USO DEI DOACs NEL TRATTAMENTO DELLA MALATTIA TROMBOEMBOLICA VENOSA NEL PAZIENTE NEOPLASTICO

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- 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)

CHEST 2016 (Antithrombotic therapy for VTE disease)

In patients with VTE and cancer ("cancer-associated thrombosis"), as noted earlier in this section, we still suggest LMWH over VKA. 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. Factors that may influence which anticoagulant is chosen for initial and long-term treatment of VTE are summarized in Table 6. This decision is also expected to be sensitive to patient preferences.

CHEST 2016 (Antithrombotic therapy for VTE disease)

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	

Quale anticoagulante?

Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer.

Akl EA[1], Cochrane Database Syst Rev. 2014 Jul 8;(7):

OBJECTIVES:

To compare the efficacy and safety of low molecular weight heparin (LMWH) and oral anticoagulants for the long-term treatment of venous thromboembolism (VTE) in patients with cancer.

MAIN RESULTS:

10 RCTs (11 reports) were eligible and reported data for 1981 patients with cancer.. Meta-analysis of seven RCTs comparing LMWH with VKA found no statistically significant survival benefit (hazard ratio (HR) 0.96; 95% confidence interval (CI) 0.81 to 1.14) but a statistically significant reduction in VTE (HR 0.47; 95% CI 0.32 to 0.71). The remaining findings did not exclude a beneficial or harmful effect of LMWH compared with VKA for the outcomes of major bleeding (RR 1.07; 95% CI 0.52 to 2.19), minor bleeding (RR 0.89; 95% CI 0.51 to 1.55), or thrombocytopenia (RR 0.98; 95% CI 0.57 to 1.66). We judged the quality of evidence as low for mortality, major bleeding, and minor bleeding, and as moderate for recurrent VTE..

AUTHORS' CONCLUSIONS:

For the long-term treatment of VTE in patients with cancer, LMWH compared with VKA reduces venous thromboembolic events but not mortality. The decision for a patient with cancer and VTE to start long-term LMWH versus oral anticoagulation should balance the benefits and harms and integrate the patient's values and preferences for the important outcomes and alternative management strategies.

Low-Molecular-Weight Heparin versus a Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer -CLOT 2003 676 pz

Chest. 2015 Feb;147(2):475-83. doi: 10.1378/chest.14-0402.

Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis.

Vedovati MC, Germini F, Agnelli G, Becattini C

RESULTS:

Overall, 10 studies comparing DOAs with conventional anticoagulation for treatment of VTE including patients with cancer were included in the review. Six studies were included in the meta-analysis (two with dabigatran, two with rivaroxaban, one with edoxaban, and one with apixaban), accounting for a total of 1,132 patients. VTE recurred in 23 of 595 (3.9%) and in 32 of 537 (6.0%) patients with cancer treated with DOAs and conventional treatment, respectively (OR, 0.63; 95% CI, 0.37-1.10; I2, 0%). MB occurred in 3.2% and 4.2% of patients receiving DOAs and conventional treatment, respectively (OR, 0.77; 95% CI, 0.41-1.44; I2, 0%).

CONCLUSIONS:

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.

Thromb Res. 2015 Sep;136(3):582-9.

Treatment of venous thromboembolism in patients with cancer: A network meta-analysis comparing efficacy and safety of anticoagulants.

Posch F[1], Königsbrügge O[1], Zielinski C[2], Pabinger I[1], Ay C[3].

METHODS:

A pre-specified search protocol identified 10 randomized controlled trials including 3242 cancer patients. Relative risks (RR) of recurrent VTE (efficacy) and major bleeding (safety) were analyzed using a random-effects meta-regression model.

RESULTS:

LMWH emerged as significantly superior to VKA with respect to risk reduction of recurrent VTE (RR=0.60, 95%CI:0.45-0.79, p<0.001), and its safety was comparable to VKA (RR=1.08, 95%CI:0.70-1.66, p=0.74). For the DOAC vs. VKA efficacy and safety comparison, the relative risk estimates were in favor of DOAC, but had confidence intervals that still included equivalence (RR for recurrent VTE=0.65, 95%CI:0.38-1.09, p=0.10; RR for major bleeding=0.72, 95%CI:0.39-1.37, p=0.32). In the indirect network comparison between DOAC and LMWH, the results indicated comparable efficacy (RR=1.08, 95%CI:0.59-1.95, p=0.81), and a non-significant relative risk towards improved safety with DOAC (RR=0.67, 95%CI:0.31-1.46, p=0.31). The results prevailed after adjusting for different risk of recurrent VTE and major bleeding between LMWH vs. VKA and DOAC vs. VKA studies.

CONCLUSION:

The efficacy and safety of LMWH and DOACs for the treatment of VTE in cancer patients may be comparable.

Am J Med. 2016 Jun;129(6):615-9.

Efficacy and Safety of Rivaroxaban in Patients with Venous Thromboembolism and Active Malignancy: A Single-Center Registry.

Bott-Kitslaar DM[1]

The purpose of this study is to evaluate the efficacy and safety of rivaroxaban in patients with venous thromboembolism and active malignancy.

PATIENTS AND METHODS:

Consecutive patients treated with rivaroxaban for deep vein thrombosis or pulmonary embolism, enrolled into Mayo Thrombophilia Clinic Direct Oral Anticoagulants Registry between March 1, 2013, and April 30, 2015, were followed prospectively to evaluate the efficacy and safety of this therapy.

RESULTS:

Of the 404 venous thromboembolism patients in the registry, 296 received rivaroxaban and had at least 3 months of follow-up. Of these, 118 (40%) had active malignancy (51% female, mean age 66 ± 10 years) and 178 had no cancer (47% female, mean age 55 ± 15 years). The 3 most common cancer locations were genitourinary (23.6%), gastrointestinal (20.3%), and lung (13.5%). There was no difference in venous thromboembolism recurrence between the malignant (3.3%) and the nonmalignant (2.8%) venous thromboembolism groups (P = .533). Borderline higher rates for major bleeding (P = .06) and nonmajor clinically relevant bleeding (P = .08) were observed in patients with cancer.

CONCLUSIONS:

The "real world" effectiveness and safety of rivaroxaban is similar for venous thromboembolism patients with and without active malignancy.

J Thromb Haemost. 2015 Dec;13(12):2187-91.

Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial.

Agnelli G[1],

The AMPLIFY trial compared apixaban with enoxaparin followed by warfarin for the treatment of acute venous thromboembolism (VTE).

To perform a subgroup analysis to compare the efficacy and safety of apixaban and enoxaparin followed by warfarin for the treatment of VTE in patients with cancer enrolled in AMPLIFY.

PATIENTS/METHODS:

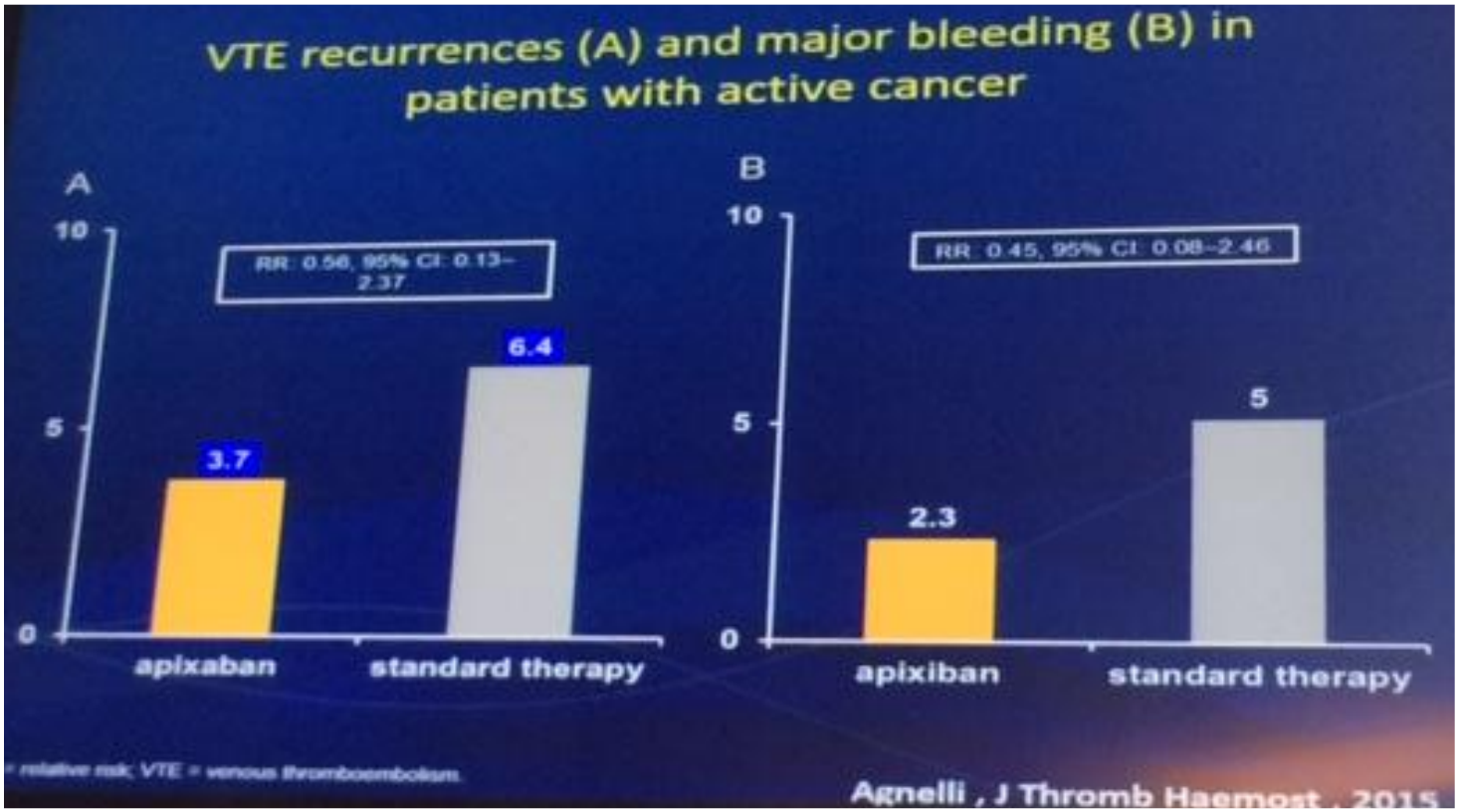
Patients with symptomatic VTE were randomized to a 6-month course of apixaban or enoxaparin followed by warfarin. The primary efficacy outcome and principal safety outcome were recurrent VTE or VTE-related death and major bleeding, respectively.

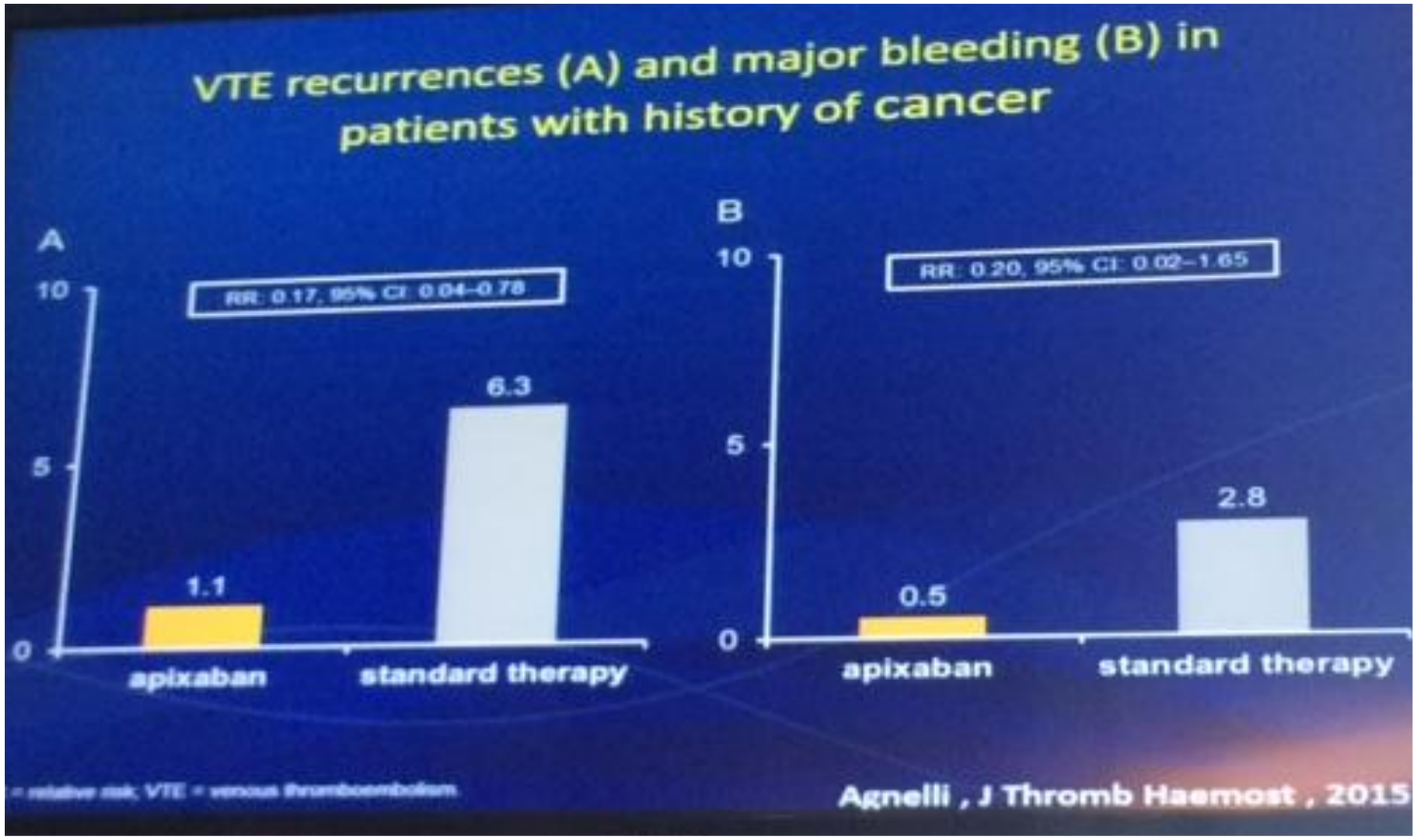
RESULTS:

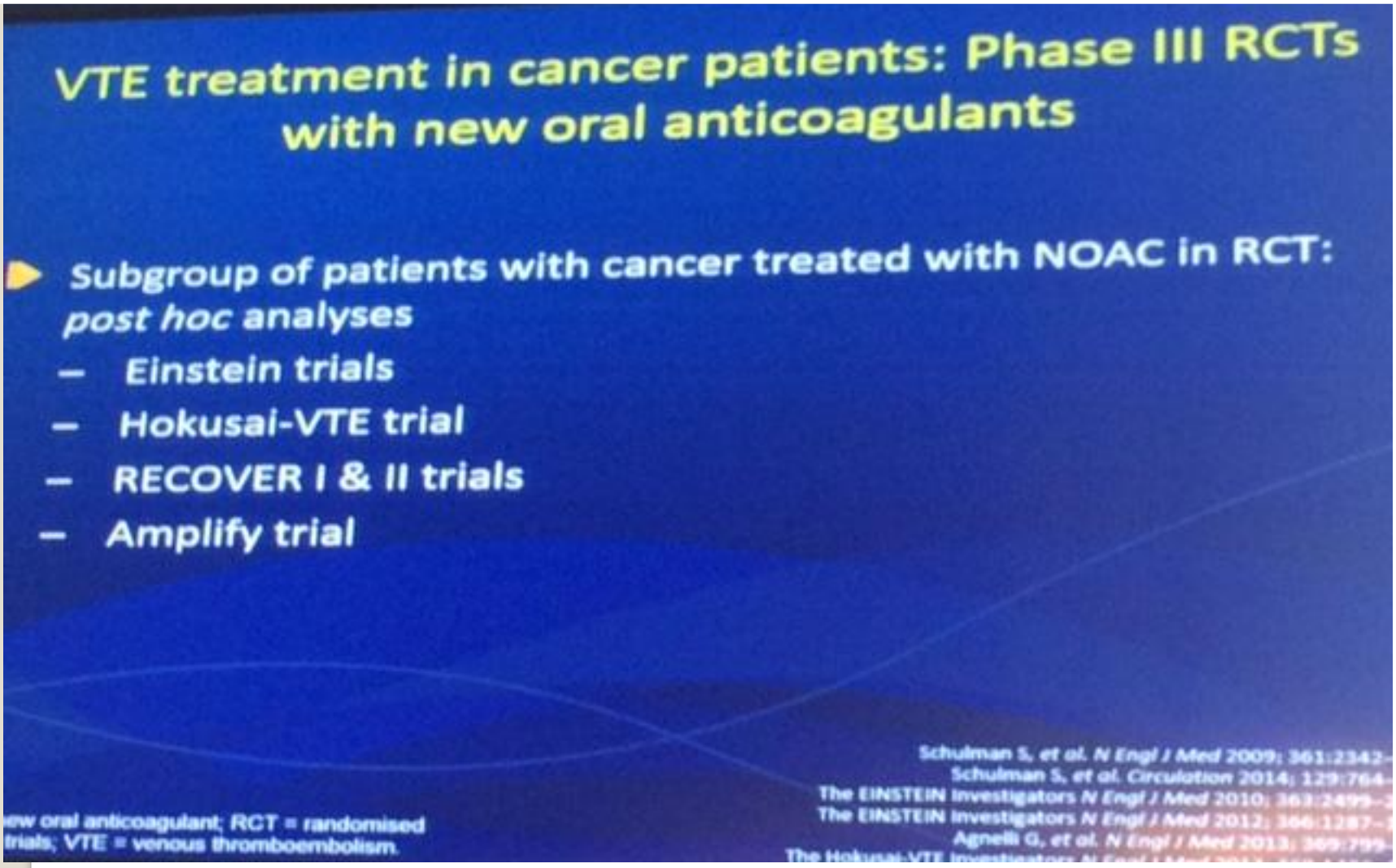
Of the 5395 patients randomized, 169 (3.1%) had active cancer at baseline, and 365 (6.8%) had a history of cancer without activecancer at baseline. Among patients with active cancer, recurrent VTE occurred in 3.7% and 6.4% of evaluable patients in the apixaban and enoxaparin/warfarin groups, respectively (relative risk [RR] 0.56, 95% confidence interval [CI] 0.13-2.37); major bleeding occurred in 2.3% and 5.0% of evaluable patients, respectively (RR 0.45, 95% CI 0.08-2.46). Among patients with a history of cancer, recurrent VTE occurred in 1.1% and 6.3% of evaluable patients in the apixaban and enoxaparin/warfarin groups, respectively (RR 0.17, 95% CI 0.04-0.78); major bleeding occurred in 0.5% and 2.8% of treated patients, respectively (RR 0.20, 95% CI 0.02-1.65).

CONCLUSIONS:

The results of this subgroup analysis suggest that apixaban is a convenient option for cancer patients with VTE. However, additional studies are needed to confirm this concept and to compare apixaban with low molecular weight heparin in these patients.

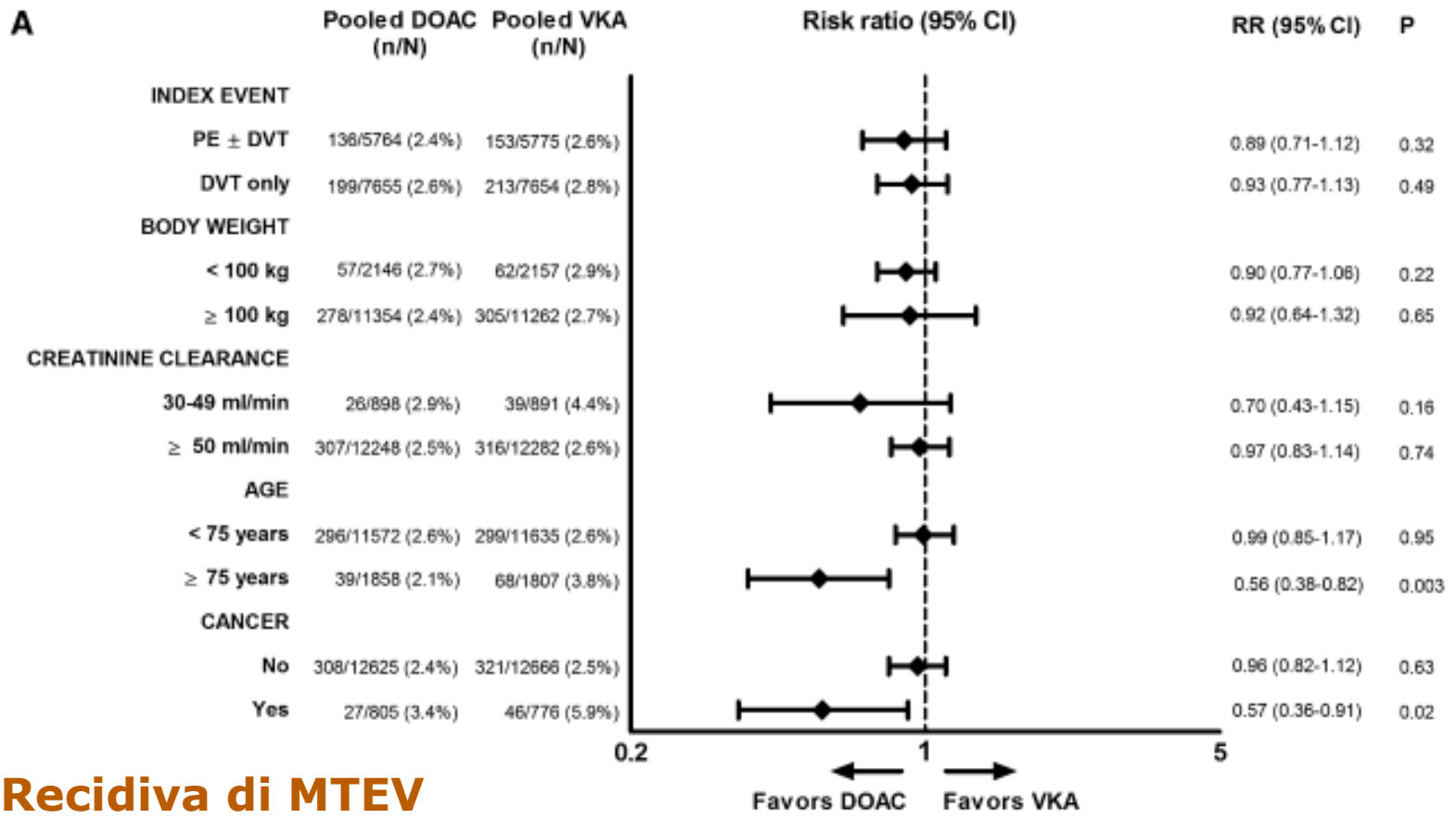

VTE recurrences (A) and major bleeding (B) in patients with active cancer
A
10
5
0
RR: 0.56, 95% CI: 0.13–2.37
3.7
6.4
apixaban
standard therapy
B
10
5
0
RR: 0.45, 95% CI: 0.08–2.46
2.3
5
apixiban
standard therapy
= relative risk; VTE = venous thromboembolism
Agnelli , J Thromb Haemost , 2015


VTE recurrences (A) and major bleeding (B) in patients with history of cancer
A
10
5
0
RR: 0.17, 95% CI: 0.04–0.78
6.3
1.1
apixaban
standard therapy
B
10
5
0
RR: 0.20, 95% CI: 0.02–1.65
2.8
0.5
apixaban
standard therapy
Agnelli , J Thromb Haemost , 2015


VTE treatment in cancer patients: Phase III RCTs with new oral anticoagulants
Subgroup of patients with cancer treated with NOAC in RCT: post hoc analyses
– Einstein trials
– Hokusai-VTE trial
– RECOVER I & II trials
– Amplify trial
Schulman S, et al. N Engl J Med 2009; 361:2342–
Schulman S, et al. Circulation 2014; 129:764–
The EINSTEIN Investigators N Engl J Med 2010; 363:2499–
The EINSTEIN Investigators N Engl J Med 2012; 366:1287–
Agnelli G, et al. N Engl J Med 2013; 369:799–
ew oral anticoagulant; RCT = randomised
trials; VTE = venous thromboembolism.

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 di MTEV

NOA for VTE: pooled analyses

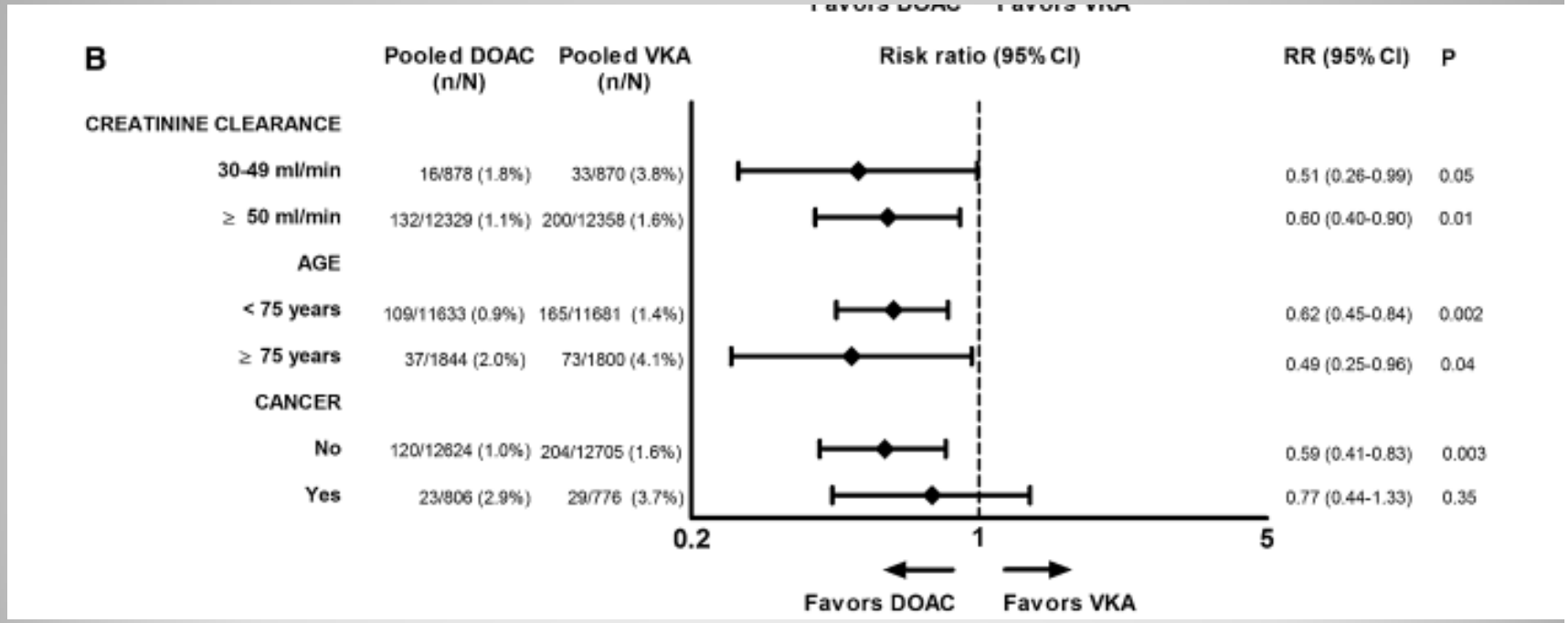
Recurrent VTE	NOAC	Conv. Treat.	RR (95% CI), p
Body weight ≥ 100 kg	2.4%	2.7%	0.92 (0.64-1.32), 0.65
Age ≥ 75 years	2.1%	3.8%	0.56 (0.38-0.82), 0.003
CrCl 30-49 ml/min	2.9%	4.4%	0.70 (0.43-1.15), 0.16
Cancer	3.8%	5.9%	0.63* (0.37-1.10),

* OR

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]



Sanguinamenti maggiori

NOA for VTE: pooled analyses

Major Bleeding	NOAC	Conv. Treat.	RR (95% CI), p
Major GI bleeding	0.5%	0.6%	0.78 (0.47-1.31), 0.35
Age ≥ 75 years	2.0%	4.1%	0.49 (0.25-0.96), 0.04
CrCl 30-49 ml/min	1.8%	3.8%	0.51 (0.26-0.99), 0.05
Cancer	3.2%	4.2%	0.77 (0.41-1.44),

* OR

The treatment of cancer-associated venous thromboembolism in the era of the novel oral anticoagulants

Paolo Prandoni

To cite this article: Paolo Prandoni (2015) The treatment of cancer-associated venous thromboembolism in the era of the novel oral anticoagulants, Expert Opinion on Pharmacotherapy, 16:16, 2391-2394, DOI: 10.1517/14656566.2015.1088003

To link to this article: http://dx.doi.org/10.1517/14656566.2015.1088003

What about the DOAC? Although available findings are encouraging [14,15], their benefit–risk profile is currently difficult to evaluate. Whether the dose–response in cancer patients is consistent with that found in patients free from malignancy is uncertain. Indeed, poor nutrition, infection, concomitant medication, vomiting and impaired liver function can cause unpredictable changes in the dose–response of the DOAC, in analogy with that expected with the use of VKA. Available

with a good chance of successful development. Accordingly, they cannot be currently recommended on a routine basis for the treatment of patients with CAT. There is the need for proper future clinical trials in which they are directly compared to LMWH. If they prove to be at least non-inferior to LMWH, the oral administration of drugs that do not require laboratory monitoring has the potential to open new scenarios for the initial and long-term treatment of CAT.

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],

Direct oral anticoagulants may be effective and safe for treatment of venous thromboembolism (VTE) in cancer patients, but they have not been compared with low-molecular-weight heparin (LMWH), the current recommended treatment for these patients. The Hokusai VTE-cancer study is a randomised, open-label, clinical trial to evaluate whether edoxaban, an oral factor Xa inhibitor, is non-inferior to LMWH for treatment of VTE in patients with cancer. We present the rationale and some design features of the study. One such feature is the composite primary outcome of recurrent VTE and major bleeding during a 12-month study period. These two complications occur frequently in cancer patients receiving anticoagulant treatment and have a significant impact. The evaluation beyond six months will fill the current gap in the evidence base for the long-term treatment of these patients. Based on the observation that the risk of recurrent VTE in patients with active cancer is similar to that in those with a history of cancer, the Hokusai VTE-cancer study will enrol patients if whose cancer was diagnosed within the past two years. In addition, patients with incidental VTE are eligible because their risk of recurrent VTE is similar to that in patients with symptomatic disease. **The unique design features of the Hokusai VTE-cancer study should lead to enrolment of a broad spectrum of cancer patients with VTE who could benefit from oral anticoagulant treatment.**

La Ricerca Clinica FADOI: Promotore di uno studio Investigator-Initiated internazionale

Giancarlo Agnelli – Mauro Campanini

- Ricerca promossa e coordinata da FADOI, con collaborazione scientifica dell'Università di Perugia (Coordinatore Prof. G. Agnell
- Studio randomizzato controllato con utilizzo di un DOAC (Apixaban) per il trattamento del tromboembolismo venoso in pazienti con cancro, vs terapia standard (EBPM)
- Arruolamento di circa 1200 Pazienti in 8 Paesi Europei + Israele + USA+ Canada
- Inizio studio previsto IIIQ-2016

STUDIO CARAVAGGIO

In corso di valutazione al CE ASLTO2 Ospedale Giovanni Bosco

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

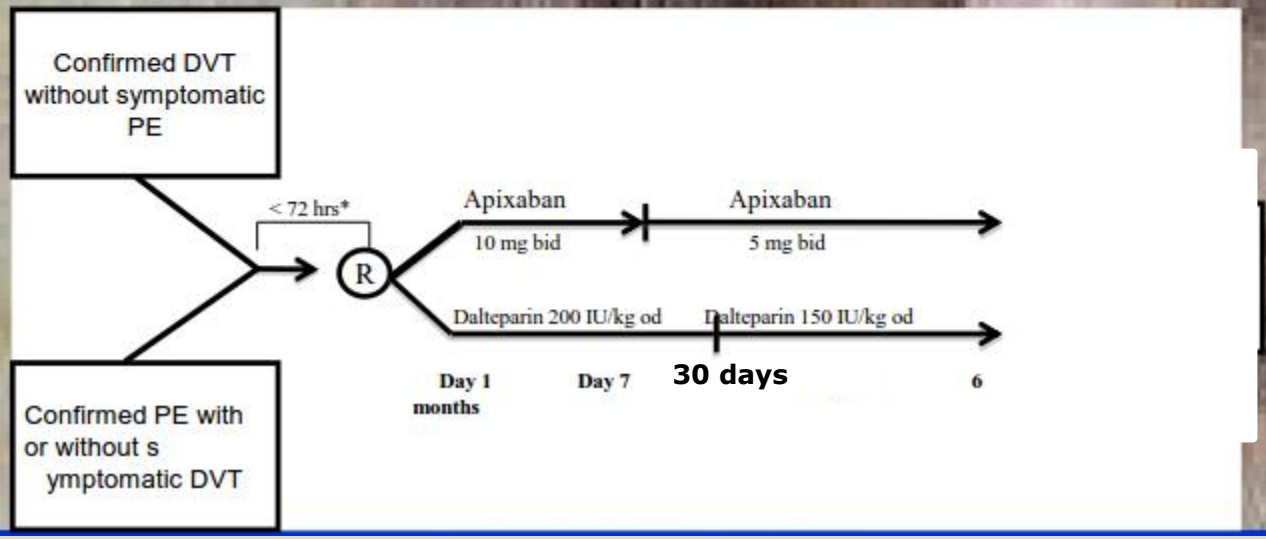


Table 4. Oncology drugs with CYP3A4 and P-glycoprotein interactions

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

(continued)

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						
Hormonal agents						
Tamoxifen	+++		+			●
Raloxifene						
Anastrozole			+			
Letrozole	+					
Fulvestrant	+					
Leuprolide						
Flutamide	+++					
Bicalutamide			++			
Enzalutamide	+++	+++				●
Abiraterone	+++		++			●
Mitotane						
Immune-modulating agents						
Cyclosporine	+++		++	●		●
Sirolimus	+++		+	●		
Everolimus	+++			●		
Temsirolimus	+++		+	●		
Tacrolimus	+++		+	●		●
Dexamethasone	+++	+++		●	●	●
Prednisone	+	++				

Oncology drugs	CYP3A4 interactions[a]			P-glycoprotein interactio	
	Substrate	Inducer	Inhibitor	Substrate	Inducer
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					

Proposta di valutazione pazienti candidabili a NOACs

- **Valutazione del rischio emorragico**

No eventi emorragici nei precedenti 2-3 mesi

Assenza di neoplasie intracraniche o viscerali a rischio emorragico

- **Piastrine**

Piastrine> 80000-100000/mm3

No se precedenti piastrinopenia da chemio o chemio potenzialmente piastrinopenizzanti

- **Esclusa coagulopatia**: PT, PTT e fibrinogeno nn
- **Funzione renale**:

No se terapie potenzialmente nefrotossiche o precedenti nefrotossicità

Controindicati in pz con Pz con CrCl <30

- **Funzione epatica**:

Controindicato in pz con insuff eaptica moderata/severa

- **Interazioni farmacologiche (vedi tabelle)**
- **Selezionare i pazienti con buona compliance**

Criteria for NOAC 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