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

30 GIORNATE CARDIOLOGICHE TORINESI

TURIN,
October
25th-27th
2018
Starhotels Majestic

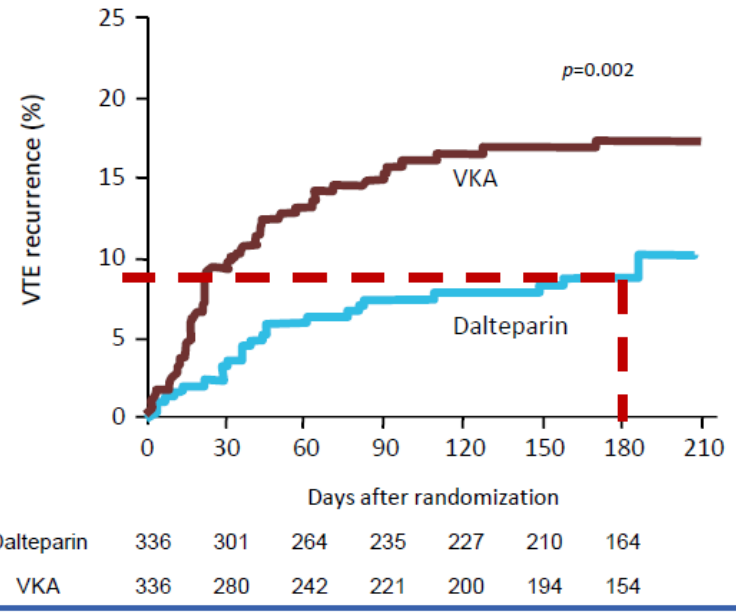
Use of DOAC in cancer patients: is it time to finally legitimize their use?

Paolo Colonna, MD FESC,
Cardiology Hospital,
Policlinico of Bari - Italy
Past-president SIECVI

DOI: Research fundings (Institutional)
from Bayer, Boehringer, BMS / Pfizer, Daiichi

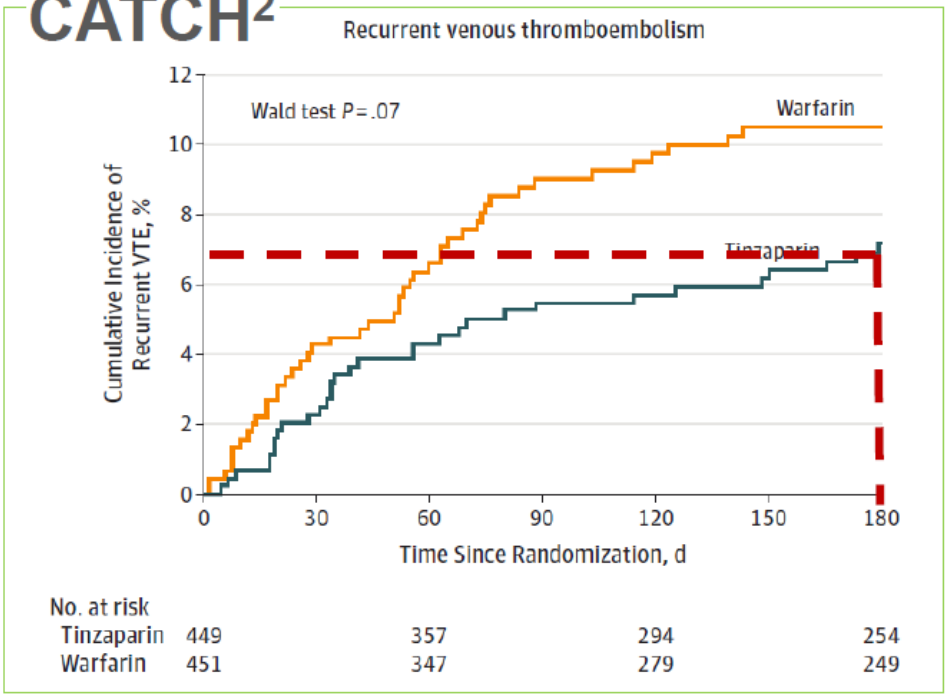
CLOT and CATCH Studies: LMWH vs VKA in CAT

CLOT[1]



Major bleeding (6% vs 4%) and mortality (39% vs 41% at 6 months)

CATCH[2]



Major bleeding similar 2.7% (LMWH) vs 2.4% (VKA) (p=0.77)

1, Lee AY et al, N Engl J Med 2003;349:146-153; 2. Lee AY et, JAMA 2015;314:677-686

Terapie antitrombotiche della TEV nei pz con cancro

	ESC 2014[1]	ACCP 2016[2]	ESMO 2011[3]
Trattamento acuto del TEV	LMWH (*Classe IIa Livello B*)	LMWH > VKA (*Grado 2B*)> Dabigatran, Rivaroxaban, Apixaban, Edoxaban (*Grado 2C*)	LMWH or IV UFH per almeno 5 giorni, dopo dosi più basse di LMWH in monoterapia > VKA monotherapia (IA)
Durata anticoagulazione	3–6 mesi anticoagulazione estesa va considerata per indefinito o finchè cancro curato	Terapia estesa indipendentemente dal rischio di sanguinamento	Dosi più basse di LMWH[a] per 6 mesi > VKA per 3-6 mesi

Standard treatment of VTE with LMWH in cancer according to guidelines

Initial treatment:

LMWH therapeutic dose (200UI/kg/die)

Continue for 1 months

↓

Long-term treatment:

Reduce LMWH to 75% of the initial dosage

Continue LMWH for 3-6 months

↓

Indefinite treatment:

In case of "active cancer" or during chemotherapy

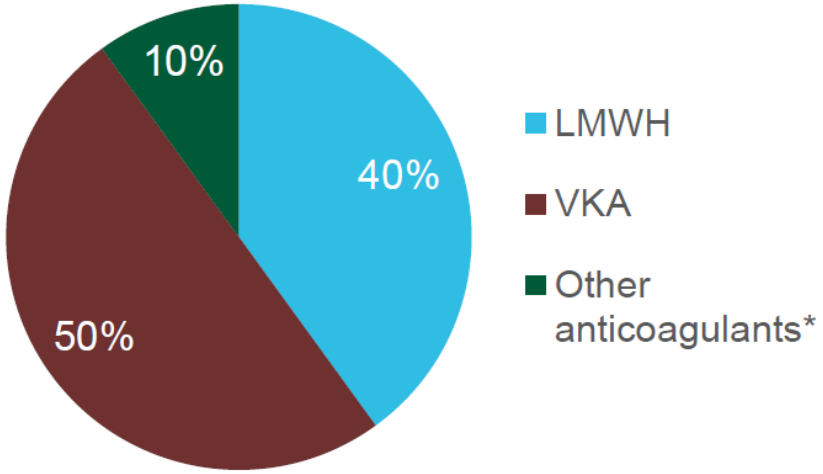
continue with LMWH,VKA……?

Database Analysis: Utilization of Anticoagulants for VTE Treatments in Patients with Active Cancer

Retrospective analysis of US healthcare claims

- High levels of VKA use despite US oncology guidelines recommending LMWH for 3-6 months
- fewer patients initiated on LMWH remained on treatment compared to OACs

Use of anticoagulants among patients with active cancer and VTE (**2009-2014**) (N=52,911)



*Including NOACs and fondaparinux

Khorana AA et al, Thromb Res 2016;145:51-53

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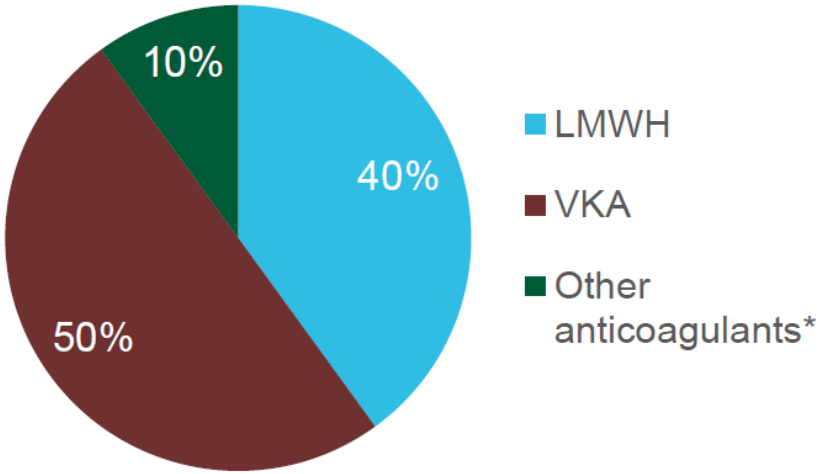
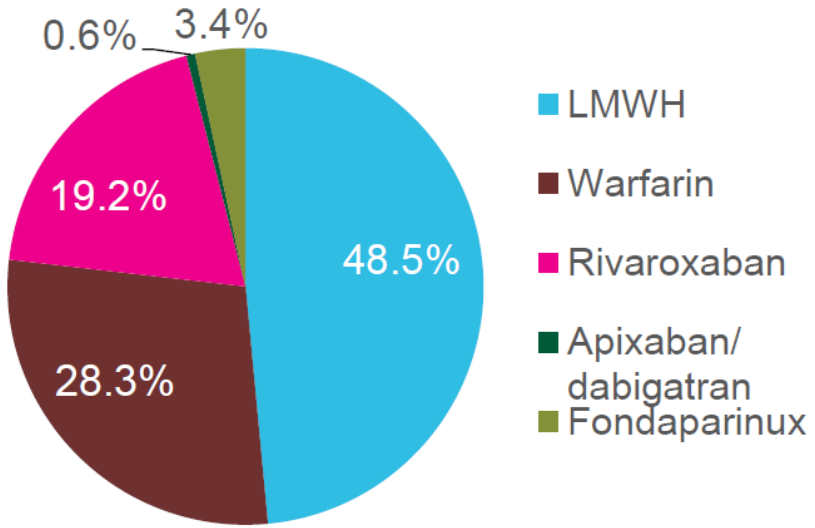


Use of anticoagulants among patients with active cancer and VTE (**2013-2014**)



Khorana AA et al, Thromb Res 2016;145:51-53

Trattamento a lungo termine con NOAC del tromboembolismo venoso

- Sottoanalisi pazienti con cancro attivo in studi di registrazione clinica
- Registri di vita reale in pazienti con cancro
- Trial clinici randomizzati di soli pazienti con cancro attivo

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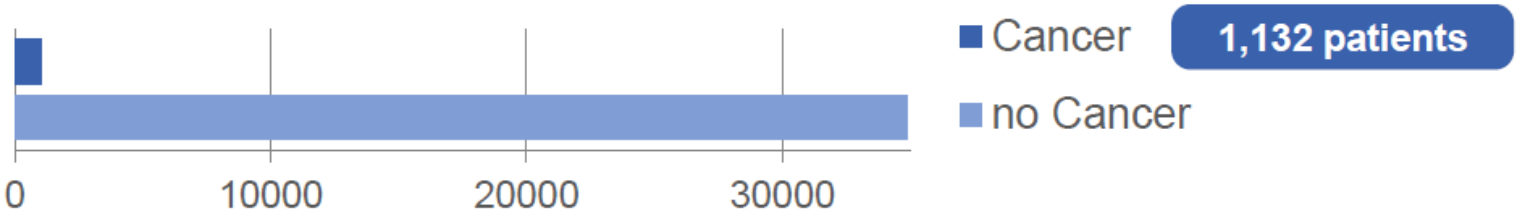
Treatment of VTE in cancer patients: NOACs

Phase III NOAC trials including more than 30,000 patients



Drug	Trial name	cancer patients (%)
Rivaroxaban	EINSTEIN-DVT	5,2
	EINSTEIN-PE	4.6
	EINSTEIN-extension	4.5
Dabigatran	RE-COVER	4.8
	RE-COVERII	0
	RE-MEDY	2.1
	RE-SONATE	
Apixaban	AMPLIFY	2.7
	AMPLIFY-EXT	1.7
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.

Direct Oral Anticoagulants in Patients With VTE and Cancer

CHEST 2015; 147:475- 483

A Systematic Review and Meta-analysis

Maria Cristina Vedovati, MD; Federico Germini, MD; Giancarlo Agnelli, MD; and Cecilia Becattini, MD, PhD

Study	Study design	Study Phase	Study drug	Dose	Study period	Patients	Patients with cancer, n (%)	TTR (%)
AMPLIFY 2013	DB	III	Apix.	10 mg bid for 7 days followed by 5 mg bid	6 mo	5395	169 (3.1)	61
BOTTICELLI 2008	Open (DB for apix. doses)	II	Apix.	5 mg or 10 mg bid or 20 mg qd	3 mo	520	37 (7.1)	57
EINSTEIN DVT 2010	Open	III	Riv.	15 mg bid 3 weeks followed by 20 mg qd	12 mo	3449	207 (6.0)	57.7
EINSTEIN DVT DOSE RANGING 2008	Open (DB for riv. doses)	II	Riv.	20 mg or 30 mg or 40 mg qd	3 mo	543	51 (9.4)	50.3
EINSTEIN PE 2012	Open	III	Riv.	15 mg bid 3 weeks followed by 20 mg qd	12 mo	4832	223 (4.6)	62.7
HOKUSAI 2013	DB	III	Heparin/ Edox.	60 mg od or 30 mg od	12 mo	8240	208 (2.5)	63.5
ODIXA DVT 2007	Open (DB for riv. doses)	II	Riv.	10 or 20 or 30 mg bid or 40 mg qd	3 mo	528	16 (3.0)	60
RECOVER 2009	DB	III	Heparin/ Dab.	150 mg bid	6 mo	2539	121 (4.8)	60
RECOVER II 2013	DB	III	Heparin/ Dab.	150 mg bid	6 mo	2589	100 (3.9)	57
REMEDY 2013	DB	III	Dab.	150 mg bid	6 - 36 mo	2856	119 (4.2)	65.3

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HOKUSAI 2013	DB	III	Heparin/ Edox.	60 mg od or 30 mg od	12 mo	8240	208 (2.5)	63.5
ODIXA DVT 2007	Open (DB for riv. doses)	II	No dosage used in phase III			528	16 (3.0)	60
RECOVER 2009	DB	III	Heparin/ Dab.	150 mg bid	6 mo	2539	121 (4.8)	60
RECOVER II 2013	DB	III	Heparin/ Dab.	150 mg bid	6 mo	2589	100 (3.9)	57
REMEDY 2013	DB	II	Data on extended treatment			2856	119 (4.2)	65.3

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Maria Cristina Vedovati, MD; Federico Germini, MD; Giancarlo Agnelli, MD; and Cecilia Becattini, MD, PhD

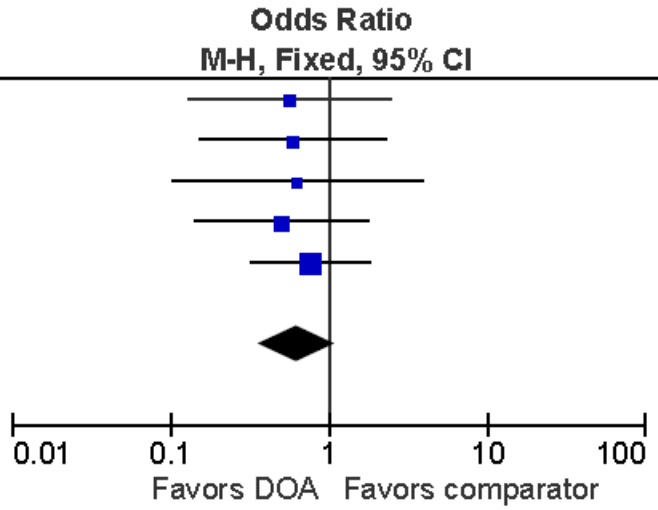
Recurrent VTE in DOA 23 / 595 (3.8%)

in conv. antic. 32 / 537 (5.9%)

Study or Subgroup	DOA Events	DOA Total	Comparator Events	Comparator Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AMPLIFY 2013	3	81	5	78	15.2%	0.56 [0.13, 2.43]
EINSTEIN-DVT 2010	4	118	5	89	17.1%	0.59 [0.15, 2.26]
EINSTEIN-PE 2012	2	114	3	109	9.4%	0.63 [0.10, 3.85]
HOKUSAI 2013	4	109	7	99	22.0%	0.50 [0.14, 1.77]
RECOVER I & II 2013	10	173	12	162	36.3%	0.77 [0.32, 1.83]
Total (95% CI)		**595**		**537**	**100.0%**	**0.63 [0.37, 1.10]**
Total events	23		32			

Heterogeneity: $Chi^2 = 0.36$, $df = 4$ ($P = 0.99$); $I^2 = 0\%$

Test for overall effect: $Z = 1.62$ ($P = 0.10$)



Direct Oral Anticoagulants in Patients With VTE and Cancer

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A Systematic Review and Meta-analysis

Maria Cristina Vedovati, MD; Federico Germini, MD; Giancarlo Agnelli, MD; and Cecilia Becattini, MD, PhD

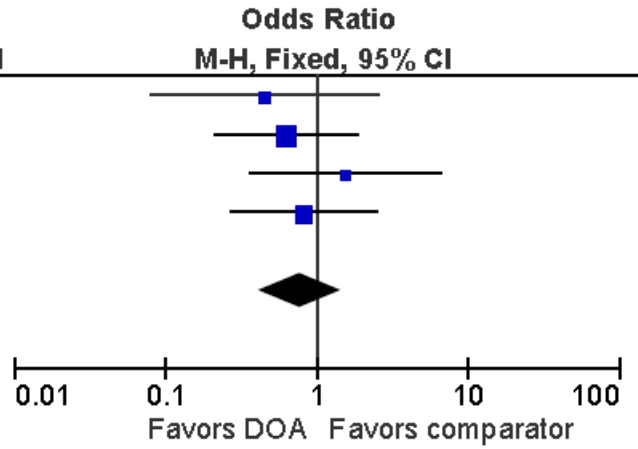
Major Bleeding in DOA 19 / 587 (3.2%)

in conv. antic. 22 / 527 (4.2%)

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)



Direct Oral Anticoagulants in Patients With VTE and Cancer

A Systematic Review and Meta-analysis

CHEST 2015; 147:475- 483

Maria Cristina Vedovati, MD; Federico Germini, MD; Giancarlo Agnelli, MD; and Cecilia Becattini, MD, PhD

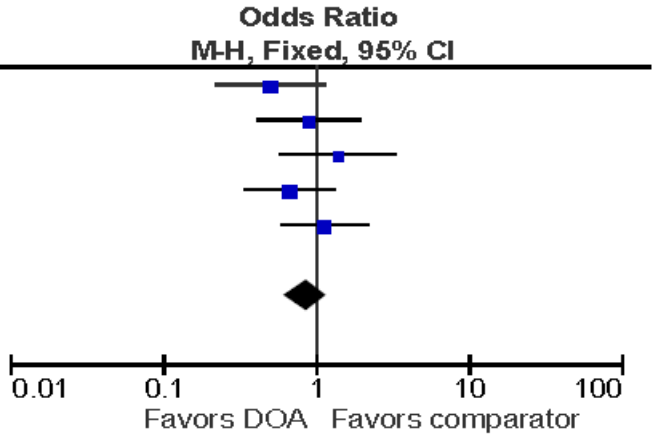
Clinically relevant bleeding in DOA 85 / 587 (14.4%)

in conv. antic. 87 / 527 (16.5%)

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			

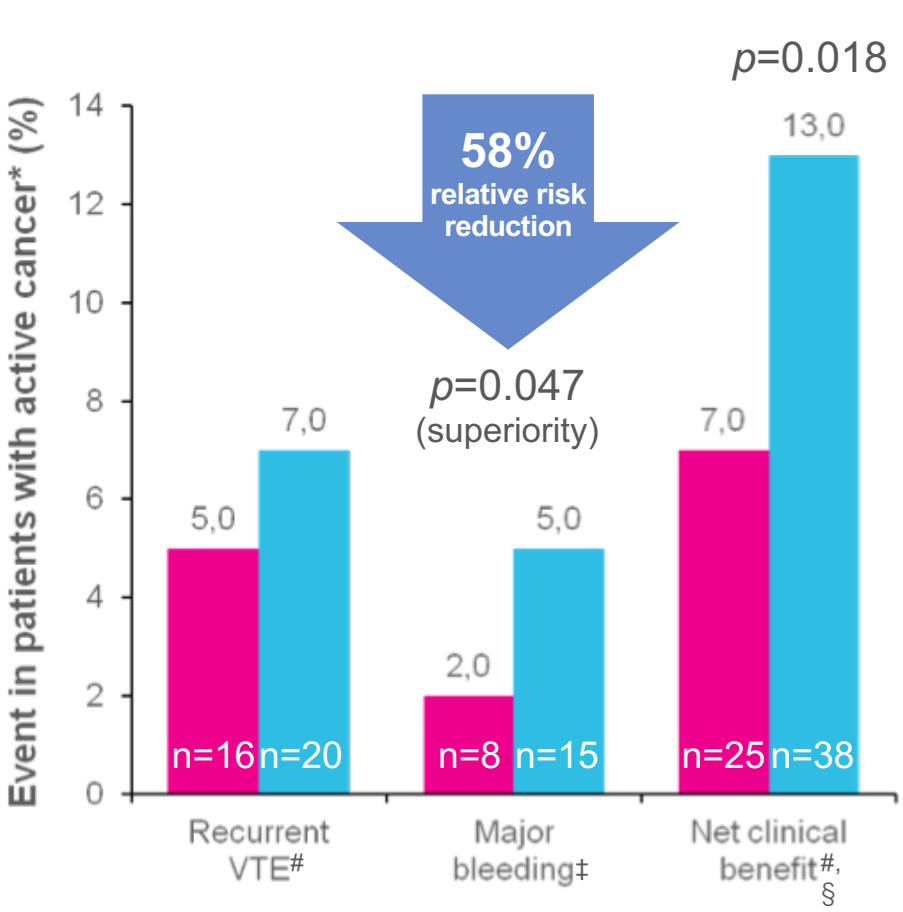
Heterogeneity: Chi² = 4.04, df = 4 (P = 0.40); I² = 1%

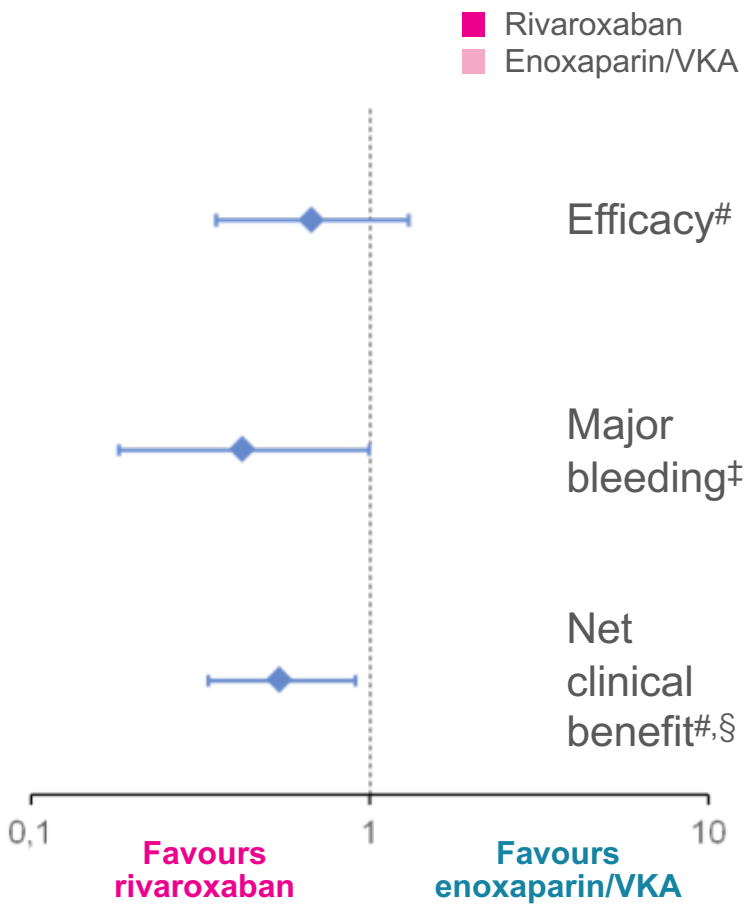
Test for overall effect: Z = 0.96 (P = 0.34)



EINSTEIN DVT/PE Pooled Analysis: Patients with Active Cancer

Prins M et al. Lancet Haematol 2014





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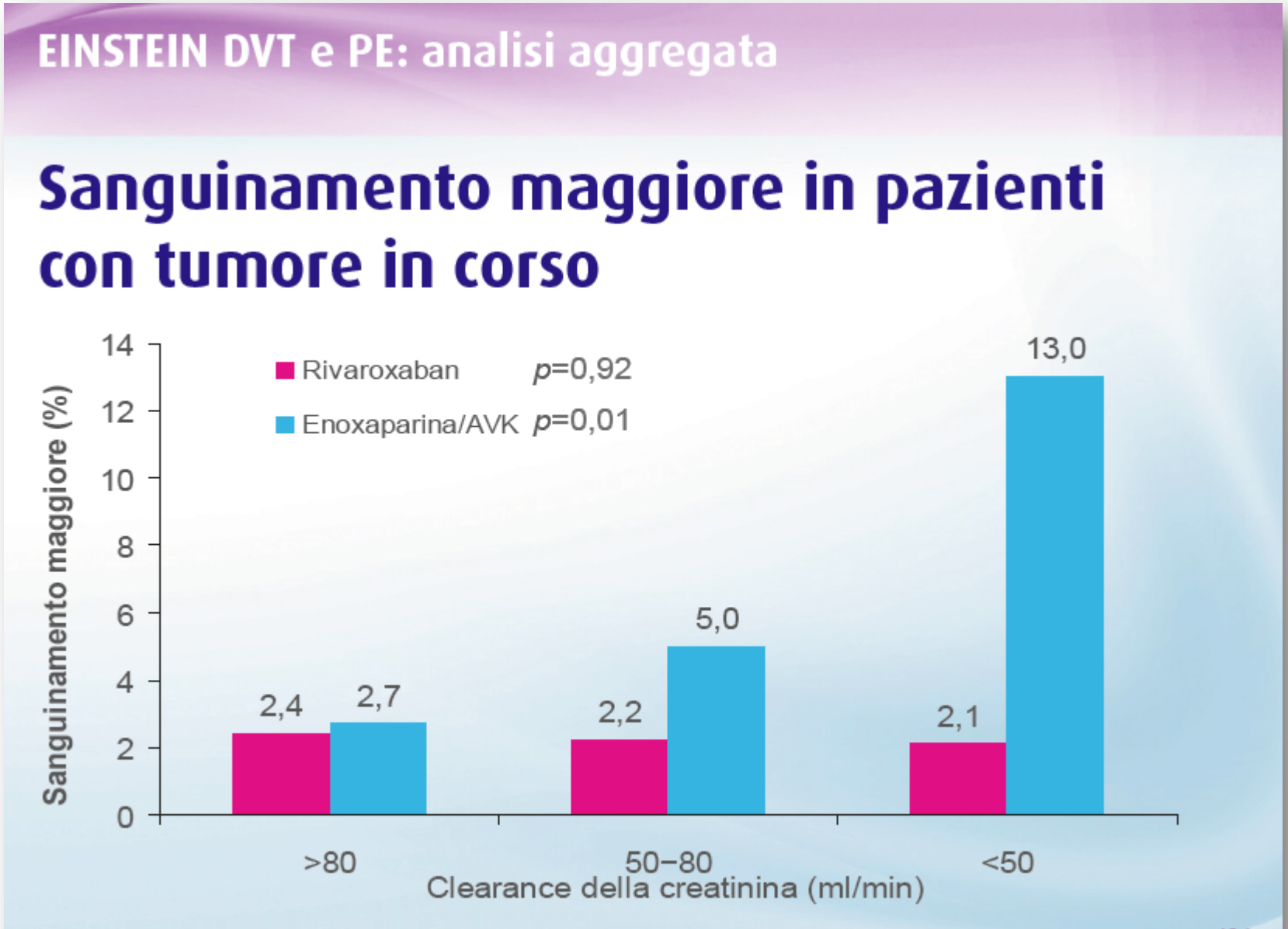


Journal of Thrombosis and Haemostasis, **13**: 2187–2191 2015 DOI: 10.1111/jth.13153

BRIEF REPORT

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

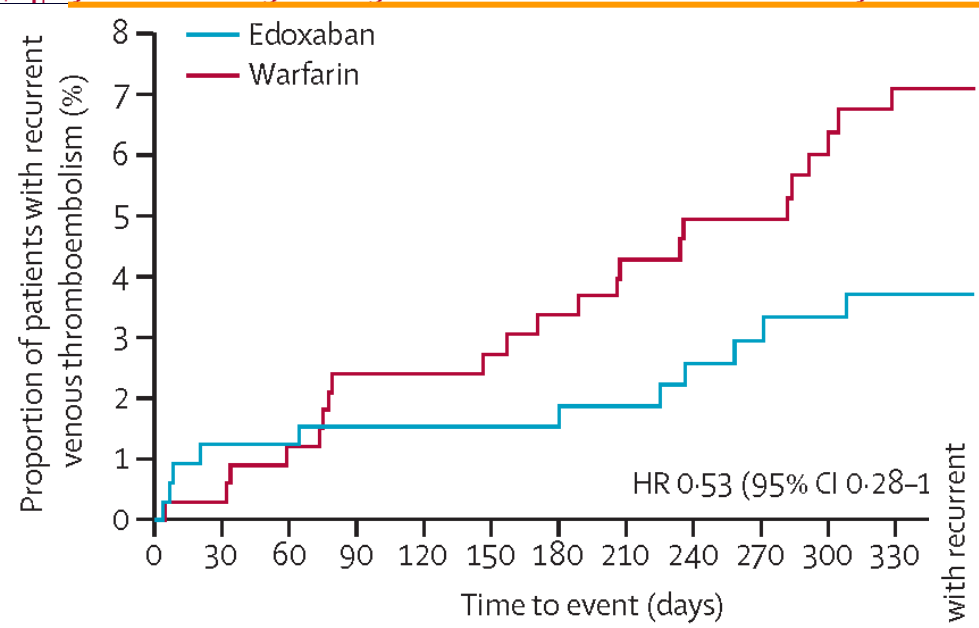
G. AGNELLI,* H. R. BULLER,† A. COHEN,‡ A. S. GALLUS,§ T. C. LEE,¶ R. PAK,** G. E. RASKOB,†† J. I. WEITZ‡‡ and T. YAMABE**

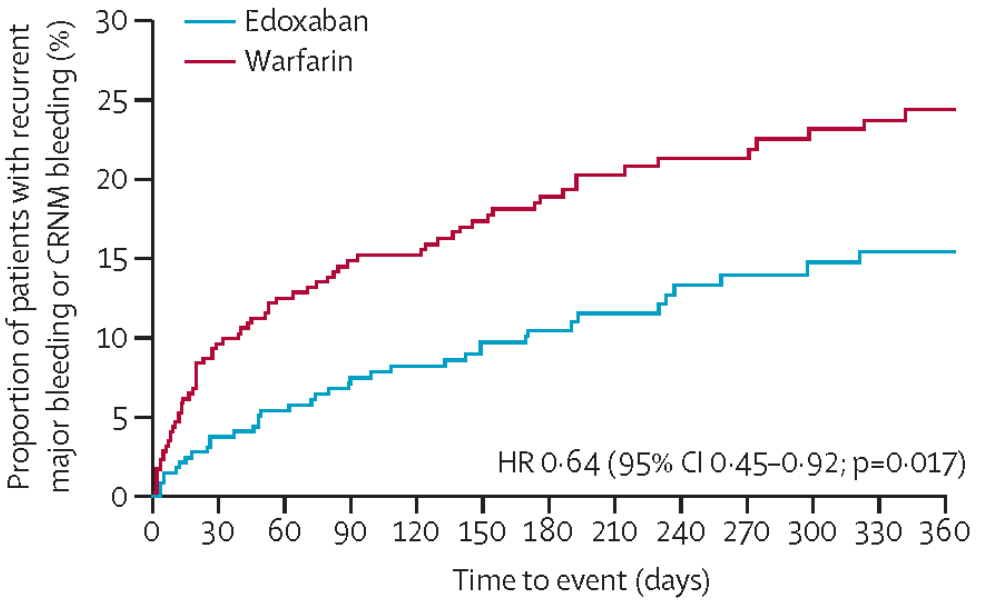
	VTE/VTE-related death		Major bleeding		MB/CRNMB	
	Patients, *n*/*N* (%)		Patients, *n*/*N* (%)		Patients, *n*/*N* (%)	
	RR (95% CI)		RR (95% CI)		RR (95% CI)	
	Apixaban	Enoxaparin/warfarin	Apixaban	Enoxaparin/warfarin	Apixaban	Enoxaparin/warfarin
Active cancer	3/81 (3.7)	5/78 (6.4)	2/87 (2.3)	4/80 (5.0)	11/87 (12.6)	18/80 (22.5)
	0.56 (0.13 2.37)		0.45 (0.08 2.46)		0.57 (0.29 1.12)	
Cancer history (without active cancer)	2/179 (1.1)	11/175 (6.3)	1/184 (0.5)	5/179 (2.8)	11/184 (6.0)	27/179 (15.1)
	0.17 (0.04 0.78)		0.20 (0.02 1.65)		0.40 (0.20 0.78)	
Active cancer and cancer history*	5/260 (1.9)	16/253 (6.3)	3/271 (1.1)	9/259 (3.5)	22/271 (8.1)	45/279 (17.4)
	0.30 (0.11 0.82)		0.32 (0.09 0.16)		0.47 (0.29 0.75)	
No cancer history/no active cancer	54/2349 (2.3)	55/2382 (2.3)	12/2405 (0.5)	40/2430 (1.7)	93/2405 (3.9)	216/2430 (8.9)
	0.99 (0.69 1.44)		0.30 (0.16 0.58)		0.43 (0.34 0.55)	
Interaction†	$P = 0.07$		$P = 0.83$		$P = 0.84$	

Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial

Gary E Raskob, Nick van Es, Annelise Segers, Pantep Angchaisuksiri, Doyeun Oh, Zoltan Boda, Roger M Lyons, Karina Meijer, Ivan Gudz, Jeffrey I Weitz, George Zhang, Hans Lanz, Michele F Mercuri, Harry R Büller, for the Hokusai-VTE investigators

Lancet Hematol 2016





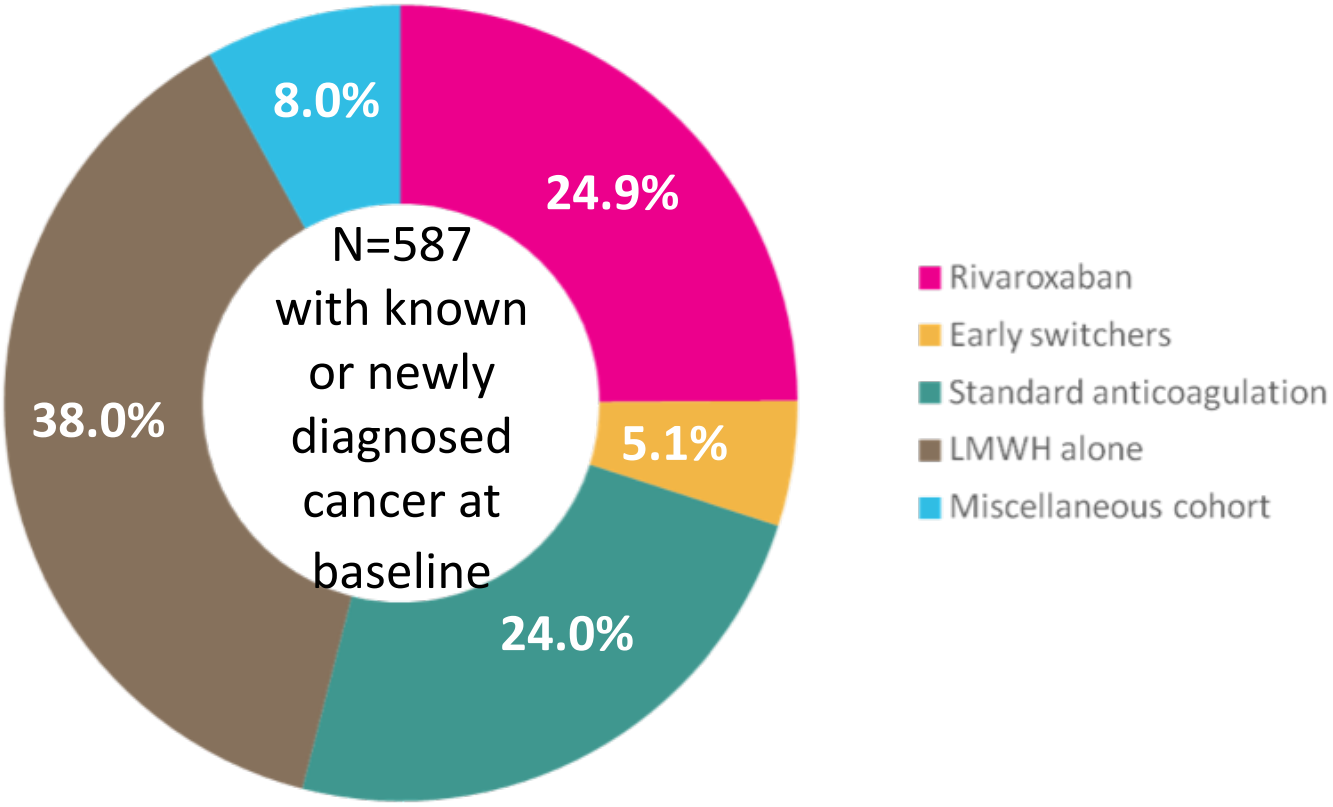
Trattamento a lungo termine con NOAC del tromboembolismo venoso

- Sottoanalisi pazienti con cancro attivo in studi di registrazione clinica
- Registri di vita reale in pazienti con cancro
- Trial clinici randomizzati di soli pazienti con cancro attivo

XALIA: A Prospective, Non-interventional Phase IV Study

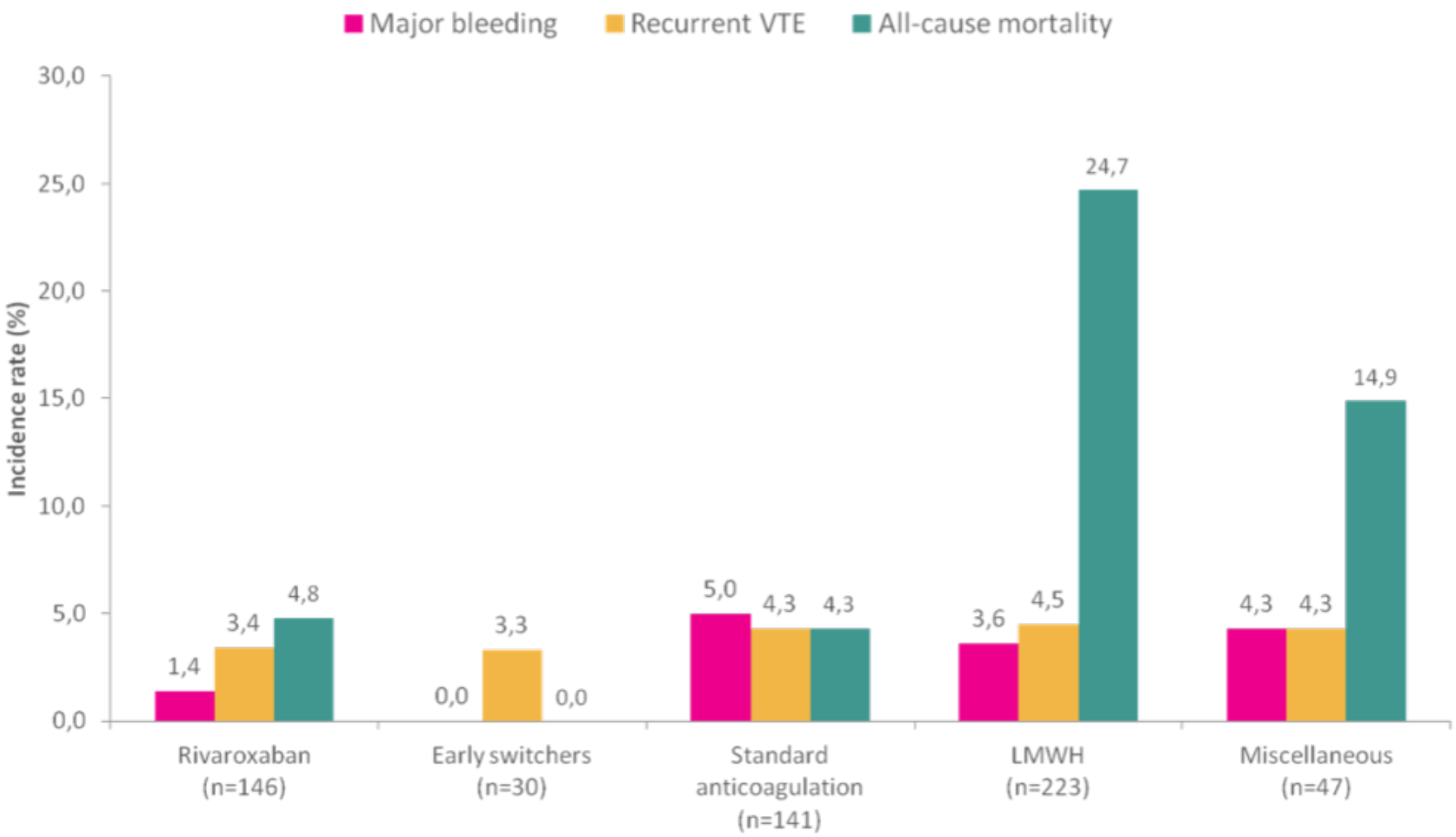
Ageno W et al. TH Open 2017

Objective: collect real-life data in patients with acute DVT treated with rivaroxaban or standard anticoagulation

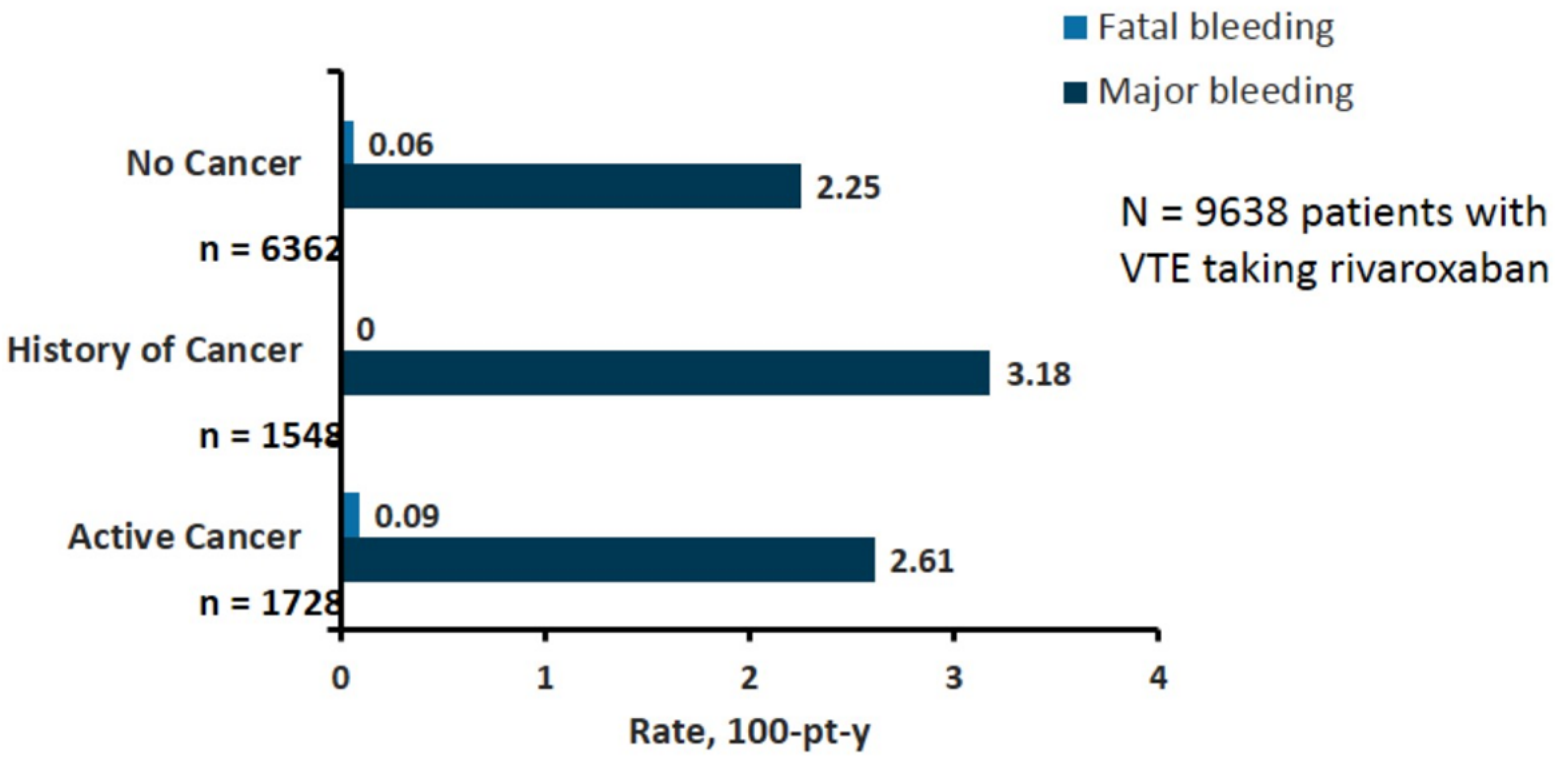


XALIA – Primary Outcomes

Ageno W et al. TH Open 2017



Major Bleeding Among Patients With and Without Cancer Taking Rivaroxaban: *a DoD Cohort Analysis*



- No significant difference in the incidence of major bleeding between the 3 groups.

Khorana AA, et al. ASH 2016. Abstract 1447.

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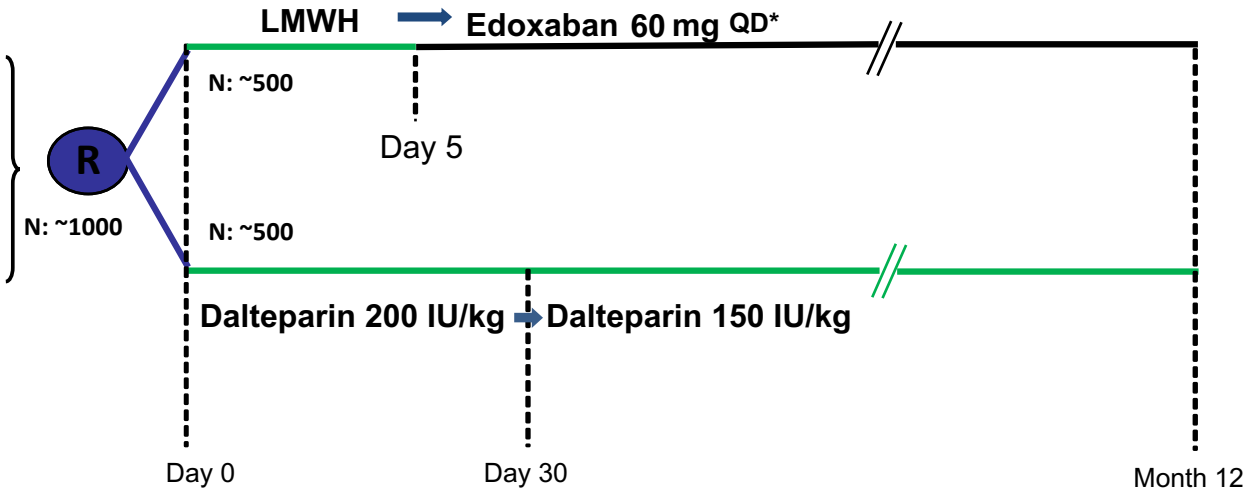
- Trial clinici randomizzati di soli pazienti con cancro attivo

	Hokusai-VTE cancer	SELECT-D	CARAVAGGIO
Drug	Lixiana (Edoxaban)	Xarelto (rivaroxaban)	Eliquis (apixaban)
DOAC dose	60mg (with 30mg dose reduction)	15mg BD x 3 weeks, 20mg QD remainder of trial	10mg BID Day 1-6, 5mg BID from 7 days to 6 months
Comparator	Dalteparin (CLOT regimen)	Dalteparin (CLOT regimen)	Dalteparin (CLOT regimen)
Heparin in DOAC arm	5 day heparin lead-in	Up to 3 days parenteral AC prior to randomization	Up to 3 days parenteral AC prior to randomization
Indication	Active cancer (or diagnosed within 2 y)	Active Cancer	Active Cancer
No. of patients	1,050	406	1,168
Primary endpoint	Composite: VTE recur and major bleeding	VTE recurrence	VTE recurrence
Treatment duration	12M	6M primary endpoint 6-12M placebo ext	6M
End date	Dec 2017	Dec 2017	Sep 2018
Design	PIII: Randomized open label	Open label, bleeding blinded adjudicated	PIII: Randomized open label
Powered for non-inferior	yes	no	Yes?
Sponsor	Daiichi-Sankyo	Warwick University, UK (IIR, part of CALLISTO program)	University of Perugia, Italy G. Agnelli IIR (BMS

Hokusai VTE - Cancer Disegno dello studio

Raskob G.E. et al, NEJM, 2017

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



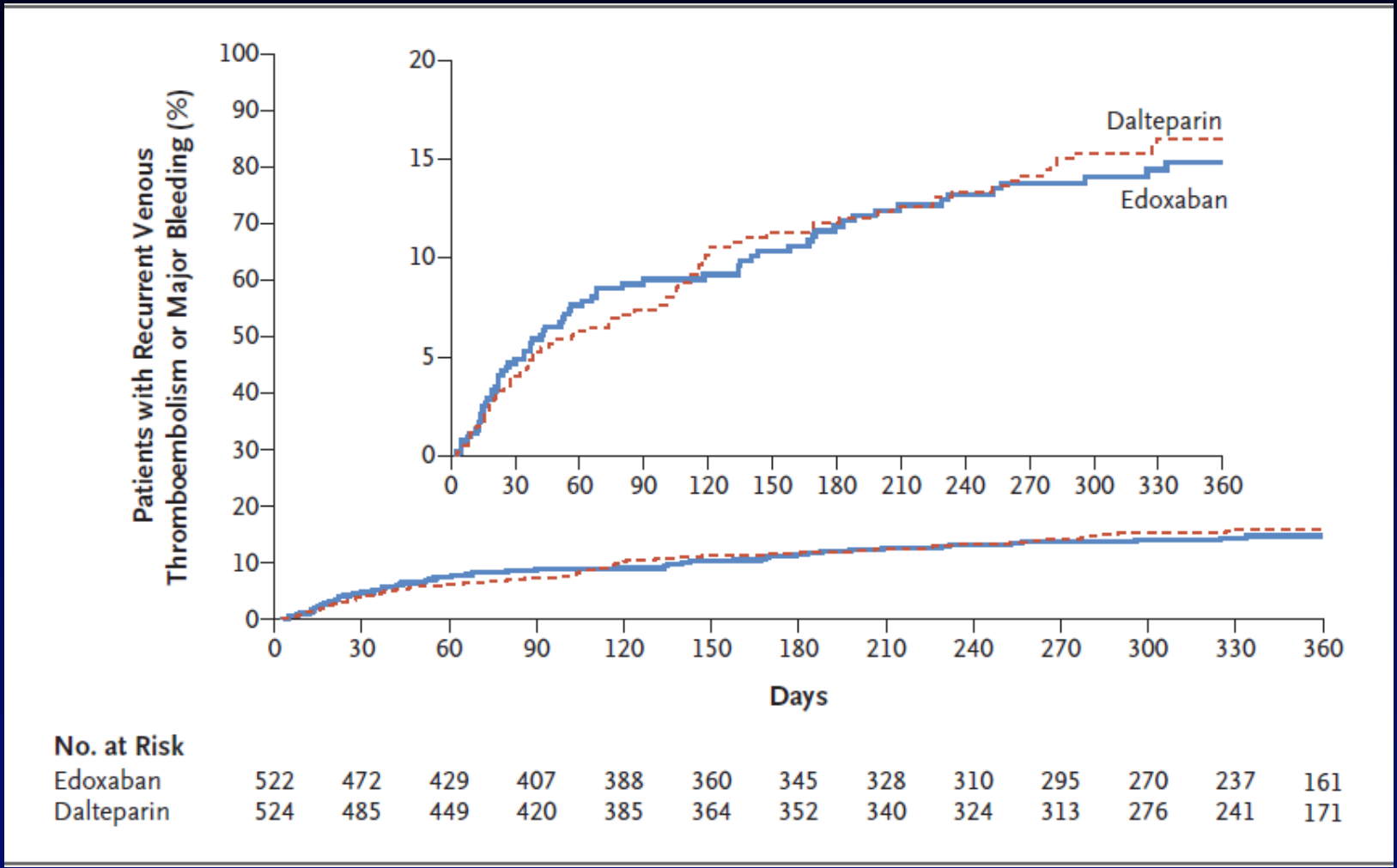
- Trattamento fino a 12 mesi (con un minimo di 6 mesi)
- I dati di efficacia e sicurezza sono stati raccolti per tutta la durata dello studio
- Gli outcomes sono stati giudicati in cieco da una Commissione Indipendente
- È stata inoltre prespecificata la severità dei sanguinamenti maggiori

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Edoxaban (N=522)	Dalteparin (N=524)
Age — yr	64.3±11.0	63.7±11.7
Male sex — no. (%)	277 (53.1)	263 (50.2)
Weight		
Mean — kg	78.8±17.9	79.1±18.1
≤60 kg — no. (%)	83 (15.9)	78 (14.9)
Creatinine clearance of 30–50 ml/min — no. (%)	38 (7.3)	34 (6.5)
Platelet count of 50,000–100,000 per μl — no. (%)	32 (6.1)	23 (4.4)
Met criteria to receive lower dose of edoxaban — no. (%)†	122 (23.4)	117 (22.3)
Qualifying diagnosis of venous thromboembolism — no. (%)		
Pulmonary embolism with or without deep-vein thrombosis	328 (62.8)	329 (62.8)
Deep-vein thrombosis only	194 (37.2)	195 (37.2)
Symptomatic deep-vein thrombosis or pulmonary embolism	355 (68.0)	351 (67.0)
Incidental deep-vein thrombosis or pulmonary embolism‡	167 (32.0)	173 (33.0)
Active cancer — no. (%)	513 (98.3)	511 (97.5)
Metastatic disease — no. (%)	274 (52.5)	280 (53.4)
Recurrent cancer — no. (%)	163 (31.2)	152 (29.0)
Cancer treatment within previous 4 wk — no. (%)§	374 (71.6)	383 (73.1)

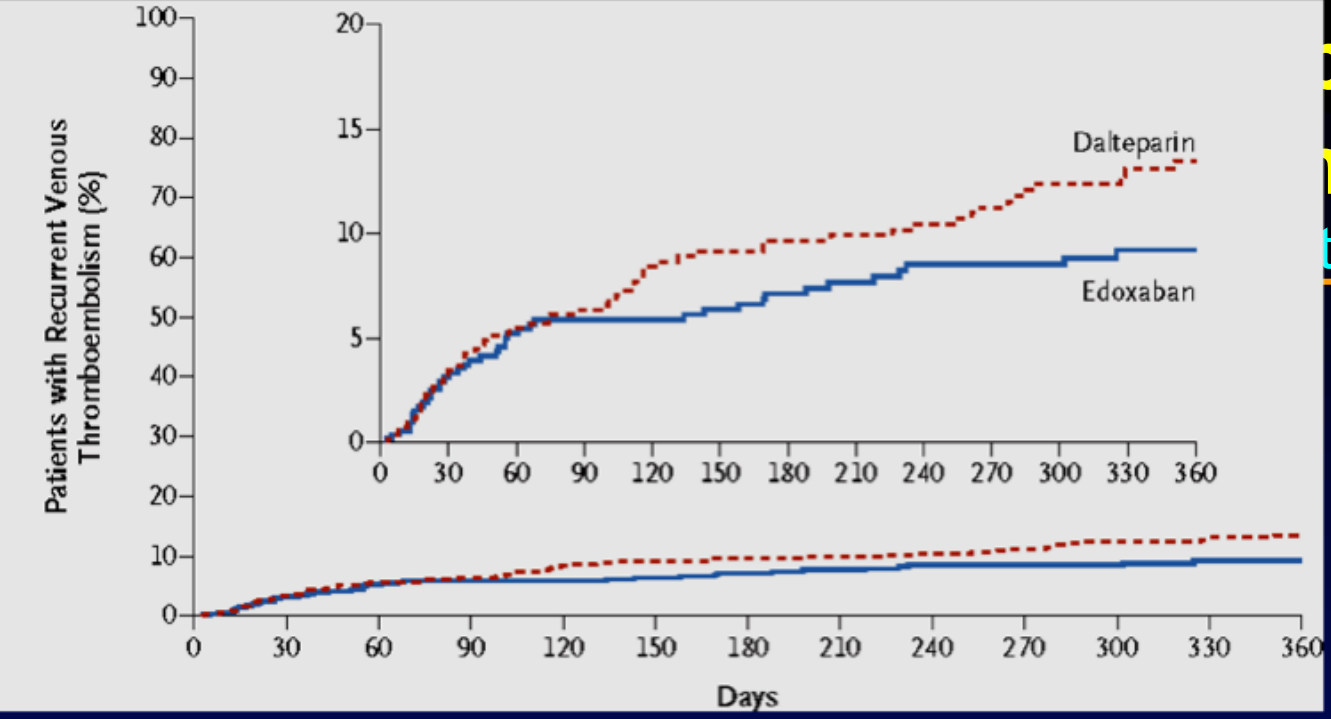
Endpoint primario composito (recidiva di TEV o sanguinamento maggiore)

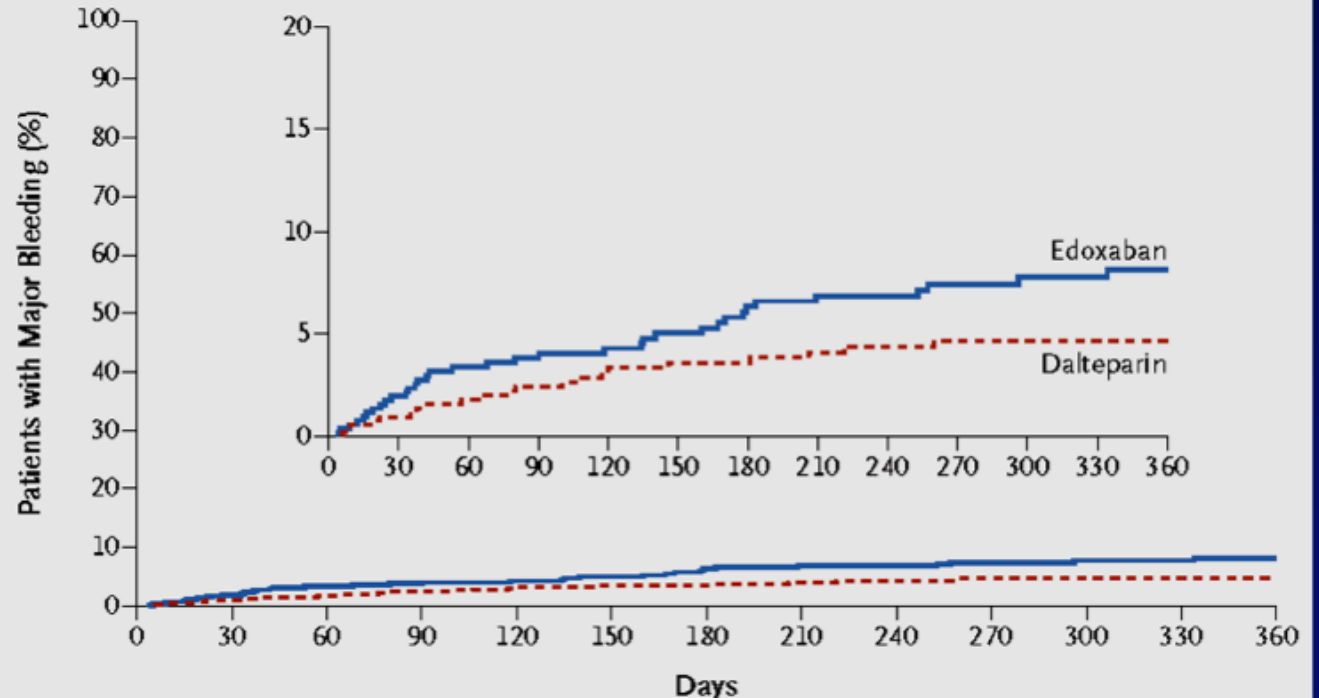
Raskob G.E. et al, NEJM, 2017



Edoxaban	Dalteparin	
67 / 522 (12.8%)	71 / 524 (13.5%)	0.97 (0.70, 1.36) *P = 0.006*

posito
nto maggiore)
t al, NEJM, 2017





Hokusai VTE Cancer. *Results.*

Secondary outcomes: bleeding

	EDOXABAN N = 522	DALTEPARIN N = 524	HR (95% CI)
Major bleeding (n, %)	36 (6.9)	21 (4)	**1.77 (1.03, 3.04) p = 0.04**

Severity	EDOXABAN N = 522	DALTEPARIN N = 524	
Category 1 (n, %)	0	0	
Category 2 (n, %)	**24 (67)**	8 (38)	**=> treatment, no emergency**
Category 3 (n, %)	12 (33)	12 (57)	**=> clinical emergency**
Category 4 (n, %)	0	1 (5)	**=> fatal bleeding**

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

Hokusai VTE-Cancer: Types of Major Bleeds Contributing to Primary Outcome

	Edoxaban (n = 522)	Dalteparin (n = 524)
Major bleeding, no. (%)	33 (6.3)	17 (3.2)
Fatal	0	2 (0.4)
Intracranial	2 (0.4)	4 (0.8)
Gastrointestinal	20 (3.8)	6 (1.1)
Upper	17 (3.3)	3 (0.6)
Lower	3 (0.6)	3 (0.6)
Urogenital	5 (1.0)	0
Other	6 (1.1)	7 (1.3)

Raskob GE, et al. *N Engl J Med.* 2017. [Epub ahead of print]

CALLISTO: Addressing Evidence Gaps in CAT

Data gaps	Ongoing or concluded
Effectiveness and safety of rivaroxaban for the prevention and treatment of CAT	CASSINI[1], select-d[2], CONKO-011[3], QAI[4], CASTA-DIVA[5]
Treatment satisfaction, treatment persistence and quality of life in cancer patients receiving rivaroxaban	select-d[2], COSIMO[6], CONKO-011[3]
Effectiveness and safety of rivaroxaban for extended treatment (>6 months) of CAT	select-d[2]
Drug–drug interactions between rivaroxaban and commonly used cancer therapies	
Dosing in patients with chemotherapy-induced side effects	COSIMO[6]
Current strategies for thromboprophylaxis and management	Frontline2[7]
How to?	
Manage temporary interruptions of rivaroxaban for invasive procedures	COSIMO[6]
Provide continuous anticoagulation for patients with chemotherapy-induced side effects	COSIMO[6]

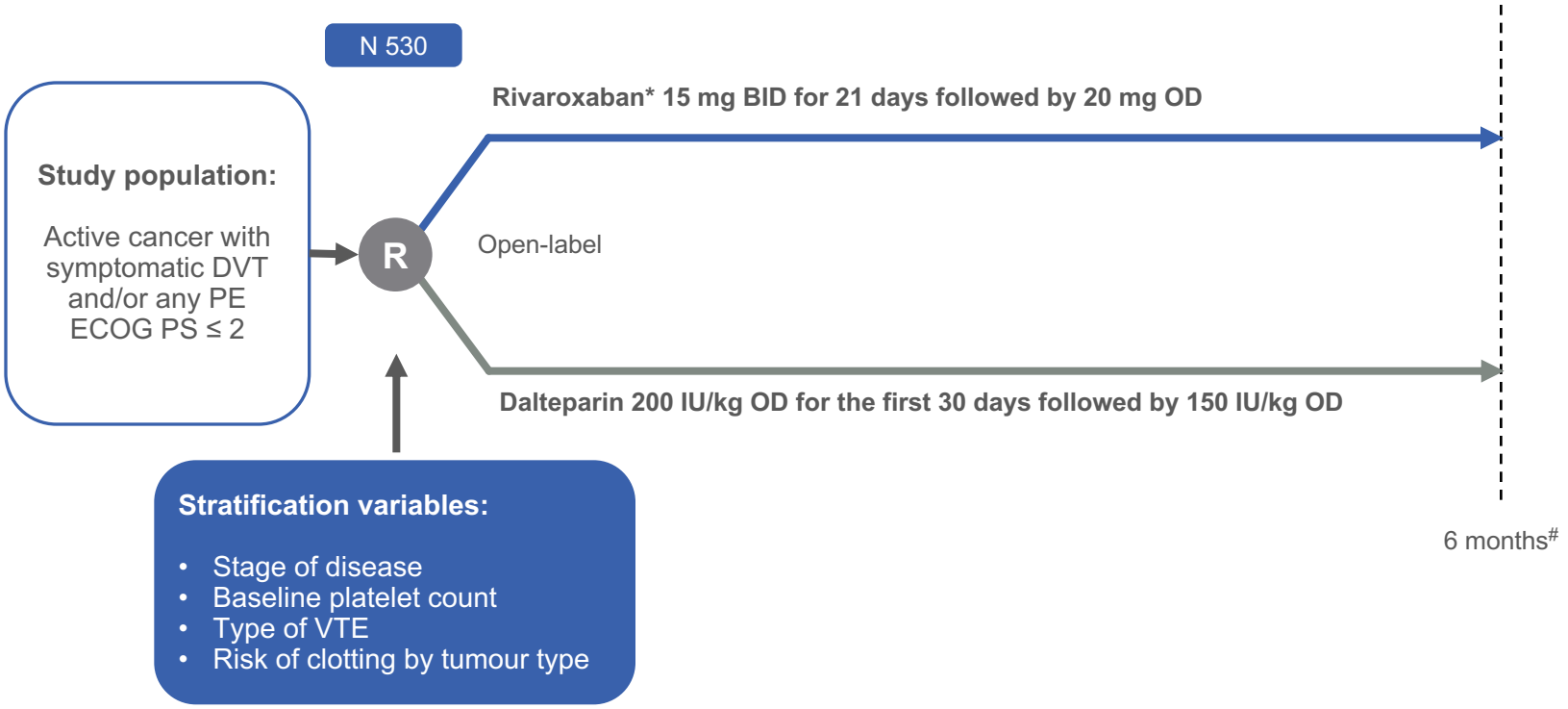
1. www.clinicaltrials.gov/ct2/show/NCT02555878; 2. http://www2.warwick.ac.uk/fac/med/research/hscience/ctu/trials/cancer/select-d/; EudraCT: 2012-005589-3;
3. Riess H, *et al. Dtsch med Wochenschr* 2015;140(S 01): S22-S23; www.clinicaltrials.gov/ct2/show/NCT02583191
4. QAI, Quality Assessment Initiative/Clinical Pathway; Mantha S, et al. *J Thromb Thrombolysis* DOI 10.1007/s11239-016-1429-1;
5. https://clinicaltrials.gov/ct2/show/NCT02746185; 6. https://clinicaltrials.gov/ct2/show/NCT02742623; 7. http://frontline2.tri-london.ac.uk/;
Survey link: https://secure.surveylab.co.uk/Frontline2/

CALLISTO

select-d: Pilot Phase III Comparing Rivaroxaban vs. Dalteparin for the Treatment of Cancer Associated Thrombosis

Young et al. J Clin Oncol '18

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

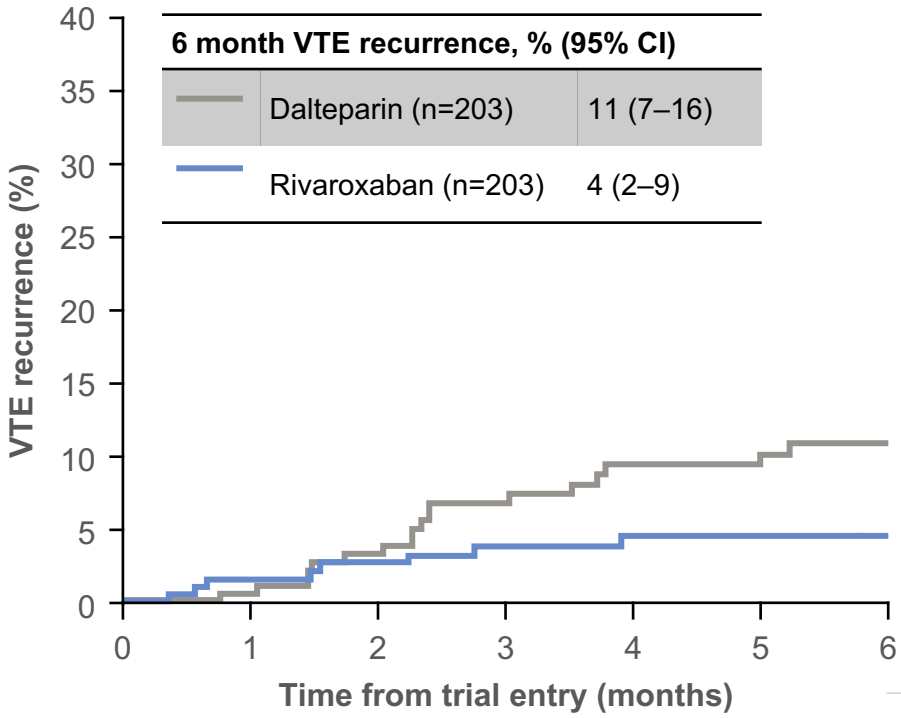


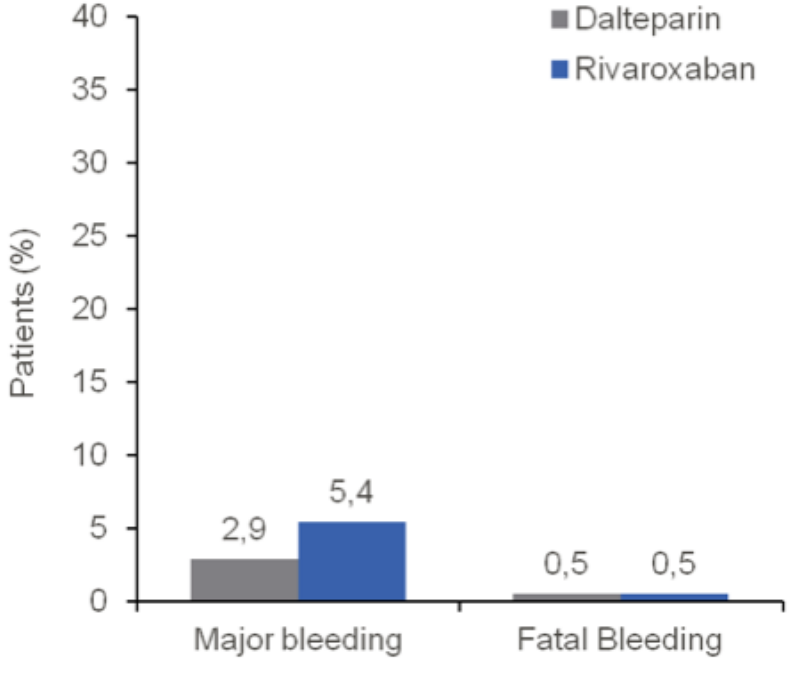
select-d

Emerging Data of Rivaroxaban vs LMWH from select-d Reinforces Applicability in CAT Patients

Young et al. J Clin Oncol '18

Primary and secondary outcomes





select-d

Rivaroxaban for SPAF in patients with Active Cancer

Laube ES, et al. Am J Cardiol 2017

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)

- safety and efficacy similar to general population in ROCKET-AF
- mortality attributable to underlying malignancy and lower than in the CLOT study (similar population with dalteparin for VTE)

DOAC CLINICAL TRIALS FOR TREATMENT OF CANCER-ASSOCIATED VTE ***ONGOING***

- **CARAVAGGIO TRIAL (Agnelli G et al) - 1168 pz.**
  - phase 3, multicentre, randomized, open label, noninferiority trial
  - apixaban *vs* dalteparin for 6-12 months

- **CASTA-DIVA TRIAL (Meyer G et al) – 200 pz.**
  - phase 3, multicentre, randomized, single-blind trial
  - rivaroxaban *vs* dalteparin for 6 months

- **ADAM VTE TRIAL (McBane Ii R et al) – 300 pz.**
  - phase 3, multicentre, randomized, open label, superiority trial
  - apixaban *vs* dalteparin for 6 months

- **CANVAS TRIAL (Schrag D et al) – 940 pz.**
  - multicentre, randomized, open label, superiority trial
  - DOAC (rivaroxaban, apixaban, edoxaban or dabigatran) *vs* dalteparin, enoxaparin or fondaparinux (with or without a transition to warfarin) for 6 months

Cancro attivo nelle schede tecniche

stato fine ottobre 2018

- Edoxaban
  - Pazienti con neoplasie attive: L'efficacia e la sicurezza di edoxaban nel trattamento e/o prevenzione del TEV nei pz con neoplasie attive non sono state stabilite
- Apixaban
  - Pazienti con neoplasie attive: L'efficacia e la sicurezza di apixaban nel trattamento delle TVP, trattamento dell'EP e prevenzione di recidive TVP ed EP (TEV) nei pz con neoplasie attive non sono state stabilite
- Dabigatran
  - Pazienti con neoplasie attive (TVP/EP): L'efficacia e la sicurezza non sono state stabilite per TVP/EP nei pazienti con neoplasia attive
- Rivaroxaban
  - Nessuna menzione di controindicazione per neoplasie attive (sezione 4.4)

NOAC nei paz con cancro attivo

- LG fino al 2016 raccomandano LMWH
- Dati da sottoanalisi, registri e trial specifici → ridotto rischio ricorrenza TEV
- Incrementato rischio emorragico (meno grave) per tumori GI alti
- Esclusi qs tumori, no limitazioni per uso NOAC in paz con cancro attivo
- Meglio compliance e tolleranza alla terapia rispetto a LMWH (tx estesa)
- Attendiamo aggiornamento LG e foglietti illustrativi