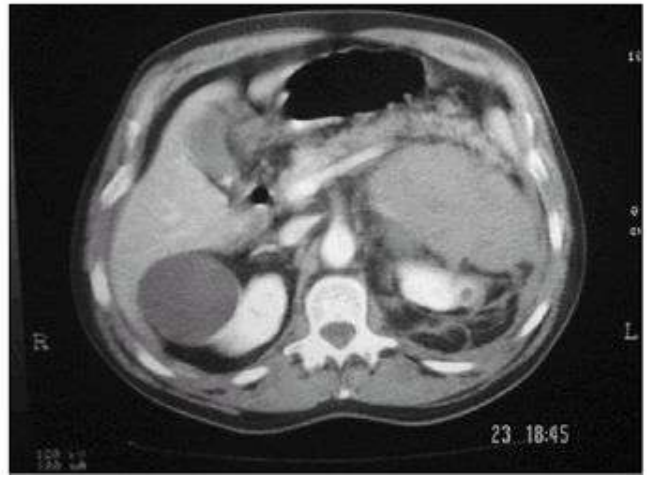
CASO CLÍNICO



- Varón 75a.
- AP: FRCV: HTA, DM2, DL.
- FA no valvular anticoagulada con Apixaban. CHADS2VASC2 5ptos.
- Enfermedad renal crónica moderada.
- **LLC estadio II- B, con del 17p.** Inicio tratamiento con Ibrutinib en julio 2016 con excelente respuesta en SP y RC en ganglios y bazo;
- Ingreso en Enero 2020 por **hematoma retroperitoneal**, con afectación de psoas y paresia de MII, en el seno de AC con heparina + IBR + I.Renal.
- Requerimiento transfusional y embolización arterial.

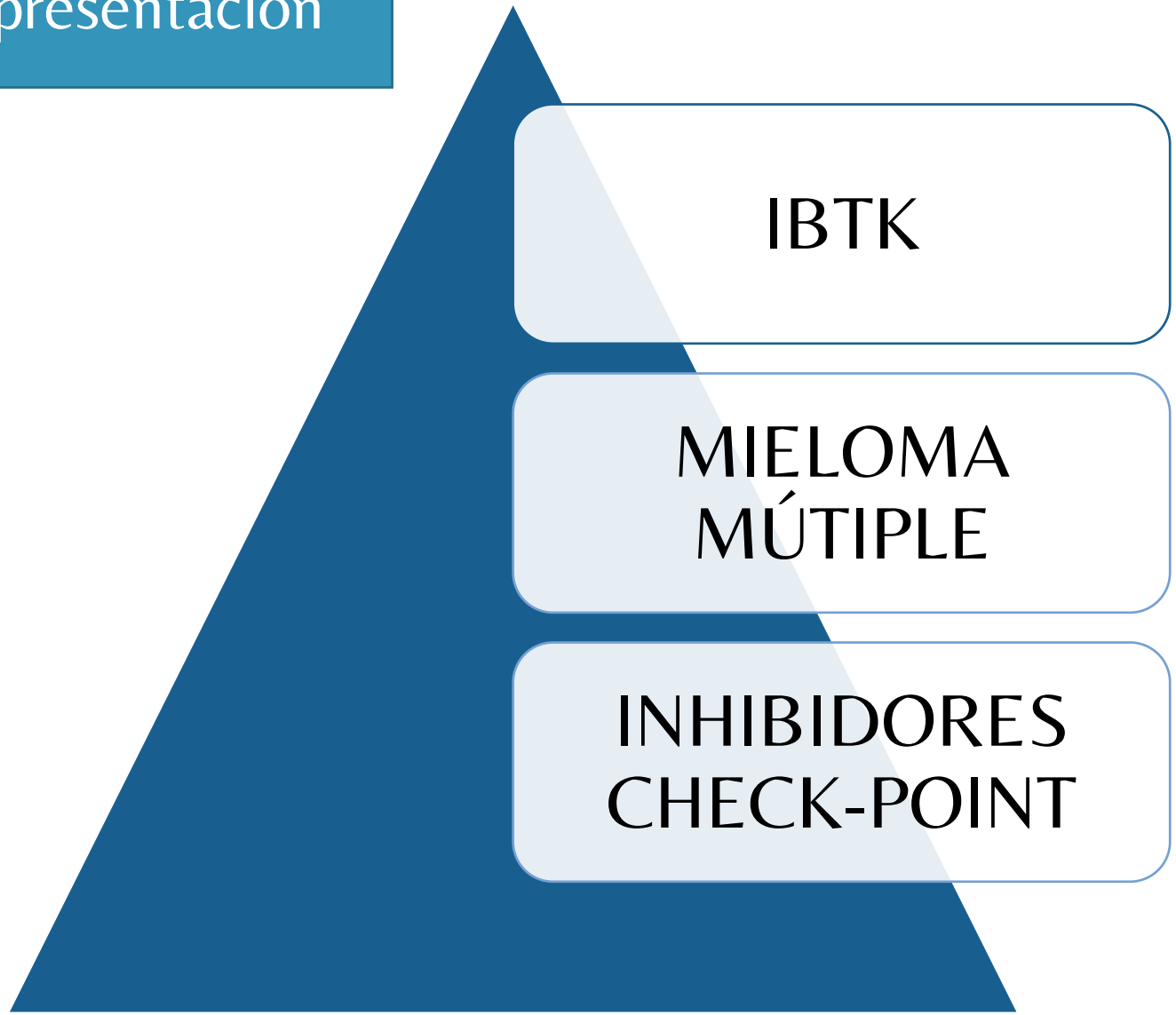
MAYO formación

Alteraciones de la hemostasia inducidas por los tratamientos oncológicos

Dra. Cristina Pascual Izquierdo, MD, PhD
Jefe Sección Servicio de Hematología y Hemoterapia.
Profesor Asociado UCM
Hospital General Universitario Gregorio Marañón
Instituto de Investigación Gregorio Marañón

Madrid, 26 de mayo 2023

Esquema de presentación



INTRODUCCIÓN

- En las últimas décadas han aparecido **fármacos antineoplásicos** que proponen alternativas diferentes a los clásicos agentes citostáticos empleados en quimioterapia.
- Son terapias más selectivas, que reciben el nombre de tratamientos dirigidos o biológico.
- El sistema hemostático, puede verse afectado con cierta frecuencia por estos nuevos fármacos.
- Complicaciones trombo-hemorrágicas frecuentes.

Ke X, Shen L. Molecular targeted therapy of cancer: The progress and future prospect. Front Lab Med 2017;1:69-75.
Khalil DN, Smith EL, Brentjens RJ, et al. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. Nat Rev Clin Oncol 2016;13:273-90.
Guri Y, Hall MN. mTOR signaling confers resistance to targeted cancer drugs. Trends Cancer 2016;2:688-97.

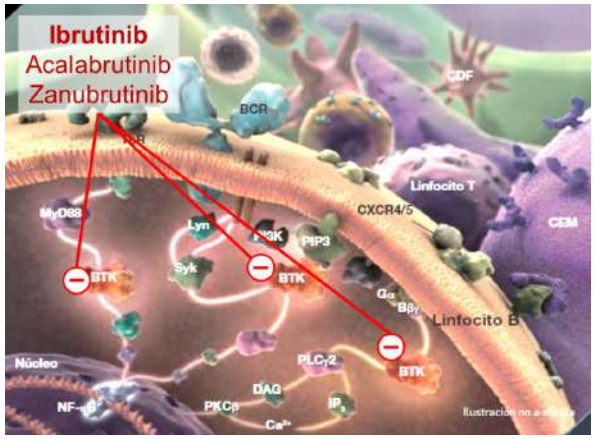
Tabla I. Alteraciones hemostáticas asociadas al uso de tratamientos dirigidos frente a cánceres hematológicos

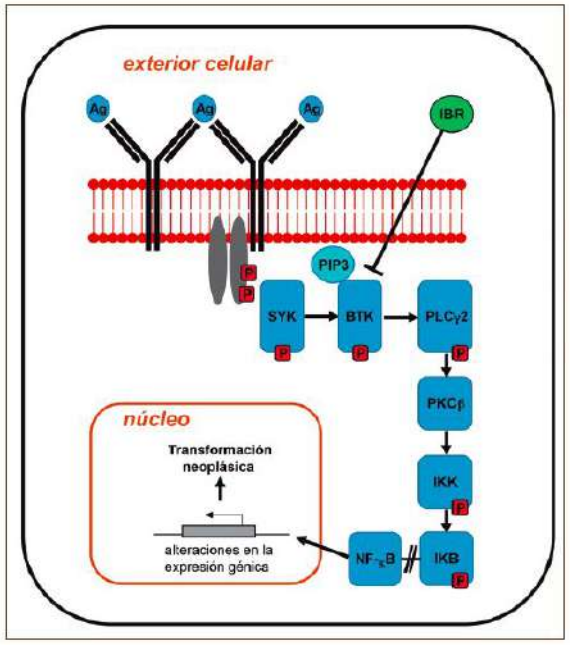
Fármaco	Mecanismo	Indicación	Disfunción hemostática: Trastorno (frecuencia)*	Disfunción hemostática: Manejo	Disfunción hemostática: Prevención
Ibrutinib (9,17)	Inhibidor de BTK/TEC	• LCM si ≥ 1 TP • LLC/LLP con deleción 17p • MW • LZM si ≥ 1 TP anti-CD20 • EICHc tras ≥ 1 TS	• Disfunción plaquetaria (muy frecuente) • Trombocitopenia (muy frecuente) • Hematomas leves (muy frecuente) • Hemorragias – Totales, ~19-22/100 p.a. – Mayores/fatales, < 10% / < 1%	• Trombocitopenia: si plaquetas < 25 × 10^9/L, suspender/modificar dosis según FT† • Hemorragia mayor: interrumpir temporalmente Ibrutinib y transfundir plaquetas ≥ 3 horas tras última dosis, repitiendo si fuera necesario	(del sangrado) • Evitar AVK concomitante • Evitar >1 ACG o/y AP (si irrenunciable, sustituir Ibrutinib por otro antineoplásico) • Considerar interacciones con otros fármacos, especialmente antiarrítmicos • Cirugía mayor: interrumpir Ibrutinib 7 días antes, hasta 1-3 días después; transfundir plaquetas ante procedimientos no programados
Dasatinib (5,27)	Inhibidor de BCR/ABL	• LMC Ph+ crónica recién diagnosticada • LMC Ph+ crónica, acelerada o blástica resistente/intolerante a TP, imatinib incluido • LLA Ph+ y crisis blástica • Linfoide procedente de LMC resistente/intolerante a TP	• Disfunción plaquetaria (muy frecuente) • Trombocitopenia (muy frecuente) • Hematomas/hemorragias leves (muy frecuente) • Hemorragias Grado ≥ 3 – Grado 3/4, 5,8% – Grado 5, 0,4% …ión sobre todo GI; en SNC	• Trombocitopenia, si LMC crónica y plaquetas < 50 × 10^9/L; si LMC acelerada/crisis blástica o LLA Ph+, y plaquetas < 10 × 10^9/L: suspender/modificar dosis según FT† • Hemorragia – Si Grado ≥ 3, interrumpir temporalmente Dasatinib y transfundir plaquetas o/y hematíes	(del sangrado) • Si plaquetas < 50 × 10^9/L en fase crónica, < 10 × 10^9/L en fases acelerada o blástica, interrumpir temporalmente Dasatinib hasta recuperación y considerar reducción de dosis (FT†) • Evitar ACG o AP concomitantes • Considerar interacciones con inhibidores de CYP3A4 • Cirugía: interrumpir Dasatinib 7 días antes, reanudar cuando se considere que no existe riesgo
			…plaquetaria (muy …openia (poci frecuente) …s, hematomas …s (poco frecuente) …as (frecuente); …as gastrointestinales …uente), habitualmente …es con GIST, también …a EVAG en LMC y LLA …a desconocida)	• Trombocitopenia, si SHE/LEC, LMC crónica, SMD/SMP, GIST o DFSP, y plaquetas < 50 × 10^9/L; si LMC acelerada/blástica o LLA Ph+, y plaquetas < 10 × 10^9/L: suspender/modificar dosis según FT† • Hemorragia GI, incluida la motivada por EVAG: aplicar procedimientos estándar para esta patología como los ya citados; considerar interrupción del tratamiento	(del sangrado) • Si se produce trombocitopenia, aplicar las pautas expuestas en la sección dedicada a su manejo • Evitar el tratamiento concomitante con antiagregantes o anticoagulantes • Cirugía: interrumpir Imatinib 7 días antes, reanudar cuando se considere que no existe riesgo

- Desde hace unos años se han depositado grandes esperanzas en los inhibidores de las tirosina cinasas (ITC) para tratar cánceres hematológicos, en especial los que cursan con proliferación anómala de células B.
- Uno de ellos, **Ibrutinib,** se autorizó en nuestro país a finales de 2014, y a raíz de los prometedores resultados obtenidos en los ensayos iniciales, su uso se ha extendido de manera considerable.

JR G Porras, SEHH 2018

Inhibidores de la Tirosin Quinasa de Bruton (BTKi)



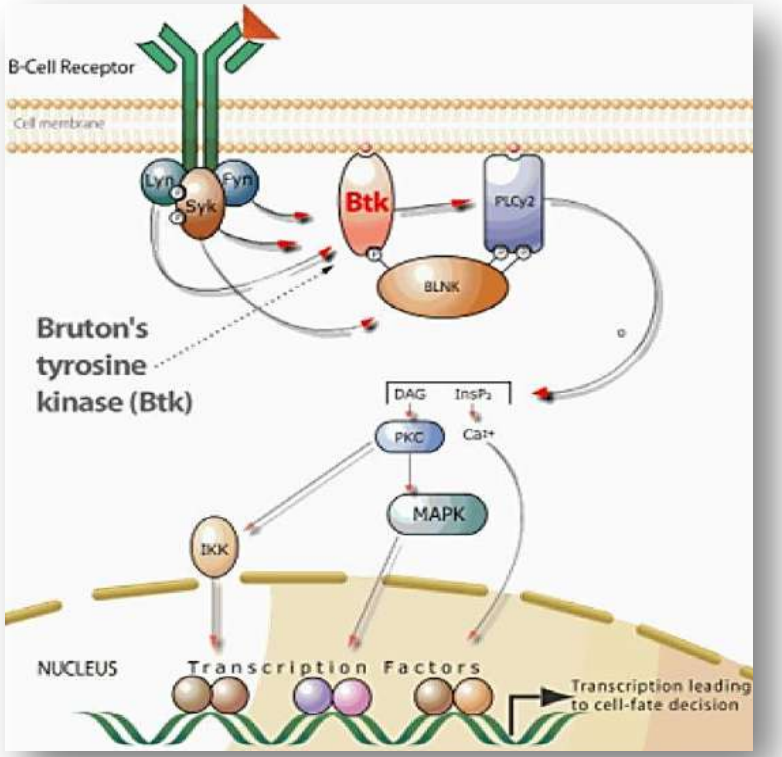


BTK is a cytoplasmic protein involved in transmitting the B-cell antigen receptor signal cascade, which regulates normal B-cell processes and promotes the survival and proliferation of malignant cells

Ibrutinib: first-in-class irreversible oral inhibitor of BTK in the B-cell receptor signaling pathway

Liu J, Fitzgerald ME, Berndt MC, et al. Bruton tyrosine kinase is essential for botrocetin/VWF-induced signaling and GPIb-dependent thrombus formation in vivo. Blood

Efectos adversos del ibrutinib



- Irreversible inhibition of BTK and TEK
- Downregulation of the PI3K-Akt signaling pathway

- Fibrilación auricular (6-15%)
- Hipertensión (6-70%)
- Hemorragia menor (45%)
- Hemorragia mayor (4%)
- Trombopenia (2-13%)

Shatzel et al J Thromb Haemost 2017 Feb 9; Blood 2014; 124: 5657; Blood 2014; 124: 1990;Clin Cancer Investig J 2016; 5:203-7

Hemorragia e IBT

THROMBOSIS AND HEMOSTASIS

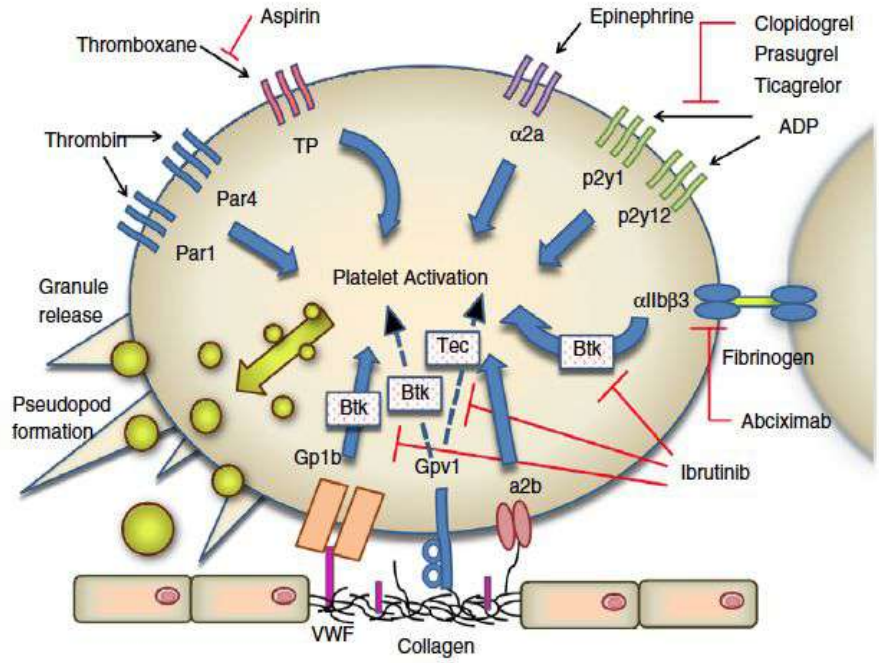
Ibrutinib treatment affects collagen and von Willebrand factor-dependent platelet functions

Marie Levade,[1,2] Elodie David,[2] Cédric Garcia,[2] Pierre-Alexandre Laurent,[1] Sarah Cadot,[2] Anne-Sophie Michallet,[3] Jean-Claude Bordet,[4] Constantine Tam,[5] Pierre Sié,[1,2] Loïc Ysebaert,[6] and Bernard Payrastre[1,2]

ORIGINAL ARTICLE

Ibrutinib inhibits collagen-mediated but not ADP-mediated platelet aggregation

S Kamel[1], L Horton[1], L Ysebaert[2], M Levade[3,4], K Burbury[5], S Tan[1], M Cole-Sinclair[1], J Reynolds[6], R Filshie[1], S Schischka[1], A Khot[5], S Sandhu[5], MJ Keating[7], H Nandurkar[1,8] and CS Tam[1,5,8]



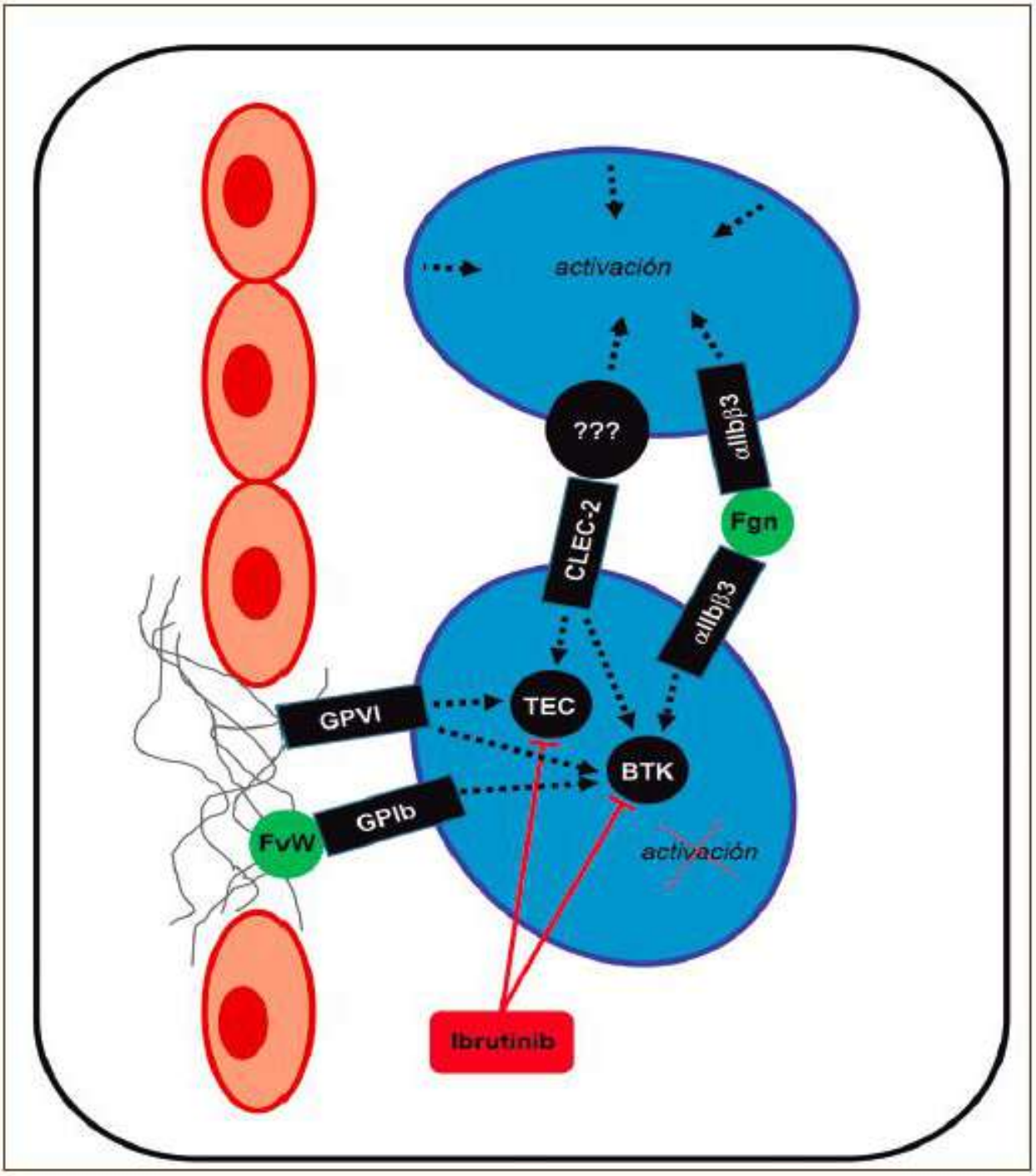


Figura 3. Acciones de Ibrutinib sobre la plaqueta. Se exponen las interacciones entre receptores plaquetares y sus ligandos cuyos mecanismos de señalización intracelular, por depender de BTK o/y TEC, son inhibidos por Ibrutinib. A la izquierda de la imagen se representa el endotelio vascular con un área lesionada de la que emergen fibras de colágeno. BTK, tirosina cinasa de Bruton; TEC, tyrosine kinase expressed in hepatocellular carcinoma; GPVI, glicoproteína VI; αIIbβ3, integrina αIIbβ3; GPIb, glicoproteína Ib; CLEC-2, C-type lectin-like receptor 2; FvW, factor von Willebrand; Fgn, fibrinógeno.

Arthur JF, Dunkley S, Andrews RK. Platelet glycoprotein VI-related clinical defects. Br J Haematol 2007;139:363-72.
Liu J, Fitzgerald ME, Berndt MC, et al. Bruton tyrosine kinase is essential for botrocetin/VWF-induced signaling and GPIb-dependent thrombus formation in vivo. Blood 2006;108:2596-603.
Navarro-Núñez L, Langan SA, Nash GB, Watson SP. The physiological and pathophysiological roles of platelet CLEC-2. Thromb Haemost 2013;109:991-8.

Hemorragia e IBTK

- St, en los 3 primeros meses de inicio de TTº.
- La mayor parte son cutáneos y mucosos en forma de petequias/hematomas/epixtasis/hematuria, leves.
- Se produce en 40-70% de enfermos.
- Las hemorragías graves : 4% - 8% en los ensayos principales. Hemorragia mortal <1%.
- Ocasionales hemorragias del SNC.
- Tb se ven transformaciones hemorrágicas de ictus, HSA y hemorragias vítreas.

von Hundelshausen P, Siess W. Bleeding by Bruton Tyrosine Kinase-Inhibitors: Dependency on Drug Type and Disease. Cancers (Basel). 2021 Mar 4;13(5):1103.

Puede IBR ser protector desde el puno de vista CV?:

- Modelos experimentales sugieren que el bloqueo de la vía GPVI puede reducir riesgo trombótico. En cualquier caso a dia de hoy no hay datos suficientes para recomendar dejar solo IBR como antiagregante.
- Con doble antiagregación el riesgo de sangrado aumenta un 40-50% respecto a un solo antiagregante.

von Hundelshausen P, Siess W. Bleeding by Bruton Tyrosine Kinase-Inhibitors: Dependency on Drug Type and Disease. Cancers (Basel). 2021 Mar 4;13(5):1103.

Manejo de las complicaciones hemorrágicas.

- Intentar evitar AINES, aceites de pescado, vitamina E.
- Valorar suspender AAS al introducir IBR en pacientes con indicación “débil”: riesgo CV bajo o moderado
- Pacientes que requieren doble antiagregación temporal por stent reciente: valorar retrasar IBR hasta que solo requieran uno.
- Para pacientes que requieren doble antiagregación a largo plazo considerar fármacos alternativos.
- Algunos autores recomiendan en pacientes con antiagregantes y anticoagulantes empezar a 280 mg y después subir si no sangran. No hay datos clínicos que avalen esta estrategia.
- En procedimientos invasivos: pautas de suspensión de 3 días para procedimientos menores y 7 días para mayores.
- Para procedimientos invasivos mayores urgentes se recomienda la trnasfusión de plaquetas.

von Hundelshausen P, Siess W. Bleeding by Bruton Tyrosine Kinase-Inhibitors: Dependency on Drug Type and Disease. Cancers (Basel). 2021 Mar 4;13(5):1103.

Tratamiento en sangrado mayor.

- En sangrados severos que no incluyan el SNC : suspensión de IBR + **transfusión de plaquetas**.
- Datos in vitro que muestran que plaquetas frescas con BTK y TEC no inhibido puede corregir la hemostasia.
- IBR puede seguir inhibiendo las plaquetas transfundidas en las 3-4 hrs posteriores a la toma.
- Solo suspendiendo IBR se calcula que el efecto se pierde en las plaquetas en 2,5 días.
- En sangrados cerebrales es dudoso si deben administrarse.
- Hay casos descritos con buena evolución, pero alguna evidencia que muestra aumento de mortalidad con Tx de plaquetas en este contexto. No esta claro si esto es aplicable a los pacientes con IBR. Individualizar
- Tras un sangrado grave la decisión de retomar o no IBR dependerá de la situación de la enfermedad, disponibilidad de alternativas, etc.
- Si la enfermedad está bien controlada se puede suspender y esperar progresión.

von Hundelshausen P, Siess W. Bleeding by Bruton Tyrosine Kinase-Inhibitors: Dependency on Drug Type and Disease. Cancers (Basel). 2021 Mar 4;13(5):1103.

Manejo de anticoagulación con IBR

- Intentar evitar la combinación si es posible. Si hay que utilizarlos, no hay contraindicación absoluta
- AVK: desconsejados, parecen implicar mayor riesgo, pero sin contraindicación absoluta. Habría que mantenerlos en válvulas protésicas y valorarlo si era un tratamiento previo con INR muy estable. La interacción por CYP3A no es muy alta (se metabolizan poco por esa vía). El INR nos permite saber que está pasando
- HPBPM : más segura pero tiene el inconveniente de su vía de administración.
- ACODS : atractivos pero hay que considerar las interacciones: IBR y apixaban y rivaroxaban interacciona por la vía de CYP3A: IBR puede aumentar sus niveles. Apix y Rivarox no aumentan los niveles de IBR

	LMWH/ heparin	VKA	NOAC	Other AC*	Use of any AC
Number of patients on AC during ibrutinib treatment	243	45	49	9	311
Median duration of AC treatment† (range), days	9.0 (1.0–596.0)	57.0 (1.0–519.0)	116.0 (1.0–619.0)	4.0 (1.0–667.0)	16.0 (1.0–667.0)
With major haemorrhage during treatment, n (%)	15 (6.2)	5 (11.1)	1 (2.0)	1 (11.1)	20 (6.4)

	NSAIDs	ADP receptor inhibitors	Other (nearly all ASA)	Use of any AP
Number of patients on AP during ibrutinib treatment	356	55	409	677
With major haemorrhage during treatment, n (%)	14 (3.9)	3 (5.5)	18 (4.4)	30 (4.4)

…r lo que su asociación
…vo, y alterar sus niveles.

…ser el menos

4 EECC aleatorizados:
- PCYC-1112 [RESONATE],
- PCYC-1115 [RESONATE-2
- CLL3001 [HELIOS]
- MCL3001 [RAY]

FA asociada al tratamiento con ibrutinib

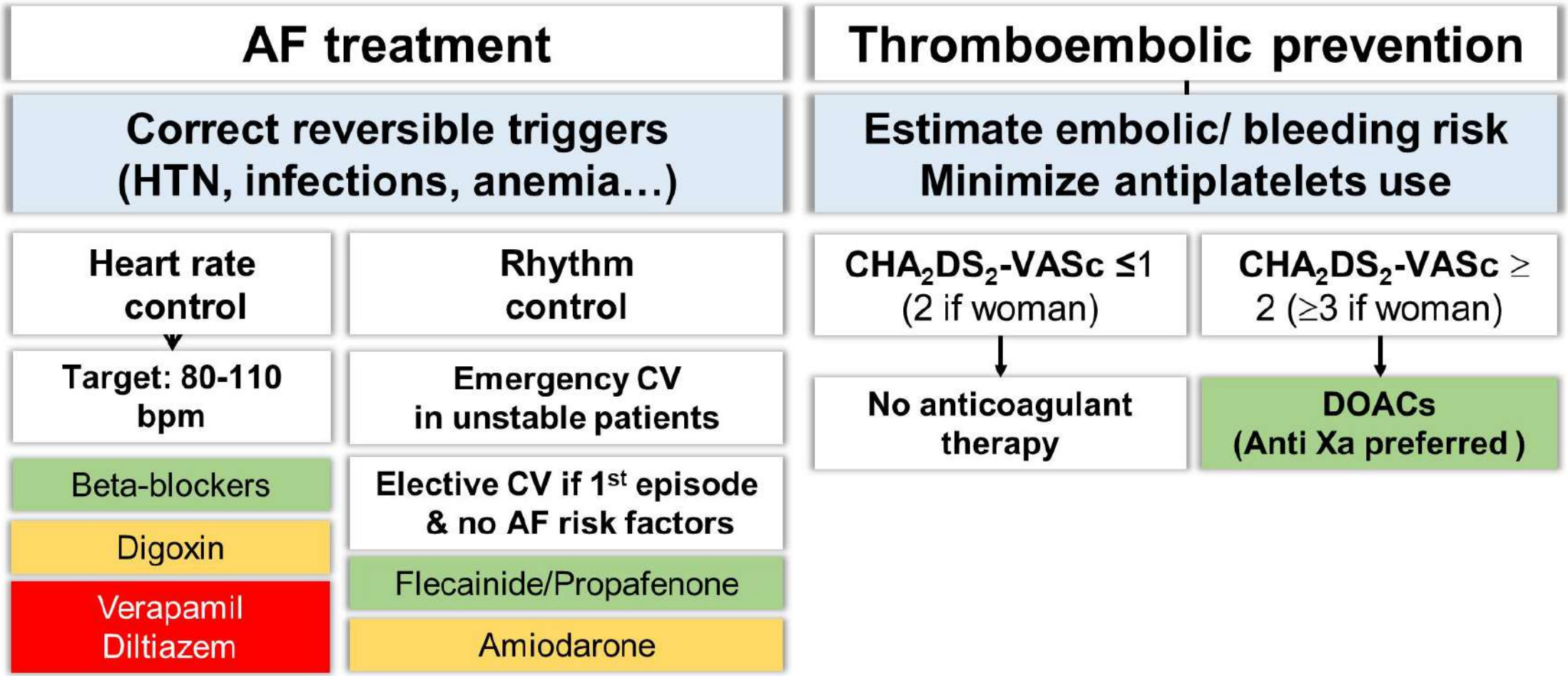
First Author, Year of Publication (Ref. #)	Population	Average Age (yrs)	Median Follow-Up (months)	Number of Subjects Who Received Ibrutinib (Sample Size Weight)	Ibrutinib Dose (mg)	Number of Subjects Who Developed AF in Ibrutinib Arm	Number of Subjects Who Developed AF in Control Arm	Number of Subjects Who Developed Grade 3 or Higher Bleeding
Byrd, 2013 (9)	Relapsed/refractory CLL	66	20.9	85 (3.92)	420 (n =51) 840 (n =34)	3 (3.5)	No control arm	4 (4.7)
Wang, 2013 (11)	Relapsed/refractory MCL	68	15.3	111 (5.12)	560	5 (4.5)	No control arm	5 (4.5)
O'Brien 2014 (20)	Frontline CLL	71	22.1	31 (1.43)	420-840	2 (6.5)	No control arm	Not reported
Byrd, 2014 (RESONATE Study) (10)	Relapsed/refractory CLL	67	9.4	195 (9.8)	420	10 (5)	1 (1)	2 (1)
Treon, 2015 (12)	Relapsed/refractory WM	63	19.1	63 (2.9)	420	3 (5)	No control arm	4 (6.3)*
Burger, 2014 (21)	Frontline and relapsed/ refractory CLL	63.2	18	40 (1.84)	420	2 (5)	No control arm	5 (12.5)†
Burger, 2015 (RESONATE-II Study) (8)	Frontline CLL	73	18.4	136 (6.27)	420	8 (5.9)	1 (0.75)	6 (4)
Farooqui, 2015 (19)	Frontline and relapsed/ refractory CLL	>65 (35) >18 (51)	28	86 (3.97)	420	14 (16) [11 (79) patients were >65 yrs of age and 3 (21) were <65 yrs of age]	No control arm	Not reported (study is ongoing)
Stilgenbauer, 2015 (RESONATE-17 trial) (24)	Relapsed/refractory CLL with del 17p	64	11.5	144 (6.64)	420	11 (6)	No control arm	7 (5)‡
Jaglowski, 2015 (25)	CLL/SLL/PLL	>65	12.5	71 (3.27)	420	6 (8.4)	No control arm	7 (10)
Romisher, 2015 (28)	CLL/MCL	65	Not stated	32 (1.47)	Not stated	5 (16)	No control arm	Not stated
Chahan-Khan, 2016 (22)	Relapsed/refractory CLL/SLL	64	17	289 (13.34)	420	21 (7.2)	7 (2.4)	12 (4)
Dreyling, 2016 (23)	Relapsed/refractory MCL	68	20	139 (6.41)	560	5 (3.5)	2 (1.4)	14 (10)
Wang, 2016 (26)	Relapsed/refractory MCL	67	16.5	50 (2.35)	560	7 (14)	No control arm	3 (6)
Gustine, 2016 (27)	WM	66	14.2	112 (5.17)	420	12 (10.7)	No control arm	Not reported
Wiczer, 2017 (6)	CLL, MCL, WM, other	65	32	582 (26.86)	420-560	76 (13)	No control arm	34 (5.8)§
Total			18.32	2,166		190 (8.15)‖		

Incidencia de FA aumenta con el tiempo

Incidencia: 5.77 por 100 pac/año

J Am Coll Cardiol EP 2018;4:1491–500

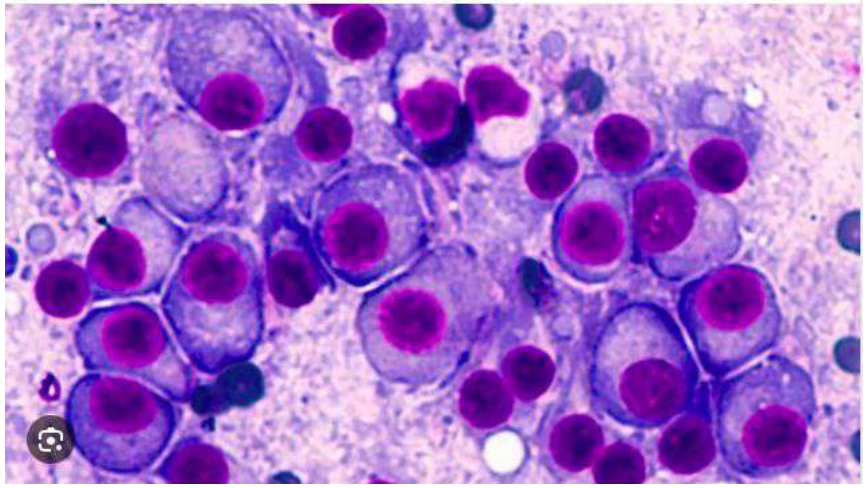
Non-valvular atrial fibrillation management under ibrutinib

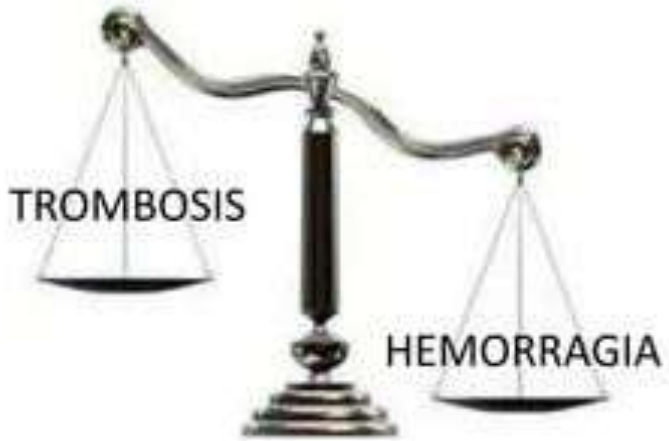


López-Fernández T, Canales M, Farmakis D et al Ann Hematol Oncol. 2018; 5(4): 1203

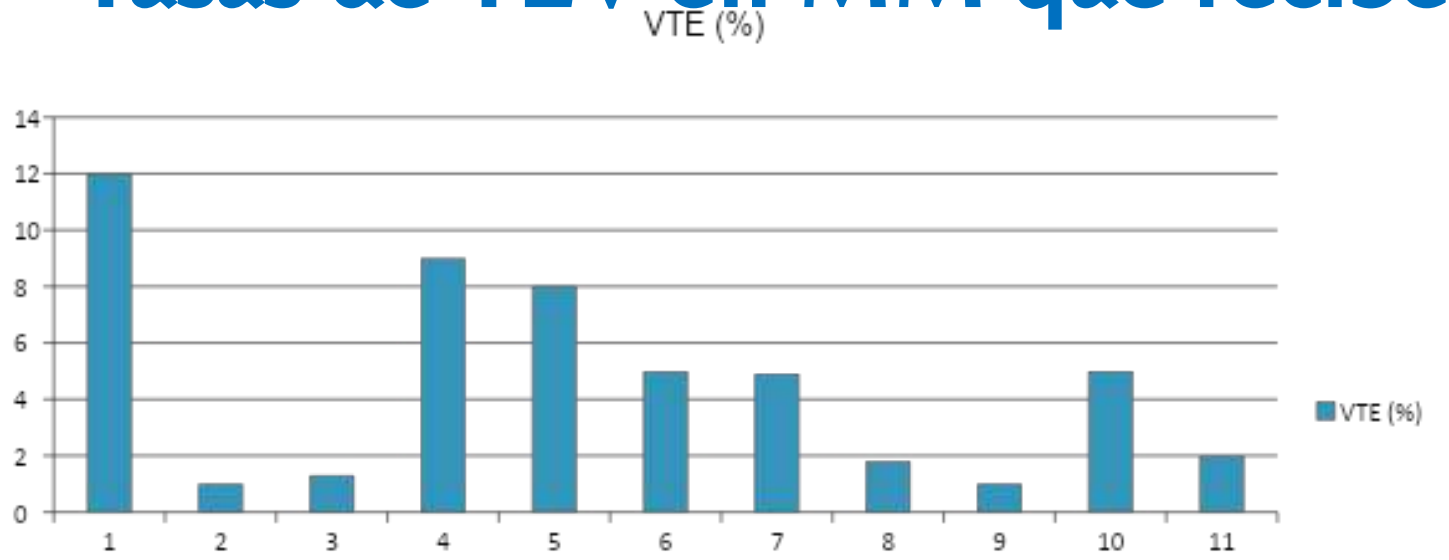
MIELOMA MÚLTIPLE – INMUNOMODULADORES (IMiD).

Riesgo de eventos trombóticos en la era de la terapia actual del mieloma múltiple.
¿Cuándo hacer tromboprofilaxis farmacológica?
¿AAS, HBPM o ACOD?





Tasas de TEV en MM que reciben IMiD



HGUGM+I. LEONOR:
EN 470 PACIENTES:
INCIDENCIA DE ETEV
12,9%
50% con IMID
Juarez et al, EHA 2018

Table 1
Risk factors for venous thrombosis in multiple myeloma patients

MM related factors	Patient related factors	Treatment related factors	Pro-coagulant related changes in MM or during treatment
Hyperviscosity	History of VTE	Multi agent chemotherapy	High FVIII and VWF levels
Newly diagnosed disease	Immobility	Use of thalidomide	High P-Selectin levels
Renal failure	High age	Use of lenalidomide	Increased fibrinogen
CRP	Obesity	High-dose dexamethasone	Increased MP-associated tissue factor activity
Chromosome 11 abnormalities	Paraplegia	Use of pomalidomide	Hypofibrinolysis
Light-chain disease	Genetic predisposition for VTE	Recombinant erythropoietin	Acquired protein C resistance
			Decreased protein S levels

Leebeek FW. Update of thrombosis in multiple myeloma. Thromb Res. 2016 Apr;140 Suppl 1:S76-80. doi: 10.1016/S0049-3848(16)30103-7. PMID: 27067983

La puntuación de Khorana no predice TEV en MM

- Cohorte de 2870 pacientes con MM
  - 1328 con riesgo bajo (0 puntos),
  - 1521 con riesgo intermedio (1-2 puntos)
  - 21 con riesgo alto (≥3 puntos)

6-month cumulative incidence of VTE stratified by Khorana Score point	
Khorana Score	6-Month Cumulative Incidence (95% CI)
0	5.1% (4.0%, 6.4%)
1	3.9% (3.0%, 5.1%)
2	3.6% (1.8%, 6.5%)
3-4	4.8% (0.3%, 20.2%)

c-statistic 0.53 at 6-months

Sanfilippo KM, Res Pract Thromb Haemost. 2022;6:e12634

Modelo de riesgos para el manejo de la tromboprofilaxis en MM que reciben talidomida-lenalidomida (IMWG)

Factores relacionados con el paciente

- Obesidad
- Previa ETV
- Catéter venoso central
- Comorbilidades: cardiaca, renal, DM
- Cirugía
- EPO
- Trombofilia

Factores relacionados con el MM

- MM al Diagnóstico
- Hiperviscosidad

Factores relacionados con el tratamiento

- Altas dosis de Dexametasona
- Doxurrubicina
- PoliQuimioterapia

ACCION

- ≤ 1 factor de riesgo: AAS
- ≥ 2 factor de riesgo: HBPM (enoxaparina 40 mg/día) ó AVK (INR: 2-3)
- Si altas dosis de Dex, Doxurrubicina o poliquimioT: HBPM o AVK

Palumbo A. *Leukemia.* 2008;22:414-23

Modelo de riesgos para el manejo de la tromboprofilaxis en MM que reciben talidomida-lenalidomida (IMWG)

ACCION

Palumbo A. Leukemia. 2008;22:414-23

- ≤ 1 factor de riesgo: AAS
- ≥ 2 factor de riesgo: HBPM (enoxaparina 40 mg/día) ó AVK (INR: 2-3)
- Si altas dosis de Dex, Doxurrubicina o poliquimioT: HBPM o AVK

- Los criterios del IMWG resultaron tener una capacidad discriminativa baja
  - Estadístico c de 0.52 en una cohorte Medicare
  - Estadístico c de 0.55 en una cohorte de veteranos estadounidenses.

Sanfilippo KM, Am J Hematol. 2019;94:1176-1184; Li A. Natl Compr Canc Netw. 2019;17:840-847

Score de riesgo ETEV MM

Table 1. International Myeloma Working Group risk assessment model.[7]

Individual risk factors
Obesity (BMI ≥30 kg/m²)
Previous venous thromboembolism
Central venous catheter or pacemaker
Associated diseases
Cardiac disease
Chronic renal disease
Diabetes
Acute infection
Immobilization
Blood clotting disorders
Surgery
General surgery
Any anesthesia
Trauma
Medications
Erythropoietin
Myeloma-related risk factors
Diagnosis
Hyperviscosity
Myeloma therapy
High-dose dexamethasone (≥480 mg/month)
Doxorubicin
Recommendations from the IMWG:
If no risk factor or any one risk factor is present:
Aspirin 81-325 mg once daily
If two or more risk factors are present:
LMWH (enoxaparin 40 mg once daily)
Full-dose warfarin (target INR 2-3)

BMI: body mass index; IMWG: International Myeloma Working Group; LMWH: low molecular weight heparin; INR: International Normalized Ratio.

Table 3. SAVED risk assessment model.[46]

Predictor	Acronym	Score
Surgery (within 90 days)	S	+ 2
Asian race	A	- 3
History of venous thromboembolism	V	+ 3
Eighty (age ≥80 years)	E	+ 1
Dexamethasone	D	
High dose (>160 mg/cycle)		+ 2
Standard dose (120-160 mg/cycle)		+ 1

Table 2. IMPEDE VTE risk assessment model.[45]

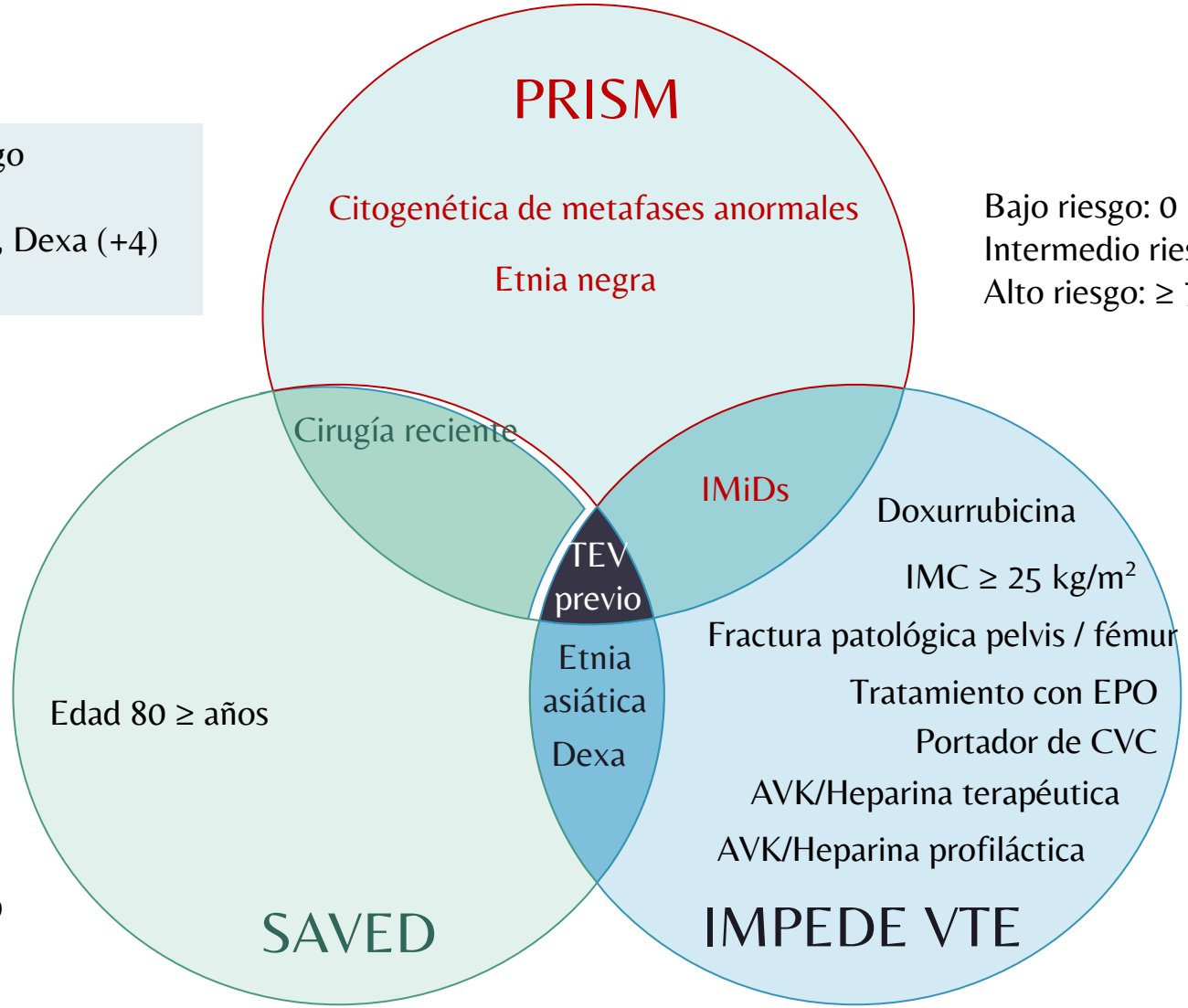
Predictor	Acronym	Score
Immunomodulatory drug	I	+ 4
Body Mass Index ≥ 25 kg/m²	M	+ 1
Pelvic, hip or femur fracture	P	+ 4
Erythropoiesis-stimulating agent	E	+ 1
Doxorubicin	D	+ 3
Dexamethasone		
High-dose (>160 mg/month)		+ 4
Low-dose (≤160 mg/month)		+ 2
Ethnicity/race = Asian/Pacific Islander	E	– 3
History of Venous thromboembolism before MM	V	+ 5
Tunneled line/central venous catheter	T	+ 2
Existing thromboprophylaxis: therapeutic LMWH or warfarin	E	- 4
Existing thromboprophylaxis: prophylactic LMWH or aspirin		- 3

MM: multiple myeloma; LMWH: low molecular weight heparin.

De Stefano V, Larocca A, Carpenedo M, Cavo M, Di Raimondo F, Falanga A, Offidani M, Petrucci MT, Ruggeri M, Santi RM, Barosi G. Thrombosis in multiple myeloma: risk stratification, antithrombotic prophylaxis, and management of acute events. A consensus-based position paper from an *ad hoc* expert panel. Haematologica. 2022 Nov 1;107(11):2536-2547.

Scores de riesgo trombótico en MM

PRISM: Dexa (+2) □ Intermedio riesgo
SAVED: Dexa (+2) □ Alto riesgo
IMPEDE VTE: IMiDs (+4), IMC (+1), Dexa (+4) □ Alto riesgo



Bajo riesgo: 0
Intermedio riesgo: 1-6
Alto riesgo: ≥ 7

Bajo riesgo: ≤ 1
Alto riesgo: ≥ 2

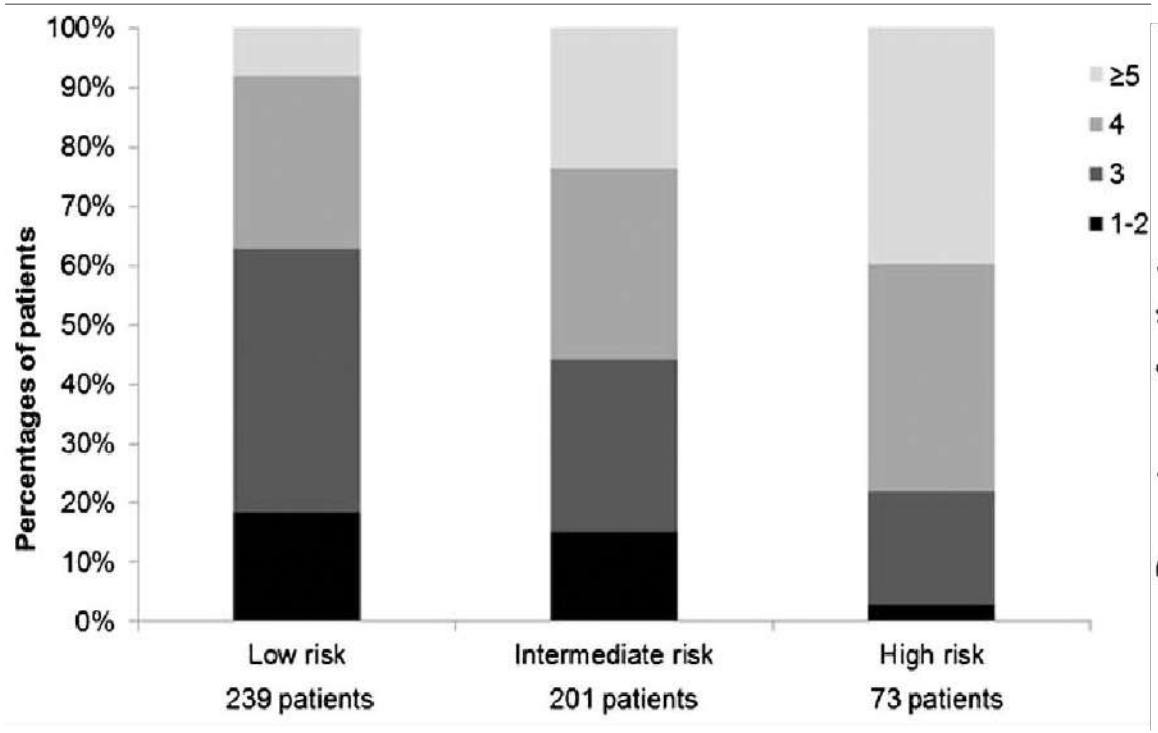
Bajo riesgo: ≤ 3
Intermedio riesgo: 4-7
Alto riesgo: ≥ 8

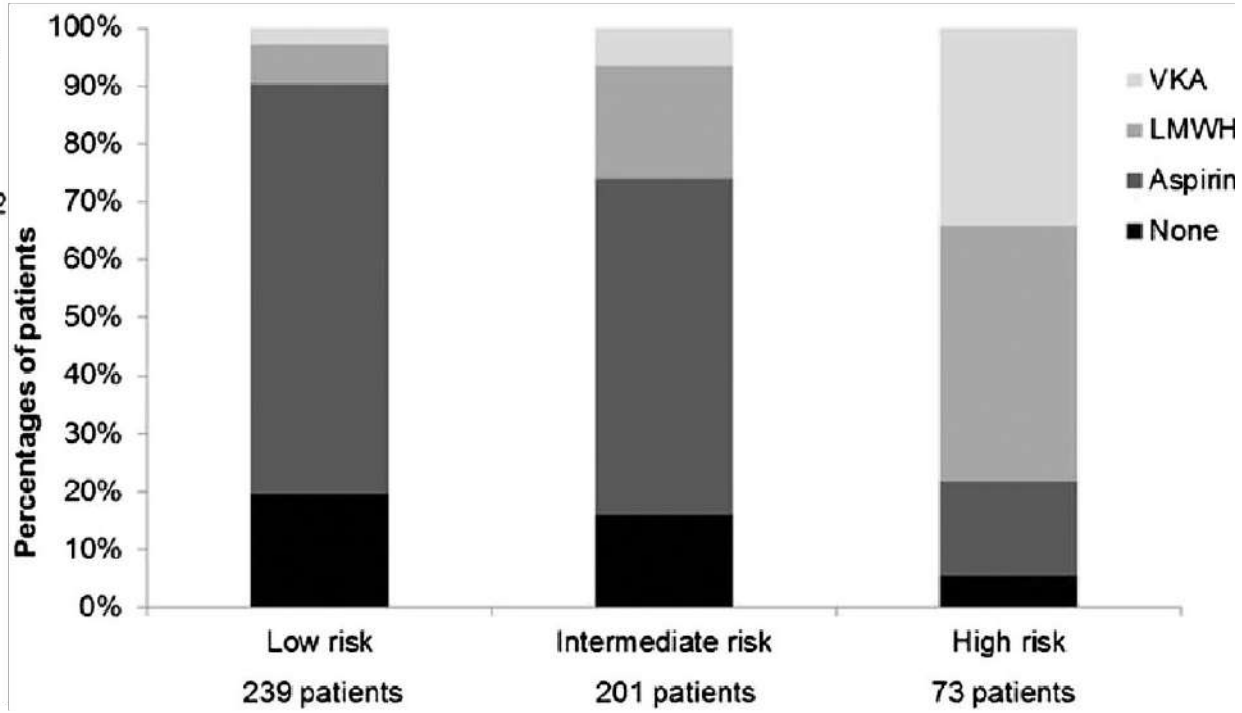
c-statistic, 0.60

c-statistic, 0.64

Chakraborty R. Blood. Ahead of print; Sanfilippo KM, Am J Hematol. 2019;94:1176-1184.; Li A. Natl Compr Canc Netw. 2019;17:840-847

¿Depende la elección de tromboprofilaxis de los factores de riesgo de TEV en la práctica clínica?





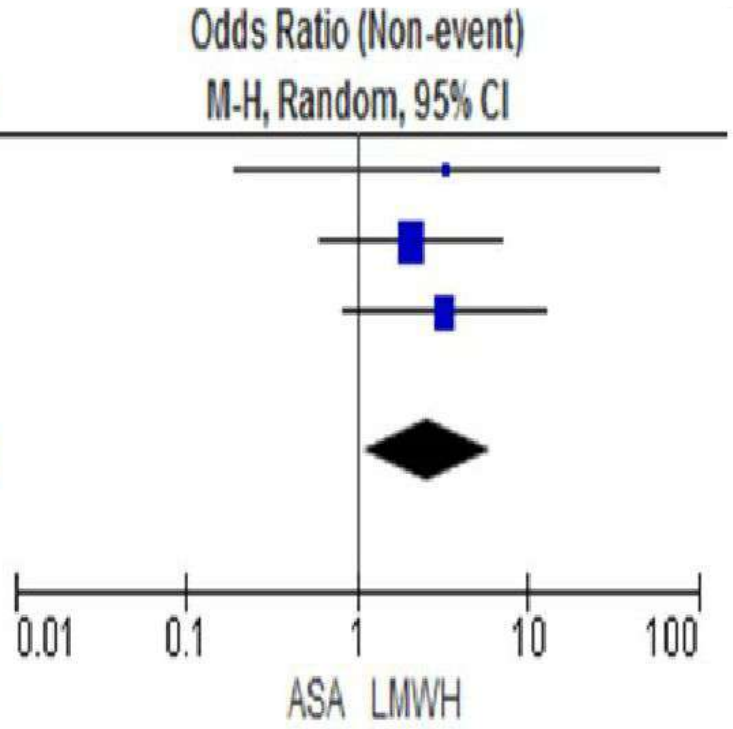
Chalayer E. Thromb Res.2016;143:101-102

La aspirina se asoció a mayor riesgo de TEV en comparación con HBPM en estudios longitudinales

Study or Subgroup	LMWH Events	LMWH Total	ASA Events	ASA Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
Bagratuni et al. 2013	0	20	12	165	9.4%	3.34 [0.19, 58.54]
Leleu et al. 2013	3	88	21	307	50.4%	2.08 [0.61, 7.14]
Zervas et., 2007	4	82	5	35	40.2%	3.25 [0.82, 12.93]
Total (95% CI)		**190**		**507**	**100.0%**	**2.60 [1.08, 6.25]**
Total events	7		38			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.26$, $df = 2$ ($P = 0.88$); $I^2 = 0\%$

Test for overall effect: $Z = 2.14$ ($P = 0.03$)



Zoppellaro G. Semin Hematol.2018;55:182-4

Tromboprofilaxis primaria con ACODs en MM

- AVERT[1] (Apixaban vs placebo) en Khorana ≥ 2 (25% linfoma) (1.1% MM)
  - Disminuye el riesgo de TEV / Aumenta el riesgo de hemorragia mayor
- CASSINI[2] (Rivaroxaban vs placebo) en Khorana ≥ 2 (7% linfoma) (No MM)
  - No reduce el riesgo de TEV / No aumenta el riesgo de hemorragia mayor
- Estudios observacionales de ACODs en MM con IMiDs

HNMCR: Hemorragia no mayor clínicamente relevante
HM: Hemorragia mayor

Autor	Diseño	Tromboprofilaxis	TEV	Hemorragia
Louzada[3] (2021) (análisis interino)	Ensayo aleatorizado	Rivaroxaban 10 mg (n=17) vs AAS (n=17)	Riva 0 AAS 1	0 1 HNMCR
Sayar[4] (2022)	Prospectivo brazo único	Apixaban 2.5 mg/12h (n=60)	0	1 HNMCR
Cornell[5] (2019)	Prospectivo brazo único	Apixaban 2.5 mg/12h (n=50)	0	3 HNMCR
Pegourie[6] (2019)	Prospectivo brazo único	Apixaban 2.5 mg/12h (n=50)	2	1 HM, 11 HNMCR
Piedra[7] (2022)	Retrospectivo	Rivaroxaban 10 mg/día (n=82)	4	1 HNMCR
Storrar[8] (2018)	Retrospectivo	Apixaban 2.5 mg/12h (n=70)	0	1 HM

1.- Carrier M. N Engl J Med. 2019;380:711-719; 2.- Khorana AA, N Engl J Med. 2019;380:720-72; 3.- Louzada M. Blood. 2021;138(suppl 1):323; 4.- Sayar Z. Thromb Res. 2022;213:27-29; 5- Cornell RF. Front Oncol. 2019;9:45; 6.- Pegourie B. Am J Hematol. 2019;94:635-640; 7.- Piedra K. J Haematol. 2022;196:105-109; 8.- Storrar NPF. Br. J Haemtol. 2019;185:142-144

GUIDELINE ARTICLE

Thrombosis in multiple myeloma: risk stratification, antithrombotic prophylaxis, and management of acute events. A consensus-based position paper from an *ad hoc* expert panel

De Stefano V, Larocca A, Carpenedo M, Cavo M, Di Raimondo F, Falanga A, Offidani M, Petrucci MT, Ruggeri M, Santi RM, Barosi G. Thrombosis in multiple myeloma: risk stratification, antithrombotic prophylaxis, and management of acute events. A consensus-based position paper from an *ad hoc* expert panel. Haematologica. 2022 Nov 1;107(11):2536-2547..

Box 1. Recommendations regarding thrombo-hemorrhagic risk factors and risk stratification in patients with multiple myeloma.

- *All patients with multiple myeloma who are candidates for active anti-myeloma treatment need evaluation for risk of thrombosis in order to prevent thromboembolic complications appropriately.*
- *Patient-, disease- and treatment-related factors should be evaluated.*
- *Patient-related factors include advanced age, personal and family history of venous thromboembolism, obesity, immobility, central venous catheter, acute infection or hospitalization, comorbidities, race (being Caucasian is a risk factor), recent surgery, and ongoing hormone therapy.*
- *There is no evidence to recommend universal laboratory testing for inherited thrombophilia. However, in the presence of a strong family history of venous thromboembolism, i.e. with one first-degree relative <50 years with one episode of venous thromboembolism or two first-degree relatives with one episode of venous thromboembolism, laboratory investigation for genetic thrombophilia should be considered, i.e. deficiency of antithrombin, protein C, protein S, factor V Leiden mutation, prothrombin G20210A mutation.*
- *Disease-related factors include: active multiple myeloma, evidence of hyperviscosity, pathological fracture of the pelvis, femur or spine conditioning immobilization or requiring surgery.*
- *Treatment-related factors include immunomodulatory drugs, especially in combination with high-dose dexamethasone, multiagent chemotherapy, or exposure to erythropoietin-stimulating agents.*
- *Even though risk assessment models such as the International Myeloma Working Group model and the IMPEDE and SAVED scores were validated for use in clinical prospective studies, the panel of experts agreed that there are not sufficient data to recommend one specific risk assessment model in clinical practice. The panel recommended that application of a risk assessment model should be consistent in a single center for all the patients.*
- *Besides thrombotic risk, it is recommended that bleeding risk is also assessed before anti-myeloma therapy is started. An accurate history should be collected from the patient and bleeding history investigated; prothrombin time, partial thromboplastin time, platelet count and fibrinogen level should be evaluated.*
- *Patients with alterations of first-line diagnostic tests indicative of a bleeding predisposition, or with a history of bleeding should be carefully evaluated by second-line diagnostic tests in cooperation with an expert in coagulation.*

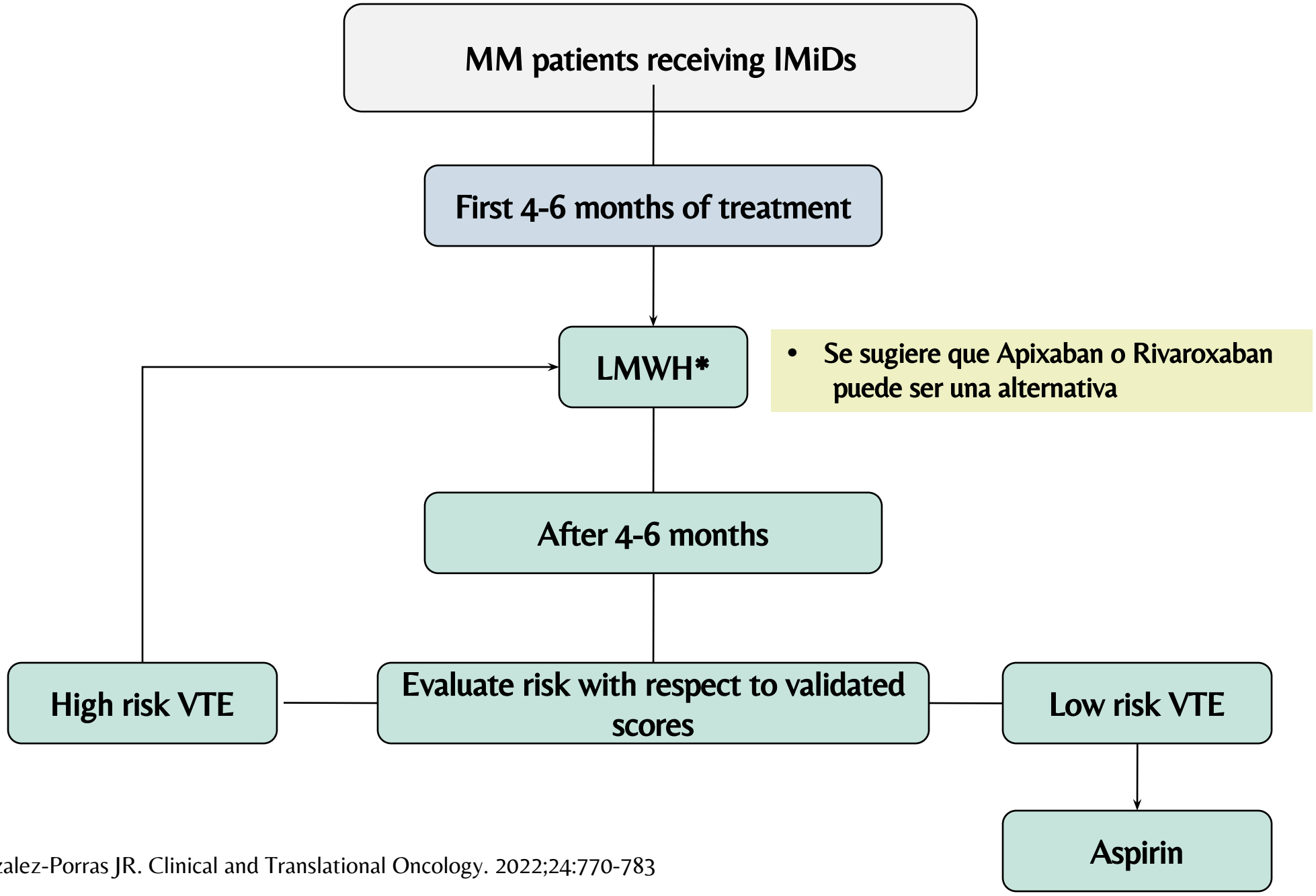
Box 2. Recommendations regarding primary antithrombotic prophylaxis in patients with multiple myeloma.

- *All patients with multiple myeloma who are candidates for active anti-myeloma treatment should be considered for thromboprophylaxis.*
- *The type, intensity and duration of thromboprophylaxis should be tailored according to the individual's baseline thrombotic and hemorrhagic risk profiles.*
- *Severe thrombocytopenia (platelet count <20x10^9/L), active bleeding, congenital bleeding disorders (hemophilia, von Willebrand disease, severe deficiency of coagulation factors), and acquired coagulopathy that cannot be corrected (e.g. severe liver disease) are absolute contraindications to thromboprophylaxis.*
- *Mild thrombocytopenia (platelet count <50x10^9/L), a history of bleeding, and acquired coagulopathy with a chance of correction are relative contraindications to thromboprophylaxis.*
- *To ensure appropriate, safe and effective thromboprophylaxis and to avoid the risks of bleeding and potential thrombotic complications, it is recommended that the drug-drug interactions of antithrombotic agents and anti-myeloma drugs are considered.*
- *Patients' compliance and patients' preferences should be considered in the choice of thromboprophylaxis, and patients should be adequately informed about their thrombotic risk.*
- *Patients at low risk of thrombosis, i.e. those aged less than 75 years, with a normal body mass index, without fractures, a central venous catheter, or co-morbidities and not planned to receive therapy with immunomodulatory drugs, should not be given thromboprophylaxis or can be given thromboprophylaxis with low-dose aspirin. The criterion for the choice is the individual hemorrhagic risk.*
- *All other patients should receive thromboprophylaxis, with low molecular weight heparin as the first choice.*
- *Patients without other risk factors for thrombosis except for a planned therapy containing an immunomodulatory drug and with a contraindication, strong aversion or documented poor compliance to low molecular weight heparin therapy, could be given aspirin as thromboprophylaxis.*

• *Preliminary data on the efficacy and safety of apixaban and rivaroxaban as primary thromboprophylaxis in patients receiving immunomodulatory drugs are promising. However, there is no strong evidence in favor of direct oral anticoagulants instead of a low molecular weight heparin.*
• *Off-label prescription of apixaban as primary antithrombotic prophylaxis in patients with contraindications to low molecular weight heparin (e.g., for allergy) should be considered.*

• *The duration of thromboprophylaxis should be modulated according to the length of anti-myeloma treatment and evolving risk factors. Prophylaxis should continue as long as a thrombotic risk is present (e.g., active disease or assumption of drugs with a thrombotic risk).*

• *Patients with relapsed multiple myeloma should receive thromboprophylaxis during the treatment according to the indications recommended for newly diagnosed patients.*
• *For patients under lenalidomide maintenance, thromboprophylaxis is indicated even if thromboembolic events are less frequent than during newly diagnosed disease. In these patients, prophylactic aspirin 100 mg/day is recommended.*
• *In patients with renal insufficiency, the most appropriate prophylaxis should be chosen according to the degree of renal function. For patients with a creatinine clearance below 30 mL/min, low molecular weight heparin with dose adjustments is the preferred prophylaxis. Dose adjustments of low molecular weight heparin according to creatinine clearance value are recommended (Table 5).*
• *During antithrombotic prophylaxis, the platelet count should be monitored, particularly in patients receiving anti-myeloma therapeutic combinations that are at high risk of causing thrombocytopenia.*
• *Thromboprophylaxis should be stopped if the platelet count decreases to less than 20-30x10^9/L. Dose reductions should be applied when the platelet count is 30-50x10^9/L. Full-dose thromboprophylaxis can be used when the platelet count is over 50x10^9/L.*
• *Primary thromboprophylaxis should be stopped in the case of clinically relevant or major bleeding. In this circumstance, the cause of bleeding should be evaluated and eventually corrected before restarting thromboprophylaxis.*

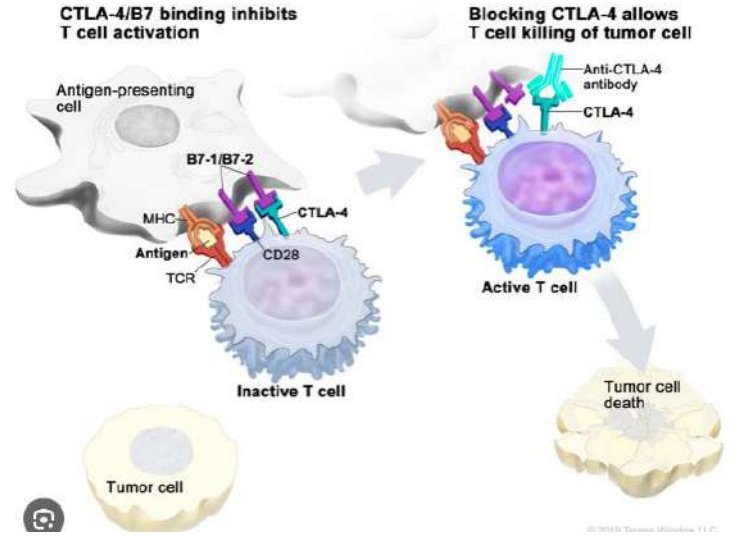


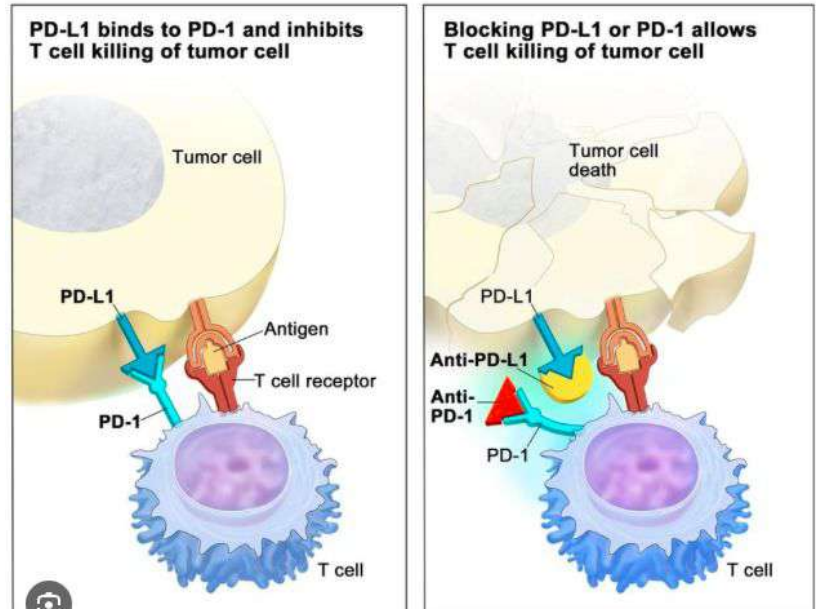
Gonzalez-Porras JR. Clinical and Translational Oncology. 2022;24:770-783

Inhibidores del punto de control ("checkpoint inhibitors")

- Diferentes fármacos:
  - Anti-CTLA-4: ipilimumab, tremelimumab
  - Anti-PD1: nivolumab, pembrolizumab, cemiplimab
  - Anti-PD-L1: atezolizumab, avelumab, durvalumab

- Aprobados en tumores de alto y bajo riesgo de ETV:
  - En monoterapia IO
  - En combinación con inmunoterapia IO + IO
  - En combinación con quimioterapia QT + IO





Current Oncology

MDPI

Review

Immune Checkpoint Inhibitors-Associated Thrombosis: Incidence, Risk Factors and Management

Tzu-Fei Wang * and Marc Carrier

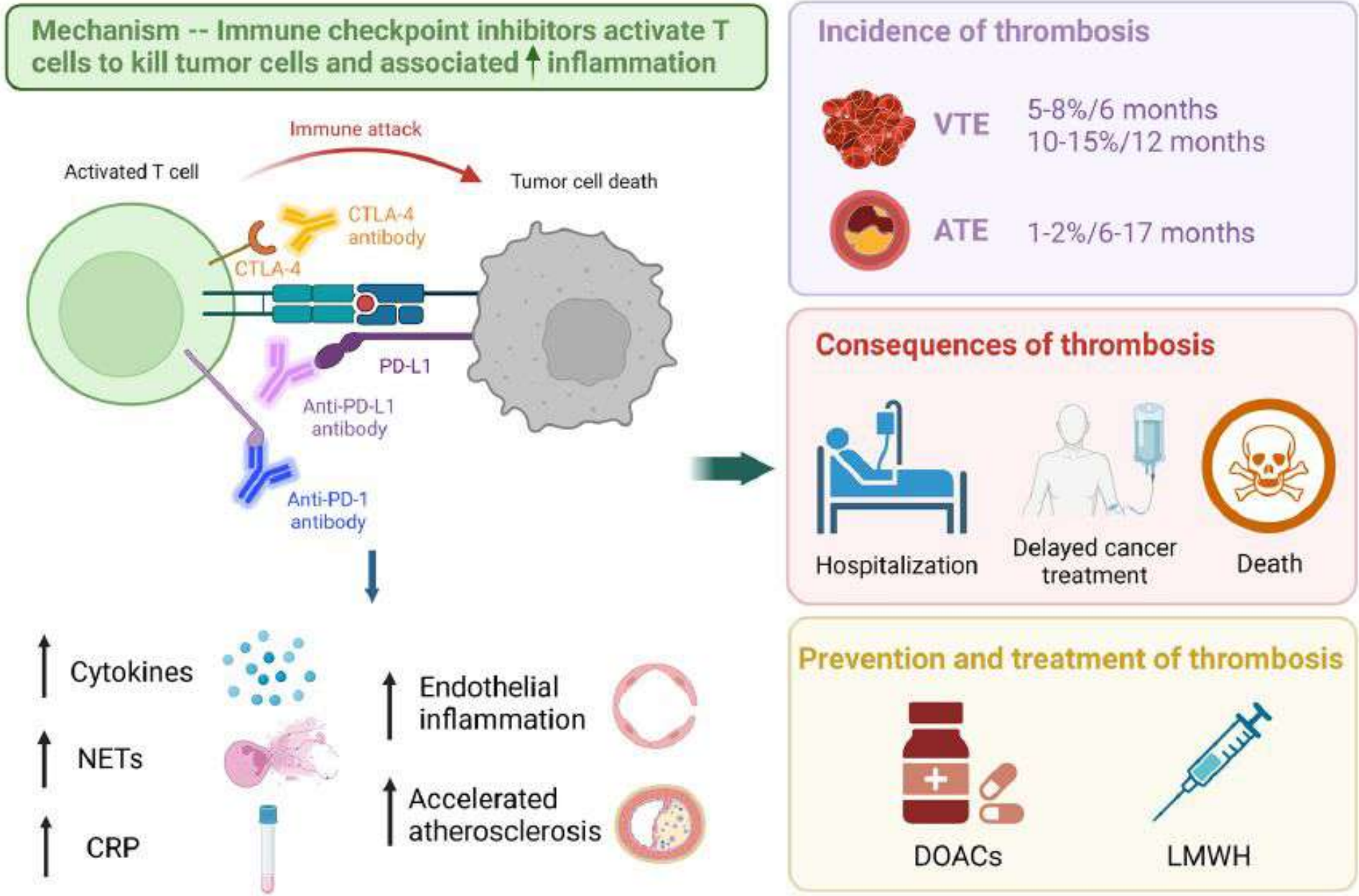
Department of Medicine, University of Ottawa at The Ottawa Hospital and Ottawa Hospital Research Institute, Ottawa, ON K1H 8L6, Canada
* Correspondence: tzwang@toh.ca; Tel.: +1-613-737-8899

Table 1. Summary of approved immune checkpoint inhibitors (and their indications).

Immune Checkpoint Inhibitors	Target	Approved Indication
Ipilimumab	CTLA-4	Melanoma NSCLC RCC Colorectal cancer Malignant pleural mesothelioma
Pembrolizumab	PD-1	Melanoma NSCLC Urothelial carcinoma RCC Bladder cancer Esophageal/esophagogastric junction cancer Colorectal cancer Endometrial cancer Cervical cancer Breast cancer Head and neck squamous cell carcinoma Hodgkin lymphoma Primary mediastinal B cell lymphoma
Nivolumab	PD-1	Melanoma NSCLC RCC Head and neck squamous cell carcinoma Classical Hodgkin lymphoma Hepatocellular carcinoma
Cemiplimab	PD-1	NSCLC Cutaneous squamous cell carcinoma Cutaneous basal cell carcinoma Cervical cancer
Atezolizumab	PD-L1	NSCLC Small cell lung cancer Urothelial carcinoma
Avelumab	PD-L1	Urothelial carcinoma Merkel cell carcinoma
Durvalumab	PD-L1	NSCLC Urothelial carcinoma

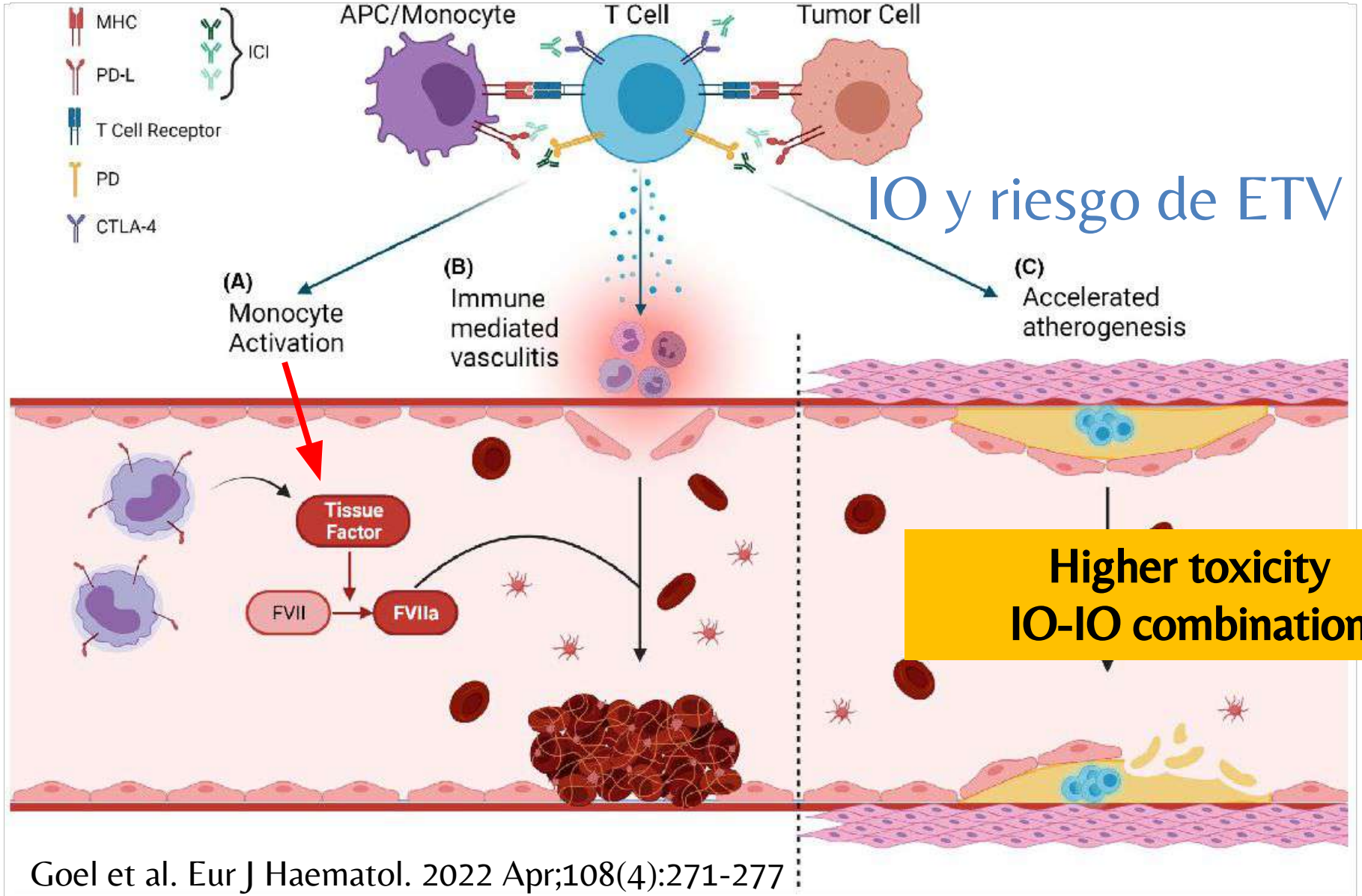
Mostly approved for unresected or metastatic cancers, refer to individual monographs for detailed approval indications for each cancer. Abbreviations: NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma.

Wang TF, Carrier M. Immune Checkpoint Inhibitors-Associated Thrombosis: Incidence, Risk Factors and Management. Curr Oncol. 2023 Mar 4;30(3):3032-3046.



Wang TF, Carrier M. Immune Checkpoint Inhibitors-Associated Thrombosis: Incidence, Risk Factors and Management. Curr Oncol. 2023 Mar 4;30(3):3032-3046.

IO y riesgo de ETV



Higher toxicity
IO-IO combination

Goel et al. Eur J Haematol. 2022 Apr;108(4):271-277

FIGURE 1 Possible mechanism by which immune checkpoint inhibitors may lead to thrombosis. T-cell activation after anti-PD-1/PD-L1 or anti-CTLA-4 leads to (A) monocyte activation, which leads to the release of tissue factor that initiates the coagulation cascade, (B) immune-mediated vasculitis, which causes endothelial damage and initiates vascular events to form a thrombus at the site of damage, and (C) deficiency in PD-1, which is known to aggravate hypercholesterolemia and increase macrophage infiltration of atherosclerotic plaques and enhance vascular inflammation and accelerate atherosclerosis

Inhbidores del punto de control ("checkpoint inhibitors") y ETtrombótica

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma

Y. Doki, J.A. Ajani, K. Kato, J. Xu, L. Wyrwicz, S. Motoyama, T. Ogata, H. Kawakami, C.-H. Hsu, A. Adenis, F. El Hajbi, M. Di Bartolomeo, M.I. Braghiroli, E. Holtved, S.A. Ostoich, H.R. Kim, M. Ueno, W. Mansoor, W.-C. Yang, T. Liu, J. Bridgewater, T. Makino, I. Xynos, X. Liu, M. Lei, K. Kondo, A. Patel, J. Gricar, I. Chau, and Y. Kitagawa, for the CheckMate 648 Trial Investigators*

Supplementary Appendix

Decenas de ECA fase II y III
sin encontrar aumento del riesgo

No descrito en la toxicidad
¿Infrarreportado?

Otras tox infrecuentes
SI descritas (por ej. neuritis óptica)

Table 3. Treatment-Related Adverse Events in All the Patients Who Received Trial Treatment.*

Event	Nivolumab plus Chemotherapy (N=310)		Nivolumab plus Ipilimumab (N=322)		Chemotherapy (N=304)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)					
Any treatment-related adverse event	297 (96)	147 (47)	256 (80)	102 (32)	275 (90)	108 (36)
Treatment-related serious adverse event	74 (24)	57 (18)	103 (32)	73 (23)	49 (16)	38 (12)
Treatment-related adverse event leading to trial-drug discontinuation†	106 (34)	29 (9)	57 (18)	41 (13)	59 (19)	14 (5)
Treatment-related adverse event leading to death‡	5 (2)	—	8 (2)	—	6 (2)	—
Treatment-related adverse events reported in ≥10% of patients in any group						
Nausea	182 (59)	11 (4)	26 (8)	1 (<1)	158 (52)	8 (3)
Decreased appetite	132 (43)	13 (4)	19 (6)	5 (2)	130 (43)	9 (3)
Stomatitis	98 (32)	20 (6)	14 (4)	0	71 (23)	5 (2)
Anemia	93 (30)	30 (10)	12 (4)	2 (1)	67 (22)	17 (6)
Decreased neutrophil count	65 (21)	25 (8)	2 (1)	0	52 (17)	24 (8)
Fatigue	61 (20)	7 (2)	29 (9)	4 (1)	50 (16)	11 (4)
Diarrhea	60 (19)	3 (1)	32 (10)	2 (1)	46 (15)	6 (2)
Constipation	59 (19)	2 (1)	7 (2)	1 (<1)	66 (22)	1 (<1)
Vomiting	56 (18)	7 (2)	18 (6)	4 (1)	49 (16)	9 (3)
Malaise	50 (16)	1 (<1)	12 (4)	0	45 (15)	0
Decreased white-cell count	43 (14)	11 (4)	3 (1)	0	28 (9)	6 (2)
Hiccups	42 (14)	0	2 (1)	0	53 (17)	0
Increased blood creatinine level	39 (13)	1 (<1)	5 (2)	0	32 (11)	1 (<1)
Decreased platelet count	36 (12)	3 (1)	6 (2)	0	32 (11)	5 (2)
Mucosal inflammation	33 (11)	8 (3)	4 (1)	0	26 (9)	4 (1)
Alopecia	31 (10)	0	2 (1)	0	32 (11)	0
Rash	24 (8)	1 (<1)	55 (17)	7 (2)	5 (2)	0
Pruritus	23 (7)	0	43 (13)	3 (1)	2 (1)	0
Hypothyroidism	18 (6)	0	43 (13)	0	0	0

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 1, 2021 VOL. 384 NO. 13

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer

R.J. Kelly, J.A. Ajani, J. Kuzdzal, T. Zander, E. Van Cutsem, G. Piessen, G. Mendez, J. Feliciano, S. Motoyama, A. Lièvre, H. Uronis, E. Elimova, C. Grootscholten, K. Geboes, S. Zafar, S. Snow, A.H. Ko, K. Feeney, M. Schenker, P. Kocon, J. Zhang, L. Zhu, M. Lei, P. Singh, K. Kondo, J.M. Cleary, and M. Moehler, for the CheckMate 577 Investigators*

Table 2. Adverse Events in the Safety Population.*

Event	Nivolumab (N = 532)		Placebo (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event†	510 (96)	183 (34)	243 (93)	84 (32)
Serious adverse event	158 (30)	107 (20)	78 (30)	53 (20)
Adverse event leading to discontinuation of trial regimen	68 (13)	38 (7)	20 (8)	16 (6)
Any adverse event related to nivolumab or placebo†‡	376 (71)	71 (13)	119 (46)	15 (6)
Serious adverse event related to nivolumab or placebo§	40 (8)	29 (5)	7 (3)	3 (1)
Related adverse event leading to discontinuation of trial regimen‡	48 (9)	26 (5)	8 (3)	7 (3)
Adverse event related to nivolumab or placebo in ≥5% of patients in either group†				
Fatigue	90 (17)	6 (1)	29 (11)	1 (<1)
Diarrhea	88 (17)	2 (<1)	39 (15)	2 (<1)
Pruritus	53 (10)	2 (<1)	9 (3)	0
Rash	52 (10)	4 (<1)	10 (4)	1 (<1)
Hypothyroidism	50 (9)	0	4 (2)	0
Nausea	47 (9)	0	13 (5)	0
Hyperthyroidism	35 (7)	0	1 (<1)	0
Arthralgia	30 (6)	1 (<1)	4 (2)	0
Increase in AST level	29 (5)	2 (<1)	10 (4)	0
Asthenia	28 (5)	0	4 (2)	0
Decreased appetite	26 (5)	0	5 (2)	0

Table 2. Summary of incidence rates of venous and arterial thrombosis from retrospective studies of cancer patients receiving immune checkpoint inhibitors (studies missing follow-up durations were not included).

Study	Country	N	Type of Cancer	Stage IV	Follow-up [Median (IQR)]	VTE Incidence % (95% CI)	ATE Incidence % (95% CI)
Hegde et al. 2017 [20] Abstract	USA	76	Lung	N/A	10.8 mo	18.4	2.6
Ibrahimi et al. 2017 [21] Abstract	USA	154	Lung 20.8% Melanoma 20.1% Ovarian 12.3%	92%	7 mo (198 days)	10.4	0
Bar et al. 2019 [22]	Israel	1215	All cancers Melanoma 40.5% Lung 28.7%	N/A	12 mo	AVE (MI, stroke, PE, DVT) 6 mo: 4.9 12 mo: 5.8	
Nichetti et al. 2019 [23]	Italy	217	NSCLC	95.4%	37.8 mo	7.4	6.5
Ando et al. 2020 [24]	Japan	122	Lung, kidney, stomach, urothelial, melanoma	N/A	N/A Time to thrombosis 90 days (range 6–178)	4.1	4.9
Drobni et al. 2020 [25]	USA	2842	All cancers NSCLC 28.8% Melanoma 27.9%	N/A	2 years	N/A	Composite: 5.35/100 person-yrs MI: 2.49 Stroke: 2.08
Deschênes-Simard et al. 2021 [26]	Canada	593	NSCLC	87.2%	12.7 (4.9–22.7) mo	9.9 (7.5–12.3) 76.5 (59.9–97.8) per 1000 person-years	1.3

Wang TF, Carrier M. Immune Checkpoint Inhibitors-Associated Thrombosis: Incidence, Risk Factors and Management. Curr Oncol. 2023 Mar 4;30(3):3032-3046.

Study	Country	N	Type of Cancer	Stage IV	Follow-up [Median (IQR)]	VTE Incidence % (95% CI)	ATE Incidence % (95% CI)
Gong et al. 2021 [27]	USA	2854	All cancers NSCLC 28.4% Melanoma 28.2%	N/A	194 days (IQR 65–412)	6 mo: 7.4 12 mo: 13.8	N/A
Gutierrez-Sainz et al. 2021 [28]	Spain	229	Lung 48% Melanoma 23.6% RCC 11.8%	96.5%	9.8 mo	7 (4–10)	N/A
Guven et al. 2021 [29]	Turkey	133	RCC 26.3% Melanoma 24.1% NSCLC 18.8%	100%	10.1 (5.8–18.5) mo	11.3	N/A
Haist et al. 2021 [30]	Germany	280	Melanoma	100%	28 mo (95% CI 23.4–32.6)	12.5	4.3
Hill et al. 2021 [31]	USA	435 (a) ICI: 171 (b) ICI+chemo: 157 (c) chemo then durvalumab: 107	NSCLC	47%	N/A	6 mo: (a) 7.6 (4.3–12.2) (b) 9.9 (5.8–15.3) (c) 9.4 (4.8–15.8) 12 mo: (a) 9.0 (5.3–14.0) (b) 12.8 (7.8–19.0) (c) 12.2 (6.8–19.2)	N/A
Icht et al. 2021 [32]	Israel	176	NSCLC	85.8%	6 mo (187 days)	4.5 (2.1–8.3)	N/A
Kewan et al. 2021 [33]	USA	552	All cancers NSCLC 47.3%	100%	12.1 mo	12.1	1.3
Madison et al. 2021 [34] ^	USA	6127	Lung	N/A	6 mo	6.3	2.6
Moik et al. 2021 [35]	Austria	672	Melanoma 30.4% NSCLC 24.1% RCC 11%	85.8%	8.5 mo	6 mo: 5.0 (3.4–6.9) 12mo: 7.0 (5.1–9.3) Overall: 12.9	6 mo: 1.0 (0.4–2.0) 12 mo: 1.8 (0.7–3.6) Overall 1.8

Wang TF, Carrier M. Immune Checkpoint Inhibitors-Associated Thrombosis: Incidence, Risk Factors and Management. Curr Oncol. 2023 Mar 4;30(3):3032-3046.

Table 2. *Cont.*

Study	Country	N	Type of Cancer	Stage IV	Follow-up [Median (IQR)]	VTE Incidence % (95% CI)	ATE Incidence % (95% CI)
Canovas et al. 2022 [38]	Spain	665	Lung	91.2%	14 mo	6.9	1.5
						All thrombosis: 8.4 (6.23–10.6)	
		291	Melanoma	82.5%	17 mo	4.8	1.0
						All thrombosis: 5.8 (3.34–9.18)	
Endo et al. 2022 [39]	Japan	120	Lung	62.5%	within 6 mo	2.5	4.2
Khorana et al. 2023 [40] ^	USA	(a) ICI: 605 (b) ICI+chemo: 602	NSCLC	100%	9.1 mo	6 mo: (a) 8.1 (b) 12.8 12 mo: (a) 13.5 (10.6–16.5) (b) 22.4 (20.2–24.5)	N/A
May et al. 2022 abstract [41] ^	USA	1823	All cancers	N/A	6 mo	7.3	N/A
Sanfilippo et al. 2022 abstract [42] ^	USA	1754	All cancers	77.9%	6 mo	4.1	N/A
Sheng et al. 2022 [19]	USA	279	Urothelial	100%	5.6 mo	13	2
						Total thromboembolism: 6 mo: 9.1 (6.0–13.0)	

Wang TF, Carrier M. Immune Checkpoint Inhibitors-Associated Thrombosis: Incidence, Risk Factors and Management. Curr Oncol. 2023 Mar 4;30(3):3032-3046.

Factores de riesgo

Table 4. Risk factors for thrombosis and mortality identified in patient cohorts receiving immune checkpoint inhibitors.

Study	Risk factors for Thrombosis (Multivariable)	Risk Factors for Mortality
Hegde et al. 2017 [20] (Abstract)	Female	VTE before ICI
Bar et al. 2019 [22]	NSCLC H/o AVE Hypertension Dyslipidemia	AVE
Nichetti et al. 2019 [23]	Current smoker PD-L1 > 50%	TE
Ando et al. 2020 [24]	h/o thromboembolism	N/A
Drobni et al. 2020 [25]	Overall study: ICIs, age, h/o stroke, diabetes, hypertension, NSCLC, male, h/o radiation	N/A
Deschênes-Simard et al. 2021 [26]	Age < 65 Higher PD-L1 level Smoking <12 mo from diagnosis to ICIs	VTE is not correlated with survival
Gong et al. 2021 [27]	Age ≤ 65 Khorana score ≥ 2 h/o hypertension Strong trend: h/o VTE (HR 1.42, 95% CI 0.99–2.06) (melanoma is associated with decreased risks)	N/A
Gutierrez-Sainz et al. 2021 [28]	Female Melanoma	VTE is not an independent risk factor
Guven et al. 2021 [29]	ECOG ≥ 1	VTE (trend, not significant)

Khorana no buen predictor de ETEV

Wang TF, Carrier M. Immune Checkpoint Inhibitors-Associated Thrombosis: Incidence, Risk Factors and Management. Curr Oncol. 2023 Mar 4;30(3):3032-3046.

Consequences of Thrombosis in Patients on Immune Checkpoint Inhibitors

La trombosis puede dar lugar a hospitalizaciones, retrasos en el tratamiento oncológico y otras formas de morbilidad y mortalidad.

Wang TF, Carrier M. Immune Checkpoint Inhibitors-Associated Thrombosis: Incidence, Risk Factors and Management. Curr Oncol. 2023 Mar 4;30(3):3032-3046.
Sheng, I.Y.; Gupta, S.; Reddy, C.A.; Angelini, D.; Funchain, P.; Sussman, T.A.; Sleiman, J.; Ornstein, M.C.; McCrae, K.; Khorana, A.A. Thromboembolism in Patients with Metastatic Renal Cell Carcinoma Treated with Immunotherapy. Target Oncol. 2021, 16, 813–821.
19. Sheng, I.Y.; Gupta, S.; Reddy, C.A.; Angelini, D.; Funchain, P.; Sussman, T.A.; Sleiman, J.; Ornstein, M.C.; McCrae, K.; Khorana, A.A. Thromboembolism in Patients with Metastatic Urothelial Cancer Treated with Immune Checkpoint Inhibitors. Target Oncol. 2022, 17, 563–569.

Prevention and Treatment of Thrombosis in Patients on Immune Checkpoint Inhibitors

AVERT y CASSINI han demostrado la eficacia y la seguridad de las dosis profilácticas de apixabán y rivaroxabán, respectivamente, en la prevención de ETEV asociada al cáncer con riesgo intermedio-alto (puntuación de Khorana 2).

Desde entonces, las principales directrices internacionales han sugerido que se considere la profilaxis primaria de la TEV en esta población.

No está claro si puede aplicarse también a los pacientes que reciben ICI.

Score Khorana, derivada de una población tratada con quimioterapia, ha demostrado ser subóptima en la estratificación del riesgo para los pacientes que reciben ICI.

Los pacientes con una puntuación de Khorana de 2 en quimioterapia se asocian con un riesgo de TEV a los 6 meses del 9-10%, y si la población tratada con ICI con un riesgo de TEV a los 6 meses del 5-8% puede obtener suficientes beneficios para garantizar la tromboprofilaxis primaria en todos los pacientes que reciben ICI sigue siendo objeto de investigación.

Wang TF, Carrier M. Immune Checkpoint Inhibitors-Associated Thrombosis: Incidence, Risk Factors and Management. Curr Oncol. 2023 Mar 4;30(3):3032-3046.

Treatment of Thrombosis in Patients on Immune Checkpoint Inhibitors

- El tratamiento de la TEV asociada al cáncer en pacientes que reciben ICI no suele diferir del resto de trombosis asociadas al cáncer.
- La anticoagulación es el pilar del tratamiento, siendo los **ACODS** y la **HBPM** los anticoagulantes más utilizados en la población oncológica;
- La ele… …características del pa… …rragia, las prefe…

FINANCIACIÓN

Lyman, G.H.; Carrier, M.; Ay, C.; Di Nisio, M.; Hicks, L.K.; Khorana, A.A.; Leavitt, A.D.; Lee, A.Y.Y.; Macbeth, F.; Morgan, R.L.; et al. American Society of Hematology 2021 guidelines for management of venous thromboembolism: Prevention and treatment in patients with cancer. Blood Adv. 2021, 5, 927–974.

Carrier, M.; Blais, N.; Crowther, M.; Kavan, P.; Le Gal, G.; Moodley, O.; Shivakumar, S.; Suryanarayan, D.; Tagalakis, V.; Wu, C.; et al. Treatment Algorithm in Cancer-Associated Thrombosis: Updated Canadian Expert Consensus. Curr. Oncol. 2021, 28, 5434–5451.

Conclusiones

- El equilibrio hemostático puede verse afectado por múltiples causas.
- Los fármacos antineoplásicos son uno de ellos.
- El hematólogo, especialmente el "***Hemostasiologo***" que en la mayoría de los casos actuaremos de interconsultor debemos de conocer perfectamente estos riesgos.
- IBTK, riesgo hemorrágico.
- La profilaxis de ETEV es la mejor estrategia.
- La trombosis arterial, a tener en cuenta en los pacientes con Check-point inhibitors.
- ACODs cada vez mas consilidados tb en este escenario.

crisizquierdo3@yahoo.es
@crisizquierdo3