Anticoagulación en las neoplasias mieloproliferativas

♣

Eduardo Arellano Rodrigo

Servicio de Hemoterapia y Hemostasia

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Frequency of major thrombosis in myeloproliferative neoplasms (MPNs)

MPNs type and study	Events at diagnosis			Events during follow-up			Annual incidence of thrombosis (100 patient-years)
	Total (%)	Arterial (%)	Venous (%)	Total (%)	Arterial (%)	Venous (%)	
Polycythemia vera (ECLAP, n= 1638)	39	75	25	14	55	42	5.5
Essential thrombocythemia (n= 891)	20	72	30	12	73	34	1.9
Primary myelofibrosis (n= 707)	10	46	54	7	48	53	1.75

Marchioli et al. J Clin Oncol 2005;23:2224, Carobbio et al. Blood 2011;117:5857 & Barbui et al. Blood 2010;115:778

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Frequency and prognostic factor of venous thrombosis in myeloproliferative neoplasms

Variable	Barbui et al, 2014 PV (n= 1545)	Carobbio et al, 2011 ET (n= 891)	Barbui et al, 2010 PMF (n= 707)
At diagnosis	7.4%	6%	5%
- Venous thromboembolism	5%	?	4.5%
- Splanchnic thrombosis	2%	?	0.6%
- Others	0.4%	?	?
Years of follow-up	6.9	6.2	2.9
During follow-up	9% (1.05 % pts-year)	4% (0.6 % pts-year)	3.1% (0.7 % pts-year)
- Venous thromboembolism	6%	?	3.1%
- Splanchnic thrombosis	2%	?	?
- Others	1%	?	?
Overall Survival	HR 1.90 (CI: 1.2-3.0), p= 0.007	HR 1.78 (CI: 0.8-3.6), p= 0.119	?

Tefferi et al. Leukemia 2013;27:1874, Barbui et al. Blood 2014;124:3021, Carobbio et al. Blood 2011;117:5857, Barbui et al. JCO 2011;29:3179, Barbui et al. Blood 2012;120:5128 & Barbui et al. Blood 2010;115:778

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How Long To Treat With Anticoagulation?

Acute phase (~7 days)

Heparin (unfractionated or low molecular heparin)
Vitamin K antagonists (VKA)
Direct oral anticoagulants (DOAC)?

Maintenance (~3 months)

VKA with INR 2-3 or DOAC; LMWH in cancer

Provoked by surgery or nonsurgical transient risk factor

Unprovoked with high bleeding risk

Extended (>3 months)

VKA with INR 2-3 or DOAC
LMWH is recommended in cancer

Unprovoked with low bleeding risk

Life-threatening thrombosis
Multiple recurrent events
Major thrombophilia
Thrombosis of the splanchnic veins

Guyatt et al. Chest 2012;141(2 Suppl):7S, Kearon et al. Chest 2016;149:315

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Case Records of the Hospital Clínic of Barcelona (I)

An 48-year-old man with long-term and low-risk JAK2 V617F ET presented with swelling, tenderness and pain in the left calft after a trip to Japan. He ommitted aspirin during the trip. The platelet count was 800x10^9/L.
Distal deep vein thrombosis (DVT) is diagnosed by compression ultrasonograhpy (popliteal and posterior tibial). How would you treat this patient?

a. **Start low-dose Aspirin.**
b. **Start LMWH at least 5 days and VKA with a target INR at 2-3 for at least 3 months.**
c. **Start hydroxyurea, LMWH at least 5 days and VKA with a target of INR at 2-3 for at least 3 months.**
d. **Start hydroxyurea, LMWH at least 5 days and VKA with a target of INR at 2-3 during extended period.**
e. **Start hydroxyurea and DOAC for at least 3 months.**

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Anticoagulant Therapy for VTE

	Initial (~7 days)	Maintenance (~3 months)	Extended (>3 months)
Unfractionated heparin	Maintain aPTT 1.5 times upper limit of normal	--	--
LMWH	Weight-based dosing	Weight-based dosing	--
Vitamin K antagonists	Target at INR at 2-3 and parallel heparin therapy for at least 5 days	Maintain INR at 2-3	Maintain INR at 2-3
Dabigatran	At least 5 days of heparin	150 mg/12 h	150 mg/12 h
Rivaroxaban	15 mg/12 h for 3 weeks	20 mg/24 h	20 mg/24 h 10 mg/24 h
Apixaban	10 mg/12 h for 1 week	5 mg/12 h	2.5 mg/12 h
Edoxaban	At least 5 days of heparin	60 mg/24 h*	60 mg/24 h*

*The recommended dose of edoxaban is 30 mg for patients with creatinine clearance of 30-50 mL/min, weight <60 Kg or use of cyclosporine, dronedarone, erythromycin or ketaconazole

Di Nisio et al. Lancet 2016;388:3060

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Choice of Anticoagulant Therapy

[Evidence-Based Medicine]

CHEST

Antithrombotic Therapy for VTE Disease

CHEST Guideline and Expert Panel Report

CrossMark

***2. In patients with DVT of the leg or PE and no cancer, as long-term (first 3 months) anticoagulant therapy, we suggest dabigatran, rivaroxaban, apixaban, or edoxaban over vitamin K antagonist (VKA) therapy (all Grade 2B).**

***3. In patients with DVT of the leg or PE and cancer ("cancer-associated thrombosis"), as long-term (first 3 months) anticoagulant therapy, we suggest LMWH over VKA therapy (Grade 2B), dabigatran (Grade 2C), rivaroxaban (Grade 2C), apixaban (Grade 2C), or edoxaban (Grade 2C).**

Kearon et al. Chest 2016;149:315

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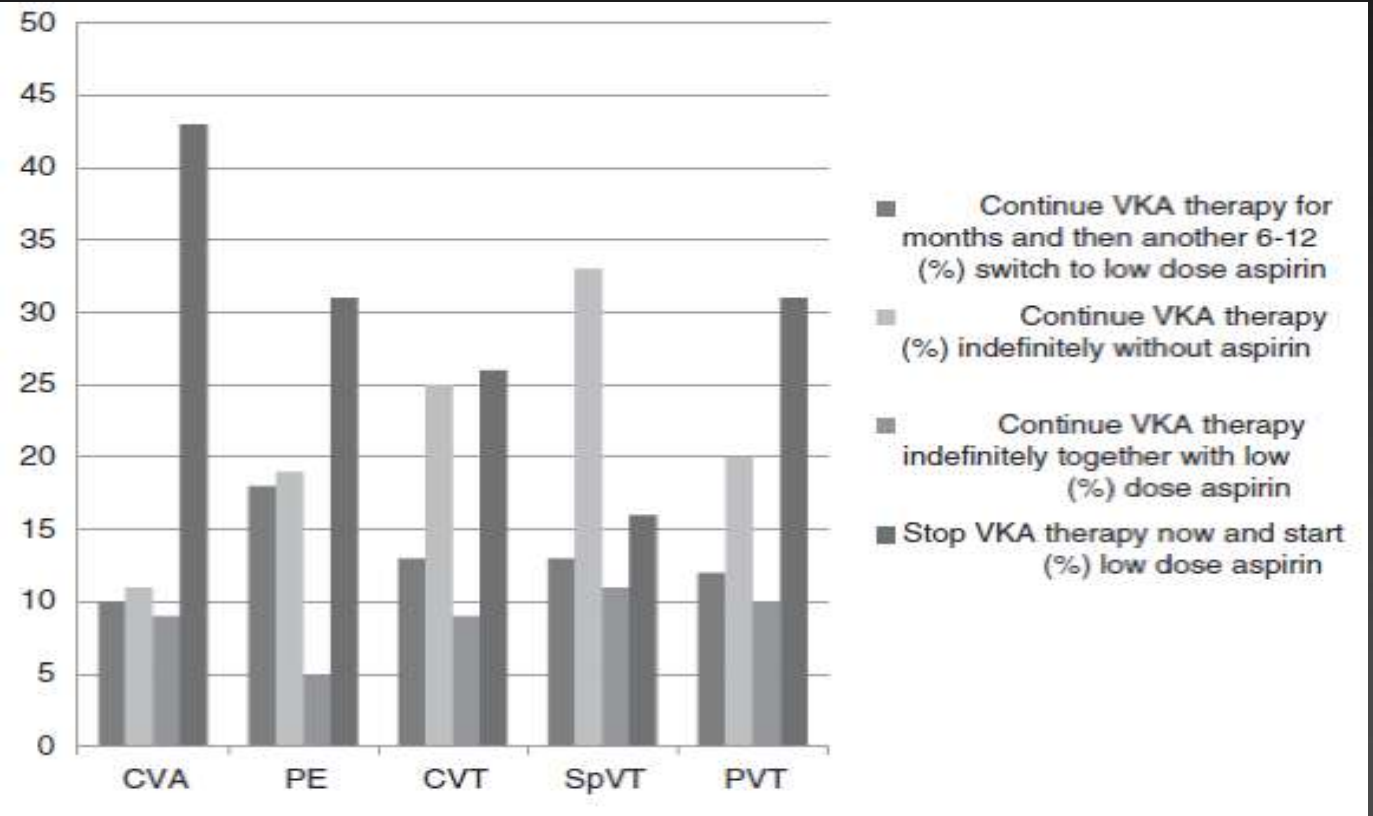
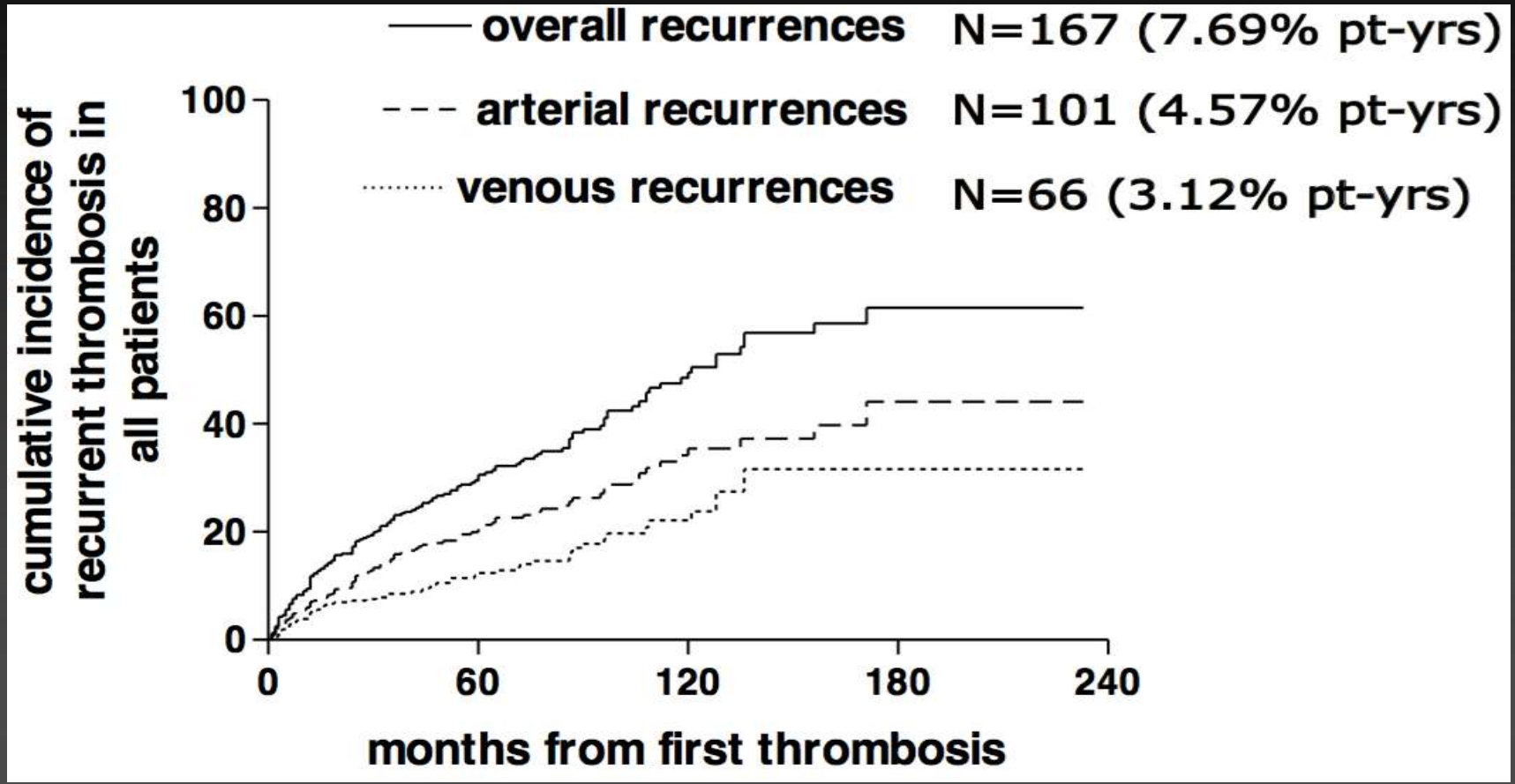
Heterogeneity of anticoagulant therapy duration for thromboembolic events coincident with PV or ET diagnosis (survey in seventy-three physicians)



Ellis et al. Thromb Res 2014;134:251

Recurrent thrombosis in 235 PV and 259 ET patients



De Stefano et al. Haematologica 2008;93:372

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Risk factors for recurrent venous thromboembolism in general population

Variable	Hazard Ratio
Unprovoked vs provoked VTE	2.3 (CI: 1.8-2.9)
Proximal vs distal (infrapopliteal) DVT	1.8 (CI: 1.1-3.0)
Pulmonary embolism vs distal DVT	3.1 (CI: 1.9-5.1)
Obesity	1.6 (CI: 1.1-2.4)
Male sex	2.8 (CI: 1.4-5.7)
Positive D-dimer	2.6 (CI: 1.9-3.5)
Residual thrombosis	1.5 (CI: 1.1-2.0)
Hereditary thrombophilia	1.5 (CI: 1.1-1.9)
Antiphospholipid antibodies	2.4 (CI: 1.3-4.1)

Agrawal et al. Curr Cardiol Reports 2019;21:24, Fahrni et al. Vasc Health Risk Manag 2015;11:451

Predictors of VTE recurrence among Olmsted County residents with cancer, 1966-2005

Characteristic	HR	95% CI	*P* value
Stage IV pancreatic cancer*	6.38	2.69, 15.13	<.0001
Brain cancer*	4.57	2.07, 10.09	.0002
Myeloproliferative or myelodysplastic disorder*	3.49	1.59, 7.68	.002
Ovarian cancer*	3.22	1.57, 6.59	.001
Stage IV cancer (non pancreas)*	2.85	1.74, 4.67	<.0001
Lung cancer*	2.73	1.63, 4.55	.0001
Neurological disease with leg paresis	2.38	1.14, 4.97	.02
Cancer stage progression	2.14	1.30, 3.52	.003
Multiple active cancers	1.78	0.87, 3.63	.12
Gastrointestinal (noncolorectal) cancer*	1.94	0.90, 4.17	.09
Stage III cancer, ALL or AML*	1.47	0.95, 2.27	.09
Warfarin therapy	0.43	0.28, 0.66	<.0001

Chee *et al*. *Blood* 2015;123:3972

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Risk factors for recurrent venous thromboembolism in MPNs

Variable	Hazard Ratio
Previous venous event in PV (n= 1545)	2.60 (CI: 1.5-4.4)
Age > 65 years in PV (n= 1545)	1.70 (CI: 1.2-2.5)
Male sex in ET (n= 891)	1.99 (CI: 1.03-3.83)
Leukocyte count > $15x10^9$/L in PV (n= 1545)	1.80 (CI: 1.1-2.8)
JAK2 V617F in ET (n= 1388)	1.95 (CI: 1.08-3.53)
Factor V Leiden in ET/PV (n= 304)	2.05 (CI: 1.3-2.5)
JAK2 V617F & thrombophilia in ET/PV for thrombosis (n= 132)	7.66 (CI: 2.66-22.03)

Tefferi et al. Leukemia 2013;27:1874, Barbui et al. Blood 2014;124:3021, Carobbio et al. Blood 2011;117:5857 & Qin et al. Intern J Hematol 2015;102:170; Ruggeri et al. Am J Hematol 2002;71:1, De Stefano et al. Haematologica 2009;94:733

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Case Records of the Hospital Clínic of Barcelona (II)

After 3 months of anticoagulant therapy with VKA due to provoked DVT without bleeding events, the patient received hydoxyurea and the platelet count was 475x10^9/L.
How would his case be managed?

a. **Stop anticoagulant VKA therapy and start high-dose Aspirin.**
b. **Start LMWH for at least 3 months.**
c. **Low-dose Aspirin plus VKA during long-term period.**
d. **Use VKA with a target of INR at 2-3 during an extended period.**
e. **Stop anticoagulant VKA therapy and start low-dose Aspirin.**

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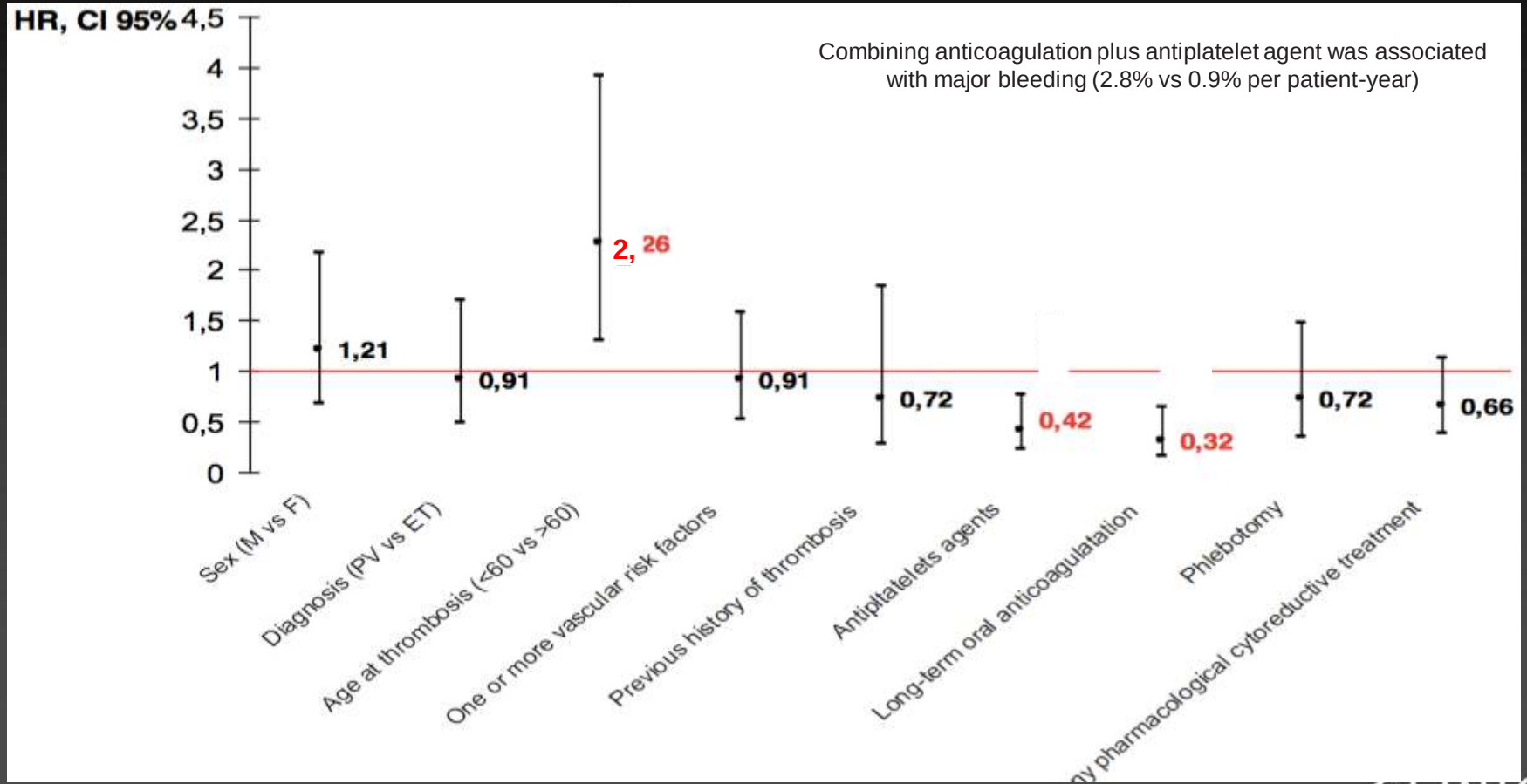
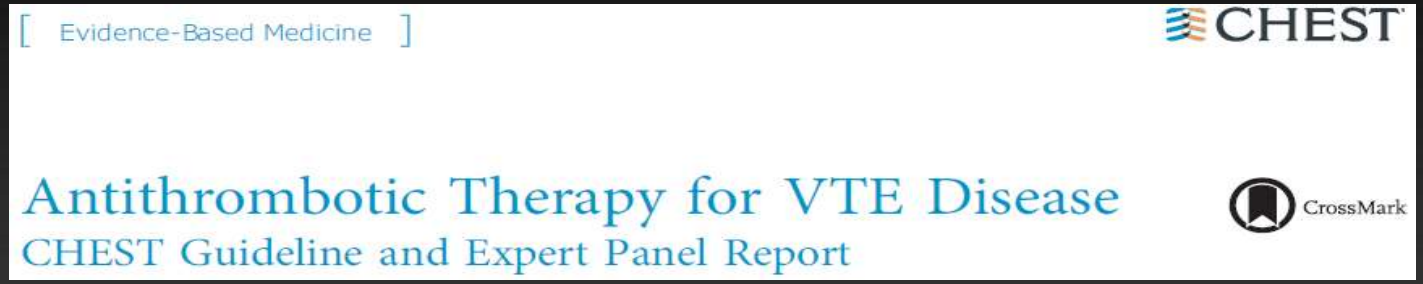
Risk factors for venous thrombotic recurrence in multivariable analysis (235 PV and 259 ET)



Combining anticoagulation plus antiplatelet agent was associated with major bleeding (2.8% vs 0.9% per patient-year)

De Stefano et al. Haematologica 2008;93:372

Aspirin for Extended Treatment of VTE



***12. In patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy and do not have a contraindication to aspirin, we suggest aspirin over no aspirin to prevent recurrent VTE (Grade 2B).**

Kearon et al. Chest 2016;149:315

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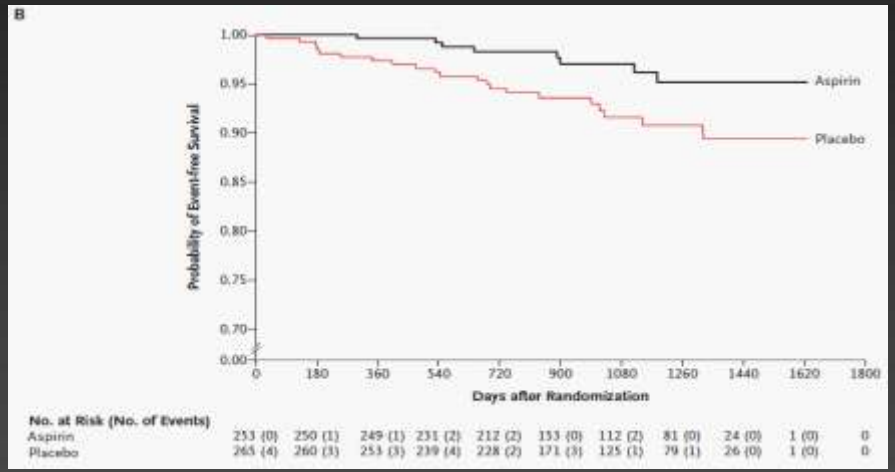
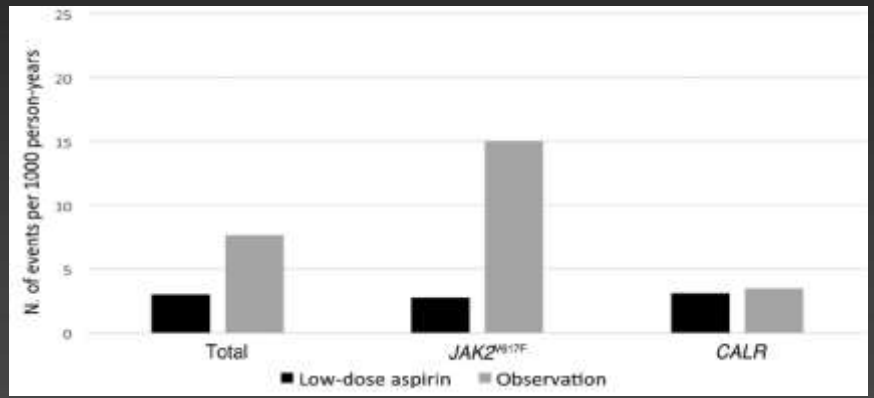
Primary Prevention of VTE with Aspirin in PV and ET





Landolfi et al. N Engl J Med 2004;350:114 & Alvarez-Larrán et al. Haematologica 2016;101:926

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Case Records of the Hospital Clínic of Barcelona (III)

Seven months after stopping VKA, the patient presented with chest pain and dysnea. He received hydoxyurea and aspirin as therapy and the thrombophilia study was negative. The platelet count was 600x10^9/L.
Pulmonary embolism (PE) is diagnosed by CT angiography. How would his case be managed?

a. **Stop low-dose Aspirin.**
b. **Start LMWH at least 5 days and VKA with a target INR at 2-3 for at least 3 months.**
c. **Improved cytoreduction, LMWH at least 5 days and VKA with a target of INR at 2-3 for at least 6 months.**
d. **Improved cytoreduction, LMWH at least 5 days and VKA with a target of INR at 2-3 during an extended period.**
e. **Combing low-dose Aspirin plus VKA during long-term period.**

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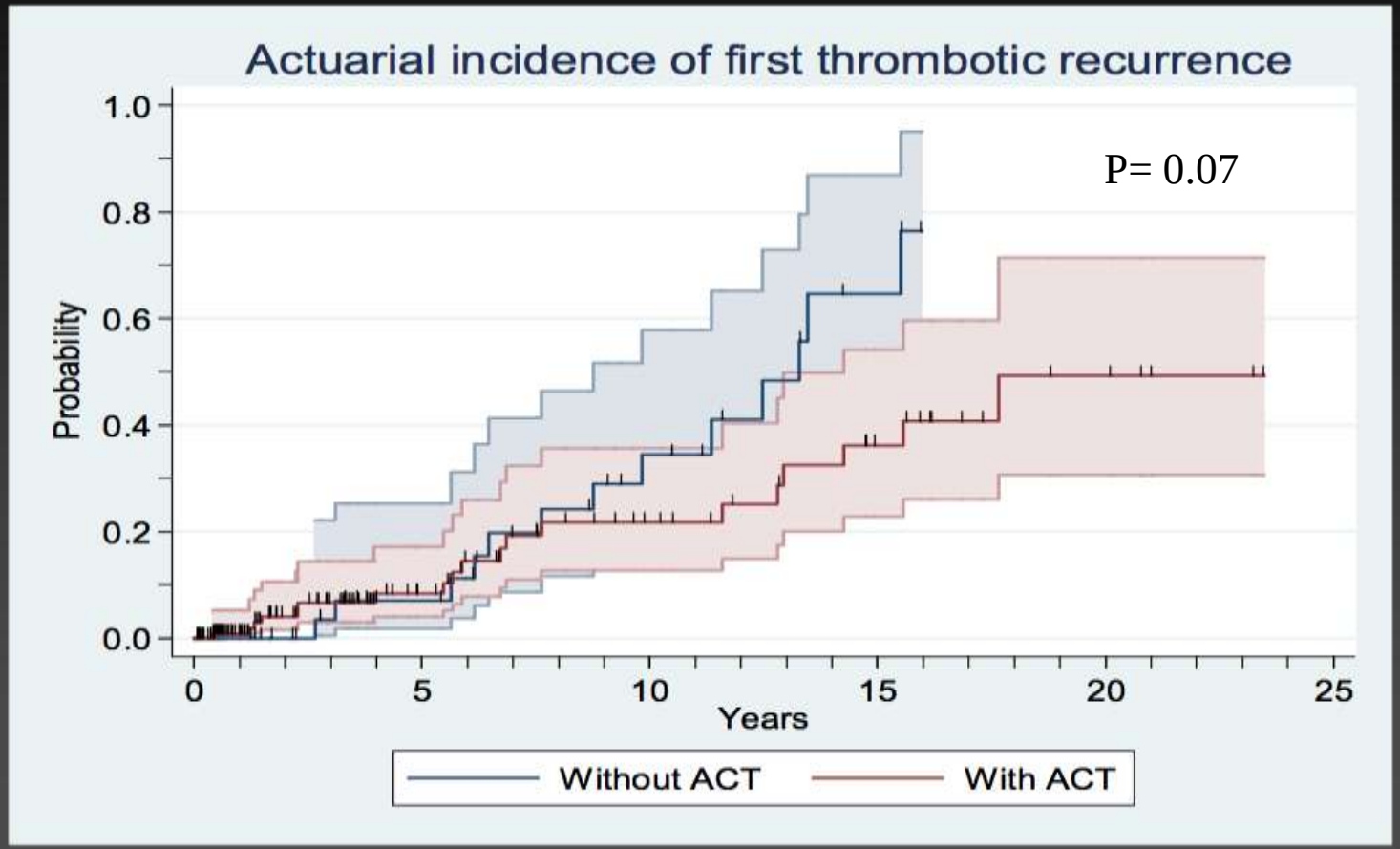
Effect of anticoagulant therapy on thrombotic recurrence in 79 PV and 71 ET



Hernandez-Boluda JC, Arellano-Rodrigo E, et al. Ann Hematol 2015;94:991

Effect of anticoagulant therapy on thrombotic recurrence and bleeding in 79 PV and 71 ET

	On-VKA 764 patient-years		Off-VKA 199 patient-years		
	No. of Events	Incidence rate* (95% CI)	No. of Events	Incidence rate* (95% CI)	p
Major thrombosis	34	4.5 (3.0 - 6.2)	24	12.0 (7.7 - 18)	<0.0005
Arterial thrombosis	13	1.7 (0.9 - 2.7)	9	4.5 (2.0 - 8.5)	0.03
Venous thrombosis	21	2.7 (1.7 - 4.2)	15	9.0 (4.2 - 12)	<0.0005
Major bleeding	14	1.8 (1.0 - 3.0)	3	1.5 (0.3 - 4.4)	0.8

*Events per 100 patient-years

Hernandez-Boluda JC, Arellano-Rodrigo E, et al. Ann Hematol 2015;94:991

Multivariate analysis for recurrent thrombosis in 79 PV and 71 ET

Variable	All thrombosis	Arterial thrombosis	Venous thrombosis
Previous thrombosis	2.8, 95% CI: 1.2-6.6 p= 0.015	–	9.8, 95% CI: 3.3-29 p< 0.001
Cardiovascular risk factors	–	7.0, 95% CI: 1.8-26 p= 0.004	–
JAK2 V617F mutation	5.9, 95% CI: 1.3-26.1 p= 0.018	10.0, 95% CI: 1.5-80 p= 0.03	–
Cytoreductive therapy	–	–	0.34, 95% CI: 0.15-0.70 p= 0.013
Anticoagulant therapy	0.26, 95% CI: 0.13-0.53 p< 0.001	–	–

Expressed in incidence rate ratios (IRRs)

Hernandez-Boluda JC, Arellano-Rodrigo E, et al. Ann Hematol 2015;94:991

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Effect of anticoagulant therapy on thrombotic venous recurrence and bleeding in 206 MPNs patients

	Vitamin K antagonists[a]		*P*	*Vitamin K antagonists*[b]		*P*
	Yes (N = 155)	*No (N = 44)*[c]		*Not discontinued (N = 108)*	*Discontinued (N = 47)*	
Pt-years	404	279		352	125[d]	
Thrombosis, N[c]	19	25	0.03	19	16	0.008
Incidence rate	4.7	8.9		5.3	12.8	
% pt-yrs (95% CI)	2.8–7.3	5.72–13.2		3.2–8.4	7.3–20.7	
Venous thrombosis, N	15	20	0.04	15	12	0.03
Incidence rate	3.7	7.1		4.2	9.6	
% pt-yrs (95% CI)	2.0–6.1	4.3–11.0		2.3–7.0	4.9–16.7	
Major bleeding, N	10[e]	2	0.08	6[e]	4	0.32
Incidence rate	2.4	0.7		1.7	3.2	
% pt-yrs (95% CI)	1.1–4.5	0.08–2.5		0.6–3.7	0.8–8.1	

De Stefano et al. Leukemia 2016;30:2032

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Effect of long-term therapy on the risk of thrombotic recurrences in 1500 MPNs patients

	Overall recurrent thromboses (HR, 95% CI)		Arterial recurrent thrombosis (HR, 95% CI)*	*p*	Venous recurrent thrombosis (HR, 95% CI)*	*p*
Age > 60 years	1.23 (0.99–1.52)	0.06	1.18 (0.89–1.57)	0.23	1.28 (0.91–1.79)	0.15
Male sex	0.94 (0.76–1.17)	0.60	0.97 (0.73–1.28)	0.99	0.91 (0.65–1.28)	0.61
Antiplatelet treatment	**0.58 (0.43–0.79)**	**0.0005**	**0.54 (0.35–0.82)**	**0.003**	0.64 (0.40–1.03)	0.07
Oral anticoagulation (VKA or DOACs)	**0.58 (0.41–0.81)**	**0.001**	**0.58 (0.35–0.96)**	**0.03**	**0.60 (0.37–0.95)**	**0.03**
Hydroxyurea	**0.75 (0.57–1.00)**	**0.05**	**0.67 (0.46–0.98)**	**0.04**	0.87 (0.56–1.33)	0.52
Cytoreduction with agents other than hydroxyurea#	1.04 (0.74–1.45)	0.80	0.94 (0.61–1.46)	0.80	1.22 (0.72–2.04)	0.44

De Stefano et al. Blood Cancer J 2018;8:112

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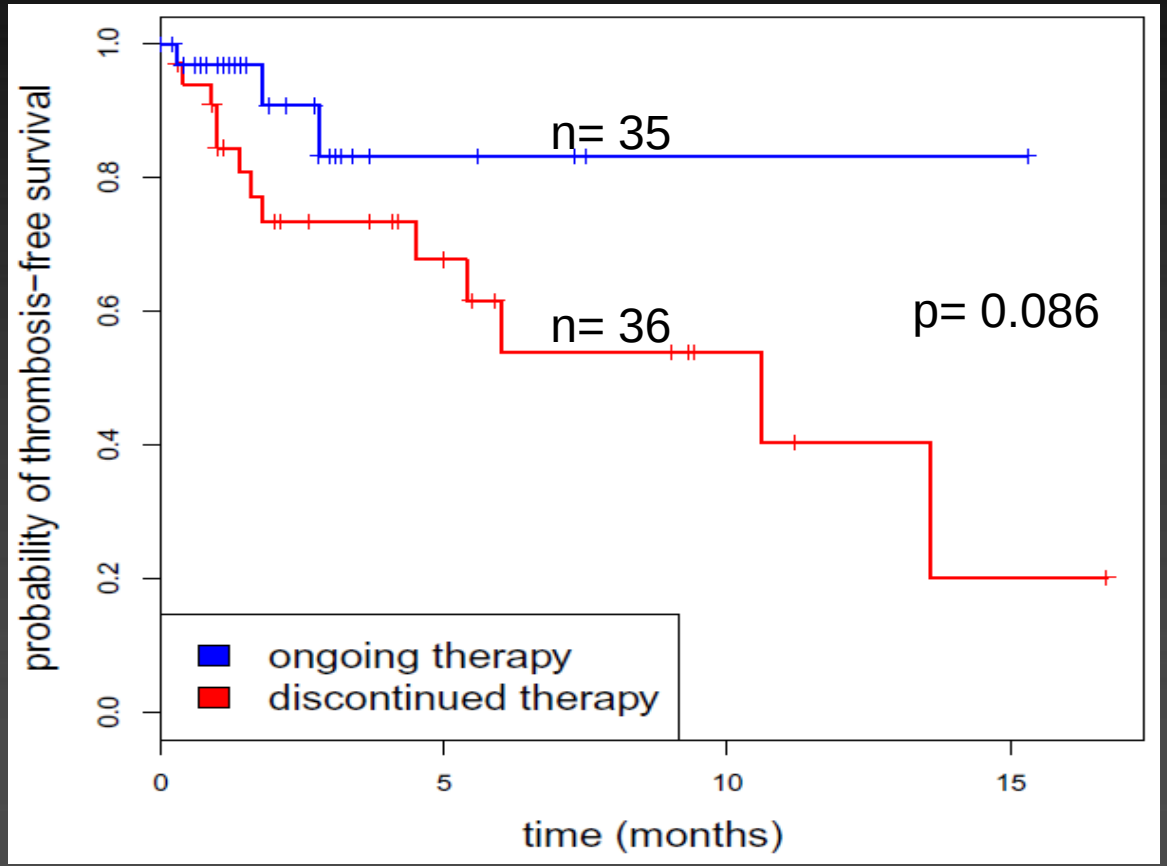
Cumulative Probability of Thrombosis-free Survival in MPN Patients



Wille et al. Ann Hematol 2019;98:93

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Case Records of the Hospital Clínic of Barcelona (IV)

Ten months after starting the VKA therapy (percent time in therapeutic range 70%), the patient presented with calf pain in the same leg. The platelet count was 450x10^9/L with an INR of 2.10.
DVT is diagnosed by compression ultrasonograhpy. How would his case be managed?

a. **Combing low-dose Aspirin plus VKA during long-term period.**
b. **Stop VKA , start LMWH for at least 1 month and start extended VKA.**
c. **Improved anticoagulation with VKA.**
d. **Stop VKA and start LMWH for at least 6 months.**
e. **Stop VKA, start LMWH for at least 1 month and change to DOAC during long-term period .**

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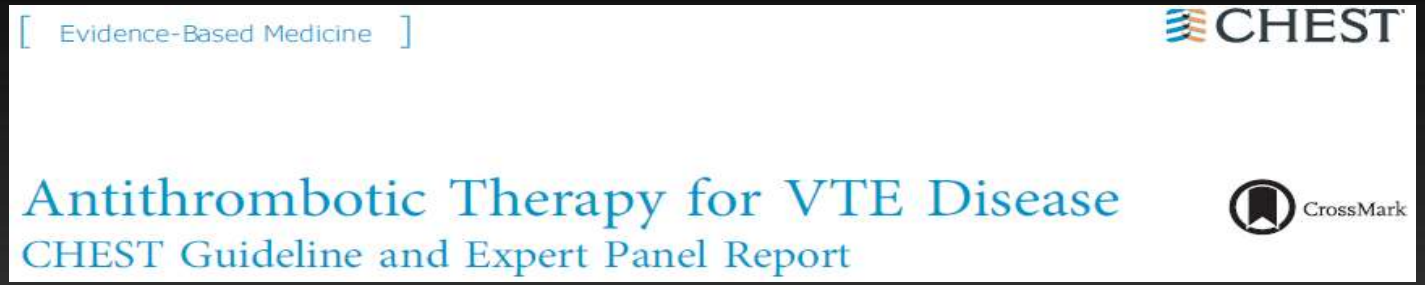
Management of Recurrent VTE on Anticoagulant Therapy



***29. In patients who have recurrent VTE on VKA therapy (in the therapeutic range) or on dabigatran, rivaroxaban, apixaban, or edoxaban (and are believed to be compliant), we suggest switching to treatment with LMWH at least temporarily (Grade 2C).**

***30. In patients who have recurrent VTE on long-term LMWH (and are believed to be compliant), we suggest increasing the dose of LMWH by about one-quarter to one-third (Grade 2C).**

Kearon et al. Chest 2016;149:315

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Case-Control comparison between MPNs patients treated with DOAC or Low-dose Aspirin (LDA)

Parameters	DOAC group	LDA group	*p*
Nb	25	25	
Median age at diagnosis of MPN (year)	70.6 (49.1–91.9)	70.6 (43.1–92.1)	1
Sex ratio	13/12	13/12	1
MPN diagnosis (ET/PV)	17/8	17/8	1
JAK2V617F Driver mutation	18	18	1
Cardio-vascular RF (nb/%)	19 (76)	18 (72)	0.75
MPN high risk classification (nb/%)	22 (88)	25 (100)	0.23
Thrombosis history	9 (36)	11 (44)	0.56
Type of events	5art/2vn/2mix	6art/3vn/2mix	
New events under DOAC/LDA (nb/%)	11	11	1
Thrombosis	1 (art) (4)	2 (art) (8)	1
Major Hemorrhage	3 (12)	3 (12)	1
Death	7 (28)	6 (24)	0.75
Median follow-up under DOAC/LDA (year)	2.1 (0.12–4.3)	2 (0.18–4.3)	0.95

Ianotto et al. Intern J Hematol 2017;106:517

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Efficay and Safety of Direct Oral Anticoagulants in Cancer-associated VTE

	Hokusai VTE Cancer			SELECT-D		
Variable	**Edoxaban 60 mg/24 h**	**Dalteparina 150 UI/Kg**	**P (sup.)**	**Rivaroxaban 20 mg/24 h**	**Dalteparina 150 UI/Kg**	**P (sup.)**
Number	522	524	--	203	203	--
Age, median	64,3	63,7	--	67	67	--
Male, %	53,1	50,2	--	57	48	--
Metastatic cancer, %	52,5	53,4	--	58	58	--
Solid cancer /hematologic, %	89,1/10,7	89,1/10,5	--	98/2	98/3	--
Terapia anticancerosa, %	71,6	73,1	--	69	70	--
VTE or major bleeding, %	12,8	13,5	0,87	9,3	11,8	0,12
Recurrent VTE, %	7,9	11,3	0,09	**4,0**	11,0	0,001
Major bleeding, %	**6,9**	4,0	0,04	6,0	4,0	0,58
Digestive bleeding, %	**3,8**	1,1	0,02	3,9	1,97	0,12
Non major bleeding, %	14,6	11,1	0,12	**13,0**	4,0	0,001
Death, %	39,5	36,6	0,15	23,6	27,5	0,16

Raskob et al. N Engl J Med 2018;378:615 & Young et al. JCO 2018;36:2017

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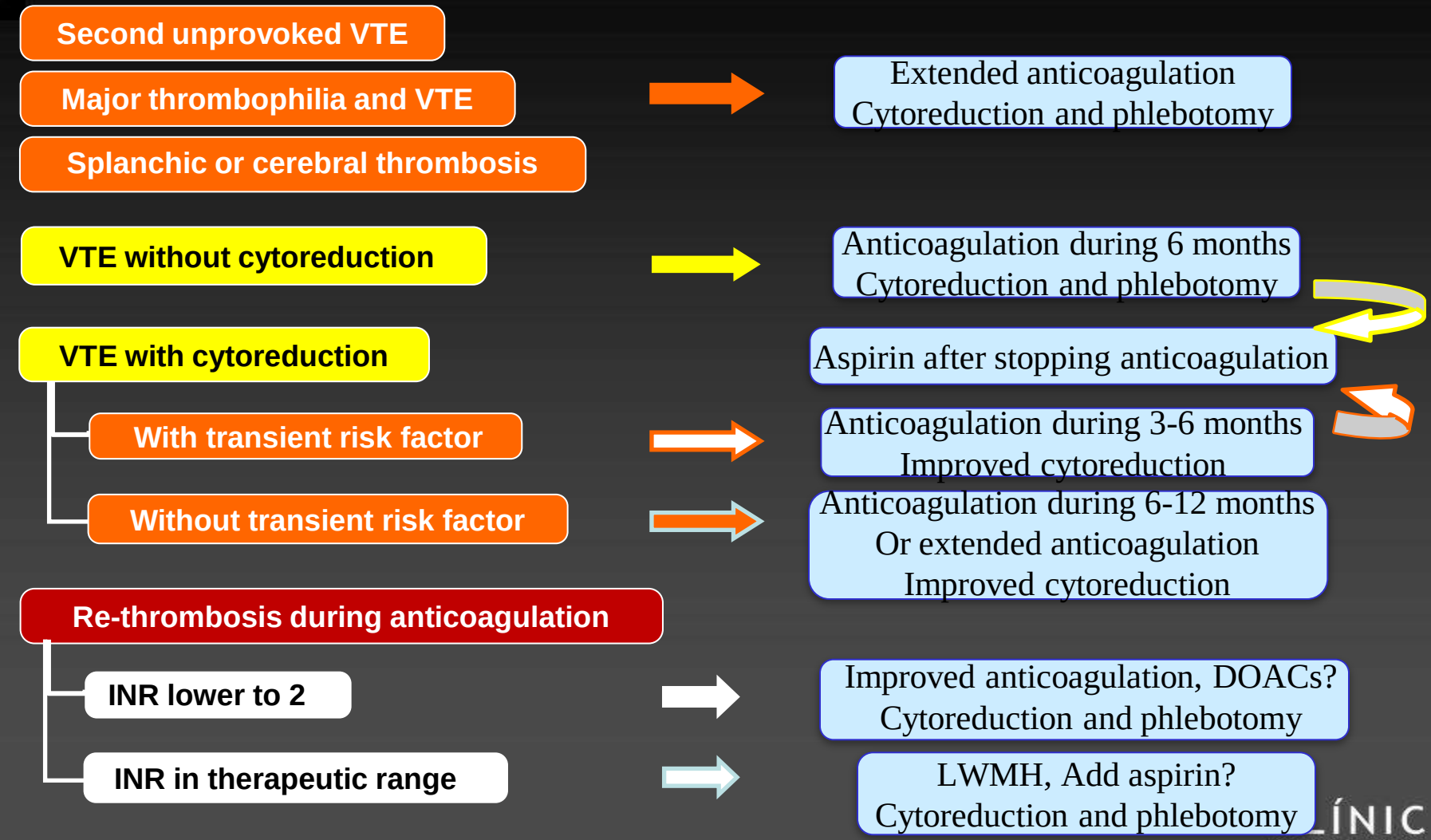
Proposed Management of Venous Thromboembolism (VTE) in MPNs



Kreher et al. Ann Hematol 2014;93:1953 & De Stefano et al. Blood Cancer J 2018;8:65