PLACE

PLATFORM OF LABORATORIES FOR ADVANCES IN CARDIAC EXPERIENCE

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FIBRILLAZIONE ATRIALE E TEV NEL PAZIENTE ONCOLOGICO: QUALE DOAC PER QUALE NEOPLASIA

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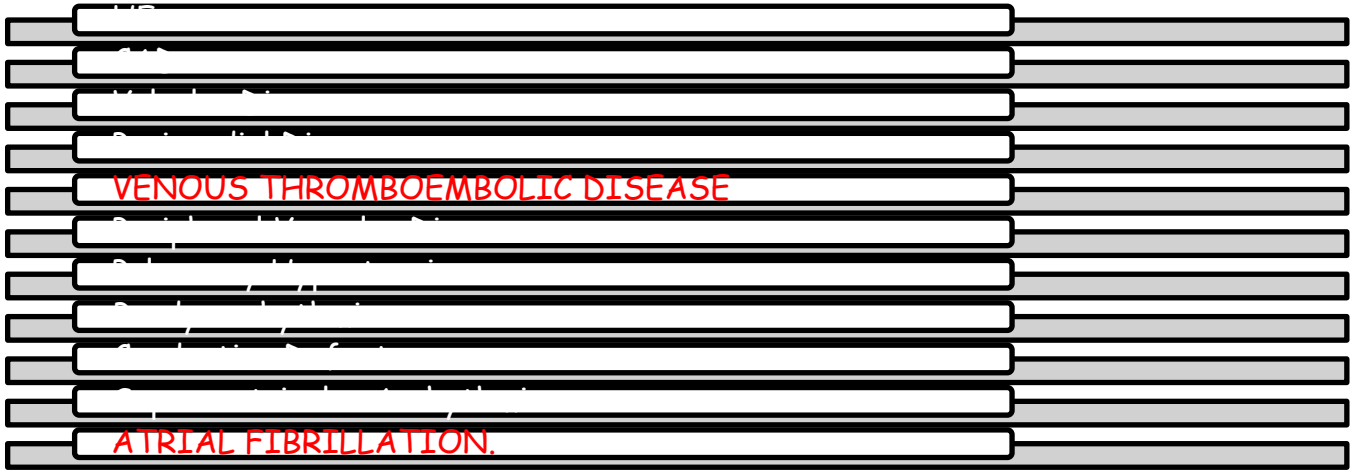
Association between Cancer and Cardiovascular Deseases

- The number of patients with cancer in USA is >26 million by 2040
- Advances in screening and treatments → ↑ Survival of Cancer pts
- Cardiovascular disease is the second most common cause of late morbidity and death among cancer survivors
- ↑ Risk of developing CVD compared with non-cancer pts

The most common CVD in cancer patients

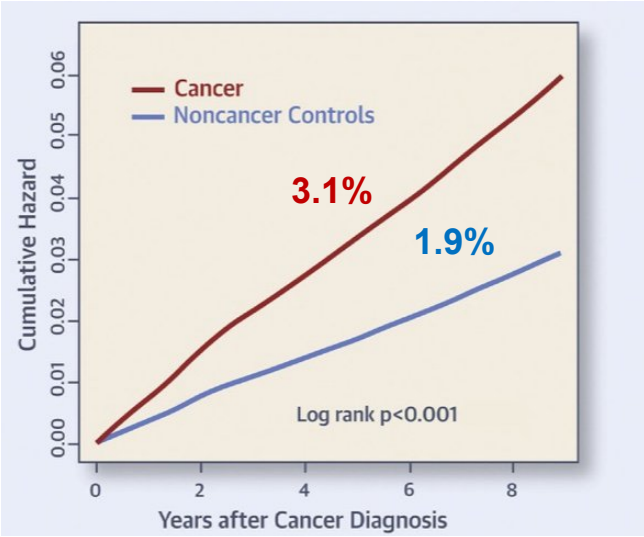


Benoite M. International Journal of Cardiology 240 (2017) 196–202

Cancer associated with increased risk of AF

Adjusted subdistribution HR 1.63, 95% CI 1.61-1.66

- **Patients with cancer have a 1.6-fold higher AF risk than the general population** even after adjusting for risk factors (hypertension, diabetes, dyslipidemia,obesity, chronic kidney disease, smoking, alcohol consumption, physical exercise status)



- Yun et al. J Am Coll Cardiol CardioOnc. 2021 (2) 221–232

Atrial Fibrillation and Cancer

- Cancer and AF share **common pathophysiological mechanisms** and **risk factors**
- Cancer is an independent risk factor for AF
- 20% prevalence of AF in patients with cancer regardless of the type of cancer
- Patients with cancer 47% HIGHER RISK OF AF compared with patients without cancer

The HIGHEST RISK OF developing NEW AF IS IN THE FIRST THREE MONTHS after the diagnosis of cancer

EARLY DETECTION OF AF

- **Relationship between cancer and AF** appears to be **BIDIRECTIONAL**
- **AF could be a marker of occult cancer**

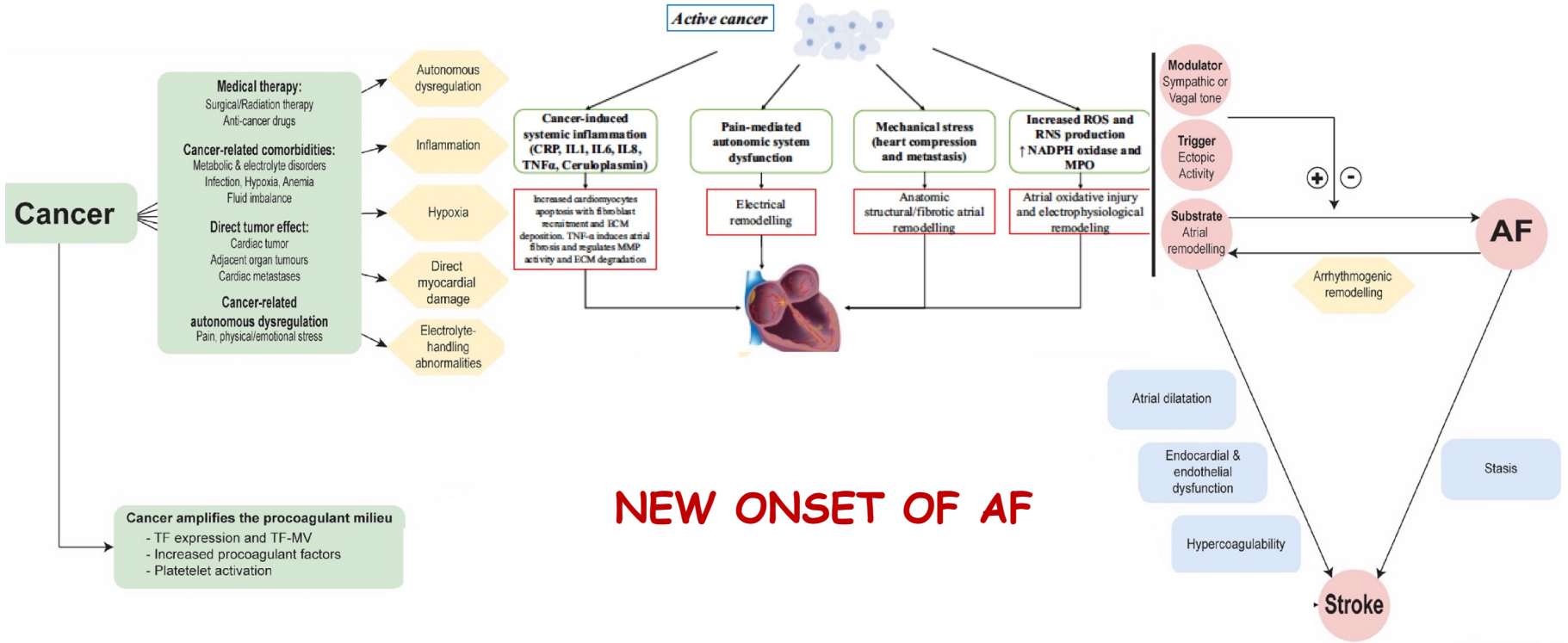
1) O'Neal WT Am J Cardiol 2015;115:1090-1094
2) Hu YF, Int J Cardiol 2013;165:355-357 3) Yuan et al. Cardiol Res Pract. 2019;2019:8985273

Atrial Fibrillation and Cancer Type

- The onset of AF may be promoted by the presence of cancer and by cancer treatments such as surgery, chemotherapy and radiotherapy
- There are several mechanisms potentially linking AF and cancer
- Systemic inflammation which seems to represent a common milieu for these two conditions
- Cancer is a heterogeneous disease, and the impact of cancer on AF risk may vary depending on the cancer type

- Siontis KC et al. J Am Coll Cardiol CardioOnc. 2021(2) 233-235
- Menichelli D e t al. Review Prog Cardiovasc Dis. 2021;S0033-0620(21)00041-4

Link between Cancer and Atrial Fibrillation



Menichelli D et al. Review Prog Cardiovasc Dis. 2021;S0033-0620(21)00041-4

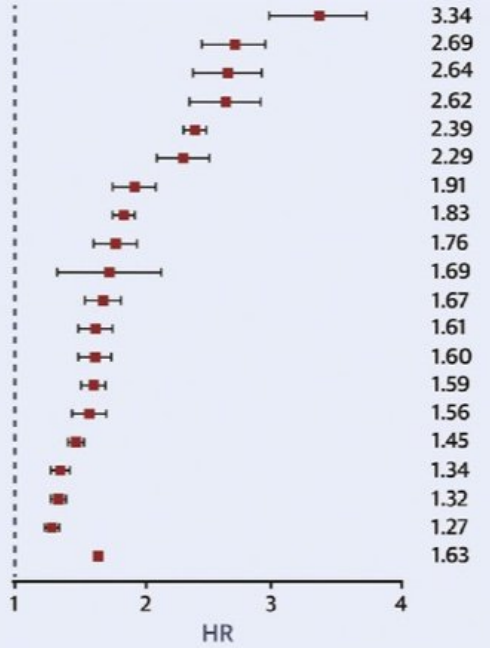
Risk of Atrial Fibrillation According to Cancer Type

A Nationwide Population-Based Study

Jun Pil Yun, MD,[a] Eue-Keun Choi, MD, PhD,[a] Kyung-Do Han, PhD,[b] Sang Hyun Park, BS,[c] Jin-Hyung Jung, PhD,[c] Sang Hyeon Park, MD,[a] Hyo-Jeong Ahn, MD,[a] Jae-Hyun Lim, MD,[a] So-Ryoung Lee, MD, PhD,[a] Seil Oh, MD, PhD[a]

Increased AF risk according to malignancy type

Type of cancer	Number	Events	Time to event	Incidence*	HR (95% CI)†
Multiple myeloma	4,058	299	1.74	19.76	3.34
Esophagus	6,587	481	1.45	19.59	2.69
Leukemia	8,563	384	1.75	12.37	2.64
CNS	8,241	360	1.5	10.91	2.62
Lung	49,435	3,017	1.57	17.59	2.39
Non-Hodgkin lymphoma	12,166	502	1.79	9.43	2.29
Renal	14,608	520	1.64	7.35	1.91
Liver	46,601	1,896	1.63	11.30	1.83
Head & neck	11,638	442	1.74	8.32	1.76
Melanoma	1,964	70	2.11	8.00	1.69
Biliary	12,125	546	1.55	12.77	1.67
Pancreatic	15,020	578	1.47	14.06	1.61
Bladder	14,039	650	1.97	9.27	1.60
Breast	81,066	1,212	1.76	3.04	1.59
Gynecologic	31,474	566	1.89	3.72	1.56
Colorectal	101,603	3,356	1.8	6.64	1.45
Prostate	29,010	1,349	2.07	8.80	1.34
Thyroid	153,923	1,949	1.95	2.27	1.32
Stomach	124,740	3,691	1.81	5.96	1.27
All	816,811	25,356	1.72	6.65	1.63



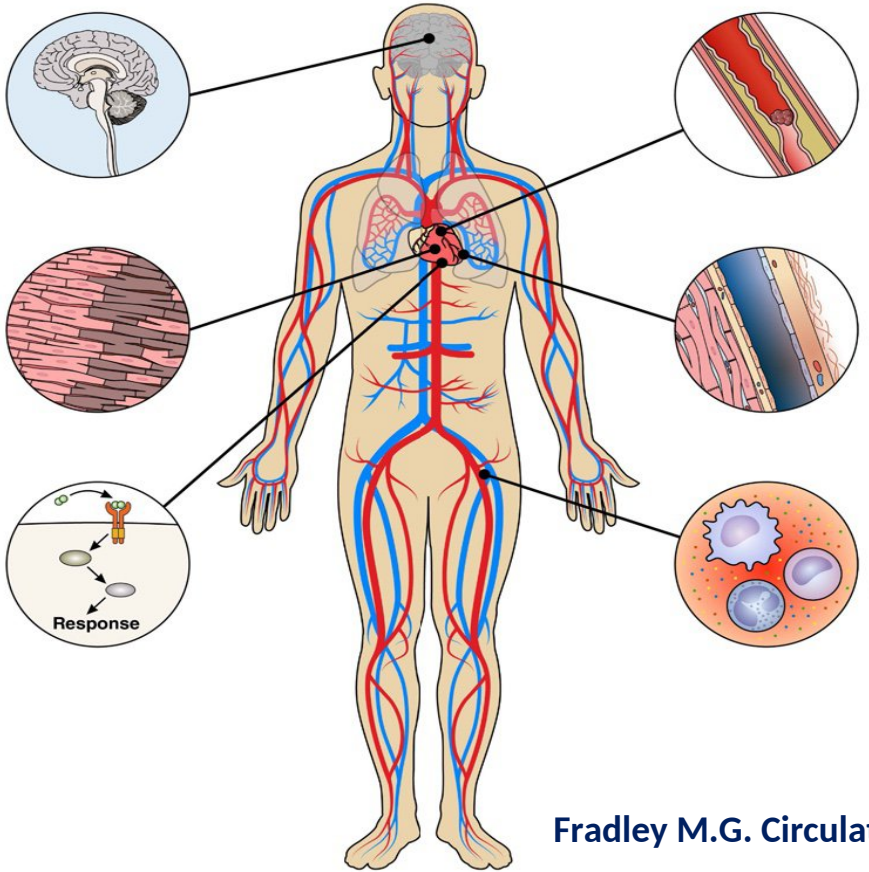
Yun et al. J Am Coll Cardiol CardioOnc. 2021 (2) 221-232

Mechanisms of systemic cancer therapy–induced arrhythmias

Autonomic dysfunction
- Anthracyclines
- Platinum
- Vinca alkaloids

Myocardial dysfunction:
Cardiomyopathy; myocarditis
- Anthracyclines
- Immune checkpoint inhibitors

Ion channel and/or intracellular signaling dysfunction:
- Tyrosine kinase inhibitors



Ischemia
- 5-fluorouracil

Pericardial disease
- Platinum compounds

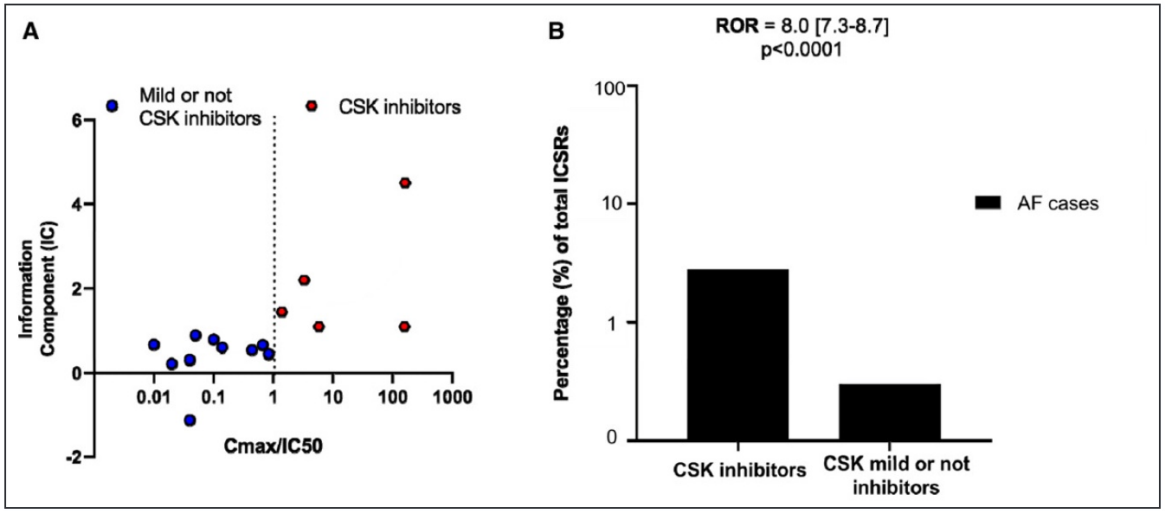
Systemic inflammatory response/cytokine release
- CAR-T therapy

Fradley M.G. Circulation. 2021;144(3):e41-e55

Circulation
Volume 142, Issue 25, 22 December 2020; Pages 2443-2455
https://doi.org/10.1161/CIRCULATIONAHA.120.049210

ORIGINAL RESEARCH ARTICLE

Ibrutinib-Mediated Atrial Fibrillation Attributable to Inhibition of C-Terminal Src Kinase



IBRUTINIB, a tyrosine kinase inhibitor that is used to treat chronic lymphocytic leukemia and other hematologic malignancies, can lead to a **10-fold risk of incident AF** due to the off-target inhibition of the C-terminal Src kinase causing deleterious downstream proarrhythmic effects

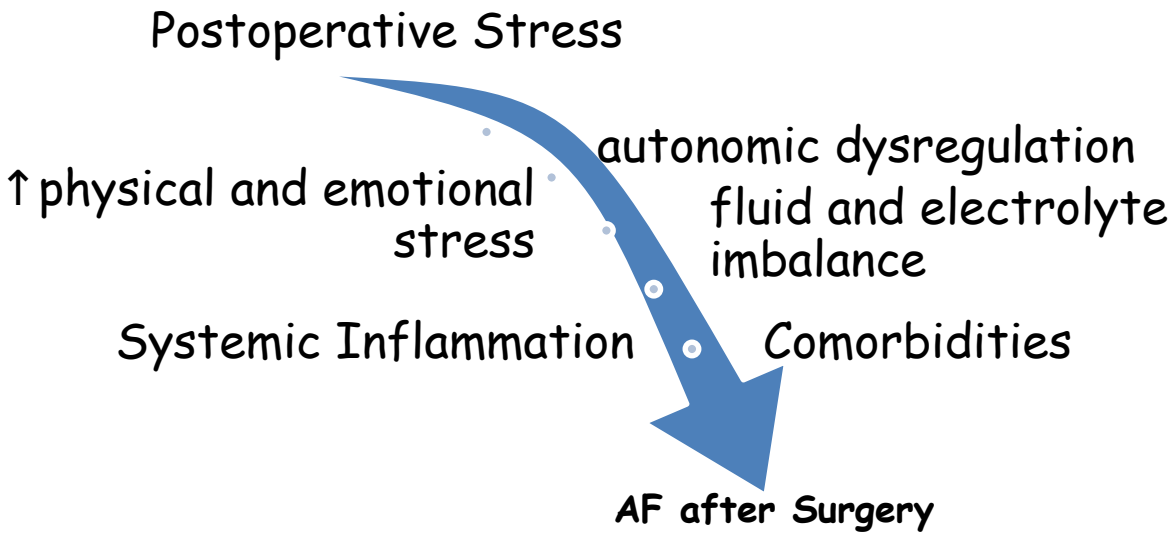
Xiao L et al. Circulation 2020;142:2443-55

Radiotherapy

- Routinely used in the treatment of patients with cancer
- ↑ Inflammatory processes at the vascular level, including coronary circulation
- ↑ Fibrosis in the atrial tissue
- ↑ Risk of cardiovascular complications including AF. .
- Myocardial injury is strongly related to
    - Total cumulative dose of radiation
    - Body area irradiated
    - Patient's age
    - Time of exposure

Menichelli D et al. Review Prog Cardiovasc Dis. 2021;S0033-0620(21)00041-4

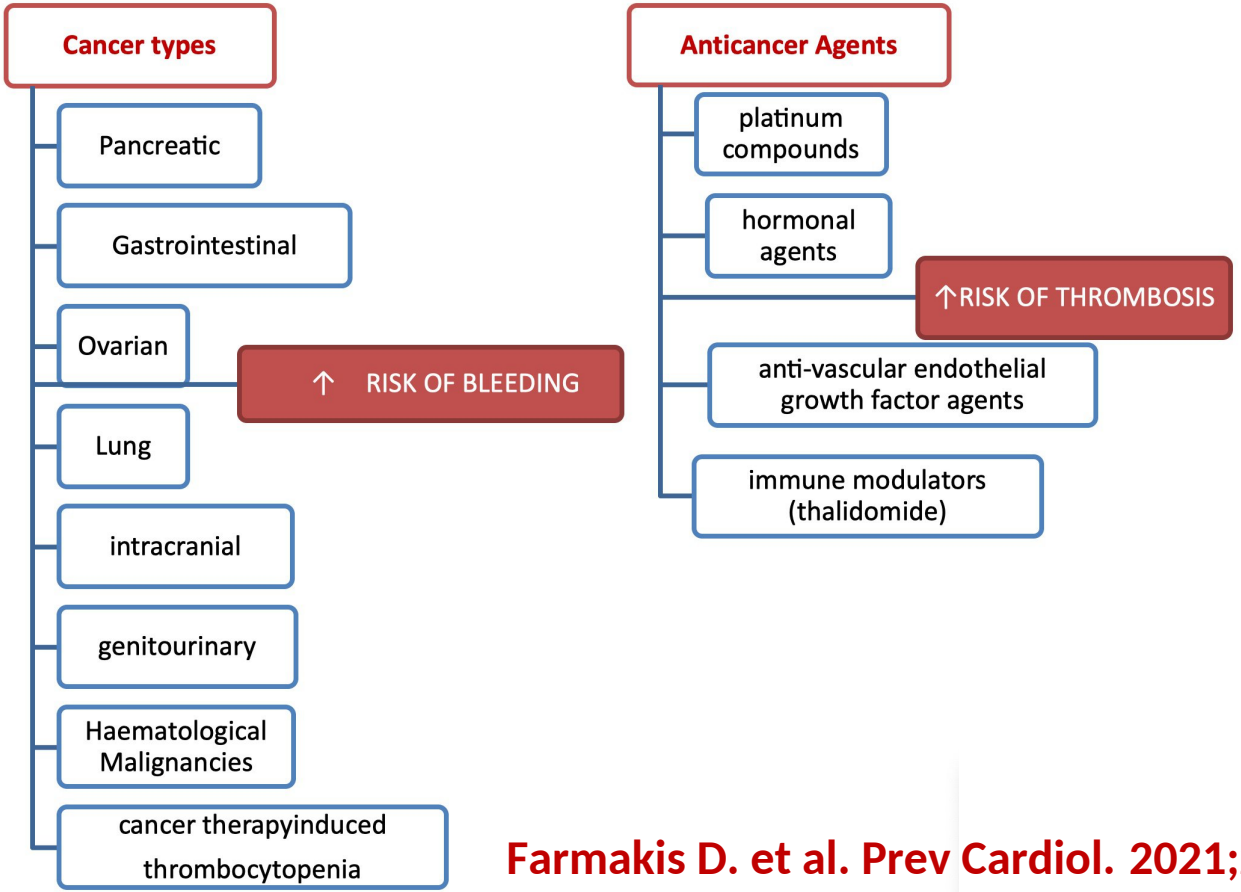
Surgery



- Surgery, especially **thoracic surgery for lung cancer**, is a strong risk factor for the development of AF
- Increased risk of AF after thoracic surgery as a result of direct myopericardial irritation
- The prevalence of postoperative AF in these patients ranges from 9.9%to 23%

Nojiri T et al. J Thorac Cardiovasc Surg 2010;140:764-768

Thromboembolic and Bleeding Risk in Active Cancer



Farmakis D. et al. Prev Cardiol. 2021;28(6):608-610

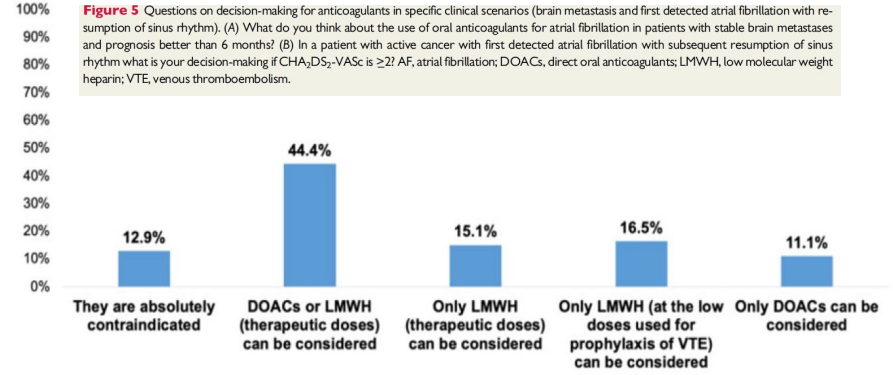
ESC European Society of Cardiology
European Journal of Preventive Cardiology (2021) 28, 611–621
doi:10.1093/eurjpc/zwaa054
CLINICAL PRACTICE

Anticoagulation in patients with atrial fibrillation and active cancer: an international survey on patient management

Giuseppe Boriani[1]*, Geraldine Lee[2], Iris Parrini[3], Teresa Lopez-Fernandez[4], Alexander R. Lyon[5], Thomas Suter[6], Peter Van der Meer[7], Daniela Cardinale[8], Patrizio Lancellotti[9,10], Jose Luis Zamorano[11], Jeroen J. Bax[12], and Riccardo Asteggiano[13,14]; for the Council of Cardio-Oncology of the European Society of Cardiology

Decision-making for anticoagulants in specific clinical scenarios

Figure 5 Questions on decision-making for anticoagulants in specific clinical scenarios (brain metastasis and first detected atrial fibrillation with resumption of sinus rhythm). (*A*) What do you think about the use of oral anticoagulants for atrial fibrillation in patients with stable brain metastases and prognosis better than 6 months? (*B*) In a patient with active cancer with first detected atrial fibrillation with subsequent resumption of sinus rhythm what is your decision-making if CHA_2DS_2-VASc is ≥2? AF, atrial fibrillation; DOACs, direct oral anticoagulants; LMWH, low molecular weight heparin; VTE, venous thromboembolism.



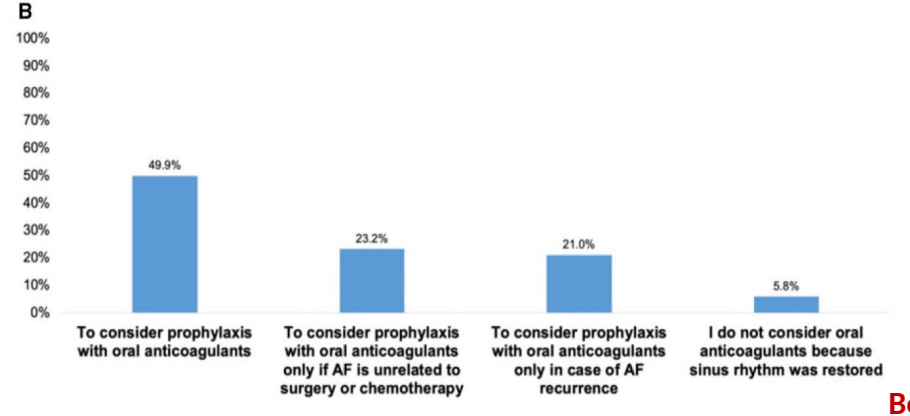
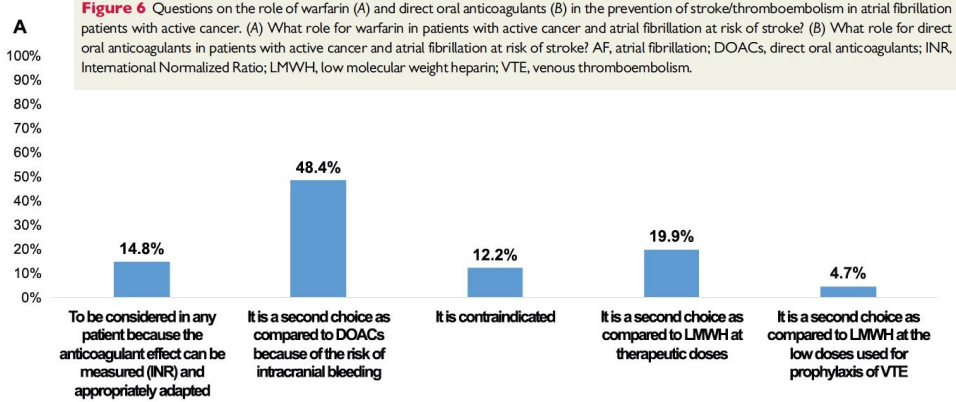
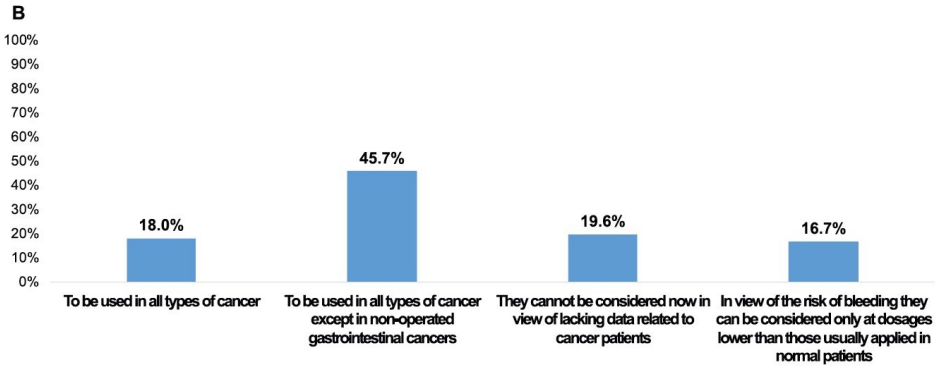


Figure 6 Questions on the role of warfarin (*A*) and direct oral anticoagulants (*B*) in the prevention of stroke/thromboembolism in atrial fibrillation patients with active cancer. (*A*) What role for warfarin in patients with active cancer and atrial fibrillation at risk of stroke? (*B*) What role for direct oral anticoagulants in patients with active cancer and atrial fibrillation at risk of stroke? AF, atrial fibrillation; DOACs, direct oral anticoagulants; INR, International Normalized Ratio; LMWH, low molecular weight heparin; VTE, venous thromboembolism.



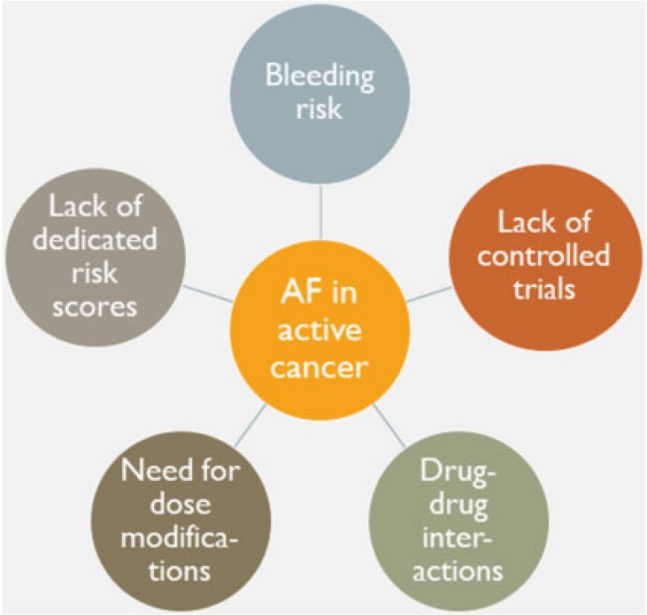


Boriani et al. European Journal of Preventive Cardiology (2021) 28, 611–621

The challenging decision and choice of anticoagulation therapy in patients with AF and active cancer

ACTIVE CANCER ➤HYPERCOAGULABLE STATE➤ ↑ RISK OF THROMBOEMBOLIC COMPLICATIONS + RISK OF BLEEDING

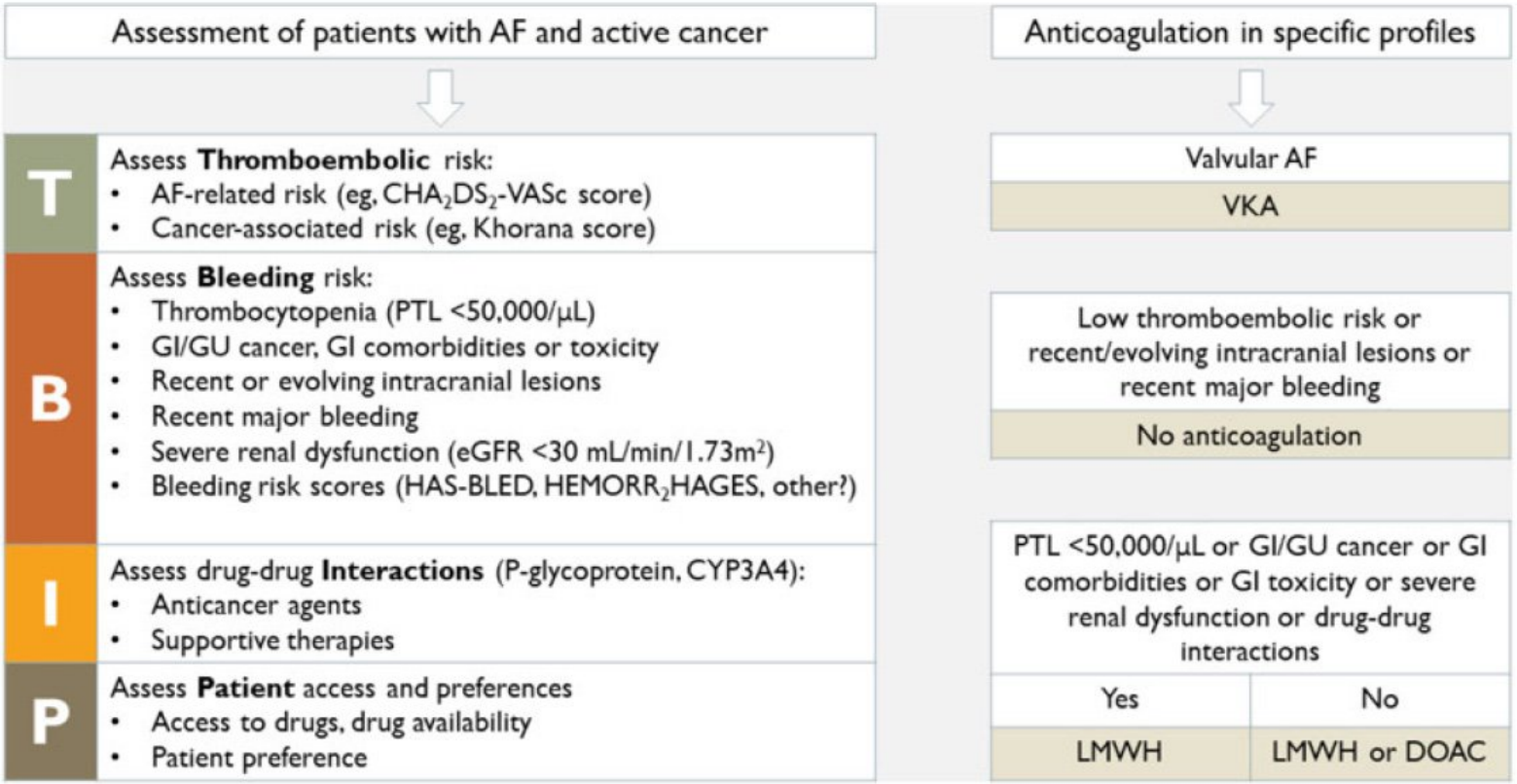
The main concerns of cardiologists



the main thromboembolic and bleeding risk assessment scores, widely used to guide the decision of anticoagulation inAF, have not been validated in patients with cancer

Farmakis D. et al. Prev Cardiol. 2021;28(6):608-610

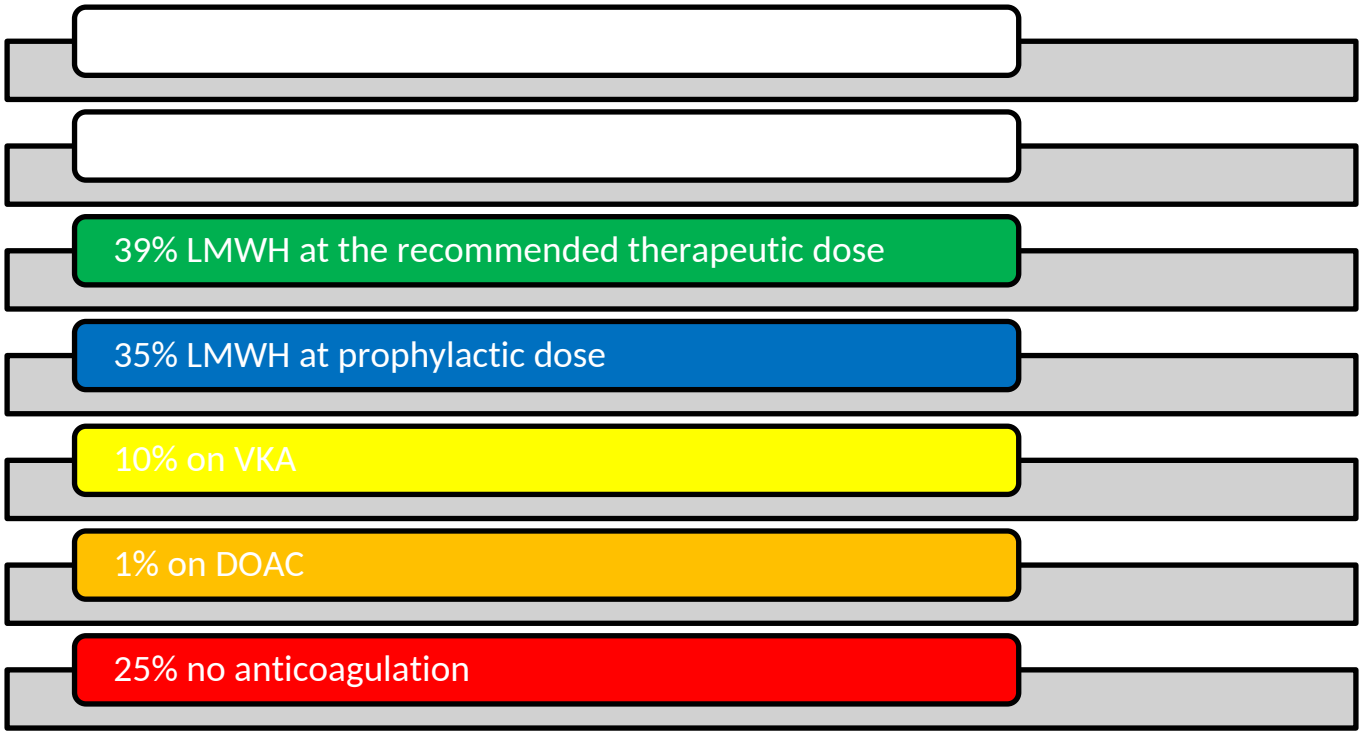
A practical approach to anticoagulation decision making in patients with atrial fibrillation and active cancer



Farmakis D. et al. Prev Cardiol. 2021;28(6):608-610

Atrial fibrillation in patients with active malignancy and use of anticoagulants: Under-prescription but no adverse impact on all-cause mortality

A real-world analysis in an Oncology Unit: Suboptimal prescription of anticoagulants



Malavasi VL et al. Eur J Intern Med 2019;59:27–33.

Table I **Pros and cons of different anticoagulation agents for stroke and systemic embolism prevention in patients with atrial fibrillation and active cancer**

Anticoagulant class	Pros	Cons
Vitamin K antagonists	• The only indicated for valvular AF	• Multiple drug–drug interactions • Narrow therapeutic window • Low likelihood to achieve optimal TTR due to vomiting, malnutrition, hepatic dysfunction • Difficult to handle peri-operatively
Low molecular weight heparins	• Long experience in cancer-associated VTE • Few known interactions • Parenteral route (no absorption issues in vomiting) • Potential antineoplastic properties	• No evidence for stroke or systemic embolism prevention in AF • Parenteral route (low compliance)
Direct oral anticoagulants	• Preferred agents for stroke or systemic embolism prevention in general AF • Recommended as alternatives to LMWH for cancer-associated VTE • Low risk of intracranial bleeding • Reversal agents • Indirect evidence for AF in cancer by secondary analyses of RCTs or observational studies	• Multiple drug–drug interactions • Impaired metabolism in renal or hepatic dysfunction • Unpredictable absorption in vomiting • Increased risk of GI bleeding • Poor monitoring of anticoagulant activity by standard assays

Farmakis D. et al. Prev Cardiol. 2021;28(6):608-610

Predicted pharmacokinetic drug interactions between main oral anticancer agents and direct oral anticoagulants

		DDIs with DOACs (PK or PD prediction)				
		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	
P-gp substrate		Yes	Yes	No (minimal)	Yes	
CYP3A4 substrate		No	Yes (moderate – 18%)	Yes (moderate – 25%)	No (minimal – 4%)	
BCRP substrate		No	Yes	Yes	No	
OATP1B1 substrate		No	No	No	Yes	
Oral anti-cancer agents	**Metabolic pathway**					**Clinical relevance and literature data**
Inhibitors of vascular endothelial growth factor receptor (VEGFR)-associated tyrosine kinases						
Axitinib	CYP1A2/2C8 inhibition (in vitro)					
Lenvatinib	No activity on CYP or P-gp					
Pazopanib	Weak inhibitor of CYP3A4/2C8					Monitoring for apixaban and rivaroxaban toxicity
Regorafenib	P-gp inhibitor (in vitro)					
Sorafenib	P-gp inhibitor					Monitoring for DOACs toxicity
Sunitinib	P-gp inhibitor					Monitoring for DOACs toxicity
Tivozanib	Weak inhibitor of CYP2C8 (in vitro) BCRP inhibitor					Increased risk of bleeding (PD interaction)

Red box: avoid co-administration (contraindicated or not recommended).
Orange box: potential interaction (caution should be exercised and consider dose adjustment or alternative drugs).
Yellow box: potential weak interaction (monitoring for potential underexposure or toxicity).
Green box: no interaction expected based on pharmacokinetic properties, although no clinical data exist.

		DDIs with DOACs (PK or PD prediction)				
		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	
P-gp substrate		Yes	Yes	No (minimal)	Yes	
CYP3A4 substrate		No	Yes (moderate – 18%)	Yes (moderate – 25%)	No (minimal – 4%)	
BCRP substrate		No	Yes	Yes	No	
OATP1B1 substrate		No	No	No	Yes	
Oral anti-cancer agents	**Metabolic pathway**					**Clinical relevance and literature data**
Inhibitor of EGFR-associated tyrosine kinases						
Afatinib*	P-gp inhibitor (moderate) BCRP inhibitor					No expected relevant interaction due to P-gp pathway Increased risk of bleeding (PD interaction)
Erlotinib*	CYP3A4/2C8 inhibitor P-gp inhibitor (strong) BCRP inhibitor (moderate)					A case report described extensive subcutaneous bleeding with concomitant use of erlotinib and dabigatran
Gefitinib*	CYP2D6/2C19 inhibitor P-gp inhibitor (strong) BCRP inhibitor (strong)					Potential increase of AUC and risk of bleeding
Lapatinib	Weak inhibitor of intestinal CYP3A4 P-gp inhibitor					Potential increase of AUC and risk of bleeding
Neratinib	P-gp inhibitor (in vitro)					Monitoring for DOACs toxicity
Osimertinib*	P-gp inhibitor (in vitro) BCRP inhibitor (in vitro)					Monitoring for DOACs toxicity
Inhibitors of BCR-ABL tyrosine kinase						
Bosutinib	No activity on CYP or P-gp					No differences in AUC, C_{max} and T_{max} between dabigatran vs dabigatran+bosutinib were found in a PK study in healthy volunteers
Dasatinib	CYP3A4 inhibitor (weak)					Increased risk of bleeding due to thrombocytopenic effect and decreased platelet aggregation (PD interaction)
Imatinib	CYP3A4-2C9 inhibition (moderate)					Potential increase of AUC and risk of bleeding

Predicted pharmacokinetic drug interactions between main oral anticancer agents and direct oral anticoagulants

		DDIs with DOACs (PK or PD prediction)				
		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	
P-gp substrate		Yes	Yes	No (minimal)	Yes	
CYP3A4 substrate		No	Yes (moderate – 18%)	Yes (moderate – 25%)	No (minimal – 4%)	
BCRP substrate		No	Yes	Yes	No	
OATP1B1 substrate		No	No	No	Yes	
Oral anti-cancer agents	**Metabolic pathway**					**Clinical relevance and literature data**
Inhibitors of cyclin-dependent protein kinases (CDK)						
Abemaciclib	P-gp inhibitor BCRP inhibitor					Monitoring for DOACs toxicity
Palbociclib	CYP3A4 inhibitor (weak) Intestinal P-gp inhibition					Monitoring for DOACs toxicity
Ribociclib*	CYP3A4 inhibitor (moderate/strong based on dosage) CYP1A2 (weak) P-gp inhibitor (in vitro) BCRP inhibitor (in vitro)					Avoid concomitant use of apixaban and rivaroxaban if ribociclib is used at 600 mg/day. Monitoring for DOACs toxicity when ribociclib is used at 400 mg/day
Inhibitors of FGFR						
Pemigatinib*	P-gp inhibitor					Monitoring for DOACs toxicity
Inhibitors of ROS1/Trk						
Entrectinib*	CYP3A4 inhibitor P-gp inhibitor (in vitro)					Potential increase of AUC and risk of bleeding
Inhibitors of Trk						
Larotrectinib*	CYP3A4 inhibitor (weak) CYP2B6/2C8/2C9/2C19 inducer (in vitro) OATP1B1 inhibitor (in vitro)					Potential increase of AUC and risk of bleeding

		DDIs with DOACs (PK or PD prediction)				
		Dabigatran	Rivaroxaban	Apixaban	Edoxaban	
P-gp substrate		Yes	Yes	No (minimal)	Yes	
CYP3A4 substrate		No	Yes (moderate – 18%)	Yes (moderate – 25%)	No (minimal – 4%)	
BCRP substrate		No	Yes	Yes	No	
OATP1B1 substrate		No	No	No	Yes	
Oral anti-cancer agents	**Metabolic pathway**					**Clinical relevance and literature data**
Other protein kinase inhibitors						
Everolimus	P-gp inhibitor BCRP inhibitor					Monitoring for DOACs toxicity
Ibrutinib	P-gp inhibitor in GI tract					Increased risk of bleeding (PD interaction) Consider benefit-risk of ibrutinib in patients requiring DOACs (see text for details) TDM may be helpful
Ruxolitinib*	CYP3A4 inhibitor P-gp inhibitor (in vitro)					Potential increase of AUC and risk of bleeding
c-MET inhibitors						
Cabozantinib	CYP2C8 inhibitor (weak) P-gp inhibitor (in vitro)					A case report described haematological toxicity due to saturated CYP3A4 by apixaban in a patient affected by CKD
Capmatinib*	CYP1A2 inhibitor P-gp inhibitor BCRP inhibitor					Monitoring for DOACs toxicity
Phosphatidylinositol-3-kinase inhibitors						
Idelalisib	CYP3A4 inhibitor (strong) P-gp inhibitor (in vitro)					Avoid concomitant use of apixaban. Monitoring toxicity for rivaroxaban and dabigatran
Sonic-Hedgehog pathway inhibitors						
Vismodegib*	CYP2C8/2C9/2C19 inhibitor BCRP inhibitor					Impact of BRCP inhibition on exposure of apixaban and rivaroxaban is unknown
Sonidegib*	BCRP inhibitor					Impact of BRCP inhibition on exposure of apixaban and

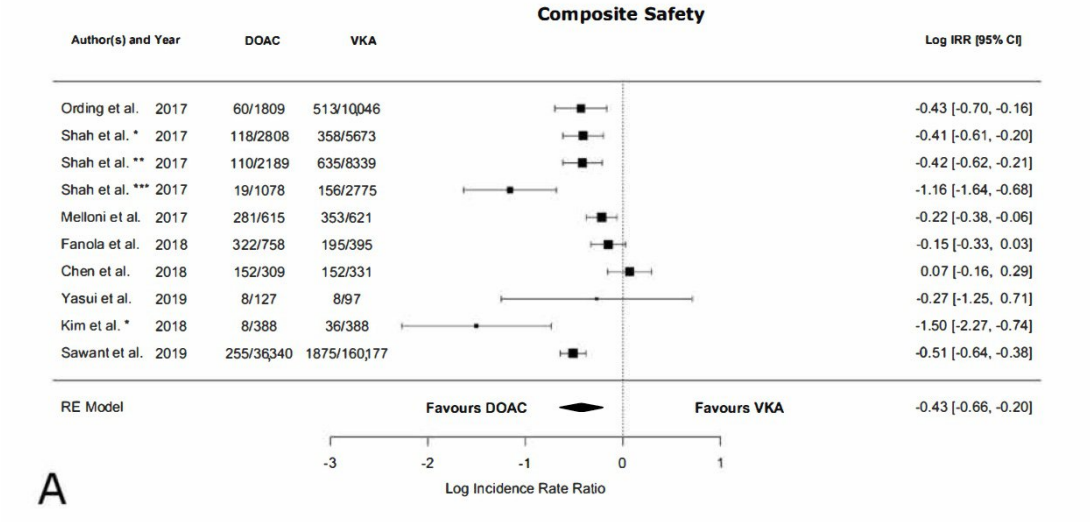
Journal of *Clinical Medicine*

MDPI

Systematic Review

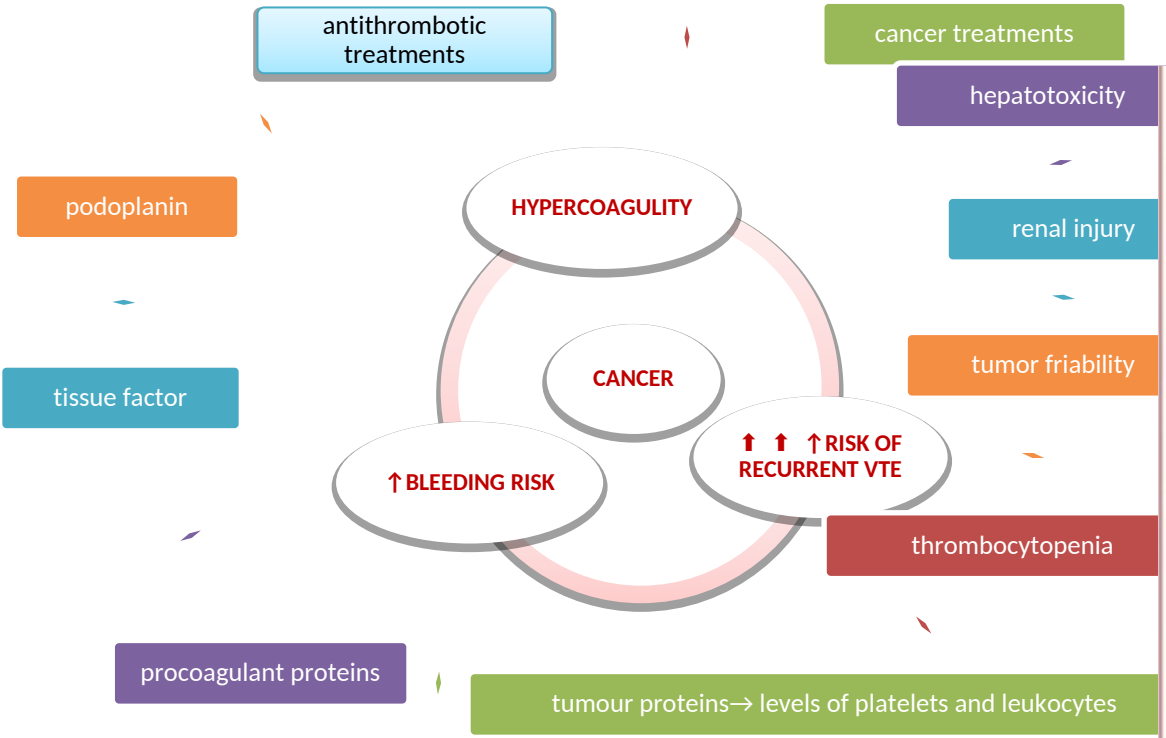
Superiority of Direct Oral Anticoagulants over Vitamin K Antagonists in Oncological Patients with Atrial Fibrillation: Analysis of Efficacy and Safety Outcomes

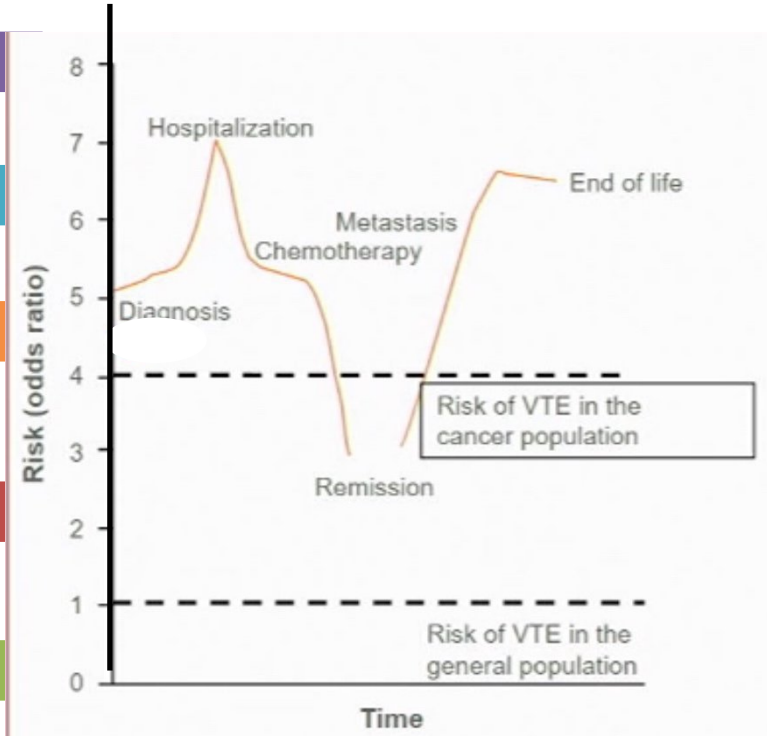
Iris Parrini [1,*], Fabiana Lucà [2], Carmelo Massimiliano Rao [2], Gianmarco Parise [3], Linda Renata Micali [3], Giuseppe Musumeci [1], Mark La Meir [4], Furio Colivicchi [5], Michele Massimo Gulizia [6,†] and Sandro Gelsomino [3,†]



JCM October 2022

Cancer and Venous Thromboembolism (VTE)





Khorana AA et al Nat Rev Dis Primers. 2022;8(1):11.

Mulder FI,.Blood. 2021;137(14):1959-1969

CLINICAL RISK FACTORS AND CANDIDATE BIOMARKERS FOR CANCER-ASSOCIATED VENOUS THROMBOEMBOLISM

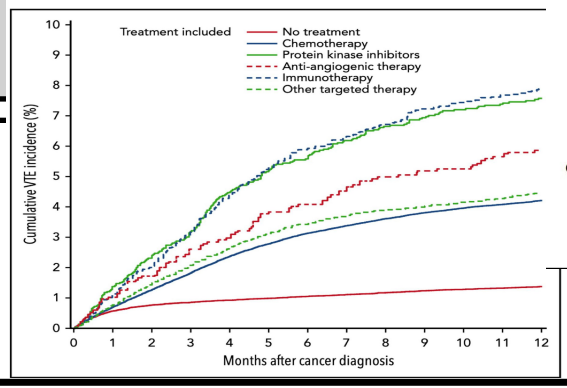
TYPE OF CANCER

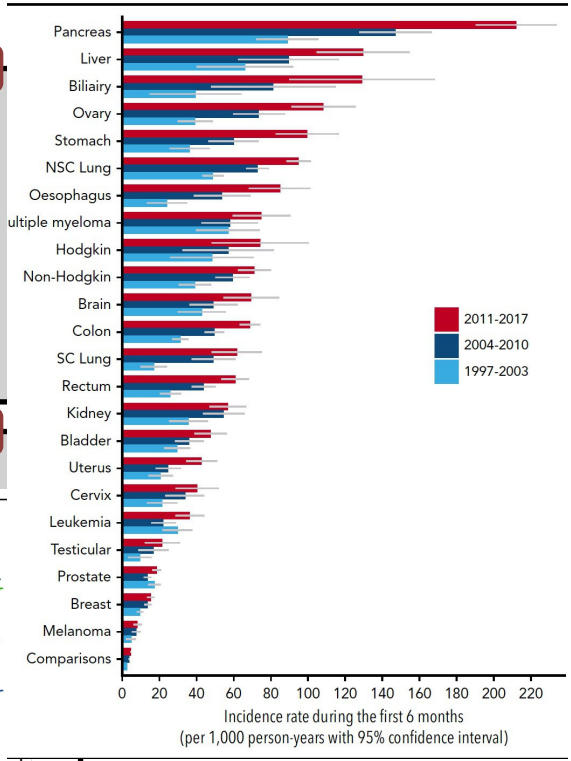
- pancreas
- Stomach
- primary brain tumours
- brain
- kidney
- lung
- gynecologic
- lymphoma
- myeloma
- Advanced cancer stage
- Initial period after cancer diagnosis
- Histology (worse with adenocarcinoma)

INDIVIDUAL PATIENT'S

- **Older age**
- -Female
- -RaceComorbiditiesInherited prothrombotic mutations
- -Prior history of venous thromboembolism
- -Poor performance status

-Major surgery
-Hospitalization
-Chemotherapy
-Hormonal therapy
-Antiangiogenic agents: thalidomide, lenalidomide, bevacizumab
-Immune checkpoint inhibitors





Gervaso L, et al. JACC CardioOncol. 2021, Mulder FI,.Blood. 2021;137(14):1959-1969

BIDIRECTIONAL RELATIONSHIP

15% of patients with cancer will experience VTE

20% of unprovoked VTEs are the first sign of an underlying malignancy

Eichinger S. Thromb Res 2016;140Suppl 1:S12–7.

RISK ASSESSMENT MODELS to determine which patients with cancer are at greater risk for VTE

TABLE 2 Comparison of Risk Assessment Models

Item	Khorana Score*	Vienna CATS Score	PROTECHT Score	CONKO Score
Pancreatic or gastric cancer (very-high-risk tumors)	+2	+2	+2	+2
Lung, gynecologic, lymphoma, bladder, or testicular (high-risk tumors)	+1	+1	+1	+1
Pre-chemotherapy Hb of <10 g/dl or erythropoietin-stimulating agents	+1	+1	+1	+1
Pre-chemotherapy white blood cell count of $>1 \times 10^9$/l	+1	+1	+1	+1
Pre-chemotherapy platelet count of $\geq 350 \times 10^9$/l	+1	+1	+1	+1
Body mass index of >35 kg/m^2	+1	+1	+1	–
D-dimer of >1.44 mg/l	–	+1	–	–
Soluble P-selectin of >53.1 ng/l	–	+1	–	–
Platinum-based or gemcitabine chemotherapy	–	–	+1	–
WHO performance status ≥2	–	–	–	+1

KHORANA: 1)type of cancer2)hemoglobin,platelet, and white blood cells
3)body mass index
Vienna CAT score adds D-dimer and soluble Pselectin
PROTECHT (Prophylaxis Thromboembolic Events
Chemotherapy) includes platinum-based orgemcitabine-based chemotherapy as additional variables

Khoran a. et al. Blood. 2008;111(10):4902-7.

Dickmann B. Haematologica 2013;98:1309–14.

Documento di consenso della Consulta delle Società Cardiologiche HCF-ANMCO/AICPR/GIEC/ITAHFA/SICOA/SICP/SIMG/SIT:

La terapia anticoagulante nel tromboembolismo venoso e nella fibrillazione atriale del paziente con cancro. Le attuali conoscenze e le nuove evidenze

Michele Massimo Gulizia (Chairperson)[1,2], Iris Parrini (Co-Chairperson)[3], Furio Colivicchi (Co-Chairperson)[4], Irma Bisceglia[5], Francesco Caiazza[6], Gian Franco Gensini[7], Gian Francesco Mureddu[8], Maurizio Santomauro[9], Walter Ageno[10], Marco Ambrosetti[11], Nadia Aspromonte[12], Sandro Barni[13], Fulvio Bellocci[14], Pasquale Caldarola[15], Monica Carletti[16], Leonardo De Luca[17], Stefania Angela Di Fusco[4], Andrea Di Lenarda[18], Marcello Di Nisio[19], Stefano Domenicucci[20], Iolanda Enea[21], Giuseppina Maura Francese[1], Chiara Lestuzzi[22], Fabiana Lucà[23], Nicola Maurea[24], Daniele Nassiacos[25], Roberto Franco Enrico Pedretti[26], Enrico Pusineri[27], Giancarlo Roscio[28], Roberta Rossini[29], Antonio Russo[30], Maurizio Volterrani[31], Domenico Gabrielli (Co-Chairperson)[32]

Tabella 17. Fattori di rischio di emorragia nei pazienti con cancro.

FR correlati al paziente	FR correlati alla neoplasia	Biomarcatori
Età	Tipo (istologia)	Conta piastrinica <50 000/mm^3
Peso corporeo <50 kg	Sede/estensione	ClCr <30 ml/min
Comorbilità (insufficienza renale, insufficienza epatica, piastrinopenia, ulcera gastroduodenale, ecc.)	Stadio avanzato della malattia	Transaminasi >3 volte il valore normale
Fragilità (rischio cadute)	Terapia antineoplastica embricata	

ClCr, clearance della creatinina; FR, fattori di rischio.

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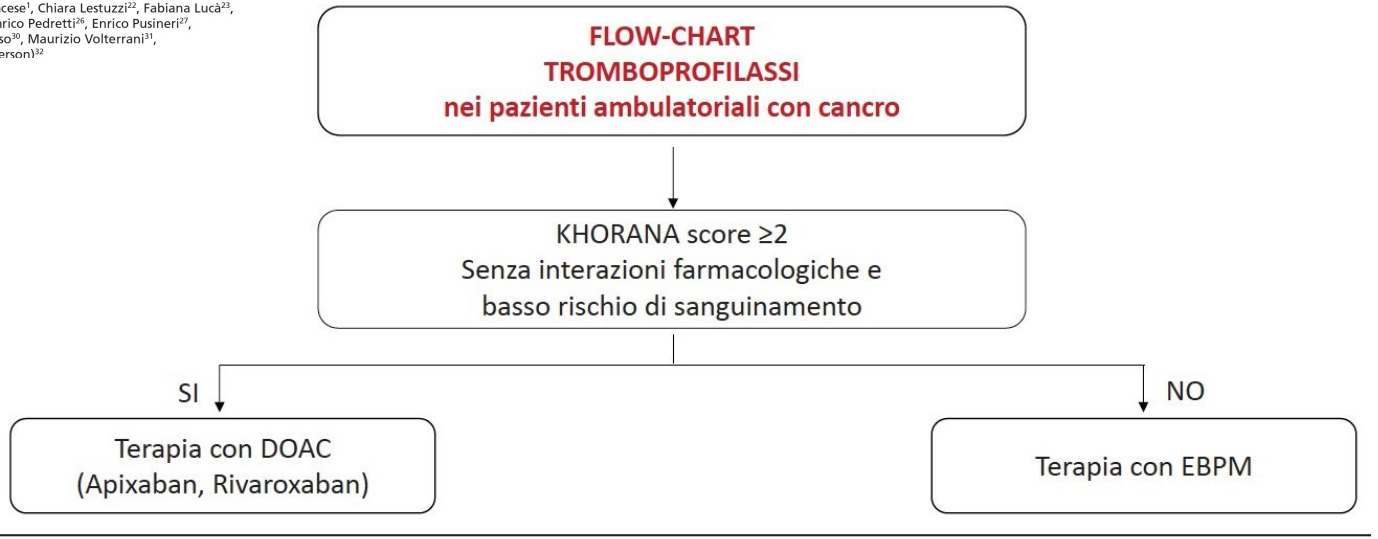

Figura 1. Flow-chart per la tromboprofilassi nei pazienti ambulatoriali con cancro. DOAC, anticoagulanti orali diretti; EBPM, eparina a basso peso molecolare.

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LLGG per la Profilassi del TEV nel paziente con CANCRO

LLGG	NICE 2018	ASCO 2019	ISTH 2019	NCCN 2021	ASH 2021
Società	National Institute for Health and Care Excellence	American Society of Clinical Oncology	International Society on Thrombosis and Haemostasis	National Comprehensive Cancer Network	American Society of Hematology
Paziente chirurgico	Preferire ove possibile anestesia regionale; profilassi TEV nei pazienti da sottoporre a Ch. addominale con EBPM over UFH tranne nei casi di I. Renale severa. Prevenzione meccanica se la anticoagulazione è controindicata	Tutti i pazienti devono ricevere profilassi anche pre operatoria con EBPM over UFH tranne nei casi di I. renale severa. Profilassi meccanica nei casi di controindicazione assoluta alla anticoagulazione	**Nel Paziente ambulatoriale con Khorana≥2 che deve iniziare chemioterapia si consiglia l'uso di profilassi con Apixaban o Rivaroxaban per 6 mesi dall'inizio della chemioterapia nei pazienti senza interazione farmacologica severa e senza K gastrointestinale, nel caso di impossibilità all'utilizzo DOAC si consiglia uso EBPM**	Si consiglia prevenzione TEV in tutti i pazienti sottoposti a intervento chirurgico fino a 4 settimane post intervento EBPM, se ClCr<30ml/min UFH	Si consiglia profilassi TEV in tutti i pazienti con Cancro che si sottopongono a ch. Addomino-pelvica con EBPM o fondaparinux over UFH tranne che per ClCr<30ml/min per 4 settimane
Paziente ospedalizzato	**Sì** se il paziente ha cancro attivo, con EBPM	**Sì** se è presente cancro attivo, con EBPM		Per i pazienti ospedalizzati si consiglia profilassi con EBPM (enoxaparina, dalteparina), fondaparinux, se ClCr <30ml/min UFH.	Per i pazienti ospedalizzati si consiglia EBPM over UFH tranne che nel caso di ClCr <30ml/min,
Ambulatoriale	Non si prevede prevenzione per i pazienti ambulatoriali anche se in chemioterapia a meno che non abbiano mieloma multiplo o K pancreas (EBPM)	**Sì** se il paziente ha un Khorana≥2 e deve iniziare chemioterapia, con apixaban, rivaroxaban o EBPM		**Sì** se il paziente ha un Khorana≥2 e deve iniziare chemioterapia, con Apixaban, Rivaroxaban per 6 mesi dall'inizio della chemio e, se inadatti, EBPM	Nel paziente ambulatoriale che si deve sottoporre a chemioterapia a rischio intermedio alto di TEV si consigliano DOAC (Apixaban o Rivaroxaban) o EBPM

The NEW ENGLAND JOURNAL of MEDICINE

Appropriate treatment of VTE in patients with cancer

ORIGINAL ARTICLE

Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer

Agnes Y.Y. Lee, M.D., Mark N. Levine, M.D., Ross I. Baker, M.D., Chris Bowden, M.D., Ajay K. Kakkar, M.B., Martin Prins, M.D., Frederick R. Rickles, M.D., Jim A. Julian, M.Math., Susan Haley, B.Sc., Michael J. Kovacs, M.D., and Michael Gent, D.Sc., for the Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators*

Randomized Comparison of Low-Molecular- Weight Heparin Versus Oral Anticoagulant Therapy or the Prevention of Recurrent Venous Thromboembolism in Patients With Cancer

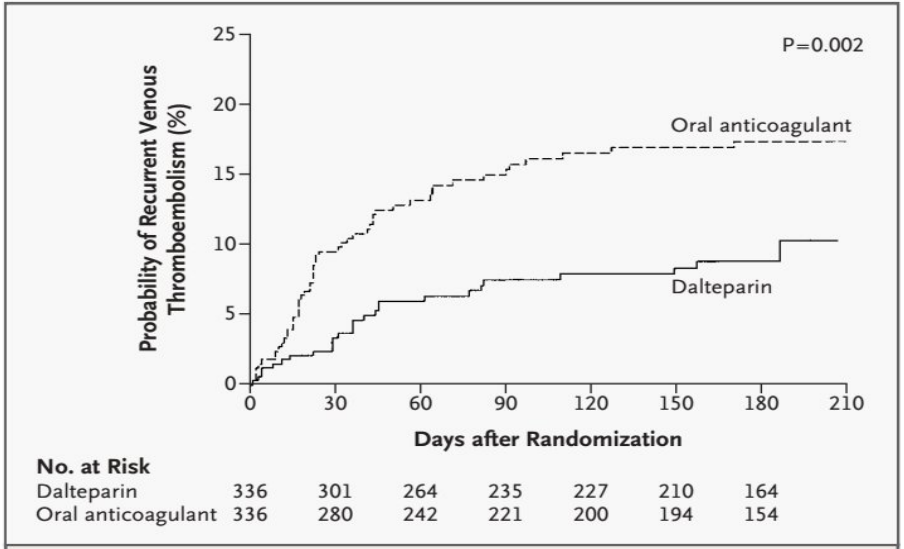

Figure 1. Kaplan–Meier Estimates of the Probability of Symptomatic Recurrent Venous Thromboembolism among Patients with Cancer, According to Whether They Received Secondary Prophylaxis with Dalteparin or Oral Anticoagulant Therapy for Acute Venous Thromboembolism.

An event was defined as an objectively verified, symptomatic episode of recurrent deep-vein thrombosis, pulmonary embolism, or both during the six-month study period. The hazard ratio for recurrent thromboembolism in the dalteparin group as compared with the oral-anticoagulant group was 0.48 (95 percent confidence interval, 0.30 to 0.77; P=0.002 by the log-rank test).

CLOT study randomly assigned 672 patients with cancer and acute symptomatic VTE to receive initial treatment with dalteparin at a dose of 200 IU/kg subcutaneous once daily for 5 to 7 days, followed by a coumarin derivative with a target international normalized ratio of 2.5

CENTRAL ILLUSTRATION Prophylaxis and Treatment of Cancer-Associated Thrombosis

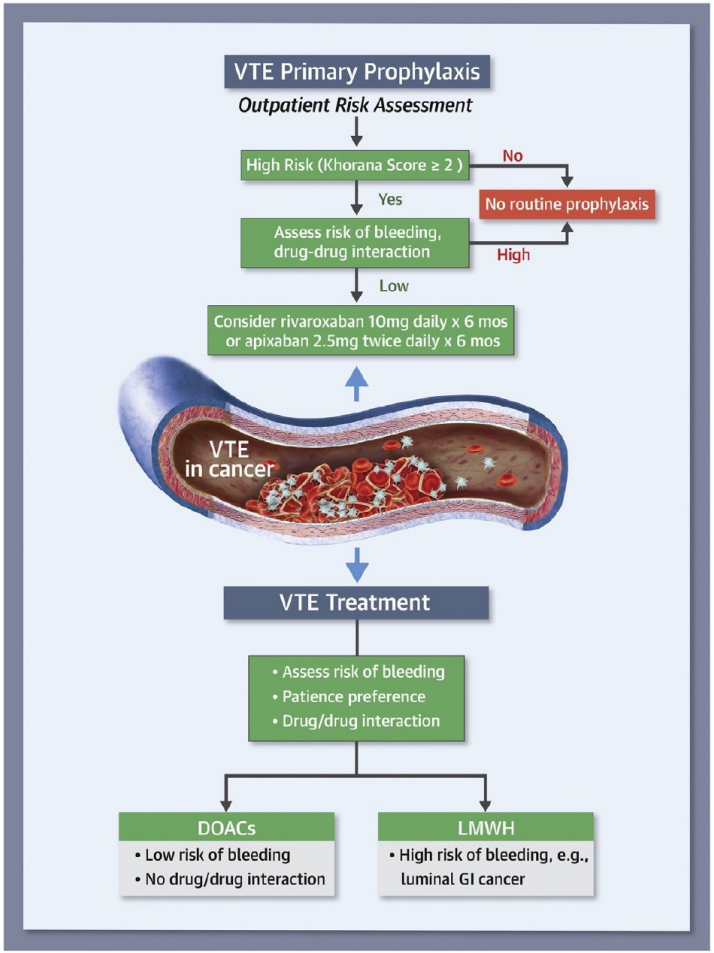

TABLE 3 Direct Oral Anticoagulants Dosing Regimens for Prophylaxis and Treatment of Venous Thromboembolism

Drug	Prophylaxis	Treatment
Apixaban	2.5 mg orally twice daily	10 mg twice daily for the first 7 days, followed by 5 mg twice daily
Rivaroxaban	10 mg orally once daily	15 mg orally every 12 h for 21 days, followed by 20 mg once daily
Edoxaban	Not applicable	60 mg daily after at least 5 days of low-molecular-weight heparin

Gervaso L, et al. JACC CardioOncol. 2021

TABLE 1 Study Characteristics

Study First Author (Ref. #); Year	N	Mean Age (yrs)	Design	Intervention	Control	Outcome
CARAVAGGIO Agnelli et al. (12); 2020	1,155	67	Open-label RCT (non-inferiority)	Apixaban	Dalteparin	Primary efficacy outcome: VTE recurrence. Primary safety outcome: major bleeding
SELECT-D Young et al. (10); 2018	406	67	Open-label RCT (pilot trial)	Rivaroxaban	Dalteparin	Primary outcome: thromboembolic recurrence. Secondary outcome: major bleeding and CRNMB
Hokusai VTE Cancer Roskab et al. (9); 2018	1,046	64	Open-label RCT (non-inferiority)	Edoxaban	Dalteparin	Primary outcome: composite of recurrent VTE or major bleeding
ADAM-VTE McBane et al. (11); 2020	300	64	Open-label RCT (superiority)	Apixaban	Dalteparin	Primary outcome: major bleeding. Secondary outcome: VTE recurrence

ADAM VTE = Apixaban and Dalteparin in Active Malignancy Associated Venous Thromboembolism: The ADAM VTE Trial; CARAVAGGIO = Apixaban for the Treatment of Venous Thromboembolism trial; CRNMB = clinically relevant non-major bleeding; Hokusai VTE Cancer = Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism; RCT = randomized clinical trial; SELECT-D = Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial; VTE = venous thromboembolism.

Gervaso L, et al. JACC CardioOncol. 2021.

Comparison of an Oral Factor Xa Inhibitor With Low Molecular Weight Heparin in Patients With Cancer With Venous Thromboembolism: Results of a Randomized Trial (SELECT-D)

Annie M. Young, Andrea Marshall, Jenny Thirlwall, Oliver Chapman, Anand Lokare, Catherine Hill, Danielle Hale, Janet A. Dunn, Gary H. Lyman, Charles Hutchinson, Peter MacCallum, Ajay Kakkar, F.D. Richard Hobbs, Stavros Petrou, Jeremy Dale, Christopher J. Poole, Anthony Maraveyas, and Mark Levine

SELECT-D

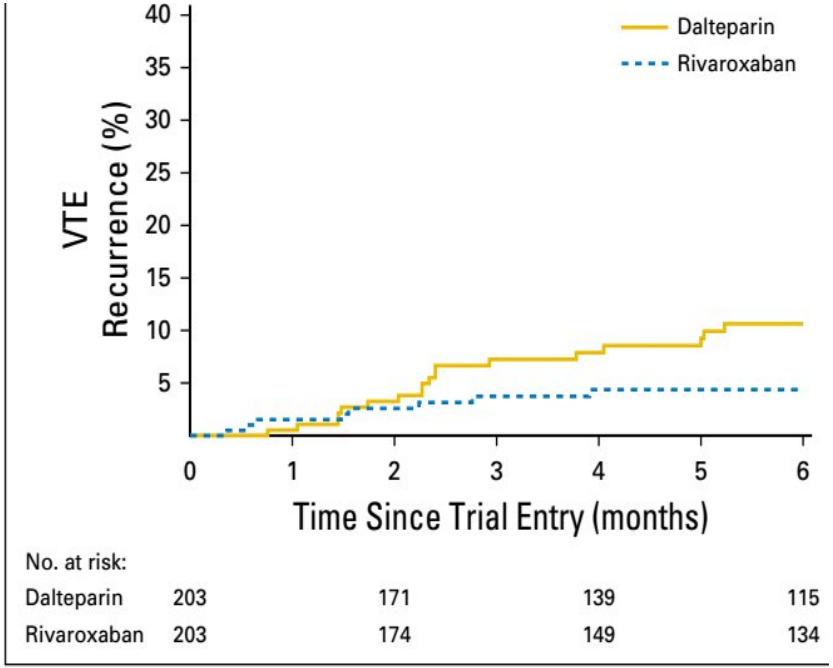

Fig 2. Time to venous thromboembolism (VTE) recurrence within 6 months.

The results of our trial provide evidence that rivaroxaban is an effective alternative to LMWH for the treatment of VTE in cancer. Rivaroxaban reduced the rate of recurrent VTE compared with LMWH, but at the cost of more bleeding. Oral administration is more convenient than daily subcutaneous injections. It should be used with particular caution in patients with esophageal cancer. At the end of the day, a patient's preference for a specific anticoagulant is based on a careful discussion between patient and physician about the benefits and risks of the treatment alternatives.

Young AM, J Clin Oncol 2018;36:2017–23.

HOKUSAI

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Gary E. Raskob, Ph.D., Nick van Es, M.D., Peter Verhamme, M.D., Marc Carrier, M.D., Marcello Di Nisio, M.D., David Garcia, M.D., Michael A. Grosso, M.D., Ajay K. Kakkar, M.B., B.S., Michael J. Kovacs, M.D., Michele F. Mercuri, M.D., Guy Meyer, M.D., Annelise Segers, M.D., Minggao Shi, Ph.D., Tzu-Fei Wang, M.D., Erik Yeo, M.D., George Zhang, Ph.D., Jeffrey I. Zwicker, M.D., Jeffrey I. Weitz, M.D., and Harry R. Büller, M.D., for the Hokusai VTE Cancer Investigators*

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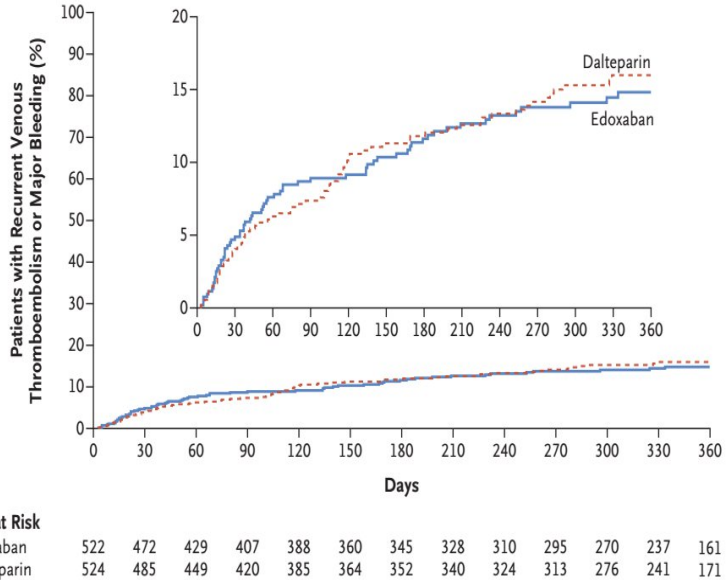


Figure 2. Kaplan–Meier Cumulative Event Rates for the Primary Outcome.

The primary outcome was a composite of recurrent venous thromboembolism or major bleeding. The inset shows the same data on an enlarged y axis.

Raskob GE, N Engl J Med 2018;378:615–24.

CARAVAGGIO

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Apixaban for the Treatment of Venous Thromboembolism Associated with Cancer

Giancarlo Agnelli, M.D., Cecilia Becattini, M.D., Guy Meyer, M.D., Andres Muñoz, M.D., Menno V. Huisman, M.D., Jean M. Connors, M.D., Alexander Cohen, M.D., Rupert Bauersachs, M.D., Benjamin Brenner, M.D., Adam Torbicki, M.D., Maria R. Sueiro, M.D., Catherine Lambert, M.D., Gualberto Gussoni, M.D., Mauro Campanini, M.D., Andrea Fontanella, M.D., Giorgio Vescovo, M.D., and Melina Verso, M.D., for the Caravaggio Investigators*

findings, we concluded that oral apixaban was noninferior to subcutaneous dalteparin for the treatment of cancer-associated venous thrombo-embolism without an increased risk of major bleeding.

Agnelli G, et al. N Engl J Med. 2020.

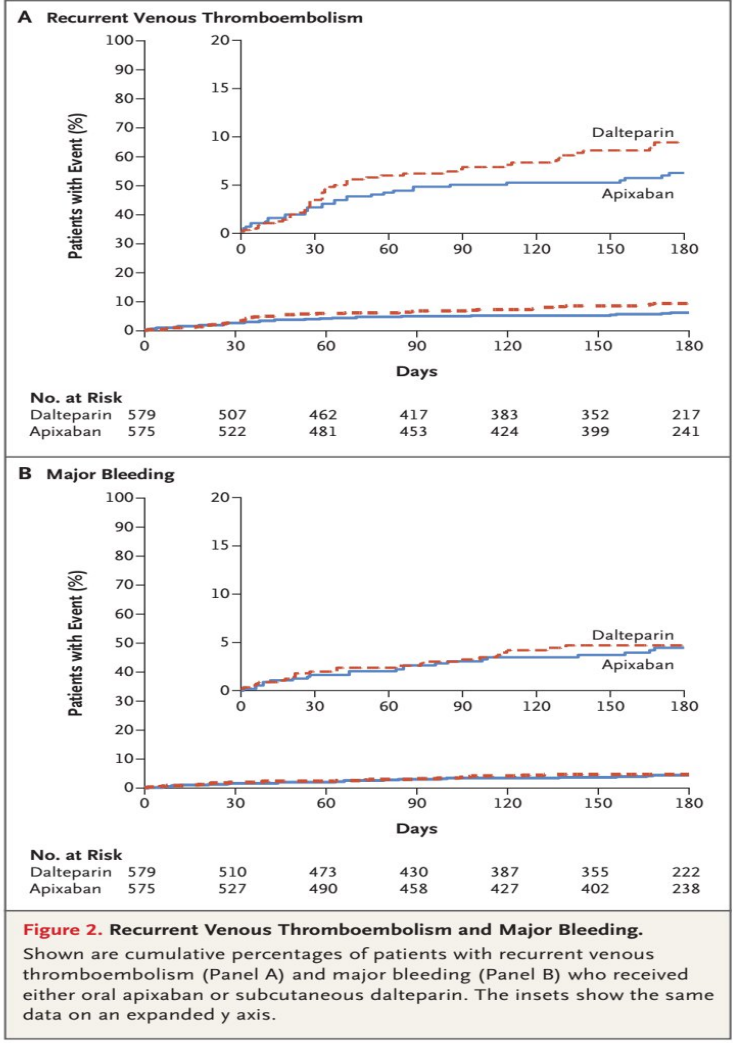
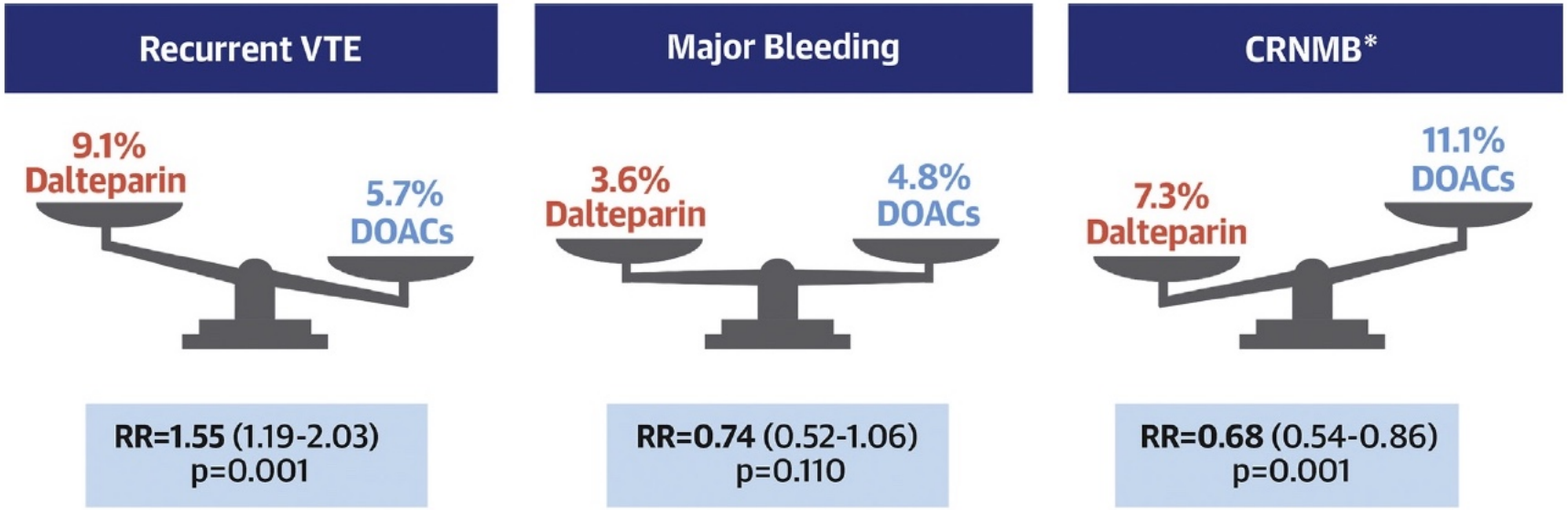


Figure 2. Recurrent Venous Thromboembolism and Major Bleeding.
Shown are cumulative percentages of patients with recurrent venous thromboembolism (Panel A) and major bleeding (Panel B) who received either oral apixaban or subcutaneous dalteparin. The insets show the same data on an expanded y axis.

CENTRAL ILLUSTRATION **DOACs Are Associated With Lower Recurrent VTE and Higher Nonmajor Bleeding Compared to Dalteparin**



Sabatino, J. et al. J Am Coll Cardiol CardioOnc. 2020;2(3):428-40.

Direct oral anticoagulants (DOACs) are noninferior to dalteparin to prevent venous thromboembolism (VTE) recurrence in cancer patients, with similar rates of major bleeding but higher clinically relevant nonmajor bleeding (CRNMB) events, particularly in studies in which a larger proportion of patients with gastrointestinal (GI) cancer was enrolled.

Gervaso L, et al. JACC CardioOncol. 2021.

FIGURE 2 Measures of Efficacy

A Recurrent venous thromboembolism

Study	Dalteparin Events	Dalteparin Total	DOACs Events	DOACs Total	P value	Risk Ratio
Hokusai VTE Cancer	59	524	41	522	0.063	1.43 [0.98, 2.10]
SELECT-D	18	203	8	203	0.050	2.25 [1.00, 5.06]
ADAM VTE	9	150	1	150	0.036	9.00 [1.15, 70.16]
CARAVAGGIO	46	579	32	576	0.108	1.43 [0.92, 2.21]
Total (95% CI)	**132**	**1,456**	**82**	**1,451**	**0.001**	**1.55 [1.19, 2.03]**

Heterogeneity: Chi² = 3.93, df = 3 (P = 0.270); I² = 24%

Risk Ratio IV, Fixed, 95% CI

0.01 0.1 1 10 100

Dalteparin DOACs

B Recurrent pulmonary embolism

Study	Dalteparin Events	Dalteparin Total	DOACs Events	DOACs Total	P value	Risk Ratio
Hokusai VTE Cancer	28	524	27	522	0.901	1.03 [0.62, 1.73]
SELECT-D	9	203	4	203	1.171	2.25 [0.70, 7.19]
ADAM VTE	1	150	0	150	0.503	3.00 [0.12, 73.06]
CARAVAGGIO	32	579	19	576	0.069	1.68 [0.96, 2.92]
Total (95% CI)	**70**	**1,456**	**50**	**1,451**	**0.08**	**1.38 [0.96, 1.97]**

Heterogeneity: Chi² = 2.59, df = 3 (P = 0.459); I² = 0%

Risk Ratio IV, Fixed, 95% CI

0.01 0.1 1 10 100

Dalteparin DOACs

C All-cause death

Study	Dalteparin Events	Dalteparin Total	DOACs Events	DOACs Total	P value	Risk Ratio
Hokusai VTE Cancer	192	524	206	522	0.348	0.93 [0.80, 1.08]
SELECT-D	56	203	48	203	0.364	1.17 [0.84, 1.63]
ADAM VTE	7	150	23	150	0.004	0.30 [0.13, 0.69]
CARAVAGGIO	153	579	135	576	0.241	1.13 [0.92, 1.38]
Total (95% CI)	**408**	**1,456**	**412**	**1,451**	**0.714**	**0.95 [0.73, 1.24]**

Heterogeneity: Tau² = 0.05; Chi² = 11.25, df = 3 (P = 0.010); I² = 73%

Risk Ratio IV, Random, 95% CI

0.01 0.1 1 10 100

Dalteparin DOACs

Forest plots illustrating results of meta-analysis on the rate of recurrent venous **(A)** thromboembolism, **(B)** pulmonary embolism, and **(C)** all-cause death. CI = confidence interval; DOAC = direct oral anticoagulants; I^2 = inconsistency index.

FIGURE 4 Measures of Safety

A Major bleeding

Study	Dalteparin Events	Dalteparin Total	DOACs Events	DOACs Total	P value	Risk Ratio
Hokusai VTE	21	524	36	522	0.043	0.58 [0.34, 0.98]
Cancer SELECT-D	6	203	11	203	0.223	0.55 [0.21, 1.45]
ADAM VTE	2	150	0	150	0.298	5.00 [0.24, 103.28]
CARAVAGGIO	23	579	22	576	0.893	1.04 [0.59, 1.84]
Total (95% CI)	**52**	**1,456**	**69**	**1,451**	**0.110**	**0.74 [0.52, 1.06]**

Heterogeneity: Chi² = 4.08, df = 3 (P = 0.253); I² = 26%

Risk Ratio IV, Fixed, 95% CI

0.01 0.1 1 10 100

Dalteparin DOACs

B Gastrointestinal bleeding

Study	Dalteparin Events	Dalteparin Total	DOACs Events	DOACs Total	P value	Risk Ratio
Hokusai VTE Cancer	6	524	20	522	0.009	0.30 [0.12, 0.74]
SELECT D	4	203	8	203	0.251	0.50 [0.15, 1.63]
CARAVAGGIO	10	579	11	576	0.816	0.90 [0.39, 2.11]
Total (95% CI)	**20**	**1,306**	**39**	**1,301**	**0.020**	**0.53 [0.31, 0.92]**

Heterogeneity: Chi² = 3.07, df = 2 (P = 0.21); I² = 35%

Risk Ratio IV, Fixed, 95% CI

0.01 0.1 1 10 100

Dalteparin DOACs

C Clinically relevant nonmajor bleeding (CRNMB)

Study	Dalteparin Events	Dalteparin Total	DOACs Events	DOACs Total	P value	Risk Ratio
Hokusai VTE Cancer	58	524	76	522	0.093	0.76 [0.55, 1.05]
SELECT-D	7	203	25	203	0.002	0.28 [0.12, 0.63]
ADAM VTE	7	150	8	150	0.791	0.88 [0.33, 2.35]
CARAVAGGIO	35	576	52	576	0.057	0.67 [0.45, 1.02]
Total (95% CI)	**107**	**1,453**	**161**	**1,451**	**0.001**	**0.68 [0.54, 0.86]**

Heterogeneity: Chi² = 5.27, df = 3 (P = 0.153); I² = 43%

Risk Ratio IV, Fixed, 95% CI

0.01 0.1 1 10 100

Dalteparin DOACs

Forest plots illustrating results of meta-analysis on the rate of **(A)** major bleeding, **(B)** GI bleeding, and **(C)** clinically relevant nonmajor bleeding (CRNMB). Abbreviations as in Figures 2 and 3.

Gervaso L, et al. JACC CardioOncol. 2021

Tabella 11. Criteri per la selezione dei pazienti con priorità all'impiego di anticoagulanti orali diretti per tromboembolismo venoso associato a neoplasia.

• Conferma di neoplasia ad alto rischio trombotico
• Alto rischio di recidiva trombotica
• Basso rischio emorragico
• Previsione di lunga durata della terapia (>3 mesi)
• Basso rischio di interazione con la terapia antineoplastica
• Consenso informato

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Note di pratica clinica
• Sulla base dell'evidenza attualmente disponibile, i DOAC potrebbero rappresentare una valida alternativa alle EBPM nella maggior parte dei pazienti oncologici con TEV. I dati più convincenti vengono dallo studio Hokusai VTE Cancer che ha mostrato una riduzione del TEV ricorrente con edoxaban al costo di un aumento dei sanguinamenti maggiori, prevalentemente gastrointestinali superiori in pazienti con tumori del tratto gastrointestinale. In questi ultimi, la scelta tra edoxaban ed EBPM andrà valutata individualmente considerando il rischio e la severità dei sanguinamenti, la potenziale riduzione del TEV ricorrente e non da ultimo le preferenze del paziente per una terapia orale o parenterale.
• L'impiego di edoxaban, rivaroxaban o apixaban potrebbe essere preferibile a quello delle EBPM nei pazienti con tumori non gastrointestinali, i quali potrebbero beneficiare di simile sicurezza e maggiore efficacia. Grazie alla monosomministrazione orale giornaliera, indipendente dall'assunzione di cibo, ed i semplici criteri per l'aggiustamento posologico, l'impiego dei DOAC potrebbe rappresentare una importante semplificazione del trattamento anticoagulante di questi pazienti con un impatto positivo sull'aderenza terapeutica e qualità di vita.
• L'uso dei DOAC dovrà attentamente considerare le differenze farmacocinetiche e le potenziali interazioni con agenti antitumorali inibitori, induttori o substrati della P-glicoproteina o del citocromo CYP3A4. Se da un lato la P-glicoproteina influisce in modo similare sull'eliminazione dei vari DOAC, il citocromo CYP3A4 condiziona la clearance epatica soprattutto di rivaroxaban e apixaban, con effetti minimi o assenti sull'eliminazione di edoxaban e dabigatran.
• Le EBPM dovrebbero essere considerate in preferenza ai DOAC in tutti quei casi nei quali le concomitanti terapie antineoplastiche potrebbero interferire in maniera rilevante con la P-glicoproteina e soprattutto con il citocromo CYP3A4.
• Va comunque sottolineato come il reale significato clinico di molte interazioni farmacologiche rimanga a tutt'oggi poco chiaro per via del numero relativamente ridotto di pazienti sottoposti ad alcune terapie, le possibili modifiche terapeutiche nel corso di malattia e le poche informazioni su associazioni di chemioterapici.