TURIN,
October
25th-27th
2018
Starhotels
Majestic

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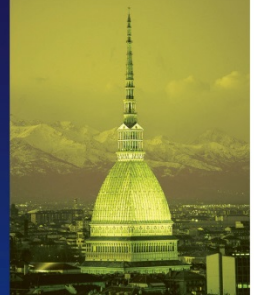
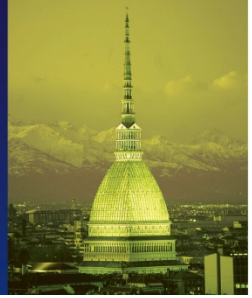


UNIVERSITÁ DEGLI STUDI DI TORINO

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

Thromboembolic complications and anticoagulants: Traditional therapies and new proposals

Eloise Beggiato
Ematologia U
Città della Salute e della Scienza di Torino



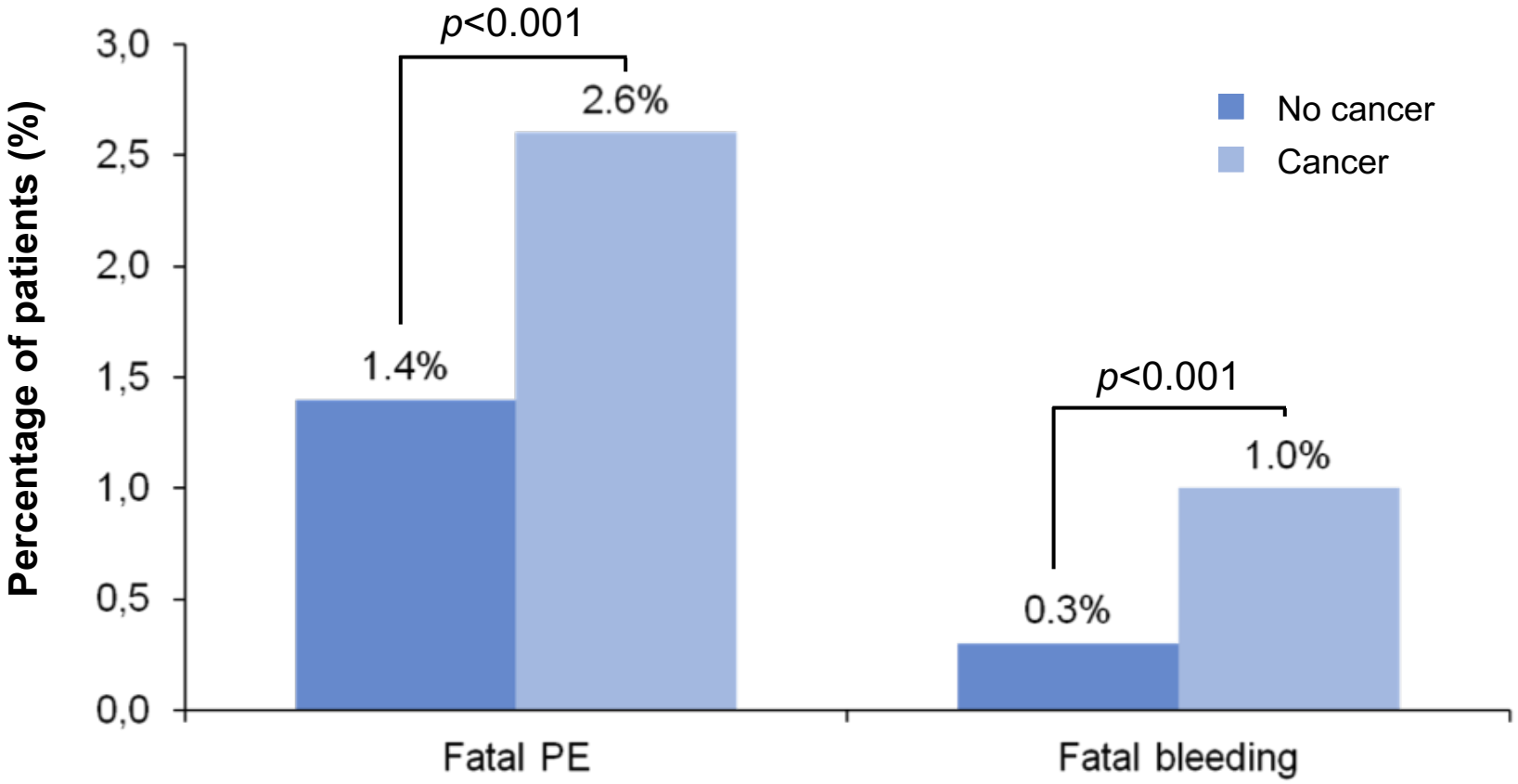
Cancer-associated Thrombosis (CAT)

- Epidemiology
- Risk factors
- Mechanism
- Treatment of VTE and guidelines

- Risk for VTE increased up to 4-7 fold in cancer[1]
  - 10-20% patients with cancer develop symptomatic VTE
  - 20% of all patients diagnosed with VTE have active cancer
  - Unusual site VTE
- "Idiopathic" VTE
  - 2-4 fold increased risk of cancer diagnosis within next 12 months
- Cancer patients with VTE have shorter life expectancy
  - VTE is second leading cause of death after cancer itself
  - More likely advanced/disseminated malignancy at diagnosis than in patients without VTE
  - 3-fold lower survival than in cancer patients without VTE

[1] Barsam SJ, Patel R, Arya R. B J Haem 2013;161:764-777; [2]Laporte S et al Circulation 2008;117:1711-1716

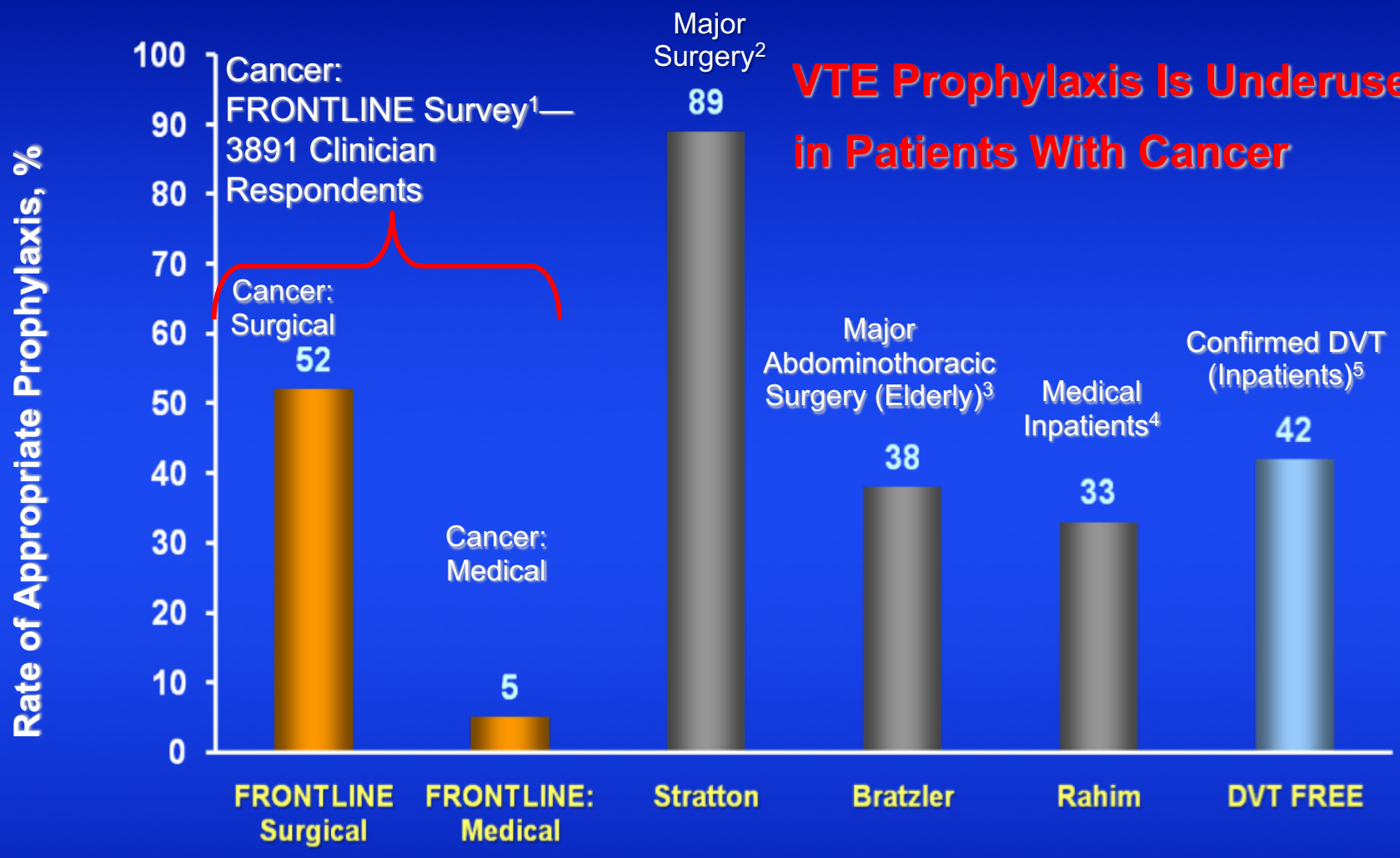
Higher rates of fatal PE and fatal bleeding in patients with cancer: data from the RIETE registry



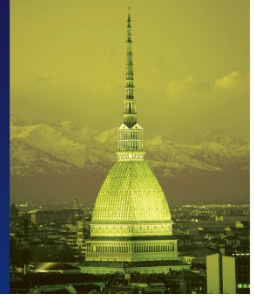
Risk of fatal PE or fatal bleeding in the RIETE registry[1]

1. Monreal M *et al*. *J Thromb Haemost* 2006;4:1950–1956

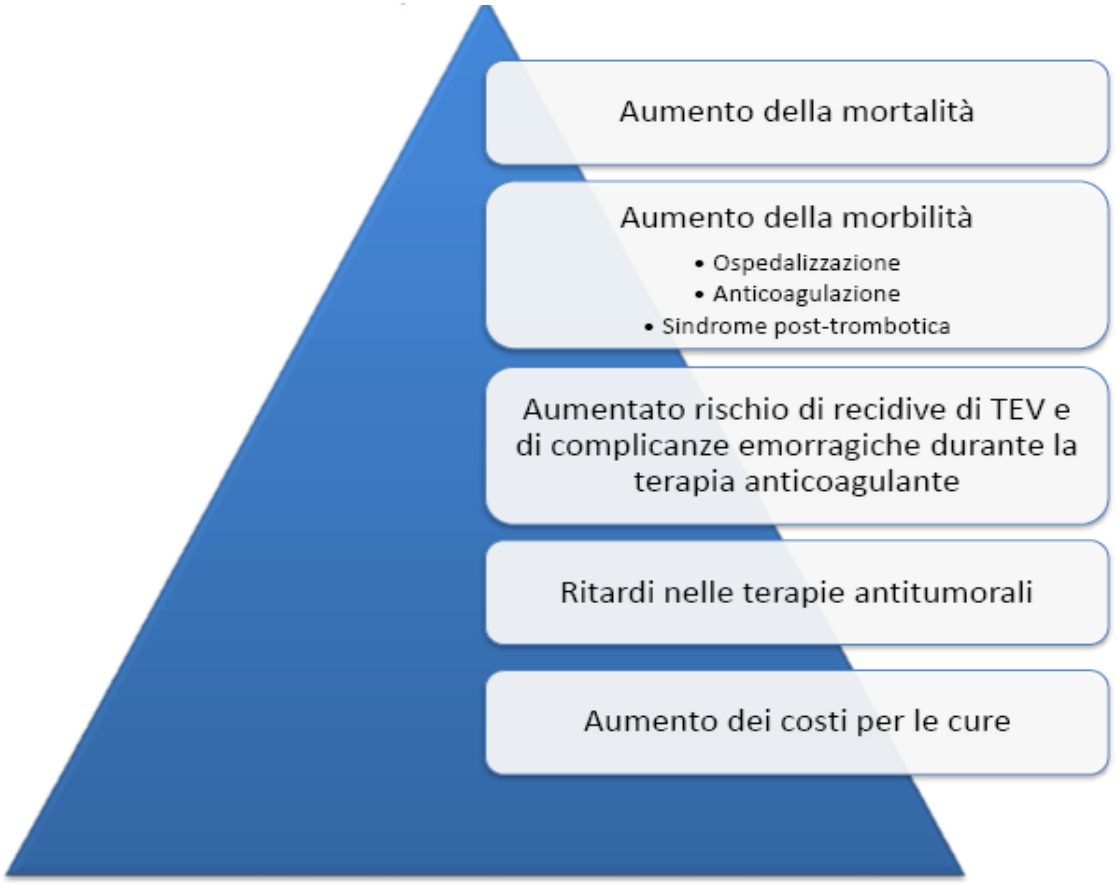
VTE Prophylaxis Is Underused in Patients With Cancer



1. Kakkar AK et al. *Oncologist*. 2003;8:381-388
2. Stratton MA et al. *Arch Intern Med*. 2000;160:334-340
3. Bratzler DW et al. *Arch Intern Med*. 1998;158:1909-1912
4. Rahim SA et al. *Thromb Res*. 2003;111:215-219
5. Goldhaber SZ et al. *Am J Cardiol*. 2004;93:259-262



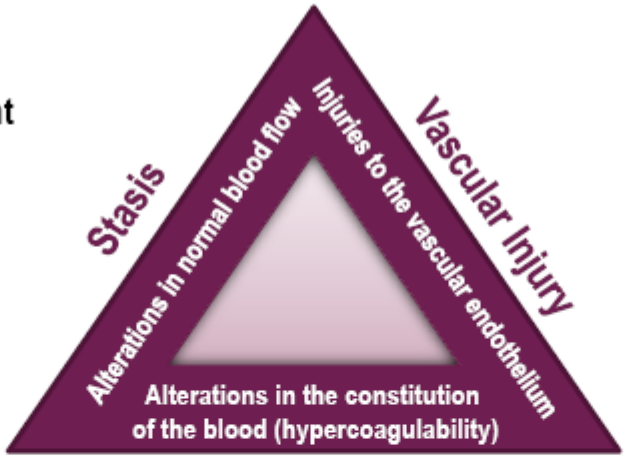
Conseguenze del TEV nel paziente oncologico



Agnelli G and Verso M, J Thromb Haemost 2011; Prandoni et al, Blood 2002

VIRCHOW'S TRIAD IN CANCER PATIENTS

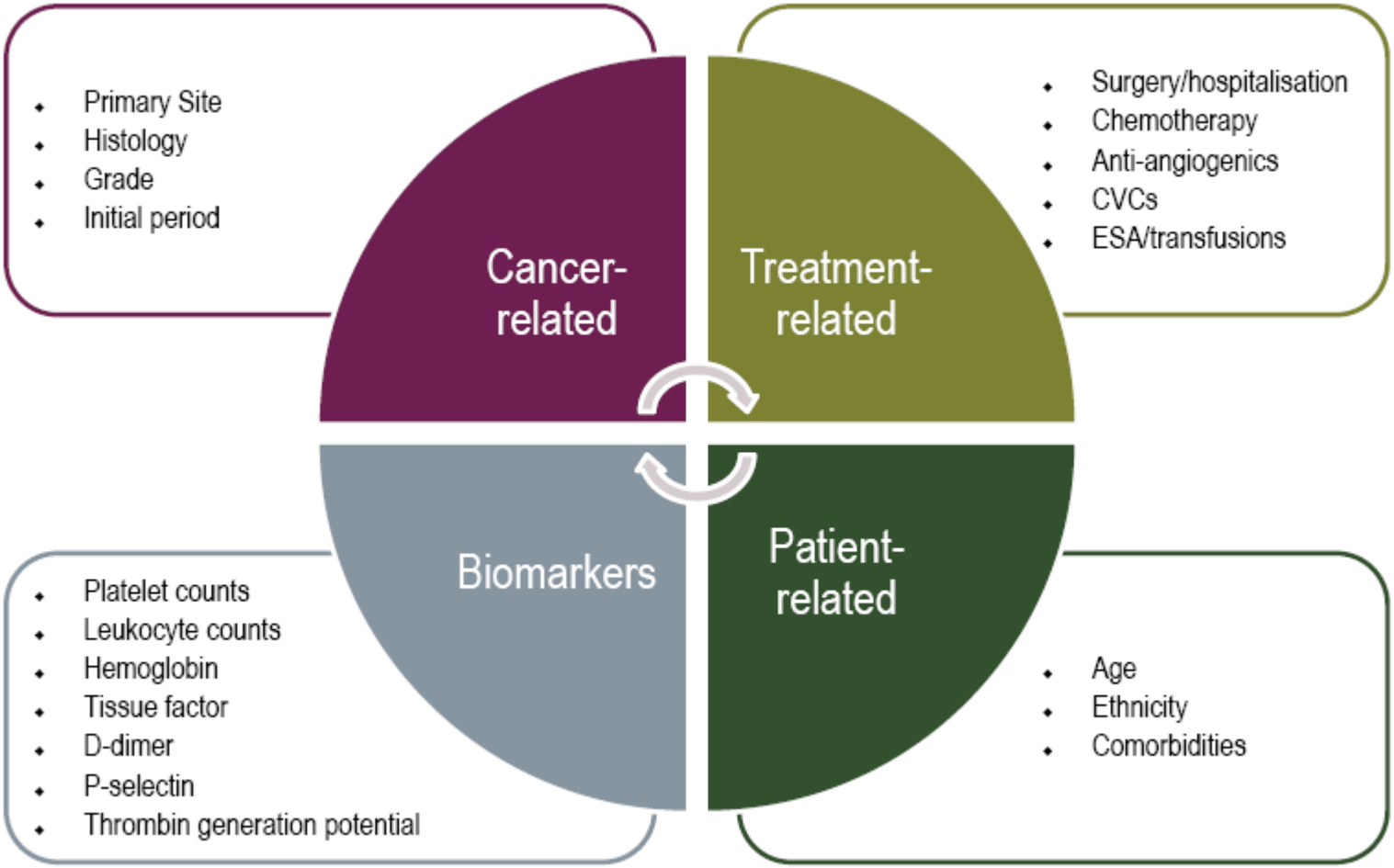
- **Prolonged bed rest – patient immobility**
- **Surgical procedures**
- **Extrinsic compression of blood vessels by tumour**
- Increased blood viscosity



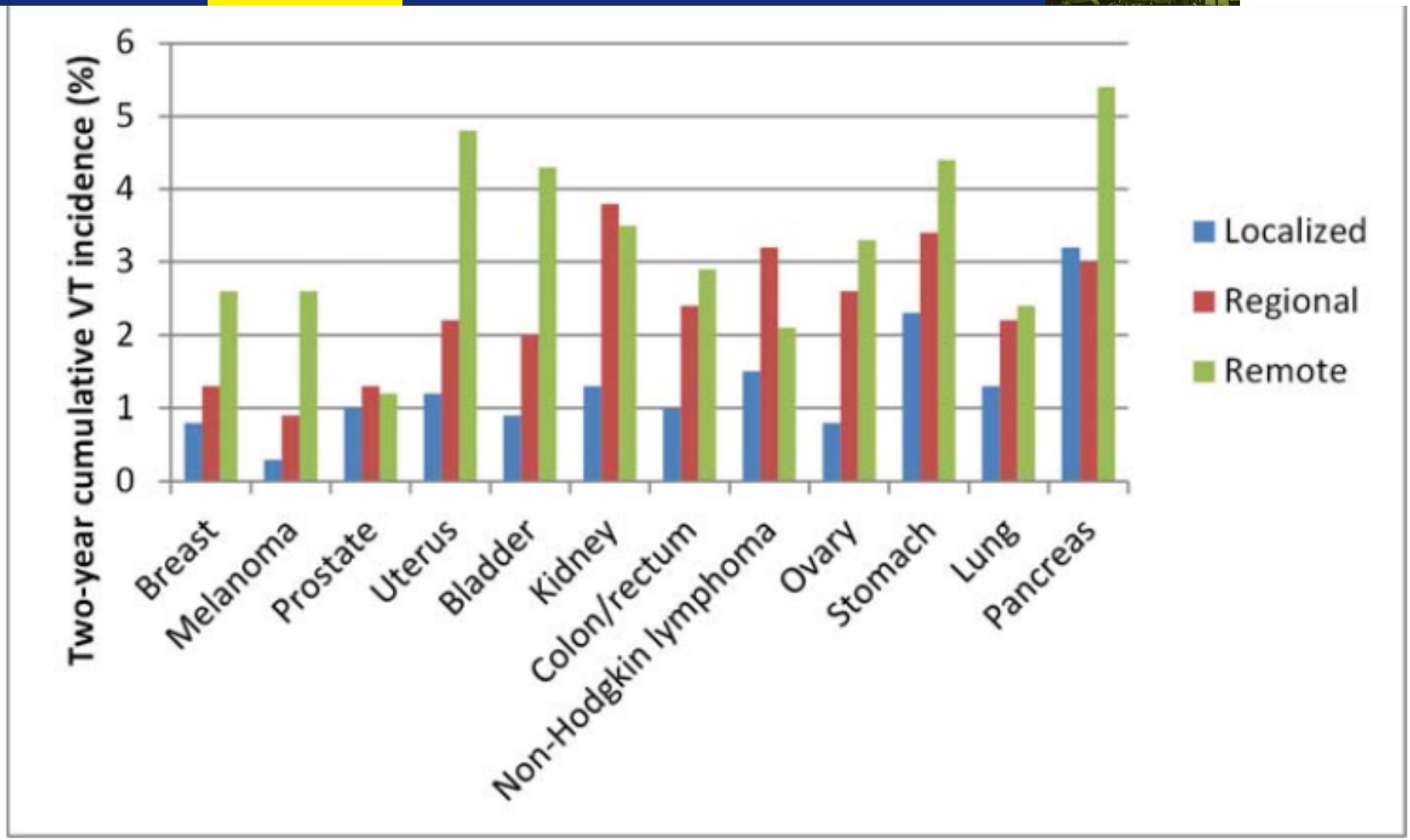
- **Direct invasion by tumour**
- **Prolonged use of CVC**
- **Endothelial damage by chemotherapy**
- Effect of tumour cytokines on vascular endothelium

Changed blood composition

- More procoagulation factors due to **hypoxia and/or inflammation**
- **Microparticles with Tissue Factor**
- Pro angiogenic factors
- Increase in overall platelet activity
- Decrease in anticoagulant activities
- Decrease in fibronolytic activity

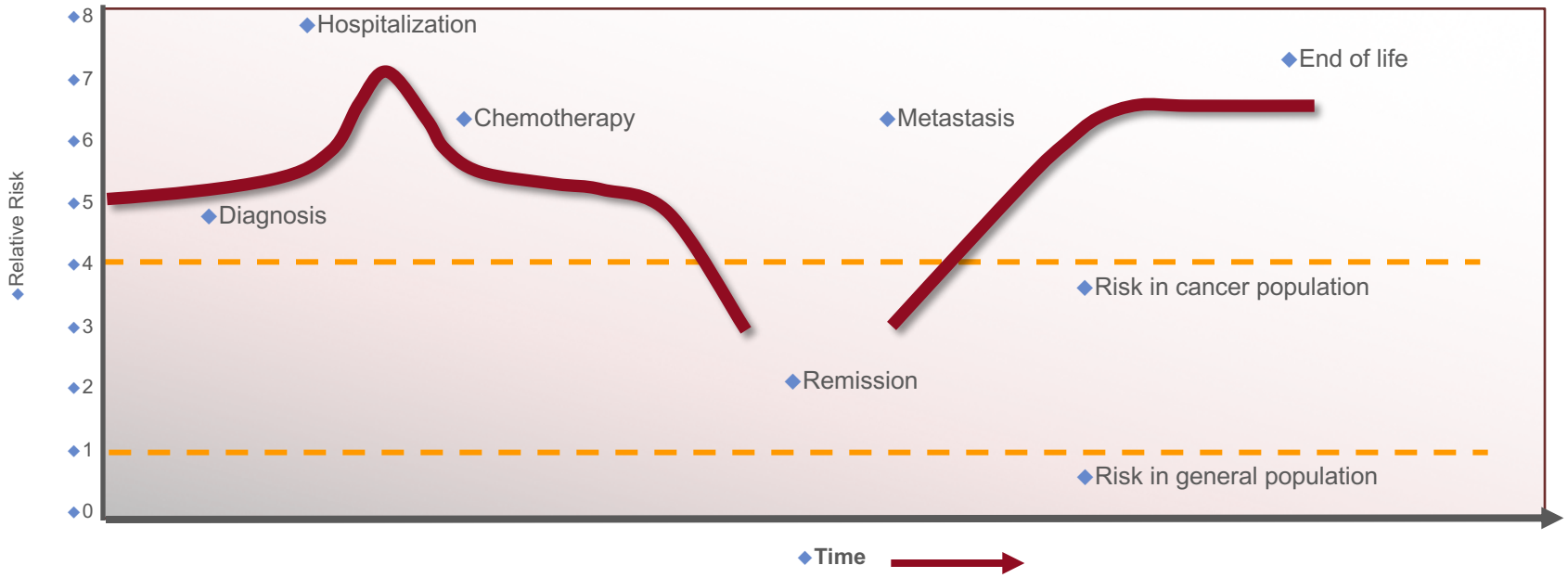


Khorana presentation in HeSMO Conference 2017, Athens



Tipo e stadio di malattia come fattori di rischio

Timp et al, Blood 2013



TVE risk and cancer natural history

Rao MV, et al. In: Khorana and Francis, eds. Cancer-Associated Thrombosis; 2007

THERAPY AS RISK FACTOR FOR VTE

Endothelial Damage

Mechanical injury to endothelium
5-FU, contrast media

Apoptosis of endothelial cells
VEGF antagonists

Induction of hypersensitivity reaction
Drug-eluting stents

Proteloysis of endothelial cell contact
Tissue plasminogen activator

Expression of pro-inflammatory mediators
Cis-platinum

Expression of tissue factor
Rapamycin

Decreased expression of anticoagulation mediators
COX-2 inhibitors

Expression of pro-coagulation mediators
Thalidomide, sildenafil

Platelets

Increased platelet adhesion
Tissue plasminogen activator

Aggregation of platelets
Erythropoietin, nanoparticles

Increased platelet reactivity
Ciclosporin

Autoantibodies against platelet factors
Heparin

Red Blood Cells

Phosphatidylserine exposure
Phenylhydrazine

White Blood Cells

Increased adhesion molecules
All-trans retinoic acid, interferon-α

Coagulation System

Increased coagulation factors
Hormone replacement therapy

Antiphospholipid antibodies
IVIG

Decreased anticoagulation factors
L-asparaginase, sildenafil

Decreased fibrinolysis
Corticosteroids, erythropoietin

Blood Flow

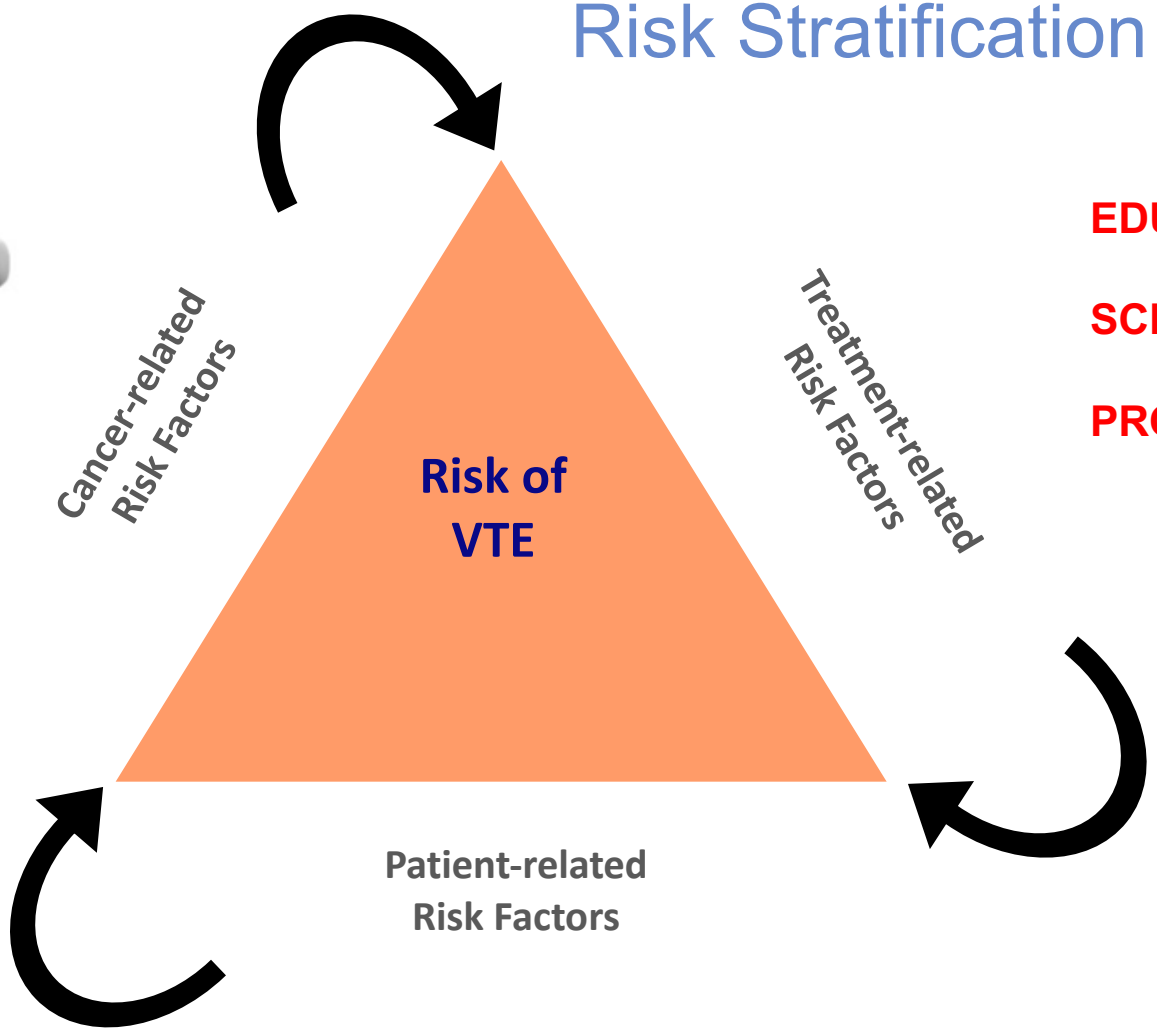
Vasoconstriction
SSRIs, ephedra

Blood stasis
IVIG, erythropoietin

Fig. 2 A list of the different mechanisms through which drugs can cause thrombosis. Examples of drugs for each mechanism are listed in italics. *5-FU* 5-fluorouracil, *COX-2* cyclo-oxygenase-2, *IVIG* intravenous immunoglobulin, *SSRI* selective serotonin reuptake inhibitor, *VEGF* vascular endothelial growth factor

Ramot et al, Drug Saf 2013

Risk Stratification



EDUCATION

SCREENING

PROPHYLAXIS

Modello di Rischio Clinico per il TEV associato a chemioterapia basato su fattori di rischio pretrattamento

Lo score di Khorana

FATTORI DI RISCHIO	SCORE
1. Sede del cancro	
a) Rischio Molto Alto (stomaco, pancreas)	2
b) Rischio Alto (polmone, linfoma, ginecologico, vescica, testicolo)	1
2. Piastrine $\geq 50000/mm^3$	1
3. Emoglobina < 10 g/dL o utilizzo di Fattori di Crescita Eritrocitari	1
4. Leucociti > 11000 $/mm^3$	1
5. BMI $\geq 35\ kg/m^2$	1

Low risk	**score 0**	**VTE Risk 0,8-0,3%**
Intermediate risk	**score 1-2**	**VTE Risk 1,8-2%**
High risk	**score $\geq$ 3**	**VTE Risk 7,1-6,7%**

Khorana et al, Blood. 2008

VOLUME 29 · NUMBER 17 · JUNE 10 2011
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Risk of Recurrent Venous Thromboembolism and Mortality in Patients With Cancer Incidentally Diagnosed With Pulmonary Embolism: A Comparison With Symptomatic Patients

Paul L. den Exter, José Hooijer, Olaf M. Dekkers, and Menno V. Huisman

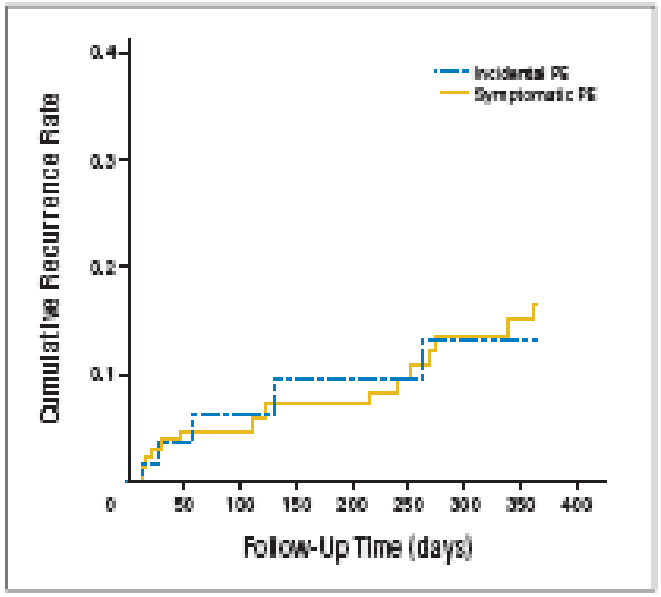


Fig 1. Cumulative risk of recurrent venous thromboembolism for patients with cancer with incidental versus symptomatic pulmonary embolism (PE; $P = .771$).

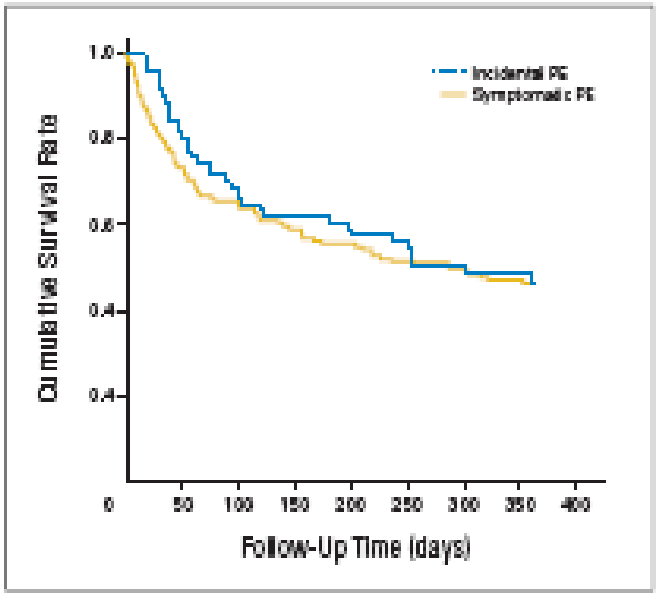
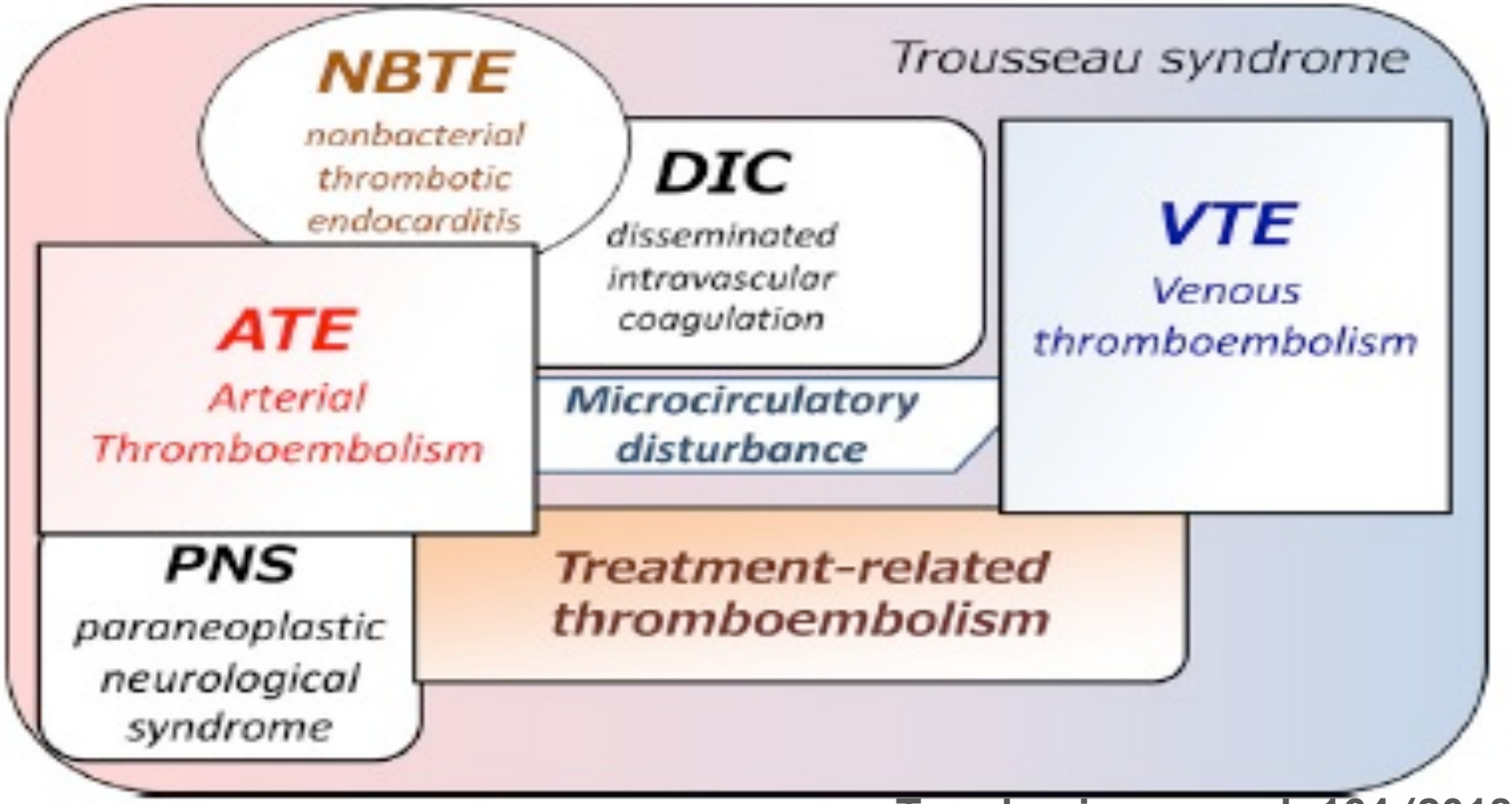


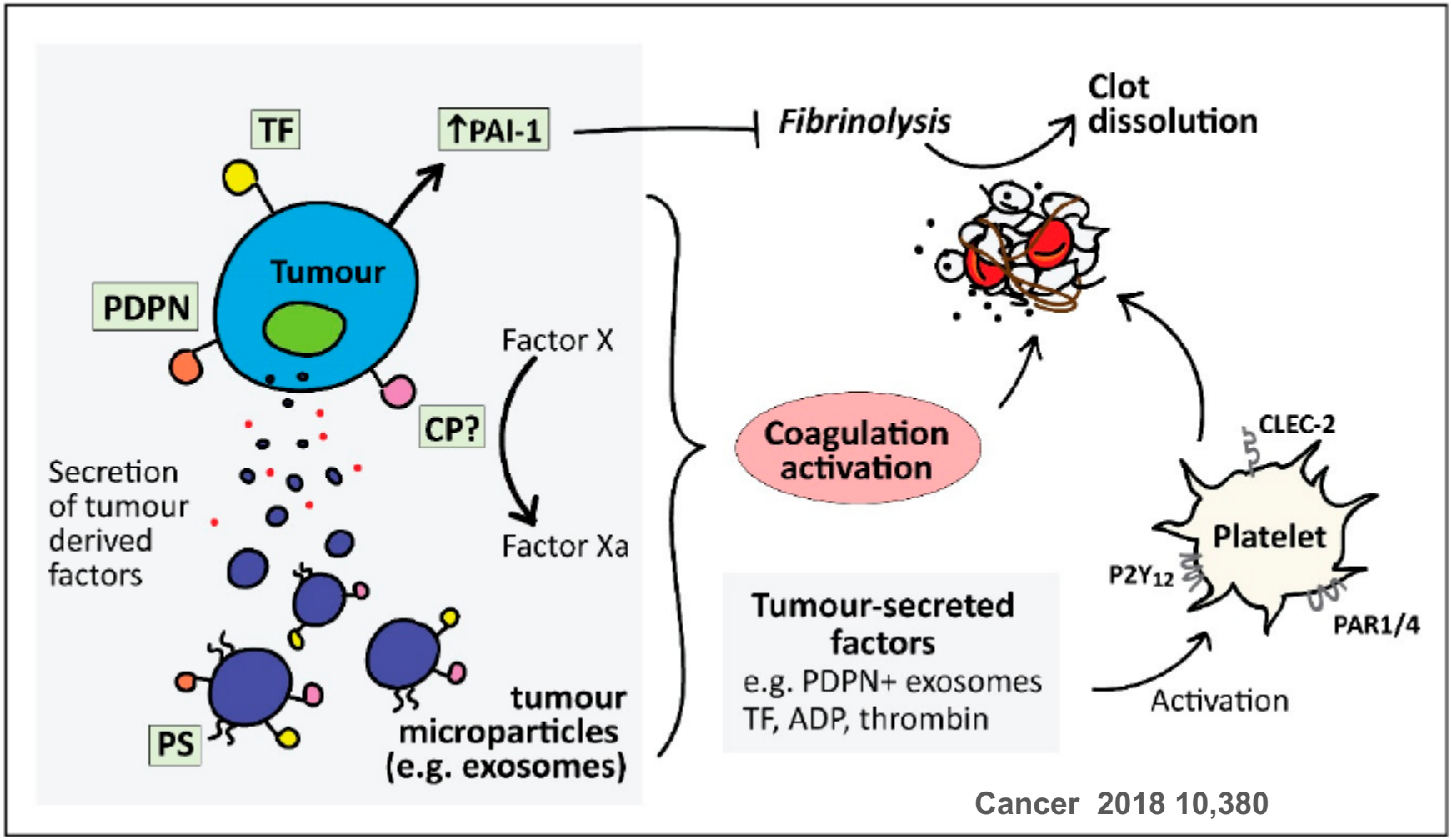
Fig 2. Kaplan-Meier cumulative survival curve until overall death for patients with cancer with incidental versus symptomatic pulmonary embolism (PE; $P = .701$).

CAT AND ITS MECHANISM

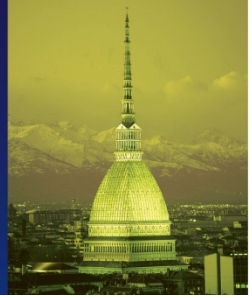


Trombosis research 164 (2018

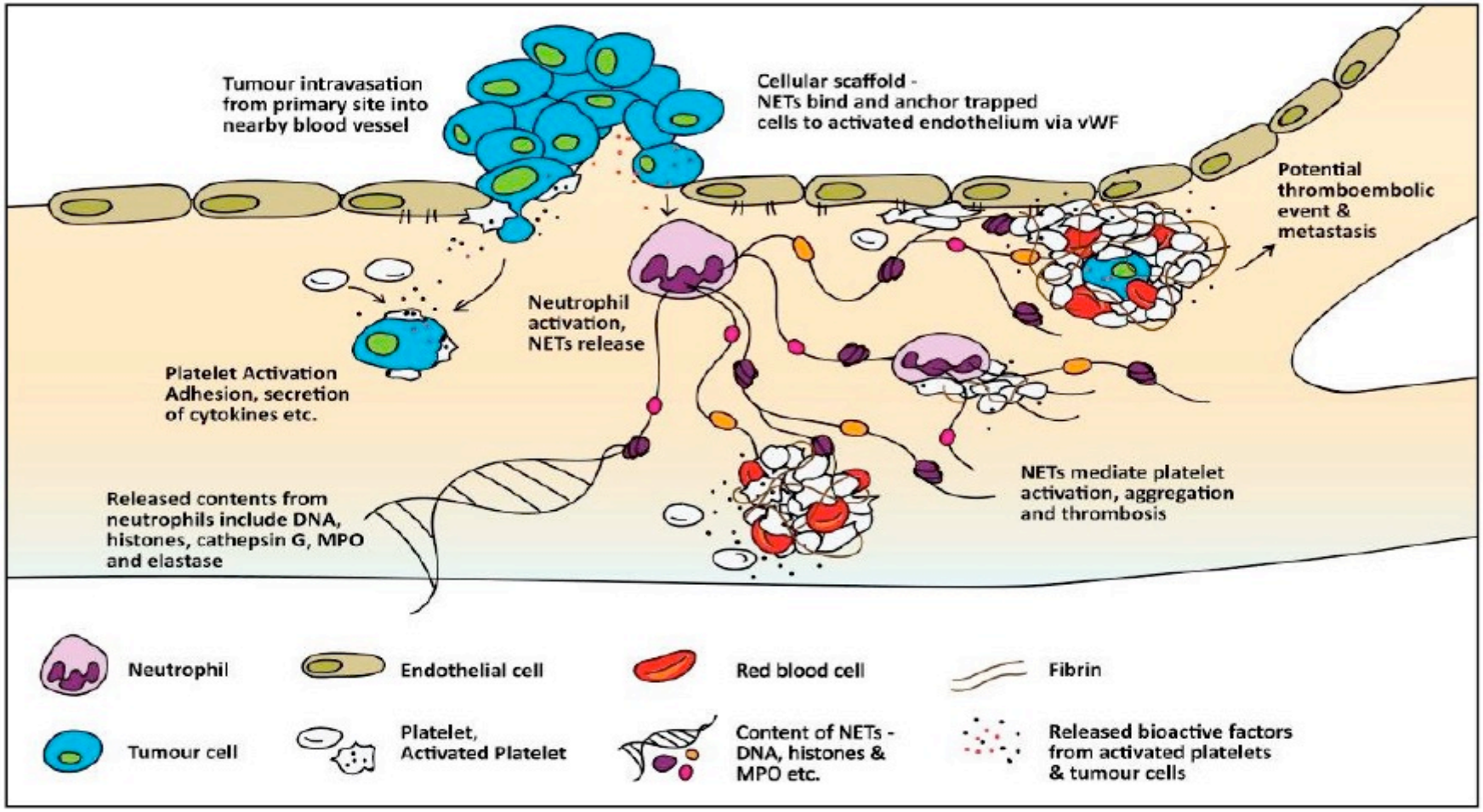
CAT AND ITS MECHANISM (Direct mechanism)



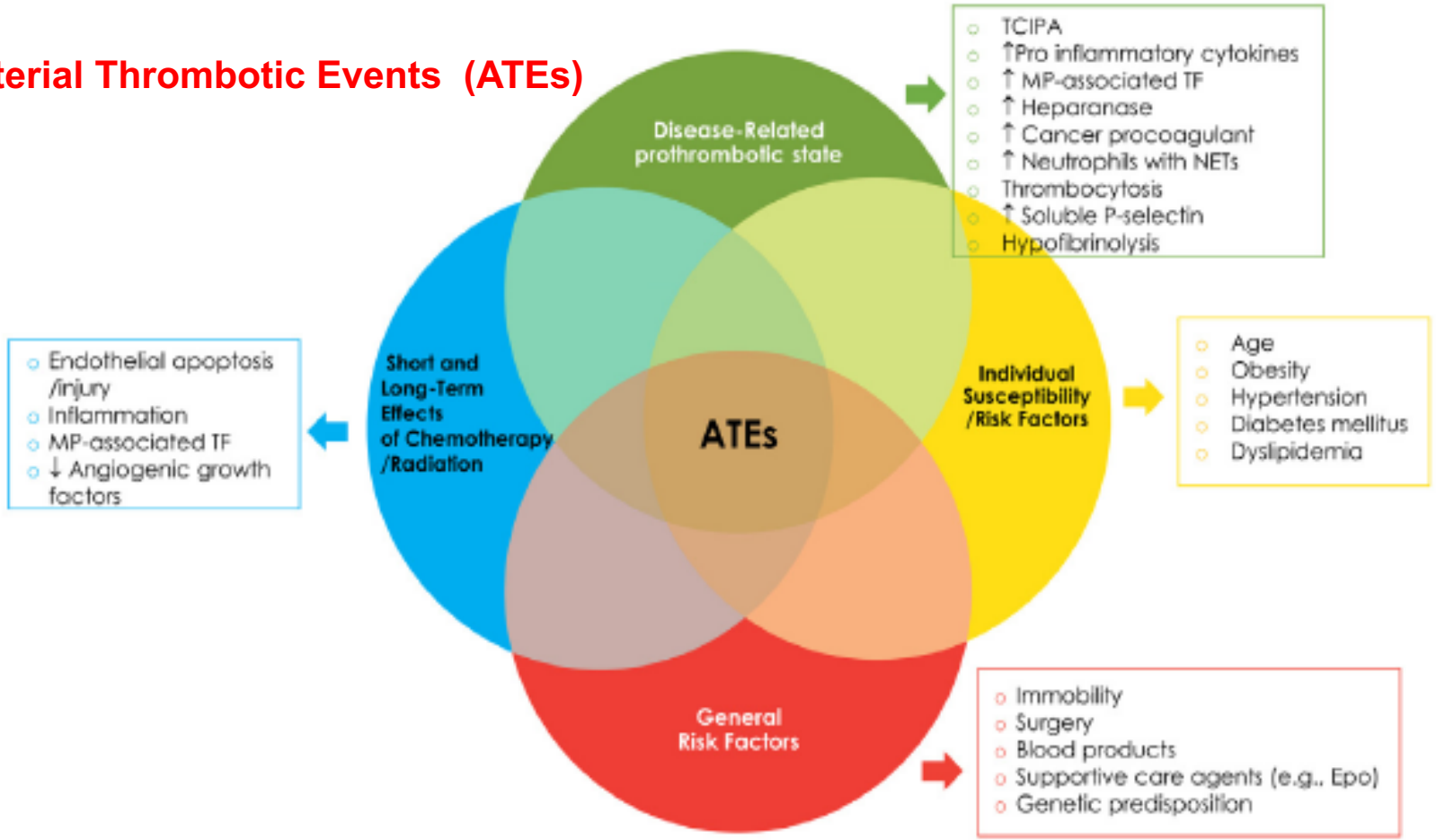
Cancer 2018 10,380



CAT AND ITS MECHANISM (Indirect mechanism)



Arterial Thrombotic Events (ATEs)



Trombosis research 164 (2018

Optimising treatment of VTE in the cancer patients

Treatment

- ↓ Recurrent VTE
- ↓ Bleeding
- ↑ Quality of life

OPEN QUESTIONS

- CHOICE OF LONG TERM AND EXTENDED ANTICOAGULANT

- DURATION OF ANTICOAGULANT THERAPY

- MANAGEMENT OF RECURRENT VTE ON ANTICOAGULANT THERAPY

TEV

Fase Iperacuta e acuta

Prevenzione Secondaria

PERCHE' NO AL TRATTAMENTO DELLA TVP CON FARMACI ANTI-VK?

LIMITI TERAPIA ANTI-VK (WARFARINA)

Factors That May In
Warfarin in the Onc

Patient characteristics
Elderly age
Debilitation
Low body weight
Patient adherence co
Infection
Nausea, vomiting
Steatorrhea
Dietary status
Inconsistency of oral i
Low albumin levels
Malabsorption
Undernourishment
Vitamin-K deficiency

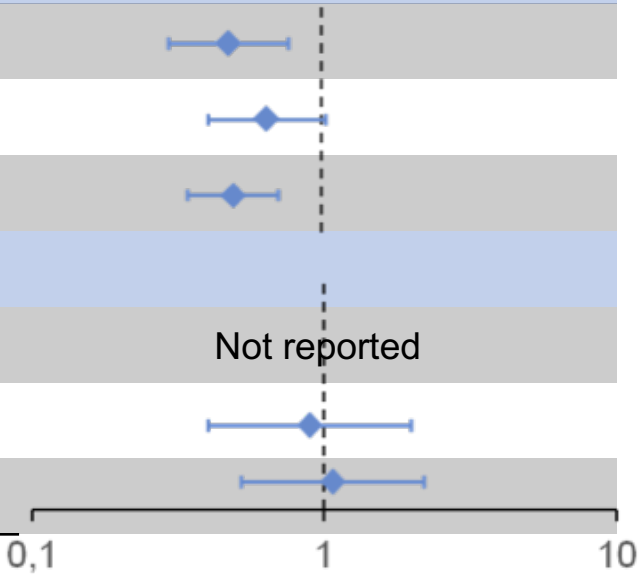
Potential Warfarin/Anticancer Drug Interactions

Increase INR
Adrenal steroid inhibitor
Aminoglutethimide[20]
Alkylating agent
Cyclophosphamide[a,18]
Antimetabolite
Hormone/hormone modifier
Androgen[9] (17-alkylated androgen)
Antiandrogen
Bicalutamide[27]
Flutamide[28]
Nilutamide[29]
Antiestrogen
Tamoxifen[30]
Toremifene[31]
Progestin[32]

Difficoltà a garantire il giusto range terapeutico e controllare il rischio di sanguinamento

Pangilinan et al, 2007

	LMWH monotherapy		LMWH overlapping with VKA		HR (95% CI)
	n/N	(%)	n/N	(%)	
Recurrent VTE					
CLOT study*[1]	27/336	8.0	53/336	15.8	
CATCH study#[2]	31/449	6.9	45/451	10.0	
Meta-analysis‡[3]	**42/591**	**7.1**	**82/571**	**14.4**	
Major bleeding					
CLOT study*[1]	19/338	5.6	12/335	3.6	Not reported
CATCH study#[2]	12/449	2.9	11/451	2.4	
Meta-analysis§[3]	**37/556**	**6.7**	**32/536**	**6.0**	



*Dalteparin versus VKA; in the VKA arm the estimated time in therapeutic range was 46% (30% below and 24% above); #tinzaparin versus warfarin; in the warfarin arm the time in therapeutic range was 47% (26% below and 27% above); ‡meta-analysis included four other small studies in addition to the CLOT study; §meta-analysis included three other small studies in addition to the CLOT study

1. Lee AYY *et al*, *New Engl J Med* 2003;349:146–153; 2. Lee AYY *et al*, *Blood* 2014:124:Abstract LBA-2; 3. Akl EA *et al*, *Cochrane Database Rev* 2014;7:CD006650

Cochrane metanalysis

Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer (Review)

For the long-term treatment of VTE in patients with cancer, ***LMWH*** *compared with VKA* ***provided no statistically significant survival benefit*** *but a* ***statistically and patient important reduction in VTE.***

The findings did not exclude a beneficial or harmful effect of LMWH compared with VKA in terms of bleeding outcomes or thrombocytopenia.

E.A. Akl et al. Cochrane Database of Systematic Reviews 2014

OPEN QUESTIONS

- CHOICE OF LONG TERM AND EXTENDED ANTICOAGULANT

- DURATION OF ANTICOAGULANT THERAPY

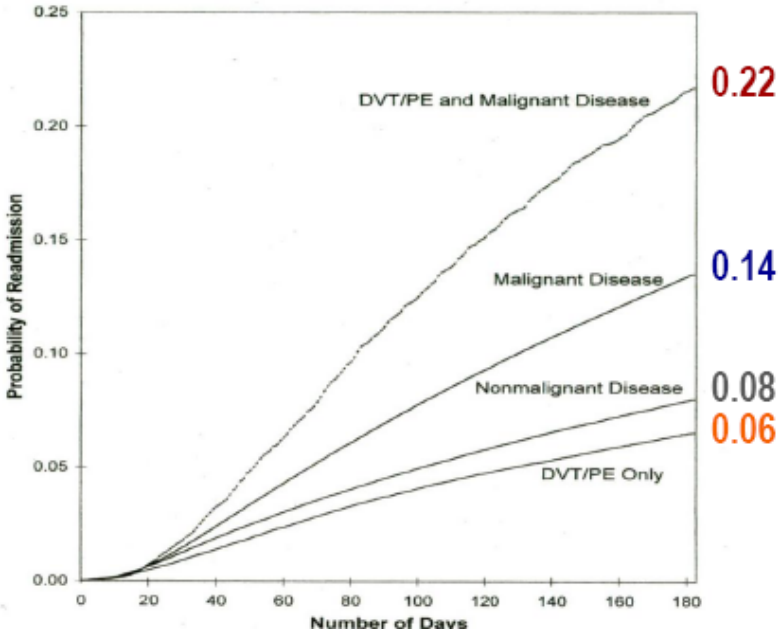
- MANAGEMENT OF RECURRENT VTE ON ANTICOAGULANT THERAPY

HOW COMMON IS RECURRENT VTE IN PATIENTS WITH CANCER?

Medicare hospital discharge data

- 46,848 cases with DVT/PE
- 1,211,944 admissions for malignancy
- 8,177,634 admissions for nonmalignant disease

Cumulative probability of re-admission with DVT/PE within 183 days of initial hospitalisation



Levitan N, *et al.*, Rates of Initial and Recurrent Thromboembolic Disease Among Patients with Malignancy Versus Those without Malignancy: Risk Analysis Using Medicare Claims Data Medicine (Baltimore) 1999;78(5):285–91. https://insights.ovid.com/pubmed?pmid=10499070

Guidelines: Treatment CAT

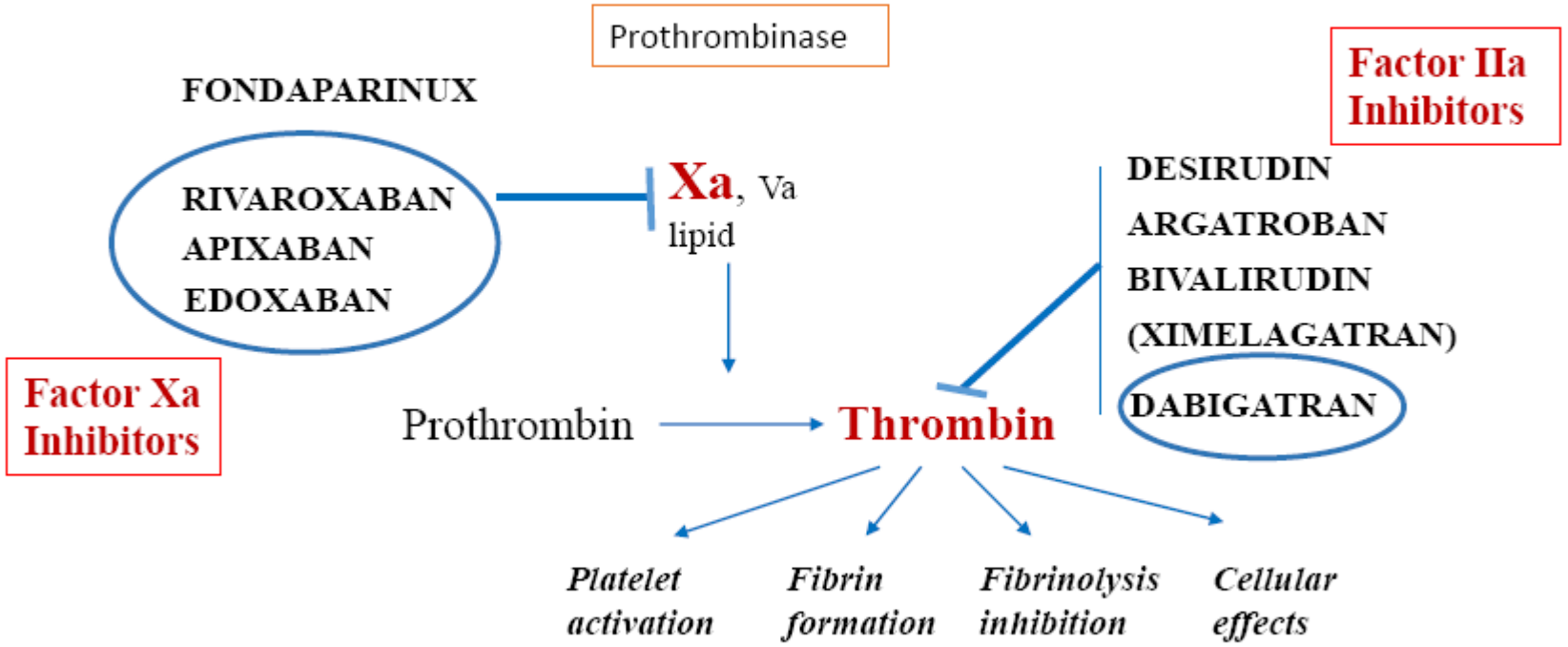
- International academic institutions consider low-molecular-weight heparins (LMWH) as the preferred option for the treatment of cancer-associated VTE

	Long-term treatment	Treatment duration
AIOM (*Italian association of medical oncology*)	LMWH	3 to 6 months then LMWH until cancer resolution
NCCN (*US national Comprehensive Cancer Network*)	LMWH or VKA	3 to 6 months for DVT; 6 to 12 month for PE
ASCO (*American Society of Clinical Oncology*)	LMWH	At least 6 months
INCa (*Institut National du Cancer*) and International	LMWH	3 to 6 months then VKA or LMWH until cancer resolution
ACCP (*American College of Chest Physicians*)	LMWH	3 to 6 months then VKA or LMWH until cancer resolution

Negli ultimi anni abbiamo a disposizione nuovi farmaci:

gli anticoagulanti orali diretti (DOA)

Direct Oral Anticoagulants (DOACs)



I DOACs nei pazienti oncologici

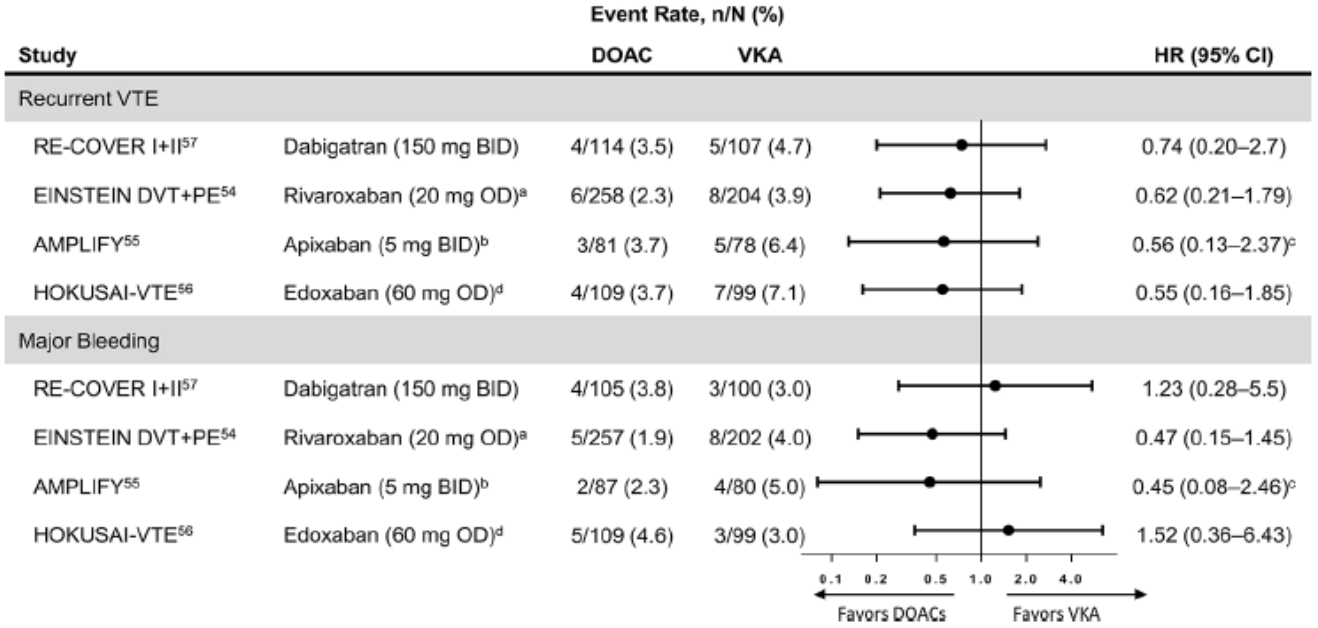


Figure 2 Forest plot of the HRs for DOACs vs warfarin for (**A**) new or recurrent VTE and (**B**) major bleeding based on the published subanalyses of the patients with active cancer at baseline included in the major DOAC phase 3 clinical trials for VTE. BID, two times per day; DOAC, direct oral anticoagulant; OD, one time per day; VKA, vitamin K antagonist; VTE, venous thromboembolism. [a]Rivaroxaban 15 mg BID for the first 21 days followed by 20 mg OD. [b]Apixaban 10 mg BID for 7 days followed by 5 mg BID. [c]Relative risk. [d]Patients with a creatinine clearance of 30 to 50 mL/min, a bodyweight of <60 kg or who were receiving concomitant treatment with select P-glycoprotein inhibitors received edoxaban 30 mg OD.

Ay C, *et al. ESMO Open* 2017;**2**:e000188. doi:10.1136/esmoopen-2017-000188

Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date) Anticoagulation

		ACCP recommendation	Grade of recommendation
2016 CHEST guidelines CHEST	**Proxymal DVT or PE**	Long-term (3 months)	1B
	DVT or PE *and NO CANCER*	NOACs over VKA	2B
	DVT or PE *with CANCER*	LMWH over VKA and NOACs	2C
	DVT or PE in extended therapy	No need to change the coiche of anticoagulant after the first 3 months	2C

"…In patients with VTE and cancer who are not treated with LMWH, we do not have a preference for either an NOAC or VKA…"

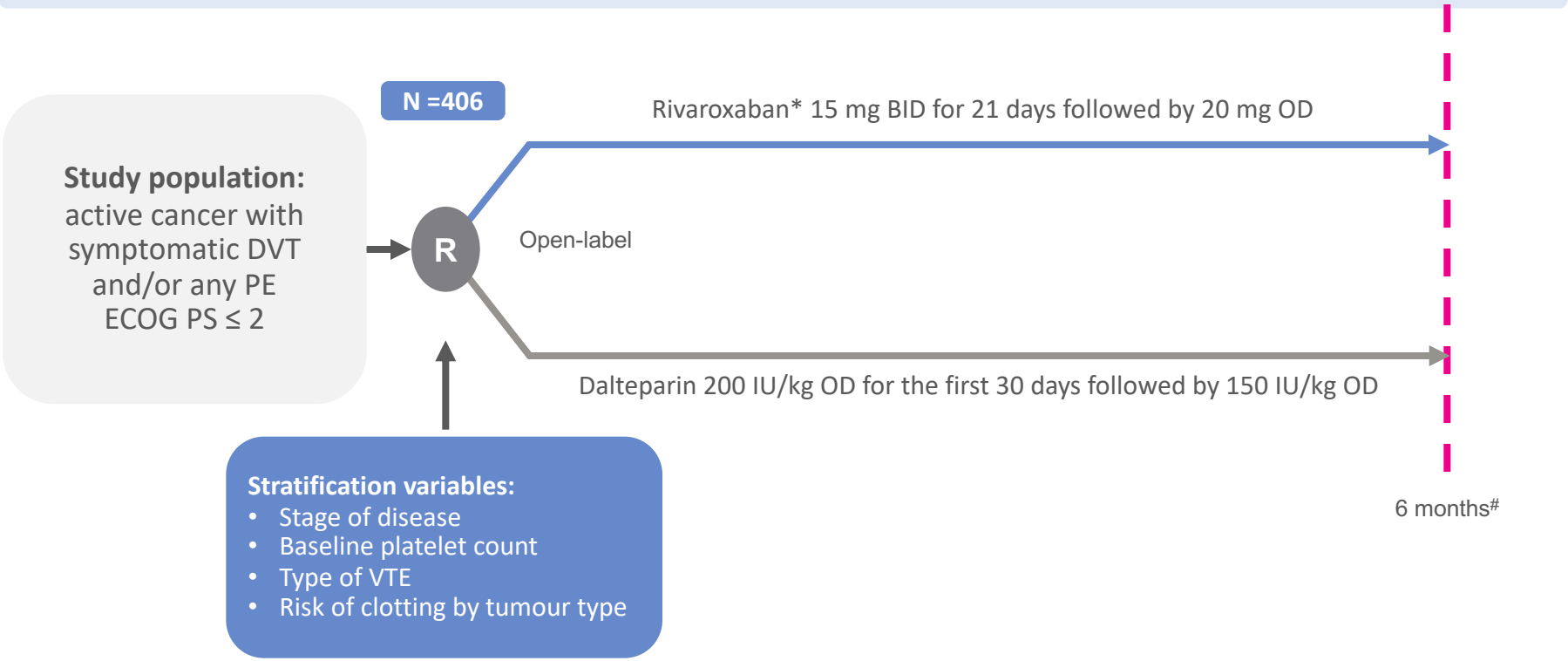
"…In the absence of direct comparisons between NOACs, and no convincing indirect evidence that one NOAC is superior to another, we do not have a preference for one NOAC over another NOAC…"

Adapted from Kearon C, et al. *Chest*. 2016;149:315-352

Current Guidelines

Select-D: Phase III Study Comparing Rivaroxaban versus Dalteparin for the Treatment of Cancer Associated Thrombosis

Study design: Prospective, randomized, open-label, multicentre pilot phase III study



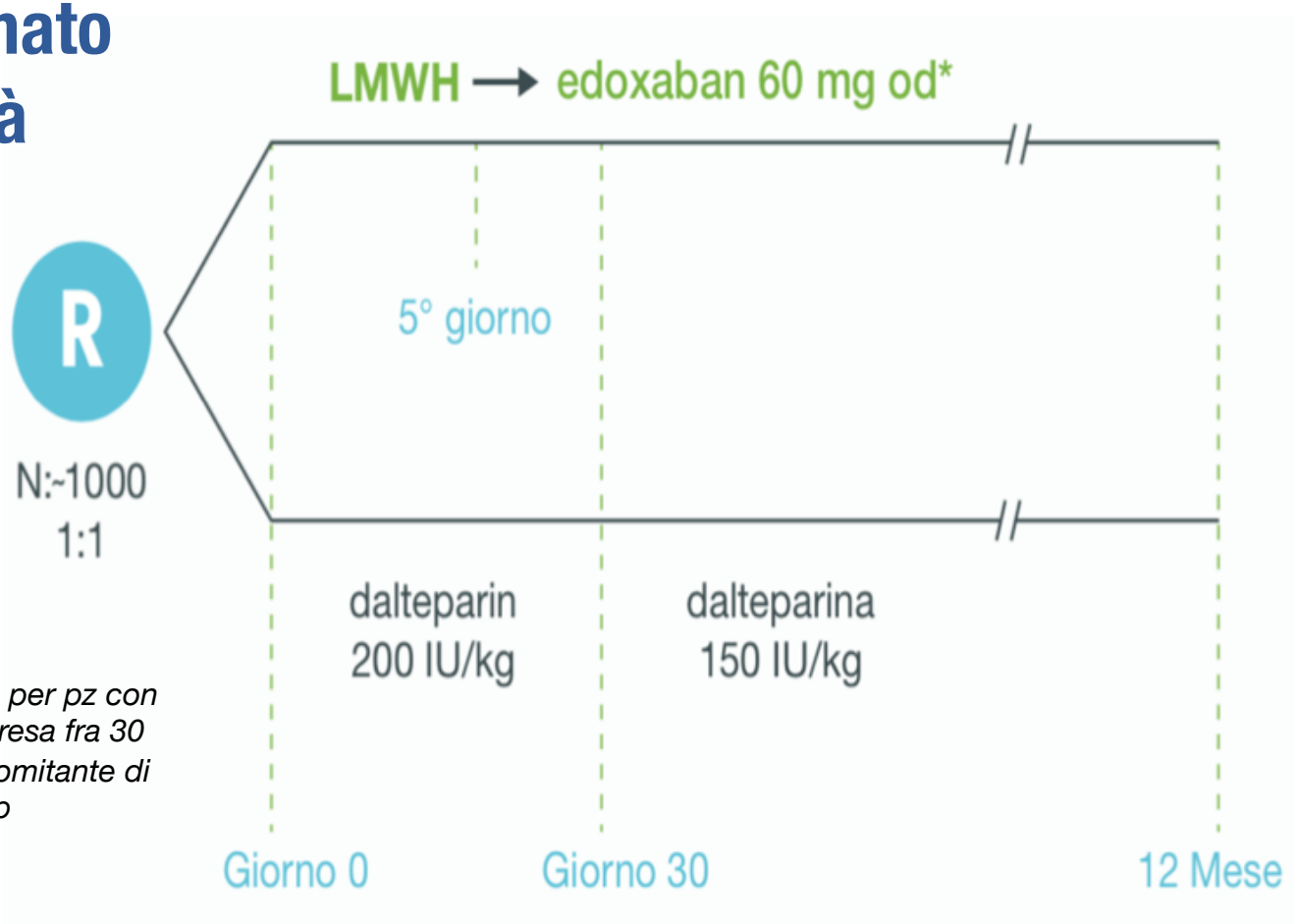
*For patients with CrCl 30–49 ml/min dosing recommendations as in rivaroxaban SmPC; #The second randomization phase for extended treatment of VTE from 6 to 12 months for patients with PE as an index event or patients with Residual DVT at 5 month assessment was closed due to low recruitment. Sample size reduced from 530 to 400 patients for main trial comparison (95% CI for VTE recurrence +/-4.5%)

Young A et al, Thromb Res 2016;140:S172–S173; EudraCT number: 2012-005589-37; Bach M et al, Thromb Haemost 2016;116:S24–S32; Data on File

HOKUSAI CANCER

TEV Confermato da obiettività

1050 pz randomizzati e stratificati per rischio di sanguinamento e necessità di riduzione del dosaggio*

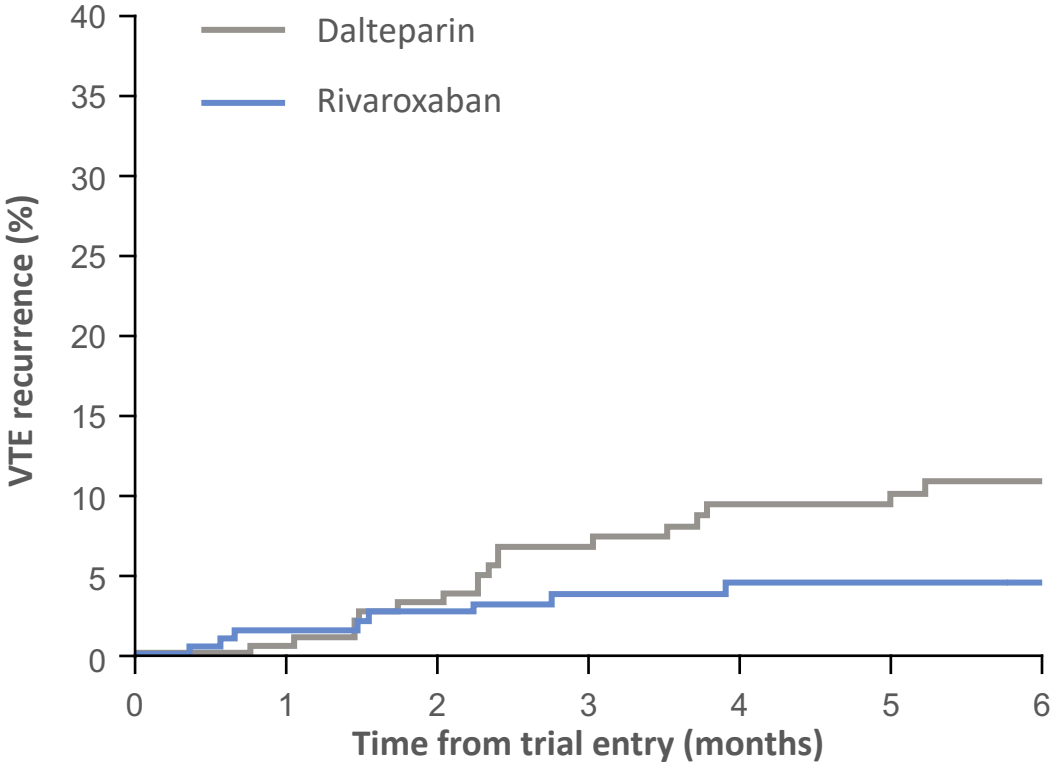


** Aggiustamento a 30 mg per pz con peso < 60 kg, ClCr compresa fra 30 e 50 mL/min, e uso concomitante di potenti inibitori della p-Gp*

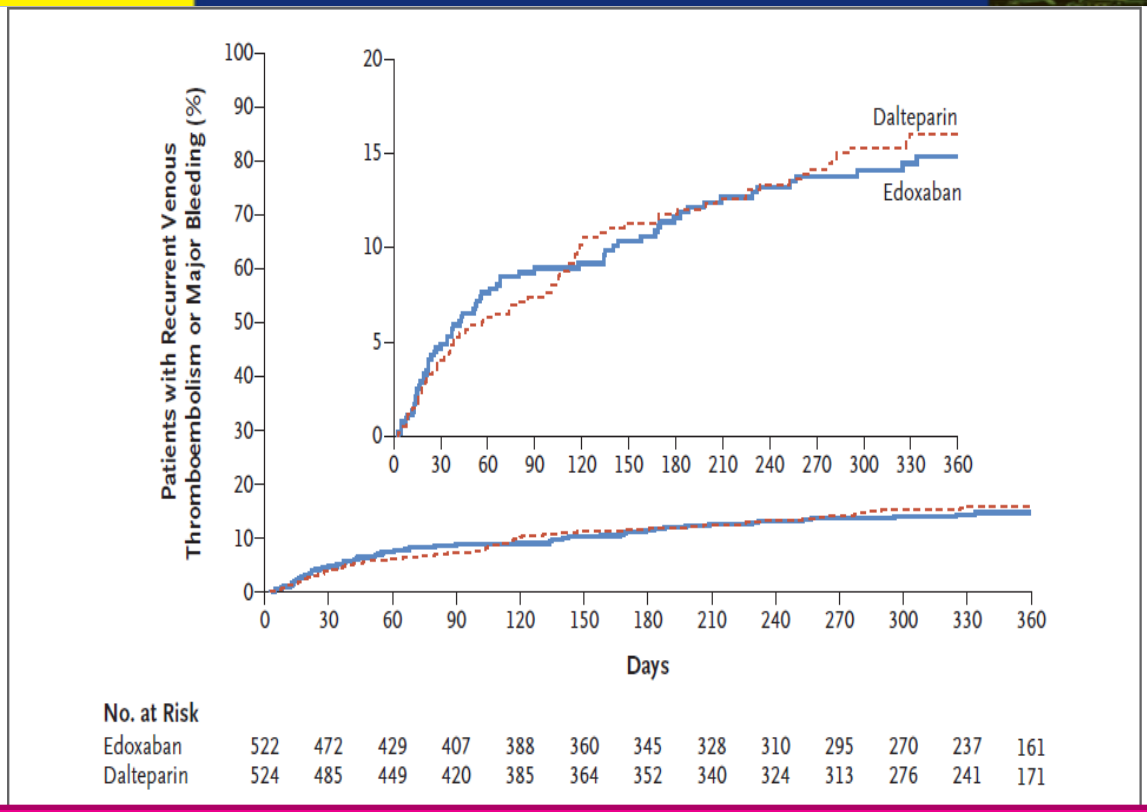
HOKUSAI CANCER Phase III Study Comparing Edoxavan versus Dalteparin for the Treatment of Cancer Associated Thrombosis

Raskob G.E. et al., NEJM, 2017

Lower Incidence of VTE Recurrence Events with Rivaroxaban Versus Dalteparin



Outcome at 6 months	Rivaroxaban (n=203)	Dalteparin (n=203)
VTE recurrence, % (95% CI)	4 (2–9)	11 (7–16)

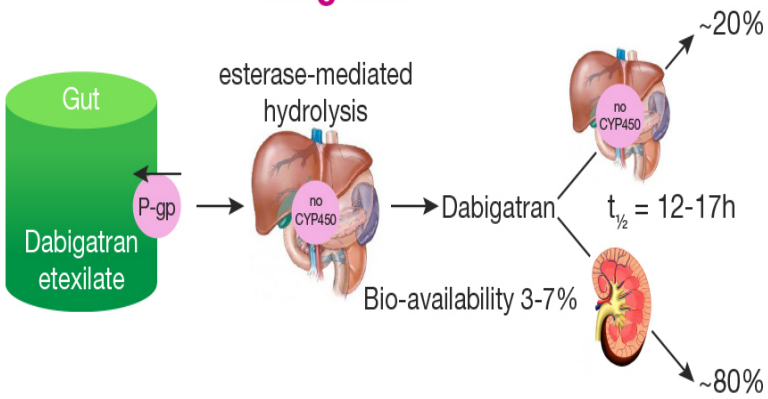


ENDPOINT PRIMARIO COMPOSITO recidiva di TEV o sanguinamento maggiore

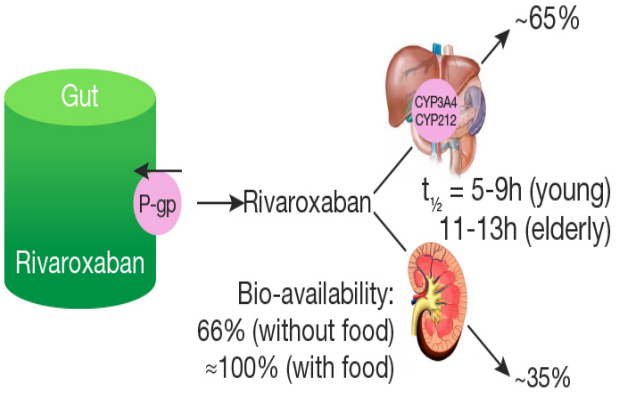
Edoxaban (522)	Dalteparina (524)	HR (95% CI)
67 (12.8%)	71 (13.5%)	0.97 (0.70, 1.36) *P = 0.006*

CHOOSING AMONGST THE DOACs

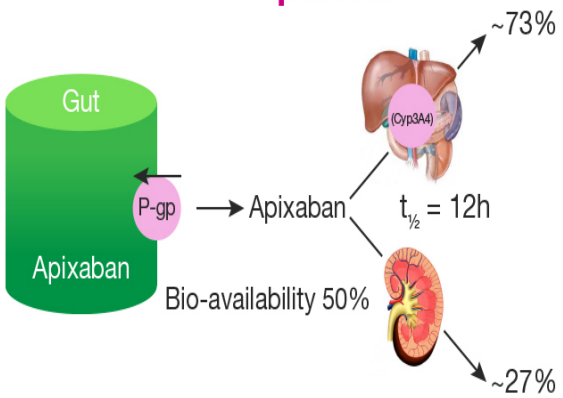
Dabigatran



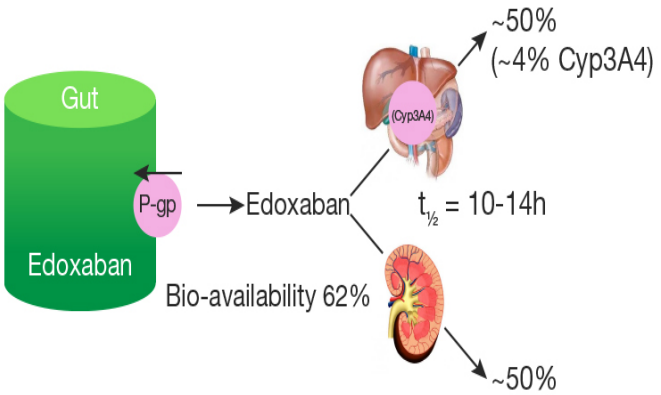
Rivaroxaban



Apixaban



Edoxaban



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

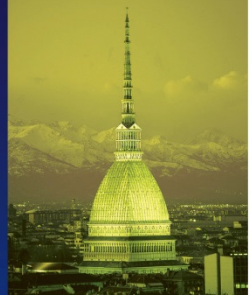
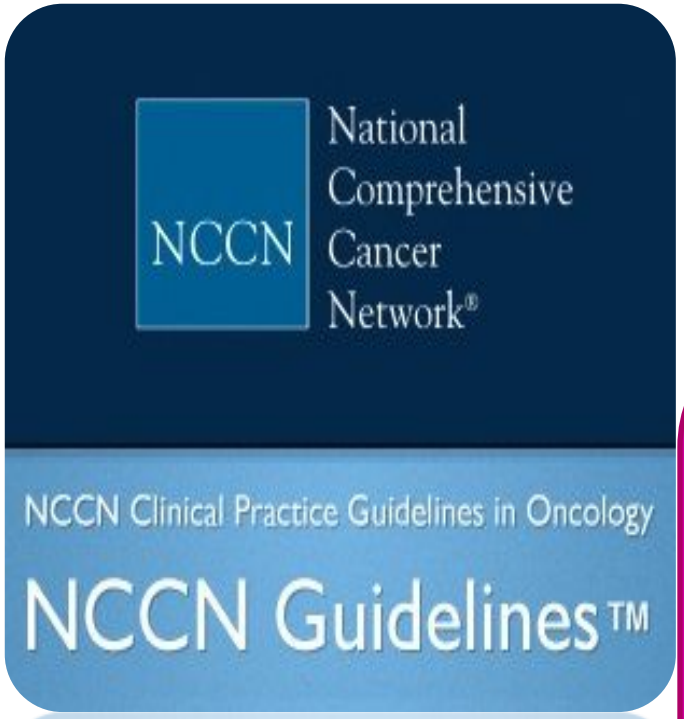


Table 3. Currently ongoing studies on DOACs for the treatment of VTE in patients with cancer (ClinicalTrials.gov.) [54].

Title, Trial Number	Study design	PHASE	Condition	Study drug	Comparator
CONKO_011/AIO-SUP-0115/Ass.: Rivaroxaban in the Treatment of Venous Thromboembolism (VTE) in Cancer Patients – a Randomized Phase III Study (NCT02583191)	RCT	III	VTE	Rivaroxaban	LMWH
A Non-interventional Study on Xarelto for Treatment of Venous Thromboembolism (VTE) and Prevention of Recurrent VTE in Patients With Active Cancer (COSIMO) (NCT027426239)	Prospective, cohort	III	DVT and PE	Rivaroxaban	-
Apixaban for the Treatment of Venous Thromboembolism in Patients With Cancer (CARAVAGGIO) NCT03045406	RCT	III	VTE	Apixaban	LMWH
Rivaroxaban Utilization for Treatment and Prevention of Thromboembolism in Cancer Patients: Experience at a Comprehensive Cancer Center (NCT02502396)	Retrospective Cohort	Not Applicable	DVT of the Lower and Upper Extremities| PE |NVAF	Rivaroxaban	
Cancer Associated Thrombosis, a Pilot Treatment Study Using Rivaroxaban (CASTA-DIVA) (NCT02746185)	rct	III	VTE	rivaroxaban	LMWH
Direct oral anticoagulants (DOACs) vs LMWH+/_warfarin for VTE in cancer: a randomized effectiveness trial (CANVAS TriaL (NCT02744092)	RCT	Not Applicable	Cumulative VTE recurrence	Apixaban Dabigatran Edoxaban Rivaroxaban	LMWH alone or with warfarin
A Study of Dabigatran Etexilate as Primary Treatment of Malignancy Associated Venous Thromboembolism (NCT03240120)	RCT	III	VTE	Dabigatran etexilate	Tinzaparin
A Randomized Phase II Study to Compare the Safety and Efficacy of Dalteparin vs. Rivaroxaban for Cancer-associated Venous Thromboembolism (PRIORITY) NCT03139487	RCT	II		Rivaroxaban	Dalteparin
Apixaban as Treatment of Venous Thrombosis in Patients With Cancer: The CAP Study (CAP) (NCT02581176)	Single Group Assignment	IV		Apixaban	-



Edoxaban già in Linee Guida

Le Linee Guida NCCN hanno recepito i risultati dell'Hokusai VTE Cancer, e raccomandano l'uso di edoxaban per il trattamento del TEV in pazienti oncologici

RECOMMENDATIONS AND GUIDELINES

Role of direct oral anticoagulants in the treatment of cancer-associated venous thromboembolism: guidance from the SSC of the ISTH

A. A. KHORANA,* S. NOBLE,† A. Y. Y. LEE,‡ G. SOFF,§ G. MEYER,¶ C. O'CONNELL** and M. CARRIER††

Guidance statement

1 We recommend individualized treatment regimens after shared decision-making with patients.

2 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. LMWHs constitute an acceptable alternative. Currently, edoxaban and rivaroxaban are the only DOACs that have been compared with LMWH in RCTs in cancer populations. A final treatment recommendation should be

Take Home Messages

THROMBOSIS AND CANCER

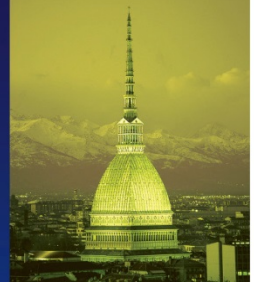
Why did this occur? CANCER-THROMBOSIS

What is the influence in patient's prognosis? POOR PROGNOSIS

What is the optimal management of this patient? LMWH

Should this patient be managed differently if this were an incidental finding? NO

Could this have been prevented? MAYBE



JOURNAL OF CLINICAL ONCOLOGY | ASCO SPECIAL ARTICLE

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014

Gary H. Lyman, Kari Bohlke, Alok A. Khorana, Nicole M. Kuderer, Agnes Y. Lee, Juan Ignacio Arcelus, Edward P. Balaban, Jeffrey M. Clarke, Christopher R. Flowers, Charles W. Francis, Leigh E. Gates, Ajay K. Kakkar, Nigel S. Key, Mark N. Levine, Howard A. Liebman, Margaret A. Tempero, Sandra L. Wong, Mark R. Somerfield, and Anna Falanga

THE BOTTOM LINE

Venous Thromboembolism Prophylaxis and Treatment in Patients with Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update

Interventions

- Pharmacologic anticoagulation

Target Audience

- Medical oncologists, surgical oncologists, hospitalists, oncology nurses

Key Recommendations

- Most hospitalized patients with active cancer require thromboprophylaxis throughout hospitalization. Data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion.
- Routine thromboprophylaxis is not recommended for ambulatory patients with cancer. It may be considered for highly select high-risk patients.
- Patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone should receive prophylaxis with either low-molecular weight heparin (LMWH) or low-dose aspirin to prevent venous thromboembolism (VTE).
- Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days.
- Extending postoperative prophylaxis up to 4 weeks should be considered in those undergoing major abdominal or pelvic surgery with high-risk features.
- LMWH is recommended for the initial 5 to 10 days of treatment of established deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis for at least 6 months.
- Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE.
- Anticoagulation should not be used to extend survival of patients with cancer in the absence of other indications.
- Patients with cancer should be periodically assessed for VTE risk.
- Oncology professionals should educate patients about the signs and symptoms of VTE.

Methods

- An update committee was convened to determine whether previous recommendations remain valid based on an updated review of evidence from the medical literature.

Additional Information

- This guideline is published in *Journal of Clinical Oncology*. Data Supplements, including evidence tables, and clinical tools and resources can be found at www.asco.org/guidelines/vte.

- **PATIENTS WITH CANCER SHOULD BE PERIODICALLY ASSESSED FOR VTE RISK**
- **ONCOLOGY PROFESSIONAL SHOULD EDUCATE PATIENTS ABOUT SIGNS AND SYMPTOMS OF VTE**

GRAZIE