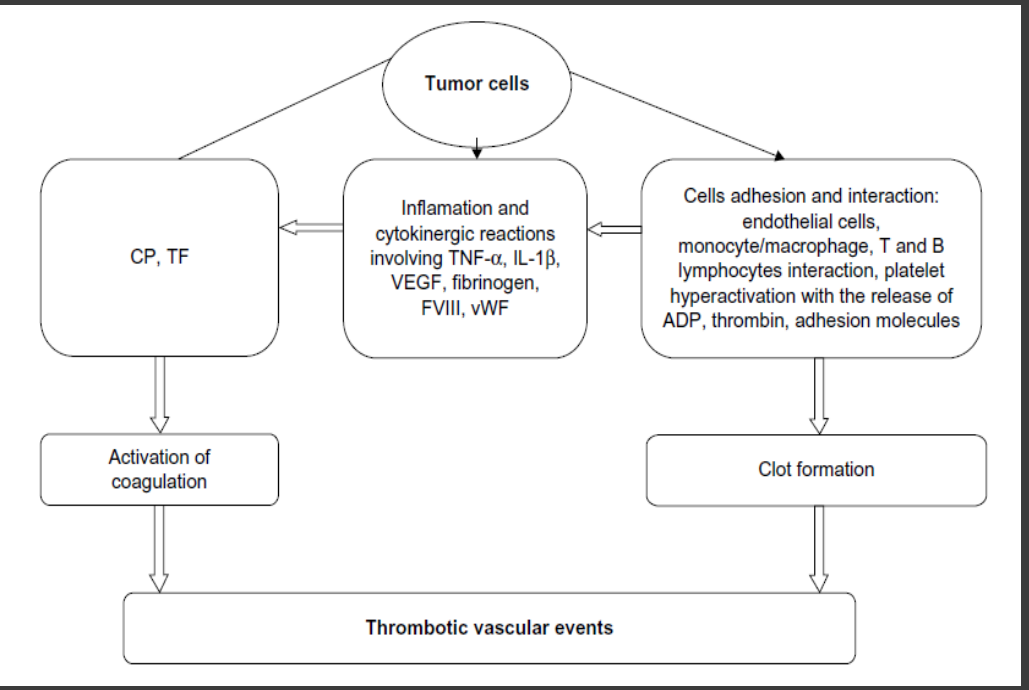
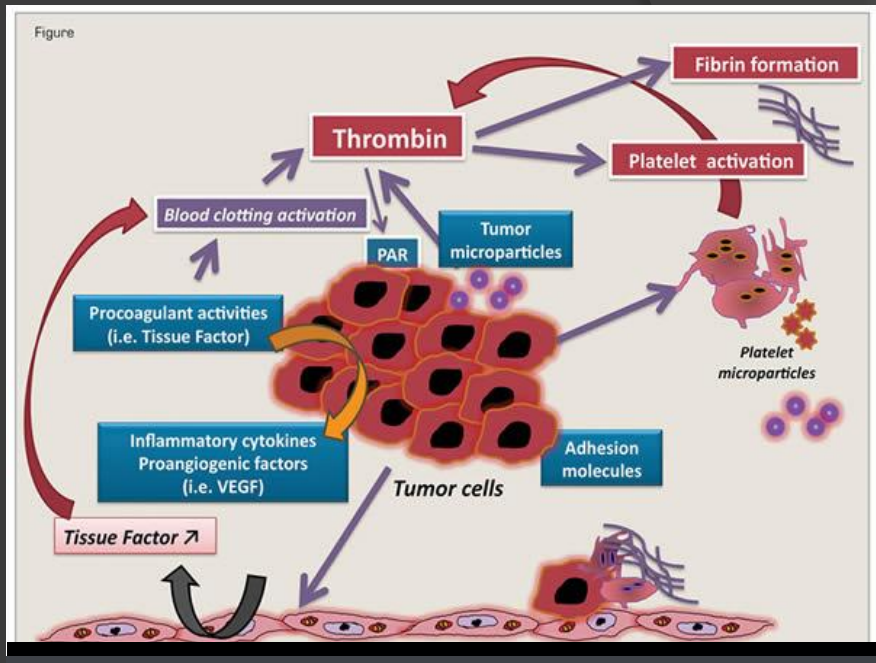
CARDIONCOLOGIA 2017, DOMANDE, RISPOSTE E….DUBBI:CONFRONTO CON GLI ESPERTI
TORINO, 1 APRILE 2017

CARDIOTOSSICITÀ E TERAPIA ANTICOAGULANTE: IL PARERE DELL'EMATOLOGO

Dott.ssa Antonella Vaccarino
SOSD Ematologia e Malattie Trombotiche
Ospedale San Giovanni Bosco - Torino

- Esistono diverse evidenze che supportano la correlazione tra cancro e trombosi.
- R di MTEV è 4-7 volte più elevato nei pz neoplastici
- Le complicanze tromboemboliche influenzano significativamente la morbilità e la mortalità della malattia neoplastica
- ***Il tromboembolismo venoso è la seconda causa di morte nei pazienti neoplastici dopo il cancro stesso***
- i pazienti con cancro che sviluppano un episodio di TEV presentano una minore sopravvivenza rispetto ai controlli oncologici senza TEV .





The Open Cardiovascular Medicine Journal 2010;4:78–82. doi:10.2174/1874192401004020078.

Fattori di rischio per MTEV

- **Fattori legati alla neoplasia**
- **Fattori legati al trattamento**
- **Fattori legati al paziente**
- **Biomarker**

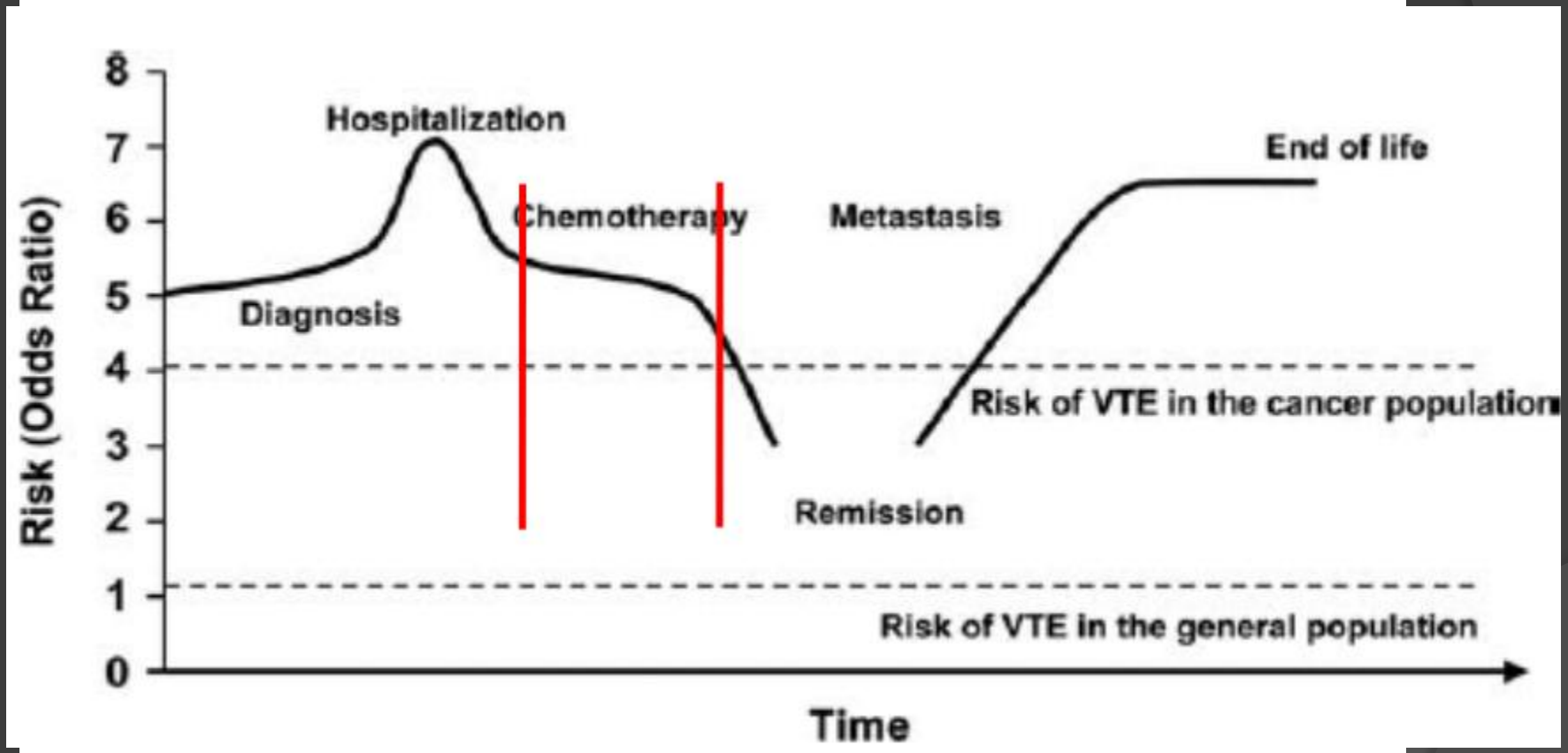
Table 1. Risk factors and biomarkers for cancer-associated thrombosis

Cancer-related factors
- Primary site of cancer
  - Pancreas, stomach, brain, kidney, lung, and ovary
- Advanced stage of cancer
- Initial period after diagnosis of cancer
- Histology

Treatment-related factors
- Major surgery
- Hospitalization
- Chemotherapy (particularly cisplatin)
- Hormonal therapy
- Anti-angiogenic agents (bevacizumab, sunitunib, sorafenib)
- Immunomodulatory drugs (thalidomide, lenalidomide)
- Erythropoiesis-stimulating agents
- Transfusions (platelets and red blood cells)
- Central venous catheters

Patient-related factors
- Older age
- Female sex
- Race (lower in Asians, higher in blacks)
- Comorbidities (Renal disease, obesity, infection)
- Prior history of VTE
- Lower performance status

Candidate biomarkers
- Platelet count $\geq$ 350 000/mm^3
- Leukocyte count $>$ 11 000/mm^3
- Hemoglobin $<$ 10 g/dL
- Elevated tissue factor
- Elevated D-dimer
- Elevated soluble P-selectin
- Elevated C-reactive protein
- Thrombin generation potential



New York, New York: Informa Healthcare USA, Inc;
2007:169-192. ©2007 Informa Healthcare.

KHORANA Risk Score

Patient Characteristics	Risk Score*
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count ≥ 350,000/mm³	1
Hemoglobin level < 100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count > 11,000/mm³	1
Body mass index ≥ 35 kg/m²	1

*High-risk score ≥ 3; intermediate-risk score = 1–2; low-risk score = 0.
Adapted from Khorana AA, Kuderer NM, Culakova E, et al. Development and validation of a predictive model for chemotherapy-associated thrombosis. Blood 2008;111:3786–4907, with permission.

Medscape Source: J Natl Compr Canc Netw © 2011 JNCCN

33.3% (5/15) of the TEs was in the high risk population

PROTECHT Risk Score

- Site of cancer
  - Stomach, Pancreas **2 points**
  - Lung, gynaecologic, testicular **1 point**
- Pre-chemotherapy platelet count 350 x 10^9L or more **1 point**
- Hemoglobin level less than 100 g/L **1 point**
- Pre-chemotherapy **Leukocyte>11000/mm3** nore **1 point**
- BMI 35 Kg/sqm or more **1 point**
- Chemotherapy regimen containing
  - Cisplatin or carboplatin or gemcitabine **1 point**
  - Platinum compound plus gemcitabine **2 points**

66.7% (10/15) of the TEs was in the high risk population

Barni S et al. MASCC 2011

RISCHIO EMORRAGICO

- Localizzazione tumore
- Trombocitosi
- Leucocitosi
- BMI > 35
- EPO
- CVC

- Chirurgia
- Danno da radiazioni
- Tumori polmonari, gastrointestinali e vescicali
- Trombocitopenia da terapia mielosoppressiva
- Fluttuazioni delle funzioni epatica e renale
- Età >75

- Prevenzione
- Trattamento

Pazienti ambulatoriali che ricevono chemioterapia

PROTECHT (Prophylaxis of Thromboembolism during Chemotherapy Trial): **NADROPARINA** (3800 U aX)

- riduce il rischio di VTE in pz con cancro metastatico o localmente avanzato (2% vs 3,9%)
- lieve aumento del rischio di emorragia maggiore (0,7 vs 0%), non di emorragia minore.

Lancet Onc. 2009 Oct ;10(10):943-9.

Se si applicano i risk score si evidenzia che i pz a rischio elevato beneficiano maggiormente della profilassi.

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Prophylaxis against Venous Thromboembolism in Ambulatory Patients with Cancer

Jean M. Connors, M.D.

Table 2. Comparison of Recommendations Regarding Prophylaxis against Venous Thromboembolism.*

Potential Indication	Recommended Use of Prophylaxis			
	Author	ACCP	ASCO	NCCN
Treatment of multiple myeloma with thalidomide or lenalidomide with high-dose dexamethasone, doxorubicin, combination chemotherapy, or other risk factors	Yes†	Suggest	Yes	Yes
Cancer associated with high risk of venous thromboembolism (pancreatic or gastric)				
With other risk factors	Yes†	Suggest	Consider	Consider
Without other risk factors	Consider‡	No	Consider	Consider
Cancer associated with intermediate risk of venous thromboembolism (lung, ovarian, primary central nervous system, bladder, lymphoma)				
With other risk factors	Consider‡	Suggest	Consider	No
Without other risk factors	No‡	No	Consider	No
Cancer associated with low risk of venous thromboembolism				
With other risk factors	Consider‡	Suggest	Consider	No
Without other risk factors	No	No	Consider	No

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

J Clin Oncol. 2015 Feb

- 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).

- 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.

Legge 648/96
Prescrivibilità di EBPM come farmaci «off-label

Le EBPM sono prescrivibili come farmaci «off-label» per l'utilizzo nella profilassi delle trombosi venose profonde in pazienti oncologici ambulatoriali a rischio (KORANA > 3)[con condizione che l'indicazione sia posta dallo specialista ematologo o oncologo]

- prescrizione mediante piano terapeutico redatto dello specialista ematologo o oncologo
- dispensazione presso i Servizi Farmaceutici dello specialista prescrittore o di afferenza dell'assistito, sulla base del distretto di sua appartenenza

- Prevenzione
- Trattamento

CHEST 2016 (Antithrombotic therapy for VTE disease)

- In patients with DVT of leg or PE and cancer (cancer associated thrombosis), as long term (first 3 months)anticoagulant therapy, we suggest LMWH over VKA therapy (grade 2C), dabigatran (grade 2C), rivaroxaban (grade 2 C), apixaban (grade 2 C) or edoxaban (grade 2 C)

Guidance for the prevention and treatment of cancer-associated venous thromboembolism

Alok A. Khorana[1] · Marc Carrier[2] · David A. Garcia[3] · Agnes Y. Y. Lee[4]

PER QUANTO TEMPO?

We suggest that patients with active cancer (i.e. known disease or receiving some form of anti-cancer therapy) and VTE be treated with LMWH for at least 6 months.

We suggest that patients with incidentally diagnosed DVT or PE be treated similarly to patients diagnosed with VTE based on symptoms i.e., with at least 6 months of LMWH monotherapy, with the exception of isolated subsegmental PE where decisions can be made on a case-by-case basis. We further suggest that treatment decisions in patients with incidentally diagnosed visceral vein thrombi be made on a case-by-case basis.

Anticoagulation with LMWH monotherapy should be prescribed for a minimum period of 6 months after diagnosis of cancer-associated VTE. Anticoagulation therapy should be continued beyond 6 months if a patient has active malignancy (i.e. persistent malignant disease) or if ongoing anti-cancer therapy is planned.

E DOPO I SEI MESI?

- *For patients at low risk of recurrence we suggest that anticoagulation be discontinued after 6 months in the absence of active malignancy (i.e. patients are cured or in complete remission), provided that no anti-cancer therapy is ongoing or planned.*
- *For patients at high risk of recurrence we suggest that anticoagulation be continued but with periodic re-evaluation of risks and benefits.*

SE RECIDIVA?

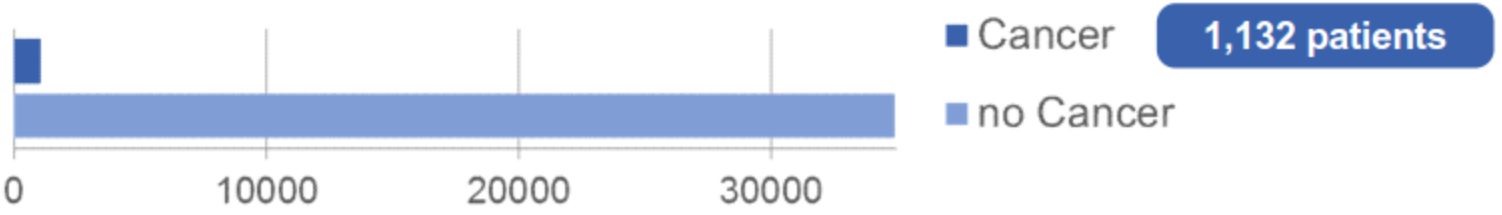
- *We suggest that cancer patients with symptomatic recurrent VTE despite therapeutic anticoagulation with an agent other than LMWH be transitioned to therapeutic LMWH, assuming no contraindications to LMWH.*
- *We suggest that cancer patients with symptomatic recurrent VTE despite optimal anticoagulation with LMWH continue with LMWH at a higher dose, starting at an increase of ~25 % of the current dose or resuming the therapeutic weight-adjusted dose if the patient was receiving a non-therapeutic dose at the time of recurrence.*

TABLE 6] Factors That May Influence Which Anticoagulant Is Chosen for Initial and Long-Term Treatment of VTE

Factor	Preferred Anticoagulant	Qualifying Remarks
Cancer	LMWH	More so if: just diagnosed, extensive VTE, metastatic cancer, very symptomatic; vomiting; on cancer chemotherapy.
Parenteral therapy to be avoided	Rivaroxaban; apixaban	VKA, dabigatran, and edoxaban require initial parenteral therapy.
Once daily oral therapy preferred	Rivaroxaban; edoxaban; VKA	
Liver disease and coagulopathy	LMWH	NOACs contraindicated if INR raised because of liver disease; VKA difficult to control and INR may not reflect antithrombotic effect.
Renal disease and creatinine clearance <30 mL/min	VKA	NOACs and LMWH contraindicated with severe renal impairment. Dosing of NOACs with levels of renal impairment differ with the NOAC and among jurisdictions.
Coronary artery disease	VKA, rivaroxaban, apixaban, edoxaban	Coronary artery events appear to occur more often with dabigatran than with VKA. This has not been seen with the other NOACs, and they have demonstrated efficacy for coronary artery disease. Antiplatelet therapy should be avoided if possible in patients on anticoagulants because of increased bleeding.
Dyspepsia or history of GI bleeding	VKA, apixaban	Dabigatran increased dyspepsia. Dabigatran, rivaroxaban, and edoxaban may be associated with more GI bleeding than VKA.
Poor compliance	VKA	INR monitoring can help to detect problems. However, some patients may be more compliant with a NOAC because it is less complex.
Thrombolytic therapy use	UFH infusion	Greater experience with its use in patients treated with thrombolytic therapy
Reversal agent needed	VKA, UFH dabigatran	
Pregnancy or pregnancy risk	LMWH	Potential for other agents to cross the placenta
Cost, coverage, licensing	Varies among regions and with individual circumstances	

Treatment of VTE in cancer patients NOACs

Phase III NOAC trials including more than 30.000 patients



Drug	Trial name	cancer patients (%)
	EINSTEIN-PE	4.6
	RE-COVER	4.8
	RE-MEDY	2.1
	AMPLIFY	2.7
Edoxaban	Hokusai-VTE	2.5

C.Wharin, V. Tagalakis / Blood Reviews 28 (2014) 1–8
Vedovati MC, Germini F, Agnelli G, Becattini C.. Chest. 2015 Sep 11.2014/09/12.

Efficacy and safety of DOACs in patients with cancer

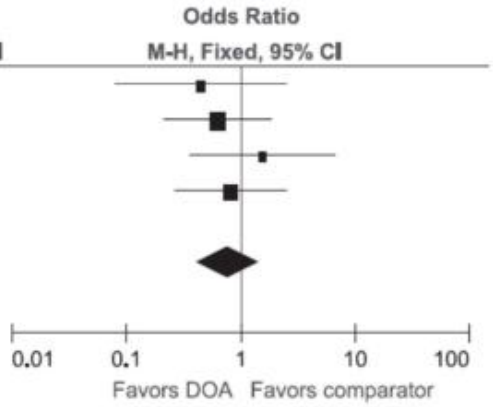
Efficacy outcomes

A

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	2	87	4	80	18.2%	0.45 [0.08, 2.51]
EINSTEIN DVT & PE 2013	6	232	8	196	37.7%	0.62 [0.21, 1.83]
HOKUSAI 2013	5	109	3	99	13.4%	1.54 [0.36, 6.61]
RECOVER I & II 2013	6	159	7	152	30.7%	0.81 [0.27, 2.47]
Total (95% CI)		**587**		**527**	**100.0%**	**0.77 [0.41, 1.44]**
Total events	19		22			

Heterogeneity: Chi² = 1.40, df = 3 (P = 0.70); I² = 0%

Test for overall effect: Z = 0.81 (P = 0.42)



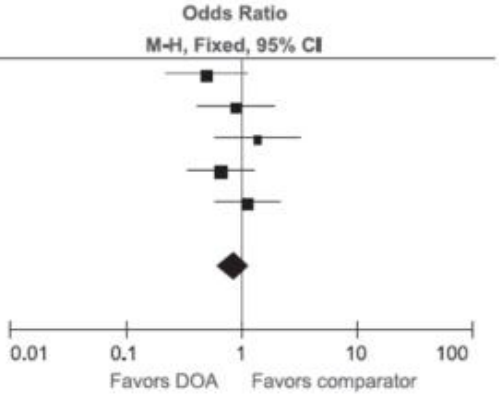
Clinically relevant bleeding

B

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	11	87	18	80	21.0%	0.50 [0.22, 1.13]
EINSTEIN-DVT 2010	17	118	14	88	17.6%	0.89 [0.41, 1.92]
EINSTEIN-PE 2012	14	114	10	108	11.5%	1.37 [0.58, 3.24]
HOKUSAI 2013	20	109	25	99	27.4%	0.67 [0.34, 1.29]
RECOVER I & II 2013	23	159	20	152	22.4%	1.12 [0.59, 2.13]
Total (95% CI)		**587**		**527**	**100.0%**	**0.85 [0.62, 1.18]**
Total events	85		87			

Heterogeneity: Chi² = 4.04, df = 4 (P = 0.40); I² = 1%

Test for overall effect: Z = 0.96 (P = 0.34)



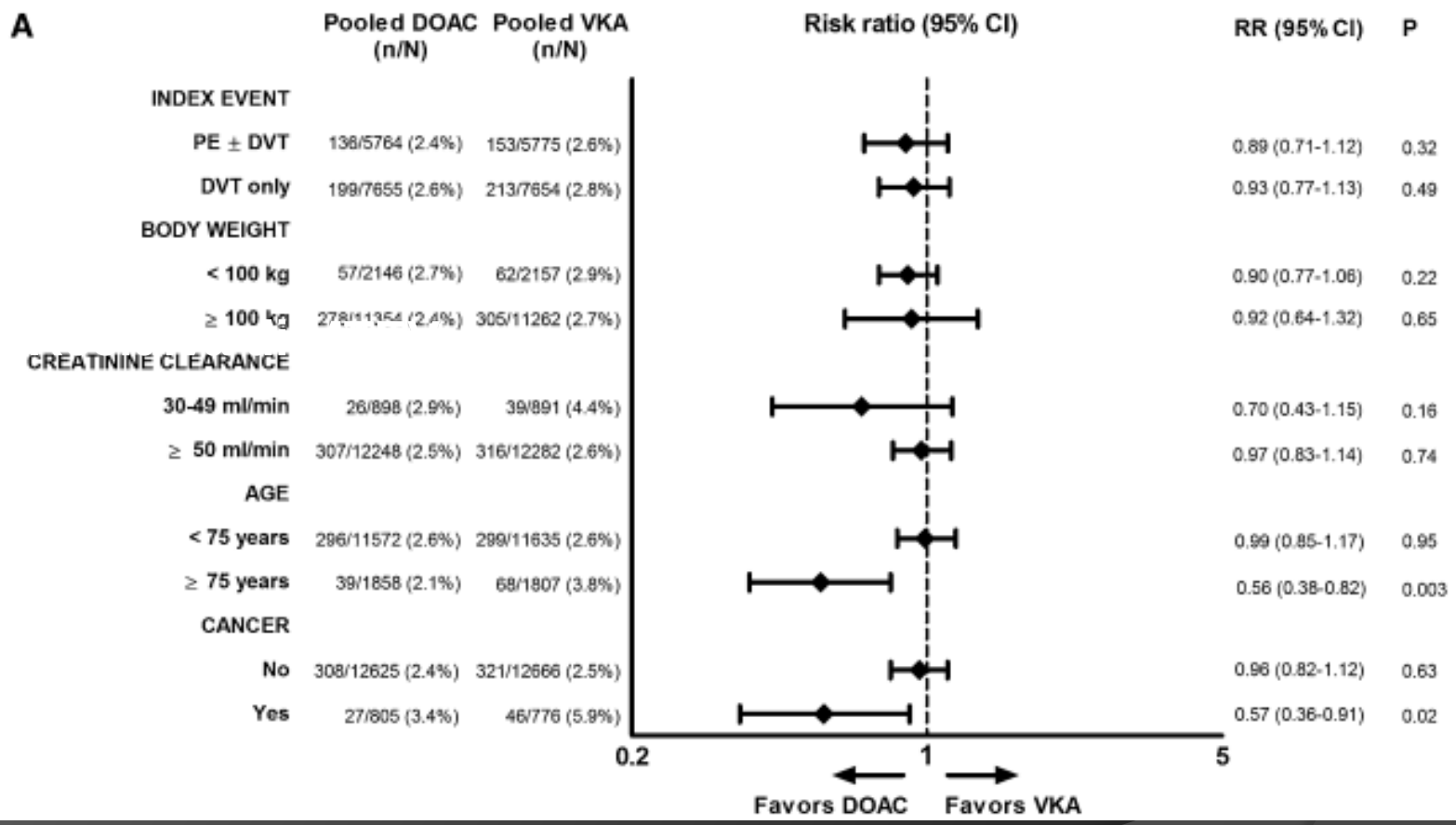
DOAs seem to be as effective and safe as conventional treatment for the prevention of VTE in patients with cancer. Further clinical trials in patients with cancer-associated VTE should be performed to confirm these results

Vedovati et al. CHEST 2015

THROMBOSIS AND HEMOSTASIS

Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials

Nick van Es,[1] Michiel Coppens,[1] Sam Schulman,[2] Saskia Middeldorp,[1] and Harry R. Büller[1]



RECIDIVA MTEV

THROMBOSIS AND HEMOSTASIS

Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials

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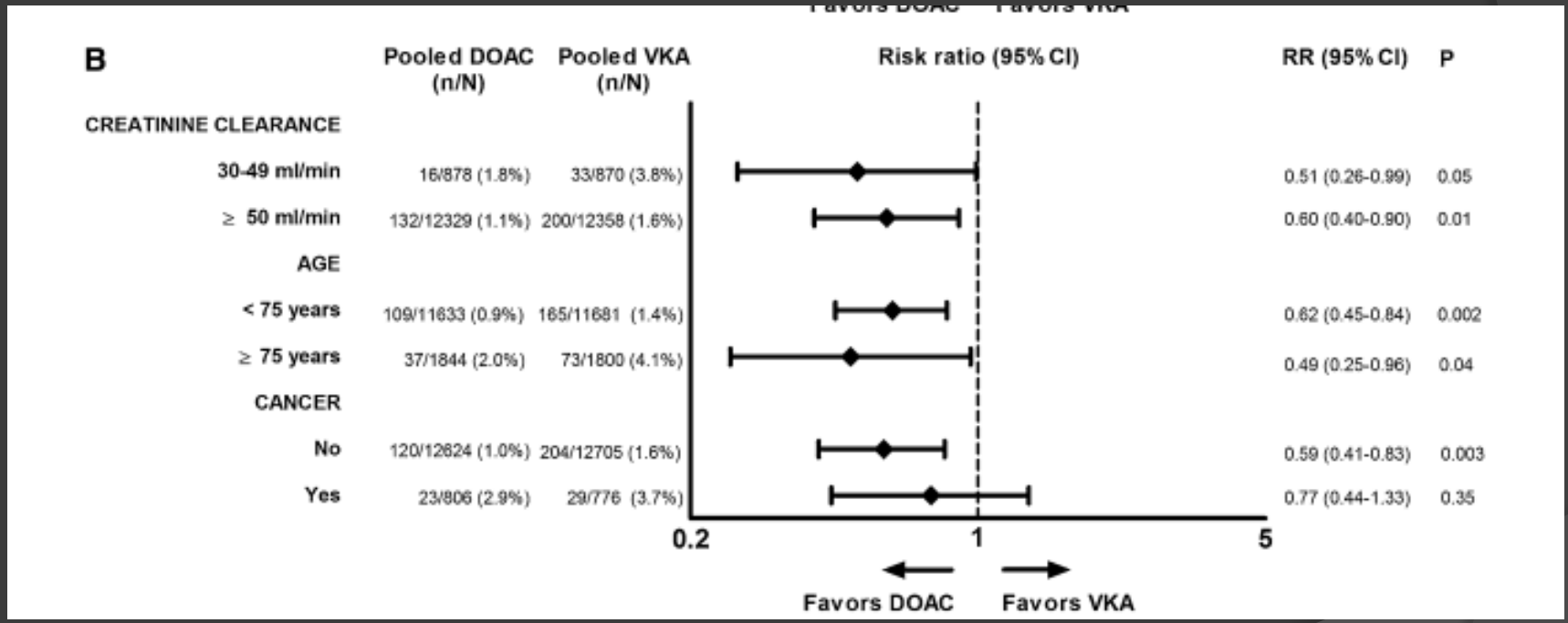

Sanguinamenti maggiori

Thromb Haemost. 2015 Nov 25;114(6):1268-76.

Edoxaban for treatment of venous thromboembolism in patients with cancer. Rationale and design of the Hokusai VTE-cancer study.

van Es N[1],

Criteria for DOAC use in cancer patients requiring anticoagulation

The Oncologist 2014;19:82–93

Patient assessment
Risk factors for bleeding No major bleeding events in the past 2 months Absence of intracranial or visceral tumor at high risk for major bleeding
Platelets Platelet count >50,000 per μL No anticipated decrease due to disease or chemotherapy
Coagulation studies Normal PT, PTT, and fibrinogen
Liver function tests No significant hepatic impairment (e.g., Child-Pugh B or C, cirrhosis)
Renal function CrCl >30 mL/min (rivaroxaban) CrCl >15 mL/min (dabigatran and apixaban) No anticipated fluctuations due to nephrotoxic chemotherapy or other drugs
Medications No concomitant use of drugs with strong effect on CYP3A4 and/or P-glycoprotein Fig. 1 lists strong CYP3A4 and/or P-glycoprotein inhibitors and inducers Table 4 lists chemotherapy drugs that modulate CYP3A4 and/or P-glycoprotein Good medication compliance


Grazie per l’attenzione