I sanguinamenti nelle sindromi mieloproliferative croniche

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VII^ Edizione "Giornate Ematologiche Vicentine"
Vicenza, 11 Ottobre 2016

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

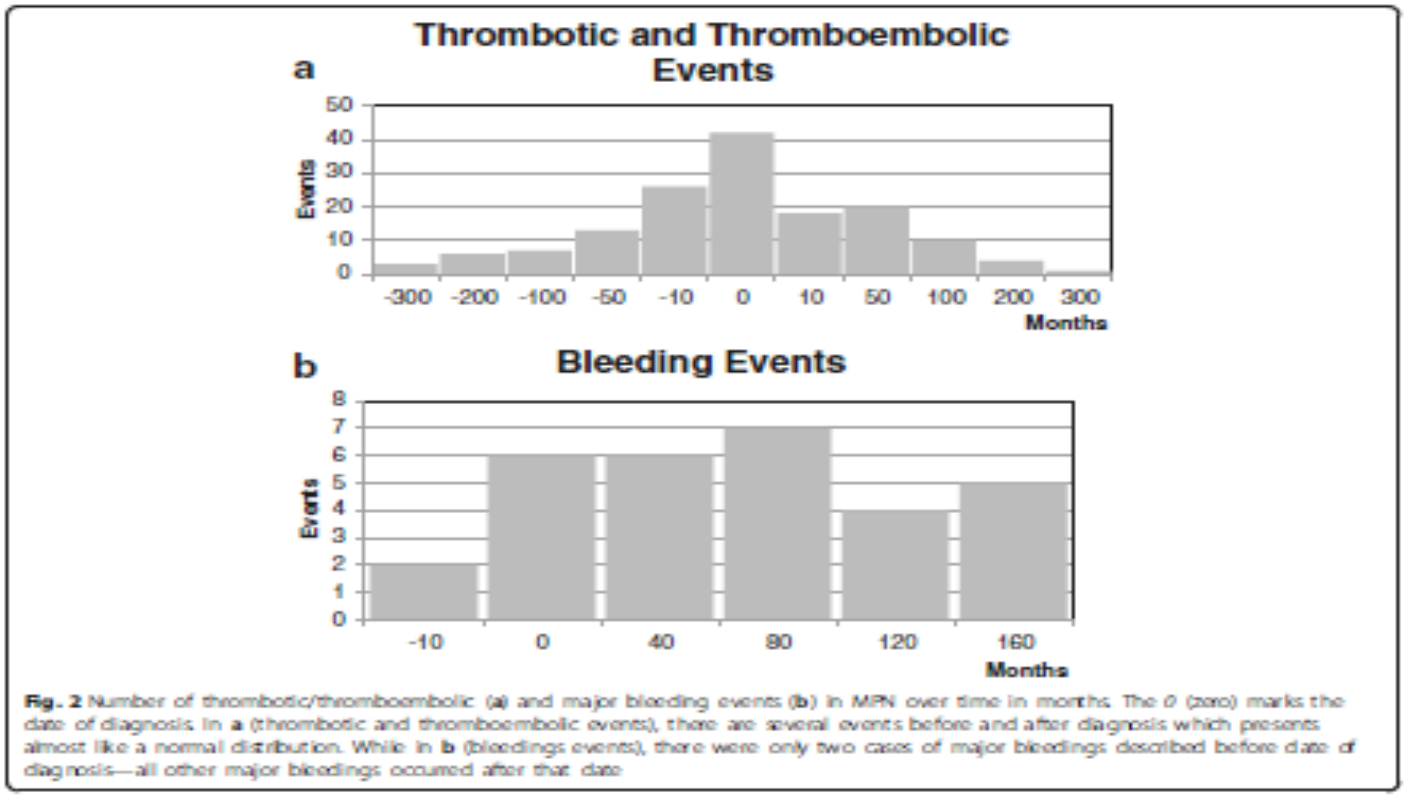


Fig. 2 Number of thrombotic/thromboembolic (**a**) and major bleeding events (**b**) in MPN over time in months. The *0* (zero) marks the date of diagnosis. In **a** (thrombotic and thromboembolic events), there are several events before and after diagnosis which presents almost like a normal distribution. 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

Major bleeding episodes were significantly **less frequent in ET patients compared to other MPN subgroups.**

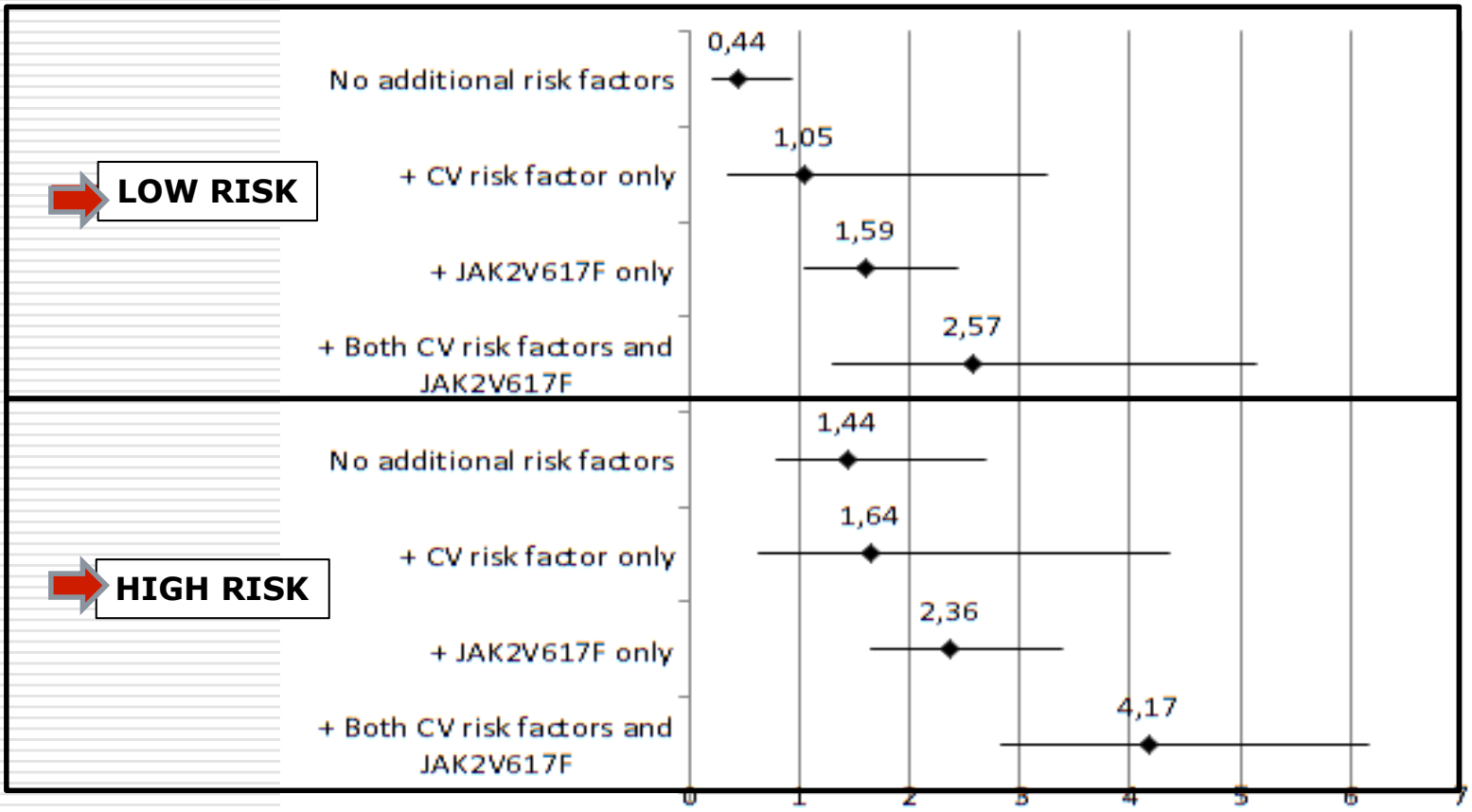
Kaifie et al. Journal of Hematology & Oncology (2016) 9:18

CASE 1

40 year- old patient JAK2V617F positive asymptomatic ET patient

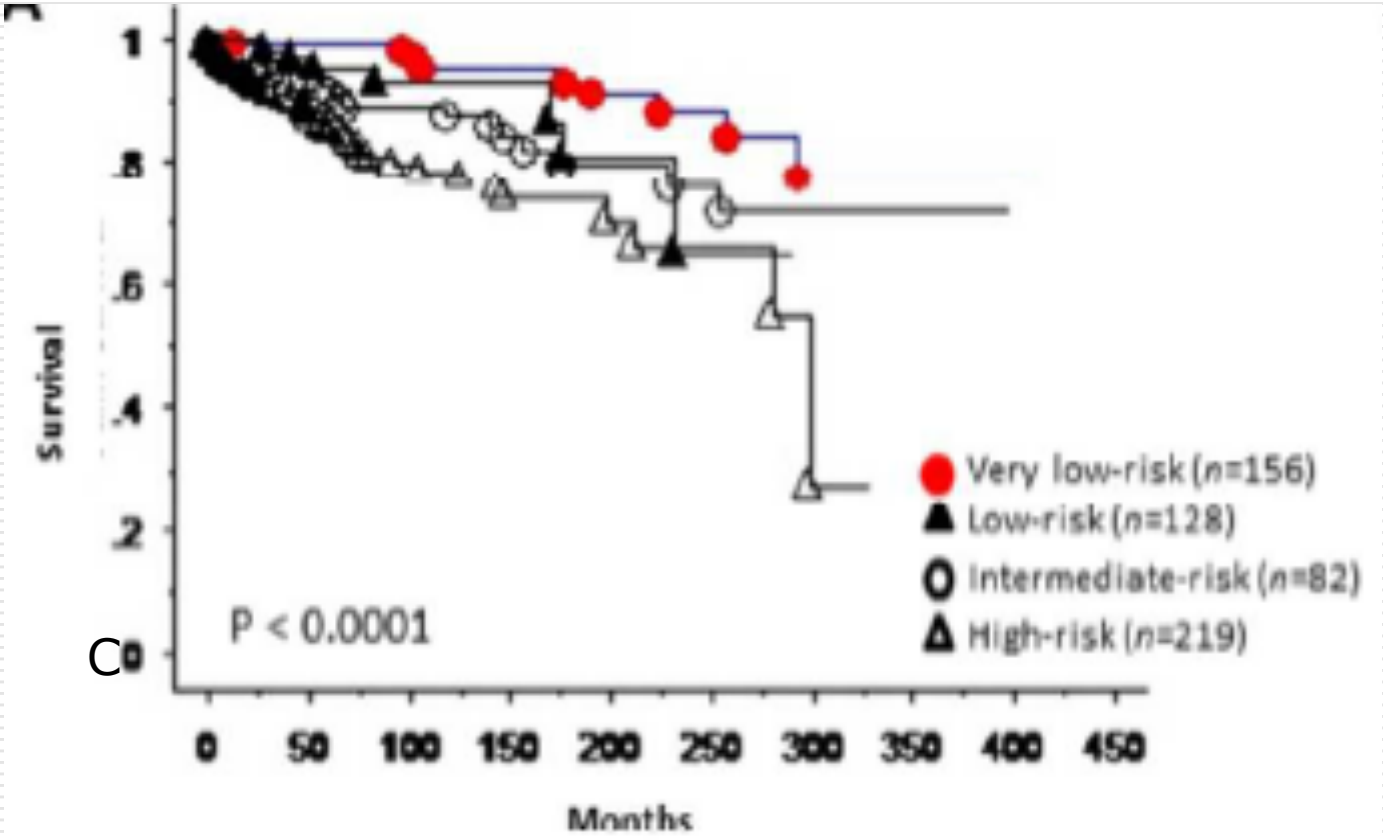
- **1,020 K/ µ L platelets**, no cardiovascular risk factors and no bleeding history
- Most physicians chose to treat this patient **with low dose aspirin (88%), and would not give cytoreductive therapy (89%).**
- Fifty-one percent of physicians recommending low dose aspirin would exclude avWD prior to initiation, **using ristocetin cofactor activity (VWF:RCo).**
- Among the physicians who would not give cytoreductive therapy for this patient, **platelet count ≥ 1,500 K/µl or ≥ 2,000 K/µl was an indication for cytoreduction** for 74% and 11% respectively, while 15% would not start treatment regardless of the platelet count, unless there is an abnormal VWF:RCo.
- **Target platelet count for patients on cytoreductive therapy was chosen as normal, ≤ 600 K/µl, ≤ 1,000 K/µl** or the count at which VWF:RCo normalized by 53%, 30%, 9% and 8% of physicians, respectively

Influence JAK2 mutation status on the rate of vascular events in a cohort of 1019 conventionally defined low and high risk patients with ET



Barbui T et al, Blood Cancer J. 2015; Barbui T. AJH 2016

Validation of the revised International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis) in 585 Mayo Clinic patients



Mahnur Haider et al, AJH 2016

Stratification of the risk of thrombosis and prophylaxis in patients with ET

Very low thrombotic risk

- No history of thrombosis
- Age <60 years
- JAK2V617F-unmutated
- No cardiovascular risk factors (CVR)

Annual rate 0,44%

Low thrombotic risk

- No history of thrombosis
- Age <60 years
- JAK2V617F-mutated and/or CVR present

Annual rate 2,57%

High thrombotic risk

- History of thrombosis and/or Age ≥ 60 year
- JAK2V617F-mutated and/or CVR present

Cerebral Hemorrhage and Aspirin in ET

	WHO-ET n=891	Early PMF n=180	p-value
Bleeding in the follow-up, N (%)	55 (6)	21 (12)	0.009
***Gastrointestinal**, n (%)*	*28 (51)*	*10 (48)*	
***Cerebral**, n (%)*	*2 (3.5)*	*3 (14)*	
***Skin/muscle hematoma**, n (%)*	*18 (33)*	*4 (19)*	
***Urologic/genital**, n (%)*	*2 (3.5)*	*3 (14)*	
***Renal**, n (%)*	*1 (2)*	*0 (0)*	
***Retinic**, n (%)*	*0 (0)*	*1 (5)*	
***Post-surgical**, n (%)*	*2 (3.5)*	*0 (0)*	
***Unknown**, n (%)*	*2 (3.5)*	*0 (0)*	
Rate of bleeding (%/pts/year)	0.79	1.39	
Incidence Rate Ratio (IRR)	1 (Reference)	1.76	0.039

Finazzi G et al, Leukemia 2011

Bleeding in ET vs early-PMF

	ET (n=891)	PMF (n=180)	P value
Follow-up, years	6.2 (0-27)	7.0 (0-27.2)	0.30
Cytoreductive therapy need, n (%)	**507 (57)**	**123 (68)**	**0.03**
Aspirin need, n (%)	602 (68)	131 (73)	0.20
Bleeding in the follow-up, n (%)	**55 (6)**	**21 (12)**	**0.009**
Rate of bleeding (% pts/year)	**0.79**	**1.39**	
Incidence Rate Ratio	**1 (ref.)**	**1.76**	**0.039**

Finazzi G, et al, Leukemia 2011

Multivariate analysis of risk factors for bleeding

	HR (95% CI)	p-value
early/prefibrotic PMF	1.74 (1.00-3.06)	**0.050**
WBC ≥11 x10^9/L	**1.74 (1.02-2.97)**	**0.041**
Previous bleeding	2.35 (1.11-4.98)	**0.025**
Aspirin use	3.16 (1.63-6.08)	**0.001**

Finazzi et al, 2011

Antiplatelet therapy *versus* observation in low-risk essential thrombocythemia with a *CALR* mutation

Total thrombosis

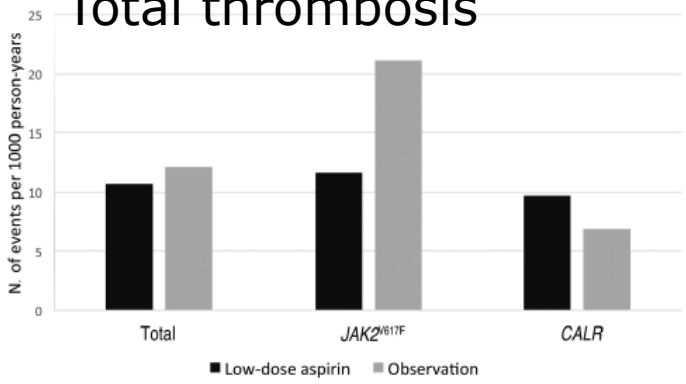


Figure 2. Incidence rate of thrombosis (arterial or venous) in ET patients treated with low-dose aspirin or careful observation. Rates according to therapy are provided for the whole cohort of patients (*P*=0.7), *JAK2*^{V617F}-mutated patients (*P*=0.2) and *CALR*-mutated patients (*P*=0.6).

Bleeding

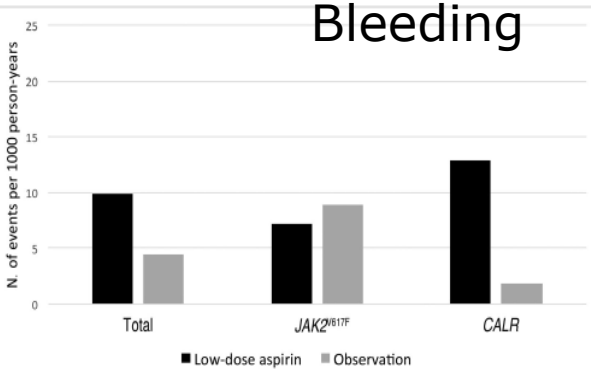


Figure 5. Incidence rate of major bleeding in ET patients treated with low-dose aspirin or careful observation. Rates according to therapy are provided for the whole cohort of patients (*P*=0.17), *JAK2*^{exon12}-mutated patients (*P*=0.8) and *CALR*-mutated patients (*P*=0.03).

Arterial thrombosis

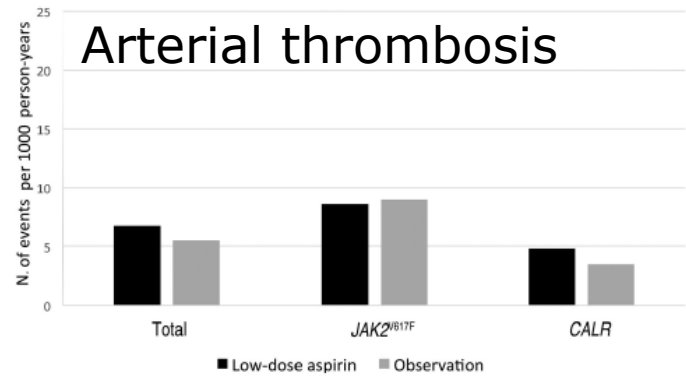


Figure 3. Incidence rate of arterial thrombosis in ET patients treated with low-dose aspirin or careful observation. Rates according to therapy are provided for the whole cohort of patients (*P*=0.7), *JAK2*^{exon12}-mutated patients (*P*=0.9) and *CALR*-mutated patients (*P*=0.7).

Conclusion

In low-Risk pts with CALR mutated ET, ASA does not reduce thrombosis and may increase the bleeding

Alvarez-Larran et al, Haematologica 2016

Gastrointestinal bleeding in patients on aspirin

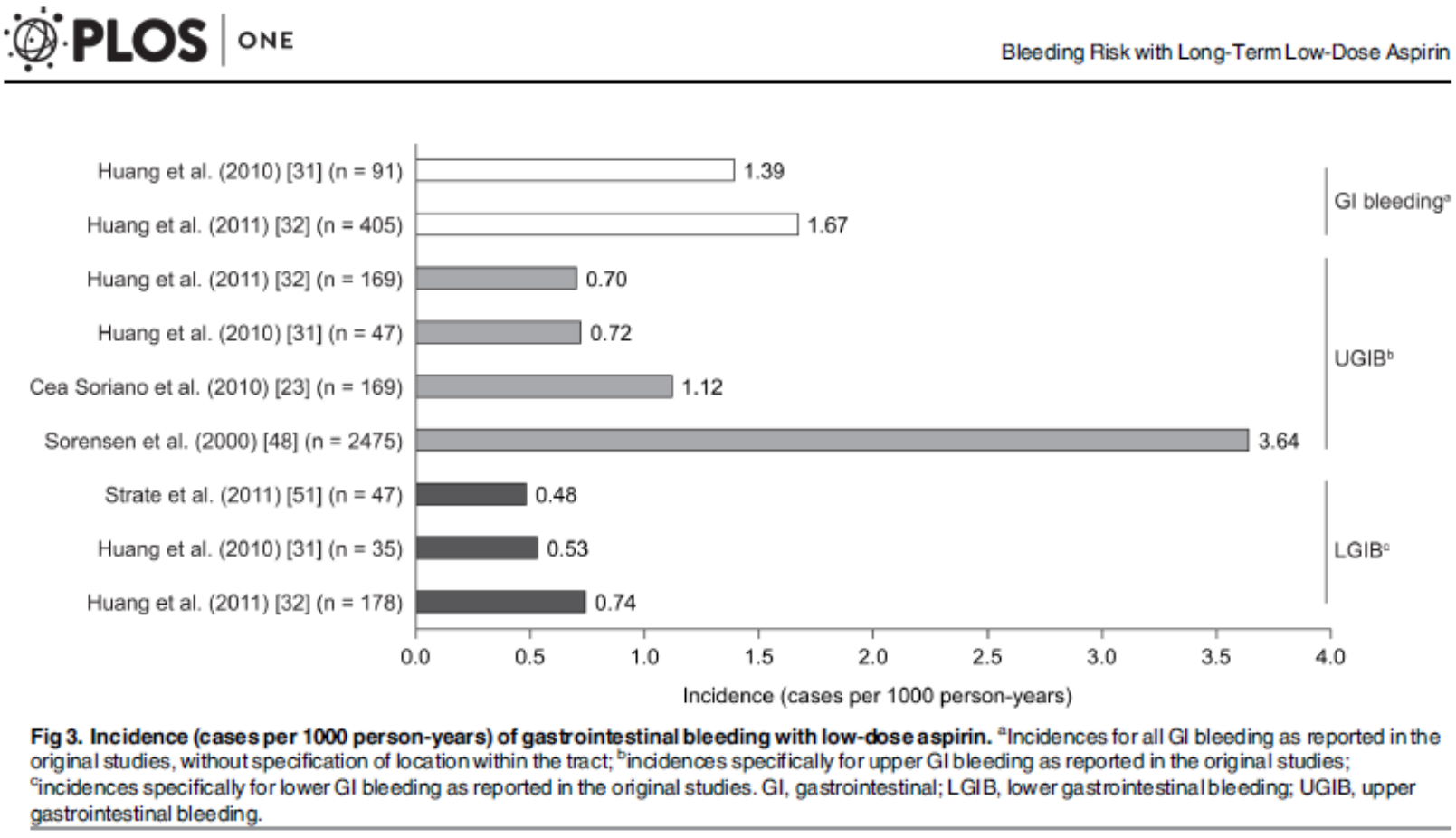
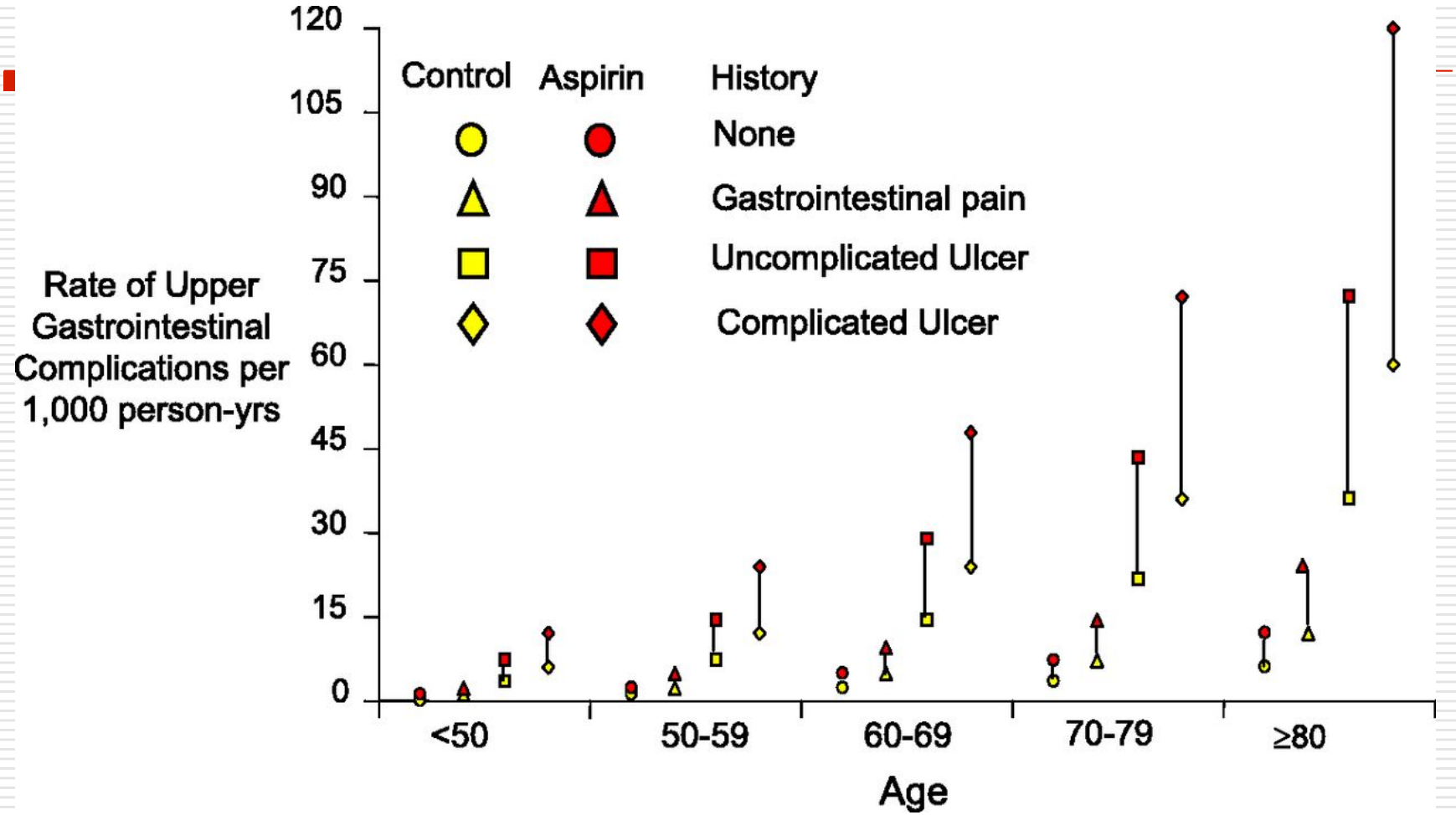


Fig 3. Incidence (cases per 1000 person-years) of gastrointestinal bleeding with low-dose aspirin. [a]Incidences for all GI bleeding as reported in the original studies, without specification of location within the tract; [b]incidences specifically for upper GI bleeding as reported in the original studies; [c]incidences specifically for lower GI bleeding as reported in the original studies. GI, gastrointestinal; LGIB, lower gastrointestinal bleeding; UGIB, upper gastrointestinal bleeding.

Garcia et al, PLOS-ONE,2016

Estimated rates of upper gastrointestinal complications in men, according to age and the presence or absence of a history of such complications and regular treatment with low-dose aspirin.



Carlo Patrono et al. Blood 2013;121:1701-1711

Bleeding to platelet dysfunction

- Indications for antiplatelet therapy should be carefully evaluated and questioned on a regular basis, especially if bleeding occurred. The regular use of aspirin is discouraged in patients with ET.

- Cytoreductive treatment improves overall bleeding risk and should, hence, be considered or optimized in patients with Ph-negative MPN and severe bleeding.

- In case of severe or life-threatening bleeding from platelet dysfunction, platelet transfusions should be administered, but treatment of the underlying disease is required in addition.

CASE 2

Patient with PV and venous thrombosis

Male, 68 year
No prior thrombosis
Arterial hypertension well controlloed with ACE inhibitors

Therapy: Phlebotomy (3 per year)Hydroxyurea and aspirin

Unprovoked DVT in the femoral vein and pulmonary embolism in 2005; heparin and then warfarin

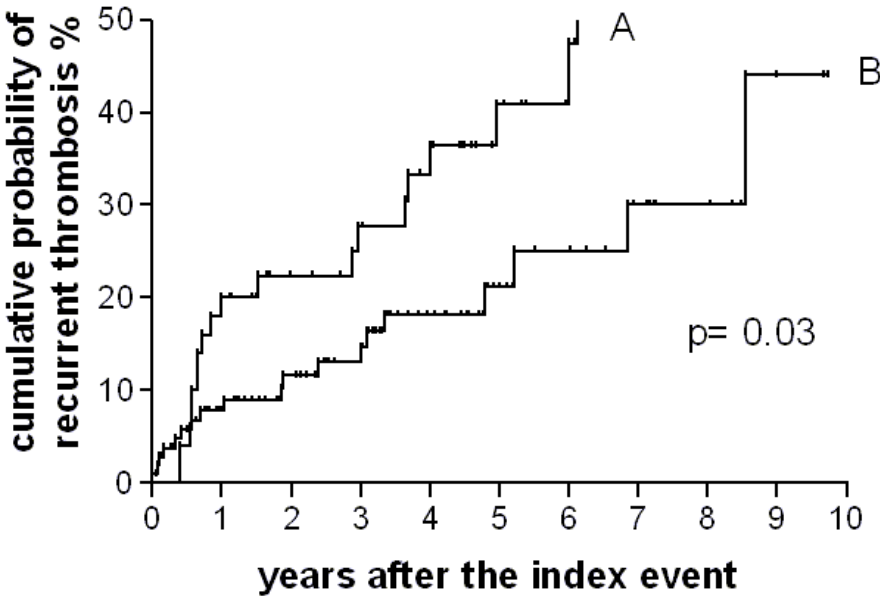
in 2010 eco-doppler escluded occlusion and warfarin was stopped

in 2012 recurrence in the same district :heparin and warfarin.

in 2016 is well on warfarin. Mild epistaxis

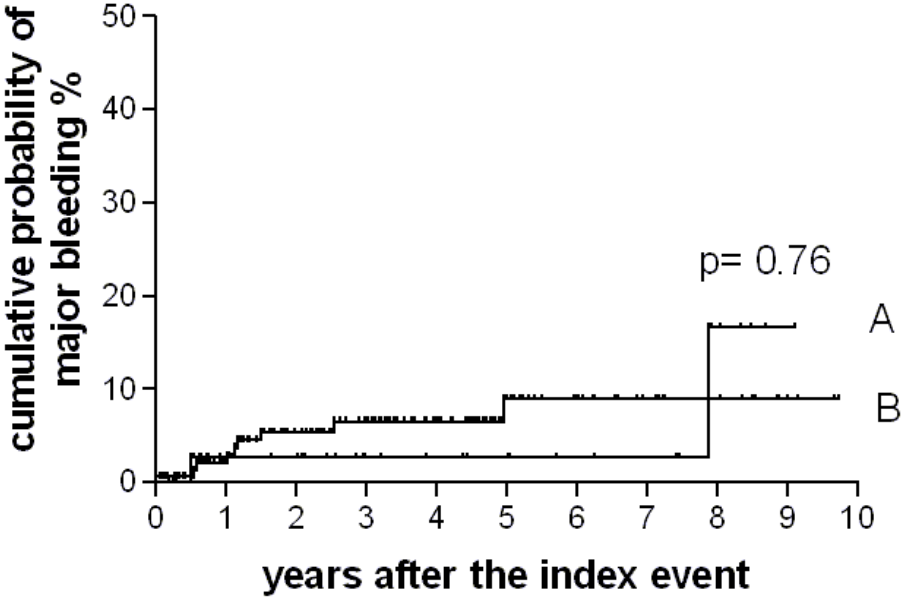
Cumulative probability of recurrent thrombosis and major bleeding in patients who discontinued VKA after index thrombosis (curve A) or did not (curve B)

Recurrent thrombosis



	Vitamin K antagonists		p
	Yes (N=155)	No (N=44)	
Pts-years	404	279	
Thrombosis, N Incidence rate % pt-yrs (95% CI)	19 4.7 (2.8-7.3)	25 8.9 (5.7-13.2)	0.03

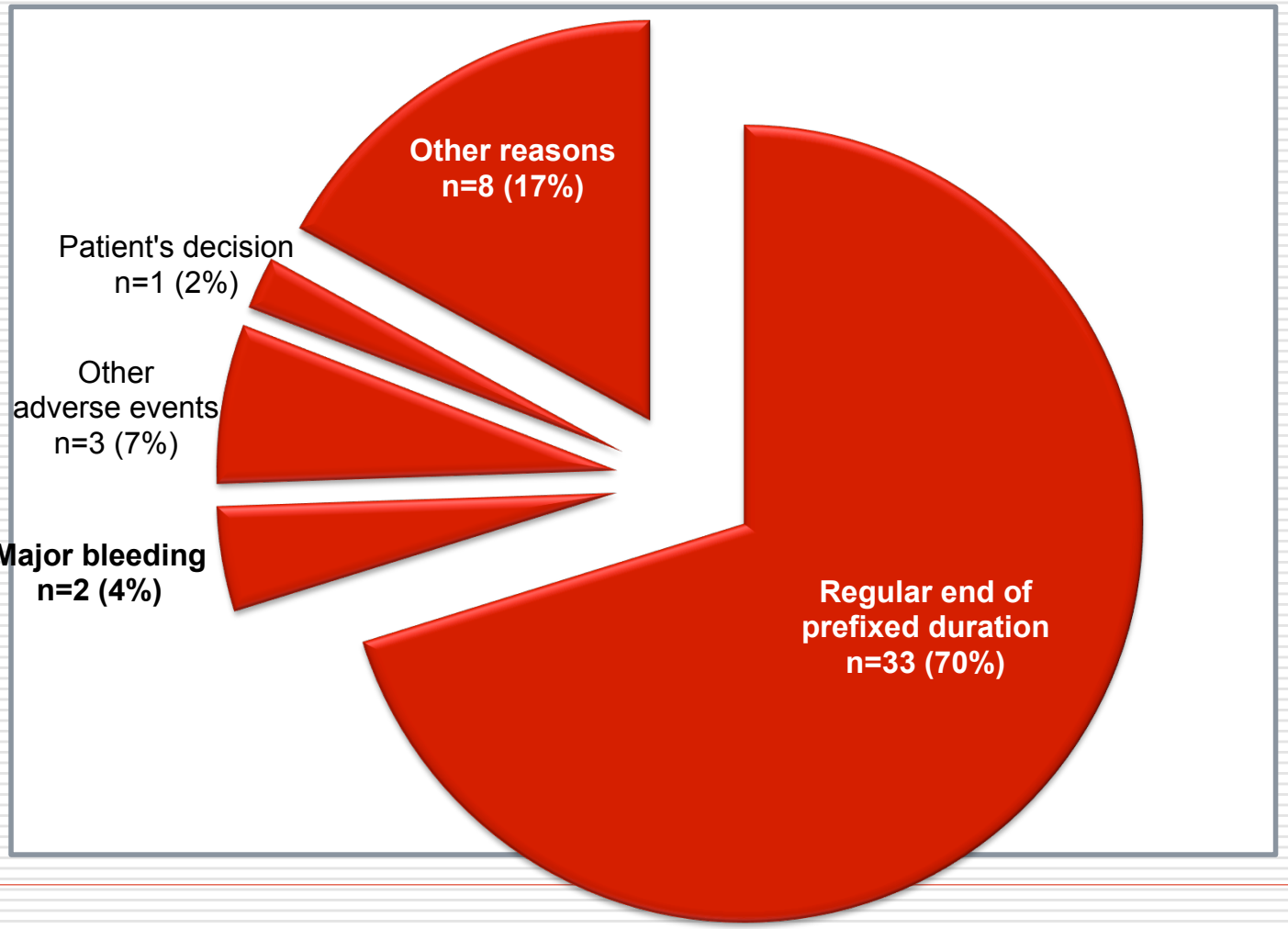
Major bleeding



	Vitamin K antagonists		p
	Yes (N=155)	No (N=44)	
Pts-years	404	279	
Major bleeding, N Incidence rate % pt-yrs (95% CI)	10 2.4 (1.1-4.5)	2 0.7 (0.08-2.5)	0.08

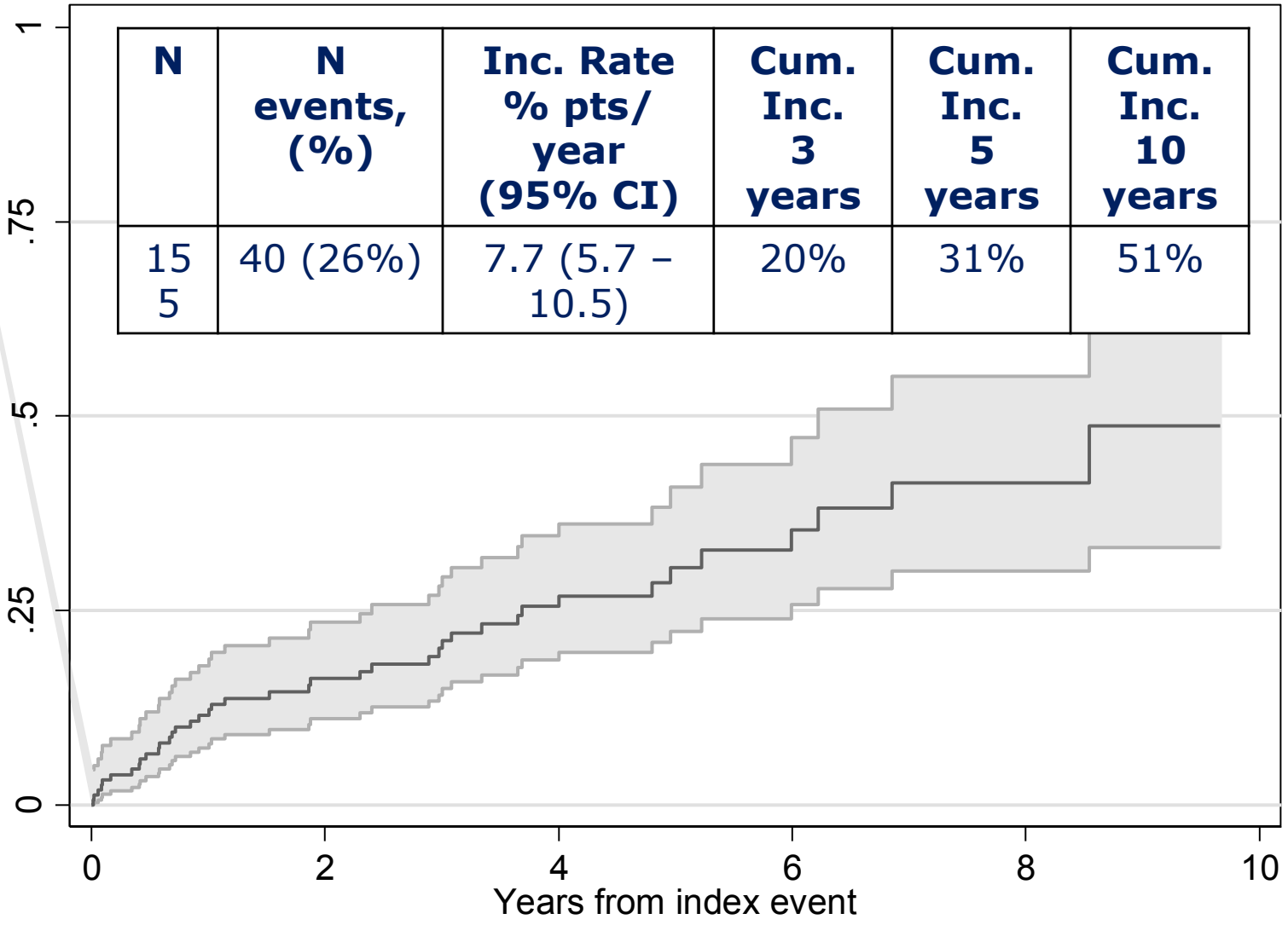
De Stefano et al. Leukemia 2016

Reasons for Warfarin discontinuation (n=47)

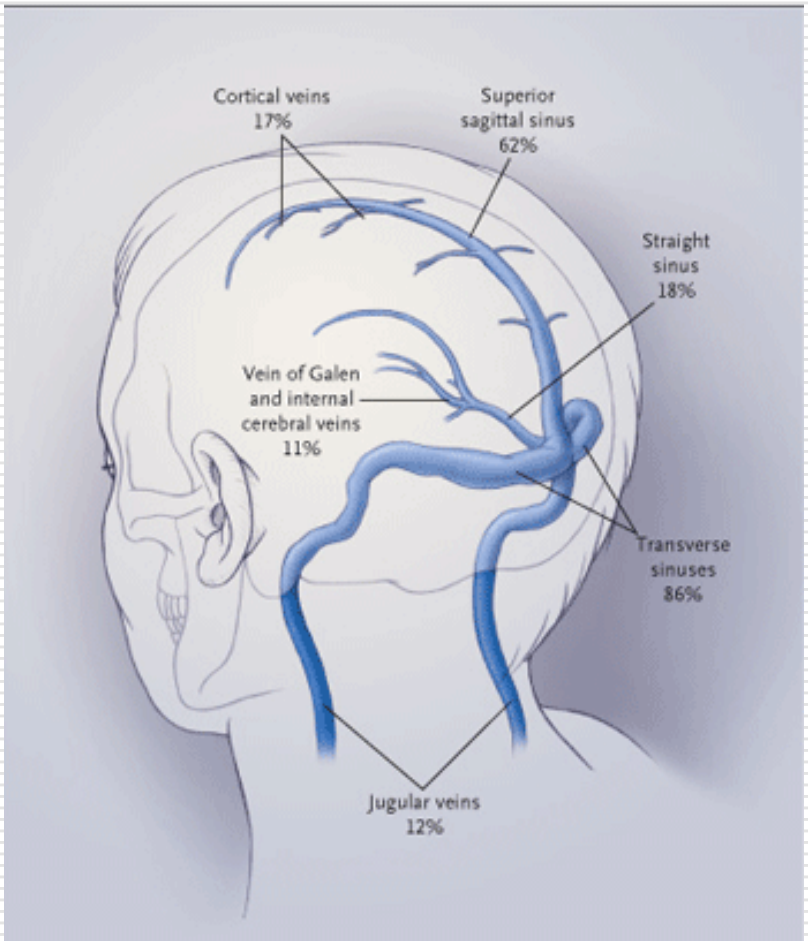


Cumulative incidence of combined thrombosis recurrence + bleeding while on Warfarin

N	N events, (%)	Inc. Rate % pts/ year (95% CI)	Cum. Inc. 3 years	Cum. Inc. 5 years	Cum. Inc. 10 years
155	40 (26%)	7.7 (5.7 – 10.5)	20%	31%	51%



Thrombosis of the cerebral veins: case-control study (n=48)

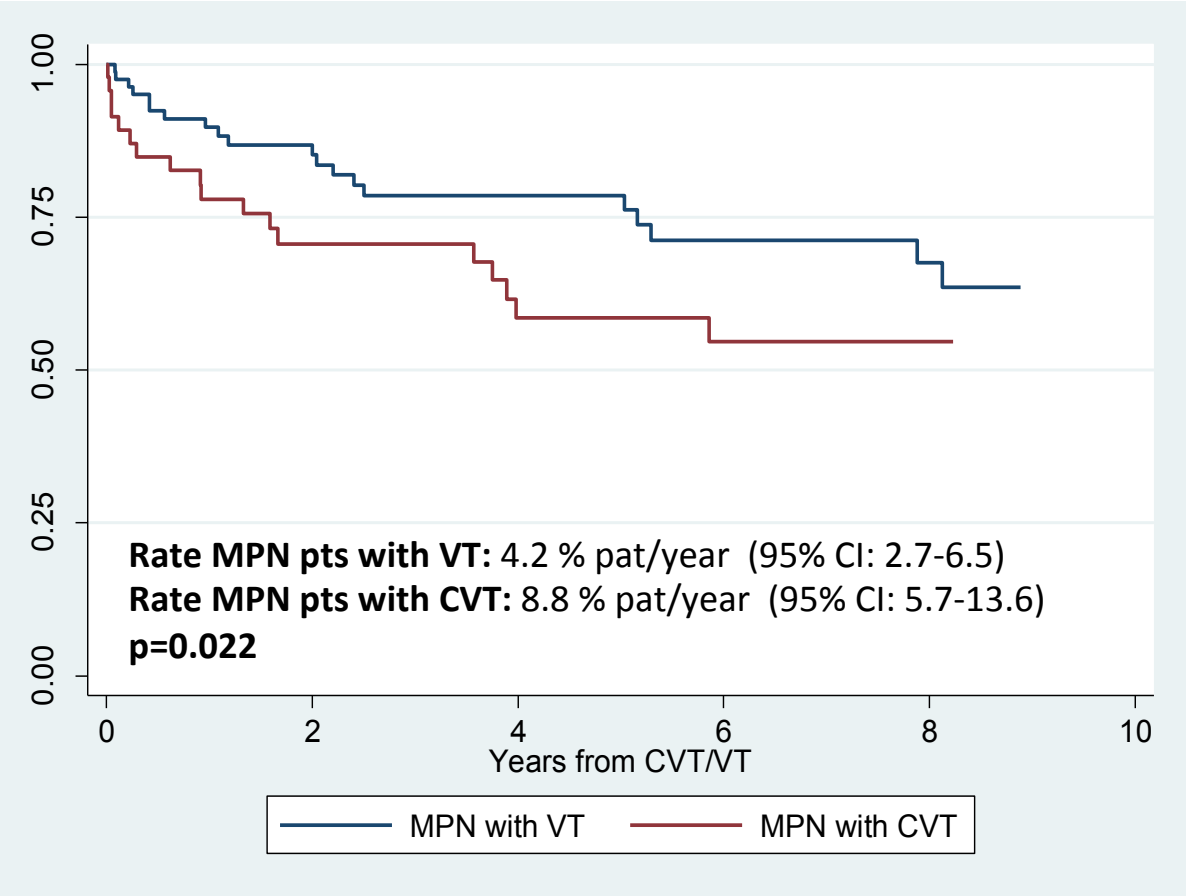


Cases: patients with CVT and MPN

Controls : pts with MPN and thrombosis at other sites

Treatment of acute VT : intravenous or subcutaneous heparin, followed by long-term antithrombotic treatment in 73 patients (84%) and consisted of VITAMIN K ANTAGONISTS in 53 (73%) or antiplatelet agents in 19 (22%) of them. Nine patients (12%) remained in subcutaneous low-molecular weight or unfractionated heparin.

Thrombosis Recurrence-Free Survival in MPN patients with previous CVT or VT.



Bleeding in cerebral veins thrombosis

	MPN-CVT patients	MPN-VT patients	*P*
Median follow-up, years (range)	6.09 (0-34)	10.3 (0-31)	*0.01*
Major bleeding, n (%)	7 (16)	9 (11)	*0.41*
central nervous system	3	2	
gastrointestinal	1	5	
muscle	1	-	
menorrhagia	-	1	
epistaxis	1	1	
hematuria	1	-	

Risk of thrombosis and hemorrhage in patients with polycythemia vera and atrial fibrillation treated with prophylactic oral anticoagulants

Ana Sofia de Freitas[1] · Alberto Alvarez-Larrán[1]

	PV + AF $n = 63$	Controls $n = 124$	p
No. of thrombotic events, n (%)	6 (9.5 %)	15 (12 %)	0.8
Stroke/TIA	3 (5)	3 (2)	0.4
Coronary artery disease	1 (2)	8 (6.5)	0.3
Peripheral artery disease	1 (2)	3 (2)	0.9
DVT/PE	2 (3)	1 (1)	0.3
Probability of thrombosis at 5 years	6 %	10 %	0.7
No. of major hemorrhagic events, n (%)	6 (9 %)	11 (9 %)	0.9
Probability of major bleeding at 5 years	12 %	8 %	0.2

Ann of Hematology 2016

CASE 3

Patient with PV in need of surgery

Male, 60 year with ET, CALR mutated

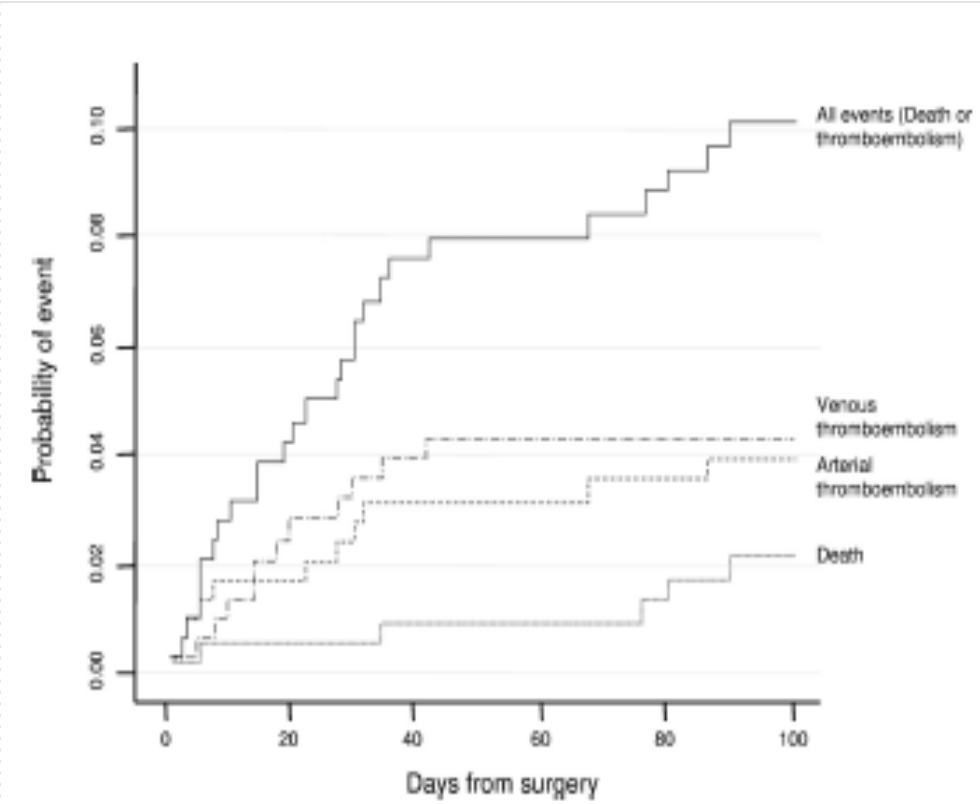
Medical history:
Arterial hypertension well controlloed with ACE inhibitors.
Treatment with HU and low dose asa started 5 years before surgery for TIA

Admitted for elective surgery to remove a small colon cancer.

Platelet number	700.000
Leukocytes	6.700
Hb	14,3 g%

Question: Which antithrombotic prophylaxis?

Postsurgery thrombosis and death in PV and ET patients



PV…… n=716
ET…….. ..n=1462
At least 1 surgery …..n= 255
Total interventions…..n= 311

Major surgery vs minor:no statistical difference

More arterial thrombosis in ET
More venous thrombosis in PV

Ruggeri et al, Blood 2008

Overall incidence of bleeding complications

(major and minor)

10.5% (30 episodes in 284 surgeries).

Clear trend for an increased bleeding risk in those subjects receiving antithrombotic prophylaxis versus no prophylaxis

- heparin versus no prophylaxis: HR, 1.7
- antiplatelet versus no prophylaxis: HR, 2.4

The hemorrhagic risk was strongly related to the immediate postsurgical period (per 1000 pts/day)

	No prophylaxis	**Yes prophylaxis**	
		ASA	*Heparin*
0 to 15 day	3.1	9.8	6.6
15 to 30 da	0.8%	0	0.2
30 to 60 days	0.2%	0	0

.

Recommendations: Perioperative prevention of venous thromboembolism in PV and ET

- *It seems appropriate to restrict the use of antithrombotic prophylaxis with LMWH in patients with PV undergoing major surgery*
- *Conversely, antiplatelet drugs may be the optimal choice in patients with ET with several arterial risk factors*
- *This approach should be weighed against the surgery specific bleeding risk (surgeries involving mucous tissue)*

LMWH, low mol. weight heparin

Ruggeri M et al. Blood 2008;111:666-71.

Surgery in ET and PV - Conclusion

- Despite the active approach, a significant proportion of surgeries (5.1% of major surgeries and 2.5% of minor surgeries) were complicated by DVT (5-fold increase with respect to the normal population)
- High rate of arterial thrombosis (3.8%) was observed after intervention (specific for patients with MPN)
- The rate of hemorrhagic complication is higher than those observed in clinical trials evaluating heparin prophylaxis and in surgical patients with cancer (predisposition in MPN)

DVT, deep venous thrombosis

Ruggeri M et al. Blood 2008;111:666-71.

Case 4

67 year old man with Myelofibrosis

Primary myelofibrosis in 2010, splenomegaly 5 cm below the costal margin; no anemia, moderate thrombocytopenia (111.000), leukocytosi 12.000 con rare peripheral erythroblasts and myelocytes

Stable condition until 2015 when he presented massive splenomegaly (15 cm below the costal margin) associated with fever , weight loss. Plateletsremained stable.

Ruxoltinib 20mgs bd.: after 2 months, significant improvement of general conditions and reduction of the spleen.
However platelet number 65.000; Hb 10.9 g%: Leucocytes 18.000

Bleeding to thrombocytopenia

Thrombocytopenia due to progression of disease

transfusion of platelets is the therapy of choice in patients with thrombocytopenia and acute hemorrhage.

Thrombocytopenia due to hypersplenism

Splenectomy remains reserved for patients with severe,refractory cytopenias and extremely large spleens (15–20 cm below costal margin or larger) who do not respond to conservative treatment.

Treatment-related thrombocytopenia

Optimize cytoreductive treatment in case of treatment-related thrombocytopenia. In myelofibrosis with low doses of ruxolitinib while closely monitoring their platelet counts.

Treatement according to general consensus guidelines.

Ruxolitinib in MF Adverse Events: 5-Year Final Study Results (exposure adjusted)

Preferred Term, n (exposure-adjusted rate)	Ruxolitinib Randomized (n = 146)	Ruxolitinib Randomized + Extension (n = 146)	BAT Randomized (n = 73)	Ruxolitinib Crossover (n = 45)	Total Ruxolitinib (n = 191)
Patient-year exposure	170.12	409.52	66.98	79.70	489.22
Bleeding events					
Bruising	24 (14.1)	38 (9.3)	6 (9.0)	12 (15.1)	50 (10.2)
GI bleeding	10 (5.9)	16 (3.9)	2 (3.0)	4 (5.0)	20 (4.1)
Intracranial	2 (1.2)	2 (0.5)	0	1 (1.3)	3 (0.6)
Other	42 (24.7)	60 (14.7)	14 (20.9)	18 (22.6)	78 (15.9)
Infections					
Herpes zoster	9 (5.3)	16 (3.9)	0	6 (7.5)	22 (4.5)
Pneumonia	8 (4.7)	21 (5.1)	7 (10.5)	4 (5.0)	25 (5.1)
Sepsis/septic shock	5 (2.9)	12 (2.9)	0	3 (3.8)	15 (3.1)
Tuberculosis	1 (0.6)	2 (0.5)	0	0	2 (0.4)
UTI	23 (13.5)	37 (9.0)	5 (7.5)	10 (12.5)	47 (9.6)
Tumors					
Malignancies	12 (7.1)	31 (7.6)	3 (4.5)	4 (5.0)	35 (7.2)
NMSC	9 (5.3)	25 (6.1)	2 (3.0)	1 (1.3)	26 (5.3)

8 patients (5.5%) in the ruxolitinib arm and 5 patients (6.8%) in the BAT arm developed AML over the course of follow-up

AML, acute myeloid leukemia; GI, gastrointestinal; NMSC, nonmelanoma

Conclusion 1

Factors influencing the risk of major bleeding due to antiplatelet drugs

- Impact of aspirin dose and duration
- Patient related factors (Age, H.pylori infection)
- Use of concomitant medications (tiklopidin, SSRI, oral anticoagulants)

Conclusion 2

Bleeding in MPN. Management Recommendations

AVWS should be suspected in patients with unexplained bleeding and/or excessive thrombocytosis and should be confirmed using vWF activity and multimer analysis.

Antiplatelet therapy should be withheld, if justifiable, unless AVWS resolves due to therapy.

Cytoreductive therapy should be initiated or optimized in patients with excessive thrombocytosis or with severe bleeding in order to normalize platelet counts and achieve remission of AVWS.

In case of acute severe bleeding, desmopressin and tranexamic acid should be administered .

Platelet transfusions, vWF-containing concentrates, and/or rFVIIa (off-label use) should be reserved for severe or life-threatening bleeding episodes.