XXIX Congresso Nazionale ANCE

QUALE NAO PUO' SOSTITUIRE IL WARFARIN E L'EPARINA NELLA FIBRILLAZIONE ATRIALE E NEL TROMBOEMBOLISMO VENOSO NEL PAZIENTE NEOPLASTICO

Nicola Maurea, MD, FACC, FESC

Direttore della Struttura Complessa di Cardiologia
Istituto Nazionale Tumori, Fondazione Pascale, Napoli
Presidente Associzione Italiana Cardioncologia (AICO)

Sorrento, 10-13 Ottobre 2019

XXIX CONGRESSO NAZIONALE ANCE

DISCLOSURE INFORMATION

Nicola Maurea

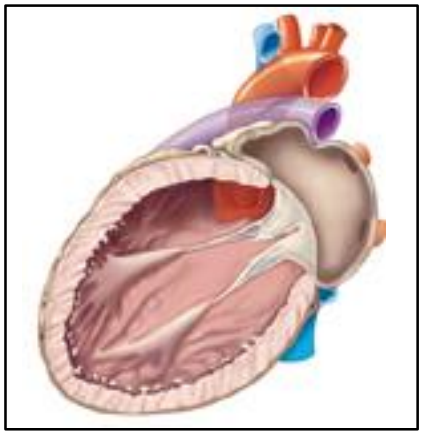
I.Grant/Research Support from the Italian Ministry of Health

II.Advisory Board for Bayer, Daiichi-Sankyo, and Clinigen

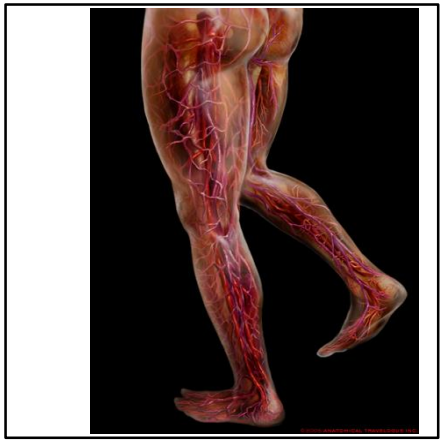
III.Speaker for Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi-Sankyo

Cardiovascular Complications in Cancer Patient

Arrhythmias
Atrial fibrillation



Cardiac Dysfunction
Heart Failure



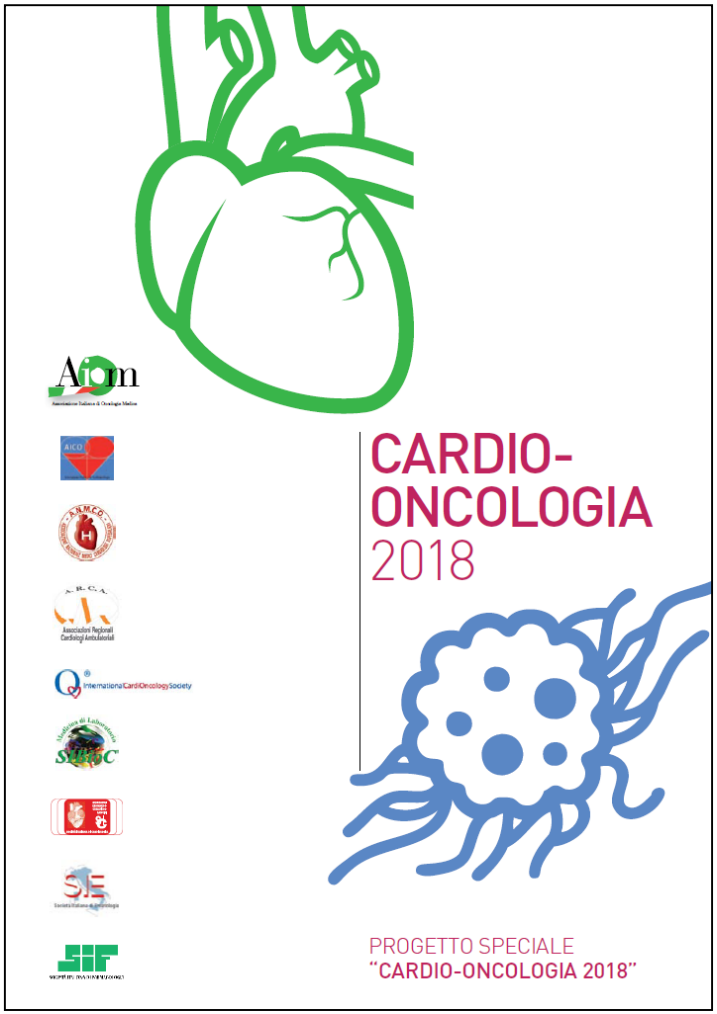
Thromboembolism

Angina pectoris
Myocardial infarction

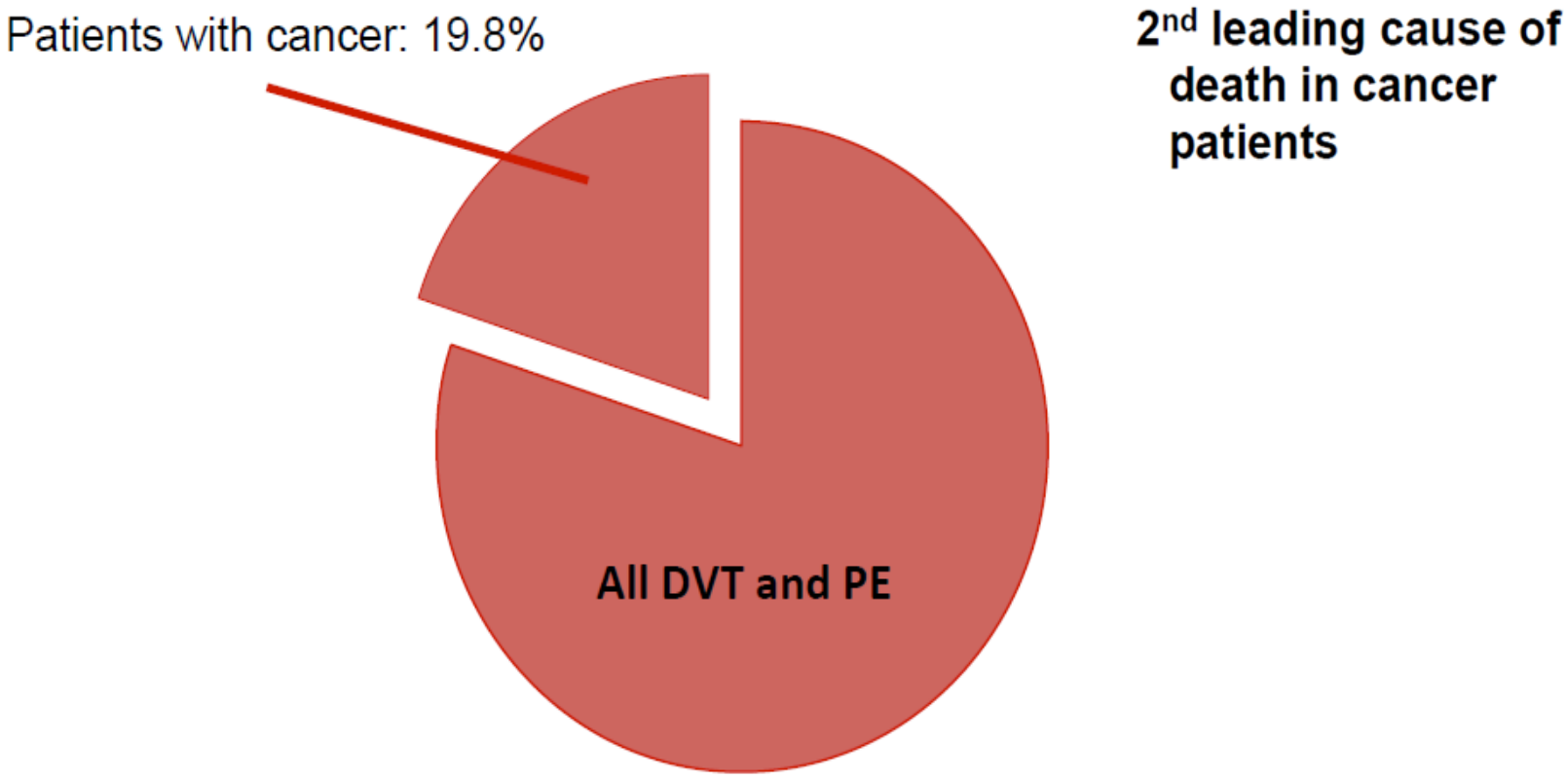
Hypertension

6 Tromboembolismo venoso e fibrillazione atriale: ruolo degli anticoagulanti orali diretti (DOA)

Nicola Maurea[1], Enrico Barbieri[2], Mario Roselli[3], Sergio Siragusa[4]

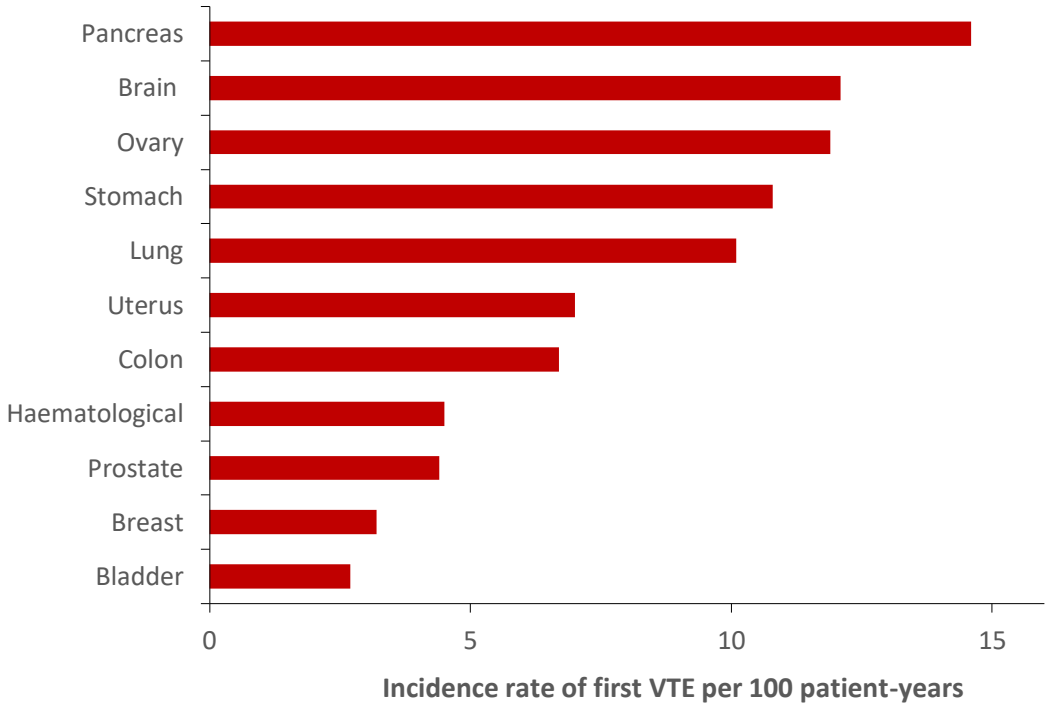


Incidence of VTE in cancer patients



One-fifth of all VTE occurs in patients with cancer

Incidence of VTE After Cancer Diagnosis



Cancer type	Incidence rate per 100 patient-years (95% CI)
Pancreas	14.6 (12.9–16.5)
Brain	12.1 (10.3–14.0)
Ovary	11.9 (10.6–13.2)
Stomach	10.8 (9.5–12.3)
Lung	10.1 (9.5–10.8)
Uterus	7 (5.9–8.3)
Colon	6.7 (6.3–7.2)
Haematological	4.5 (4.1–4.8)
Prostate	4.4 (4.0–4.7)
Breast	3.2 (2.9–3.4)
Bladder	2.7 (2.4–3.0)

Cohen AT *et al*, *Thromb Haemost* 2017;117:57–65

Prevalence of Tumour Types in Active Cancer-Associated Thrombosis

Patients with active cancer* and a first VTE

Common cancer types (%)	DVT (n=3055)	PE (n=3537)	Total (N=6592)
Prostate (men)	19.1	16.1	17.5
Breast (women)	14.0	16.0	15.1
Lung	10.3	17.0	13.9
Colon	12.6	12.5	12.5
Ovarian (women)	8.5	10.3	9.5
Haematological	11.8	8.7	10.1
Bladder	6.1	3.8	4.8
Uterus (women)	5.2	3.3	4.2
Pancreas	4.2	3.7	3.9
Stomach	3.4	3.8	3.6
Brain	2.6	2.5	2.5

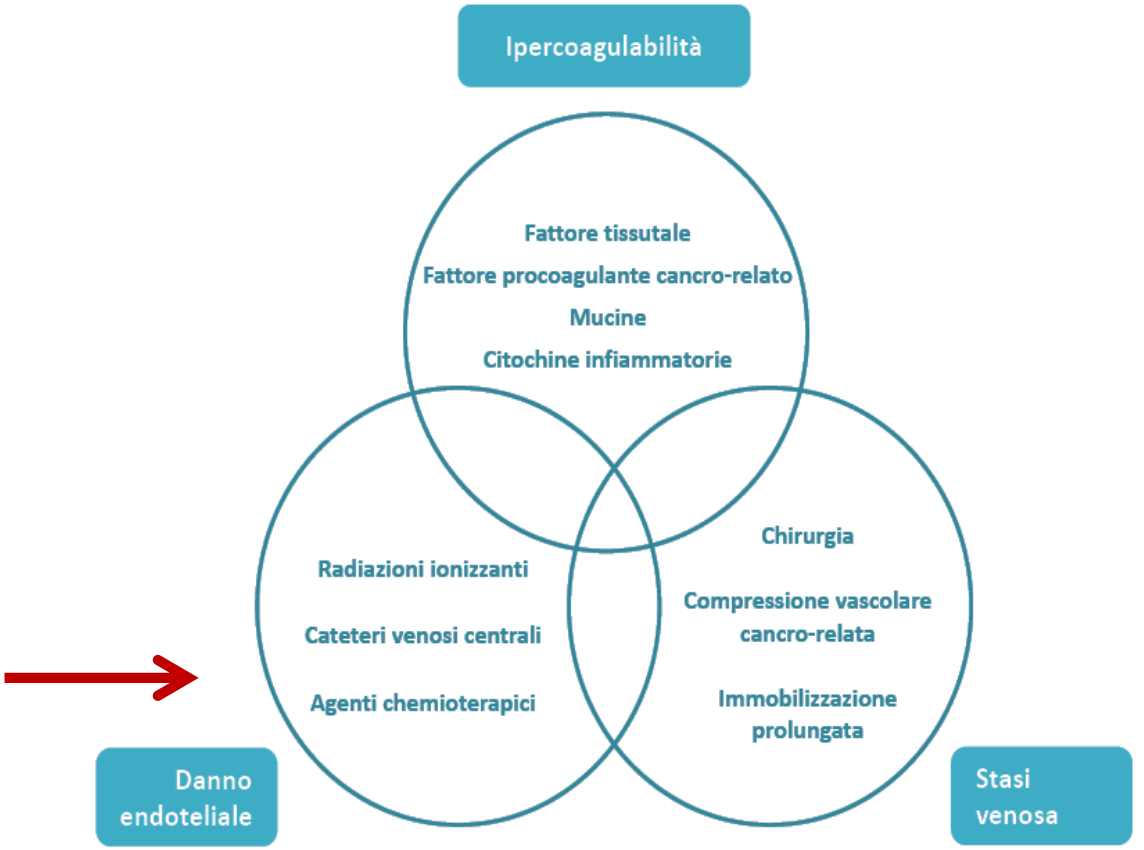
*Defined as an admission to hospital with a primary diagnosis of cancer (excluding non-melanoma skin cancer), or a recording of radiation, chemotherapy or bone marrow transplantation in HES records

Cohen AT *et al*, *Thromb Haemost* 2017;117:57–65

Tromboembolismo venoso e fibrillazione atriale nel paziente oncologico

Nicola Maurea[1], Letizia Riva[2]

Meccanismi del tromboembolismo venoso associati al cancro



cancro.

G Ital Cardiol (Rome). 2018 Sep;19(9):3-6

Tromboembolismo venoso e fibrillazione atriale nel paziente oncologico

Nicola Maurea[1], Letizia Riva[2]

Farmaci oncologici associati a tromboembolismo venoso

Inibitori dell'angiogenesi
Lenalidomide
Talidomide
Pomalidomide
Inibitori dell'istone deacetilasi
Vorinostat
Agenti alchilanti
Cisplatino
Inibitori delle tirosinchinasi
Dabrafenib
Sunitinib
Pazopanib
Axitinib
Nilotinib
Erlotinib
Ponatinib
Ziv-aflibercept
Cabozantinib
Trametinib
Anticorpi monoclonali anti-VEGF
Bevacizumab
Inibitori di mTOR
Everolimus

mTOR, mammalian target of rapamycin; VEGF, fattore di crescita endoteliale vascolare.

G Ital Cardiol (Rome). 2018 Sep;19(9):3-6

Anticoagulation in cancer patients with AF

- **What is an active cancer?**
- Anticoagulation during the first 6 months
- Duration of anticoagulation

Definizione di cancro attivo secondo l' International Society on Thrombosis and Haemostasis

Il cancro attivo è definito come:

- ❑ Cancro diagnosticato negli ultimi 6 mesi
- ❑ Recidiva di cancro, cancro regionalmente avanzato o metastatico
- ❑ Cancro per il quale è stato effettuato trattamento negli ultimi 6 mesi
- ❑ Neoplasia ematologica che non è in remissione completa

Khorana AA et al. Journal of Thrombosis and Haemostasis 2018

Anticoagulation in cancer patients with VTE

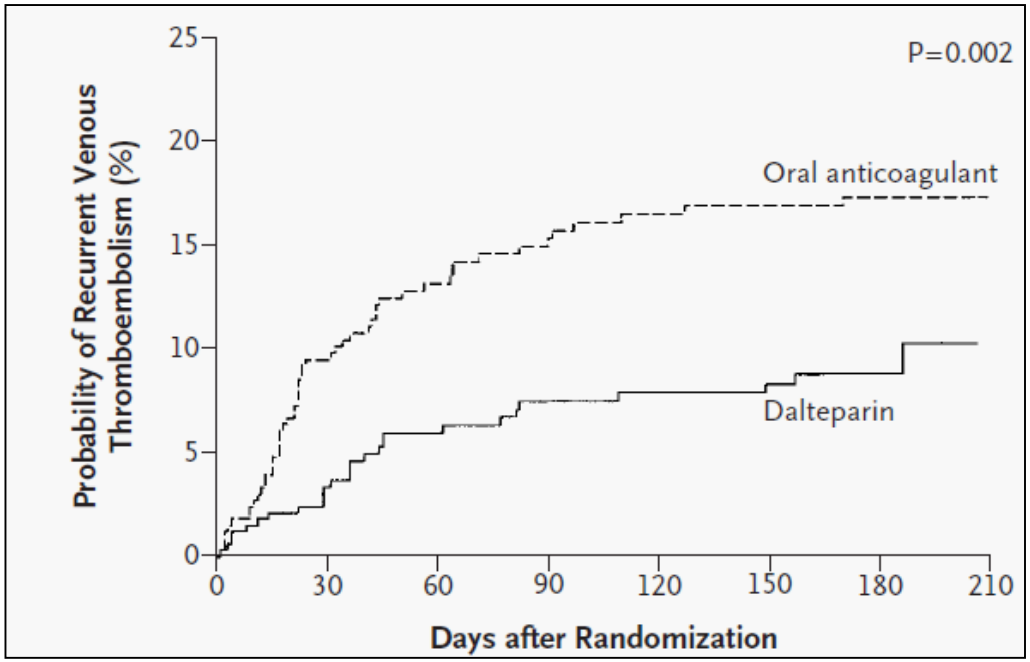
- What is an active cancer?
- **Anticoagulation during the first 6 months**
- Duration of anticoagulation

ORIGINAL ARTICLE

N Engl J Med 2003;349:146-53.

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

Gold standard del trattamento del TEV



CLOT trial

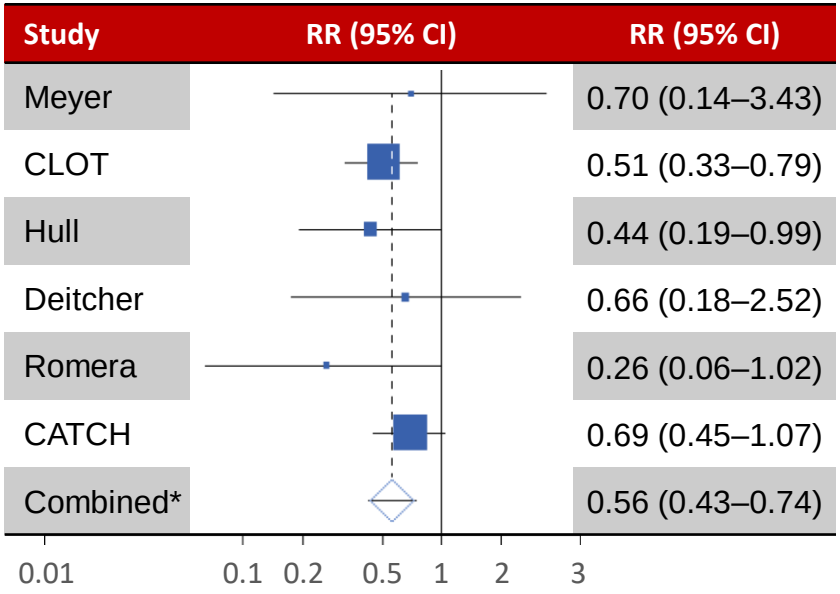
CONCLUSIONS

In patients with cancer and acute venous thromboembolism, dalteparin was more effective than an oral anticoagulant in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding.

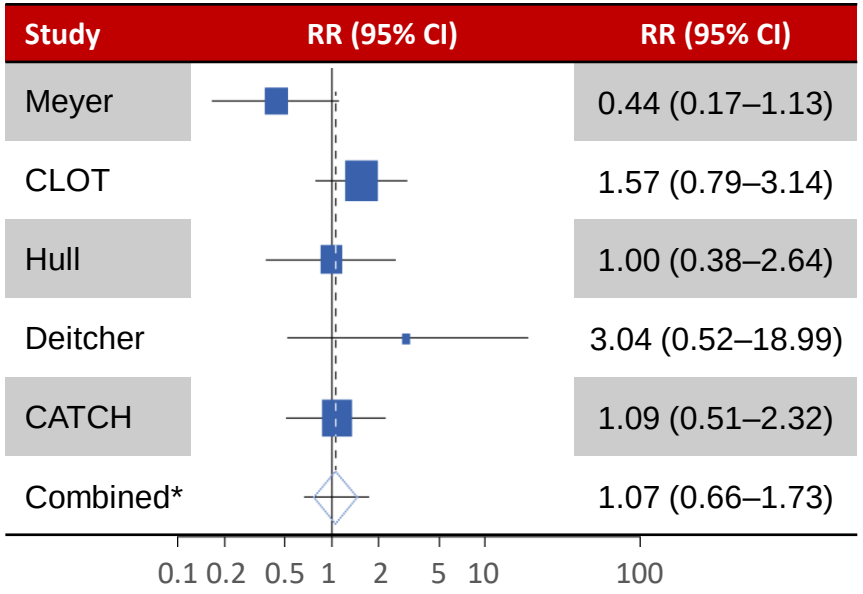
Lee AY et al.

Efficacy and Safety of LMWH Versus VKA in the Treatment of Cancer-Associated Thrombosis

Recurrent VTE



Major bleeding events



LMWH is associated with a significant reduction in the risk of recurrent VTE without a significant increase in major bleeding episodes versus VKA

*Random effects model

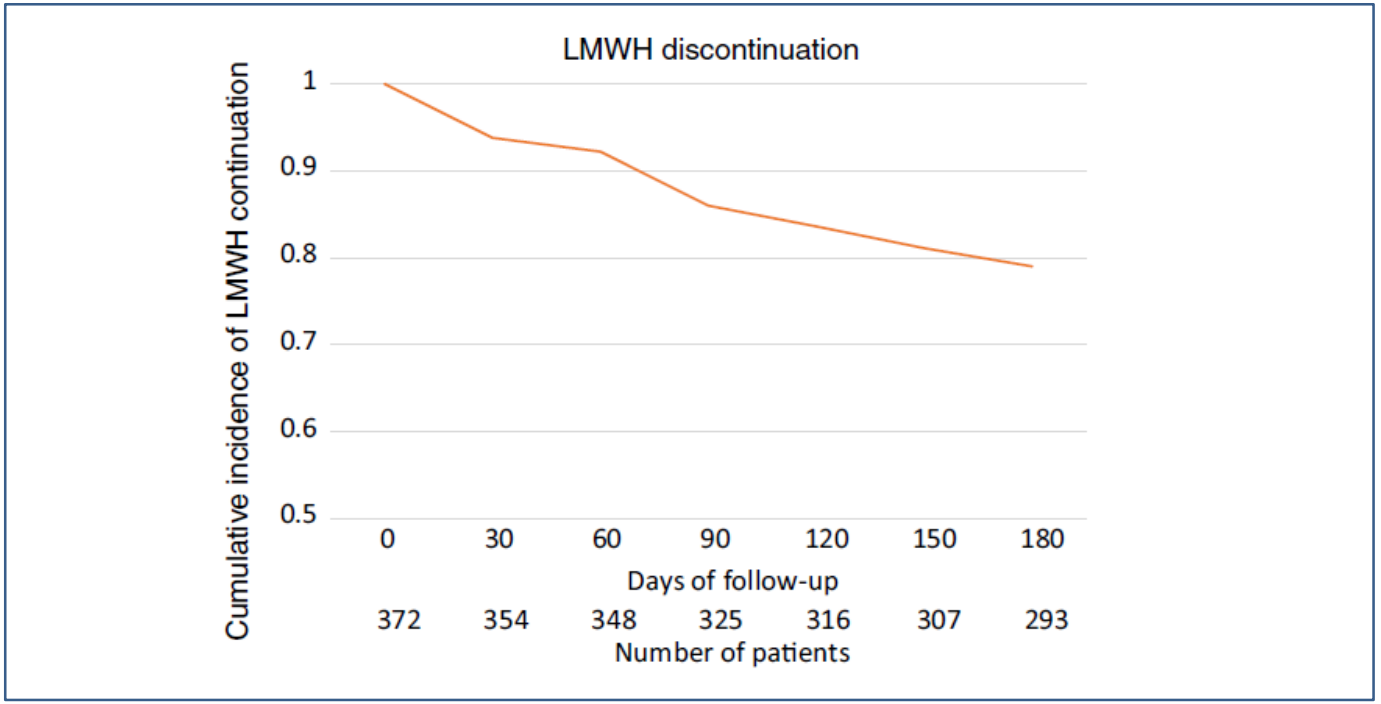
Carrier M, Prandoni P, *Expert Rev Hematol* 2017;10:15–22

Journal of Thrombosis and Haemostasis 2017

Continuation of low-molecular-weight heparin treatment for cancer-related venous thromboembolism: a prospective cohort study in daily clinical practice

S. J. VAN DER WALL,* F. A. KLOK,* P. L. DEN EXTER,* D. BARRIOS,† R. MORILLO,† S. C. CANNEGIETER,‡ D. JIMENEZ† and M. V. HUISMAN*

Results: A total of 372 patients were analyzed during LMWH treatment for a maximum of 180 days. The cumulative incidence of discontinuation was 21% (95% confidence interval [CI] 17–25) after a median period of 90 days (interquartile range 60–120 days).



Conclusion: Our study reveals that one of five patients with cancer-associated VTE stopped LMWH injections because of side-effects.

LMWH might be a burden for patients

- Daily SC injections
- Platelet count monitoring
- Local hematoma
- What about the DOACs?

Recent Clinical Trial Data and Upcoming Studies

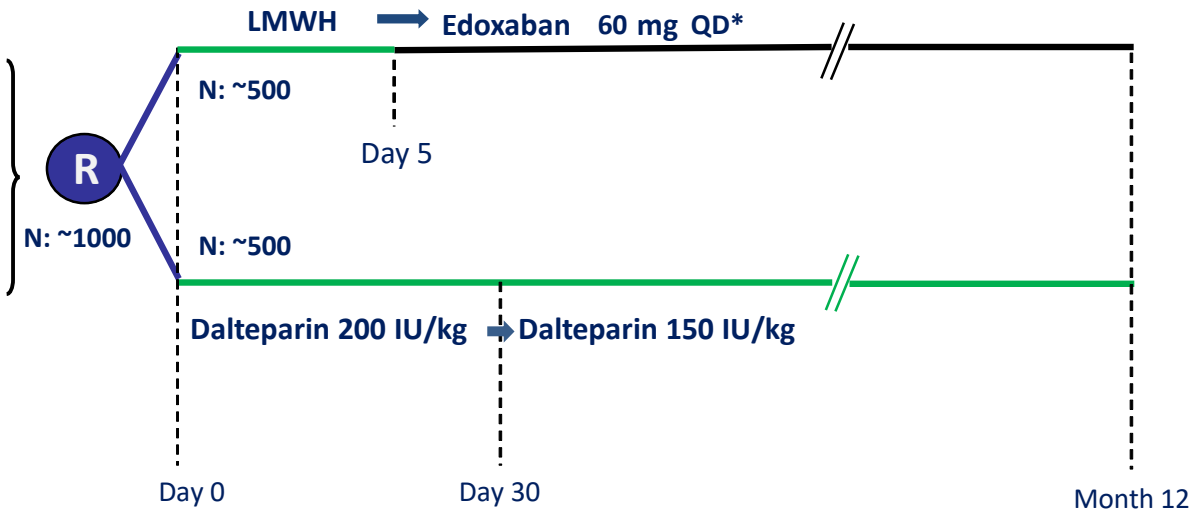
- **Hokusai-VTE-Cancer** (edoxaban versus dalteparin)[1]
- **Select-D** (rivaroxaban versus dalteparin) [2]
- **Caravaggio– ongoing** (apixaban versus dalteparin) [3]

[1] Raskob Ge et al. N Engl J Med 2016; 376:615-624
[2] Young AM et al. J Clin Oncol 2016; 36: 2017-2023
[3] Clinical Trials.gov http://clinicaltrials.gov/cl2/show/NCT03045406 [accessed 31 May 2015]

The NEW ENGLAND JOURNAL of MEDICINE

Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism

Objectively Confirmed VTE
- Stratified randomization for
  - Bleeding Risk
  - Dose Adjustment
- PROBE design
- 114 sites North America, Europe, Australia, New Zealand



Treatment for up to 12 months (at least 6 months)

CONCLUSIONS

Oral edoxaban was noninferior to subcutaneous dalteparin with respect to the composite outcome of recurrent venous thromboembolism or major bleeding. The rate of recurrent venous thromboembolism was lower but the rate of major bleeding was higher with edoxaban than with dalteparin.

Raskob GE et al. N Engl J Med. 2018

Inclusion criteria

- **Adult cancer patients with acute VTE confirmed by imaging:**
  - **symptomatic or incidentally detected proximal DVT,**
  - **symptomatic PE,**
  - **incidental PE of a segmental or larger pulmonary artery;**
- Cancer other than basal-cell or squamous-cell skin cancer
- Cancer either active or diagnosed within 2 years
- Active cancer
  - diagnosed or treatment given within last 6 months
  - recurrent or regionally advanced or metastatic
  - hematologic not in complete remission
- Intention for LMWH treatment for at least 6 months

Utilizzo concomitante di un ampio spettro di farmaci antitumorali

	Edoxaban (N=522)	Dalteparin (N=524)
Antimetabolites – no. (%)	124 (23.8)	118 (22.5)
Platinum-based chemotherapy – no. (%)	105 (20.1)	107 (20.4)
Monoclonal antibodies – no. (%)	42 (8.0)	54 (10.3)
Bevacizumab – no. (%)	13 (2.5)	17 (3.2)
Taxanes – no. (%)	40 (7.7)	47 (9.0)
Hormonal therapy – no. (%)	41 (7.9)	37 (7.1)
Topoisomerase inhibitors – no. (%)	30 (5.7)	48 (9.2)
Alkylating agents – no. (%)	30 (5.7)	38 (7.3)
Anthracyclines – no. (%)	22 (4.2)	25 (4.8)
Vinca alkaloids – no. (%)	16 (3.1)	18 (3.4)
Kinase inhibitors – no. (%)	18 (3.4)	18 (3.4)
Immunomodulating agents – no. (%)	16 (3.1)	9 (1.7)
Proteasome inhibitors – no. (%)	7 (1.3)	8 (1.5)
Antitumor antibiotics – no. (%)	5 (1.0)	5 (1.0)
Miscellaneous – no. (%)	14 (2.7)	14 (2.7)

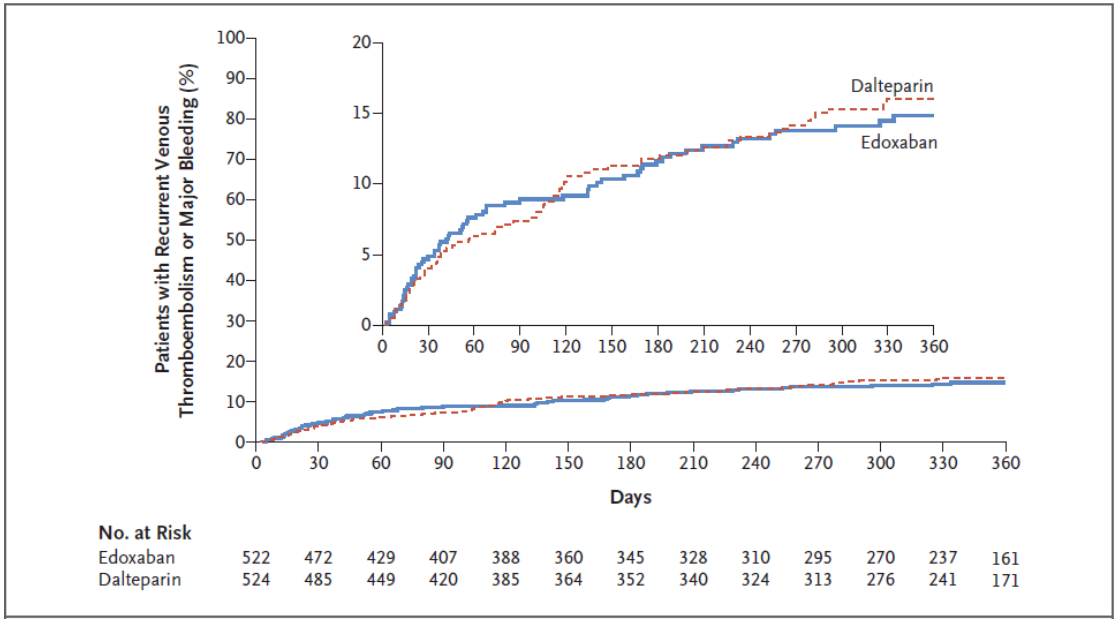
Da protocollo, i seguenti farmaci richiedevano riduzione della dose di Edoxaban a 30 mg:

- **Inibitori delle tirosinchinasi**: imatinib, nilotinib, lapatinib, sunitinib, crizotinib, vandetanib
- **Terapie ormonali**: tamoxifene, enzalutamide, abiraterone
- **Agenti immunomodulatori**: ciclosporine, tacrolimus, desametasone

Completato il trattamento con questi farmaci, andava ripreso il dosaggio pieno (60 mg)

Raskob G.E. et al., NEJM, 2018

Primary Outcome (Recurrent VTE or Major Bleeding)



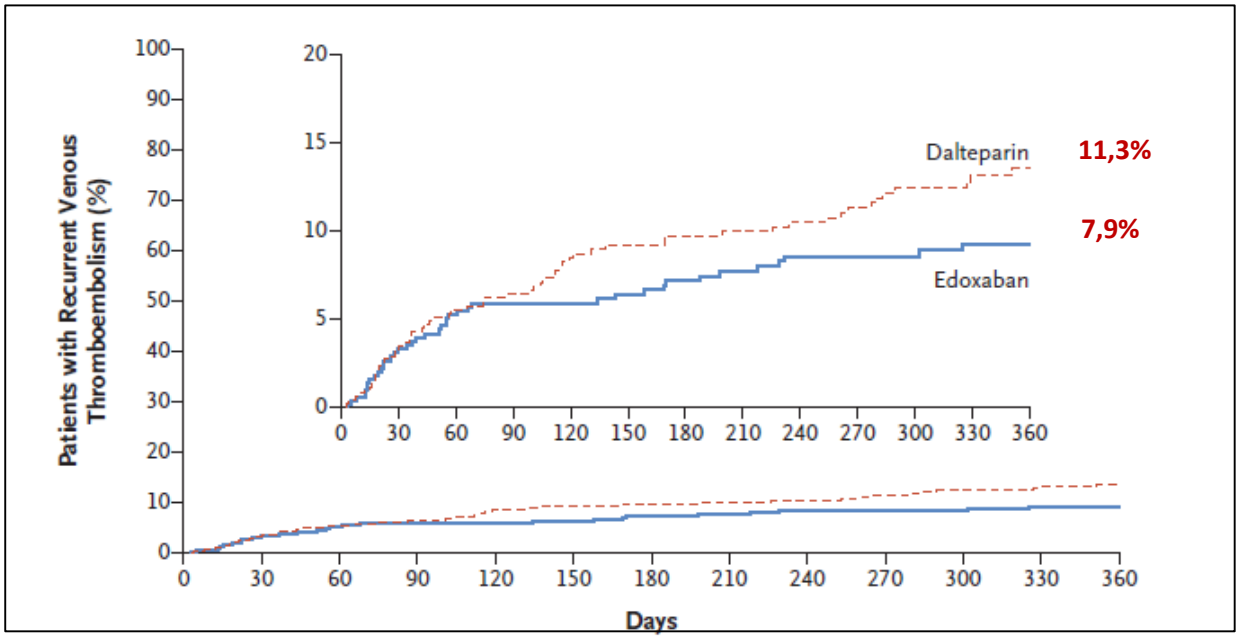
P = 0.006 for noninferiority

Edoxaban (522)	Dalteparin (524)	HR (95% CI)
67 (12.8%)	71 (13.5%)	0.97 (0.70, 1.36)

Oral edoxaban was noninferior to subcutaneous dalteparin.

Raskob G.E. et al, NEJM 2018

Secondary outcomes (Recurrent VTE)



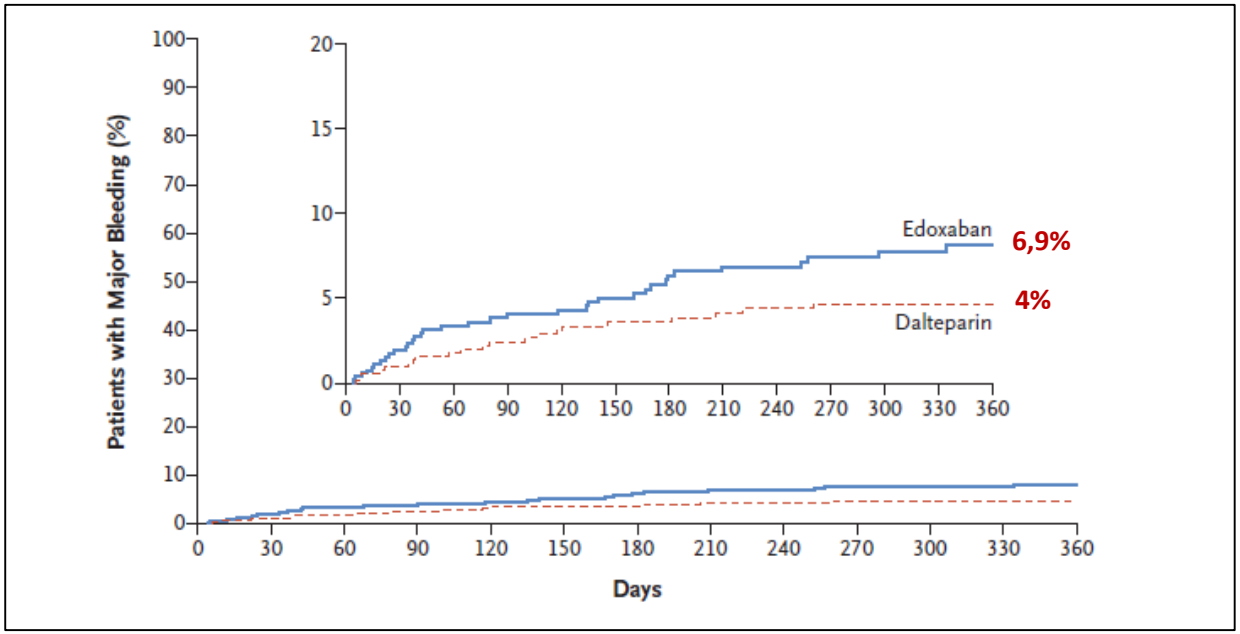
P = 0.093

	Edoxaban (N = 522)	Dalteparin (N = 524)	HR (95% CI)
Recurrent VTE	41(7.9%)	59 (11.3%)	0.71 (0.48, 1.06) **P = 0.093**
Recurrent DVT	19 (3.6%)	35 (6.7%)	0.56 (0.32, 0.97)
Recurrent PE	27 (5.2%)	28 (5.3%)	1.00 (0.59, 1.69)

Recurrent VTE was numerically lower with edoxaban, but not significantly.

Raskob G.E. et al, NEJM 2018

Secondary outcomes (major bleeding)



P = 0.04

	Edoxaban (N = 522)	Dalteparin (N = 524)	HR (95% CI)
Major Bleeding	36 (6.9%)	21 (4%)	1.77 (1.03, 3.04) ***P = 0.04***
Fatal	0	2	
Intracranial	2	4	

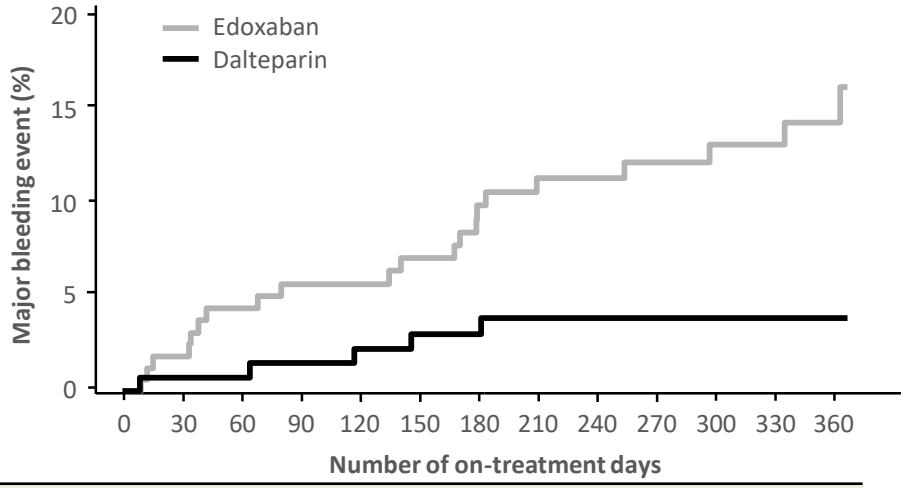
The rate of major bleeding was higher with edoxaban than with dalteparin.

Raskob G.E. et al, NEJM 2018

Tumour Type

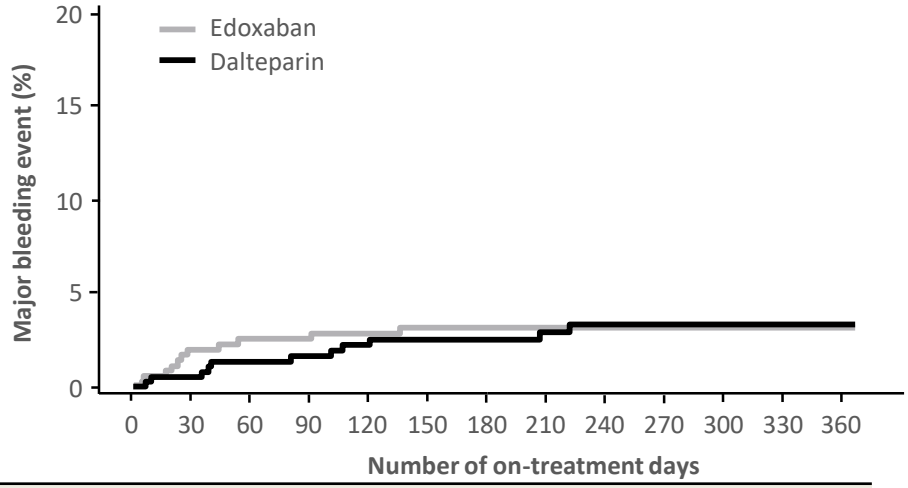
Major bleeding events (edoxaban versus LMWH) according to tumour types

Patients with GI cancer



Number at risk													
Edoxaban	165	134	121	108	97	89	79	70	64	59	48	38	28
Dalteparin	140	123	116	108	94	89	79	67	60	54	48	40	25

Patients with non-GI cancer



Number at risk													
Edoxaban	357	315	284	271	255	234	220	190	179	171	144	123	88
Dalteparin	384	347	305	278	254	236	216	151	138	131	108	95	63

Kraaijpoel N *et al*, *Thromb Haemost* 2018;118:1439–1449

EDITORIALS

Edoxaban for the Treatment of Venous Thromboembolism in Patients with Cancer

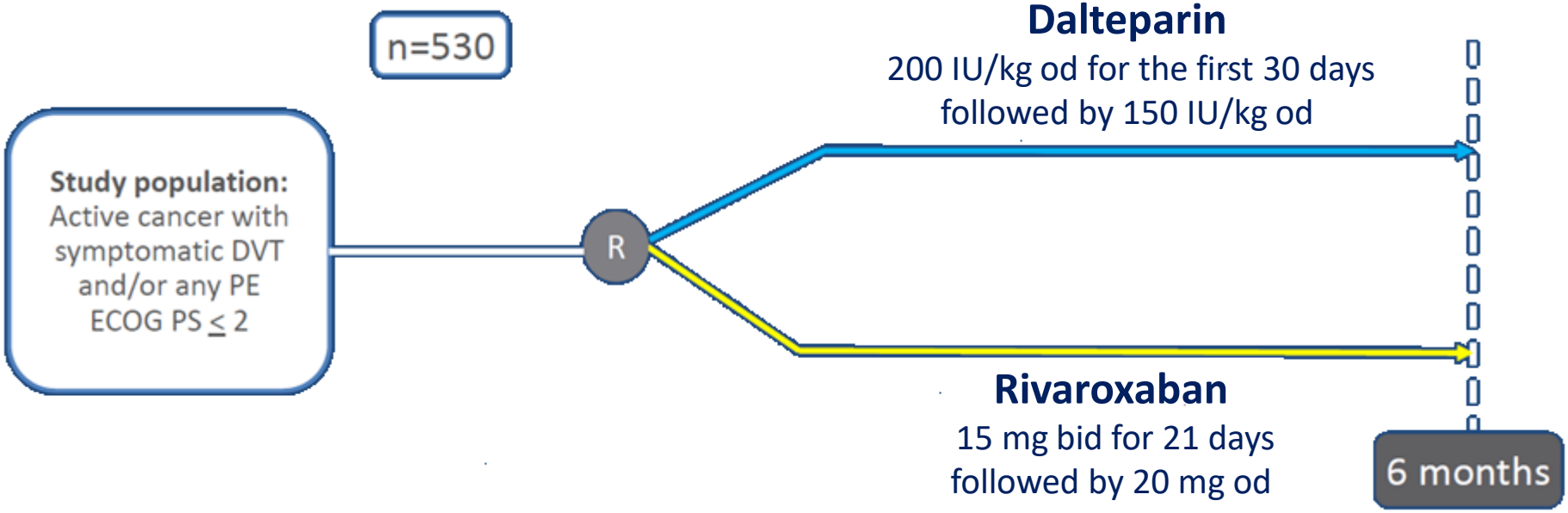
Jack Hirsh, M.D., and Jeffrey S. Ginsberg, M.D.

«Practice guidelines recommend long-term low-molecular-weight heparin therapy for patients with cancer who have venous thromboembolism. However, low-molecular-weight heparin therapy is far from ideal, because many patients do not wish to receive daily injections over the long term."

J Clin Oncol
Published at jco.org on May 10, 2018.

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

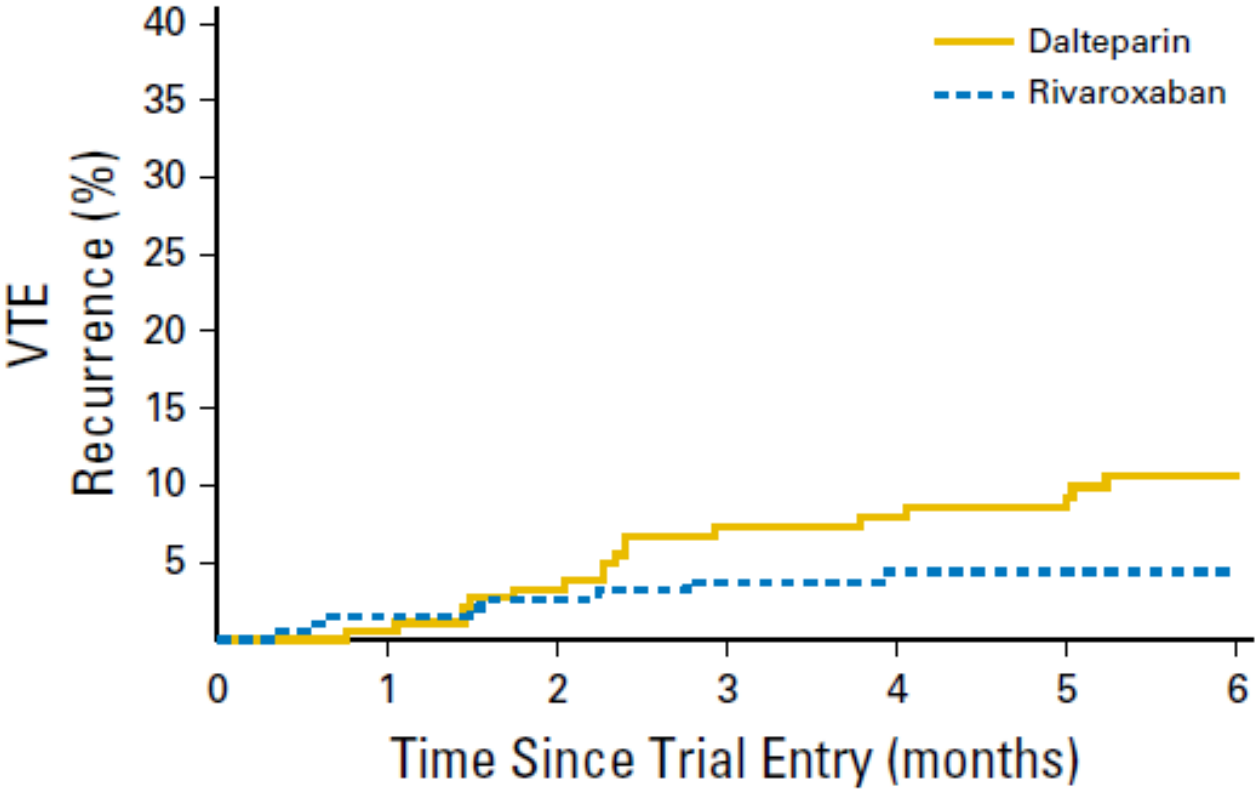


Conclusion

Rivaroxaban was associated with relatively low VTE recurrence but higher CRNMB compared with dalteparin.

SELECT D - VTE recurrence

	Dalteparin (N = 203)	Rivaroxaban (N = 203)
VTE recurrences within 6 months, n	18	8
DVT or PE	16	6
Other location	2	2
6-month VTE recurrence rate, % (95% CI)	11% (7-16%)	4% (2-9%)

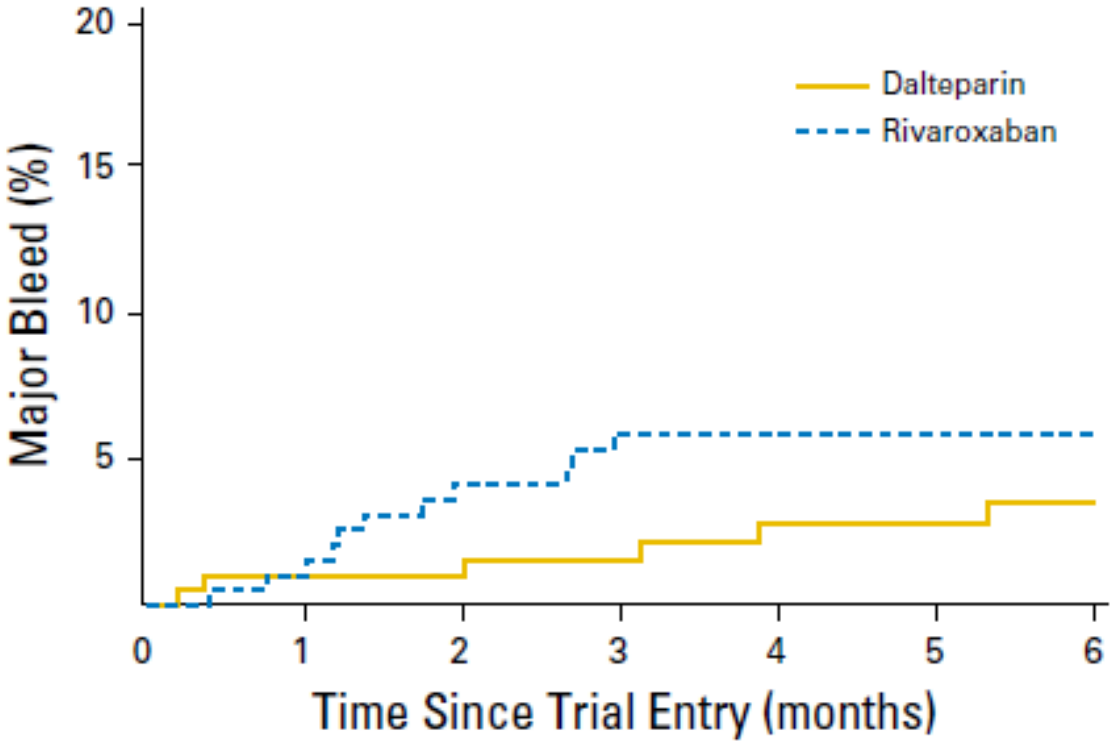


Young AM et al., JCO 2018

SELECT D - Bleeding (%)

Category	Dalteparin (N = 203)	Rivaroxaban (N = 203)
Major*	6 (4%)	11 (6%)
Clinically relevant non-major	7 (4%)	25 (13%)

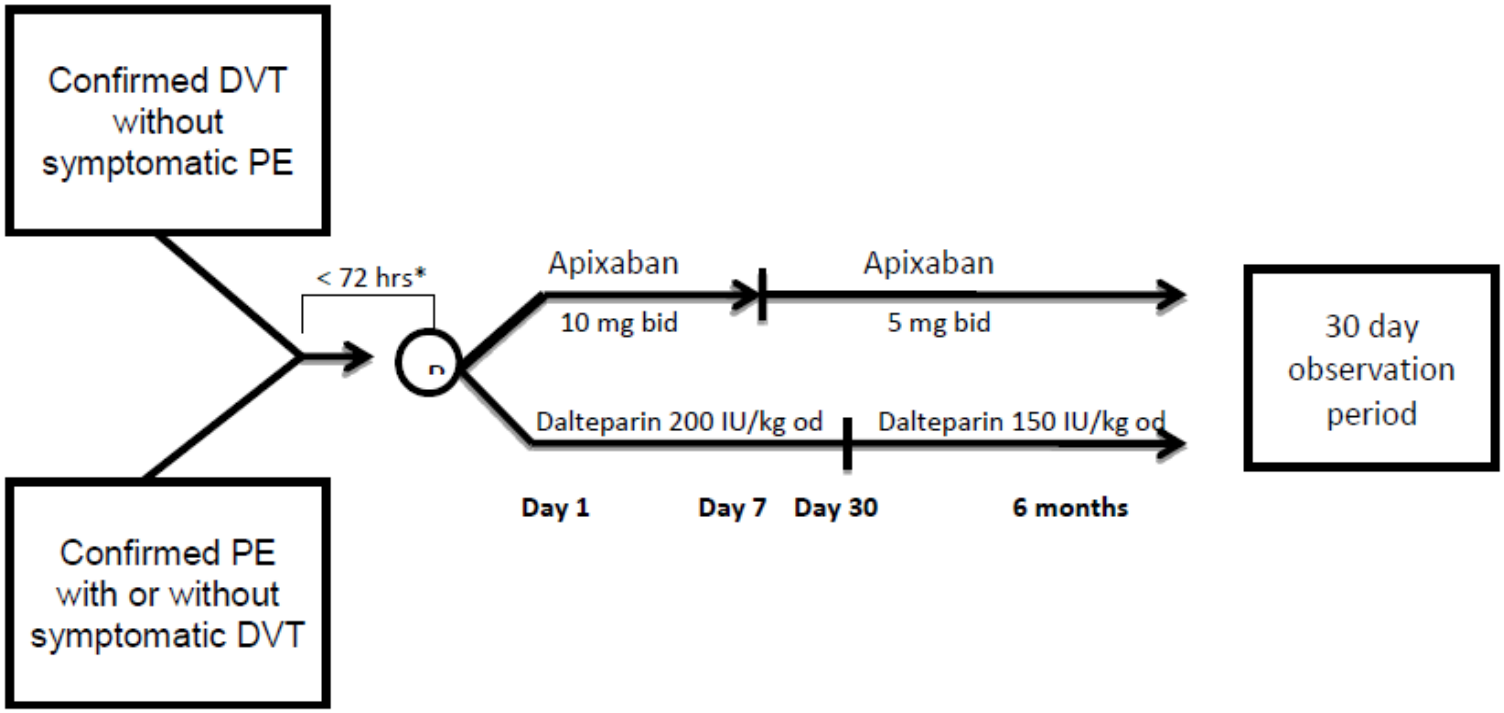
*1 fatal bleeding event in each arm
Most major bleeding events were **gastrointestinal bleeding**; no CNS bleeds
Most CRNMBs were **gastrointestinal or urological**



Young AM et al., JCO 2018

CLINICAL STUDY PROTOCOL

APIXABAN FOR THE TREATMENT OF VENOUS THROMBOEMBOLISM IN PATIENTS WITH CANCER: A PROSPECTIVE RANDOMIZED OPEN BLINDED END-POINT (PROBE) STUDY - THE CARAVAGGIO STUDY



* Maximum time allowed between diagnosis and randomization

New Guidelines from ISTH/SSC 2018

- *We suggest the use of specific DOACs for cancer patients with an acute diagnosis of VTE, a low risk of bleeding, and no drug–drug interactions with current systemic therapy. Currently,* ***edoxaban*** *and* ***rivaroxaban*** *are the only DOACs that have been compared with LMWH in RCTs in cancer populations.*

- *We suggest the use of LMWHs for cancer patients with an acute diagnosis of VTE and a high risk of bleeding, including patients with luminal gastrointestinal cancers, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis.*

Journal of Thrombosis and Haemostasis, 2018 Jun 29

National Comprehensive Cancer Network Guidelines Aprile 2019

- Category 1 recommendations (high-level evidence, uniform consensus):
  - Dalteparin monotherapy
  - LMWH followed by **edoxaban**
- Category 2A recommendations: (lower-level evidence, uniform consensus):
  - Enoxaparin monotherapy
  - Fondaparinux monotherapy
  - **Rivaroxaban** monotherapy
  - LMWH followed by warfarin
  - UFH followed by **edoxaban**

NCCN Guidelines, 1.2019 (accessed 18 aprile 2019)

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update

Nigel S. Key, MB ChB[1]; Alok A. Khorana, MD[2]; Nicole M. Kuderer, MD[3]; Kari Bohlke, ScD[4]; Agnes Y.Y. Lee, MD, MSc[5]; Juan I. Arcelus, MD, PhD[6]; Sandra L. Wong, MD, MS[7]; Edward P. Balaban, DO[8]; Christopher R. Flowers, MD, MS[9]; Charles W. Francis, MD[10]; Leigh E. Gates[11]; Ajay K. Kakkar, MBBS, PhD[12]; Mark N. Levine, MD, MSc[13]; Howard A. Liebman, MD[14]; Margaret A. Tempero, MD[15]; Gary H. Lyman, MD, MPH[16]; and Anna Falanga, MD[17]

RECOMMENDATIONS Changes to previous recommendations: Clinicians may offer thromboprophylaxis with apixaban, rivaroxaban, or LMWH to selected high-risk outpatients with cancer; rivaroxaban and edoxaban have been added as options for VTE treatment; patients with brain metastases are now addressed in the VTE treatment section; and the recommendation regarding long-term postoperative LMWH has been expanded. Re-affirmed recommendations: Most hospitalized patients with cancer and an acute medical condition require thromboprophylaxis throughout hospitalization. Thromboprophylaxis is not routinely recommended for all outpatients with cancer. Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days. Patients with cancer should be periodically assessed for VTE risk, and oncology professionals should provide patient education about the signs and symptoms of VTE.

J Clin Oncol 37. © 2019 by American Society of Clinical Oncology

Treatment of VTE in Patients with Cancer

Clinical Setting	Drug	Regimen[a]
Treatment of established VTE[i]		
Initial	UFH[j]	80 U/kg IV bolus, then 18 U/kg/h IV and adjust dose based on aPTT[k]
	Dalteparin[j,l,m]	100 U/kg every 12 hours
		200 U/kg once daily
	Enoxaparin[j,l,m,n]	1 mg/kg every 12 hours
		1.5 mg/kg once daily
	Tinzaparin[j,l,m,o]	175 U/kg once daily
	Fondaparinux[j,l,p]	< 50 kg: 5.0 mg once daily
		50-100 kg: 7.5 mg once daily
		> 100 kg: 10 mg once daily
→	Rivaroxaban	15 mg orally every 12 hours for 21 days
Long term[p,q,r]	Dalteparin[l,m,s]	200 U/kg once daily for 1 month, then 150 U/kg once daily
	Enoxaparin[l,m,n]	1.5 mg/kg once daily
		1 mg/kg every 12 hours
	Tinzaparin[m,o]	175 U/kg once daily
	Warfarin	Adjust dose to maintain INR 2-3
→	Rivaroxaban[m,t]	15 mg orally every 12 hours for 21 days, followed by 20 mg once daily thereafter (both doses with food)
→	Edoxaban[m,t]	Needs at least 5 days of parenteral anticoagulation prior to its start, then switch to 60 mg orally once daily or 30 mg orally once daily in those weighing ≤ 60 kg, who have creatinine clearance between 30 and 50 mL/min, or who need concomitant use of a P-glycoprotein inhibitor

Recommendations for the regimen and the duration of anticoagulation after PE in patients with active cancer (1)

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

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

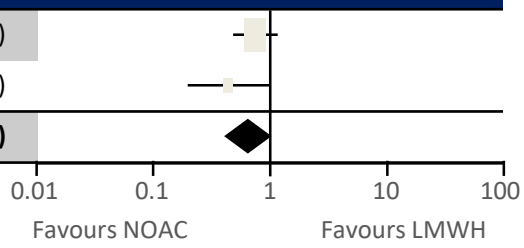
European Heart Journal (2019) **00**, 1–61
doi:10.1093/eurheartj/ehz405

Cancer-Associated Thrombosis: LMWHs Versus NOACs

Recurrent VTE

Study	NOAC		LMWH		Weight	Risk ratio M-H, random (95% CI)
	Events	Patients	Events	Patients		
Hokusai-VTE-Cancer	34	522	46	524	73.4%	0.74 (0.48–1.14)
select-d	8	203	18	203	26.6%	0.44 (0.20–1.00)
Total		**725**		**727**	**100.0%**	**0.65 (0.42–1.01)**
Total events	42		64			

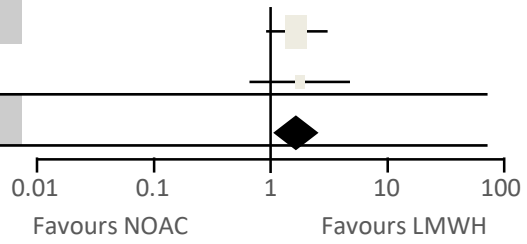
Heterogeneity: Tau^2=0.02; Chi^2=1.21, df=1 (p=0.27), I^2=17%
Test for overall effect: Z=1.92 (p=0.06)



Major bleeding

Study	NOAC		LMWH		Weight	Risk ratio M-H, random (95% CI)
	Events	Patients	Events	Patients		
Hokusai-VTE-Cancer	29	522	17	524	73.5%	1.71 (0.95–3.08)
select-d	11	203	6	203	26.5%	1.83 (0.69–4.86)
Total		**725**		**727**	**100.0%**	**1.74 (1.05–2.88)**
Total events	40		23			

Heterogeneity: Tau^2=0.00; Chi^2=0.01, df=1 (p=0.91), I^2=0%
Test for overall effect: Z=2.17 (p=0.03)



Results observed for the use of NOACs in patients with CAT need to be confirmed in a dedicated trial

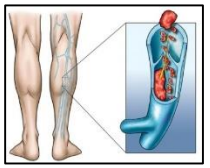
All NOACs are contraindicated in patients with lesions or conditions considered to be a significant risk for major bleeding. This may include presence of malignant neoplasms at high risk of bleeding

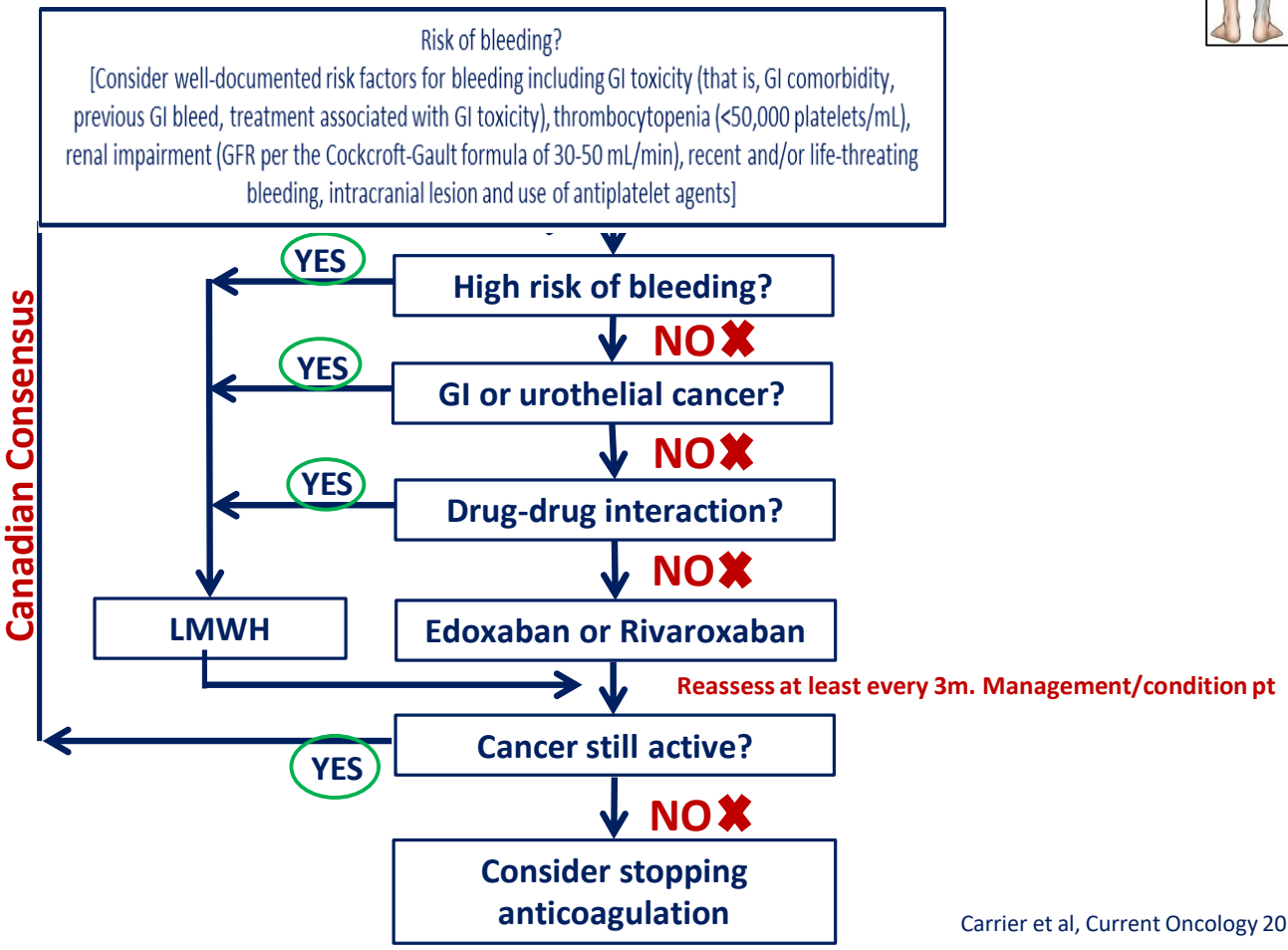
Li A *et al*, *Thromb Res* 2019;173:158–163

What are the implication of these new guidelines?

- NOACs are now clearly an option for the treatment of cancer-associated VTE
- One size fits all approach (e.g. LMWH for everyone) is no longer appropriate
- Patient selection is key, incorporating bleeding risk/renal funtion/drug-drug interactions
- Patients preferences should be taken into account

Algorithm for VTE treatment: DOACs or LMVH?





Carrier et al, Current Oncology 2018

Anticancer therapies associated with gastrointestinal (GI) toxicity

Drug class	Agent or agents	Types of toxicity
Alkylating agent (in high doses)[21]	Cyclophosphamide, bendamustine, busulfan, ifosfamide, melphalan	Stomatitis
Antimetabolite[21]	5-Fluorouracil, cytarabine, floxuridine, methotrexate	Diarrhea, stomatitis
Antimitotic agent[21]	Vinblastine, vincristine	Stomatitis, constipation
Checkpoint inhibitor[22]	Ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab	Colitis, diarrhea
EGFR inhibitor[22]	Cetuximab	Diarrhea
	Erlotinib, afatinib, gefitinib	Diarrhea, GI bleeding or perforation
Immunomodulating agent[21]	Interleukin 2	Stomatitis, colitis
MEK inhibitor[22]	Trametinib	Diarrhea
Nitrosourea[21]	Carmustine, lomustine	Diarrhea
PI3K inhibitor[22]	Idelalisib	Colitis
Topoisomerase inhibitor[21]	Etoposide	Stomatitis
	Irinotecan	Diarrhea, stomatitis
VEGF or VEGFR inhibitor[22]	Axitinib, bevacizumab	GI bleeding or perforation

[a] The list of therapies in the table is incomplete; agents are provided as examples.
EGFR = epidermal growth factor receptor; MEK = mitogen-activated protein kinase kinase; PI3K = phosphatidylinositol-4,5-bisphosphate 3-kinase; VEGF(R) = vascular endothelial growth factor (receptor).

Carrier et al, Curr Oncol 2018

Intracranial Metastatic Disease as a Risk Factor for bleeding

Risk of ICH with NOACs for patients with brain tumours and intracranial metastasis

- A cohort study evaluating the safety of NOACs in patients with CAT and intracranial metastatic disease or primary brain tumours
- 67 patients with primary brain tumours
  - NOACs (n=20); LMWH (n=47)
  - No patients with primary brain tumour receiving NOAC had ICH
- 105 patients with intracranial metastatic disease
  - NOACs (n=21); LMWH (n=84)
  - NOACs did not increase the risk of ICH relative to LMWH in patients with intracranial brain metastasis

Carney BJ *et al*, *J Thromb Haemost* 2019;17:72–76

Anticoagulation in cancer patients with VTE

- What is an active cancer?
- Anticoagulation during the first 6 months
- **Duration of anticoagulation**

Guidelines

ACCP2016	11. In patients with DVT of the leg or PE and active cancer ("cancer-associated thrombosis") and who (i) do not have a high bleeding risk, we recommend extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 1B), or (ii) have a high bleeding risk, we suggest extended anticoagulant therapy (no scheduled stop date) over 3 months of therapy (Grade 2B).		
Farge 2016	4 After 3–6 months, termination or continuation of anticoagulation (LMWH, VKA, or direct oral anticoagulants) should be based on individual assessment of the benefit-to-risk ratio, tolerability, drug availability, patient preference, and cancer activity (guidance, in the absence of data).		
ESC 2014	For patients with PE and cancer, extended anticoagulation (beyond the first 3–6 months) should be considered for an indefinite period or until the cancer is cured.	**IIa**	C

Recommendations for the regimen and the duration of anticoagulation after PE in patients with active cancer (2)

Recommendations	Class[a]	Level[b]
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
In patients with cancer, management of incidental PE in the same manner as symptomatic PE should be considered, if it involves segmental or more proximal branches, multiple subsegmental vessels, or a single subsegmental vessel in association with proven DVT.[376,377]	IIa	B

[a]Class of recommendation.
[b]Level of evidence.
[c]Refer to Supplementary Data *Table 9* for further guidance on therapeutic decisions after the first 6 months.

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) **00**, 1–61
doi:10.1093/eurheartj/ehz405

Treatment Duration

- **3-month treatment duration**: suitable for patients with transient risk factors for VTE[1,2]
  - Recent surgery or trauma
  - Immobilization
  - Use of oestrogen-containing drugs
  - Puerperium
- **Extended (>3 months) treatment**: suitable for patients with:
  - Idiopathic VTE[1,2]
  - Persistent risk factors for VTE
    - **Active cancer[1–4]**
    - Previous episodes of DVT/PE[1,2]
    - Known thrombophilic condition[1]

1. Kearon C *et al*, *Chest* 2016;149:315–352; 2. Konstantinides S *et al*, *Eur Heart J* 2014;35:3033–3069; 3. Mandala M *et al*, *Ann Oncol* 2011;22:vi85–vi92;
4. Lyman GH *et al*, *J Clin Oncol* 2015;33:654–656

NOACs in treatment of CAT

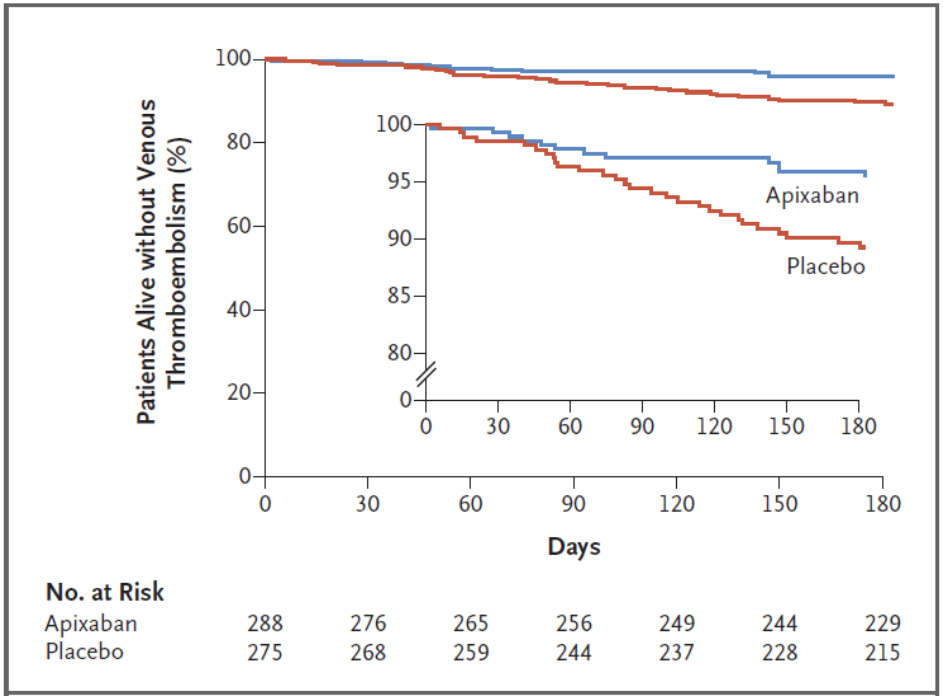
LMWH	Unstable, high bleeding risk	• E.g. Acute leukemia, active GI/UG lesion, oesophagus/ stomach, not resected • CrCl <30ml/min; LFT>3x ULN • Antiplatelet agent • CNS neoplasm: primary metastatic	• ECOG4, poor prognosis • Acute chemotherapy, sepsis, vomiting, mucositis; platelets < 50,000 per µl • Post-surgery <2 weeks • DDI
NOAC	Stable; low bleeding risk	• Pancreatic cancer • Hepatic/renal cancer • Prostate cancer • Thyroid cancer • Lung/ovarian cancer • Chronic leukaemia • Uterine/breast cancer • Melanoma	• Preventive radiotherapy • Chronic Chemotherapy • No active anticancer treatment, stable disease

LMWH vs NOAC: no permanent decision!
Adjustment to type/phase od malignancy and treatment, patient situation:
Unstable, chemotherapy, vomiting, thrombocytopenia: NOAC→ LMWH
Stable, low risk for complications and high QoL: LMWH → NOAC

In patients with high risk of bleeding LMWH are preferred over NOACs are controindicated in case of malignant neoplasms at high risk of bleeding. Expert Opinion.

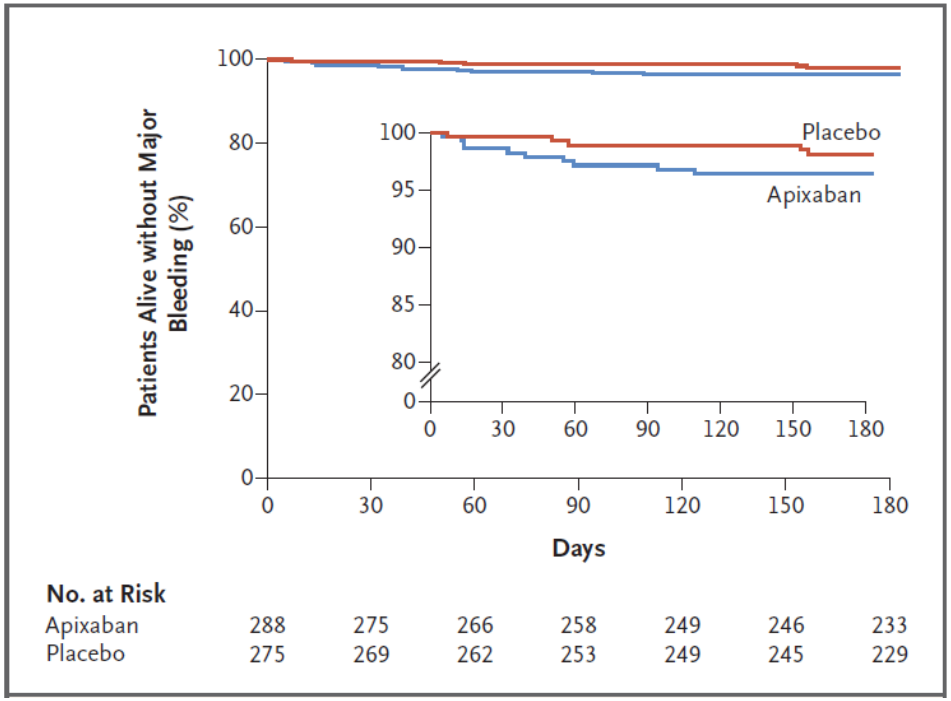
…e la prevenzione primaria nel paziente oncologico ambulatoriale ad alto rischio?

Apixaban to Prevent Venous Thromboembolism in Patients with Cancer



No. at Risk

Apixaban	288	276	265	256	249	244	229
Placebo	275	268	259	244	237	228	215



No. at Risk

Apixaban	288	275	266	258	249	246	233
Placebo	275	269	262	253	249	245	229

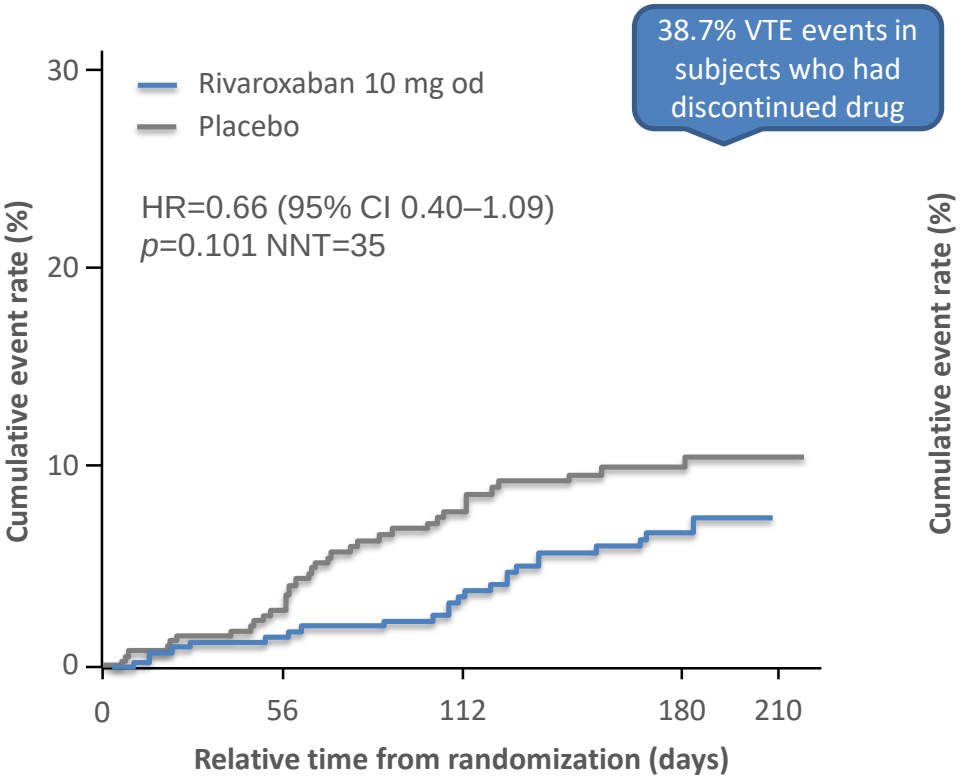
CONCLUSIONS

Apixaban therapy resulted in a significantly lower rate of venous thromboembolism than did placebo among intermediate-to-high-risk ambulatory patients with cancer who were starting chemotherapy. The rate of major bleeding episodes was higher with apixaban than with placebo.

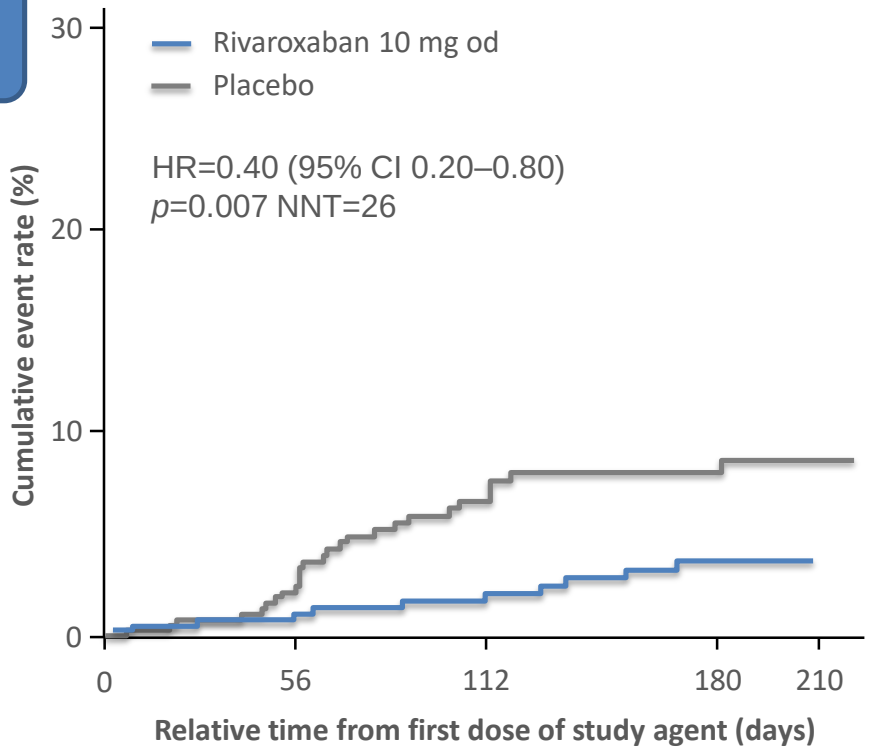
Carrier M. et al. The New England Journal of Medicine 2019

Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer

Study Period - Up to Day 180



On-treatment



Khorana A. et al. The New England Journal of Medicine 2019

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update

Nigel S. Key, MB ChB[1]; Alok A. Khorana, MD[2]; Nicole M. Kuderer, MD[3]; Kari Bohlke, ScD[4]; Agnes Y.Y. Lee, MD, MSc[5]; Juan I. Arcelus, MD, PhD[6]; Sandra L. Wong, MD, MS[7]; Edward P. Balaban, DO[8]; Christopher R. Flowers, MD, MS[9]; Charles W. Francis, MD[10]; Leigh E. Gates[11]; Ajay K. Kakkar, MBBS, PhD[12]; Mark N. Levine, MD, MSc[13]; Howard A. Liebman, MD[14]; Margaret A. Tempero, MD[15]; Gary H. Lyman, MD, MPH[16]; and Anna Falanga, MD[17]

RECOMMENDATIONS Changes to previous recommendations: Clinicians may offer thromboprophylaxis with apixaban, rivaroxaban, or LMWH to selected high-risk outpatients with cancer; rivaroxaban and edoxaban have been added as options for VTE treatment; patients with brain metastases are now addressed in the VTE treatment section; and the recommendation regarding long-term postoperative LMWH has been expanded. Re-affirmed recommendations: Most hospitalized patients with cancer and an acute medical condition require thromboprophylaxis throughout hospitalization. Thromboprophylaxis is not routinely recommended for all outpatients with cancer. Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days. Patients with cancer should be periodically assessed for VTE risk, and oncology professionals should provide patient education about the signs and symptoms of VTE.

J Clin Oncol 37. © 2019 by American Society of Clinical Oncology

KHORANA Risk Score for Venous Thromboembolism

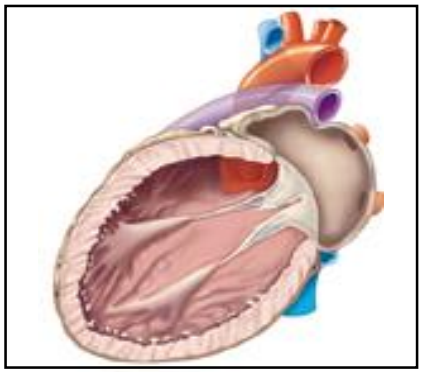
Patient Characteristic	Points
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular, renal)	1
Prechemotherapy platelet count ≥ 350,000/μL	1
Hemoglobin level < 10 g/dL or use of red cell growth factors	1
Prechemotherapy leukocyte count > 11,000/μL	1
Body mass index ≥ 35 kg/m^2	1
Calculate total score, adding points for each criterion in the model	
Interpretation	
High-risk score ≥ 3 points	
Intermediate-risk score = 1-2 points	
Low-risk score = 0 points	

Prevenzione Primaria in Pazienti ad alto rischio di TEV

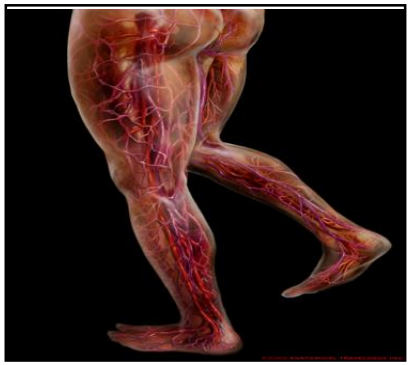
Clinical Setting	Drug	Regimen[a]
Pharmacologic (anticoagulant) prophylaxis		
Hospitalized medical patients[b]	UFH	5,000 U every 8 hours[c]
	Dalteparin	5,000 U once daily
	Enoxaparin	40 mg once daily
	Fondaparinux[d]	2.5 mg once daily
Surgical patients[b]	UFH	5,000 U 2-4 hours preoperatively and every 8 hours[c] thereafter[e]
	Dalteparin	2,500 U 2-4 hours preoperatively[e] and 5,000 U once daily thereafter[f]
		Or 5,000 U 2-4 hours preoperatively[e] or 10-12 hours preoperatively and 5,000 U once daily thereafter[f]
	Enoxaparin	40 mg 2-4 hours preoperatively[e] or 10-12 hours preoperatively and 40 mg once daily thereafter[f]
	Fondaparinux[d]	2.5 mg once daily beginning 6-8 hours postoperatively
Outpatients[b]	Dalteparin[d,g]	5,000 U once daily
	Enoxaparin[d,g]	40 mg once daily
	Fondaparinux[d,h]	2.5 mg once daily
→	Apixaban[d]	2.5 mg orally twice daily
→	Rivaroxaban[d]	10 mg orally once daily

Cardiovascular Complications in Cancer Patient

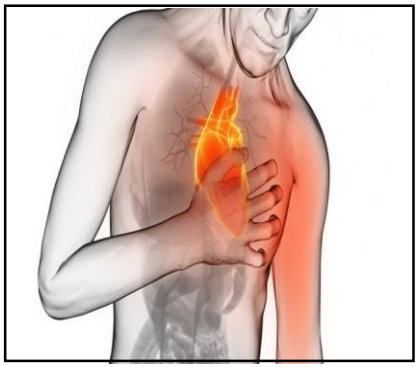
Atrial fibrillation



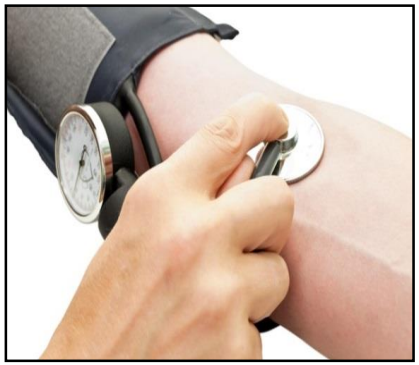
Cardiac Dysfunction
Heart Failure



Thromboembolism



Angina pectoris
Myocardial infarction



Hypertension

BOOKLET

LA FIBRILLAZIONE ATRIALE NEL PAZIENTE ONCOLOGICO

Nicola Maurea

Iris Parrini

ANMCO – Task Force Cardioncologia 2017

Heart Rhythm, Vol 16, No 3, March 2019

EDITORIAL COMMENTARY

Breast cancer and atrial fibrillation—A malignant combination?

Ankur A. Karnik, MD, FHRS, FACC,* Emelia J. Benjamin, MD, ScM, FACC, FAHA,*†‡
Ludovic Trinquart, PhD‡§

Meccanismi patogenetici potenziali che collegano cancro e fibrillazione atriale

Farmakis, JACC 2014

10 La gestione della fibrillazione atriale nel paziente oncologico

Nicola Maurea[1], Enrico Barbieri[2]

TABELLA 35. Agenti dei farmaci tumorali associati con la fibrillazione atriale

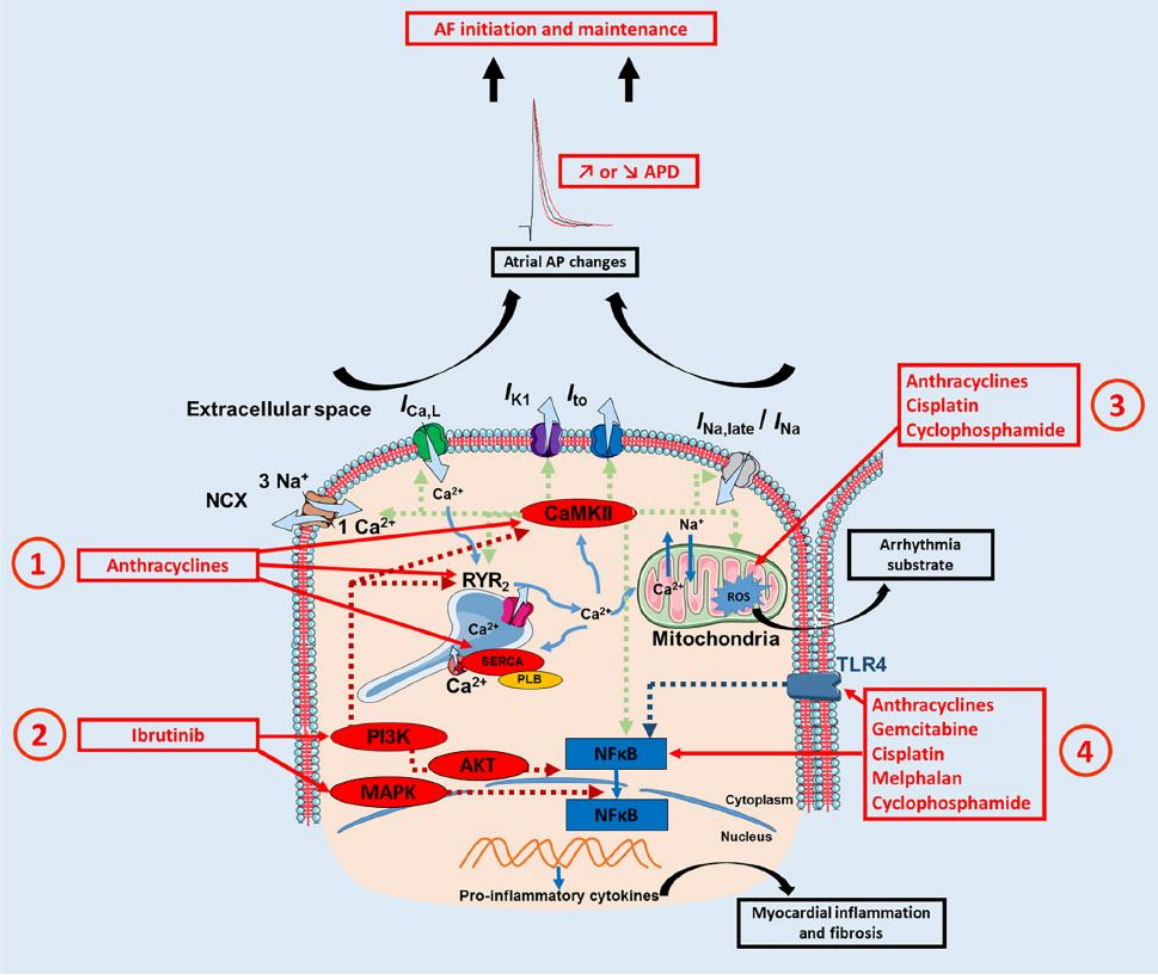
Tipi di aritmia	Farmaci che la causano
Fibrillazione Atriale	Agenti alchilanti (cisplatino, ciclofosfamide, ifosfamide melfalan), antracicline, antimetaboliti (capecitabina, 5-FU, gemcitabina), IL-2, interferoni, rituximab, romidepsin alchilanti, piccola molecola TKI (ponatinib, sorafenib, sunitinib, ibrutinib), topoisomerasi II inibitori (amsacrina, etoposide), taxani, alcaloide della vinca.

Select Cancer Therapies Associated With Atrial Arrhythmias and Thrombotic Adverse Events

Class	Anti-Cancer Mechanism	Select Drug Examples	Mechanism of Cardiovascular Toxicity
Cancer therapies associated with atrial arrhythmias			
Anthracyclines	Inhibition of DNA/RNA synthesis via topoisomerase inhibition	Doxorubicin Daunorubicin Idarubicin Epirubicin	? Direct cardiotoxicity
Alkylating agents	Inhibition of DNA/RNA synthesis via formation of carbonium ions	Melphalan	Unknown
Anti-metabolites	Inhibition of DNA/RNA synthesis via acting as a pyrimidine analog	Fluorouracil	? Ischemia
Interleukins	Immunotherapy	Il-2	Inflammation
Bruton's tyrosine kinase TKIs	Inhibition of Bruton's tyrosine kinase	Ibrutinib Acalabrutinib	? Direct kinase inhibition
Immune checkpoint inhibitors	Activation of immune system	Ipilimumab Nivolumab Pembrolizumab	Cardiac inflammation; myocarditis, pericarditis, vasculitis

Mosarla RC et al. JACC 2019

Potential mechanisms involved in anticancer drug-induced atrial fibrillation



Alexandre J et al, Pharmacology & Therapeutics 2018

JACC: CLINICAL ELECTROPHYSIOLOGY VOL. 4, NO. 12, 2018

TOPIC REVIEW

Ibrutinib-Associated Atrial Fibrillation

*"**Ibrutinib,** a novel and potent Bruton tyrosine kinase inhibitor, is an effective and well-tolerated treatment for a variety of **B-cell lymphomas and refractory chronic lymphocytic leukemia (CLL).***
*Its use is associated with an **increased incidence** of atrial fibrillation (AF), **ranging from 4% to 16%.***
Based on 16 studies included in our analysis, the incidence of ibrutinib associated AF was 5.77 per 100 person-years.
*Ibrutinib also **inhibits platelet activation and decisions regarding anticoagulation** have to be carefully weighed against this **increased risk of bleeding."***

TABLE 2 Interaction Between Ibrutinib and Common Medications Used for Management of AF

Medication	Level of Interaction	Effect	Mechanism of Interaction
Diltiazem/verapamil	Major	Increases plasma level of ibrutinib (6- to 9-fold)	CYP450 3A4 inhibition by diltiazem/verapamil
Digoxin	Moderate	Increases plasma level of digoxin	P-glycoprotein inhibition by ibrutinib
Amiodarone/dronedarone	Major	Increases plasma level of ibrutinib (6- to 9-fold)	CYP450 3A4 inhibition by amiodarone/ dronedarone
Factor Xa inhibitor (rivaroxaban, apixaban, edoxaban)	Moderate	Increases plasma level of factor Xa inhibitors	CYP450 3A4 induction and P-glycoprotein inhibition by ibrutinib
Direct thrombin inhibitor (dabigatran)	Major	Increases plasma level of dabigatran	P-glycoprotein inhibition by ibrutinib

Ganatra S et al.

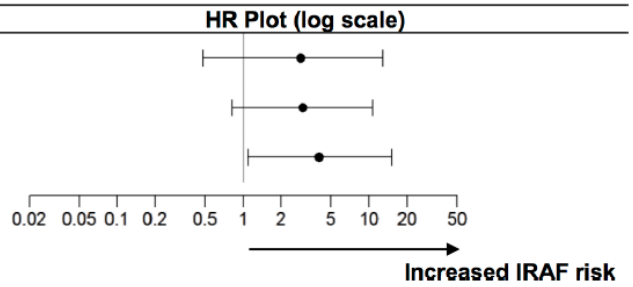
openheart

High incidence of atrial fibrillation in patients treated with ibrutinib

Results 53 patients were included. The incidence of IRAF was 38% at 2 years and the risk was 15-fold higher than the AF risk in both the general population and patients with CLL not exposed to ibrutinib ($p<0.0001$). The majority of cases occurred in asymptomatic patients within the first 6 months. Left atrial volume index ≥40 mL/m^2 at treatment initiation identified patients at high risk of developing IRAF.

Conclusions This cardio-oncology study showed that the risk of IRAF was much higher than previously reported. The majority of cases occurred in asymptomatic patients justifying close monitoring.

	HR	lower.ci	upper.ci	p-value
Heart failure history	2.84	0.48	12.83	0.2233
Age ≥75 years	2.96	0.82	10.69	0.0968
LAVI (≥ 40 mL/m²)	**4.01**	**1.10**	**15.18**	**0.0361**



Baptiste F, *et al. Open Heart* 2019;**6**:e001049. doi:10.1136/openhrt-2019-001049

Management and outcomes of patients with atrial fibrillation and *a history of* cancer: the ORBIT-AF registry

9749 pazienti:
- Cancro: 2318
- No cancro: 7431

Table 2 CV outcomes in AF patients with and without history of cancer

Outcomes	No cancer[a]	History of cancer[a]	Adjusted HR (95% CI)	*P*-values
All-cause death	4.92	7.75	1.26 (1.11–1.42)	0.0003
CV death	2.07	2.89	1.10 (0.90–1.34)	0.35
Non-CV death	2.42	4.24	1.35 (1.14–1.60)	0.0004
First stroke, non-CNS embolism, or TIA	1.48	1.96	1.04 (0.82–1.32)	0.74
First major bleed	3.45	5.13	1.21 (1.04–1.40)	0.02
New onset HF diagnosis (*N* = 6545)	1.53	1.73	0.90 (0.66–1.21)	0.47

CV, cardiovascular; CNS, central nervous system; TIA, transient ischaemic attack; HF, heart failure; HR, hazard ratio; CI, confidence interval.
[a]Event rate per 100 patient-years follow-up.

Conclusion A history of cancer is common among AF patients with up to one in four patients having both. Antithrombotic therapy, rates of cerebrovascular accident, other thrombotic events and cardiac death were similar in AF patients with or without a history of cancer. Patients with cancer, however, were at higher risk of major bleeding and non-CV death.

Melloni et al. European Heart Journal – Quality of Care and Clinical Outcomes 2017

Effectiveness of Warfarin among Patients with Cancer

Adam J. Rose, MD[1,2,5], Jeff P. Sharman, MD[3], Al Ozonoff, PhD[4], Lori E. Henault, MPH[1], and Elaine M. Hylek, MD, MPH[1]

Patients with cancer may experience especially erratic control of the international normalized ratio (INR).[1] Contributing factors may include drug interactions, fluctuations in dietary vitamin K intake, therapy interruptions, hepatic dysfunction, mucositis, and diarrhea and the hypercoagulable state induced by the cancer itself.[2–10]

CONCLUSIONS: Compared to matched controls, cancer patients receiving warfarin spend less time in the target INR range, have more variable INR values, and have more thrombotic events. These effects are not dependent on whether the patient is anticoagulated for VTE or another indication.

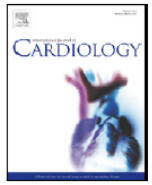
J Gen Intern Med. 2007 Jul;22(7):997-1002

International Journal of Cardiology 203 (2016) 372–378

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



Bleeding risk and major adverse events in patients with cancer on oral anticoagulation therapy

2168 consecutive non-valvular AF patients with newly diagnosed malignancies.

The **optimal INR** (2.0 to 3.0) level was achieved in **only 12% of patients**.

However, **1 year after cancer diagnosis**, only OAT+ patients **with the target therapeutic range of ≥ 60%** demonstrated **better cumulative survival free of composite end point*** than OAT−patients (p = 0.026).

Conclusion: During the first year after the cancer diagnosis, **OAT did not improve the composite end point because of poor INR control caused by cancer treatment**.

OAT: oral anticoagulant therapy

****Major adverse cardiac events (MACEs) and major bleeding***

Lee et al.

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

19. Anticoagulation in atrial fibrillation patients with a malignancy

However, evidence for stroke prevention with LMWH in AF is lacking and LMWH is contraindicated in secondary prevention in the setting of acute stroke.

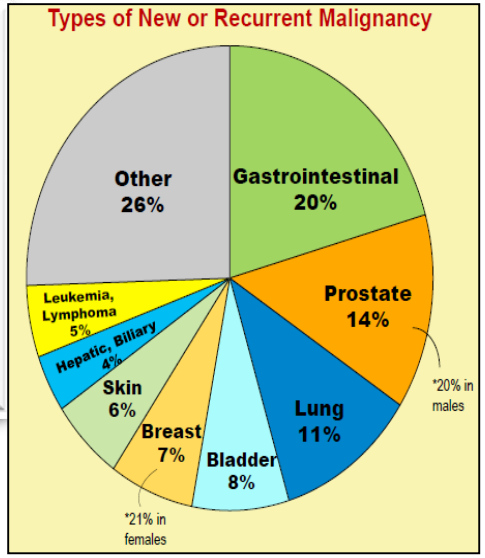
Steffel J et al. European Heart Journal 2018

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Efficacy and Safety of Edoxaban in Patients With Active Malignancy and Atrial Fibrillation: Analysis of the ENGAGE AF-TIMI 48 Trial

Christina L. Fanola, MD, MSc; Christian T. Ruff, MD, MPH; Sabina A. Murphy, MPH; James Jin, PhD; Anil Duggal, MD; Noe A. Babilonia, MD; Piyamitr Sritara, MD; Michele F. Mercuri, MD, PhD; Pieter W. Kamphuisen, MD; Elliott M. Antman, MD, Eugene Braunwald, MD; Robert P. Giugliano, MD, SM

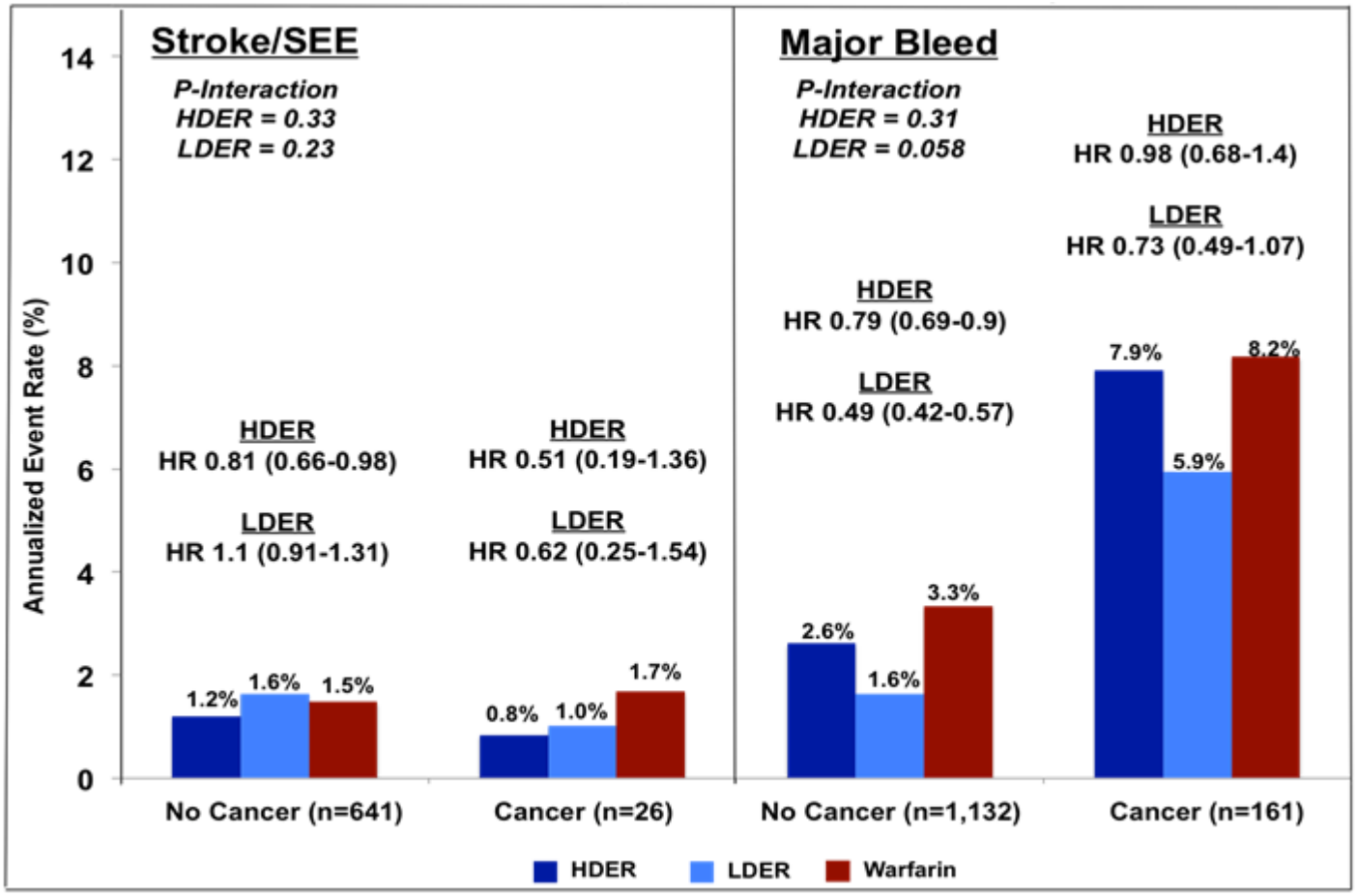


- **1153 (5,5%) patients developed cancer (new diagnosis or recurrence of remote cancer) with the most common sites GI, prostate and lung.**
- Efficacy and safety of edoxaban vs. warfarin were preserved.
- In patients with cancer, edoxaban was effective in the prevention of stroke/systemic embolic event vs. warfarin and had a similar risk of major bleeding.

J Am Heart Assoc. 2018

Efficacy and Safety of Edoxaban in Patients With Active Malignancy and Atrial Fibrillation: Analysis of the ENGAGE AF-TIMI 48 Trial

Christina L. Fanola, MD, MSc; Christian T. Ruff, MD, MPH; Sabina A. Murphy, MPH; James Jin, PhD; Anil Duggal, MD; Noe A. Babilonia, MD; Piyamitr Sritara, MD; Michele F. Mercuri, MD, PhD; Pieter W. Kamphuisen, MD; Elliott M. Antman, MD, Eugene Braunwald, MD; Robert P. Giugliano, MD, SM

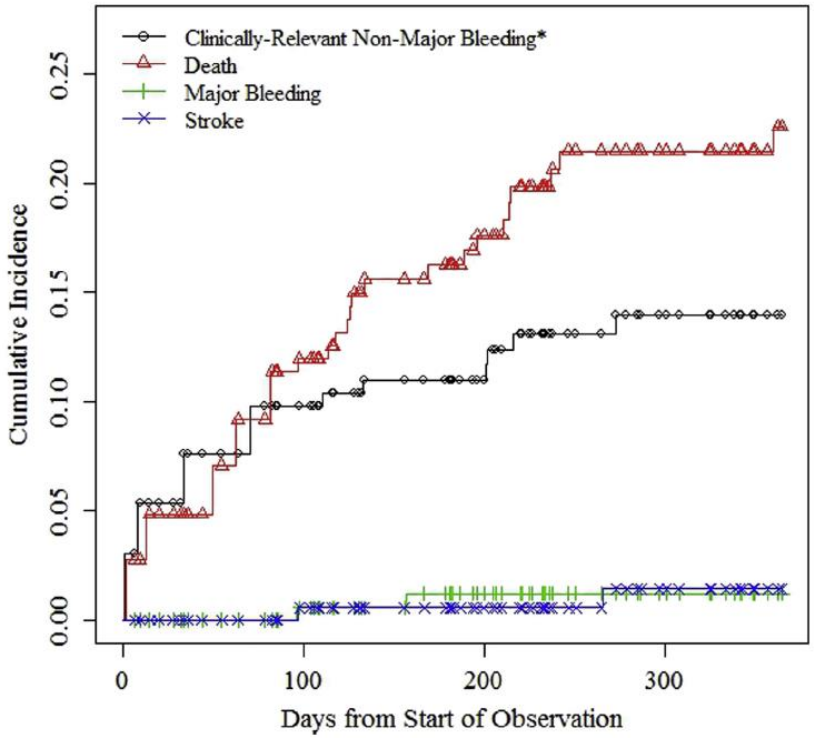


[a] SEE, systemic embolic event; HDER, higher dose edoxaban regimen; LDER, lower dose edoxaban regimen

Am J Cardiol 2017;120:213–217

Rivaroxaban for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation and Active Cancer

Eva S. Laube, MD[a], Anthony Yu, MD[b], Dipti Gupta, MD, MPH[b], Yimei Miao, BS[a], Patrick Samedy, MS[c], Jonathan Wills, BA[d], Stephen Harnicar, PharmD[e], Gerald A. Soff, MD[a], and Simon Mantha, MD, MPH[a,*]



163 pts with active cancer and Afib treated with rivaroxaban

CONCLUSIONS

The safety and efficacy of rivaroxaban treatment for nonvalvular AF in patients with active cancer is comparable to the results of **ROCKET-AF** study in the general population.

Rivaroxaban in Patients with NVAF and Active Cancer

Results

- 163 patients were included between 1 Jan 2014 and 31 Mar 2016
- Efficacy
  - **stroke rates were similar to those reported in ROCKET AF** (cumulative incidence of stroke was **1.4%** in this cohort vs **1.7%** in the rivaroxaban arm of ROCKET AF)
  - no systemic embolism episodes
- Safety
  - **1 year rate of major bleeding was 1.2% (lower than 3.6% found in the rivaroxaban arm of ROCKET AF)**

Cumulative incidence of competing risks for patients in the acute, chronic, and combined phases of anticoagulation*

	Acute Phase N=59	Chronic Phase N=138	Combined Period N=163
Ischemic Stroke (95% CI)	0	1.8% (0-4.3)	1.4% (0-3.4)
Major bleeding (95% CI)	0	1.5% (0-3.6)	1.2% (0-2.9)
Death (95% CI)	11.4% (1.4-20.3)	14.2% (7.3-20.5)	22.6% (12.2-31.7)
CRNMB (95% CI)	9.8% (0.2-18.4)	5.4% (1.1-9.5)	14.0% (4.2-22.7)

CRNMB = clinically relevant nonmajor bleeding leading to discontinuation of rivaroxaban for at least 7 days.

* Cumulative incidence estimates for the chronic phase are conditional to reaching day 90 of anticoagulation without sustaining an event. The chronic phase was defined as lasting 275 days and the combined period encompasses 365 days.

Chronic phase: > 90 days of anticoagulation
Acute phase: < 90 days of anticoagulation

Laube et al. Am J Cardiol 2017

The American Journal of Medicine (2017)

Efficacy and Safety of Apixaban Versus Warfarin in Patients with Atrial Fibrillation and a History of Cancer: Insights from the ARISTOTLE Trial

Chiara Melloni, MD, MHS,[a,b] Allison Dunning, MS,[a] Christopher B. Granger, MD,[a,b] Laine Thomas, PhD,[a] Michel G. Khouri, MD,[b] David A. Garcia, MD,[c] Elaine M. Hylek, MD, MPH,[d] Michael Hanna, MD,[e] Lars Wallentin, MD, PhD,[f] Bernard J. Gersh, MB, ChB, DPhil,[g] Pamela S. Douglas, MD,[a,b] John H. Alexander, MD, MHS,[a,b] Renato D. Lopes, MD, MHS, PhD[a,b]

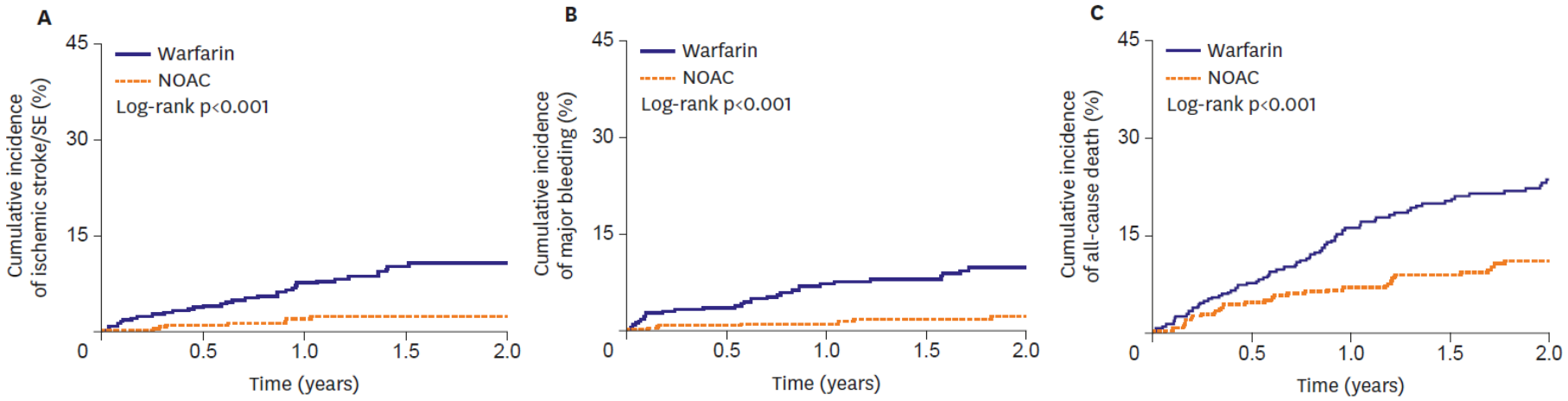
	Active/Treated			No Cancer			p-value*
	Apixaban	Warfarin	HR (95% CI)	Apixaban	Warfarin	HR (95% CI)	
Efficacy endpoints							
Stroke or SE	0 (0%)	5 (6.2%)	0 (0–infinity)	196 (2.3%)	251 (3.0%)	0.77 (0.64–0.93)	0.9469
Overall death	5 (6.6%)	11 (13.6%)	0.45 (0.16–1.29)	548 (6.5%)	626 (7.4%)	0.87 (0.77–0.97)	0.2209
Ischemic stroke	0 (0%)	3 (3.7%)	0 (0–infinity)	147 (1.7%)	166 (2.0%)	0.88 (0.70–1.10)	0.9556
MI	0 (0%)	1 (1.2%)	0 (0–infinity)	78 (0.9%)	90 (1.1%)	0.86 (0.63–1.16)	0.9668
VTE: PE/DVT	0 (0%)	1 (1.2%)	0 (0–infinity)	27 (0.3%)	33 (0.4%)	0.81 (0.49–1.35)	0.9775
Safety endpoints							
ISTH major bleeding	1 (1.3%)	5 (6.2%)	0.19 (0.02–1.59)	303 (3.6%)	430 (5.1%)	0.69 (0.59–0.80)	0.2339
Major or CRNM bleeding	6 (7.9%)	10 (12.4%)	0.56 (0.20–1.54)	560 (6.6%)	810 (9.6%)	0.67 (0.60–0.75)	0.7253
Any bleeding	27 (35.5%)	30 (37.0%)	0.93 (0.55–1.56)	2149 (25.3%)	2815 (33.3%)	0.71 (0.67–0.75)	0.3089
Intracranial bleeding	0 (0%)	2 (2.5%)	0 (0–infinity)	52 (0.6%)	113 (1.3%)	0.45 (0.32–0.63)	0.9701
Net composite endpoint							
Composite efficacy endpoint†	5 (6.6%)	16 (19.8%)	0.30 (0.11–0.83)	734 (8.6%)	841 (10.0%)	0.86 (0.78–0.95)	0.0421
Composite endpoint‡	6 (7.9%)	18 (22.2%)	0.32 (0.13–0.81)	948 (11.2%)	1124 (13.3%)	0.83 (0.76–0.90)	0.0441

*P-value for the randomized treatment-by-cancer interaction. †Stroke/SE & MI & Death; ‡Stroke/SE & MI & Death & ISTH Major bleeding. Event rate = events/100 patient-years of follow up.

Conclusion: There was no evidence of a lesser effect of apixaban vs. warfarin in patients with active cancer. Our findings are promising and warrant further evaluation in RCTs focusing on patients with cancer.

Atrial Fibrillation - Real life

- In 2,568 consecutive AF patients with newly diagnosed cancer, stroke/systemic embolism (SE), major bleeding, and all-cause death were analyzed.
- **NOACs have significantly lower incidences of ischemic stroke/systemic embolism** (p<0.001), **major bleeding** (p<0.001), **and all-cause death** (p<0.001) **than warfarin.**
  - The incidence of major bleeding was particularly lower within 1 year after cancer diagnosis
  - The incidences of all clinical events were significantly lower in the NOAC group vs warfarin group

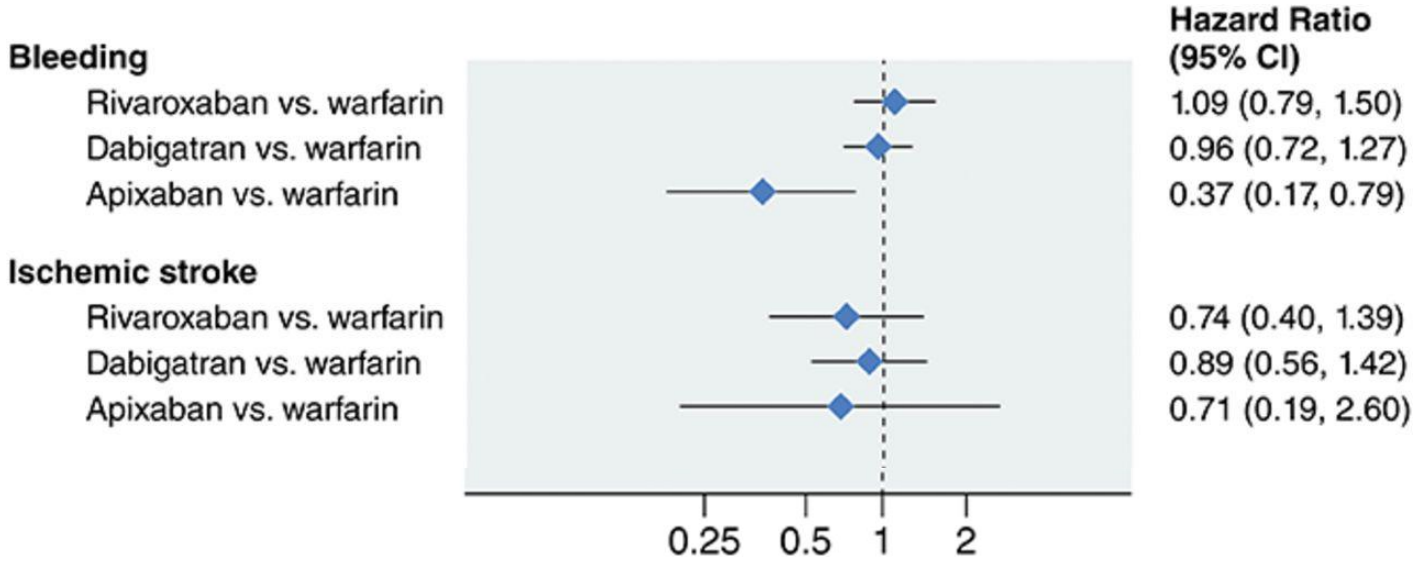


572 patients in NOAC: 140 (36.1%) dabigatran, 138 (35.6%) apixaban, and rivaroxaban 110 (28.3%) patients.

Kim K et al. Korean Circ J. 2018

DOACs in cancer and AF

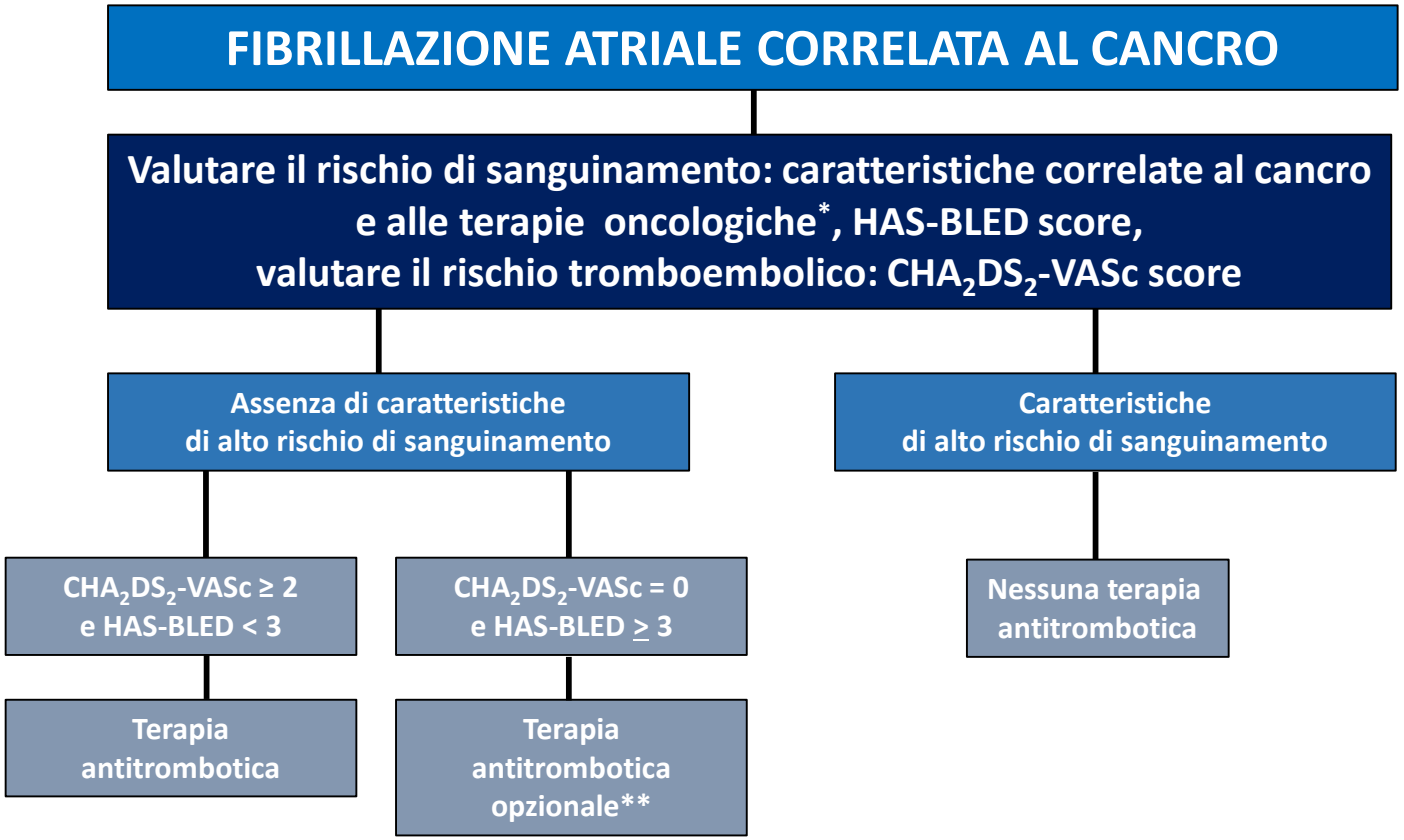
MarketScan databases, we identified 16096 AF patients (mean age, 74 years) initiating oral anticoagulant and being actively treated for cancer.



	Rivaroxaban	Dabigatran	Apixaban	Warfarin
N	2808	2189	1078	10021
Age, y	73.8 ± 10.2	74.0 ± 10.3	74.9 ± 10.3	75.4 ± 10.1
Female, %	40.7	38.3	42.5	39.4

Shah S et al. Blood Advances 2018

Algoritmo per la terapia antitrombotica nella fibrillazione atriale correlata al cancro



*Tumore intracranico, neoplasie ematologiche con difetti della coagulazione, trombocitopenia indotta dalla terapia, grave malattia epatica metastatica, terapie oncologiche a rischio di sanguinamento. **La terapia antitrombotica può essere considerata in alcuni cancri associati ad alto rischio tromboembolico (ad esempio pancreas, ovaie, polmone, fegato) o a terapie oncologiche (ad esempio cisplatino, gemcitabina, 5-fluorouracile, eritropoietina, fattori di crescita dei granulociti)

International Journal of Cardiology 269 (2018) 152–157

Contents lists available at ScienceDirect

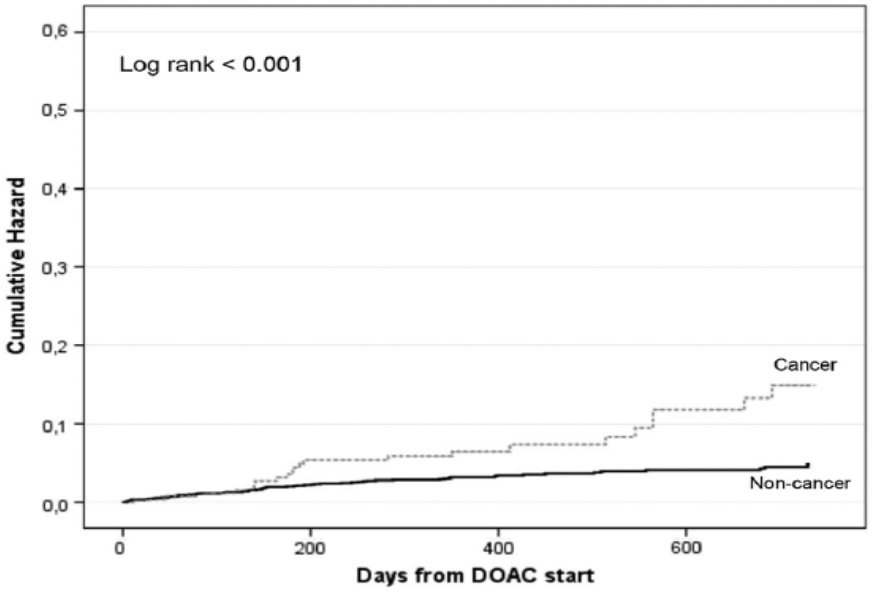
International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Patients with cancer and atrial fibrillation treated with doacs: A prospective cohort study

Maria Cristina Vedovati [a,*,1], Michela Giustozzi [a,1], Paolo Verdecchia [b,1], Lucia Pierpaoli [c,1], Serenella Conti [d,1], Melina Verso [a,1], Francesco Di Filippo [c,1], Emanuela Marchesini [a,1], Giulio Bogliari [a,1], Giancarlo Agnelli [a,1], Cecilia Becattini [a,1]

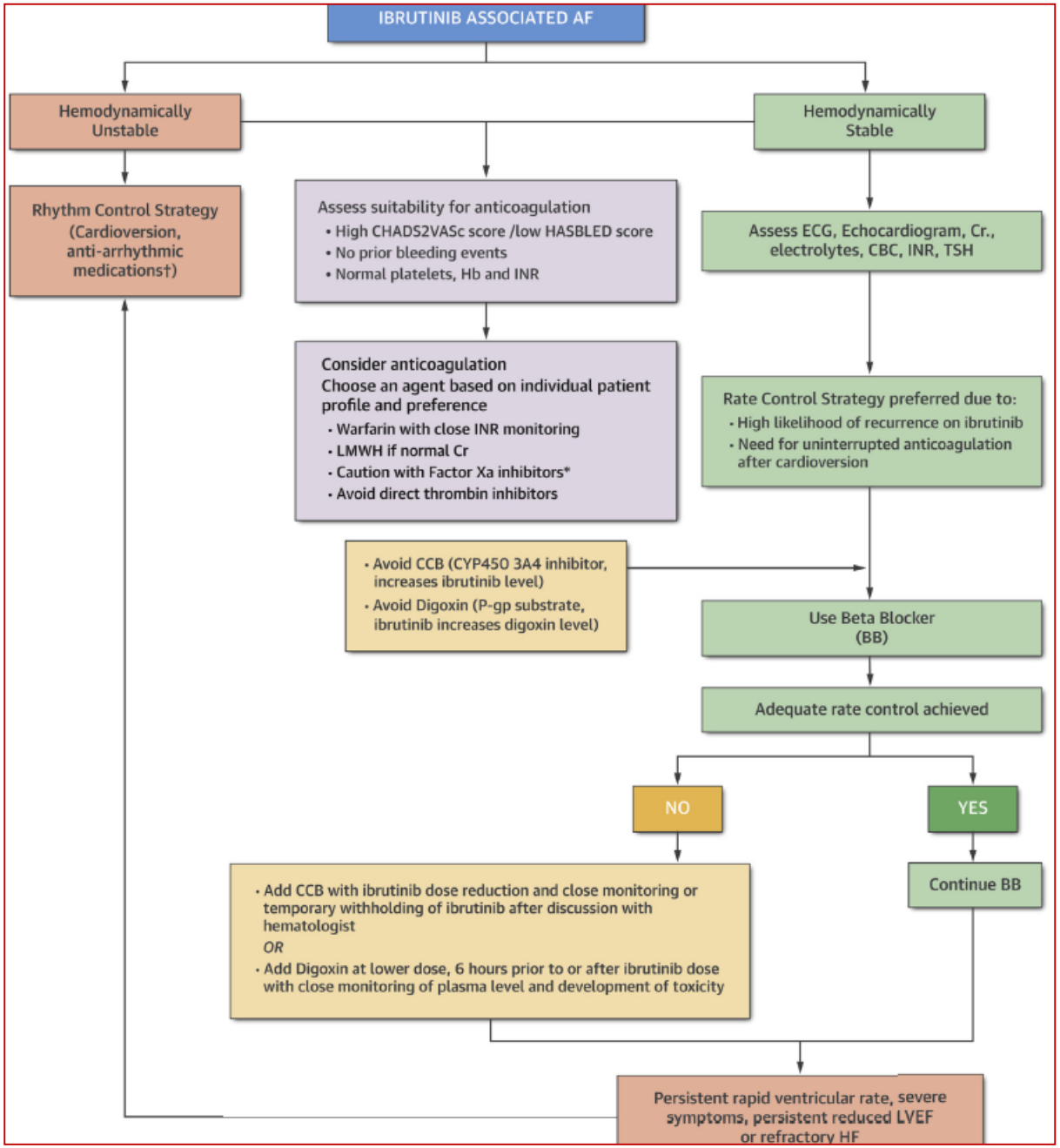
Major bleeding events in cancer and non-cancer patients



289 pazienti con cancro su 2304 in trattamento con NAO

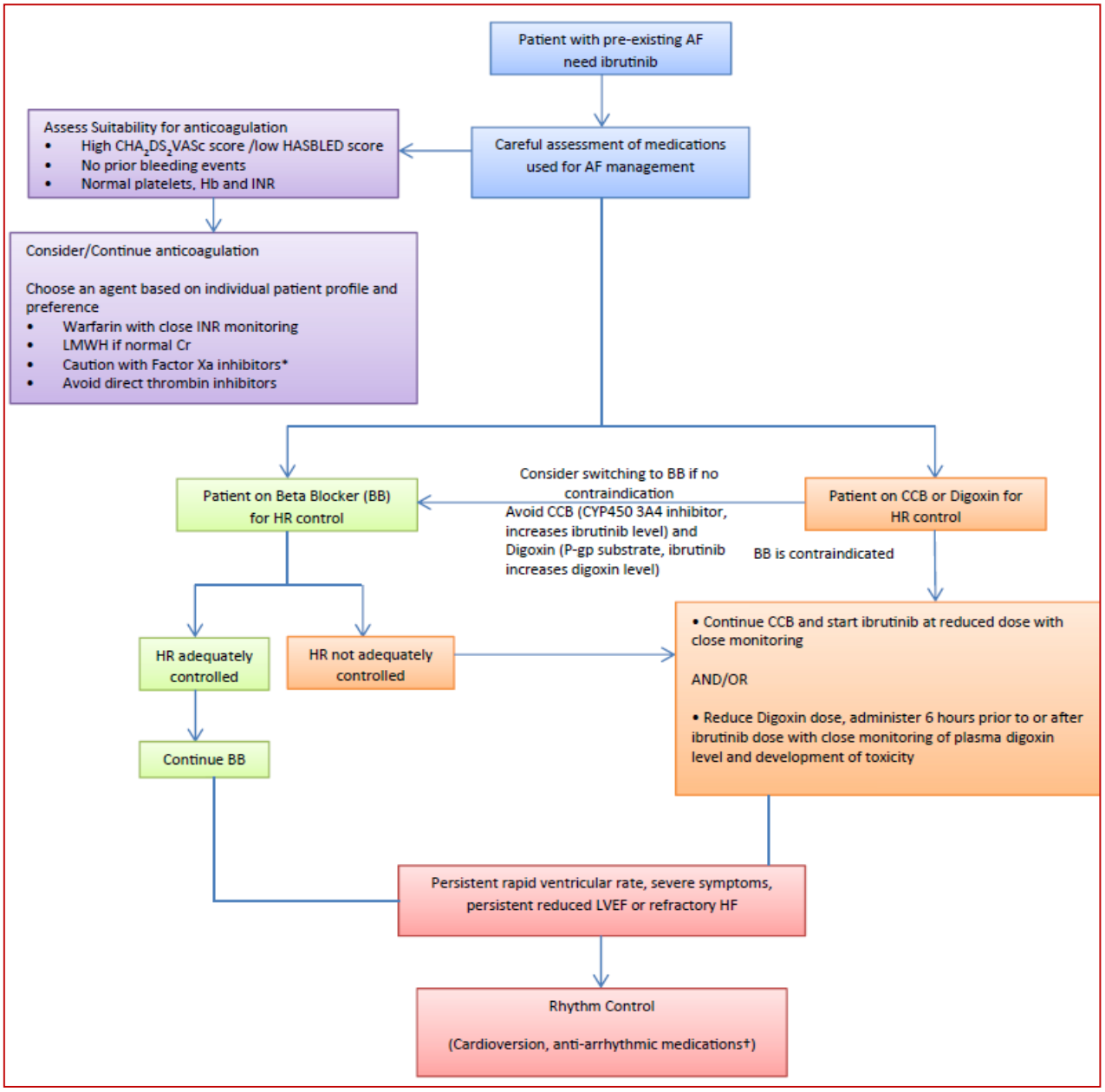
Conclusions: In this study, the higher bleeding risk found in cancer compared to non-cancer patients was mainly due to an excess of bleeding at gastrointestinal and at genitourinary sites. Larger studies on the optimal management of cancer patients with AF are needed.

Proposed algorithm for Ibrutinib-associated AF management



Ganatra S. et al. JACC 2018

Proposed algorithm for patients with pre-existing AF who require Ibrutinib



Ganatra S. et al. JACC 2018

10 La gestione della fibrillazione atriale nel paziente oncologico

Nicola Maurea[1], Enrico Barbieri[2]

Tabella 36. Criteri di utilizzo dei NAO nei pazienti oncologici

Valutazione dei pazienti
Fattori di rischio per sanguinamento Nessun evento di sanguinamento maggiore nei due mesi precedenti. Assenza di tumori intracranici o viscerali ad alto rischio di sanguinamenti maggiori
Piastrine Numero di piastrine >50,000 per µl. Nessuna previsione di riduzione dovuta alla chemioterapia
Studio di coagulazione PT, PPT e fibrinogeno normali
Test funzionali del fegato Nessuna insufficienza epatica significativa (es. Child Pugh B o C, cirrosi)
Funzione renale CrCl >30ml/min. Nessuna previsione di riduzione dovuta a chemioterapia nefrotossica
Farmaci Assenza di uso concomitante di farmaci con un forte effetto sul citocromo P450 3A4 e sulla glicoproteina P. Considerare la lista di farmaci chemioterapici, biologici, ormonali o di supporto che modulano il citocromo P450 3A4 e/o la glicoproteina P. Buona compliance.

Citocromo P450 e Glicoproteina P

	Dabigatran[1]	Rivaroxaban[2,3]	Apixaban[4]	Edoxaban[5–8]
Target	IIa (thrombin)	Xa	Xa	Xa
Bioavailability, %	3–7	100 with food	50	62
Hours to C_{max}	1–3	2–4	3–4	1–2
Half-life, h	12–17	5–13	12	10-14
Renal clearance, %	80	33	27	35-50*
→ Transporters	P-gp	P-gp	P-gp	P-gp
→ CYP-metabolism, %	No	Yes (moderate)	Yes (moderate)	Minimal (<4%)
Protein binding, %	35	92–95	87	40–59
Dosing regimen	BID	OD/BID	BID	OD

CYP, cytochrome P450; P-gp, P-glycoprotein
*absorbed dose

1.Pradaxa [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc. 2013
2. Xarelto [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc. 2011
3. Weinz et al. Drug Dispos Metab 2009;37:1056–1064
4. ELIQUIS Summary of Product Characteristics. Bristol Myers Squibb/Pfizer EEIG, UK
5. Matsushima et al. Am Assoc Pharm Sci 2011; abstract; 6. Ogata et al. J Clin Pharmacol 2010;50:743–753
7. Mendell et al. Am J Cardiovasc Drugs 2013;13:331–342; 8. Bathala et al. Drug Metab Dispos 2012;40:2250–2255
8. Heidbuchel et al. EHRA Practical Guidelines; Europace 2015

Drug–Drug Interactions

- NOACs and warfarin are substrates of key metabolic and transport pathways
- Some DDIs are well documented; clinical relevance of many potential DDIs is unknown

Anticoagulants as substrates for major pathways

Anticoagulant	CYP3A4 (metabolic)	P-gp (transport)	Other CYP-metabolizing enzymes (2C9, 2C19, 2C8, 2C18, 1A2)
LMWH[1]	No	No	No
VKA[2]	Major	No/minor	All (major: CYP2C9)
Apixaban[3]	Major	Major	Minor: 1A2, 2C8, 2C9, 2C19
Edoxaban[4]	Minor	Major	No
Rivaroxaban[5]	Major	Major	No
Dabigatran[6]	No	Moderate*	No

*Dabigatran is contra-indicated with quinidine

1. Lovenox (enoxaparin sodium injection) Prescribing Information. 2009; 2. Coumadin (warfarin sodium) Prescribing Information. 2011; 3. Eliquis (apixaban) Prescribing Information. 2019; 4. Savaysa (edoxaban) Prescribing Information. 2015; 5. Xarelto (rivaroxaban) Prescribing Information. 2019; 6. Pradxa (dabigatran etexilate mesylate) Prescribing Information. 2018.

Anticipated Drug-Drug Interaction Between Common Anticancer Drug Classes and DOACs

	P-Glycoprotein Interaction (All DOACs Affected)	CYP3A4 Interaction (Strongly Affects Rivaroxaban and Apixaban)
Inhibition	• Immune-modulating agents (e.g., tacrolimus; strong to moderate to competition to none) • Tyrosine kinase inhibitors (e.g., imatinib; strong to moderate to competition to none) • Hormonal agents (e.g., abiraterone; strong to competition to none)	• Immune modulating agents (e.g., cyclosporine; moderate to mild to competition) • Tyrosine kinase inhibitors (e.g., nilotinib; moderate to mild to competition) • Hormonal agents (e.g., bicalutamide; moderate to mild to competition to none) • Topoisomerase inhibitors (e.g., etoposide; mild to competition to none) • Anthracyclines (e.g., idarubicin; mild to competition to none) • Alkylating agents (e.g., cyclophosphamide; mild to competition to none)
Induction	• Anthracyclines (e.g., doxorubicin; strong to competition to none) • Antimitotic agents (e.g., vinblastine; strong to competition) • Immune-modulating agents (e.g., dexamethasone; strong to competition to none)	• Immune-modulating agents (e.g., dexamethasone; strong to moderate to competition) • Antimitotic agents (e.g., paclitaxel; moderate to mild to competition) • Tyrosine kinase inhibitors (e.g., vemurafenib; moderate to competition) • Hormonal agents (e.g., enzalutamide; strong to competition to none)
Minimal to no Interaction	• Alkylating agents (e.g., bendamustine; competition to none) • Antimetabolites (e.g., methotrexate; competition to none) • Monoclonal antibodies (e.g., rituximab; none) • Platinum based agents (e.g., cisplatin; none) • Intercalating agents (e.g., bleomycin; none)	• Monoclonal antibodies (e.g., brentuximab; competition to none) • Antimetabolites (e.g., pemetrexed; none) • Platinum based agents (e.g., oxaliplatin; none) • Intercalating agents (e.g., mitomycin C; none)

Anticipated interactions are offered within anticancer drug classes as no interaction, competition, or potential interaction (mild, moderate, or strong). Intraclass differences exist in inhibition/induction and presence and strength of interaction. Table 4 of the 2018 European Heart Rhythm Association practical guide (3) offers more detailed drug–drug interactions and anticipated effects on DOAC drug levels.

CYP3A4 = Cytochrome P450 3A4; DOAC = direct oral anticoagulants.

Mosarla RC et al. JACC 2019

Common drug-drug interactions with direct factor Xa inhibitors

Drug class and name	Interaction effect		
	Edoxaban[a]	Rivaroxaban[b]	Apixaban[b]
Antimitotic agents			
Vinblastine	↓	↓	↓
Anti-mycotic agents			
Azithromycin	↑	↑	↑
Clarithromycin	↑	↑	↑
Erythromycin	↑	↑	↑
Itroconazole	↑	↑	↑
Ketoconazole	↑	↑	↑
Posaconazole	—	↑	↑
Voriconazole	—	↑	↑
Anthracyclines			
Doxorubicin	↓	↓	↓
Hormonal agents			
Tamoxifen	↑	↑	↑
Immune-modulating agents			
Cyclosporine	↑	↑	↑
Dexamethasone	↓	↓	↓
Tacrolimus	↑	↑	↑
Protease inhibitors			
Indinavir	↑	↑	↑
Nelfinavir	↑	↑	↑
Ritonavir	↑	↑	↑
Saquinavir	↑	↑	↑
Tyrosine kinase inhibitors			
Imatinib	—	↓	↓
Lapatinib	↑	↑	↑
Nilotinib	↑	↑	↑
Sunitinib	↑	↑	↑

[a] Substrate of P-glycoprotein.
[b] Substrate of P-glycoprotein and CYP3A4 (cytochrome P450 3A4).
↑ = increases plasma factor Xa through P-glycoprotein or CYP3A4 inhibition; ↓ = decreases plasma factor Xa through P-glycoprotein or CYP3A4 induction; — = no effect on plasma factor Xa.

The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation

Interazioni con i farmaci concomitanti forti inibitori e induttori della glicoproteina P e del citocromo P450 3A4

	Via	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Antibiotics					
Clarithromycin; Erythromycin	Moderate P-gp competition and strong CYP3A4 inhibition	+15 to 20%	+60% AUC +30% C_{max}	+90%[SmPC]	+34% (Erythromycin)/ +54% (Clarithromycin) [SmPC129]
Rifampicin	P-gp/BCRP and CYP3A4/ CYP2J2 inducers	Minus 66%[SmPC]	Minus 54%[138]	Minus 35%, but with compensatory increase of active metabolites	Up to minus 50%[SmPc]
Antiviral drugs					
HIV protease inhibitors (e.g. ritonavir)	P-gp and BCRP competition or inducer; CYP3A4 inhibition	No data yet	Strong increase[SmPC]	No data yet	Up to +153%[139]
Fungostatics					
Fluconazole	Moderate CYP3A4 inhibition	No data yet	No data yet	No data yet	+42% (if systemically administered)[SmPC]
Itraconazole; Ketoconazole; Voriconazole	potent P-gp and BCRP competition; CYP3A4 inhibition	+140 to 150% (US: 2 x 75 mg if CrCl 30–50 mL/min)	+100%[136]	+87 to 95%[132] (reduce NOAC dose by 50%)	Up to +160%[SmPc]
Posaconasole	Mild to moderate P-gp inhibition	SmPC	SmPC		SmPC

Steffel J et al. European Heart Journal 2018

Anticipated effects of common anticancer drugs on non-vitamin K antagonist oral anticoagulants plasma levels

	Via[142]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		**Yes**	**Yes**	**Yes**	**Yes**
CYP3A4 substrate		**No**	**Yes (≈25%)**	**No (<4%)**	**Yes (≈18%)**
Antimitotic agents					
Paclitaxel	Moderate CYP3A4 induction; CYP3A4/P-gp competition				
Vinblastine	Strong P-gp induction; CYP3A4/P-gp competition				
Docetaxel, Vincristine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Vinorelbine	Mild CYP3A4 induction; CYP3A4/P-gp competition				
Antimetabolites					
Metotrexate	P-gp competition; no relevant interaction anticipated				
Pemetrexed, Purine analogs, Pyrimidine analogs	No relevant interaction anticipated				
Topoisomerase inhibitors					
Topotecan	No relevant interaction anticipated				
Irinotecan	CYP3A4/P-gp competition; No relevant interaction anticipated				
Etoposide	Mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Anthracyclines/Anthracenediones					
Doxorubicin	Strong P-gp induction, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Idarubicin	Mild CYP3A4 inhibition; P-gp competition				

Steffel J et al. European Heart Journal 2018

Anticipated effects of common anticancer drugs on non-vitamin K antagonist oral anticoagulants plasma levels

	Via[142]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
Daunorubicin	P-gp competition; No relevant interaction anticipated				
Mitoxantrone	No relevant interaction anticipated				
Alkylating agents					
Ifosfamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Ciclophosphamide	Mild CYP3A4 inhibition; CYP3A4 competition				
Lomustine	Mild CYP3A4 inhibition				
Busulfan	CYP3A4 competition; No relevant interaction anticipated				
Bendamustine	P-gp competition; No relevant interaction anticipated				
Chlorambucil, Melphalan, Carmustine, Procarbazine, Dacarbazine, Temozolomide	No relevant interaction anticipated				
Platinum-based agents					
Cisplatin, Carboplatin, Oxaliplatin	No relevant interaction anticipated				
Intercalating agents					
Bleomycin, Dactinomycin	No relevant interaction anticipated				
Mitomycin C	No relevant interaction anticipated				
Tyrosine kinase inhibitors					
Imatinib, Crizotinib	Strong P-gp inhibition, moderate CYP3A4 inhibition; CYP3A4/P-gp competition				
Nilotinib, Lapatinib	Moderate-to-strong P-gp inhibition, mild CYP3A4 inhibition; CYP3A4/P-gp competition				
Vemurafenib	Moderate CYP3A4 induction; CYP3A4/P-gp competition				

Steffel J et al. European Heart Journal 2018

	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Antimitotic agents						
Vinca alkaloids						
Vinblastine	+++		+	●	●	
Vincristine	+++		+	●		
Vinorelbine	+++		+			
Taxanes						
Docetaxel	+++		+	●		
Paclitaxel	**+++**	**++**		●		
Antimetabolites						
Antifolates						
Methotrexate				●		
Pemetrexed						
Purine analogs						
Mercaptopurine						
Thioguanine						
Pentostatin						
Cladribine						
Clofarabine						
Fludarabine						
Pyrimidine analogs						
Fluorouracil						
Capecitabine						
Cytarabine						
Gemcitabine						
Azacitadine						
Decitabine						

[a] +++, strong interaction; ++, moderate interaction; +, weak interaction.
[b] Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c] Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

Short, The Oncologist 2014

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Topoisomerase inhibitors						
Topotecan						
Irinotecan	+++			●		
Etoposide	+++		+	●		
Anthracyclines/ anthracenediones						
Doxorubicin	+++		+	●	●	
Daunorubicin				●		
Idarubicin			+	●		
Mitoxantrone						
Alkylating agents						
Cyclophosphamide	+		+			
Ifosfamide	+++		+			
Chlorambucil						
Melphalan						
Bendamustine				●		
Carmustine						
Lomustine			+			
Busulfan	+++					
Procarbazine						
Dacarbazine						
Temozolomide						

[a] +++, strong interaction; ++, moderate interaction; +, weak interaction.
[b] Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c] Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

Short, The Oncologist 2014

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Platinum-based agents						
Cisplatin						
Carboplatin						
Oxaliplatin						
Intercalating agents						
Bleomycin						
Mitomycin C				●		
Dactinomycin						
Tyrosine kinase inhibitors						
Imatinib	+++		++	●		●
Dasatinib	+++		+			
Nilotinib	+++		+	●		●
Erlotinib	+++					
Gefitinib	+++					
Lapatinib	+++		+	●		●
Sunitinib	+++					●
Sorafenib	+					
Crizotinib	+++		++	●		●
Vemurafenib	+	++		●		
Vandetanib	+++					●
Monoclonal antibodies						
Rituximab						
Brentuximab	+++					
Alemtuzumab						
Cetuximab						
Trastuzumab						
Bevacizumab						

[a] +++, strong interaction; ++, moderate interaction; +, weak interaction.
[b] Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c] Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

Short, The Oncologist 2014

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Hormonal agents						
Tamoxifen	+++		+			●
Raloxifene						
Anastrozole			+			
Letrozole	+					
Fulvestrant	+					
Leuprolide						
Flutamide	+++					
Bicalutamide			++			
Enzalutamide	+++	+++				●
Abiraterone	+++		++			●
Mitotane						
Immune-modulating agents						
Cyclosporine	+++		++	●		●
Sirolimus	+++		+	●		
Everolimus	+++			●		
Temsirolimus	+++		+	●		
Tacrolimus	+++		+	●		●
Dexamethasone	+++	+++		●	●	●
Prednisone	+	++				

[a] +++, strong interaction; ++, moderate interaction; +, weak interaction.
[b] Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c] Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

Short, The Oncologist 2014

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
	Substrate	Inducer	Inhibitor	Substrate	Inducer	Inhibitor
Miscellaneous						
Lenalidomide				●		
Bortezomib	+++		+			
Bexarotene	+	++				
Supportive care						
Prochlorperazine						
Ondansetron	+++			●		
Palonosetron	+					
Metoclopramide						
Aprepitant	+++	++	++			
Fosaprepitant	+++	++	++			
Oxycodone	+++					
Hydromorphone						
Morphine						
Fentanyl	+++		+			
Methadone	+++		+			
Acetaminophen	+		+			
Lorazepam						
Clonazepam	+++					
Filgrastim						
Epoetin alfa						
Darbepoetin alfa						

[a] +++, strong interaction; ++, moderate interaction; +, weak interaction.
[b] Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c] Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

Short, The Oncologist 2014

Anticoagulation of cancer patients with non- valvular atrial fibrillation receiving chemotherapy: guidance from the SSC of the ISTH

Guidance Statements

- We recommended **individualized anticoagulation regimens** after **shared decision-making** with patients, based wherever possible on risk of stroke, bleeding and patients values.

- In cancer patients **on chemotherapy with newly diagnosed NVAF**, with **exception** of patients with **luminal gastrointestinal cancers** with no surgery or patients with **active gastrointestinal mucosal abnormalities** such as duodenal ulcers, gastritis, esophagitis or colitis we suggest the **use of a DOAC over a VKA** or LMWH as anticoagulant therapy if no clinically relevant drug-to-drug interactions are expected

Delluc A et al, J Tromb Haemost 2019

Anticoagulation of cancer patients with non- valvular atrial fibrillation receiving chemotherapy: guidance from the SSC of the ISTH

Guidance Statements

- In cancer patients with **NVAF already on an anticoagulant** regimen before starting chemotherapy, we recommended continuing **the same anticoagulation regimen** unless there are clinically relevant drug-to-drug interaction

  a) In cancer patients on chemotherapies with **clinically relevant VKA interactions**, we suggest considering a DOAC if no additional drug-drug interaction with DOAC or close monitoring of VKA (target INR between 2 and 3)

  b) In cancer patients on chemotherapies **unable to tolerate an oral route** of admininistration (e.g. nausea and vomiting), we suggest the **use of parenteral anticoagulation** with therapeutic dosing of LMWH **with resumption of oral** anticoagulation as soon as possible.

Delluc A et al, J Tromb Haemost 2019

Anticoagulation of cancer patients with non-valvular atrial fibrillation receiving chemotherapy: guidance from the SSC of the ISTH

- DOACs are a **more practical alternative to warfarin**, with comparable clinical efficacy and safety
- **Rapid onset** (1-2 hours) **and shorter half-life** of DOACs (6-12 hours) compared with warfarin (40 hours) offer **additional practical advantages** over VKAs in cancer patients **who undergo frequent medication changes and invasive procedures.**
- As for cancer-associated VTE, **carefully consider**:
  - Bleeding risks (e.g. tumor type)
  - (Clinically revelant) drug-drug interactions
  - Thrombocytopenia ($< 50 \times 10^9\ L^{-1}$)
  - Renal and hepatic function
  - Patients preferences and values
- **Anticoagulant therapy** regularly reassessed as patient's cancer status and **management change over time**

QUALE NAO PUO' SOSTITUIRE IL WARFARIN E L'EPARINA NELLA FIBRILLAZIONE ATRIALE E NEL TROMBOEMBOLISMO VENOSO NEL PAZIENTE NEOPLASTICO?

- Trattamento del Tromboembolismo Venoso e dell'Embolia Polmonare :

  -**Edoxaban e Rivaroxaban** (trials randomizzati)

- Prevenzione del Tromboembolismo Venoso e dell'Embolia Polmonare nel paziente ambulatoriale ad alto rischio:

  -iniziali evidenze per **Apixaban e Rivaroxaban** (trials randomizzati)

- Fibrillazione Atriale:

  -assenza di trials randomizzati

  -le linee guida EHRA hanno aperto all'utilizzo di **tutti i NAO**

Istituto Nazionale Tumori
Fondazione G. Pascale

AICO

SAVE THE DATE

III INTERNATIONAL WORKSHOP ON CARDIONCOLOGY
VI CONGRESSO NAZIONALE DI CARDIONCOLOGIA

Presidenti del Congresso
Nicola Maurea, Michelino De Laurentiis

Napoli
HOTEL ROYAL CONTINENTAL
30/31 Gennaio 2020

Select-d: Patients Baseline Characteristics

Baseline characteristics

	Rivaroxaban (n=203)	Dalteparin (n=203)
Age, years, median (range)	67 (22–87)	67 (34–87)
Gender male, %	54	48
Metastatic cancer, %	59	59
ECOG performance status, % 0 or 1 2	 72 26	 76 21
Qualifying VTE, % Symptomatic VTE Incidental PE	 46 54	 48 52

Primary tumour type

Tumour type, %	Rivaroxaban (n=203)	Dalteparin (n=203)
Colorectal	27	23
Lung	11	12
Breast	9	10
Ovarian	5	9
Pancreatic	9	5
Lymphoma	5	6
Oesophageal/ gastro-oesophageal	5	9
Prostate	6	3
Bladder	5	2
Other	18	21

Young A *et al*, ASH 2017: Abstract 625; Available at: http://www.clinicaltrialresults.org/

Drug–Drug Interactions

Inducers and inhibitors of CYP3A4 and P-gp

- Inhibitors of CYP3A4 and/or P-gp may increase the risk of bleeding with NOACs

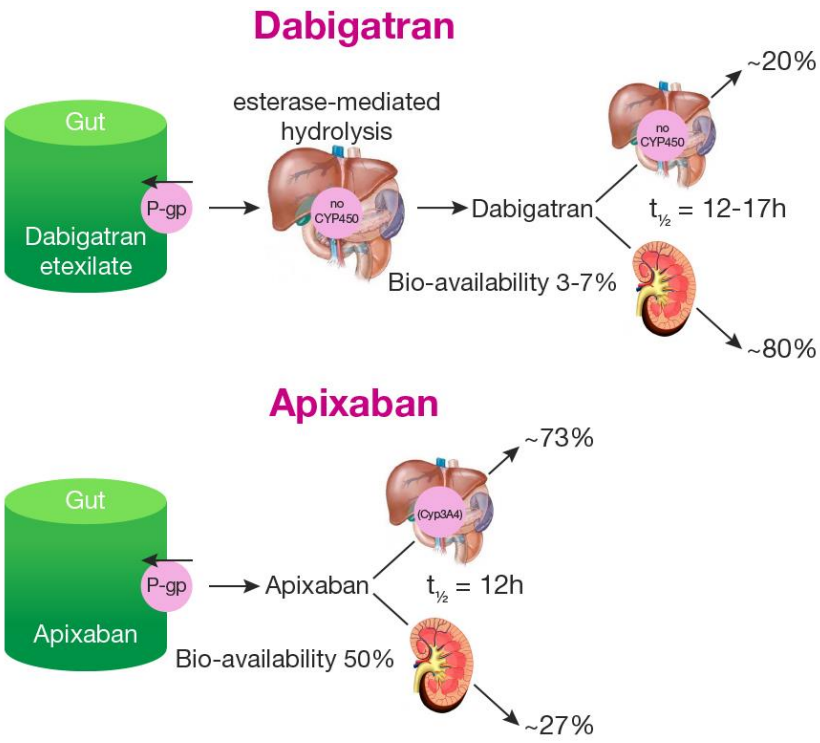
Chemotherapies	CYP3A4	P-gp
Doxorubicin[1,2]	↓	
Topotecan[3]	↓	
Vinblastine[1,2]	↓	
Mitotane[4]	↑	
Venetoclax[5]		↓

Supportive care	CYP3A4	P-gp
Aprepitant[6]	↓	
Methylprednisolone[7]	↓	
Dexamethasone[1,2]	↑	↑

Kinase inhibitors	CYP3A4	P-gp
Afatinib[8]		↓
Alectinib[9]		↓
Ceritinib[10]	↓	
Crizotinib[11]	↓	
Dasatinib[12]	↓	
Ibrutinib[13]		↓
Idelalisib[14]	↓	↓
Imatinib[1]	↓	
Lapatinib[1]	↓	↓
Nilotinib[1]	↓	↓
Osimertinib[15]	↓	
Vemurafenib[16]	↑	↓
Lenvatinib[17]	↑	↑

1. Lee AY, Peterson EA, *Blood* 2013;122:2310–2317; 2. Carrier M *et al*, *Current Oncol* 2018;25:329–337; 3. Hycamtin (topotecan hydrochloride) Product Monograph. 2016; 4. Lysodren (mitotane) SmPC. 2009; 5. Venclyxto (venetoclax) SmPC. 2018; 6. Emend (aprepitant) SmPC. 2008; 7. Methylprednisolone SmPC. 2017; 8. Giotrif (afatinib) SmPC. 2013; 9. Alecense (alectinib) SmPC. 2017; 10. Zykadia (ceritinib) SmPC. 2017; 11. Xalkori (crizotinib) SmPC. 2016; 12. Sprycel (dasatinib) SmPC. 2016; 13. Imbruvica (ibrutinib) SmPC. 2014; 14. Zydelig (idelalisib) SmPC. 2014; 15. Tagrisso (osimertinib) SmPC. 2016; 16. Zelboraf (vemurafenib) SmPC. 2016; 17. Lenvima (lenvatinib) SmPC. 2015

NOACs: Assorbimento, Metabolismo, Eliminazione



Heidbuchel H et al. EHRA Practical Guide. Europace 2015;17(10):1467-507.

NOACs: Biodisponibilità, Trasportatori e Metabolismo

	P-gp Substrate	CYP3A4 Substrate	BCRP Substrate	Biodisponibilità
DABIGATRAN	Yes	No	No	6%
RIVAROXABAN	Yes	33%	Yes	100% con cibo
APIXABAN	Yes	25%	Yes	60%
EDOXABAN	Yes	<4%	No	62%

Edoxaban nel paziente con fibrillazione atriale e cancro

Nicola Maurea[1], Letizia Riva[2]

[1]*S.C. Cardiologia, Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, Napoli*
[2]*U.O.C. Cardiologia, Ospedale Maggiore, Bologna*

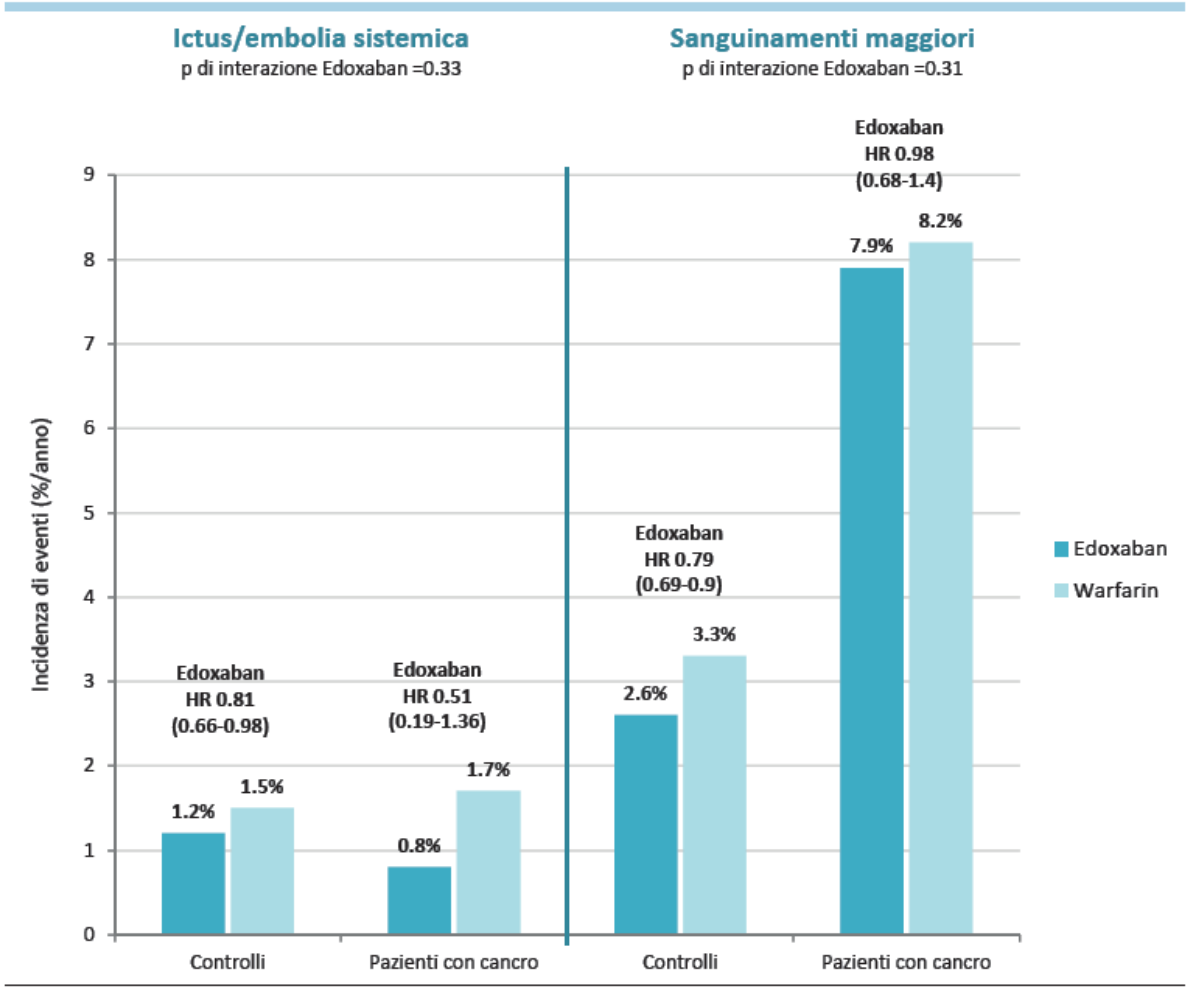


Figura 3. Efficacia e sicurezza di edoxaban vs warfarin in pazienti con fibrillazione atriale e cancro attivo.
HR, hazard ratio.

Edoxaban nel paziente con fibrillazione atriale e cancro

Nicola Maurea[1], Letizia Riva[2]

[1]*S.C. Cardiologia, Istituto Nazionale Tumori, IRCCS Fondazione G. Pascale, Napoli*
[2]*U.O.C. Cardiologia, Ospedale Maggiore, Bologna*

Tabella 2. Farmaci oncologici che interagiscono con il citocromo CYP3A4.

Substrato	Induttore	Inibitore
Abiraterone, acetaminofene, aprepitant, bexarotene, bortezomib, brentuximab, busulfan, ciclofosfamide, ciclosporina, clonazepam, crizotinib, dasatinib, desametasone, docetaxel, doxorubicina, enzalutamide, erlotinib, etoposide, everolimus, fentanil, fosaprepitant, flutamibe, fulvestrant, gefitinib, ifosfamide, imatinib, irinotecan, lapatinib, letrozolo, metadone, nilotinib, ondansetron, ossicodone, paclitaxel, palonosetron, prednisone, sirolimus, sorafenib, sunitinib, tacrolimus, tamoxifene, temsirolimus, vandetanib, vemurafenib, vinblastina, vincristina, vinorelbina	Aprepitant, bexarotene, desametasone, enzalutamide, fosaprepitant, paclitaxel, prednisone, vemurafenib	Abiraterone, acetaminofene, anastrozole, aprepitant, bicalutamide, bortezomib, ciclofosfamide, ciclosporina, crizotinib, dasatinib, docetaxel, doxorubicina, etoposide, fentanil, fosaprepitant, idarubicina, ifosfamide, imatinib, lapatinib, lomustine, metadone, nilotinib, sirolimus, tacrolimus, tamoxifene, temsirolimus, vinblastina, vincristina, vinorelbina

Tabella 3. Farmaci oncologici che interagiscono con la P-glicoproteina.

Substrato	Induttore	Inibitore
Bendamustina, ciclosporina, crizotinib, daunorubicina, desametasone, docetaxel, doxorubicina, etoposide, everolimus, idarubicina, imatinib, irinotecan, lapatinib, lenalidomide, methotrexate, mitomicina C, nilotinib, ondansetrone, paclitaxel, sirolimus, tacrolimus, temsirolimus, vemurafenib, vinblastina, vincristina	Desametasone, doxorubicina, vinblastina	Abiraterone, ciclosporina, crizotinib, desametasone, enzalutamide, imatinib, lapatinib, nilotinib, sunitinib, tacrolimus, tamoxifene, vandetanib

10 La gestione della fibrillazione atriale nel paziente oncologico

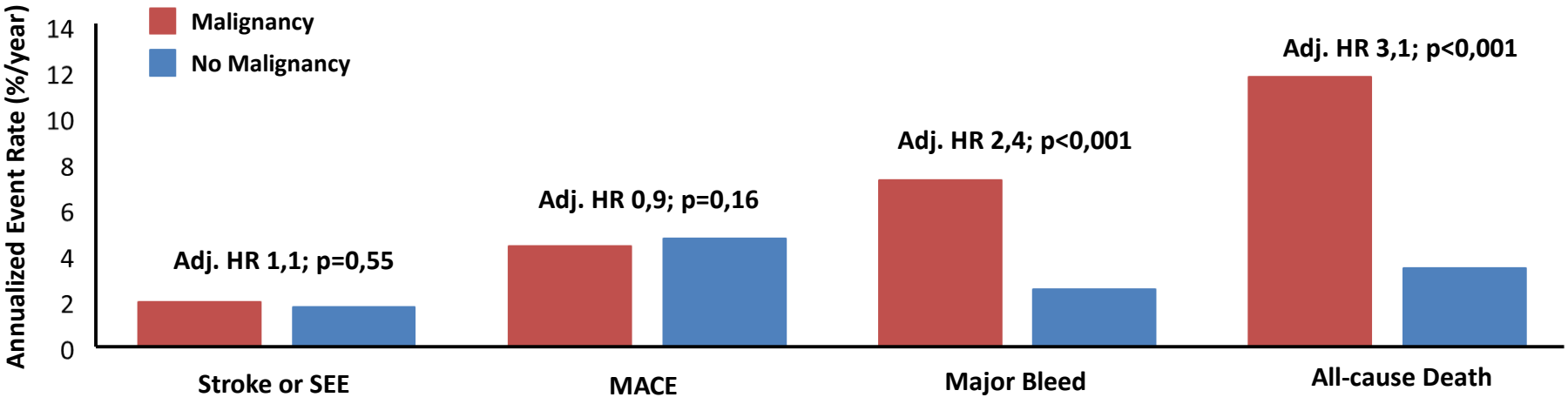
Nicola Maurea[1], Enrico Barbieri[2]

TABELLA 35. Agenti dei farmaci tumorali associati con la fibrillazione atriale

Tipi di aritmia	Farmaci che la causano
Fibrillazione Atriale	Agenti alchilanti (cisplatino, ciclofosfamide, ifosfamide melfalan), antracicline, antimetaboliti (capecitabina, 5-FU, gemcitabina), IL-2, interferoni, rituximab, romidepsin alchilanti, piccola molecola TKI (ponatinib, sorafenib, sunitinib, ibrutinib), topoisomerasi II inibitori (amsacrina, etoposide), taxani, alcaloide della vinca.

Events in cancer patients
ENGAGE AF

	Edoxaban 60/30 mg (N=7012)		Warfarin (N=7012)
First malignancy, n (%/year)	494 (2,68)		485 (2,64)
Hazard ratio vs warfarin (95%CI)		1,01 (0,895-1,150)	
p-value		0,8172	



HR adjusted for age, BMI, sex, race, region, prior VKA experience, CrCl, prior stroke/TIA, hypertension, CAD, PAD, CHF, HLD, T2DM, smoking status and randomised treatment arm, Event rates unadjusted. **MACE, major cardiovascular events (MI, stroke or Cv death)**

Fanola et al. Presented at ACC 2017

10 La gestione della fibrillazione atriale nel paziente oncologico

Nicola Maurea[1], Enrico Barbieri[2]

TABELLA 37. Lista dei farmaci concomitanti forti inibitori e induttori della glicoproteina P e del citocromo P450 3A4

Inibitori			
Antimicotici	**Inibitori delle proteasi**	**Immunosoppressori***	**Altri**
Chetoconazolo	Ritonavir	Ciclosporine	Claritromicina
Itraconazolo	Lopinavir/ritronavir	Tacrolimus	Conivaptan
Voriconazolo	Indinavir/ritronavir		
Posaconazolo			
Fluconazolo			

Induttori	
Anti-epilettici	**Altri**
Fenitoina	Claritromicina
Carbamazepina	Conivaptan

NCCN Guidelines

- Monotherapy or combination therapy
- Select patient based on renal function, inpatient/patient, FDA approval, cost, ease, monitoring, bleeding risk assessment and ability to reverse anticoagulation

Monotherapy options listed

- LMWH (delteparin or enoxaparin)
- Rivaroxaban
- UFH
- Fondaparinux
- Apixaban* (for patients who refuse or have compeling reasons to avoid LMWH

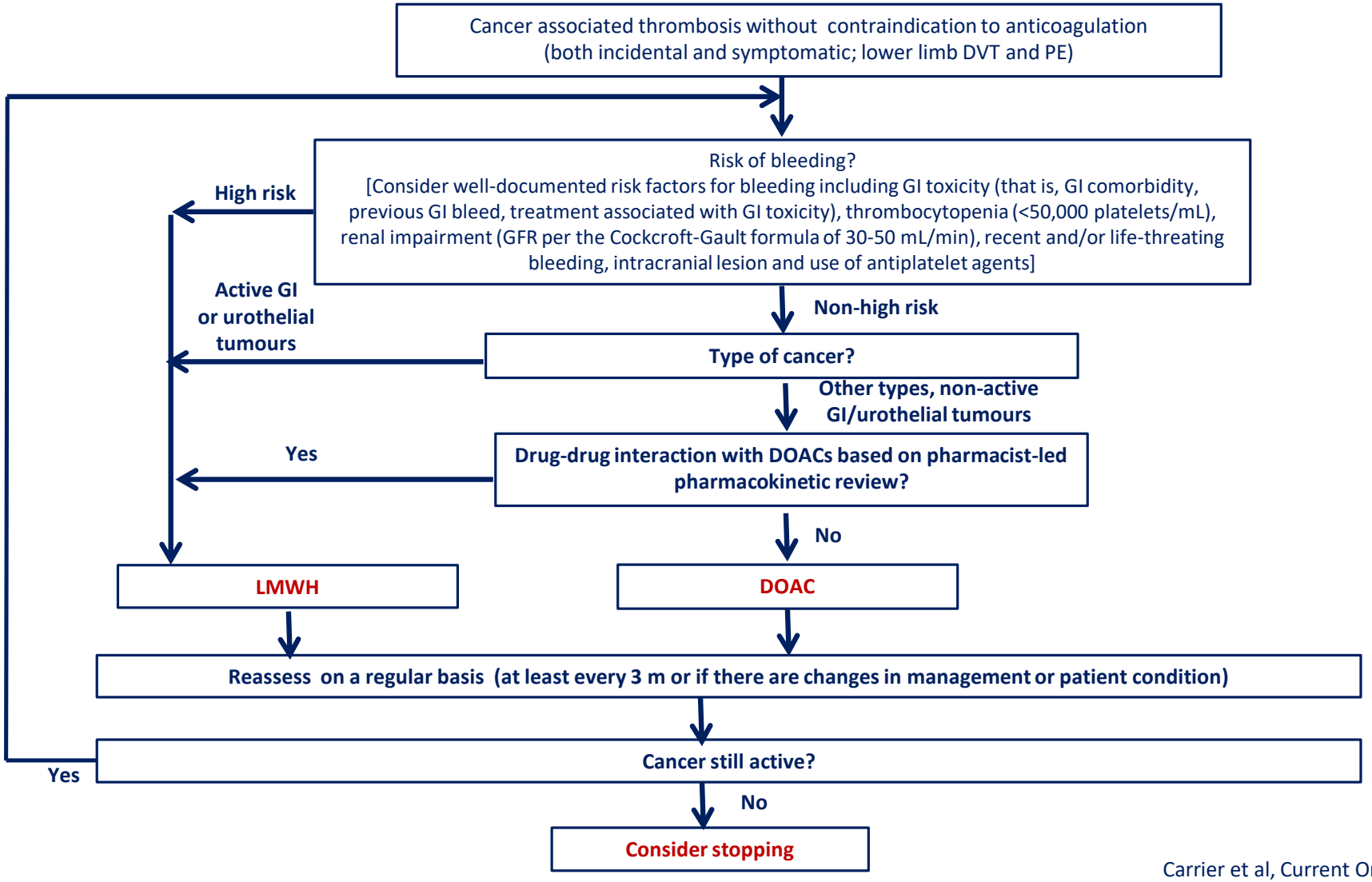
Combination therapy options listed

- LMWH or UFH with edoxaban
- LMWH or UFH with warfarin
- LMWH or UFH with dabigatran*(for patients who refuse or have compelling reasons to avoid LMWH)

*Apixaban EU label – Special warningd and precautions for use: Efficacy and safety of apixaban in the treatment of PE and prevention of recurrent DVT andPE (VTEt in patients with active cancer have not been established[2]; † Edoxaban EU label- Special warnings and precautions for use: Efficacy and safety of edoxaban in the treatment and/or prevention of VTE in patients with active cancer have not been established; Dabigatran EU label – Bleeding LMWH are preferred over NOACs; NOACS are contraindicated in case of malignant neoplasm at high risk of bleeding.

1. NCCN guidelines 2019 (assessed 16 Apr 2019); 2. Elquis (apixaban) SmPC 2017; 3. Lixana (edoxaban) SmPC 2019; 4. Pradaxa (dabigatran) SmPC 2017

Patient risk stratification algorithm for the treatment of cancer-associated thrombosis



Carrier et al, Current Oncology 2018

VTE in Patients with Cancer – Cancer-Associated Thrombosis

Risk factors:[1]

- Patient-related
- Tumour-related
- Treatment-related
- Biomarkers

Prevalence and risk ratios:

- Approximately 20% of all venous thromboembolic events occur in patients with cancer[2]
- VTE is a common cause of death in patients with cancer[3–5]
- VTE recurrence rate is ~2–5-fold higher in patients with VTE and cancer compared with those with VTE and no cancer[2,6,7]
- Common cancers have the greatest burden[2]

1. Ay C *et al*, *Thromb Haemost* 2017;117:219–230; 2. Cohen AT *et al*, *Thromb Haemost* 2017;117:57–65; 3. Horsted F *et al*, *PLoS Med* 2012;9:e1001275;
4. Khorana AA *et al*, *J Thromb Haemost* 2007;5:632–634; 5. Chew HK *et al*, *Arch Intern Med* 2006;166:458–464; 6. Sallah S *et al*, *Thromb Haemost* 2002;87:575–579;
7. Stein PD *et al*, *Am J Med* 2006;119:60–68

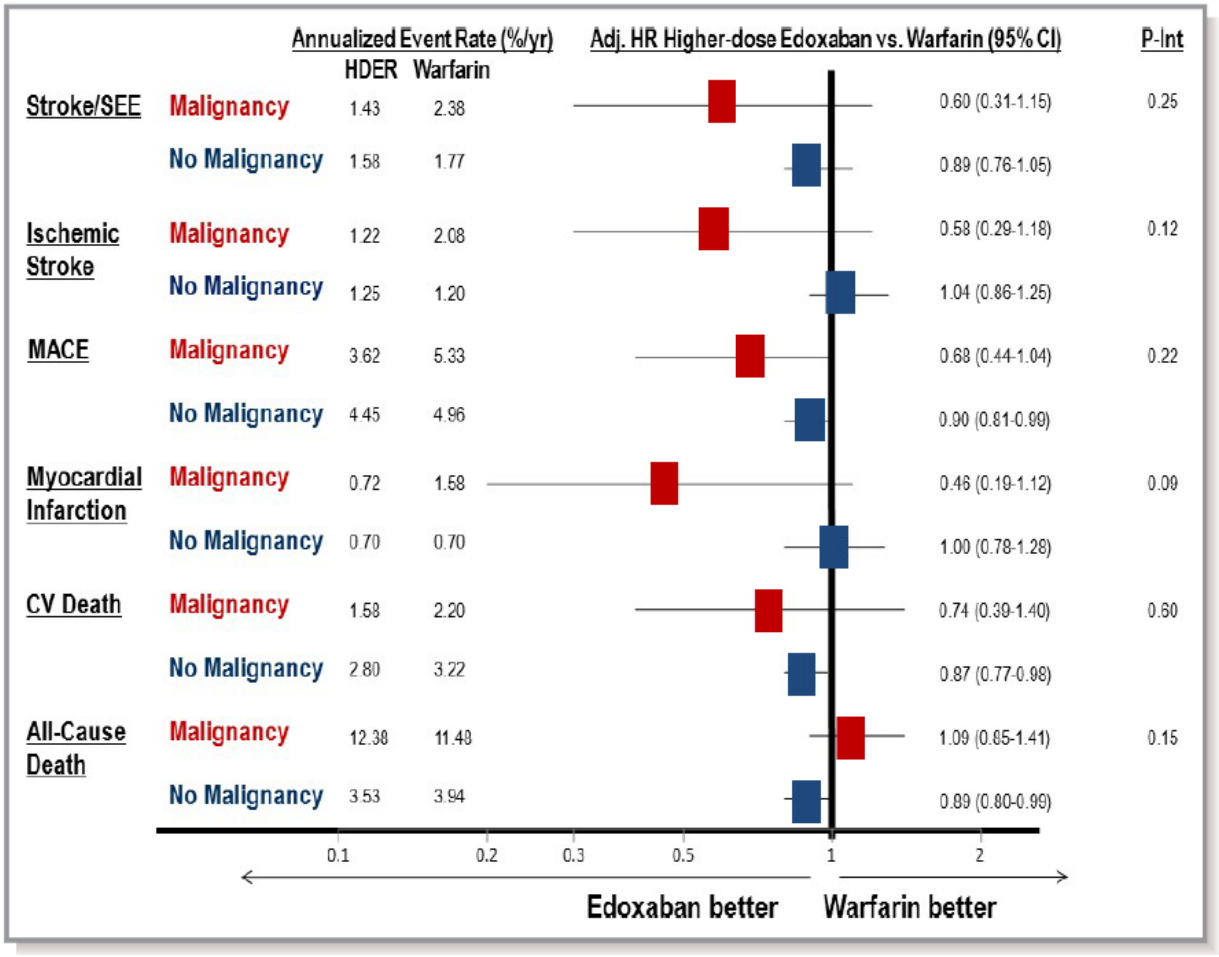
Oncology drugs with CYP3A4/P-glycoprotein interactions

	CYP3A4 interactions[a]			P-glycoprotein interactions[b,c]		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Miscellaneous						
Lenalidomide				●		
Bortezomib	+++		+			
Bexarotene	+	++				
Supportive care						
Prochlorperazine						
Ondansetron	+++			●		
Palonosetron	+					
Metoclopramide						
Aprepitant	+++	++	++			
Fosaprepitant	+++	++	++			
Oxycodone	+++					
Hydromorphone						
Morphine						
Fentanyl	+++		+			
Methadone	+++		+			
Acetaminophen	+		+			
Lorazepam						
Clonazepam	+++					
Filgrastim						
Epoetin alfa						
Darbepoetin alfa						

[a] +++, strong interaction; ++, moderate interaction; +, weak interaction.
[b] Data for strength of P-glycoprotein interactions are limited. ●, indicates that an interaction has been documented.
[c] Bold indicates the drug is either a strong or a moderate inhibitor of CYP3A4 (with or without P-glycoprotein interaction). These drugs have increased risk for interactions with the new oral anticoagulants that are metabolized by CYP3A4.

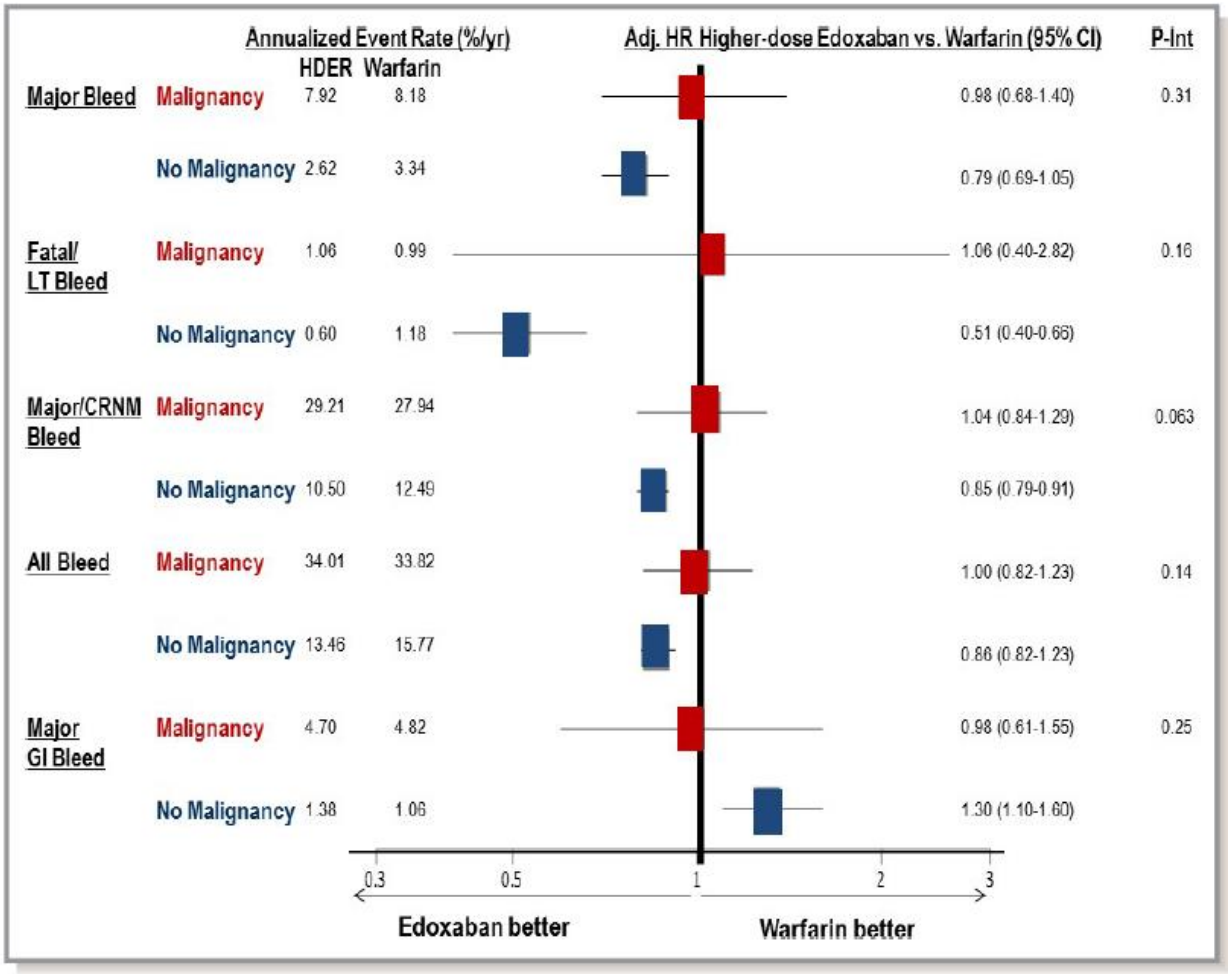
Short, The Oncologist 2014

Efficacy end points by malignancy status in the higher-dose edoxaban regimen vs warfarin groups



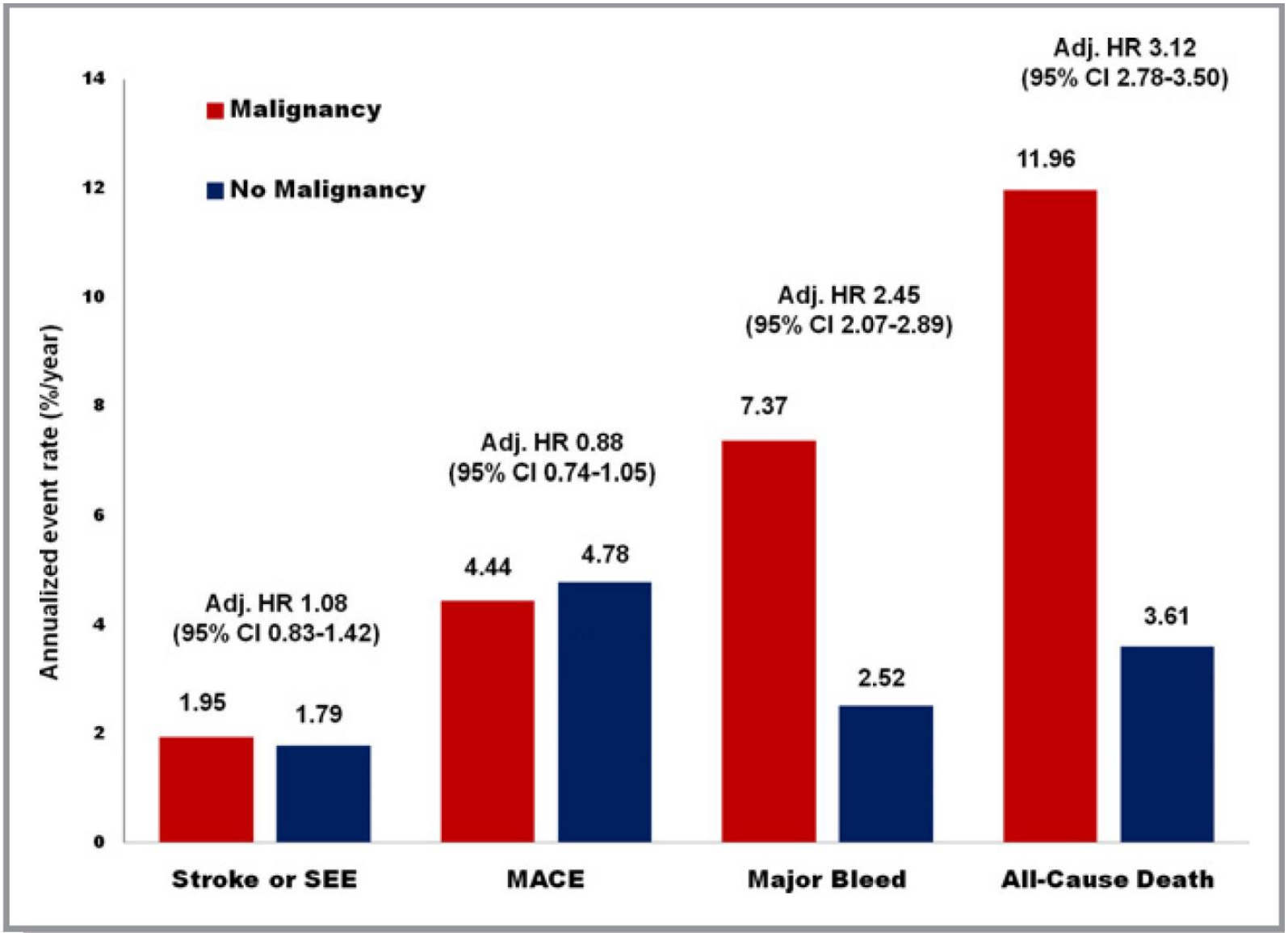
Fanola et al, J Am Heart Assoc. 2018

Safety end points by malignancy status in the higher-dose edoxaban regimen (HDER) vs warfarin groups

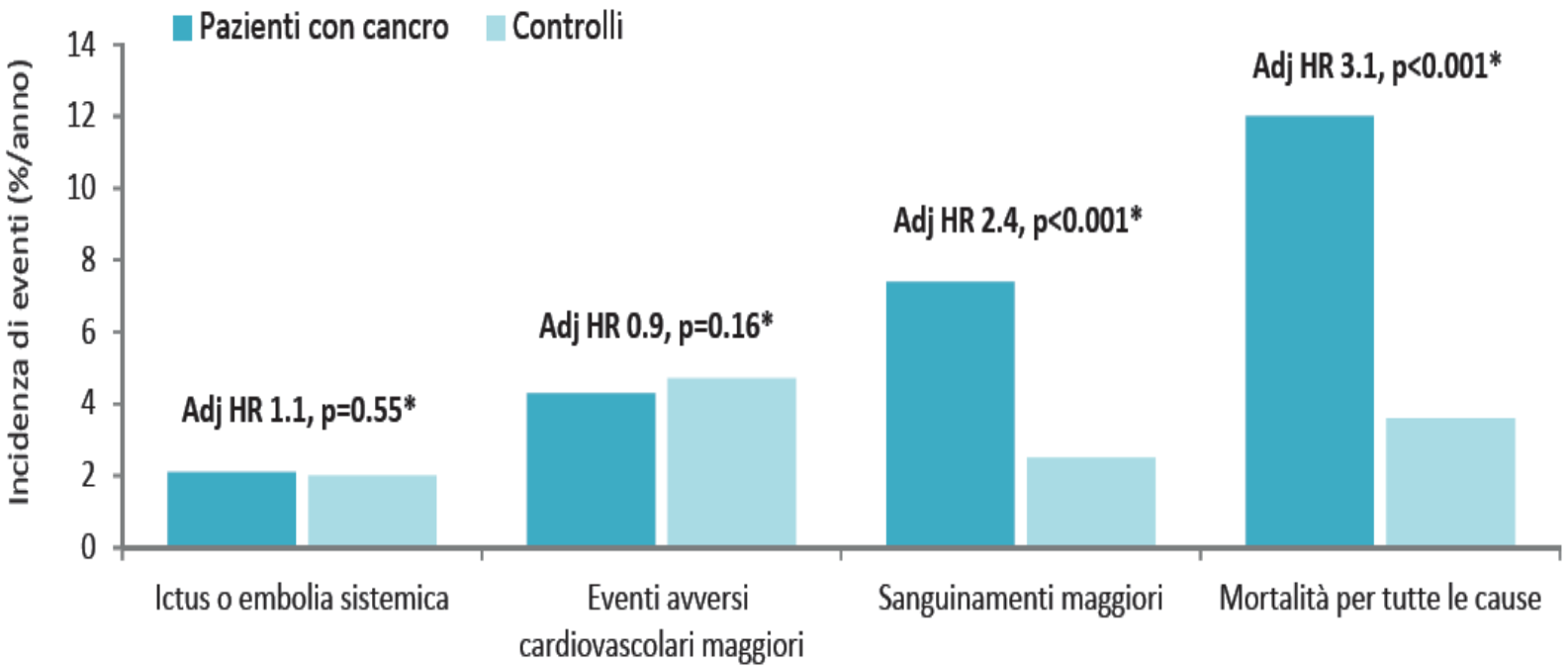


Fanola et al, J Am Heart Assoc. 2018

Incidenza di ictus ed embolia sistemica, eventi avversi cardiovascolari maggiori (infarto miocardico, ictus e morte cardiovascolare), sanguinamenti maggiori e morte per tutte le cause nei pazienti con fibrillazione atriale e cancro attivo



Incidenza di ictus ed embolia sistemica, eventi avversi cardiovascolari maggiori (infarto miocardico, ictus e morte cardiovascolare), sanguinamenti maggiori e morte per tutte le cause nei pazienti con fibrillazione atriale e cancro attivo



Maurea N, Riva L. G Ital Cardiol (Rome). 2018 Sep;19(9):13-19

Rates of major bleeding complications in patients with high-risk features in the HOKUSAI VTE Cancer trail

Risk factor	Major bleeding (%)		*p* Value
	Edoxaban	Dalteparin	
Urothelial cancer	13.2	0	NA
Creatinine clearance 30–50 mL/min	10.5	2.9	NA
Platelets 50–100×10^3/mL	12.5	4.3	NA
Use of antiplatelet agents	11.5	3.2	NA
3 Risk factors[a]	13.5	4.1	<0.05
4 Or more risk factors[a]	10.5	4.2	NA

[a] Defined as surgery within the preceding 2 weeks, use of antiplatelet agents, primary or metastatic brain tumour, regionally advanced or metastatic cancer, gastrointestinal or urothelial cancer diagnosed within the preceding 6 months, or treatment with bevacizumab within the preceding 6 weeks.

NA = not available.

Carrier et al, Curr Oncol 2018