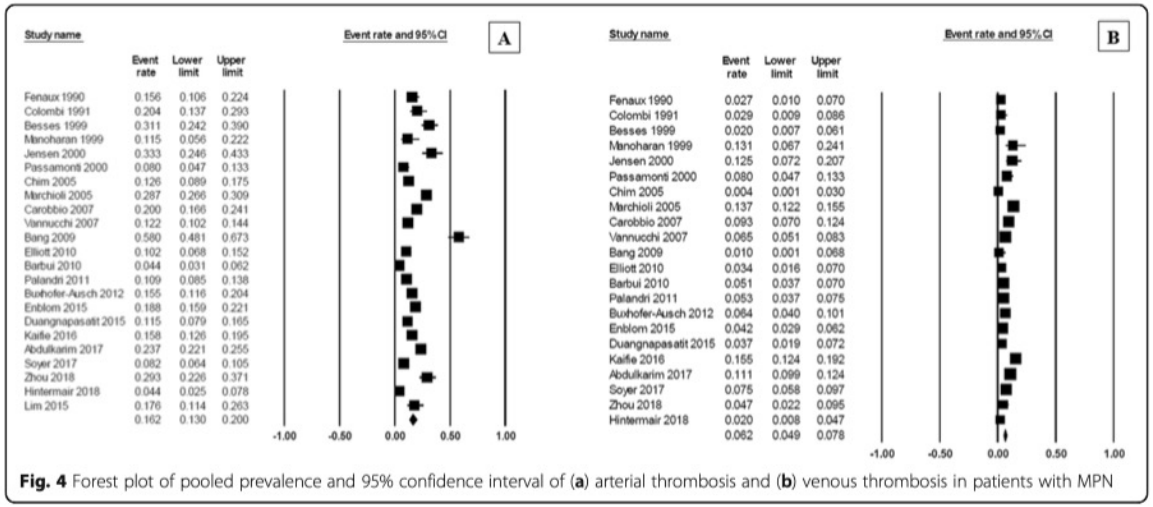


Fig. 4 Forest plot of pooled prevalence and 95% confidence interval of (**a**) arterial thrombosis and (**b**) venous thrombosis in patients with MPN

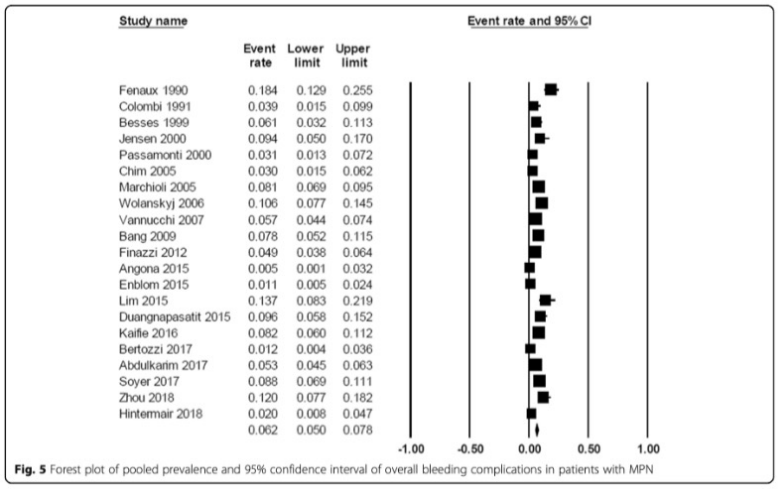
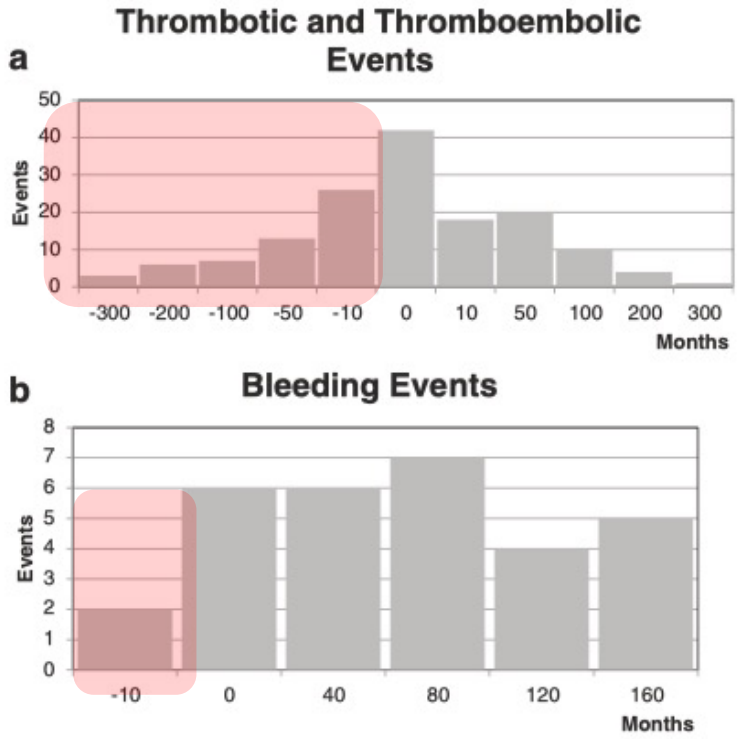


Fig. 5 Forest plot of pooled prevalence and 95% confidence interval of overall bleeding complications in patients with MPN

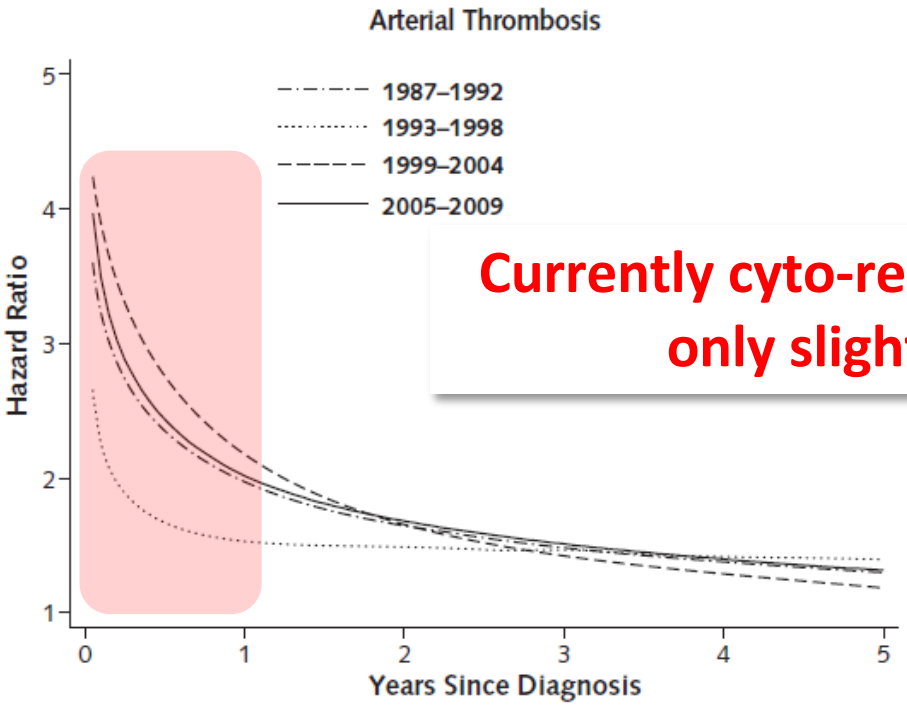
T Rungjirajittranon et al BMC 2019;19:184

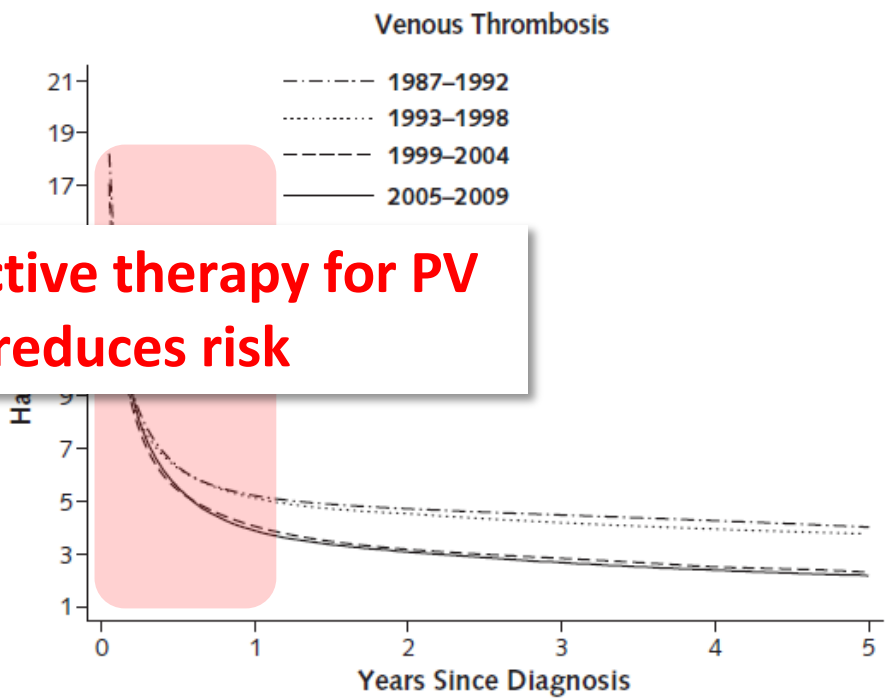
Number of thrombotic/thromboembolic (a) and major bleeding events (b) in MPN over time in months. The 0 (zero) marks the date of diagnosis



Kailfie A et al. Journal of Hematology & Oncology (2016) 9:18

Polycythemia Vera is a Thrombotic disease





Currently cyto-reductive therapy for PV only slightly reduces risk

Both arterial and venous thrombosis occur mainly at the beginning (or just before the diagnosis)

Hultcranz M et al. Ann Intern Med 2018;168:317-25

Why MPNs are thrombotic disorders?

1° Actor: Erythrocyte

	Changes in MPN	Pathophysiological consequences	Possible role of mutations
Leukocytes	• Leukocytosis • Activated neutrophils – ↑ Proteolytic enzymes – ↑ ROS • ↑ CD 11b expression • ↑ NET formation • ↑ TF on monocytes	• Endothelial injury • Formation of 'leukocyte–platelet aggregates' • Leukocyte adhesion to endothelium • Activation of extrinsic pathway and coagulation cascade	JAK2V617F
RBCs	• Erythrocytosis/increased hematocrit • Phosphorylation of surface adhesion receptor (Lu/BCAM) on RBCs • High shear stress within vessel	• Stasis of blood flow • Endothelial injury • Margination of platelets – adhesion to vWF and collagen • Enhanced adhesion of RBCs to subendothelial laminin	JAK2V617F
Platelets	• Thrombocytosis • ↑Number of immature platelets (more thrombogenic) • Epigenetic changes – promoter hypermethylation of CD 18 integrins • ↑ Expression of P-selectin • ↑ Responsiveness to ADP • ↑ TF expression on platelets	• Activation of platelets • Platelet adhesion • Platelet aggregation • Activation of coagulation cascade	JAK2V617F MPL
Endothelial cells	• ↑ Number of circulating ECFCs	• Increased adherence to mononuclear cells • Activation of coagulation cascade	JAK2V617F
Inflammation	• ↑ Lipocalin-2 • ↑ TNF-alpha and IL-6 • ↑ hs-CRP	• Widespread inflammation • Upregulation of TF – activation of extrinsic pathway of coagulation	JAK2V617F MPL
Microparticles	• ↑ Number of TF bearing MPs • ↑ PS and PSGL-1 • ↑ Procoagulant PL activity • Resistance to thrombomodulin	• PS-catalytic surface for coagulation factors • PSGL-1-platelet aggregation • Activation of TF – extrinsic pathway of coagulation • Activation of factor XII – intrinsic pathway of coagulation	JAK2V617F
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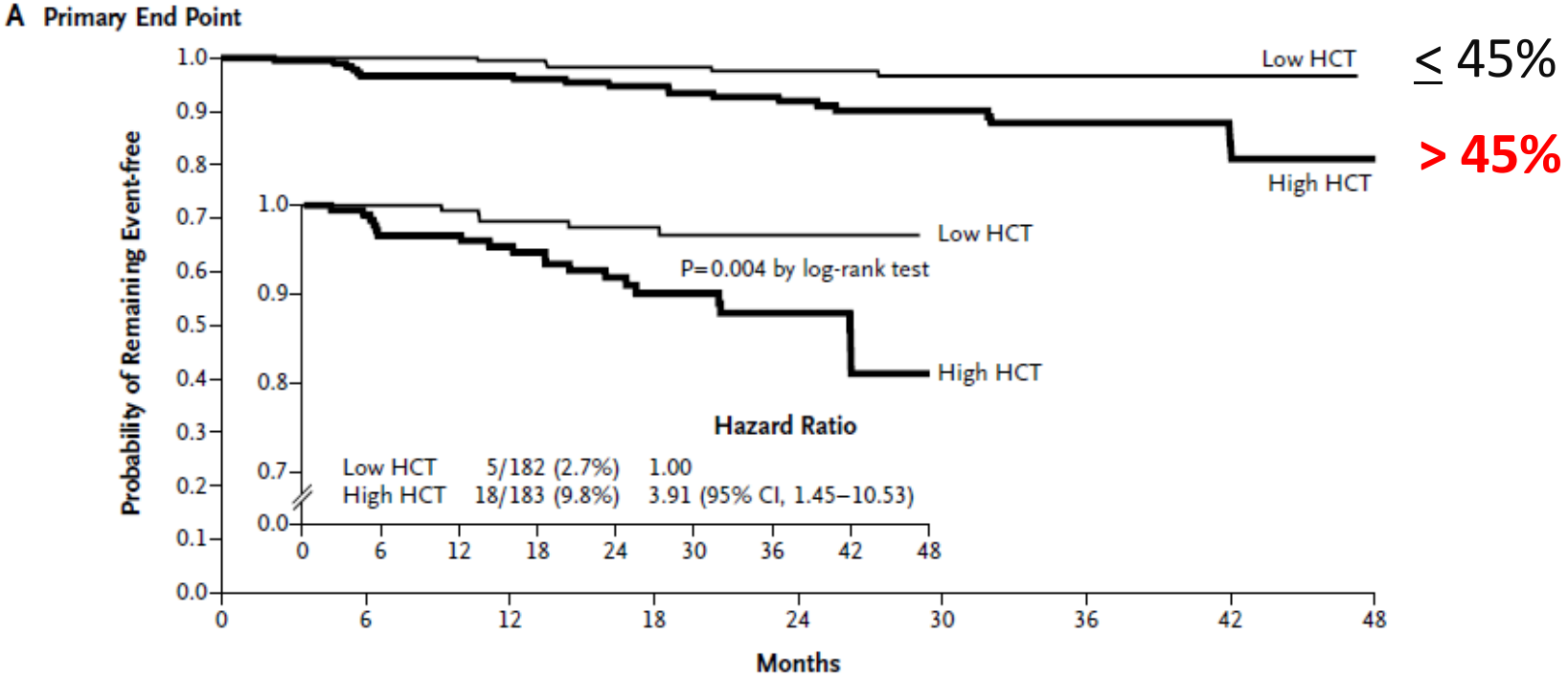
Ball S et al. J Thromb Thrombolysis 2018;45:516-28

The role of HCT:

KM Curves for Total Cardiovascular Events (including venous thrombosis)



≤ 45%

> 45%

Marchioli R et al. NEJM 2013;368:22-33

Shear rates, HCT & thrombosis

- **Several** polycythemic states are not associated with increased thrombosis (eg, emphysema), other factors and adaptive responses may modify thrombosis risk

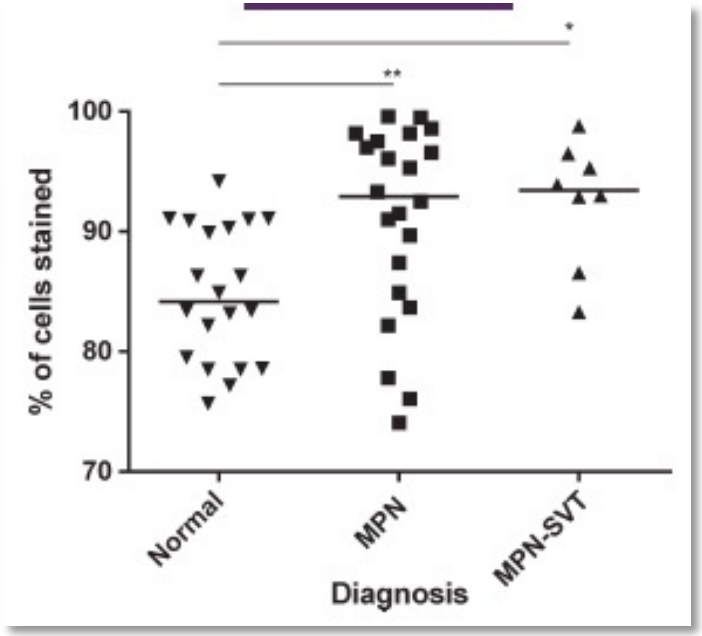
- These observations suggest **multimodal effects of hematocrit** on cardiovascular risk and imply direct but **complex relationships between hematocrit, coagulation and monoclonality**

Erythrocytes from patients with MPNs and splanchnic venous thrombosis show greater expression of Lu/BCAM

Lutheran/BCAM protein (Lu) on the surface of erythrocytes is key for their adhesion to the endothelium, and erythrocytes from individuals with JAK2V617F-mutated PV have increased endothelial adhesion

⇩

Monoclonal erythrocytes express adhesion molecules



2° Actor: leukocyte

	Changes in MPN	Pathophysiological consequences	Possible role of mutations
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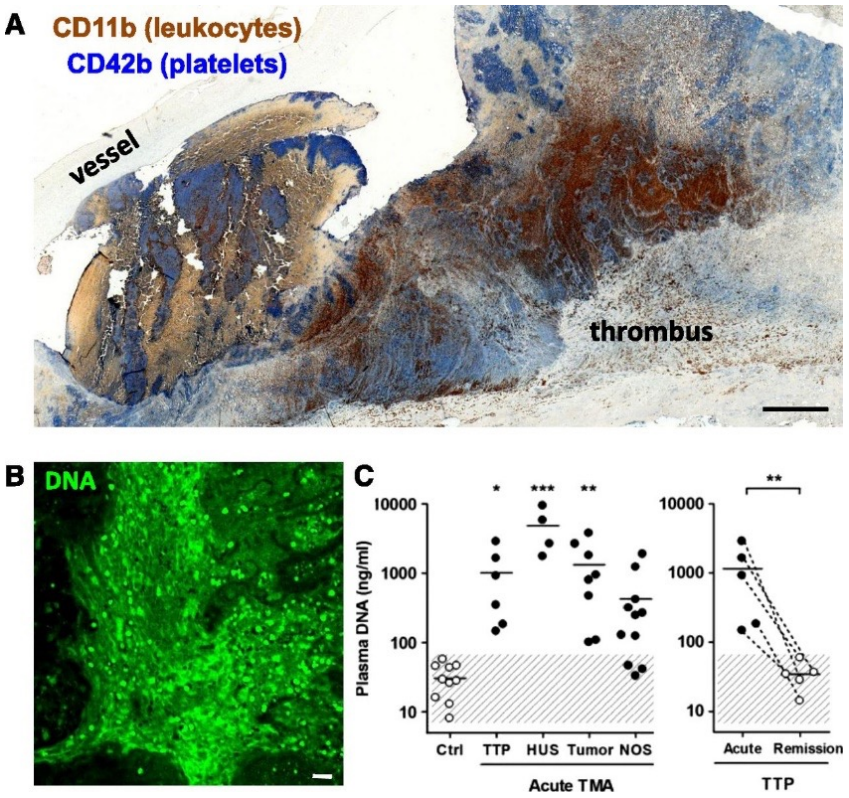
Ball S et al. J Thromb Thrombolysis 2018;45:516-28

Evidence of NETs in human pathological thrombosis - Immunothrombosis

Evidence of NETs in human pathological thrombosis.

(A) Composite image of a human pulmonary embolism specimen obtained surgically and stained by immunohistochemistry for **platelets (blue) and leukocytes (brown)** showing that areas of the thrombus are rich in both cell types

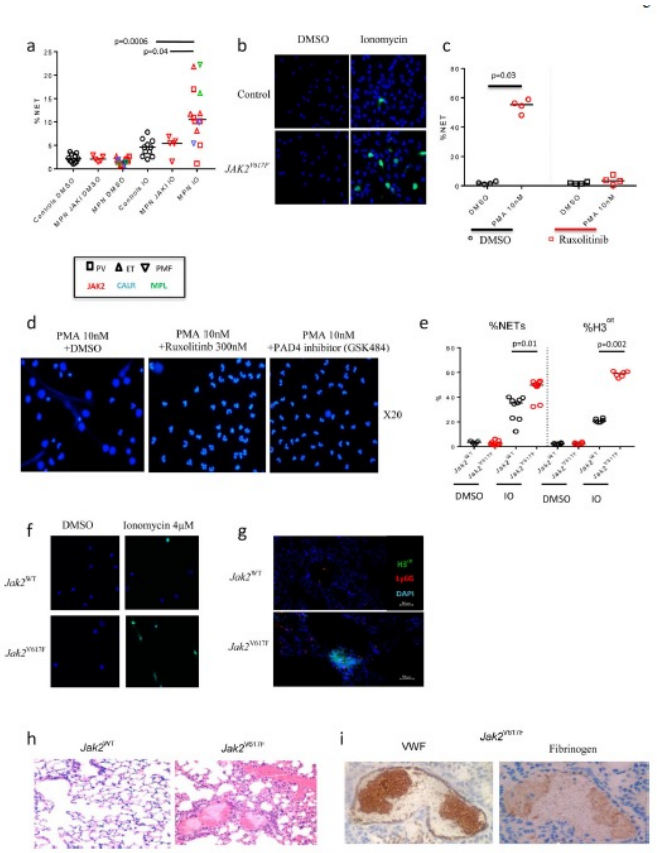
(B) Cell-free DNA, a plasma biomarker of **NETs, is elevated in patients with thrombotic microangiopathies** (left): thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), **malignancies** (tumor), and nonspecified cases (NOS).



Kimberly Martinod, and Denisa D. Wagner. Blood 2014;123:2768-2776

Neutrophils derived from patients with MPNs are associated with an increase in NET formation and a prothrombotic, NET-rich phenotype

NET formation in patients with myeloproliferative neoplasms (MPN) compared to healthy controls



3° Actor: cells & coagulation

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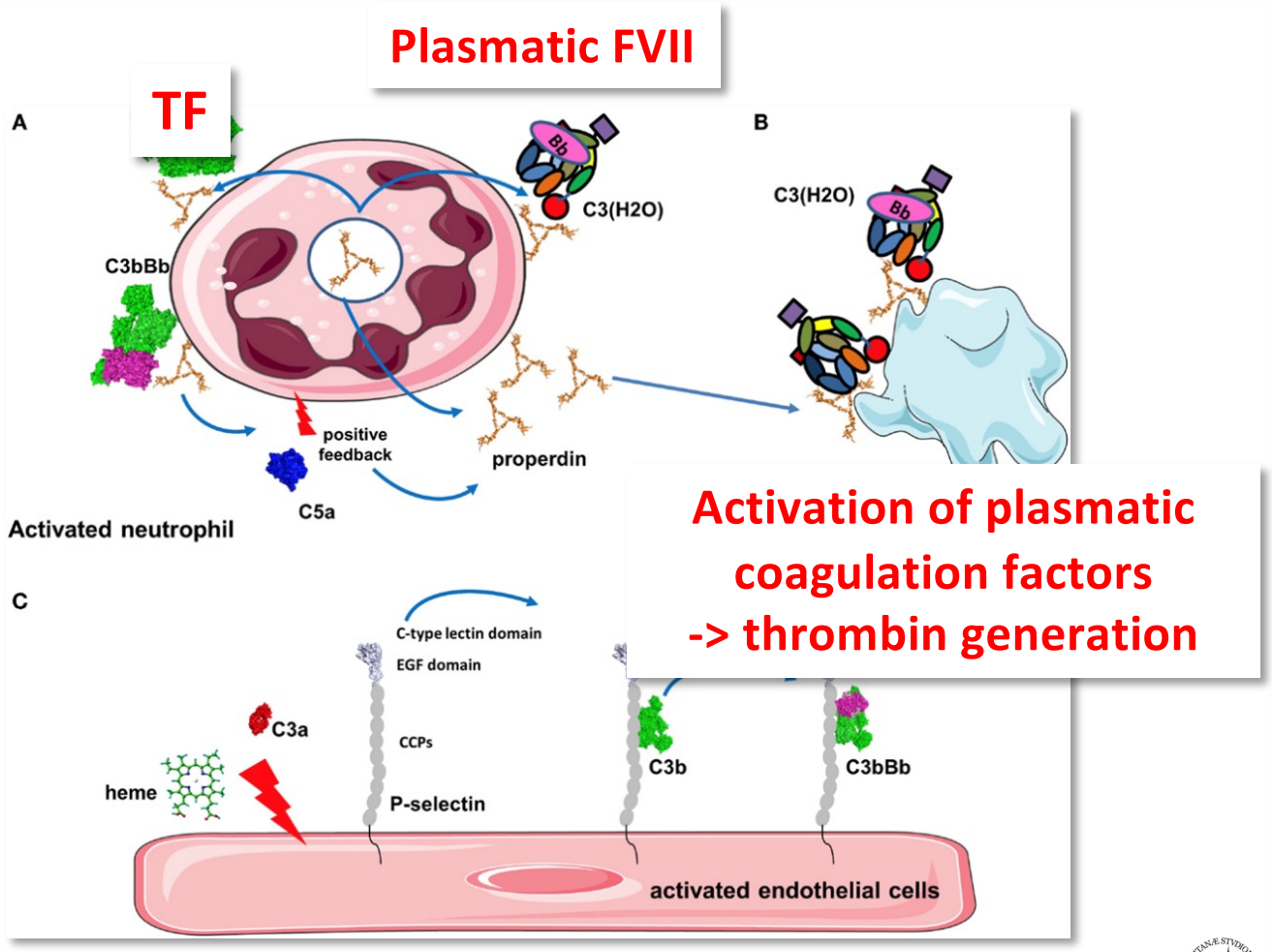
Ball S et al. J Thromb Thrombolysis 2018;45:516-28

Activated cells promote thrombin generation



Activation of plasmatic coagulation factors -> thrombin generation

James R. Byrnes, and Alisa S. Wolberg Blood 2017;130:1795-1799

4° Actor: JAK2V617F

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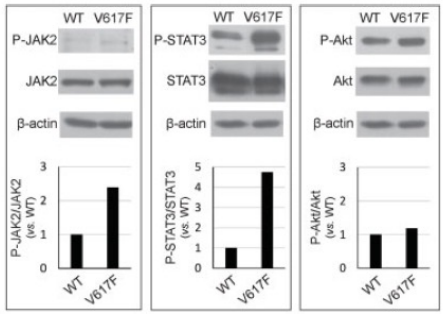
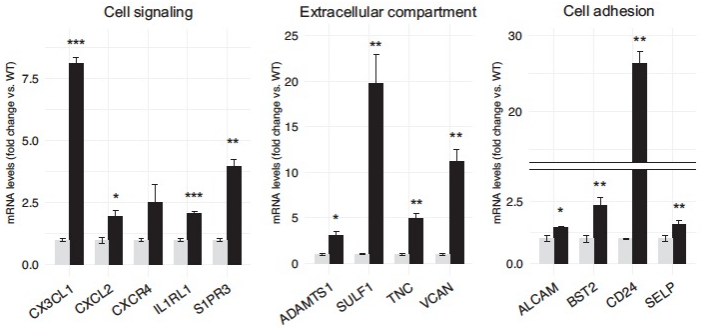
Ball S et al. J Thromb Thrombolysis 2018;45:516-28

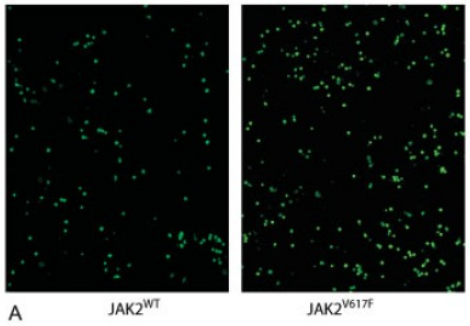
How JAK2 mutation leads to thrombosis?



1. Increase Endothelial Like-Cells (ELCs) synthesis

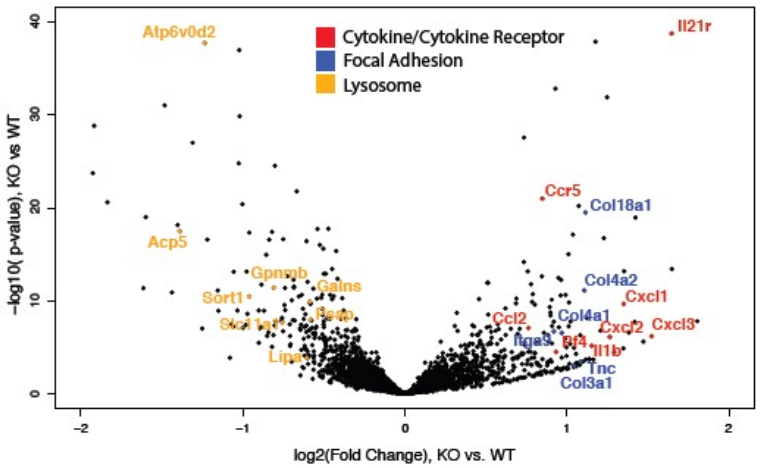


2. ELCs promote cell signaling, extracellular activity and cell adhesion



3. ELCs increase number of adhered leucocyte

Something new: monoclonal hematopoiesis (CHIP)
Gene expression in *Tet2* knockout macrophages



CHIP is associated with increased overall mortality

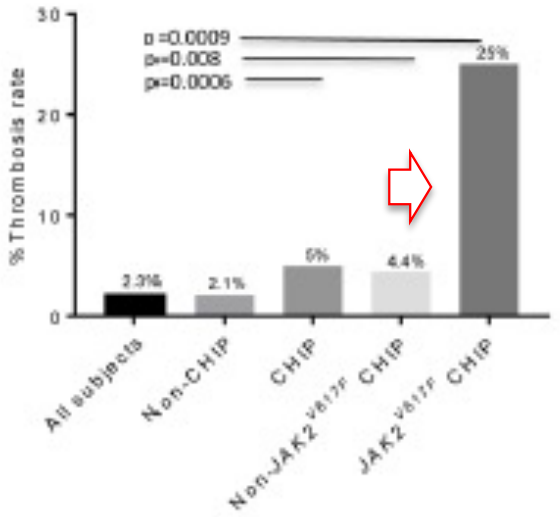
- Increased risk of hematologic malignancy
- Increased risk of therapy-related malignancy
- Increased risk of cardiovascular disease

Tet2 mutations induce atherosclerosis *in vivo*

- Accelerated atherosclerosis
- Development of xanthomas
- Altered expression of **inflammatory cytokines**

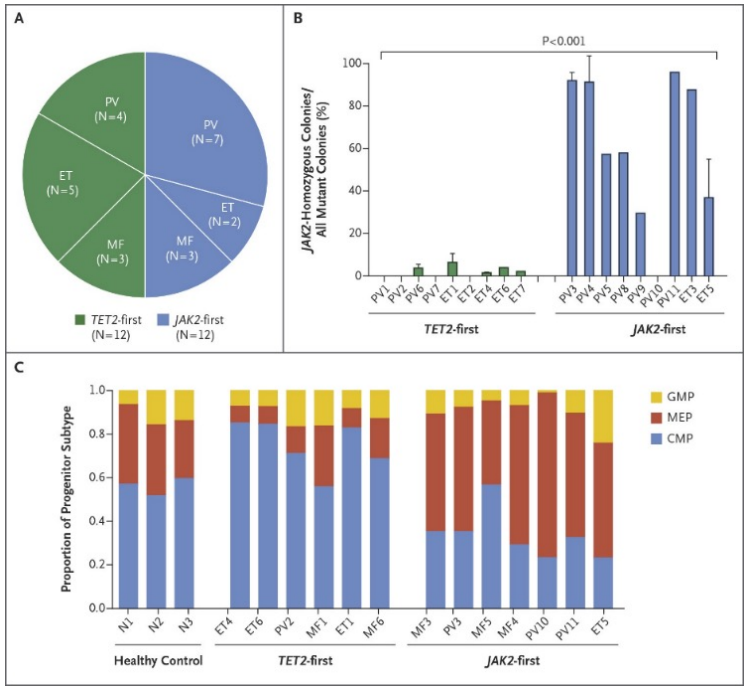
JAK2V617F positive clonal hematopoiesis is associated with increased thrombosis rates

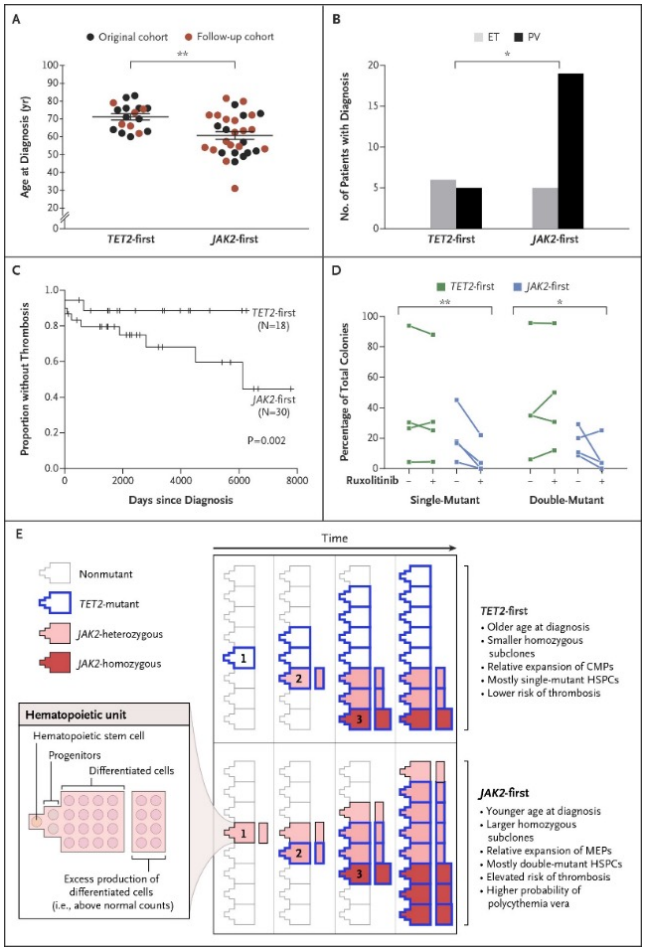
Rates of venous thrombosis in patients with or without clonal hematopoiesis of indeterminate potential (CHIP) and/or JAK2V617F mutation



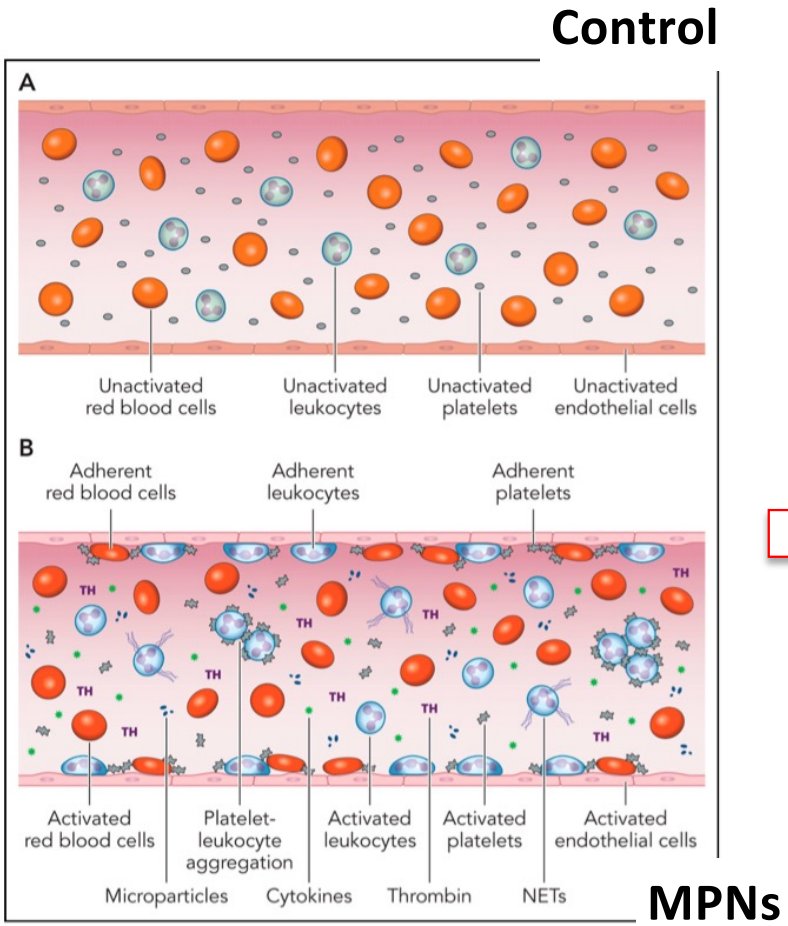
Wolach O et al. Sci Transl Med. 2018; 10(436)

Adjunctive role of TET2 & Jak2 for thrombosis?

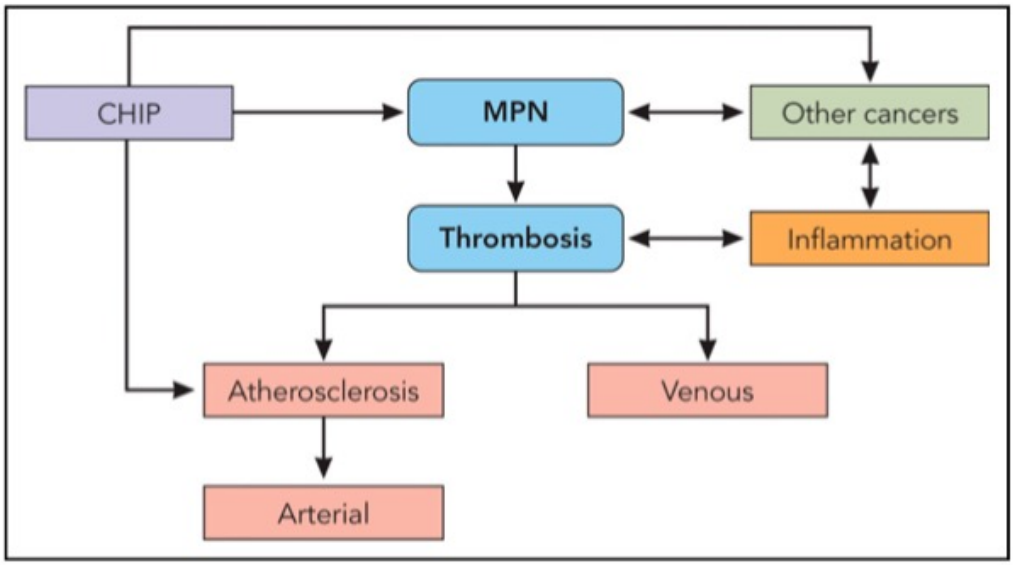




Ortmann CA et al. N Engl J Med 2015; 372:601-612



The pathogenesis of thrombosis in the MPNs



HC Hasselbalch et al. Blood 2021;137:2152-60

Why MPNs are (if any) bleeding disorders?

Overall bleeding events on MPNs

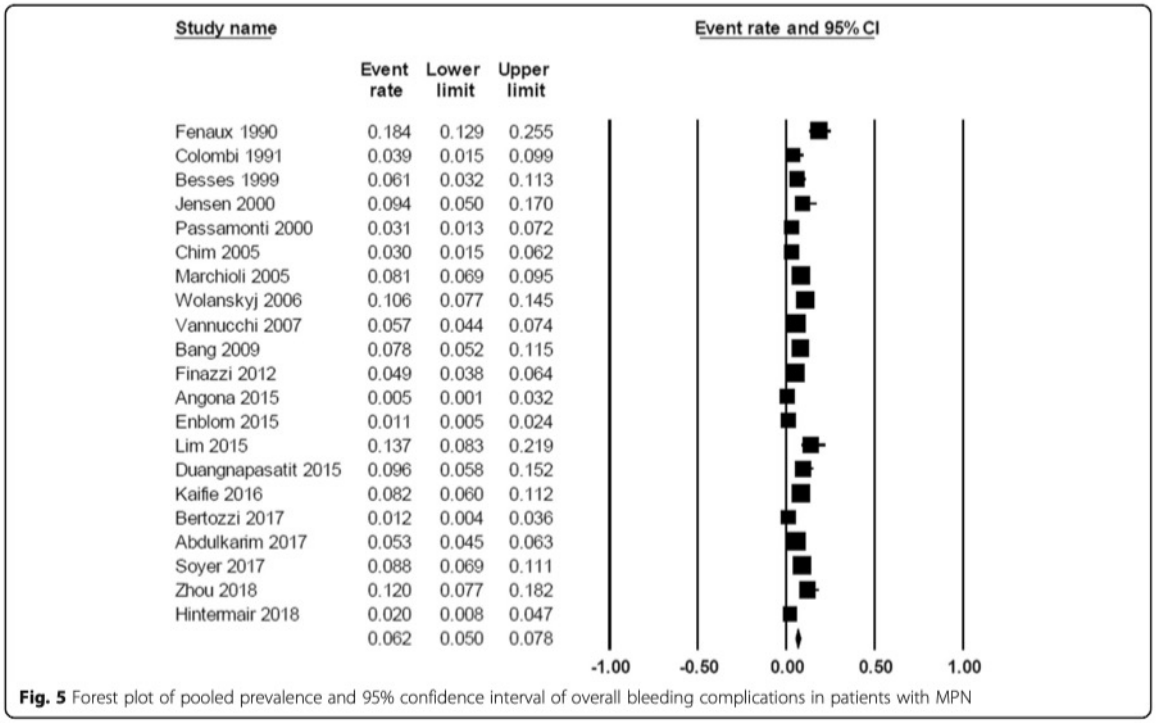
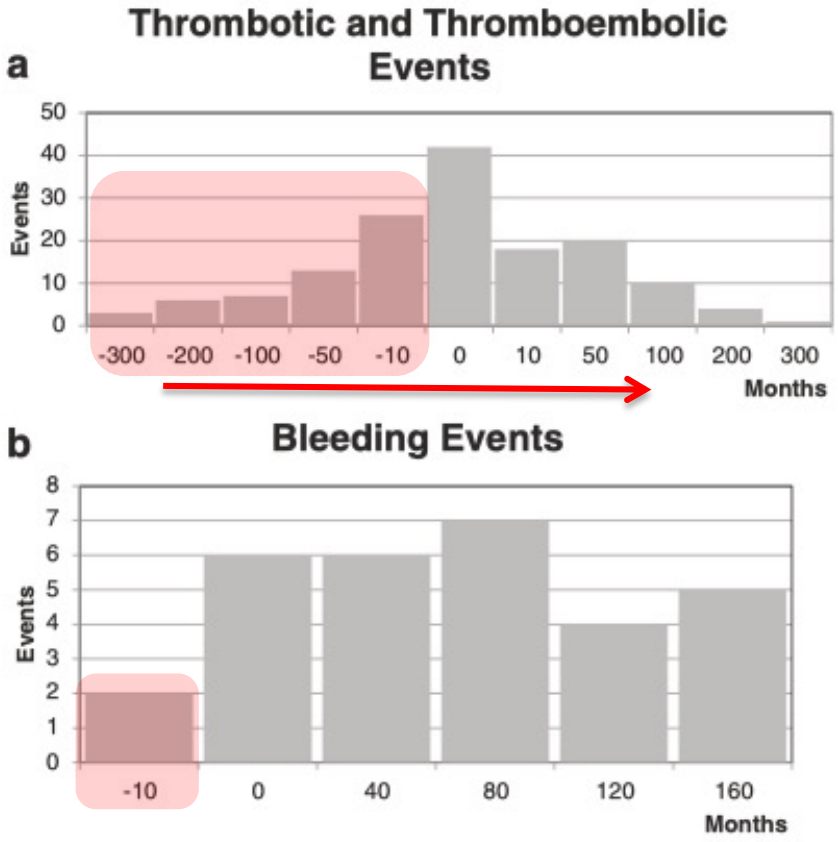


Fig. 5 Forest plot of pooled prevalence and 95% confidence interval of overall bleeding complications in patients with MPN

T Rungjirajittranon et al BMC 2019;19:184

Increased bleeding than thrombotic risk over time (clear effect of antiplatelets/anticoagulant treatment)



MPN patients are at a higher risk for bleeding complications due to:

- **Antiplatelet and anticoagulant therapy** necessary to prevent major thromboembolic complications in high-risk patients (most)

- Presence of **esophageal or gastric varices** due to portal vein hypertension and/or an **acquired von Willebrand syndrome** (AVWS) due to excessive thrombocytosis (quite rare but not exceptional)

Acquired vonWillebrand syndrome due to thrombocytosis

- May occur with PLT > 1.000.000 mm/c (range: rare to frequent)
- Mechanism still unclear (no Ab-mediated)
- More frequent in JAK2 patients (also if PLT < 1.000.000 mm/c) were platelet are more activated
- Diagnosis difficult, mainly lab detection (reduced VWF:RCo/VWF:Ag ratio due to reduction of high molecular weight multimers - HMWM)

Trotti C et al. Hematological Oncology 2021;38:859

How to manage both risks (thrombosis & bleeding)?

NCCN GL for VTE treatment in cancer patients

NCCN[a]	Category 1*	Category 2A†	Category 2B‡
	Dalteparin	Enoxaparin	UFH IV, then UFH SC
	LMWH × 5 d, then edoxaban	Rivaroxaban	UFH SC load, then UFH SC
	Tinzaparina (Italia)	Fondaparinux	
		Apixaban	
		UFH × 5 d, then edoxaban	
		LMWH, UFH, or fondaparinux × 5 d, then warfarin	

Al-Samkari H et al. BloodAdv 2019;3(22):3770:79

DOACs in MPNs

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

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

Schieppati F et al. Hematology 2021;448-52

DOACs in MPNs

Reference	Study population	N on VKA	N on DOAC	Overall thrombotic recurrence		VTE recurrence		Major bleeding		Median follow-up (years)
				VKA	DOAC	VKA	DOAC	VKA	DOAC	
Huenerbein et al[29]	PV/ET/PMF/ MPN-U on systemic anticoagulation for VTE or ATE	45	26	48.8%	15.3%	24.4%	11.5%	8.88%	7.6%	3.2
Fedorov et al[30]	PV/ET/PMF/ MPN-U on systemic anticoagulation for VTE or ATE	31	22	19.4%	22.7%	—	—	6.4%	4.5%	1.2

Retrospective studies comparing thrombosis recurrence and major bleeding in MPN patients receiving VKA or DOAC

Schieppati F et al. Hematology 2021;448-52

Recurrent Thrombosis

9% (12/133) total pts

6% (5/75) VTE pts

13% (6/46) AF pts

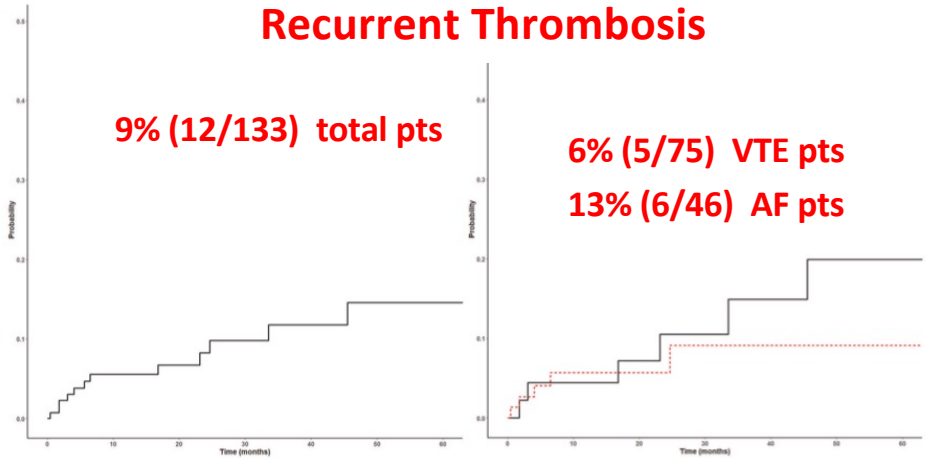


Fig. 1 Cumulative incidence of thrombosis on DOAC in all MPN patients (left) and by indication (right). A total of 12 thrombotic events occurred in 133 patients, including 6 thrombotic events in 46 patients on DOAC for atrial fibrillation (black), and 5 thrombotic events in 75 patients on DOAC for VTE (red).

Retrospective cohort studies of 133 + 65 (italian centres*) MPN patients prescribed DOACs for venous thromboembolism (VTE), atrial fibrillation, or arterial thromboembolism (ATE)

Bleeding

21% (28/133) total pts

20% (15/75) VTE pts

28% (13/46) AF pts

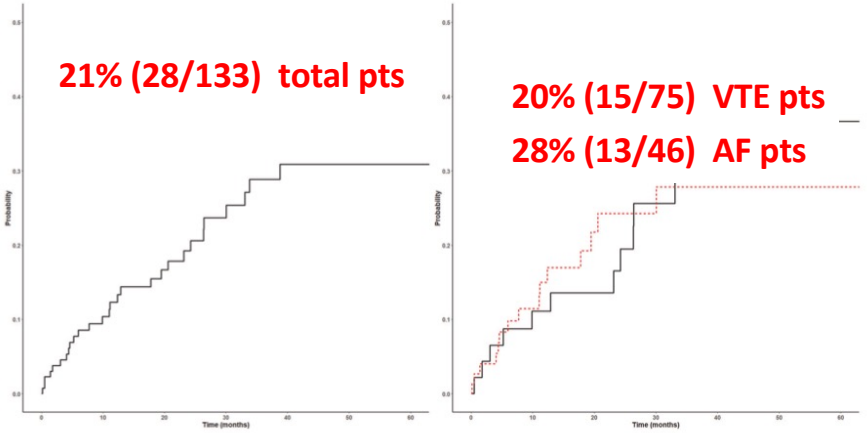


Fig. 2 Cumulative incidence of bleeding on DOAC in all MPN patients (left) and by indication (right). A total of 28 bleeding events occurred in 133 patients, including 13 bleeding events in 46 patients on DOAC for atrial fibrillation (black), and 15 bleeding events in 75 patients on DOAC for VTE (red).

*How J et al. Blood Cancer Journal 2021;11:176, *Serrao A, AJH 2020;1-3, Raso S et al, EHA 2021, EHA submitted 2022*

DOAC

Relative indications	Patient without GI malignancy
	Low risk for major bleeding*
	Ease of treatment of patient is a priority
	No strong drug-drug interactions
Relative contraindications	Active GI malignancy
	History of GI bleeding
	Extremes of weight (<50 or >150 kg)†
	Renal insufficiency/fluctuating renal status

VKA

Relative indications	Any situation in which close anticoagulant monitoring is necessary (eg, multiple prior bleeds) or concern for absorption and metabolism
	Advanced chronic kidney disease
	Extremes of weight (<50 or >150 kg)†
Relative contraindications	Lack of access to dedicated anticoagulation monitoring service with experience caring for cancer patients

LMWH

Relative indications	Frequent emetogenic chemotherapy, nausea and vomiting, difficulty with oral intake
	Concerns for GI absorption (feeding tubes, gastric or bowel resections)
	Drug-drug interactions with DOAC or VKA
	Motivated patient willing to use for extended durations
	Known increased bleeding risk
	Recurrent cancer-associated VTE while on anticoagulants‡
Relative contraindications	Strong aversion or inability to use injectable therapy
	Renal insufficiency/fluctuating renal status (unless regular anti-Xa monitoring with dose adjustment is feasible)
	Extremes of weight (<50 or >150 kg)†

Al-Samkari H et al. BloodAdv 2019;3(22):3770:79

Management of thrombosis in ET and PV

Clinical feature	Intervention
Primary prophylaxis of thrombosis	
All patients	Aspirin Once o twice daily
Unless:	Consider holding aspirin
vWF:RiCoF/vWF:Ag < 0.7 • VWF activity <30%,	
• Platelet > 1 million,	
• *CALR*-mutated low-risk ET	
PV with Hct > 45%	Add phlebotomy/cytoreduction to target Hct < 45%
Age > 60 years and/or prior history of thrombosis	Add cytoreduction
Secondary prophylaxis after thrombotic event	
All patients	Cytoreduction or DOACs
Typical VTE[a]	Consider indefinite VKA for most patients; aspirin if not on VKA
Atypical VTE[b]	Indefinite VKA or DOACs
Arterial thrombosis	Aspirin

Kalyn M. Curr Hematol Malig Rep 2017;12:389–396 *Tefferi & Barbui. Am J Hematol. 2020;95:1599–1613*

Overall Conclusions

- Thrombosis (multifactorial) is a main gap in the management of MPNs
- Few evidence of the use of (new) anticoagulants drugs (but seems safe)
- Bleeding mainly due to AC treatment
- Need for appropriate investigantions

Managing Special Situations

Splanchnic Vein Thrombosis	Bleeding	Surgery	Pregnancy
-Younger women with newly diagnosed *JAK2* V617F PV > ET, or occult MPN	-Advanced age, prior bleeding -MF > ET, PV -Thrombocytosis, acquired von Willebrand Syndrome (aVWS)	-Data from ET and PV > MF	-Data from ET >> PV >>> MF
1. Indefinite anticoagulation -Warfarin unless baseline PT prolongation -DOACs understudied, but we consider in absence of liver dysfunction 2. Cytoreduction when cytosis present (HU or peg-IFN based on age, patient preference) 3. Multi-disciplinary approach -Hepatology assistance w/ surveillance EGD, TIPS consideration, liver transplant consideration (BCS)	1. aVW Stesting prior to ASA when platelets > 1000 x 10^9/L and consider testing even with modest thrombocytosis 2. Cytoreduction to lower platelets in presence of aVWS 3. Supportive measures such as DDAVP and VWF concentrate in aVWS 4. Empirical platelet transfusion if bleeding suspected to be due to qualitative platelet dysfunction 5. Collaboration with hemophilia specialist if questions re aVWS testing/management	1. Optimization of blood counts prior to surgery 2. Cessation of antithrombotic therapy based on half-life 3. Extended VTE prophylaxis following cancer surgery, splenectomy, major orthopedic procedures 4. ASA after vascular procedures 5. Factor replacement and DDAVP in aVWS-bleeding; anti-fibrinolytics for minor bleeding 6. Multi-disciplinary collaboration (Surgery/procedural teams)	1. Antithrombotic therapy *-Low-risk pregnancy* -ASA -LMWH post-partum *-High-risk** -Antepartum + post-partum LMWH -ASA 2. If cytoreduction previously indicated, transition to peg-IFN 3. Peg-IFN in those with prior pregnancy loss/complications 4. Hct control within gestational range for women with PV 5. Multi-disciplinary collaboration (OB and anesthesia)

*Prior arterial or venous thrombosis

B Stein et al. Hematology 2019:397-406