Hôpital Européen
MARSEILLE | L'humain au cœur de nos soins

ZAPPING MEDICAL #3

Maladie veineuse thrombo-embolique et cancer : plein de nouveautés

Serge Cohen et Walfroy Radix

Mardi 6 Juin 2023

Euro FMC
La formation est une de nos missions

MVTE ET CANCER

- 2O % des patients avec cancer développent une MVTE
- 2 ème cause de mortalité
- Prévalente , complique le cancer ou les traitements
- Risque accru de récidive

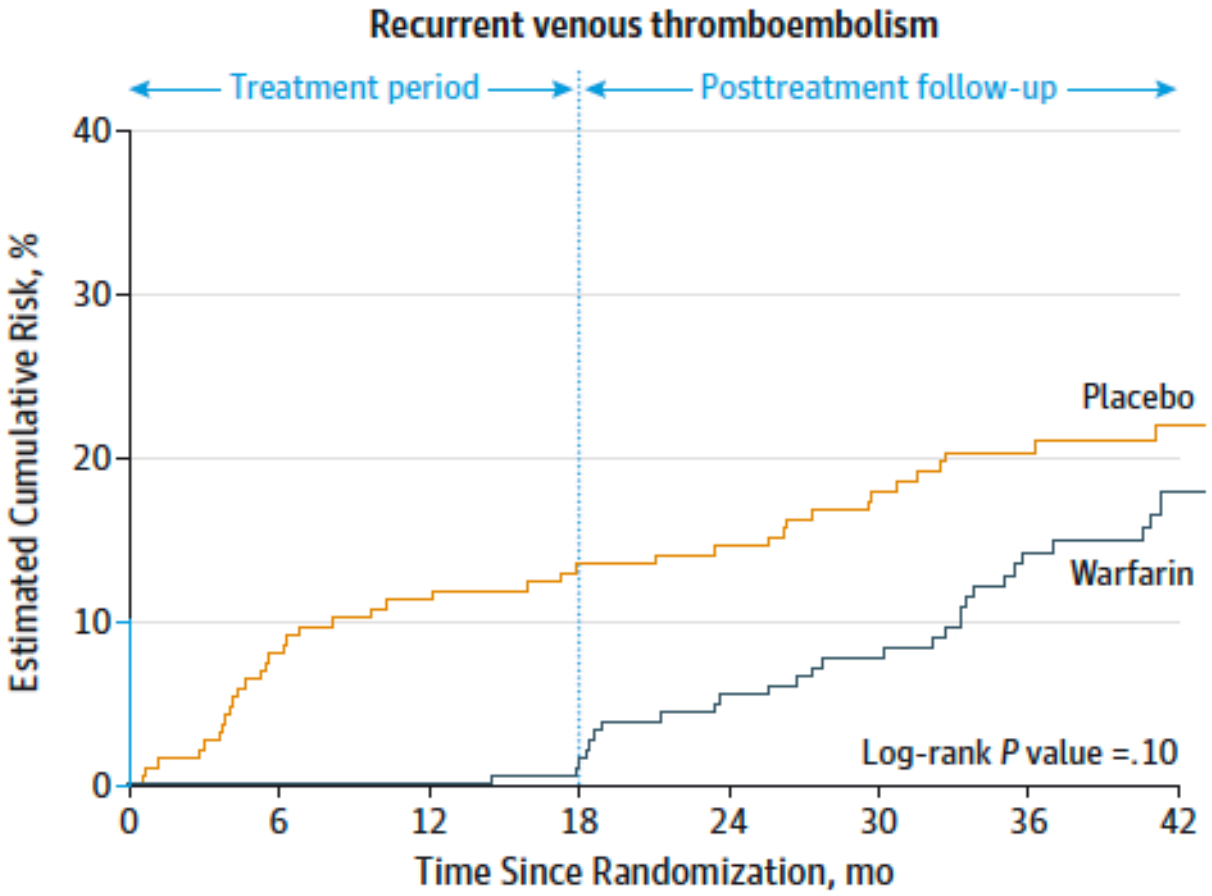
- Il faut prolonger la durée du traitement anticoagulant
- On peut utiliser très souvent les AOD
- La demi-dose peut-être prescrite en toute sécurité
- Un nouveau parcours de soin pour vos patients

Original Investigation

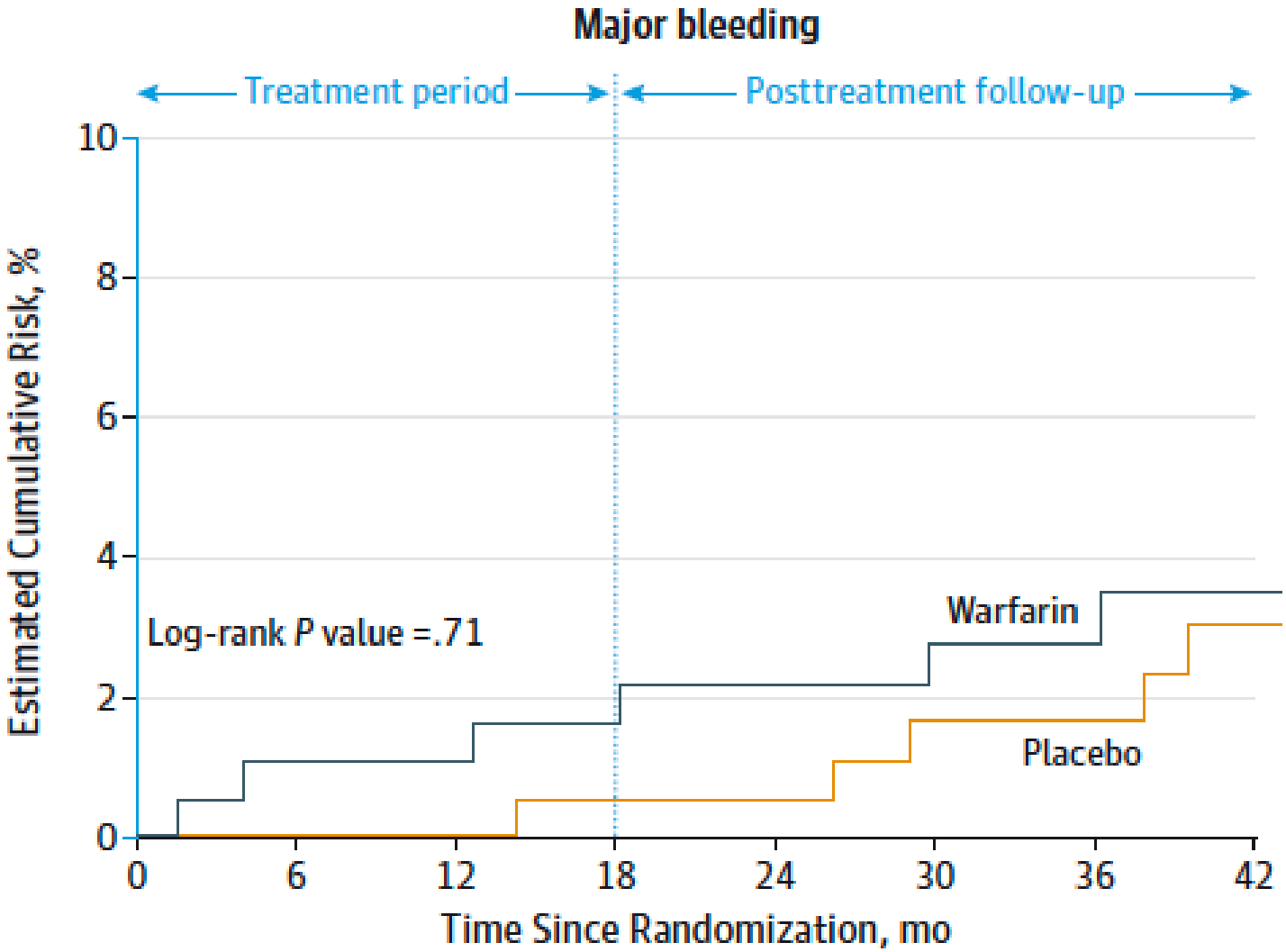
Six Months vs Extended Oral Anticoagulation After a First Episode of Pulmonary Embolism

The PADIS-PE Randomized Clinical Trial

Francis Couturaud, MD, PhD; Olivier Sanchez, MD, PhD; Gilles Pernod, MD, PhD; Patrick Mismetti, MD, PhD; Patrick Jego, MD, PhD; Elisabeth Duhamel, MD; Karine Provost, MD; Claire Bal dit Sollier, MB; Emilie Presles, MS; Philippe Castellant, MD; Florence Parent, MD; Pierre-Yves Salaun, MD, PhD; Luc Bressollette, MD, PhD; Michel Nonent, MD, PhD; Philippe Lorillon, PharmD; Philippe Girard, MD; Karine Lacut, MD, PhD; Marie Guégan, MS; Jean-Luc Bosson, MD, PhD; Silvy Laporte, MS, PhD; Christophe Leroyer, MD, PhD; Hervé Décousus, MD; Guy Meyer, MD; Dominique Mottier, MD; for the PADIS-PE Investigators



No. at risk								
Placebo	187	170	162	158	155	141	117	105
Warfarin	184	182	180	174	168	150	120	110


Major bleeding
Treatment period
Posttreatment follow-up
Estimated Cumulative Risk, %
10
8
6
4
2
0
Log-rank P value =.71
Warfarin
Placebo
0
6
12
18
24
30
36
42
Time Since Randomization, mo

MTEV ET CANCER

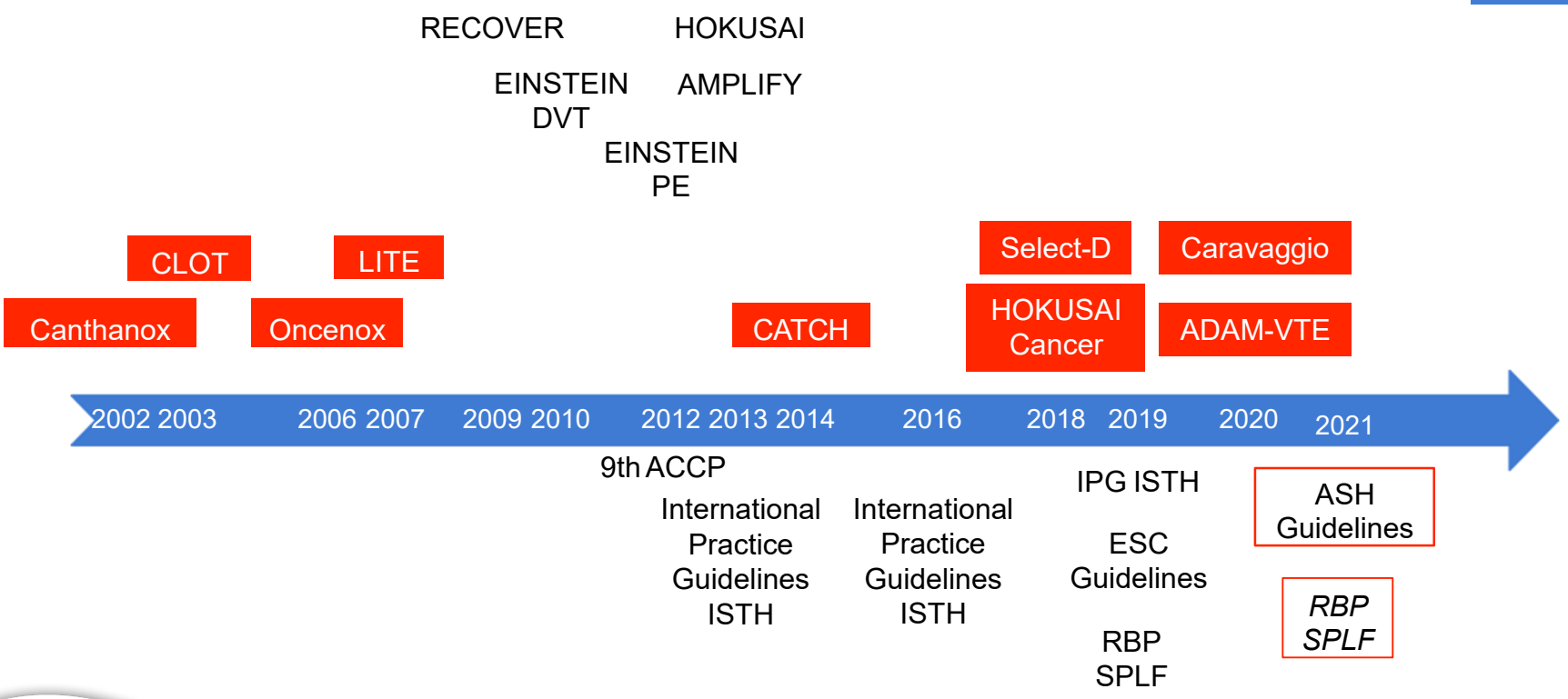
- **Maintenir le patient sous anticoagulants**
  - cancer actif
  - chimiothérapie
  - radiothérapie
  - hormonothérapie (sein , prostate)
  - chirurgie incomplète ou palliative
  - récidive MVTE sous traitement

Tableau 1. Risque de récidive de MTEV selon les circonstances de déclenchement.

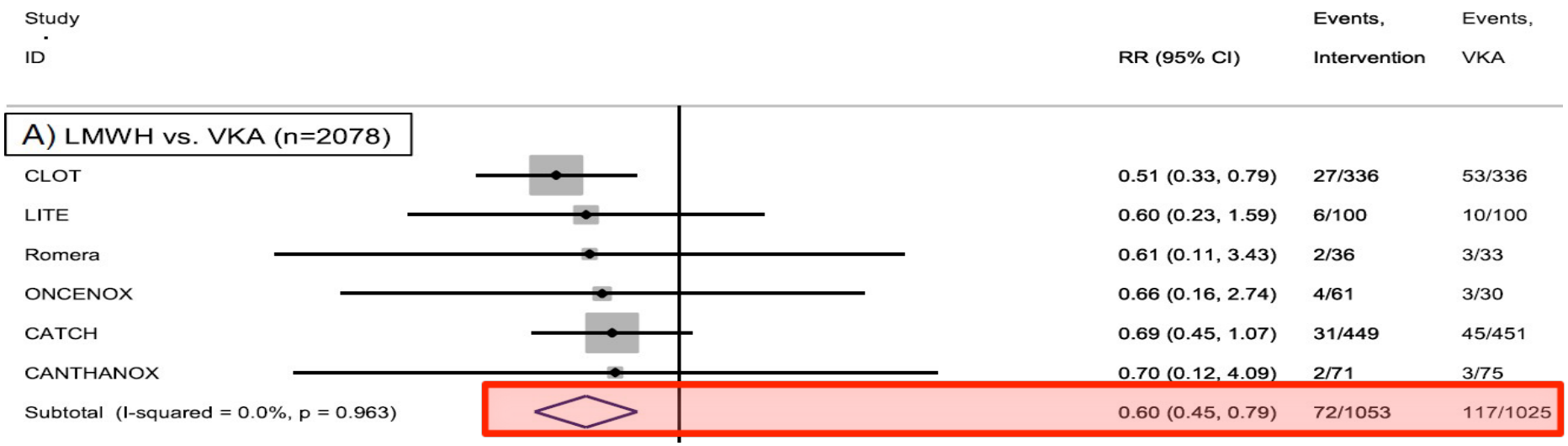
Provoquée chirurgicale	3 % à 5 ans
Provoquée non chirurgicale (estrogènes, grossesse, avion ≥ 8 h)	15 % à 5 ans
Non provoquée	30 % à 5 ans
Cancer	15 %/an
TVP distale isolée	↘ 50 %
Second épisode	↗ 50 %

Risque de récidive à 1 an selon les circonstancesde déclenchement (SSC/ISTH).		
Facteurs transitoires majeurs	Chirurgie majeure (AG > 30 min) + trauma Affection médicale aiguë + immobilisation ≥ 3 j Césarienne	< 2 %
Facteurs transitoires mineurs	Chirurgie majeure Affection médicale aiguë + immobilisation < 3 j Estrogènes, grossesse, péripartum Trauma des MI + immobilisation < 3 j	> 5 %
Facteurs persistants mineurs	Affection auto-immune, MICI	> 5 %
Non provoquée		> 5 %
Facteurs persistants majeurs	Cancer actif : sans traitement curatif ou progression sous traitement ou toujours sous traitement	> 10 %

Essais thérapeutiques et recommandations



LMWH vs VKA: meta-analysis of RCT
Efficacy: symptomatic recurrent VTE



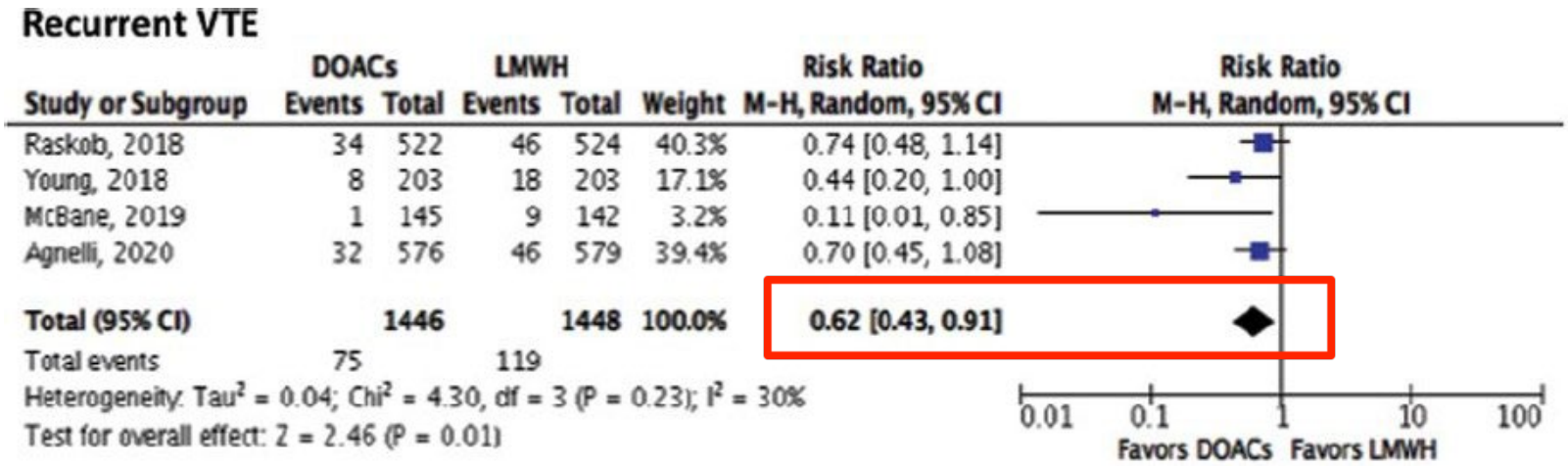
Posh F. et al. *Thromb Res* 2015;136: 582-89.

Direct Oral Anticoagulants for the Treatment of Acute Venous Thromboembolism Associated with Cancer: A Systematic Review and Meta-Analysis

Thromb Haemost 2020;120:1128–1136.

Michela Giustozzi[1] Giancarlo Agnelli[1] Jorge del Toro-Cervera[2] Frederikus A. Klok[3]
Rachel P. Rosovsky[4] Anne-Céline Martin[5,6] Joerg Herold[7] Inna Tzoran[8] Sebastian Szmit[9]
Laurent Bertoletti[10] Cecilia Becattini[1] Menno V. Huisman[3]

- Méta-analyse des 4 essais randomisés AOD vs dalteparine 2894 patients avec MVTE et cancer



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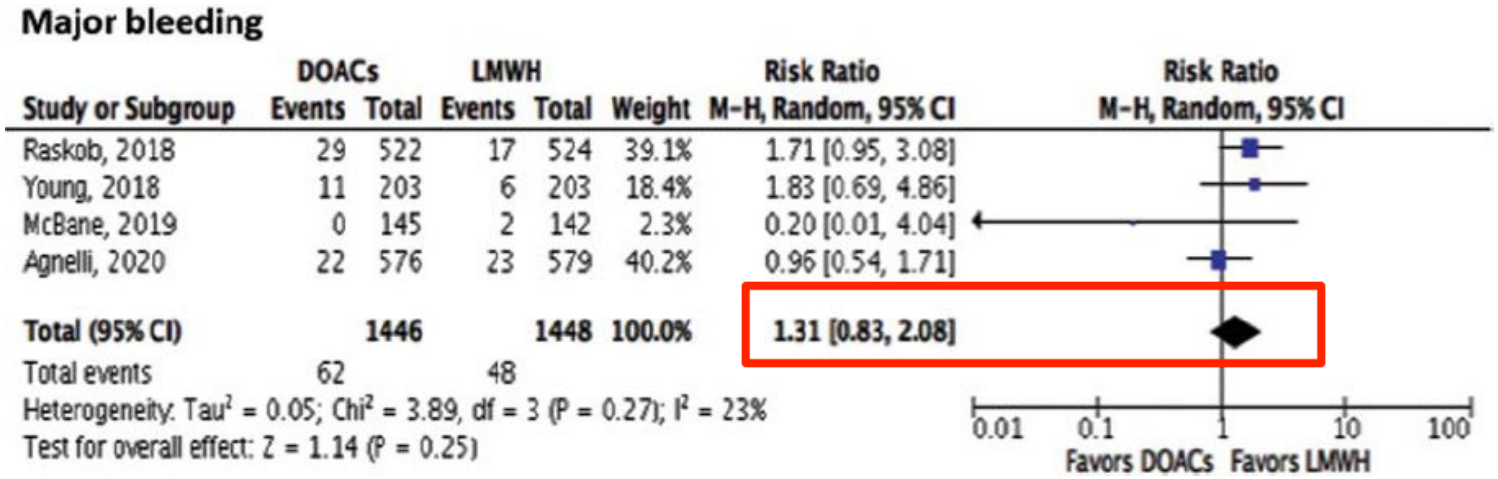


Clinical Impact of Bleeding in Cancer-Associated Venous Thromboembolism: Results from the Hokusai VTE Cancer Study

Thromb Haemost 2018;118:1439–1449.

Noémie Kraaijpoel[1] Marcello Di Nisio[2] Frits I. Mulder[1] Nick van Es[1] Jan Beyer-Westendorf[3] Marc Carrier[4] David Garcia[5] Michael Grosso[6] Ajay K. Kakkar[7] Michele F. Mercuri[6] Saskia Middeldorp[1] Cristhiam Rojas Hernandez[8] Amparo Santamaria[9] Lee Schwocho[6] Annelise Segers[10] Peter Verhamme[11] Tzu-Fei Wang[12] Jeffrey I. Weitz[13] George Zhang[6] Jeffrey I. Zwicker[14] Harry R. Büller[1] Gary E. Raskob[15]

The excess of major bleeding with edoxaban was confined to patients with gastrointestinal cancer and predominantly occured in the upper GI tract

Cancer type	Edoxaban (n=522)		Dalteparin (n=524)	
	Nb at risk	Major bleeding, n (%)	Nb at risk	Major bleeding, n (%)
Brain	30	2 (7%)	42	3 (7%)
Gastrointestinal	**165**	**21 (12.7%)**	**140**	**(3.6%)**
Genitourinary	65	3 (4.6%)	71	1 (1.4%)
Gynaecological	47	2 (4.3%)	63	2 (1.6%)
Lung	77	2 (2.6%)	75	0
Breast	64	0	60	2 (3.3)
Haematological	56	1 (1.8%)	55	2 (3.6%)

Bleeding with Apixaban and Dalteparin in Patients with Cancer-Associated Venous Thromboembolism: Results from the Caravaggio Study

Thromb Haemost

Walter Ageno[1] Maria Cristina Vedovati[2] Ander Cohen[3] Menno Huisman[4] Rupert Bauersachs[5]
Gualberto Gussoni[6] Cecilia Becattini[2] Giancarlo Agnelli[2]

Sites of bleeding in patients with cancer of the GI tract

Cancer type	Apixaban ($N = 576$)										Dalteparin ($N = 579$)									
	Number at risk	Major bleeding *n* (%)	Clinical course severity category 3 or 4	Site of bleeding							Number at risk	Major bleeding *n* (%)	Clinical course severity category 3 or 4	Site of bleeding						
				Abdominal	Genito-urinary	Lower GI	Upper GI	Muscle	Retroperitoneal	Upper airways				Abdominal	Genito-urinary	Lower GI	Upper GI	Muscle	Retroperitoneal	Upper airways
Total GI cancer	188	9 (4.8)	1	1	1	3	4	0	0	0	187	9 (4.8)	4	0	0	3	3	1	1	2
Colorectal	121	5 (4.1)	0	1	1	1	2	0	0	0	113	6 (5.3)	2	0	0	3	2	1	0	1
Resected	33	0	0	0	0	0	0	0	0	0	29	0	0	0	0	0	0	0	0	0
Nonresected	88	5	0	1	1	1	2	0	0	0	84	6	2	0	0	3	2	1	0	1
Pancreatic or hepatobiliary	44	2 (4.5)	1	0	0	1	1	0	0	0	43	0	0	0	0	0	0	0	0	0
Resected	5	0	0	0	0	0	0	0	0	0	6	0	0	0	0	0	0	0	0	0
Nonresected	39	2	1	0	0	1	1	0	0	0	37	0	0	0	0	0	0	0	0	0
Upper GI	23	2 (8.7)	0	0	0	1	1	0	0	0	31	3 (9.7)	2	0	0	0	1	0	1	1
Resected	5	0	0	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	0	0
Nonresected	18	2	0	0	0	1	1	0	0	0	29	3	2	0	0	0	1	0	1	1

No MB events occurred in patients with resected upper gastrointestinal or colorectal cancer

2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS)

European Heart Journal (2019)

The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC)

Authors/Task Force Members: Stavros V. Konstantinides* (Chairperson) (Germany/Greece), Guy Meyer* (Co-Chairperson) (France), Cecilia Becattini (Italy), Héctor

Recommendations	Class[a]	Level[b]
For patients with PE and cancer, weight-adjusted subcutaneous LMWH should be considered for the first 6 months over VKAs.[360–363]	IIa	A
Edoxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[366]	IIa	B
Rivaroxaban should be considered as an alternative to weight-adjusted subcutaneous LMWH in patients without gastrointestinal cancer.[367]	IIa	C
For patients with PE and cancer, extended anticoagulation (beyond the first 6 months)[c] should be considered for an indefinite period or until the cancer is cured.[378]	IIa	B

American Society of Hematology 2021 guidelines for management of venous thromboembolism: prevention and treatment in patients with cancer

February 2021. DOI 10.1182/bloodadvances.2020003442.

Gary H. Lyman,[1,2,*] Marc Carrier,[3,*] Cihan Ay,[4] Marcello Di Nisio,[5] Lisa K. Hicks,[6] Alok A. Khorana,[7] Andrew D. Leavitt,[8,9] Agnes Y. Y. Lee,[10,11] Fergus Macbeth,[12] Rebecca L. Morgan,[13] Simon Noble,[14] Elizabeth A. Sexton,[15] David Stenehjem,[16] Wojtek Wiercioch,[13] Lara A. Kahale,[17,†] and Pablo Alonso-Coello[18,†]

Short-term treatment for patients with active cancer (initial 3-6 months). RECOMMENDATION 23. For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* DOAC (apixaban, edoxaban, or rivaroxaban) over LMWH (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

RECOMMENDATION 24. For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* DOAC (apixaban, edoxaban, or rivaroxaban) over VKA (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 25. For the short-term treatment of VTE (3-6 months) for patients with active cancer, the ASH guideline panel *suggests* LMWH over VKA (conditional recommendation, moderate certainty in the evidence of effects ⊕⊕⊕◯).

Long-term treatment (>6 months) for patients with active cancer and VTE. RECOMMENDATION 32. For patients with active cancer and VTE, the ASH guideline panel *suggests* long-term anticoagulation for secondary prophylaxis (>6 months) rather than short-term treatment alone (3-6 months) (conditional recommendation, low certainty in the evidence of effects ⊕⊕◯◯).

RECOMMENDATION 33. For patients with active cancer and VTE receiving long-term anticoagulation for secondary prophylaxis, the ASH guideline panel *suggests* continuing indefinite anticoagulation over stopping after completion of a definitive period of anticoagulation (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

RECOMMENDATION 34. For patients with active cancer and VTE requiring long-term anticoagulation (>6 months), the ASH guideline panel *suggests* using DOACs or LMWH (conditional recommendation, very low certainty in the evidence of effects ⊕◯◯◯).

Pour diminuer ce risque hémorragique , une seule solution :

La demi-dose

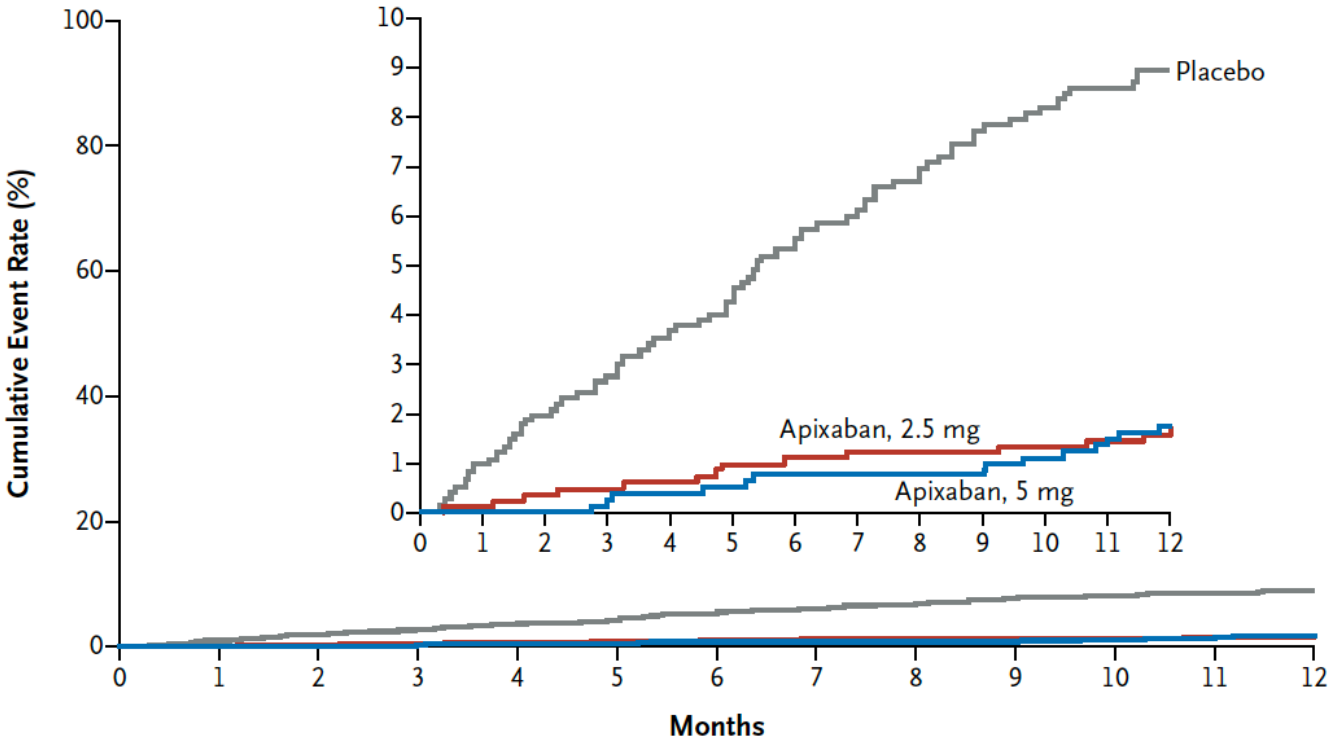
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 21, 2013 VOL. 368 NO. 8

Apixaban for Extended Treatment of Venous Thromboembolism

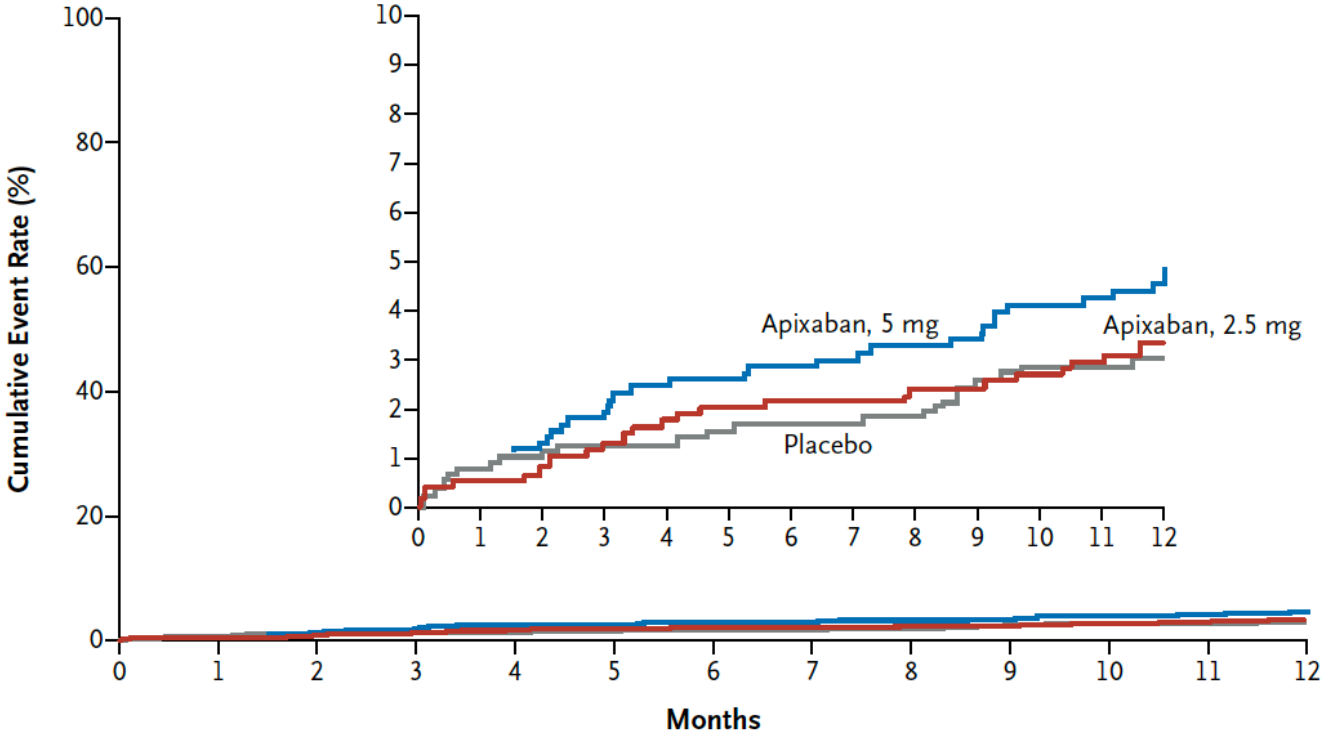
Giancarlo Agnelli, M.D., Harry R. Buller, M.D., Ph.D., Alexander Cohen, M.D., Madelyn Curto, D.V.M., Alexander S. Gallus, M.D., Margot Johnson, M.D., Anthony Porcari, Ph.D., Pharm.D., Gary E. Raskob, Ph.D., and Jeffrey I. Weitz, M.D., for the AMPLIFY-EXT Investigators*

A **Symptomatic Recurrent VTE or VTE-Related Death**



No. at Risk					
Apixaban, 2.5 mg	840	836	825	818	533
Apixaban, 5 mg	813	807	799	791	513
Placebo	826	796	768	743	471

B Major or Clinically Relevant Nonmajor Bleeding



No. at Risk					
Apixaban, 2.5 mg	840	786	759	737	354
Apixaban, 5 mg	811	751	716	689	331
Placebo	823	749	687	651	298

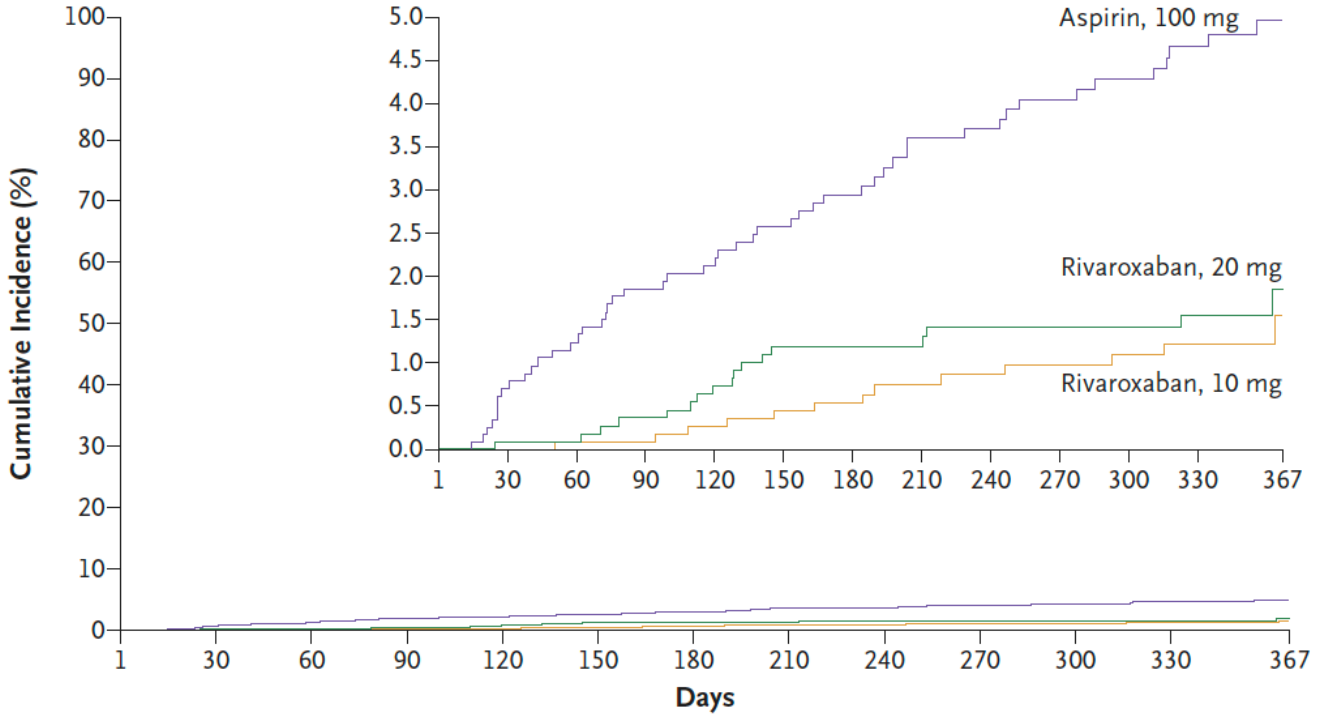
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 30, 2017 VOL. 376 NO. 13

Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

J.I. Weitz, A.W.A. Lensing, M.H. Prins, R. Bauersachs, J. Beyer-Westendorf, H. Bounameaux, T.A. Brighton, A.T. Cohen, B.L. Davidson, H. Decousus, M.C.S. Freitas, G. Holberg, A.K. Kakkar, L. Haskell, B. van Bellen, A.F. Pap, S.D. Berkowitz, P. Verhamme, P.S. Wells, and P. Prandoni, for the EINSTEIN CHOICE Investigators*

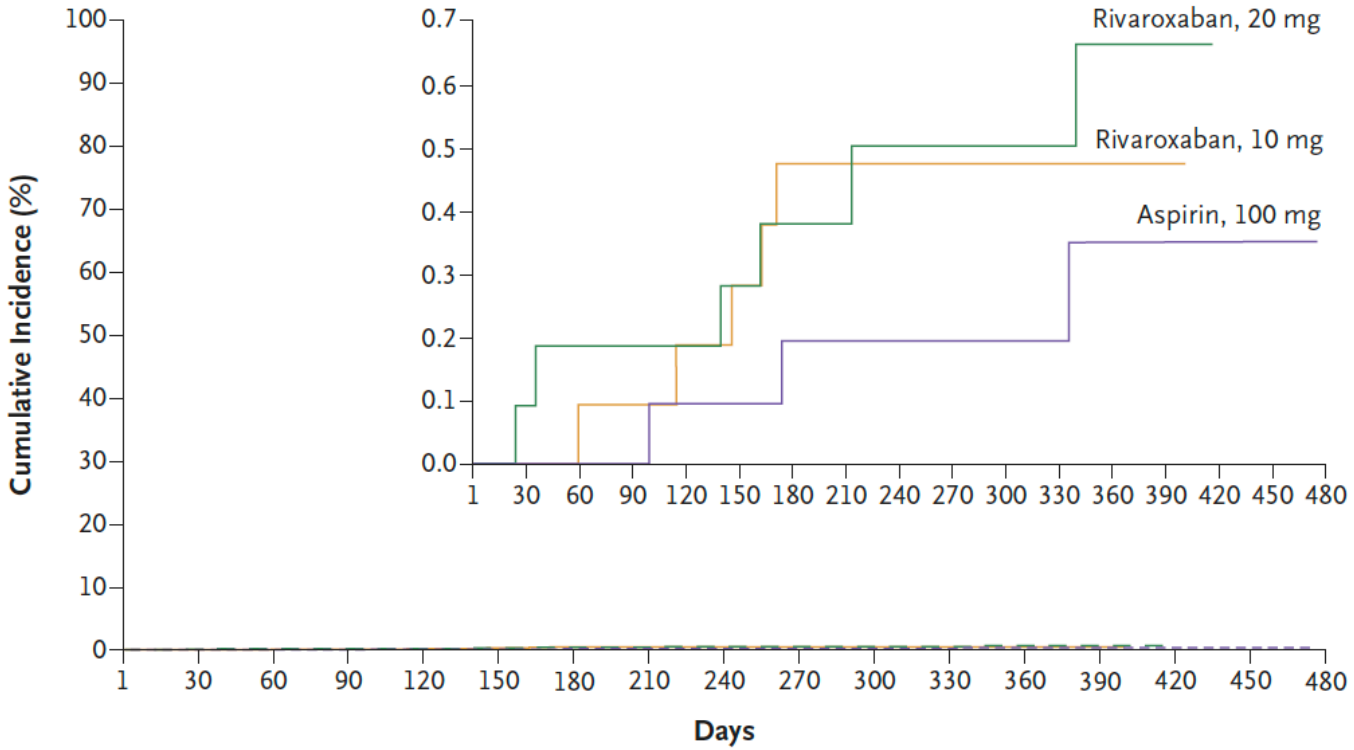
A Fatal or Nonfatal Venous Thromboembolism



No. at Risk

Rivaroxaban, 20 mg	1107	1102	1095	1090	1084	1079	997	876	872	860	794	718	0
Rivaroxaban, 10 mg	1126	1124	1119	1118	1111	1109	1029	890	886	867	812	723	0
Aspirin, 100 mg	1131	1121	1111	1103	1094	1088	1010	859	857	839	776	707	0

B Major Bleeding



No. at Risk

Rivaroxaban, 20 mg	1107	1081	1063	1048	1036	1024	963	818	801	780	712	642	449	10	0	0	0
Rivaroxaban, 10 mg	1126	1103	1080	1070	1058	1046	988	823	812	790	733	653	469	8	0	0	0
Aspirin, 100 mg	1131	1096	1075	1058	1040	1023	970	800	791	768	709	645	445	5	2	2	0

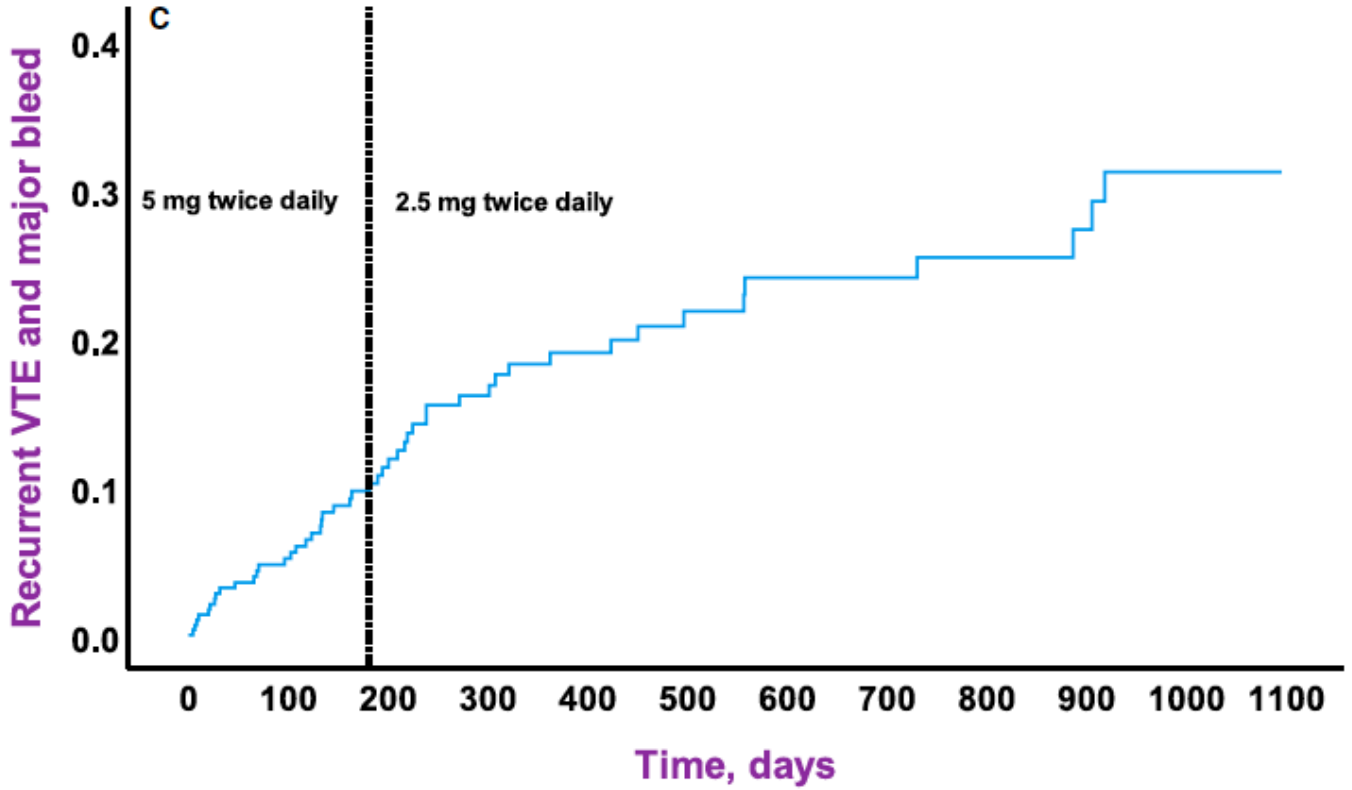
ORIGINAL ARTICLE

Low dose apixaban as secondary prophylaxis of venous thromboembolism in cancer patients – 30 months follow-up

Trine-Lise Larsen[1,2] | Herish Garresori[3] | Jorunn Brekke[4] | Tone Enden[5] | Hege Frøen[6] | Eva Marie Jacobsen[7] | Petter Quist-Paulsen[8] | Alina Carmen Porojnicu[9] | Anne Hansen Ree[1,10] | Dag Torfoss[11] | Elin Osvik Velle[12] | Hilde Skuterud Wik[7] | Waleed Ghanima[1,13] | Per Morten Sandset[1,7] | Anders Erik Astrup Dahm[1,2]

Essentials

- Low-dose anticoagulation has not been investigated in cancer associated thrombosis
- We gave patients low-dose apixaban for 30 months after 6 months of full-dose
- Low-dose apixaban resulted in low major bleeding rates from 6 to 12 months
- From 12 to 36 months there were few recurrent venous thrombosis and few bleedings


C
0.4
0.3
0.2
0.1
0.0
Recurrent VTE and major bleed
5 mg twice daily
2.5 mg twice daily
0
100
200
300
400
500
600
700
800
900
1000
1100
Time, days

API-CAT

Traitement anticoagulant prolongé d'un évènement Thrombo-embolique veineux (ETEV) associé au cancer :

Dose réduite vs Dose pleine d'APIXABAN

Critères d'inclusion :

- Patient avec un cancer du sein, de la prostate, ou colorectal
- Patient ayant présenté un ETEV: TVP proximale ou EP, traité depuis 6 mois par anticoagulant sans récidive de l'ETEV.
- Randomisation dans les 7 jours après la dernière dose du traitement initial de 6 mois

Le parcours de soins : vasculo-oncologie

- Synergie oncologue- médecin vasculaire
  - prévenir du risque artériel et veineux des traitements (chimiothérapies , radiothérapie)
  - participation aux RCP

- Consultations dédiées : une demi-journée/semaine
  S Cohen , W Radix , N El Haddad , A Yaagoubi
  oncovasc@hopital-europeen.fr
  Création de registres en vue d'améliorer la prise en charge

- Collaboration avec les pharmaciens pour les interférences drogues anticancéreuses- AOD

Take home message

- Prolonger la durée tant que le cancer est actif
- AOD chez tous les patients sauf cancers digestifs , uro-génitaux , tumeurs et métastases cérébrales , tumeurs cutanées
- Demi-dose possible après 6 mois de traitement
- Unité de vasculo-oncologie