Azienda Ospedaliero Universitaria Careggi

UNIVERSITÀ DEGLI STUDI FIRENZE

Trombocitemia Essenziale

La profilassi antitrombotica

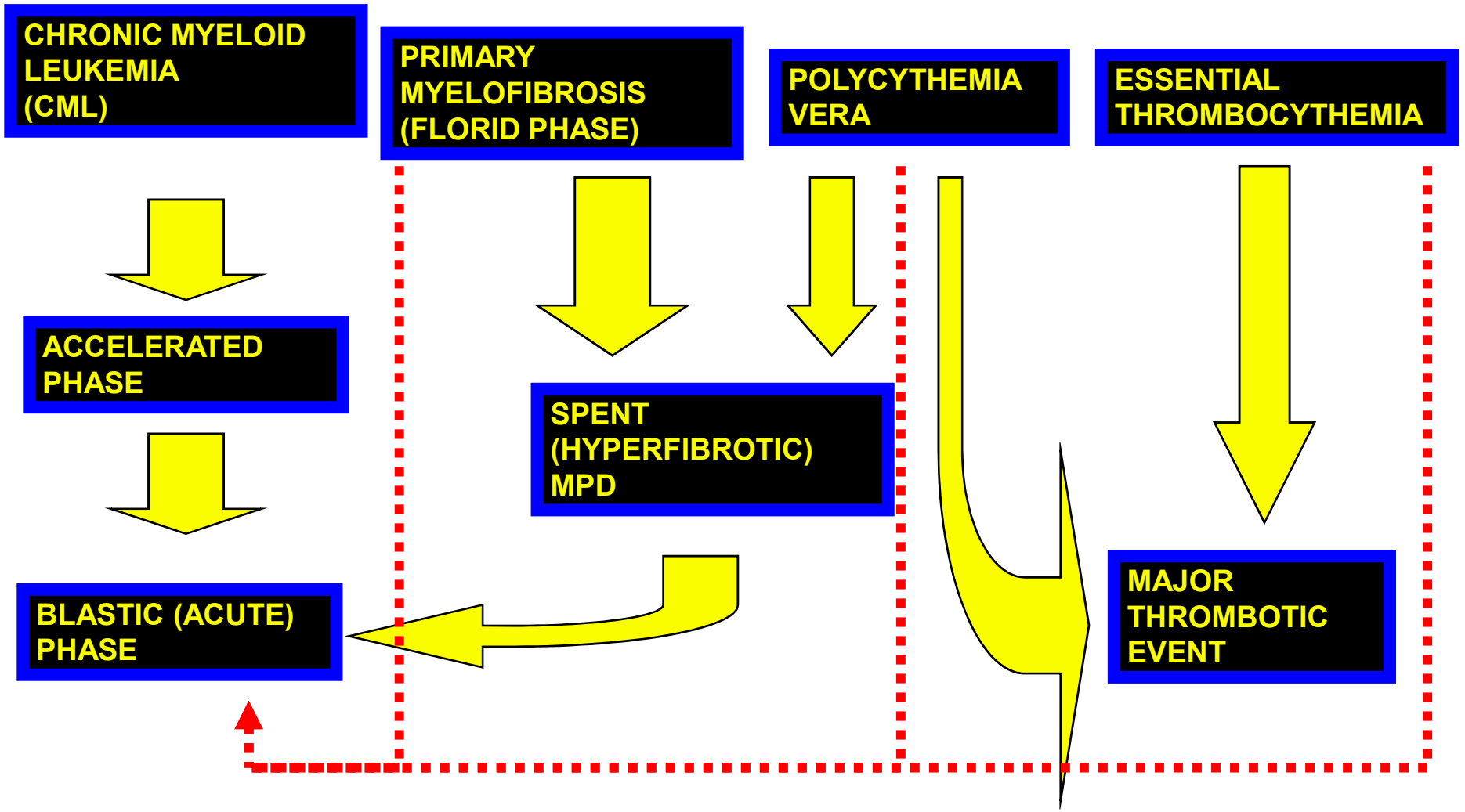
Nona Giornata Fiorentina dedicata ai pazienti con malattie mieloproliferative croniche

Sabato 20 maggio 2023

Valerio De Stefano

Sezione di Ematologia, Università Cattolica, Fondazione Policlinico A. Gemelli IRCCS Roma

NATURAL HISTORY OF MPN



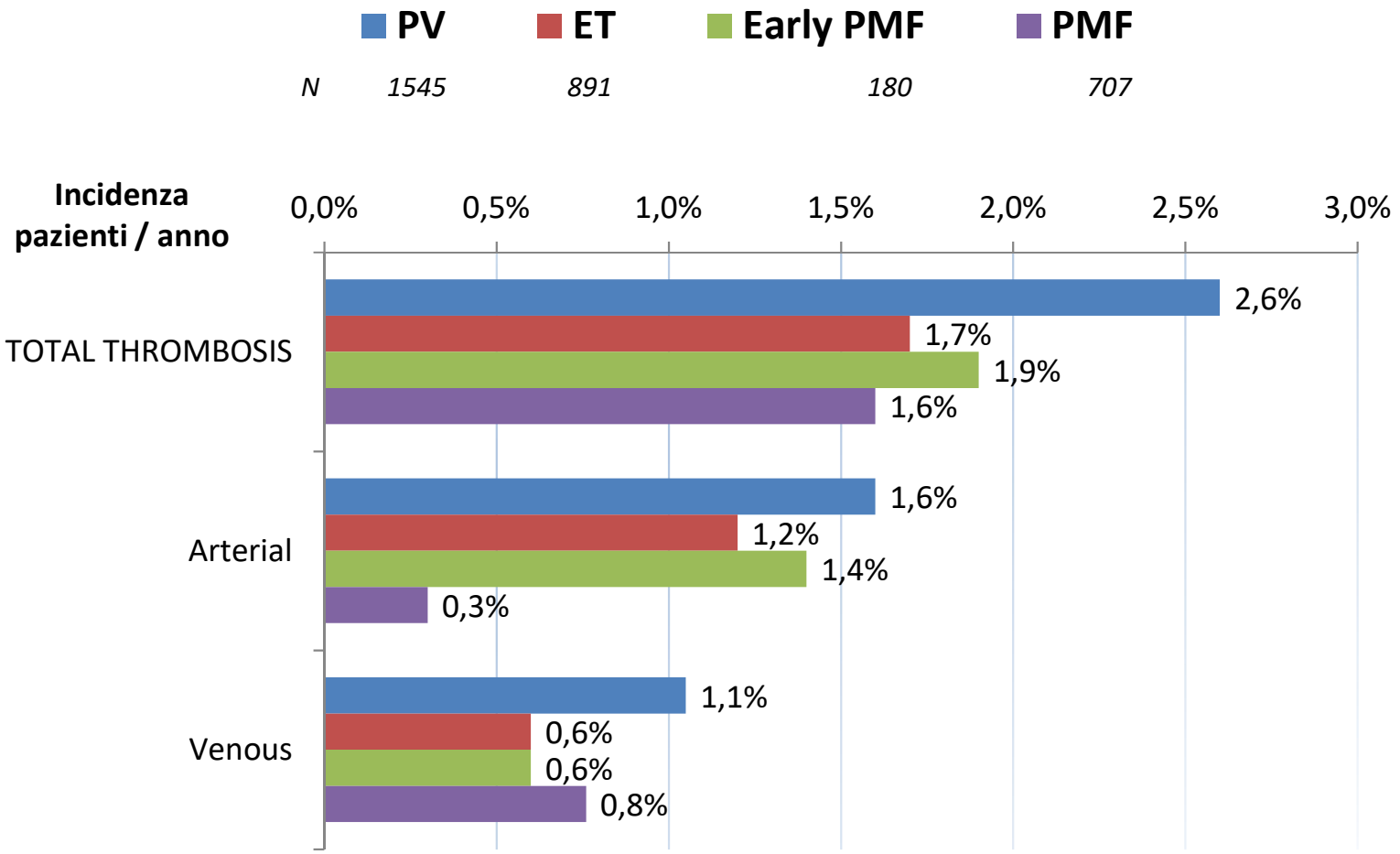
- L’incidenza annuale di Trombo-Embolismo Venoso nella popolazione generale è 1-2 per 1000

- L’incidenza annuale di Malattia Cardio-Vascolare (sindromi coronariche acute e eventi cerebrovascolari) nella popolazione generale 6-7 per 1000

Incidenza annuale totale 7-9 per 1000 (0.9 %)

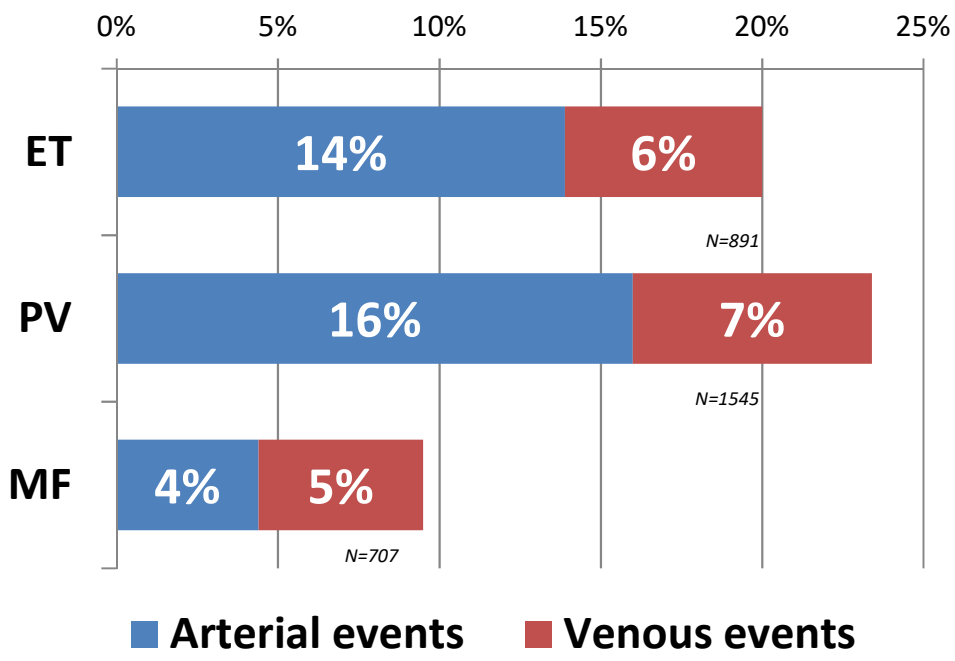
Incidenza di trombosi nelle malattie mieloproliferative croniche

(pazienti n= 3323; Incidenza % per anno)



Prevalenza di trombosi arteriose / venose nelle MMPC alla presentazione e 3 anni prima della diagnosi

Rapporto A / V circa 2 / 1



Incidenza / 100 pazienti / anno
ET 1.8 %
PV 2.6 %
MF 2.2 %

Barbui T et al, Blood. 2014 Nov 6;124(19):3021-3
Barbui et al, J Clin Oncol. 2011 Aug 10;29(23):3179-84
Carobbio et al, Blood. 2011 Jun 2;117(22):5857-9
Barbui et al, Blood. 2010 Jan 28;115(4):778-82

Fattori di rischio per trombosi

Correlati al paziente
Età (> 60 anni)
Storia di pregressa trombosi
Presenza di fattori di rischio cardiovascolari (fumo, ipertensione, dislipidemia, diabete)
Presenza di trombofilia (congenita o acquisita)
Correlati alla trombocitemia essenziale
Piastrinosi
Anomalie funzionali delle piastrine
Attivazione dell'endotelio e del sistema emostatico
Leucocitosi
Attivazione leucocitaria e piastrinica
Interazione leucociti-piastrine
Mutazione JAK2 V617F

Cervantes, Hematology 2011

Stratificazione «classica» del rischio

Basso rischio
Età ≤ 60 anni
Assenza di pregressa trombosi
Conta piastrinica < 1,500,000 / mmc
Rischio intermedio ?
+ fattori di rischio cardiovascolari (fumo, ipertensione, dislipidemia, diabete)
+ trombofilia congenita
Alto rischio
Età > 60 anni
Storia di pregressa trombosi
Conta piastrinica ≥ 1,500,000 / mmc

Fattori di rischio addizionali

- JAK2 V617F
- Cinetica piastrinica
- Attivazione piastrinica
- Leucocitosi
- Ipercoagulabilità plasmatica
- Trombofilia genetica

blood

2012 120: 5128-5133
Prepublished online October 1, 2012;
doi:10.1182/blood-2012-07-444067

Development and validation of an International Prognostic Score of thrombosis in World Health Organization –essential thrombocythemia (IPSET-thrombosis)

Tiziano Barbui, Guido Finazzi, Alessandra Carobbio, Juergen Thiele, Francesco Passamonti, Elisa Rumi, Marco Ruggeri, Francesco Rodeghiero, Maria Luigia Randi, Irene Bertozzi, Heinz Gisslinger, Veronika Buxhofer-Ausch, Valerio De Stefano, Silvia Betti, Alessandro Rambaldi, Alessandro M. Vannucchi and Ayalew Tefferi

Fattore di rischio in 891 pazienti TE	Rischio relativo	Punteggio
Età > 60 anni	1.50	1
Fattori di rischio cardiovascolare	1.56	1
Pregressa trombosi	1.93	2
JAK2 V617F	2.04	2

Rischio	Punteggio
Basso	0 – 1
Intermedio	2
Alto	≥ 3

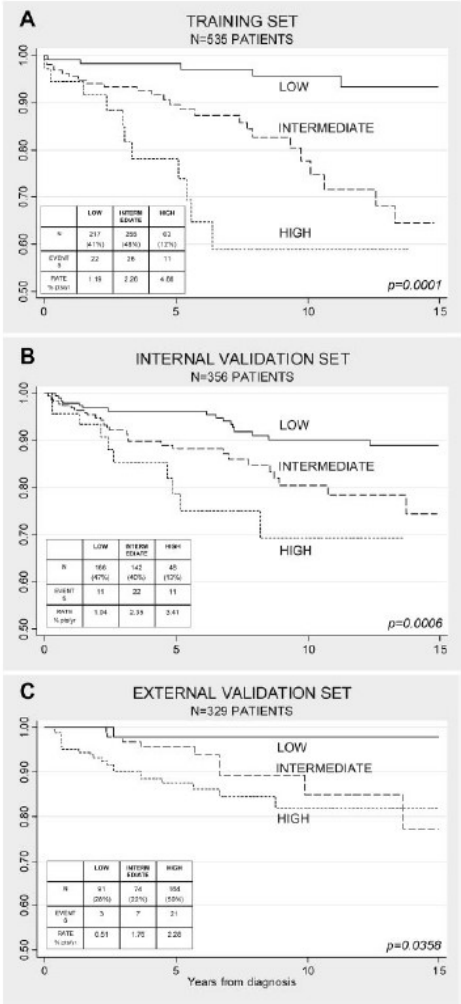


Table 1. Influence of cardiovascular risk factors and JAK2 mutation on the rate of vascular events in low- and high-risk patients

Additional risk factors	N *(%)*	*Event*	*Rate% patients/year (95% CI)*	P-*value*	P-*value*	P-*value trend*
Low risk	506 (50)					
None	200 (40)	7	0.44 (0.21–0.92)	Ref		
Cardiovascular risk factor	36 (7)	3	1.05 (0.34–3.25)	0.220	0.227	
JAK2V617F	213 (43)	21	1.59 (1.04–2.44)	0.001	0.217	
Both	52 (10)	8	2.57 (1.29–5.15)	<0.001	Ref	<0.001
High risk	513 (50)					
None	111 (22)	10	1.44 (0.78–2.68)	Ref		
Cardiovascular risk factor	44 (9)	4	1.64 (0.62–4.37)	0.909	0.067	
JAK2V617F	222 (43)	30	2.36 (1.65–3.38)	0.168	0.082	
Both	136 (27)	25	4.17 (2.82–6.17)	0.011	Ref	0.005

four categories: 'very low risk' (no thrombosis history, age $\leqslant 60$ years and *JAK2*-unmutated); 'low risk' (no thrombosis history, age $\leqslant 60$ years and *JAK2*-mutated); intermediate risk' (no thrombosis history, age >60 years and *JAK2*-unmutated) and high risk (thrombosis history or age >60 years with *JAK2* mutation).

Barbui et al, Blood Cancer J 2015

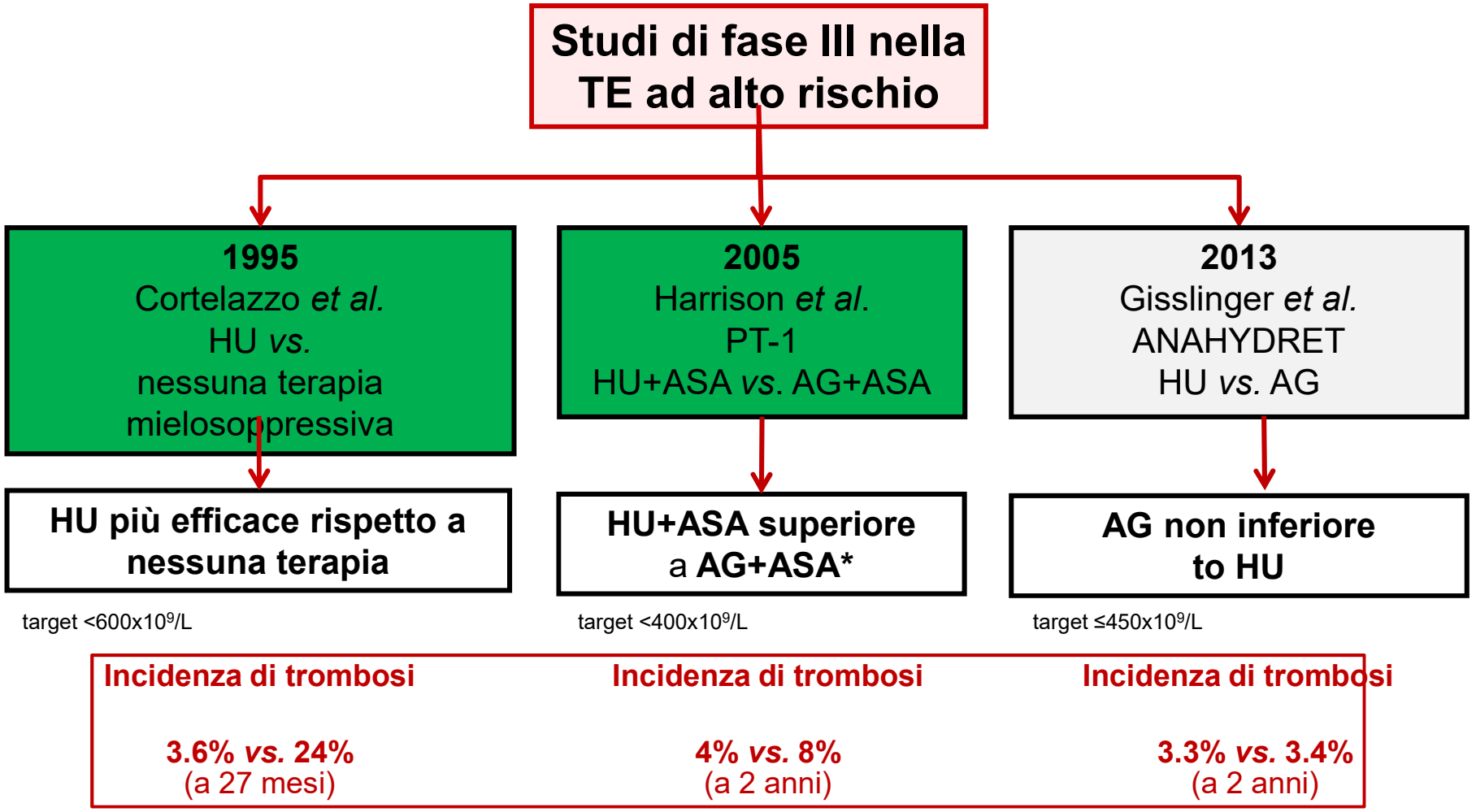
TRATTAMENTO DELLA TE

- Profilassi antitrombotica

  [primaria –secondaria]
- Citoriduzione

Profilassi antitrombotica primaria

Studi clinici prospettici randomizzati nella TE



* End point primario composito di trombosi arteriosa o venosa, emorragia maggiore, morte cardiovascolare

HU: idrossiurea
AG: anagrelide
ASA: acido acetilsalicilico

Cortelazzo *et al.* N Engl J Med 1995;332:1132
Harrison *et al.* N Engl J Med 2005;353:33
Gisslinger *et al.* Blood 2013;121:1720

HYDROXYUREA FOR PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA AND A HIGH RISK OF THROMBOSIS

SERGIO CORTELAZZO, M.D., GUIDO FINAZZI, M.D., MARCO RUGGERI, M.D., OSCAR VESTRI, M.D., MONICA GALLI, M.D., FRANCESCO RODEGHIERO, M.D., AND TIZIANO BARBUI, M.D.

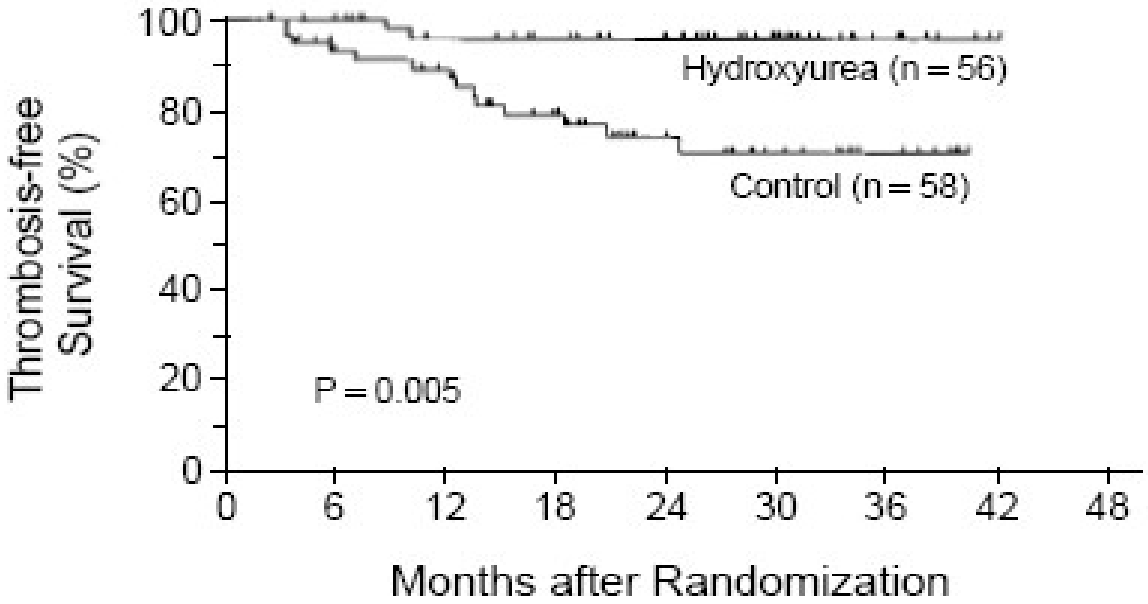
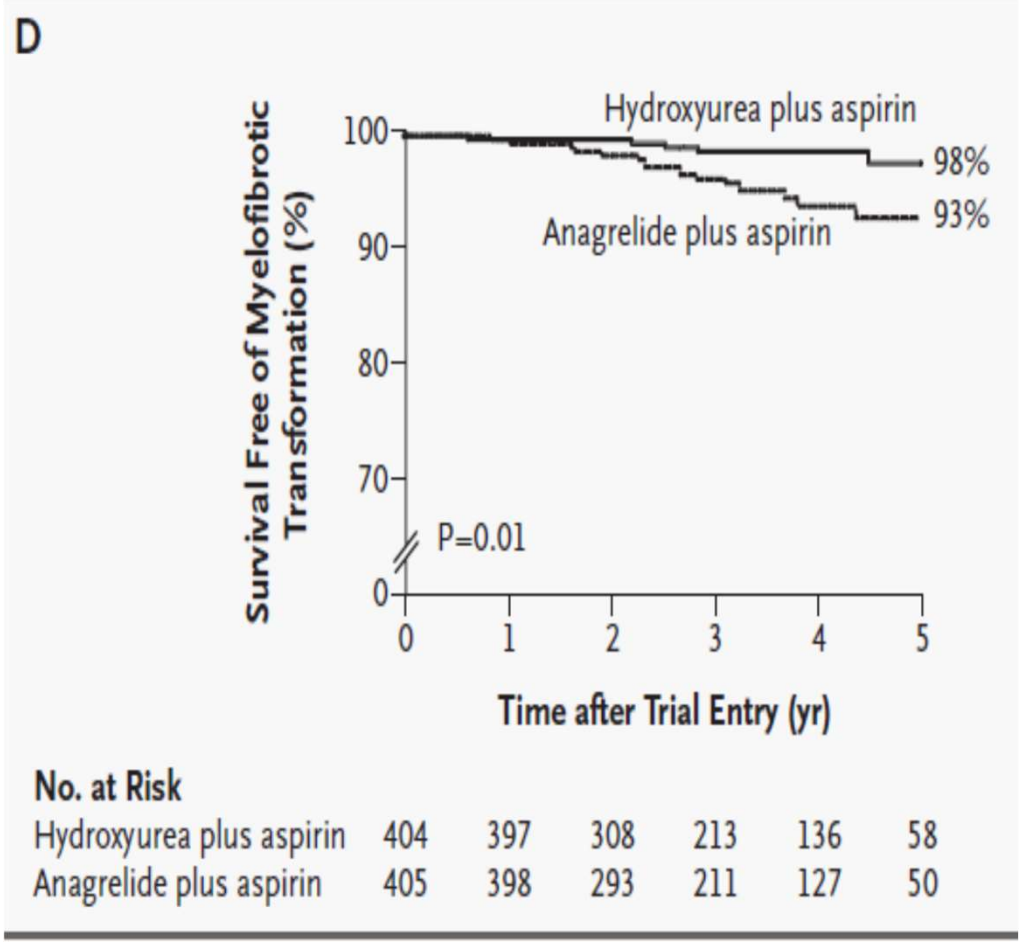
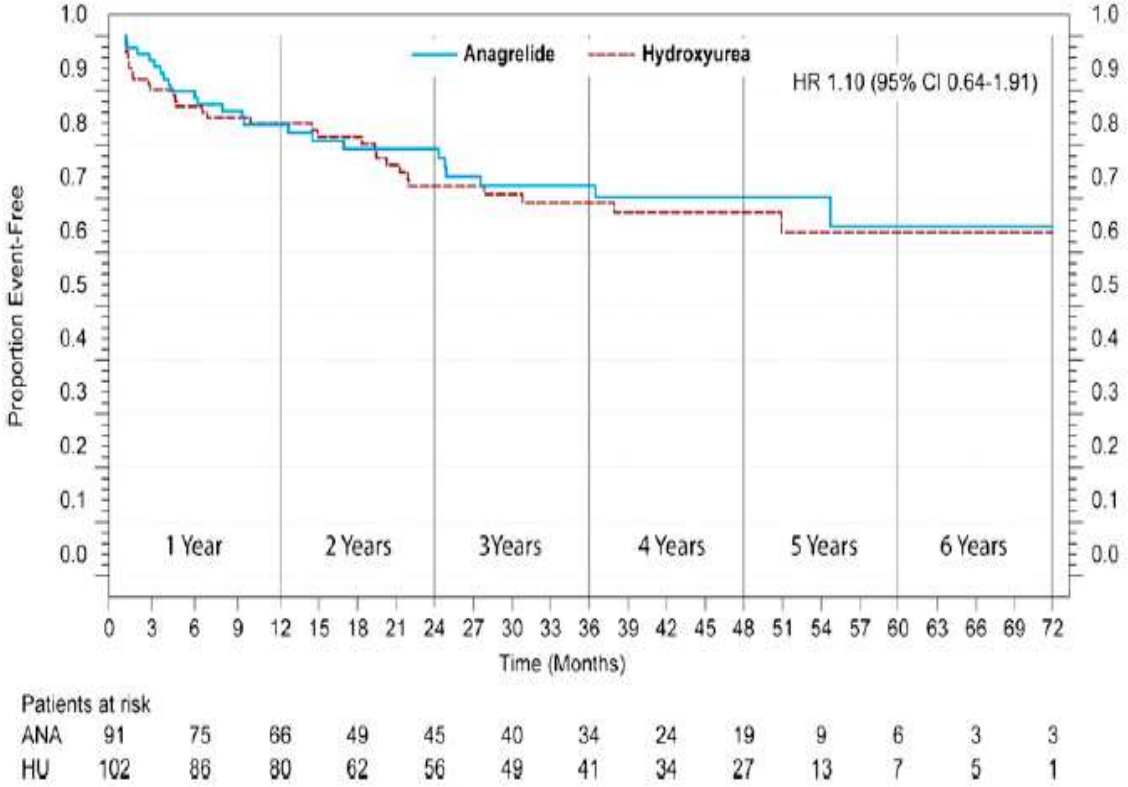


Figure 2. Probability of Thrombosis-free Survival in 114 Patients with Essential Thrombocythemia Treated with Hydroxyurea or Left Untreated.



Harrison et al, PT-1 trial, NEJM 2005



Gisslinger et al, ANAHYDRET Study, Blood 2013

Aspirina: efficacia

- A differenza che nella Policitemia, non sono disponibili studi prospettici che dimostrino in maniera controllata l'efficacia dell'aspirina nei pazienti con TE.

- In piccoli studi retrospettivi non controllati (con definizione di trombosi eterogenea, inclusiva di disturbi del microcircolo) l'ASA è stata associata a una significativa riduzione di trombosi, in particolare impiegando alti dosaggi (500 mg)

blood

2010 116: 1205-1210
Prepublished online May 27, 2010;
doi:10.1182/blood-2010-01-263319

Observation versus antiplatelet therapy as primary prophylaxis for thrombosis in low-risk essential thrombocythemia

Alberto Alvarez-Larrán, Francisco Cervantes, Arturo Pereira, Eduardo Arellano-Rodrigo, Virginia Pérez-Andreu, Juan-Carlos Hernández-Boluda, Ramón Ayats, Carlos Salvador, Ana Muntañola, Beatriz Bellosillo, Vicente Vicente, Luis Hernández-Nieto, Carmen Burgaleta, Blanca Xicoy and Carlos Besses

	Osservazione (848 pz-anno)		Antiaggreganti (802 pz-anno)		P
	Eventi	Incidenza % pz-anno	Eventi	Incidenza % pz-anno	
Trombosi	15	1.77	17	2.12	0.6
- Arteriose	8	0.94	13	1.62	0.2
- Venose	7	0.82	4	0.49	0.4
Emorragie	5	0.60	10	1.26	0.09

I pazienti JAK2 V617F-positivi senza aspirina presentano più TEV (IRR 4, 95%CI 1.2-12.9)

EUROPEAN HEMATOLOGY ASSOCIATION
Ferrata Storti Foundation

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

Alberto Alvarez-Larrán,[1] Arturo Pereira,[2] Paola Guglielmelli,[3] Juan Carlos Hernández-Boluda,[4] Eduardo Arellano-Rodrigo,[2] Francisca Ferrer-Marín,[5] Alimam Samah,[6] Martin Griesshammer,[7] Ana Kerguelen,[8] Bjorn Andreasson,[9] Carmen Burgaleta,[10] Jiri Schwarz,[11] Valentín García-Gutiérrez,[12] Rosa Ayala,[13] Pere Barba,[14] María Teresa Gómez-Casares,[15] Chiara Paoli,[3] Beatrice Drexler,[16] Sonja Zweegman,[17] Mary F. McMullin,[18] Jan Samuelsson,[19] Claire Harrison,[6] Francisco Cervantes,[20] Alessandro M. Vannucchi,[3] and Carlos Besses[1]

Haematologica 2016
Volume 101(8):926-931

433 pazienti (2215 pz-anno)	Osservazione (908 pz-anno) n= 80		Antiaggreganti (1307 pz-anno) n=353		P
	Eventi	Incidenza % pz-anno	Eventi	Incidenza % pz-anno	
Trombosi	11	1.21	14	1.07	0.7
- Arteriose	4	0.44	10	0.76	0.3
- Venose	7	0.77	4	0.31	0.1
Emorragie	4	0.46	13	0.99	0.2

bjh research paper

Cytoreduction plus low-dose aspirin *versus* cytoreduction alone as primary prophylaxis of thrombosis in patients with high-risk essential thrombocythaemia: an observational study

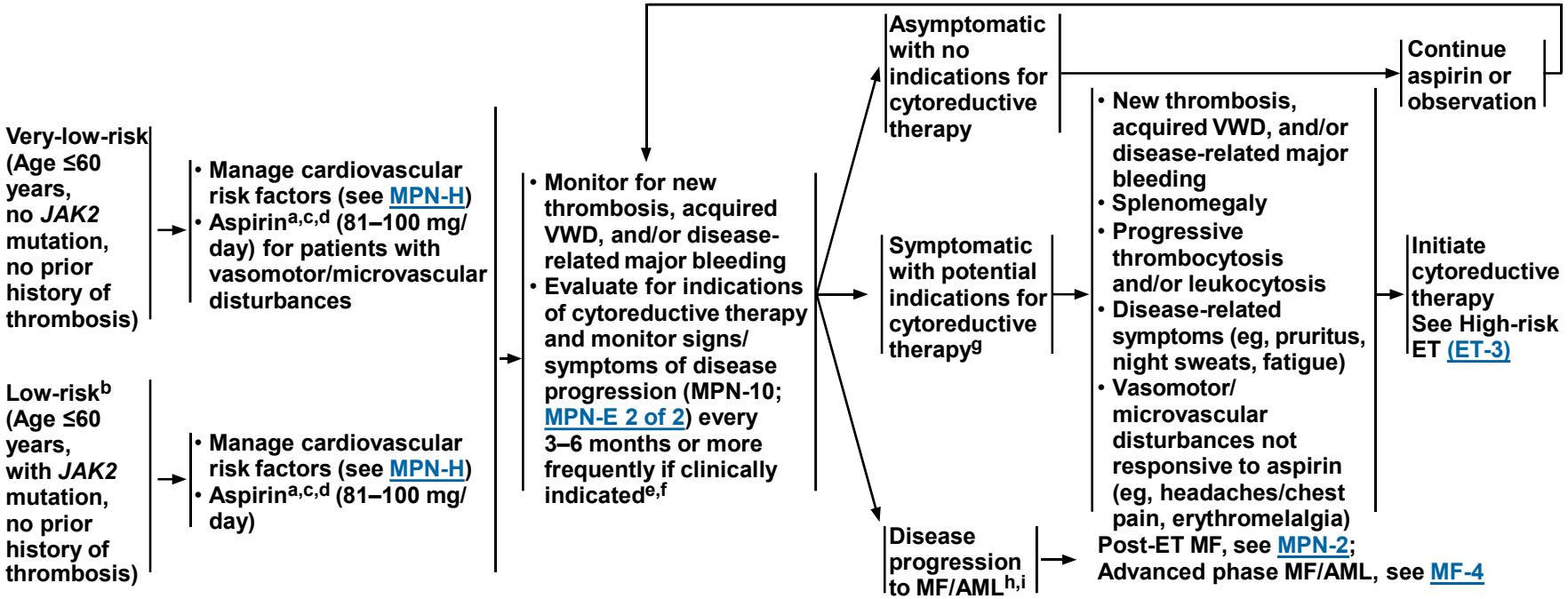
Alberto Alvarez-Larrán,[1] Arturo Pereira,[2] Eduardo Arellano-Rodrigo,[2] Juan-Carlos Hernández-Boluda,[3] Francisco Cervantes[4] and Carlos Besses[1]

2013

247 pazienti (193 > 60 anni)	**Citoriduzione (685 pz-anno) n= 79**		**Citoriduzione + aspirina (763 pz-anno) n=168**		**P**
	Eventi	Incidenza % pz-anno	Eventi	Incidenza % pz-anno	
Trombosi	17	2.48	11	1.44	0.2
Emorragie	1	0.14	11	1.44	0.006
Trombosi >60 anni	14	2.92	5	0.86	0.02
Emorragie > 60 anni	1	0.21	8	1.37	0.04

I pazienti JAK2 V617F-positivi in citoriduzione senza aspirina presentano più TEV (IRR 2.3, 95%CI 1.0-5.4)

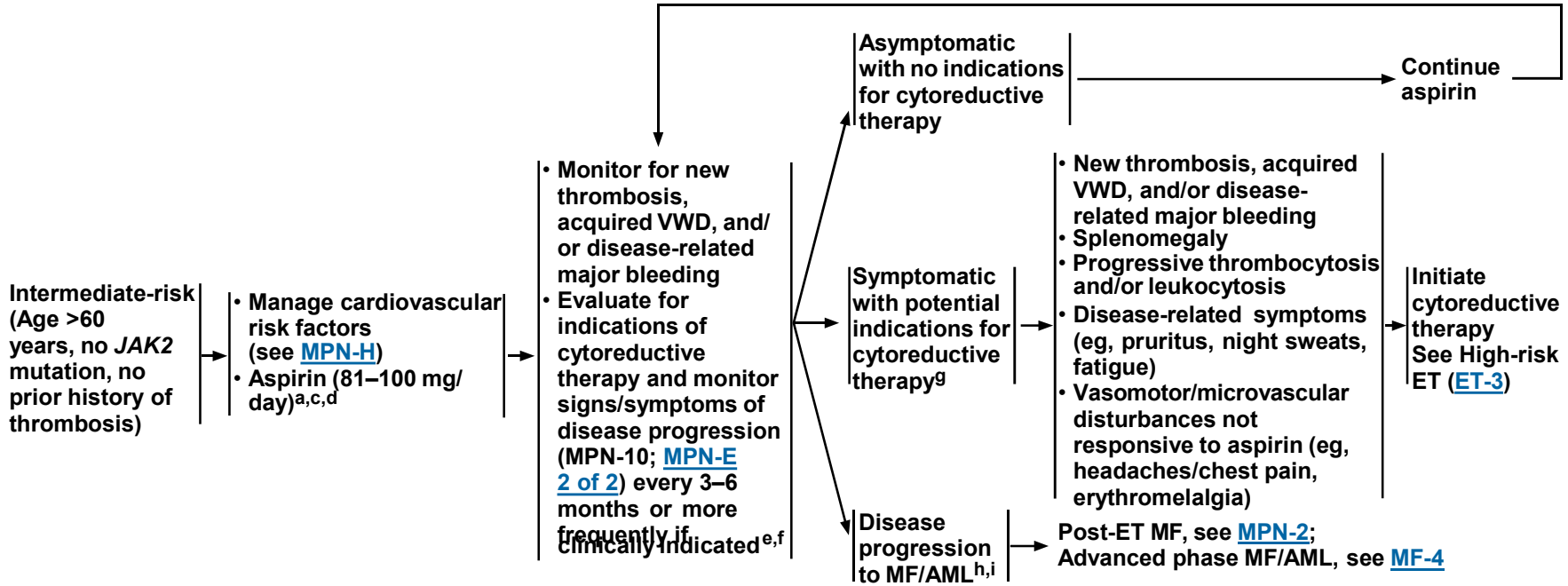
TREATMENT FOR VERY-LOW-RISK OR LOW-RISK ESSENTIAL THROMBOCYTHEMIA[a]



[a] See Special Considerations in the Treatment of PV and ET (MPN-H).
[b] Harrison CN, et al. N Engl J Med 2005;353:33-45.
[c] Aspirin should be used with caution in patients with acquired VWD. Higher-dose aspirin may be appropriate in selected patients as clinically indicated. The risks and benefits of higher-dose aspirin (>100 mg) must be weighed based on the presence of vasomotor symptoms versus the risk of bleeding.
[d] Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG, et al. Thromb Res 2012;129:91-94; Pascale S, et al. Blood 2012;119:3595-3603).
[e] See Supportive Care for Patients with MPN (MPN-F).
[f] Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[h] Diagnostic criteria for post-ET or post-PV MF. See (MPN-B).
[i] The WHO classification defines acute leukemia as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

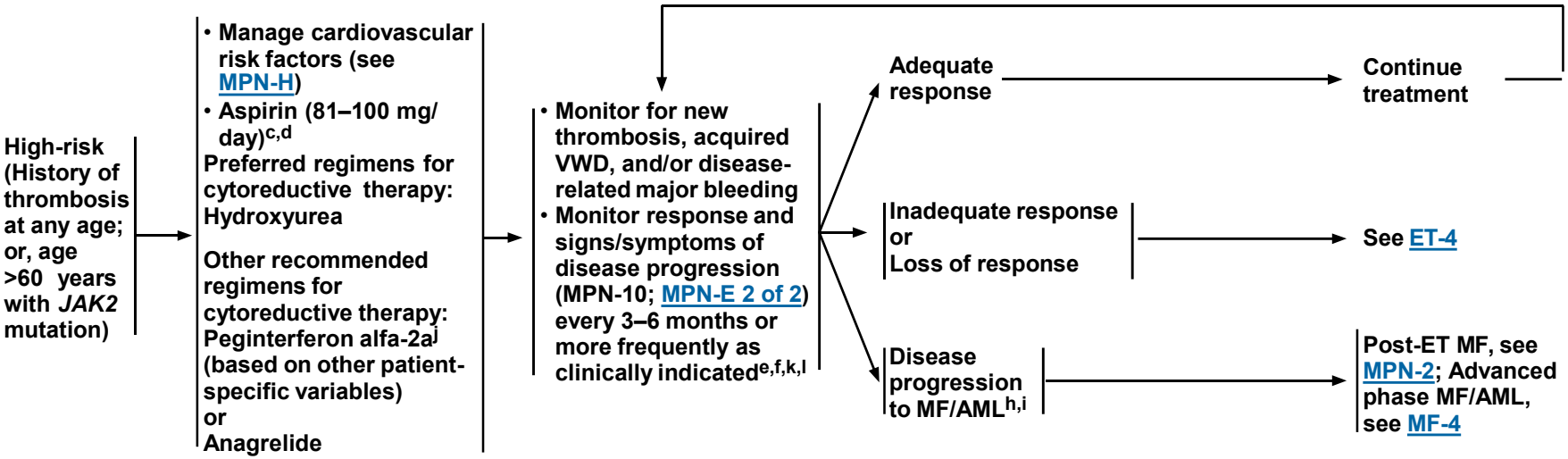
TREATMENT FOR INTERMEDIATE-RISK ESSENTIAL THROMBOCYTHEMIA[a]



[a] See Special Considerations in the Treatment of PV and ET (MPN-H).
[c] Aspirin should be used with caution in patients with acquired VWD. Higher-dose aspirin may be appropriate in selected patients as clinically indicated. The risks and benefits of higher-dose aspirin (>100 mg) must be weighed based on the presence of vasomotor symptoms versus the risk of bleeding.
[d] Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG, et al. Thromb Res 2012;129:91-94; Pascale S, et al. Blood 2012;119:3595-3603).
[e] See Supportive Care for Patients with MPN (MPN-F).
[f] Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[h] Diagnostic criteria for post-ET or post-PV MF. See (MPN-B).
[i] The WHO classification defines acute leukemia as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT FOR HIGH-RISK ESSENTIAL THROMBOCYTHEMIA[a]



[a] See Special Considerations in the Treatment of PV and ET (MPN-H).

[c] Aspirin should be used with caution in patients with acquired VWD. Higher-dose aspirin may be appropriate in selected patients as clinically indicated. The risks and benefits of higher-dose aspirin must be weighed based on the presence of vasomotor symptoms versus the risk of bleeding.

[d] Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG, et al. Thromb Res 2012;129:91-94; Pascale S, et al. Blood 2012;119:3595-3603).

[e] See Supportive Care for Patients with MPN (MPN-F).

[f] Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.

[h] Diagnostic criteria for post-ET or post-PV MF. See (MPN-B).

[i] The WHO classification defines acute leukemia as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

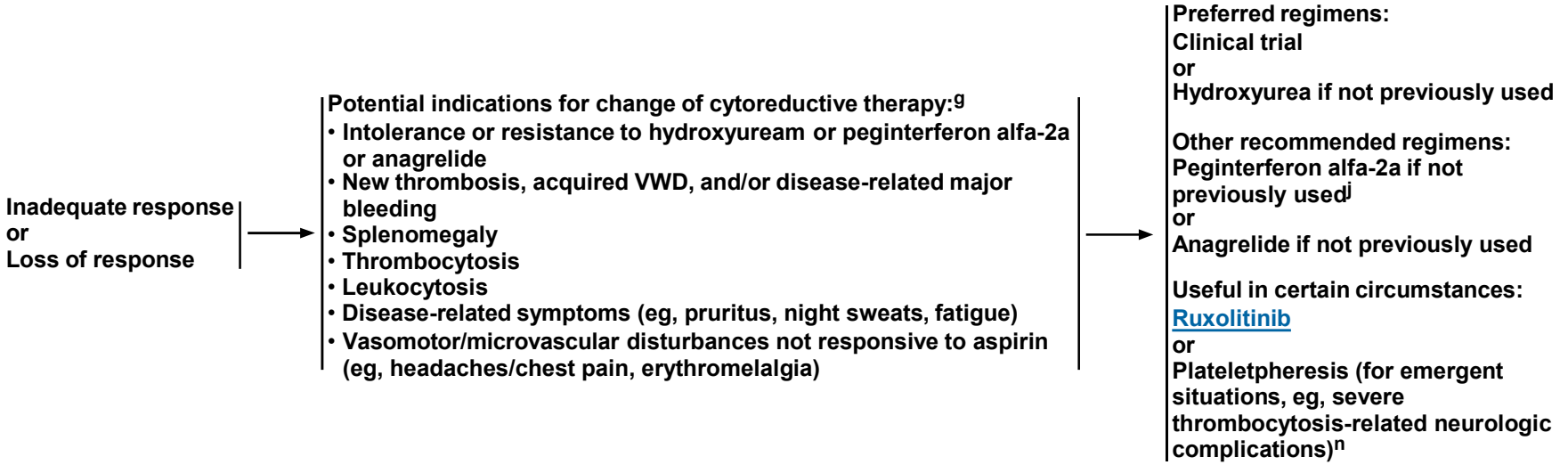
[j] Peginterferon alfa-2a can be considered for younger patients or in pregnant patients in need of cytoreductive therapy or in those in need of cytoreductive therapy who defer hydroxyurea.

[k] See 2013 IWG-MRT and ELN Response Criteria for ET (ET-A). These response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the IWG-MRT Response Criteria. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.

[l] While normalization of blood counts after initiation of treatment is usually a goal in clinical practice, it is not associated with long-term clinical benefit and there are no evidence-based data to recommend a target WBC or platelet count for patients receiving cytoreductive therapy. In selected patients with a severe thrombotic event or other disease-related symptoms, normalization of blood counts might be an essential goal of treatment.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT FOR HIGH-RISK ESSENTIAL THROMBOCYTHEMIA[a]



[a] See Special Considerations in the Treatment of PV and ET (MPN-H).
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[j] Peginterferon alfa-2a can be considered for younger patients or in pregnant patients in need of cytoreductive therapy or in those in need of cytoreductive therapy who defer hydroxyurea.
[m] Definition of intolerance/resistance to hydroxyurea (MPN-I).
[n] Padmanabhan A, et al. J Clin Apher 2019;34:171-354.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

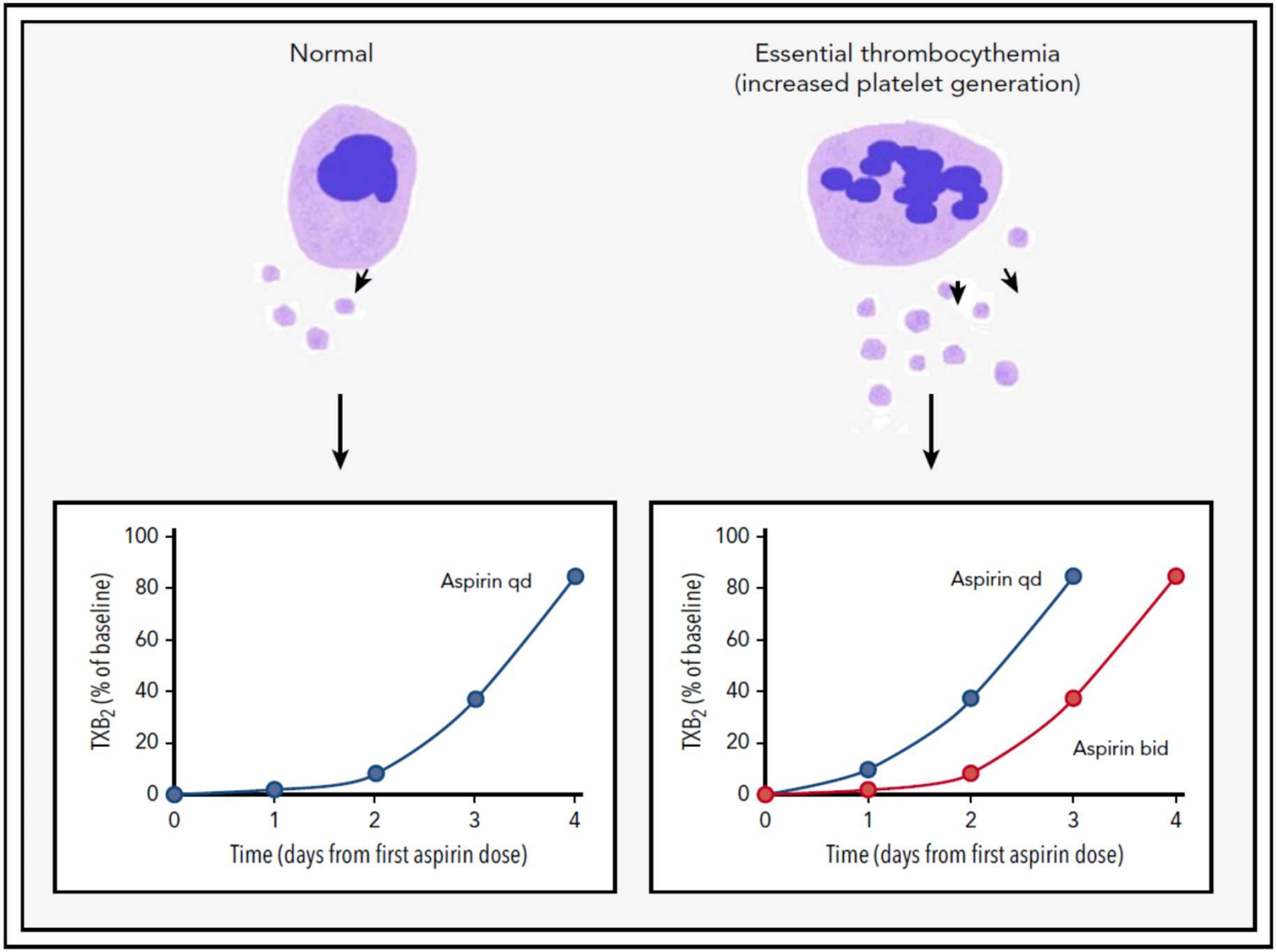
	Primary prophylaxis
Polycythemia vera	Phlebotomy (HCT < 0.45) (all patients) Hydroxyurea (age > 60 years) Low-dose aspirin (all patients)
Essential thrombocythemia	Hydroxyurea (age > 60 years) Consider anagrelide (especially age < 40 years) Low-dose aspirin (age > 60 years, CVRF, JAK2*V617F*)

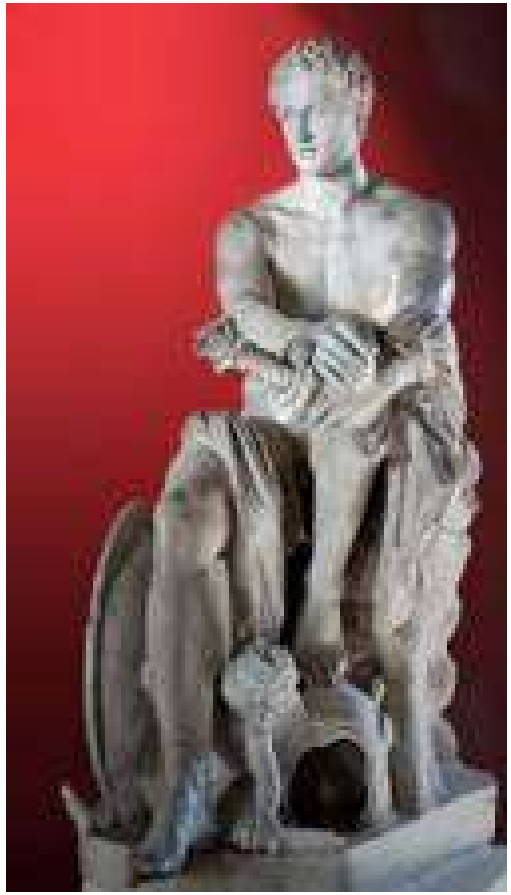
Barbui & De Stefano, Curr Opin Hematol 2016

Una significativa incidenza di eventi trombotici (1-2 % pazienti-anno) avviene nonostante l'assunzione di aspirina.

In soggetti sani ASA 100 mg al giorno inibisce il 99% di trombossano B2 sierico (indice della sintesi di trombossano A2) , mentre in soggetti con TE inibisce solo parzialmente la COX-1 piastrinica.

Nella TE una somministrazione due volte al giorno è più efficace nel ridurre il trombossano B2 sierico.


Normal
Essential thrombocythemia
(increased platelet generation)
100
80
60
40
20
0
TXB2 (% of baseline)
Aspirin qd
0
1
2
3
4
Time (days from first aspirin dose)
100
80
60
40
20
0
TXB2 (% of baseline)
Aspirin qd
Aspirin bid
0
1
2
3
4
Time (days from first aspirin dose)



Aspirin Regimens in ESsential thrombocythemia

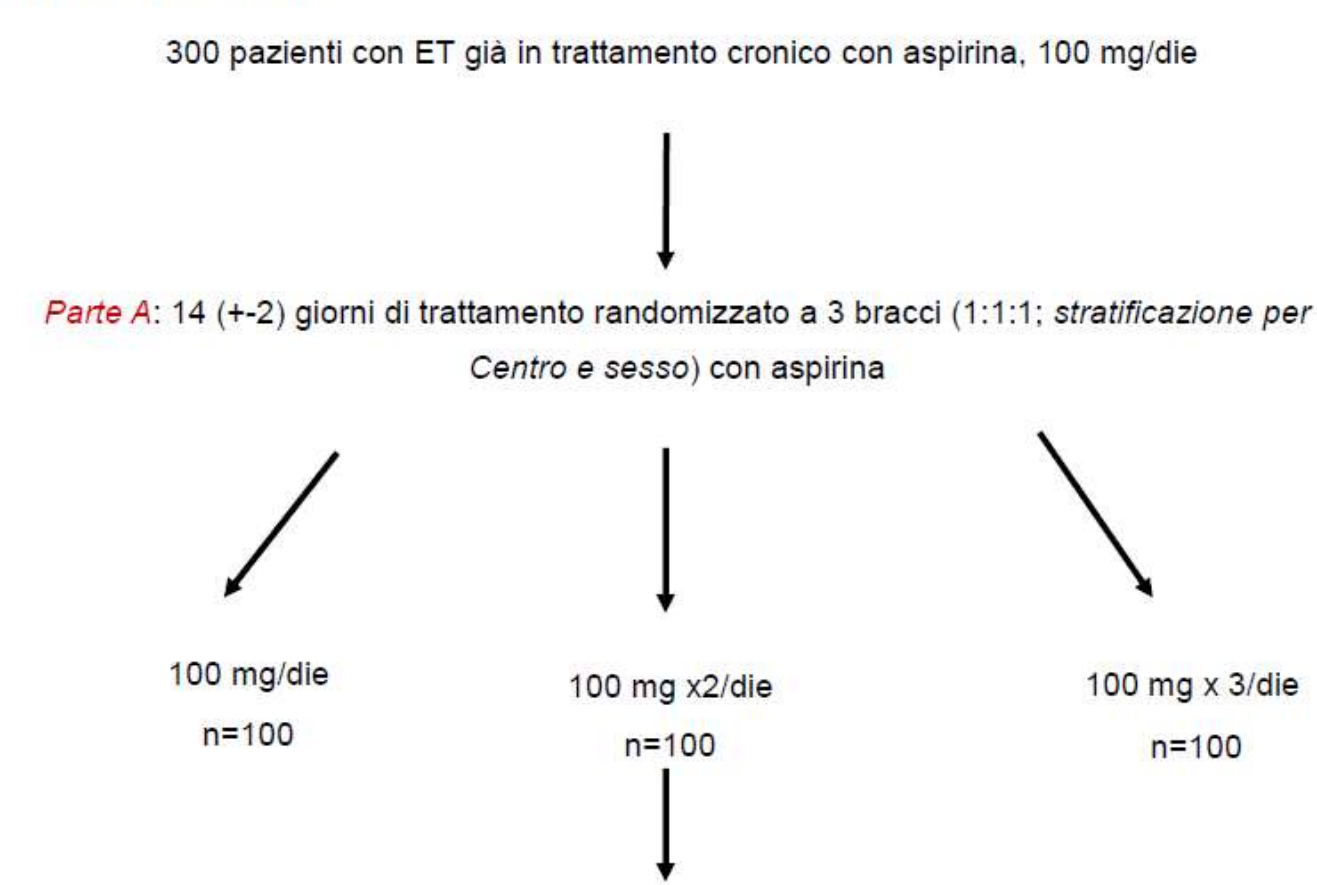
ARES Study

Sinossi in lingua Italiana

Versione 1.0 del 27 giugno 2016

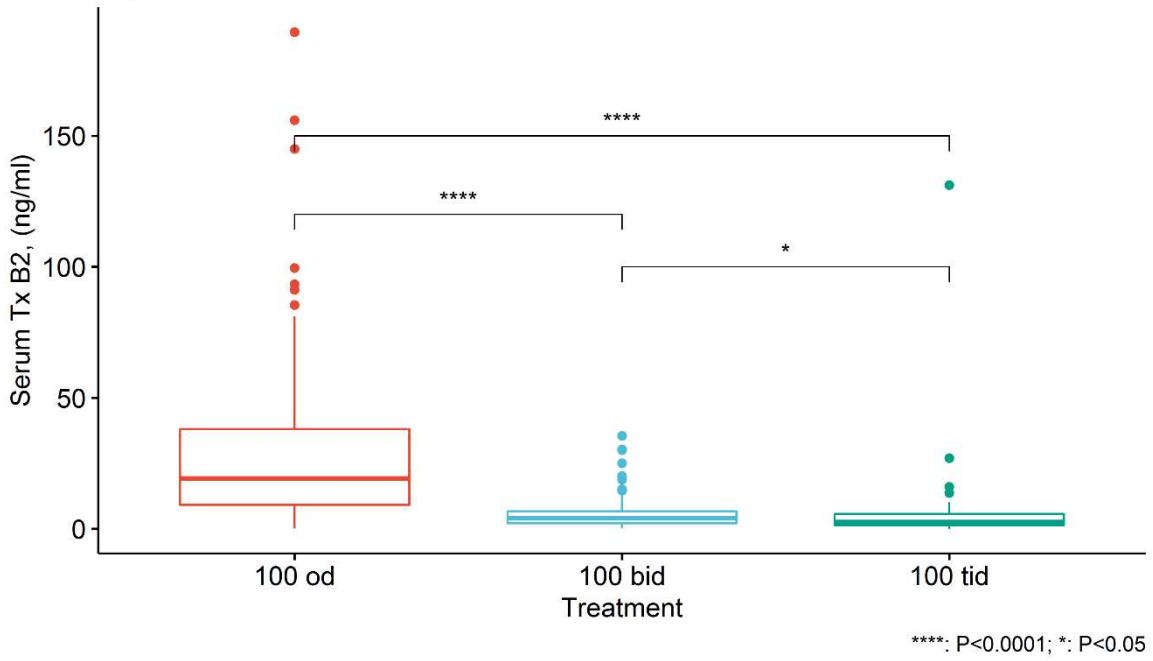
Promotore	Area di Ematologia, Università Cattolica del Sacro Cuore, Fondazione Policlinico Universitario Agostino Gemelli, Roma.
Fornitore del farmaco	Bayer S.p.A Divisione Pharmaceuticals - Viale Certosa, Milano
Finanziamento	AIFA – Agenzia Italiana del Farmaco bando ricerca indipendente anno 2012 (studio n. FARM12Y8HH)
Nome del farmaco in studio	Cardioaspirin
Nome del principio attivo	Acido acetilsalicilico
Titolo dello studio	Nuove strategie di profilassi antitrombotica in pazienti con Trombocitemia Essenziale (TE): valutazione di differenti regimi posologici di acido acetilsalicilico a basse dosi.
Acronimo dello Studio (data e versione sinossi)	Aspirin Regimens in ESsential thrombocythemia ARES Study (Versione 1.0, 27/06/2016)

Schema dello Studio



Results – TxB2 by treatment group

analysis of the 240 enrolled patients at July 30 2018



blood®
Regular Article

CLINICAL TRIALS AND OBSERVATIONS

A randomized double-blind trial of 3 aspirin regimens to optimize antiplatelet therapy in essential thrombocythemia

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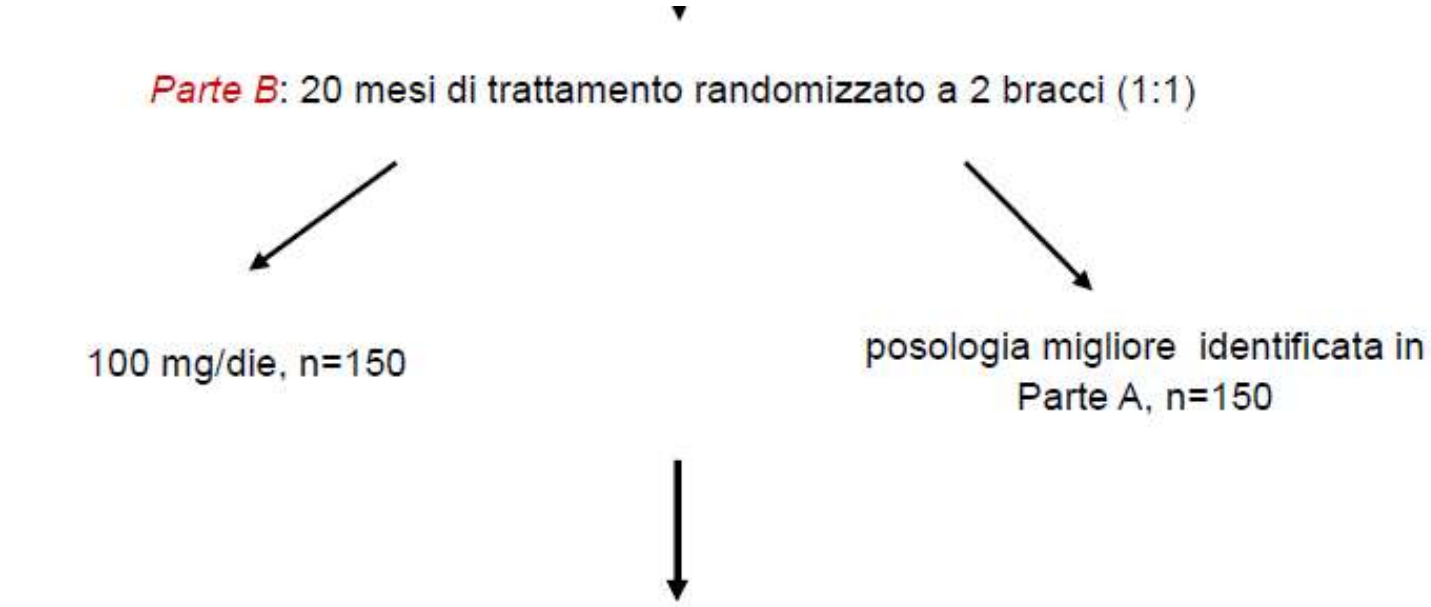
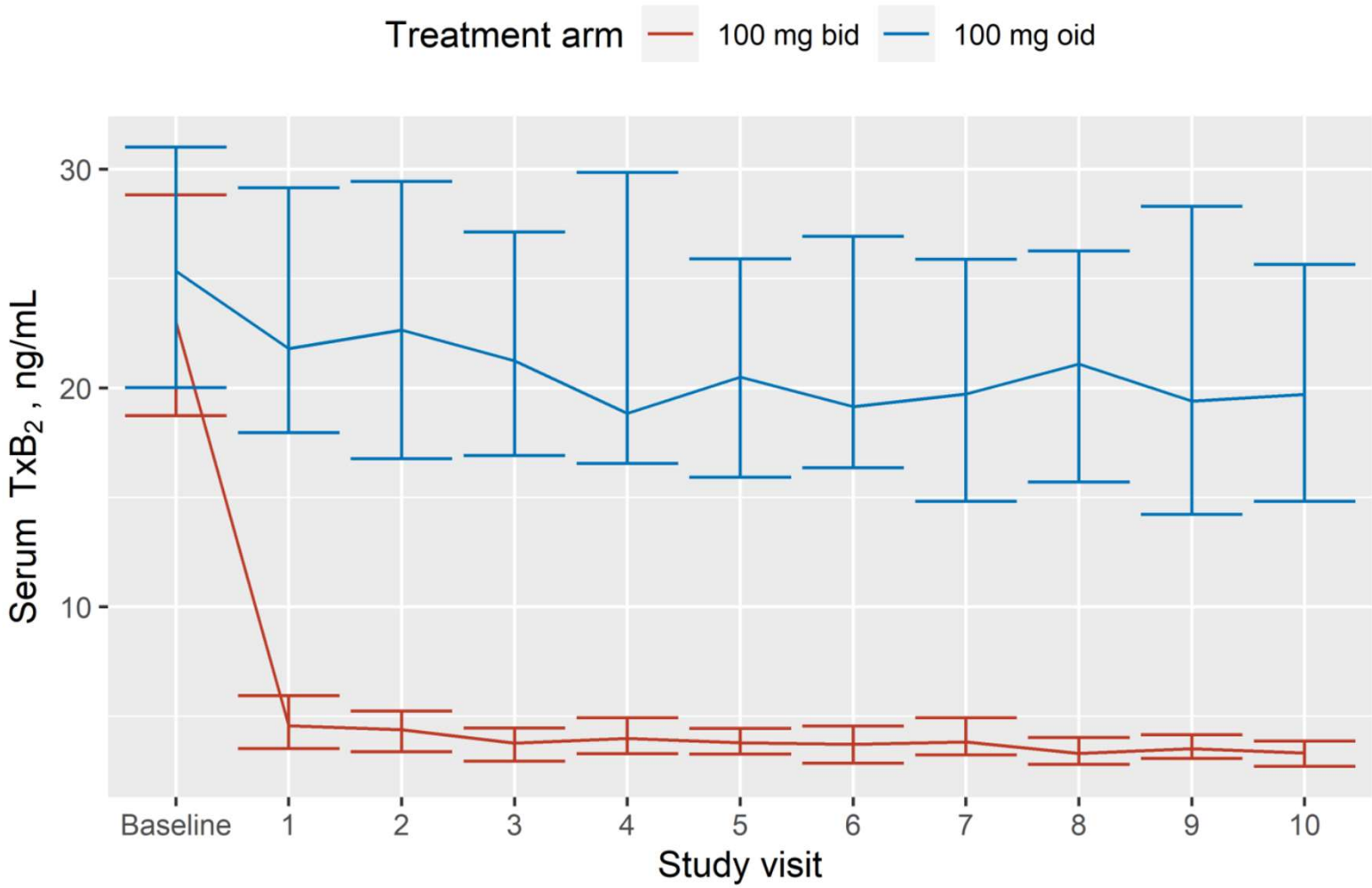

Parte B: 20 mesi di trattamento randomizzato a 2 bracci (1:1)
100 mg/die, n=150
posologia migliore identificata in Parte A, n=150
Misurare TXB_2 sierico ogni 3 mesi per verificare la persistenza della superiore efficacia biochimica del regime posologico sperimentale vs quello standard


Treatment arm
100 mg bid
100 mg oid
Serum TxB2 , ng/mL
30
20
10
Baseline
1
2
3
4
5
6
7
8
9
10
Study visit

La dimostrata superiore efficacia biochimica del regime ASA x 2 non implica automaticamente che vi sia una superiore efficacia nel prevenire trombosi.

Per dimostrare questo punto occorrono studi mirati a questo scopo.

ASA x 2 riduce in maniera significativa i disturbi severi del microcircolo

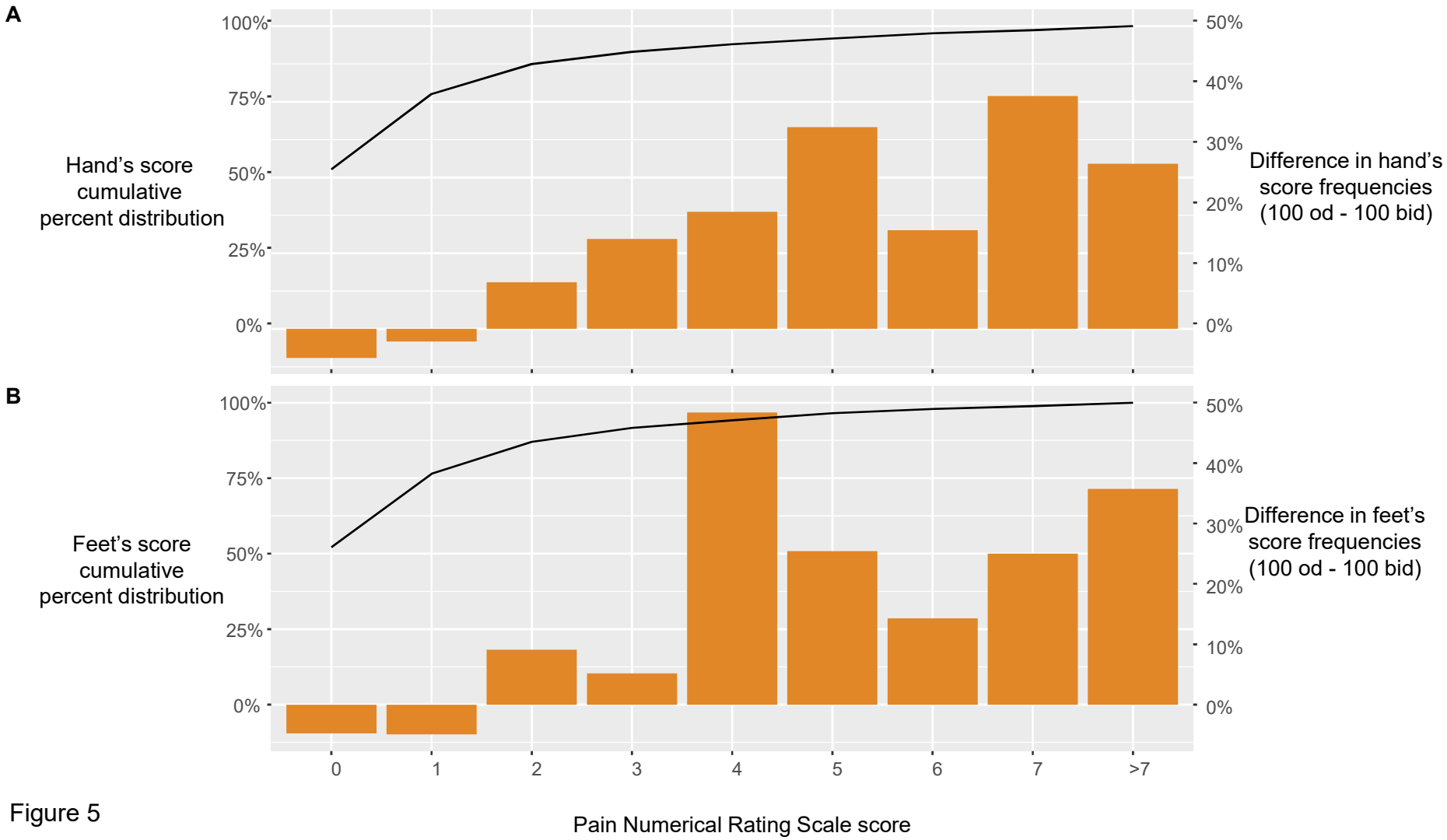


Figure 5

Profilassi antitrombotica secondaria

ELN-WP9 project
Ricorrenze trombotiche in MPN. Analisi di 1032 eventi indice

Index event	No. Centers	Design	No. Pats
Trombosi venosa cerebrale *Martinelli et al, Am J Hematol 2014*	11	**Studio caso-controllo** • Casi: MPN con TVC • Controlli: MPN con TV degli arti	135 48 87
Trombosi venosa profonda *De Stefano et al, Leukemia 2016* Trombosi venosa splancnica *De Stefano et al, Blood Cancer J 2016*	23	**Studio retrospettivo di coorte** **Studio retrospettivo di coorte**	206 181
Trombosi arteriosa cerebrale *De Stefano et al, Blood Cancer J 2018*	22	**Studio retrospettivo di coorte** • TIA • Stroke ischemico	597 270 327

Tipo di trombosi – N (%)	436 (100)
Trombosi venosa	212 (49)
TVP arti inferiori	119 (27)
TVP arti inferiori + embolia polmonare	42 (10)
Embolia polmonare	45 (10)
Totale episodi maggiori di trombosi venosa	206 (47)
TVP arti superiori	4 (1)
Trombosi vena giugulare	2 (0.5)
Circolo venoso splancnico	181 (41)
Trombosi vene epatiche	31 (7)
Trombosi venosa portale	109 (25)
Trombosi vemnosa mesenterica	18 (4)
Trombosi venosa splenica	23 (5)
Altre trombosi venose	43 (10)
Trombosi venosa cerebrale	35 (8)
Trombosi venosa retinica	8 (2)

On focus

De Stefano et al, Leukemia 2016

	Totale (%)	Citoriduzione #	
		Yes	No
VKA	136 (66.5)	125 (69.1)	11 (44.0)
VKA + aspirina	19 (9.2)	17 (9.4)	2 (8.0)
Aspirina	11 (5.3)	9 (5.0)	2 (8.0)
Eparina	19 (9.2)	14 (7.7)	5 (20.0)
DOACs	7 (3.3)	7 (3.9)	0 (0.0)
Nessun trattamento antitrombotico	14 (6.5)	9 (5.0)	5 (20.0)
Total (%)	206 (100)	181	25

De Stefano et al, Leukemia 2016

	Eventi, n (%)	Incidenza % anni-pz. (95% C.I.)
Eventi trombotici	45 (21.8)	6.5 (4.7-8.7)
Trombosi venosa	36 (17.5)	5.2 (3.6-7.2)
TVP +/- embolia polmonare **Trombosi venosa splancnica** **Trombosi venosa cerebrale** **Trombosi venosa superficiale** **Non specificato**	25 (12.1) 3 (1.5) 0 (0.0) 3 (1.5) 5 (2.4)	
Trombosi arteriosa	9 (4.4)	1.3 (0.6-2.4)
Eventi emorragici maggiori	12 (5.8)	1.7 (0.9-3.0)

De Stefano et al, Leukemia 2016

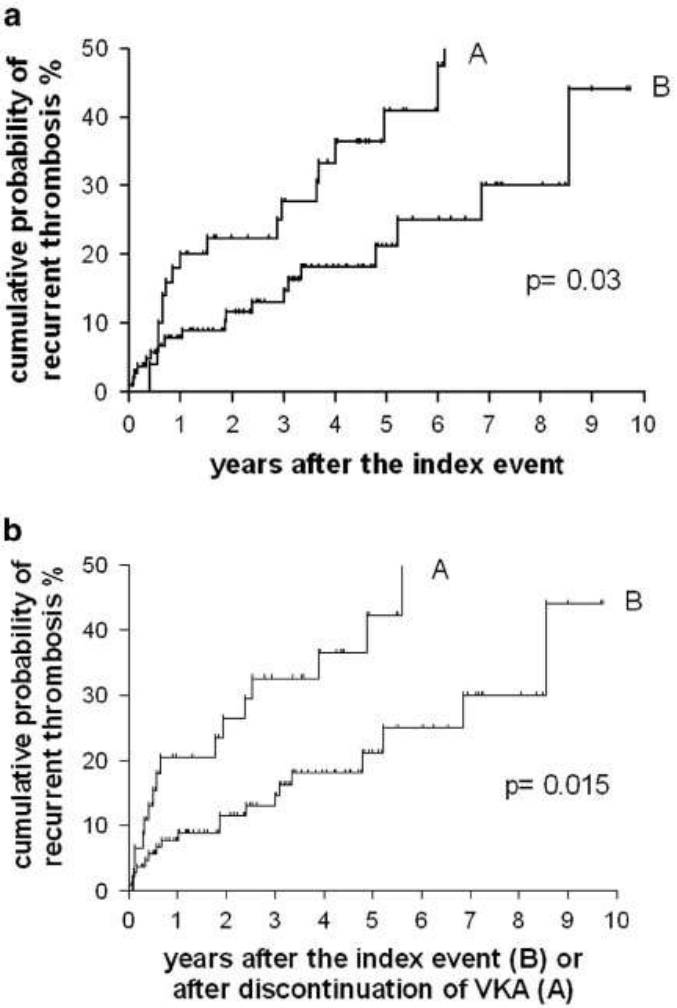
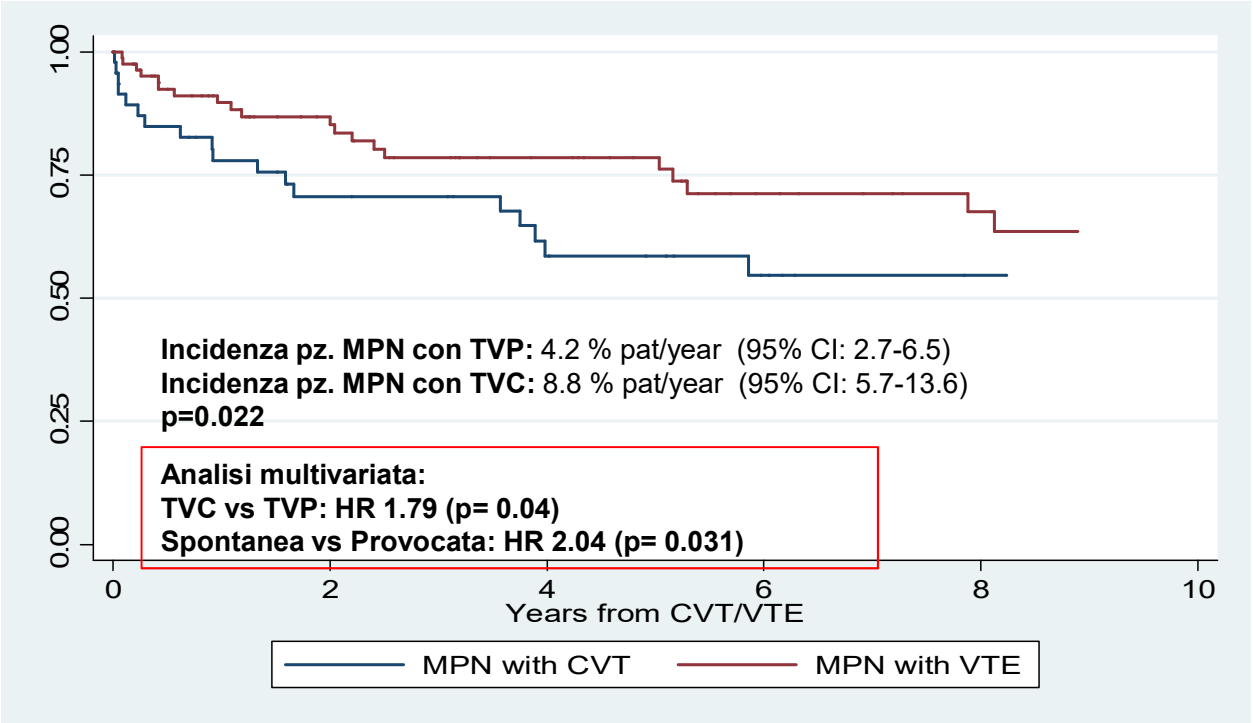


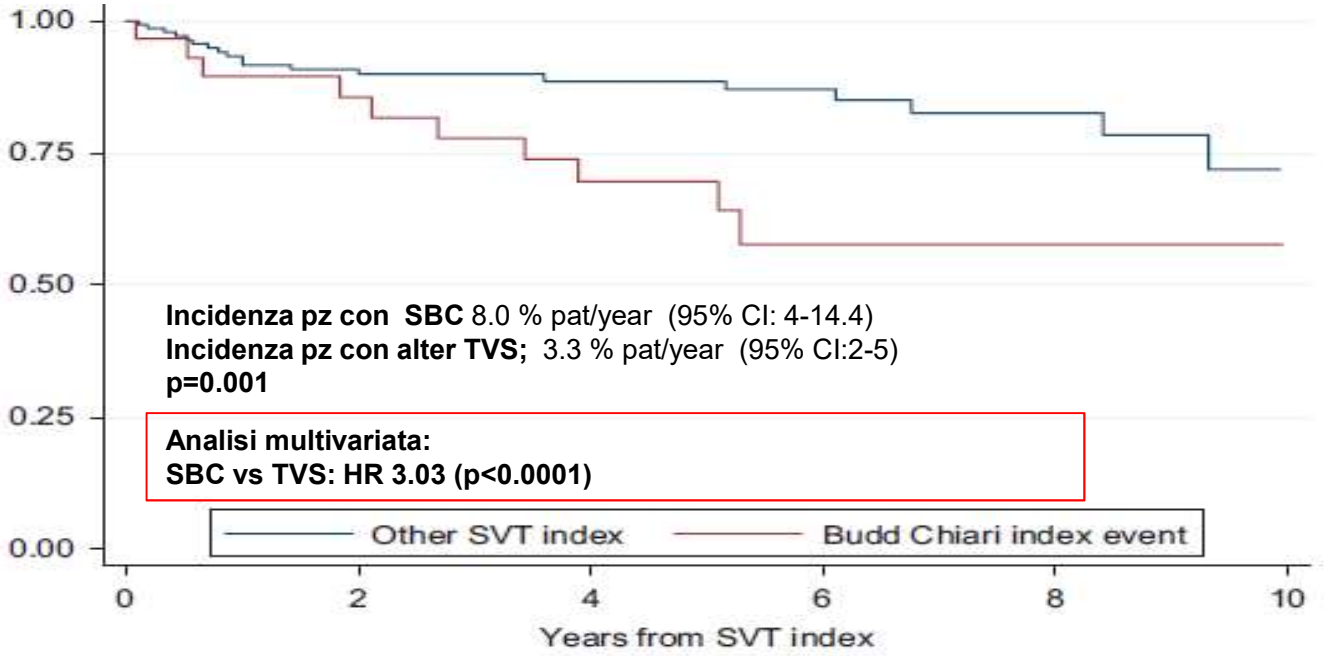
Figure 2. Cumulative probability of recurrent thrombosis in patients who discontinued VKA after index thrombosis (curve A) or did not (curve B). Analysis by intention-to-treat (**a**) and by treatment (**b**).

De Stefano et al, Leukemia 2016

Il sito della prima trombosi può influenzare il tasso di ricorrenza.
Maggiore incidenza nelle trombosi venose cerebrali versus trombosi venose degli arti.



Il sito della prima trombosi può influenzare il tasso di ricorrenza.
Maggiore incidenza nelle S. Budd-Chiari versus altre trombosi venose splancniche.



Barbui T, De Stefano V, Carobbio A et al

Direct Oral Anticoagulants for Myeloproliferative Neoplasms (MPN-DOACs): results from an international study on 442 patients

Leukemia 2021

442 MPN receiving DOACs * :

PV 178 ET 172 PMF 92

Rivaroxaban 187 Apixaban 157 Dabigatran 50 Edoxaban 48

***AF on primary / secondary prophylaxis 203**

Previous VTE 239

Incidence rate of thrombosis per 100 pt-years				
	VKA		DOACs	
	Non-MPN	MPN	Non-MPN	MPN
AF (primary prophylaxis)	1.2 – 1.8	2.7 (PV)	1.0 - 1.4	1.5
AF (secondary prophylaxis)	2.7 – 3.2		2.0 – 2.8	4.6
VTE (recurrent thromboses)		5.3		4.5
VTE (recurrent VTE) [treatment less/more than 3 months]	3.3 / 3.7	4.2	3.7 / 1.5	3.4

Incidence rate of major bleeding per 100 pt-years				
	VKA		DOACs	
	Non-MPN	MPN	Non-MPN	MPN
AF (overall)	2.4 – 3.4	2.7 (PV)	1.6 – 3.1	3.0
VTE (secondary prophylaxis) [treatment less/more than 3 months]	3.1 / 1.6	1.7	1.8 / 0.6	2.3

Atrial Fibrillation:

Connolly SJ et al, Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139.

Granger CB et al, Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365(11):981.

Hankey GJ et al, Rivaroxaban compared with warfarin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a subgroup analysis of ROCKET AF. Lancet Neurol. 2012 Apr;11(4):315-22.

Giugliano RP et al, Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013;369(22):2093.

Lip GYH et al. Antithrombotic Therapy for Atrial Fibrillation: CHEST Guideline and Expert Panel Report. Chest. 2018 Nov;154(5):1121-1201.

de Freitas AS, Alvarez-Larrán A. Risk of thrombosis and hemorrhage in patients with polycythemia vera and atrial fibrillation treated with prophylactic oral anticoagulants. Ann Hematol. 2016;95(11):1903-4.

Venous Thromboembolism:

Wu C et al. Case fatality of bleeding and recurrent venous thromboembolism during, initial therapy with direct oral anticoagulants: a systematic review. Thromb Res. 2014;134(3):627-32.

Wu C et al. Case-fatality of recurrent venous thromboembolism and major bleeding associated with aspirin, warfarin, and direct oral anticoagulants for secondary prevention. Thromb Res. 2015;135(2):243-8.

De Stefano V et al. High rate of recurrent venous thromboembolism in patients with myeloproliferative neoplasms and effect of prophylaxis with vitamin K antagonists. Leukemia. 2016;30(10):2032-2038.

Secondary prophylaxis after VTE
Phlebotomy (HCT < 0.45) (all patients)
Hydroxyurea (all patients)
Indefinite VKA treatment (especially patients with CVT and BCS)
Low-dose aspirin (selected patients after 6 months of treatment with VKA)

Polycythemia Vera

Hydroxyurea (all patients)
Consider anagrelide (especially age < 40 years)
Indefinite VKA treatment (especially patients with CVT and BCS)
Low-dose aspirin (selected patients after 6 months of treatment with VKA)

Essential Thrombocythemia

Barbui & De Stefano, Curr Opin Hematol 2016

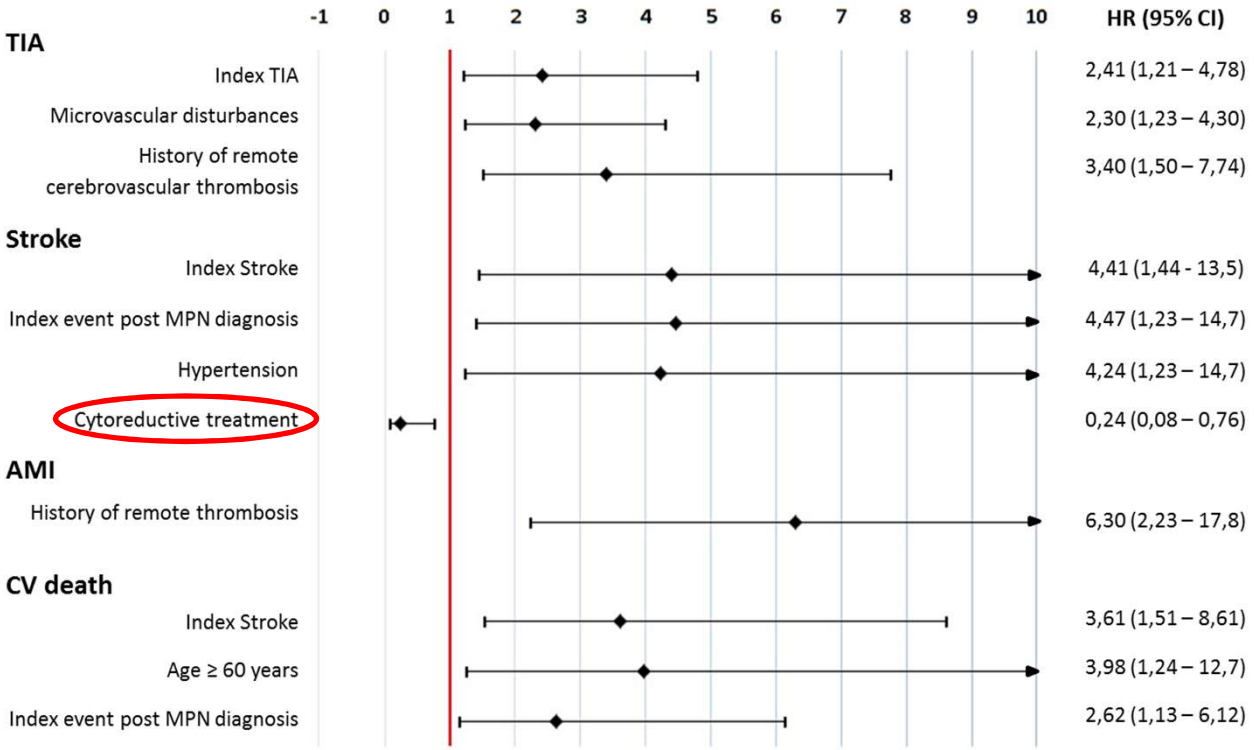
ELN-WP9 project
Thrombosis recurrences in MPN.
Analysis of 1032 index events

Index event	No. Centers	Design	No. Pts
Cerebral vein thrombosis *Martinelli et al, Am J Hematol 2014*	11	**Case-control study** • Cases: MPN with CVT • Controls: MPN and DVT	135 48 87
Deep vein thrombosis *De Stefano et al, Leukemia 2016* Splanchnic vein thrombosis *De Stefano et al, Blood Cancer J 2016*	23	**Retrospective cohort study** **Retrospective cohort study**	206 181
Cerebral arterial thrombosis *De Stefano et al, Blood Cancer J 2018*	22	**Retrospective cohort study** • TIA or • Ischemic Stroke	597 270 327

	Strokes dopo 1 anno	Strokes dopo 5 anni
Dopo TIA		
-studio PRISM	0	1.2 %
-popolazione generale *	4.4 – 5.1 %	12 – 13.2 %
Dopo Stroke ischemico		
-studio PRISM	2.0 %	6.5 %
-popolazione generale *	11.1 – 12 %	26.4 %

** References:*

Van WijK I et al, Lancet 2005;365:2098
Weimar C et al, J Neurol 2009;256:639
Mohan KM et al, Stroke 2011;42:1489
Amarenco P et al, N Engl J Med 2016;374:1533
Bergstrom L et al, Stroke 2017;48:2046



De Stefano V et al, Blood Cancer Journal 2018; 8: 25

Conclusioni

- Il tasso di trombosi nella TE è 1-3 per 100 pazienti-anno; dopo un primo evento il tasso di ricorrenza è 5-6 per 100 pazienti-anno.

- La prevenzione primaria con aspirina è indicata nei soggetti con età >60 anni e/o fattori di rischio cardiovascolari e/o presenza JAK2 V617F

- Dopo un evento trombotico venoso spontaneo (in particolare in sede cerebrale o addominale) è indicato un trattamento con anticoagulanti orali a tempo indeterminato. In linea di massima il trattamento va effettuato con anti-vitamina K (Coumadin o Sintrom); i dati su efficacia e sicurezza dei nuovi anticoagulanti diretti nei pazienti con MPN sembrano comparabili.

- Dopo un evento trombotico arterioso è indicato un trattamento con antiaggreganti secondo pratica corrente (mono o duplice antiaggregazione o anticoagulazione orale in caso di FA); è molto importante l'aggiunta di citoriduzione.