XXIV CONGRESSO NAZIONALE SISET

ABANO TERME (PD), 9-12 novembre 2016

Sessione Educazionale 1

"Controversie nella Gestione del TEV"

Terapia del tromboembolismo venoso nel paziente con cancro

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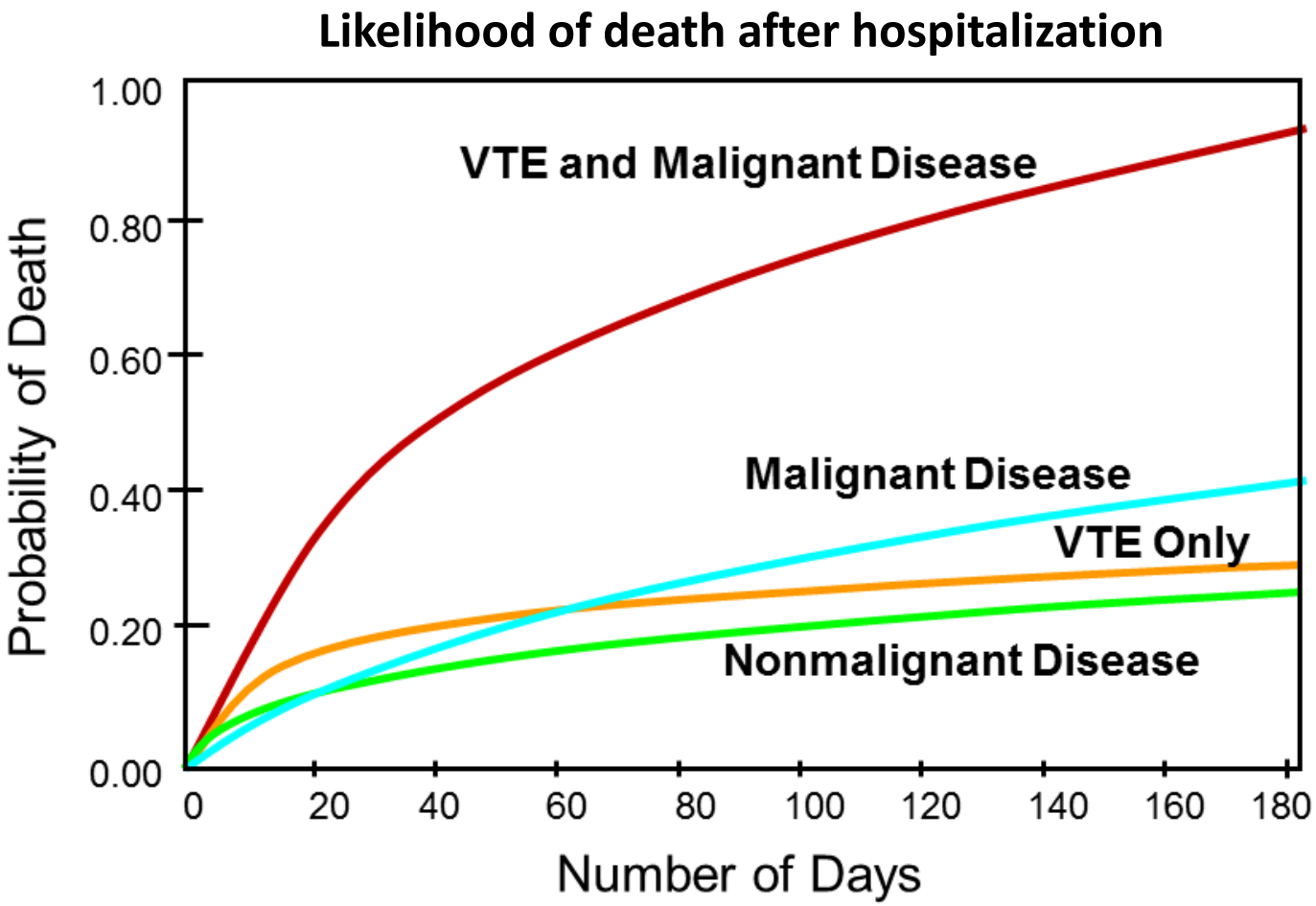
Important Consequences of VTE in Cancer

- Increased morbidity
  - Hospitalization
  - Anticoagulation
  - Postphlebitic syndrome
- Increased mortality *(reduced overall survival)*
- Increased risk of recurrent VTE *(21% vs 7% in non cancer patients)*
- Bleeding complications *(2-fold increase during anticoagulation)*
- Cancer treatment delays
- Increased healthcare costs

Decreased Survival in Cancer Patients With VTE



Levitan et al. Medicine (Baltimore) 1999

Effect of VTE on Risk of Death Stratified by Stage, Adjusted for Age and Race

- California Cancer Registry linked to Discharge Data
- Overall Mortality
  - HR=3.7 [1.3-14.4]
- Multivariate analysis
  - Stratified by stage
  - Adjusted for age, race
  - **VTE is a significant predictor for 1 year mortality for each cancer type**

Table 4. Effect of Venous Thromboembolism on the Risk of Death Within 1 Year of Cancer Diagnosis Stratified by Stage, Adjusted for Age and Race

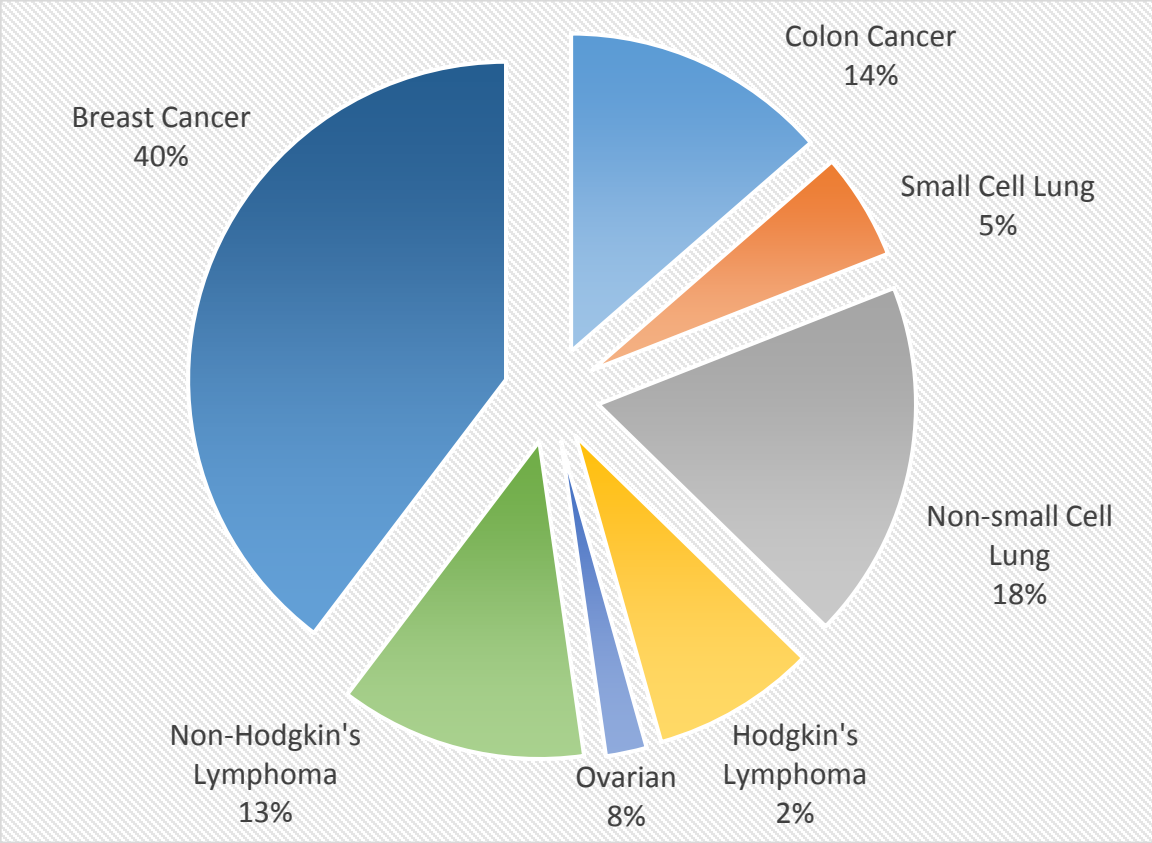
	Hazard Ratio (95% CI), by Stage		
Cancer	Local	Regional	Remote
Prostate	5.6 (3.8-8.5)*	4.7 (1.9-11.5)*	2.8 (1.5-5.0)†
Breast	6.6 (3.7-11.8)*	2.4 (1.3-4.5)†	1.8 (1.1-2.9)‡
Lung	3.1 (2.1-4.5)*	2.9 (2.3-3.5)*	2.5 (2.3-2.7)*
Colon/rectum	3.2 (1.8-5.5)*	2.2 (1.7-3.0)*	2.0 (1.7-2.4)*
Melanoma	14.4 (4.6-45.2)*	NA§	2.8 (1.5-5.3)†
Non-Hodgkin lymphoma	3.2 (1.9-5.3)*	2.0 (1.3-3.2)†	2.3 (1.7-3.1)*
Uterus	7.0 (3.4-14.2)*	9.1 (4.8-17.2)*	1.7 (1.0-3.0)‡
Bladder	3.2 (1.7-6.2)*	3.3 (1.7-6.4)*	3.3 (1.8-6.2)*
Pancreas	2.3 (1.2-4.6)‡	3.8 (2.8-5.1)*	2.3 (1.9-2.7)*
Stomach	2.4 (1.1-5.1)‡	1.5 (1.0-2.1)‡	1.8 (1.4-2.3)*
Ovary	11.3 (2.5-51.7)†	4.8 (1.1-20.4)‡	2.3 (1.7-3.0)*
Kidney	3.2 (1.2-8.8)‡	1.4 (0.6-3.2)	1.3 (0.9-2.0)

Abbreviations: CI, confidence interval; NA, not applicable.
*$P<.001$.
†$P<.01$.
‡$P<.05$.
§Not enough venous thromboembolism cases to estimate.

Chew HK, et al. Arch Intern Med. 2006

Causes of Early Death in Ambulatory Cancer Patients
Results from Prospective Study of Series

- **Patient Population**
  - Prospective study of 4466 patients starting new chemotherapy
  - Consecutive patients accrued at 117 US practices
  - Median follow-up of 75 days, 141 (3.2%) died.
- **Causes of Death, n (%)**
  - All 141 (100)
  - Progression of cancer 100 (70.9)
  - ***Thromboembolism 13 (9.2)***
    - Arterial 8 (5.6)
    - Venous 5 (3.5)
  - Infection 15 (10.6)
  - Respiratory failure 5 (3.5)
  - Bleeding 2 (1.4)
  - Other 9 (6.4)
  - Unknown 5 (3.5)



Distribution of Cancer Type

Khorana AA et al. J Thromb Haemost 2007

Issues in VTE treatment in the Cancer Patient

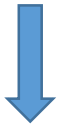
- High rate of recurrences
- High rate of bleeding with anticoagulant therapy
- Problems with VKA anticoagulation during surgery, invasive procedures (i.e. biopsies), and chemotherapy
- Is the pathogenesis different? Do we need a new treatment target?

Standard treatment of VTE with Vitamin K antagonists (VKA)

Initial treatment:

LMWH therapeutic dose + within 24 hours start VKA

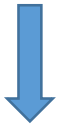
Continue both drugs for 5-7 days, until INR ≥ 2 (for 2 consecutive days)



Long-term treatment:

When INR ≥ 2 stop LMWH

Continue VKA for 3-6 months

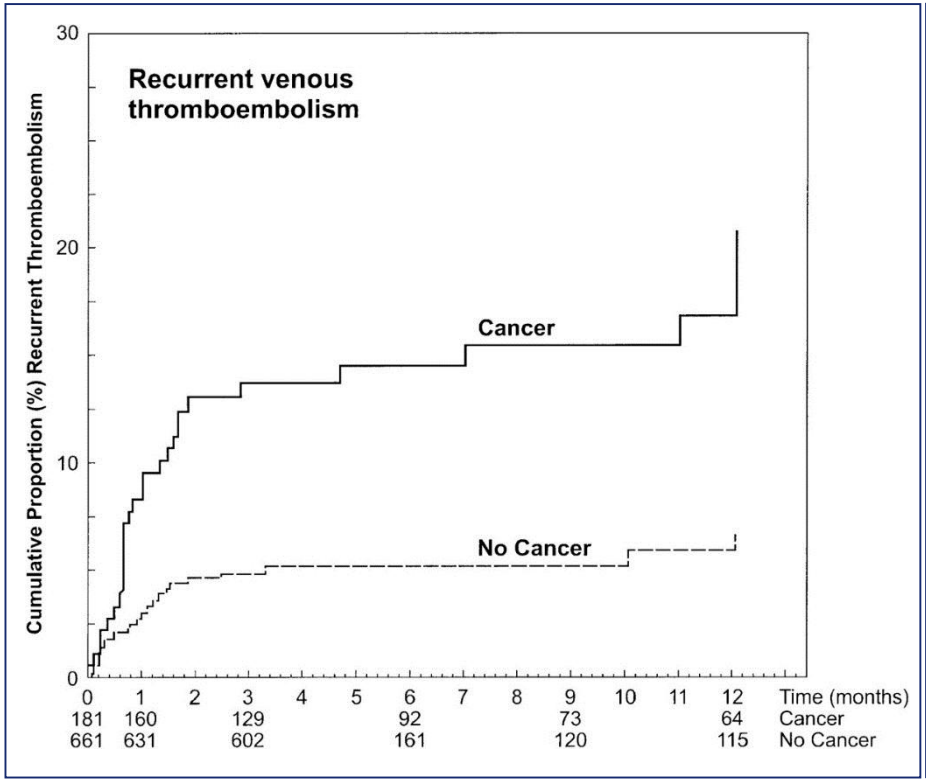


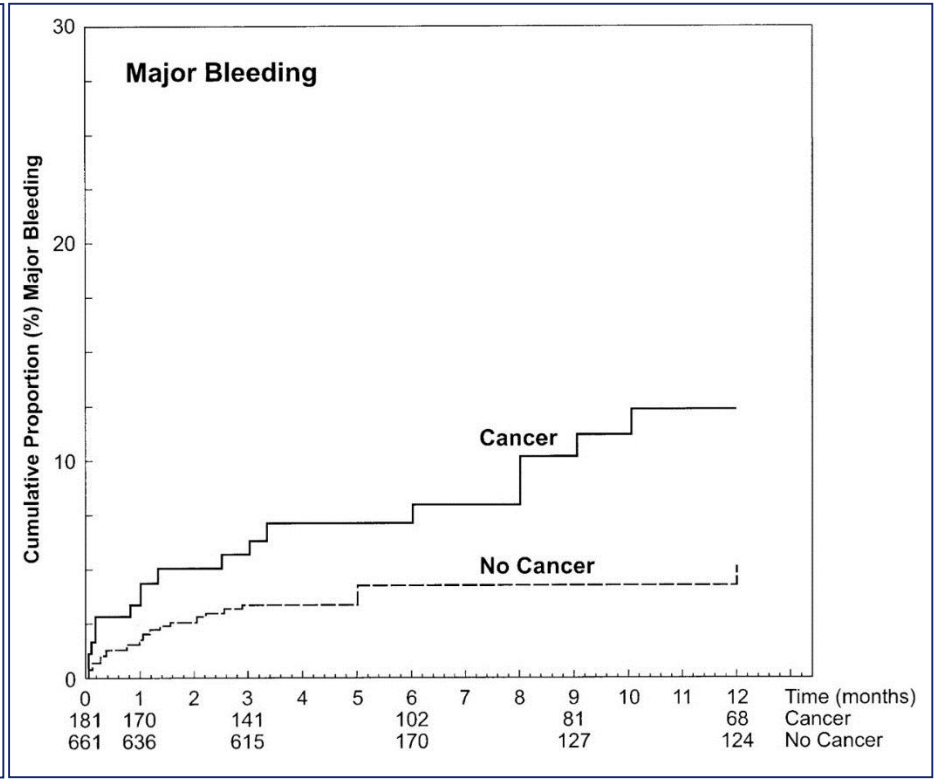
Indefinite treatment:

In case of recurrent VTE, continue VTE indefinitely

Recurrent venous thromboembolism (VTE) and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis

- Inception cohort study of 842 outpatients with confirmed deep vein thrombosis (DVT)
- Initial treatment with UFH or LMMH followed by warfarin at INR 2 – 3
- Endpoints were recurrent VTE and bleeding





Prandoni, P. et al. *Blood* 2002.

Optimising treatment of VTE in the cancer patients

Treatment 

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

NEW STRATEGIES REQUIRED FOR CANCER PATIENTS!

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

J Clin Oncol 33. © 2015

LMWH is recommended for the initial 5 to 10 days of treatment of established VTE as well as for long-term *secondary prophylaxis for at least 6 months.*

LMWH versus UFH: Initial Treatment in Cancer

- Limited number of studies published results in subgroup of cancer patients
- No difference in recurrent VTE (RR 0.78; 0.29 – 2.08)
- LMWH is associated with improved survival

3-month survival	**Cancer** OR (95% CI)	**No cancer** OR (95% CI)
Hettiarachchi 1999	0.61 (0.40 – 0.93)	0.94 (0.60 – 1.47)
van Dongen 2004	0.53 (0.33 – 0.85)	0.97 (0.61 – 1.56)
Akl 2008	0.71 (0.52 – 0.98)	-----

Hettiarachchi et al. Thromb Haemost 1999; van Dongen et al. Cochrane Syst Rev 2004; Akl et al. Cochrane Syst Rev 2008.

Cochrane metanalysis

Anticoagulation for the initial treatment of venous thromboembolism in patients with cancer (Review)

A meta-analysis performed in 2014

Included 16 RCTs

3 studies comparing LMWH and UFH,
2 studies comparing fondaparinux and heparin,
1 study comparing dalteparin and tinzaparin

Objectives:

- To compare the efficacy and safety of 3 types of parenteral anticoagulants (i.e. fixed-dose LMWH, adjusted-dose UFH, and fondaparinux) for the initial treatment of VTE in patients with cancer.

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

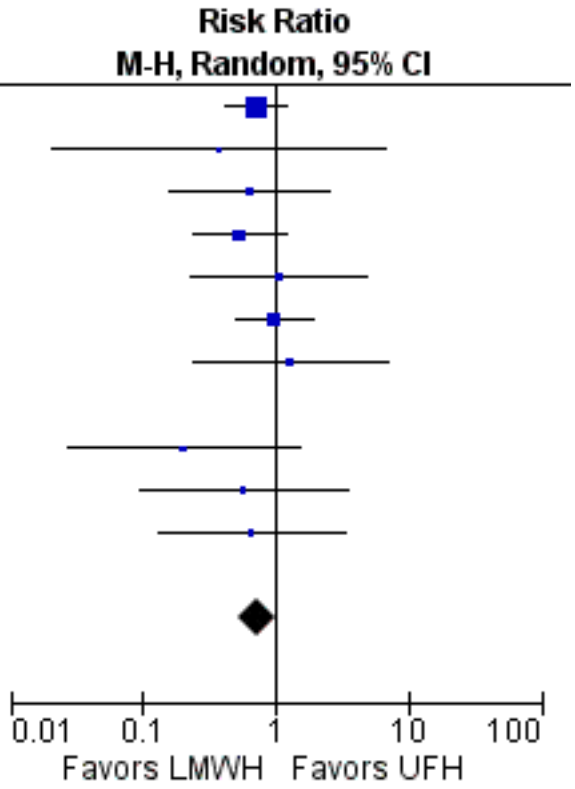
Low molecular weight heparin (LMWH) *versus* unfractionated heparin (UFH)

An analysis of 11 studies revealed a **significant reduction in 3-month fatality rates in favor of LMWH, as compared with UFH (RR, 0.71; 95% CI, 0.52–0.98).**

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Random, 95% CI
Columbus 1997	20	119	27	113	38.5%	0.70 [0.42, 1.18]
Duroux 1991	0	6	2	12	1.2%	0.37 [0.02, 6.71]
Galilei 2004	3	76	5	80	5.3%	0.63 [0.16, 2.55]
Hull 1992	7	46	14	49	15.6%	0.53 [0.24, 1.20]
Koopman 1996	3	34	3	36	4.4%	1.06 [0.23, 4.89]
Levine 1996	11	46	14	57	21.8%	0.97 [0.49, 1.94]
Lindmarker 1994	2	7	2	9	3.6%	1.29 [0.24, 6.99]
Lopaciuk 1992	0	7	0	2		Not estimable
Prandoni 1992	1	15	6	18	2.6%	0.20 [0.03, 1.48]
Simonneau 1993	2	7	1	2	3.1%	0.57 [0.09, 3.51]
Simonneau 1997	2	26	4	34	3.9%	0.65 [0.13, 3.30]
Total (95% CI)		**389**		**412**	**100.0%**	**0.71 [0.52, 0.98]**
Total events	51		78			

Heterogeneity: Tau² = 0.00; Chi² = 3.88, df = 9 (P = 0.92); I² = 0%

Test for overall effect: Z = 2.07 (P = 0.04)



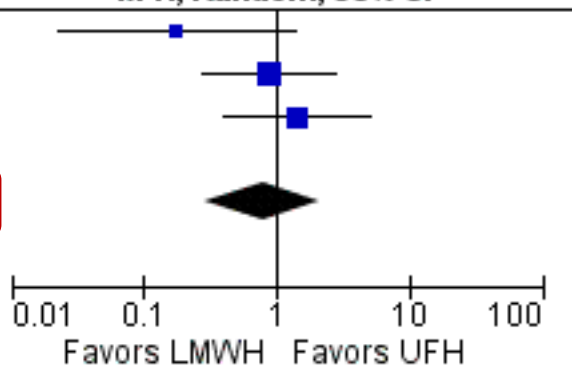
E.A. Akl et al. Cochrane Database of Systematic Reviews 2014

No difference in thrombosis recurrence rates was seen between LMWH and UFH used in an initial treatment

Study or Subgroup	LMWH Events	LMWH Total	UFH Events	UFH Total	Weight	Risk Ratio M-H, Random, 95% CI
Breddin 2001	1	33	7	41	18.9%	0.18 [0.02, 1.37]
Galilei 2004	5	76	6	80	42.8%	0.88 [0.28, 2.76]
Merli 2001	9	96	3	45	38.3%	1.41 [0.40, 4.95]
Total (95% CI)		**205**		**166**	**100.0%**	**0.78 [0.29, 2.08]**
Total events	15		16			

Heterogeneity: Tau² = 0.25; Chi² = 2.96, df = 2 (P = 0.23); I² = 32%

Test for overall effect: Z = 0.50 (P = 0.62)



The authors concluded that the initial treatment with LMWH, due to lower incidence of bleeding complications and lower fatality rates, may be superior to UFH when used in patients with Cancer Associated Thrombosis (CAT).

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

Long-term VTE treatment (3-6 months) in cancer patients

Long Term Treatment:

RCTs of LMWH vs Vit K antagonists in cancer

Study	Pt, No.	Long-Term Treatment	Rec VTE, %	Major Bleed, %	Death, %	P-value
Meyer 2002	71	Warfarin	21.1		22.7	NS
	67	Enoxaparin 1.5 mg/kg	10.5		11.3	
Lee 2003	336	Warfarin	17	4	41	0.002
	336	Dalteparin 200/150 IU/kg	9	6	39	
Deitcher 2006	30	Warfarin	10	2.9	8.8	NS
	29	Enoxaparin 1.0 mg/kg	6.9	6.5	6.5	
	32	Enoxaparin 1.5 mg/kg	6.3	11.1	19.4	
Hull 2006	100	Warfarin	10	7	19	NS
	100	Tinzaparin 175 IU/kg	6	7	20	

Lee N Engl J Med 2003;349:146-153. Meyer Arch Intern Med 2002;162:1729-1735. Deitcher Clin Appl Thromb Hemost 2006;12:389-396. Hull Am J Med 2006;119:1062-1072.

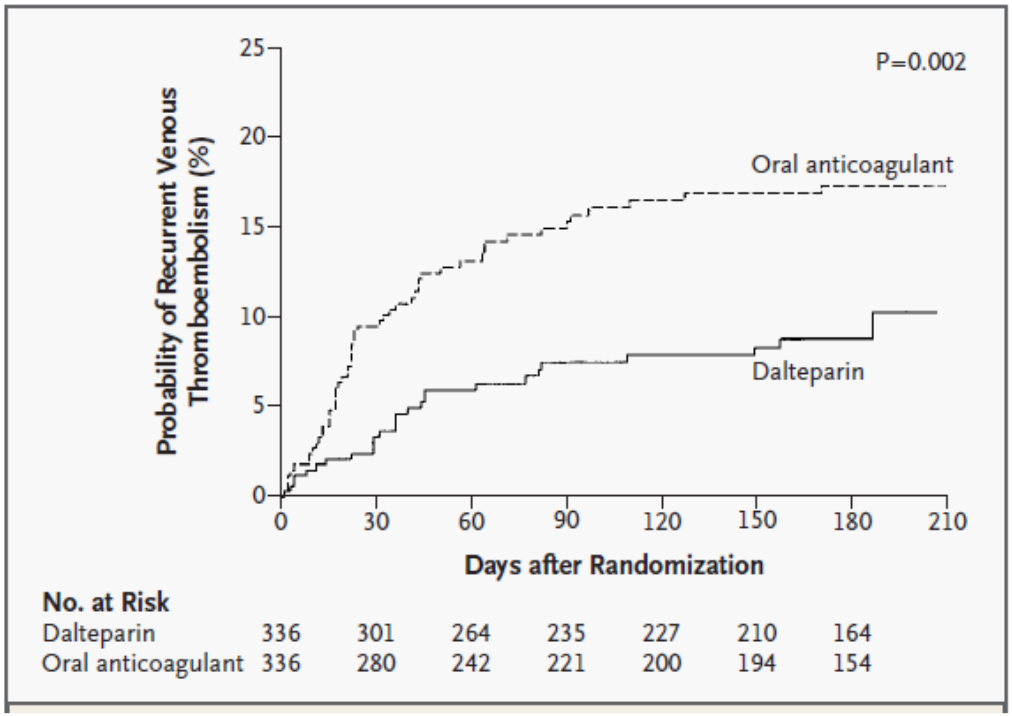
The CLOT trial

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

- The CLOT study randomized 677 subjects with cancer and VTE to the following VTE treatment regimens:
  - Experimental arm: therapeutic LMWH dalteparin dose of 200 IU/kg body weight for 1 month and subsequently 75% to 83% of the full dose (mean 150 IU/kg body weight) for 5 months
  - Control arm: LMWH dalteparin 200 IU/kg in combination with a VKA oral anticoagulant for 5 to 7 days followed by VKA alone for 6 months.

A.Y.Y. Lee et al. NEJM 2003

Probability of Symptomatic Recurrent Venous Thromboembolism among Patients with Cancer



During the 6 months of treatment, thrombosis recurred in 8% of the patients in the heparin group as compared with 15.8% of the patients in the vitamin K antagonist group (P =0.002).

A.Y.Y. Lee et al. NEJM 2003

The CATCH trial

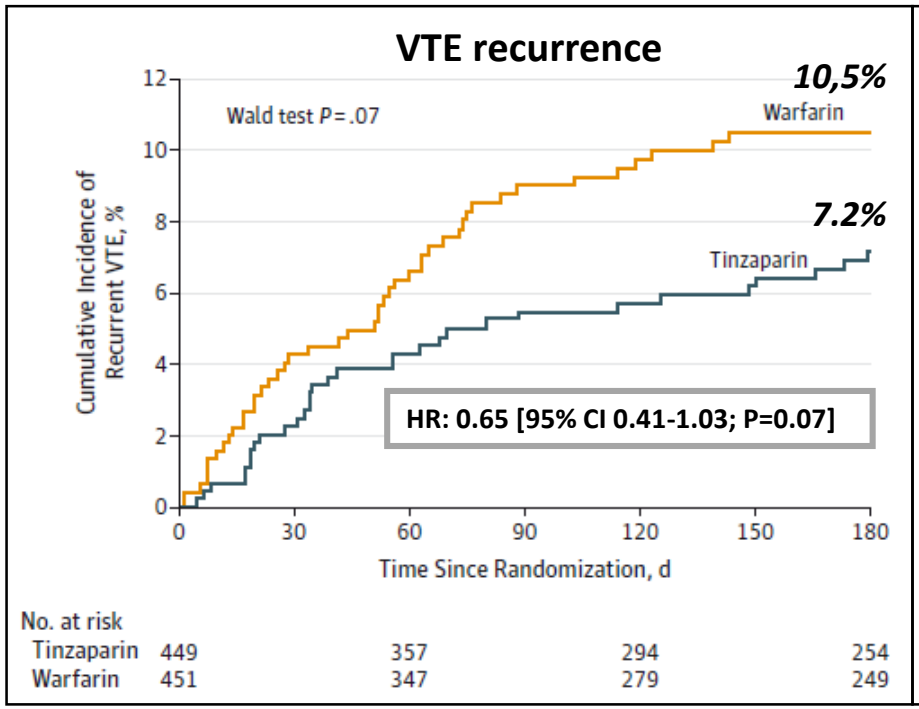
LMWH vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial

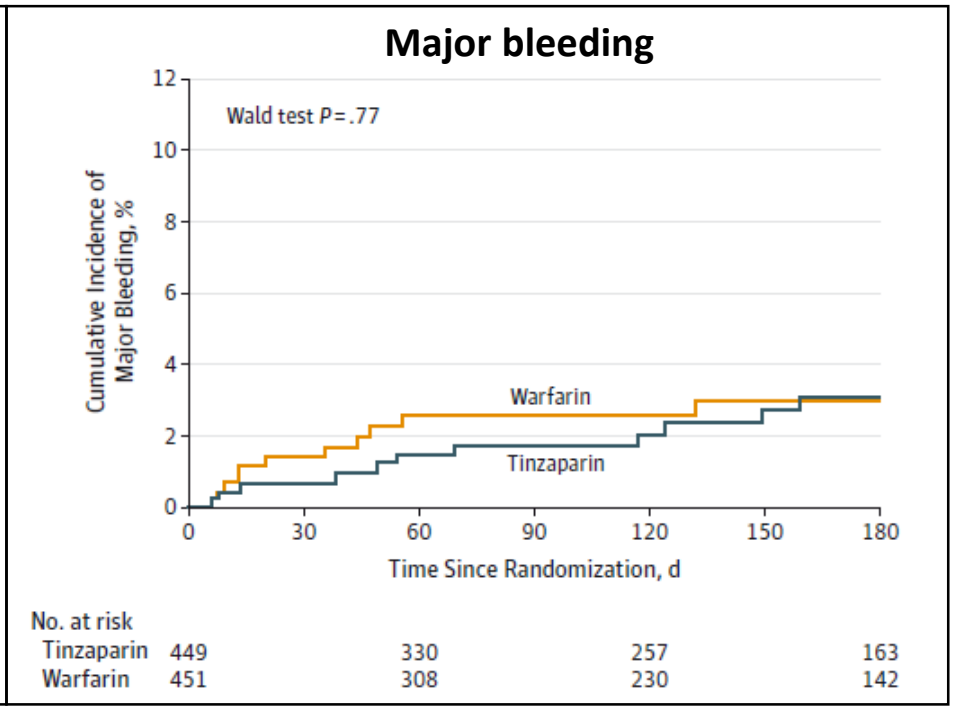
- The CATCH trial randomized 900 patients to the following arms:
  - Experimental Arm: LMWH tinzaparin, 175 IU/kg, once daily for 6 months
  - Control Arm: LMWH tinzaparin 175 IU/kg, once daily for 5 to 10 days and subsequently warfarin for 6 months.

- Primary objective: efficacy in preventing recurrent VTE in patients with active cancer and acute symptomatic proximal deep vein thrombosis or pulmonary embolism (or both).

A.Y.Y. Lee et al. JAMA 2015

CATCH study: Results





The study showed a trend towards a superior efficacy with the LMWH compared to VKA in reducing the relative risk of VTE recurrence and all bleeding thus confirming the value of LMWH therapy in patients with CAT.

A.Y.Y. Lee et al. JAMA 2015

Cochrane metanalysis

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

- This metanalysis included randomized controlled trials (RCTs) comparing long-term treatment with LMWH versus oral anticoagulants (VKA or ximelagatran) in patients with cancer and symptomatic objectively confirmed VTE.

Objectives:

- To compare the efficacy and safety of LMWH and oral anticoagulants for the long-term treatment of VTE in patients with cancer.

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

- **Recurrent venous thromboembolism:** The pooled analysis showed a statistically significant benefit of LMWH over VKA (HR 0.47; 95% CI 0.32 to 0.71)
- **Bleeding outcomes**: The pooled analysis did not exclude a beneficial or harmful effect of LMWH compared with VKA for major bleeding (RR 1.07; 95% CI 0.52 to 2.19; I2 = 46%) or minor bleeding (RR 0.89; 95% CI 0.51 to 1.55)

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.

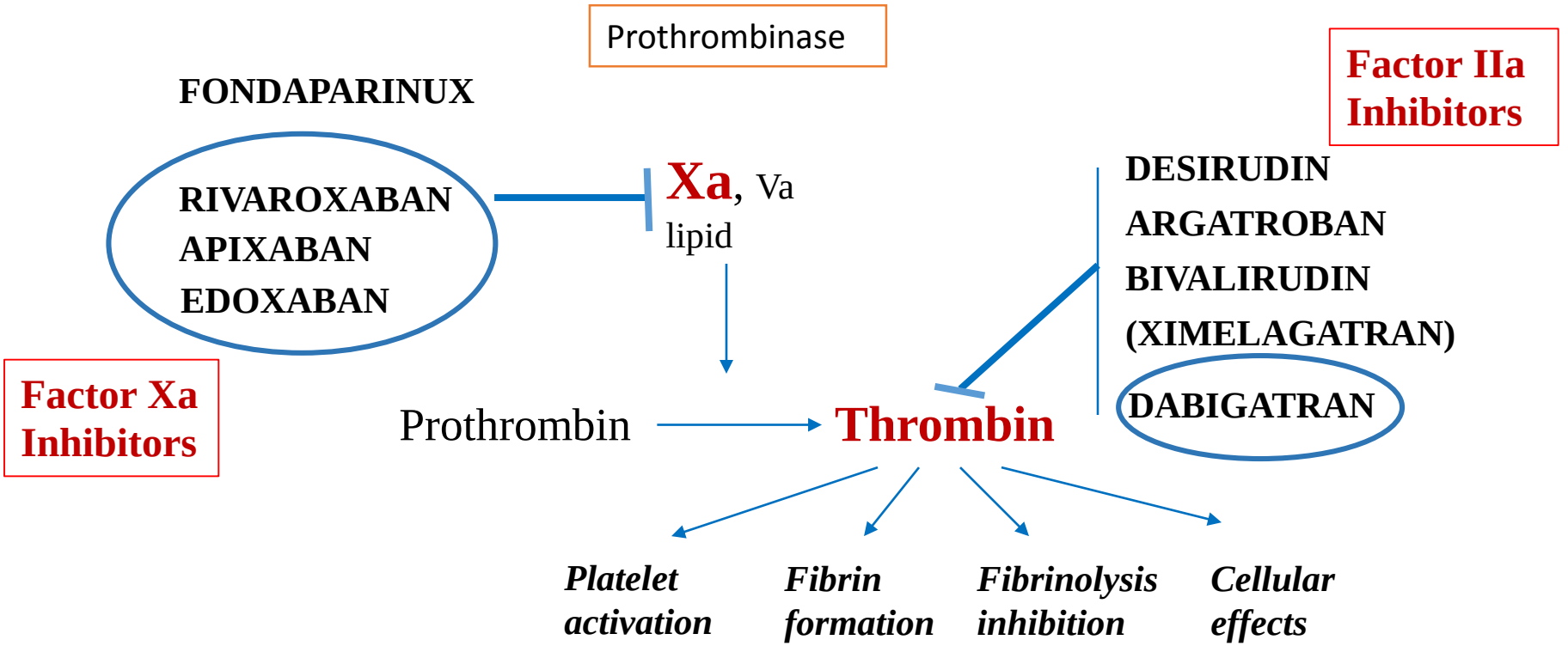
E.A. Akl et al. Cochrane Database of Systematic Reviews 2014

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

Direct Oral Anticoagulants (DOACs)



DOAC in Patients with Cancer

- The new oral anticoagulants offer an attractive option because of their oral administration, fixed-dose, and lack of routine laboratory monitoring.

- The results of phase III trials of DOACs vs Warfarin for VTE treatment support the efficacy and safety of DOACs in the management of VTE in the general population.

- However, generalizing these findings to cancer patients with VTE is difficult since very few cancer patients were included in those trials.

- Finally, in the cancer setting, their role in comparison with the current standard of care, i.e. LMWH, is still unclear.

The DOAC and the Treatment of VTE

Cancer subgroup analysis from phase III randomized controlled trials **comparing DOACs *vs* conventional treatment with Warfarin** after VTE

Agent	Trial name	Number of cancer patients randomized (%)	Dose (mg), frequency	Comparator (INR indicated if VKA)	Recurrent VTE % (vs. VKA %)	Safety analysis (major bleeding and clinically relevant non-major bleeding) % (vs. VKA %)
Rivaroxaban	EINSTEIN-DVT	207/3449 (6%)	15 BID → 20 OD	INR 2.0–3.0	3.4 (vs. 5.6)	14.4 (vs. 15.9)
	EINSTEIN-PE	223/4832 (4.6%)	15 BID → 20 OD	INR 2.0–3.0	1.8 (vs. 2.8)	12.3 (vs. 9.3)
	EINSTEIN-extension	54/1196 (4.5%)	20 OD	Placebo	n/a	n/a
Dabigatran	RE-COVER	121/2539 (4.8%)	150 BID	INR 2.0–3.0	3.1 (vs. 5.3)	n/a
	RE-COVER II	n/a	150 BID	INR 2.0–3.0	n/a	n/a
	RE-MEDY	60/2856 (2.1%)	150 BID	INR 2.0–3.0	3.3 (vs. 1.7)	n/a
	RE-SONATE	n/a	150 BID	Placebo	n/a	n/a
Apixaban	AMPLIFY	143/5395 (2.7%)	10 BID → 5 BID	Enoxaparin 1 mg/kg; INR 2.0–3.0	n/a	n/a
	AMPLIFY-EXT	42/2482 (1.7%)	2.5 BID 5.0 BID	Placebo	n/a	n/a
Edoxaban	Hokusai-VTE	208/8240 (2.5%)	60 OD	INR 2.0–3.0	3.7 (vs. 7.1)	18.3 (vs. 25.3)

1. Schulman et al. New Engl J Med 2009. Schulman ASH 2013. 2. Buller et al. New Engl J Med 2010. 3. Buller et al. New Engl J Med 2012. 4. Agnelli et al N Engl J Med 2013. 5. Hokusai N Engl J Med 2013; Raskob ASH 2013.

1. Trials included very few patients with malignant disease.

2. The strict inclusion criteria excluded from enrolling patients with end-organ dysfunction (e.g., renal and liver dysfunction) and elevated risk of bleeding, **resulting in an overall study population likely not-representative of patients with advanced cancer**.

Wharin C. and Tagalakis V. Blood Reviews 2014

DOACs and Treatment of VTE

Study	NOAC Control	All Patients, n/N (%)	Non-Cancer Patients, n/N (%)	Cancer Patients, n/N (%)
RECOVER	dabigatran control	30/1274 (2.4%) 27/1265 (2.1%)	28/1210 (2.3%) 24/1208 (2.0%)	2/64 (3.1%) 3/57 (5.3%)
EINSTEIN DVT	rivaroxaban control	36/1731 (2.1%) 51/1718 (3.0%)	32/1613 (2.0%) 46/1629 (2.8%)	4/118 (3.4%) 5/89 (5.6%)
EINSTEIN PE	rivaroxaban control	50/2419 (2.1%) 44/2413 (1.8%)	48/2305 (2.1%) 41/2304 (1.8%)	2/114 (1.8%) 3/109 (2.8%)
AMPLIFY	apixaban control	59/2609 (2.3%) 71/2635 (2.7%)	not available not available	not available not available
HOKUSAI	edoxaban control	130/4118 (3.2%) 146/4122 (3.5%)	103/3658 (2.8%) 99/3629 (2.7%)	14/378 (3.7%) 28/393 (7.1%)

n, number of patients with primary efficacy outcome; N, number of patient receiving study drug.

- There are insufficient data to show that DOACs are non-inferior to warfarin in patients with cancer. The small number of highly selected cancer patients in these studies precludes the extrapolation of the available results to the general oncology population.
- A head-to-head comparison of LMWH with DOACs is necessary to determine if DOACs is an acceptable alternative for the treatment of cancer-associated thrombosis.

A. Lee and M. Carrier. Thromb Res 2014

Efficacy and safety of DOACs in patients with active cancer

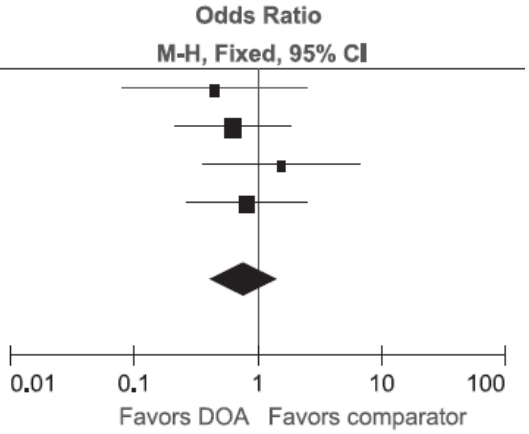
Use of DOAC and major bleeding

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)



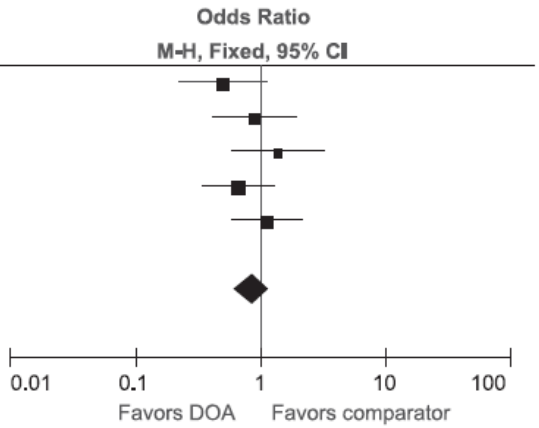
Use of DOAC and clinically relevant bleeding

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)



The efficacy and safety profile of DOAC for VTE treatment in patients with cancer is similar to that observed in patients without cancer. A favorable trend toward reduction of recurrent VTE was observed without concern in terms of clinically relevant bleedings.

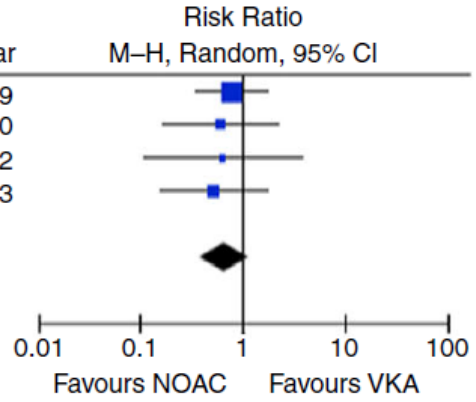
Vedovati et al. CHEST 2015

The risk of recurrent VTE (A) and major bleeding (B) in cancer patients and non-cancer patients separately

A

Study or Subgroup	NOAC Events	NOAC Total	VKA Events	VKA Total	Weight	Risk Ratio M–H, Random, 95% CI	Year
Re-Cover I and II	10	173	12	162	48.4%	0.78 [0.35, 1.76]	2009
Einstein-DVT	4	118	5	89	19.3%	0.60 [0.17, 2.18]	2010
Einstein-PE	2	114	3	109	10.2%	0.64 [0.11, 3.74]	2012
Hokusai	4	109	7	99	22.2%	0.52 [0.16, 1.72]	2013
Total (95% CI)		514		459	100.0%	0.66 [0.38, 1.17]	
Total events	20		27				

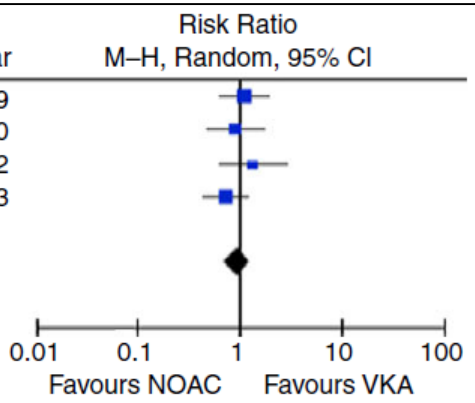
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.34$, df = 3 (P = 0.95); $I^2 = 0\%$
Test for overall effect: Z = 1.42 (P = 0.16)



B

Study or Subgroup	NOAC Events	NOAC Total	VKA Events	VKA Total	Weight	Risk Ratio M–H, Random, 95% CI	Year
Re-Cover I and II	23	159	20	152	29.5%	1.10 [0.63, 1.92]	2009
Einstein-DVT	17	118	14	88	21.5%	0.91 [0.47, 1.74]	2010
Einstein-PE	14	114	10	108	15.5%	1.33 [0.62, 2.86]	2012
Hokusai	20	109	25	99	33.6%	0.73 [0.43, 1.22]	2013
Total (95% CI)		500		447	100.0%	0.94 [0.70, 1.28]	
Total events	74		69				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.03$, df = 3 (P = 0.57); $I^2 = 0\%$
Test for overall effect: Z = 0.37 (P = 0.71)



Note: VTE: venous thromboembolism; NOAC: new oral anticoagulant; VKA: vitamin K antagonist

The most important results of this study are the RRs of 0.66 (95% CI 0.38–1.2) for recurrent VTE and 0.94 (95% CI 0.70–1.3) for major bleeding and clinically relevant non-major bleeding, indicating that both the efficacy and safety of DOACs in cancer patients were at least comparable to those of VKAs.

Van der Hulle et al. JTH 2015

Comments: DOACs in Treatment of CAT

Data come from:

- underpowered subgroup analyses in selected patients
- study population of “cancer” or “active cancer” not clearly defined and inconsistent among DOAC trials
- no details regarding prognostic factors (e.g., cancer types, treatment, stages) and no data on death
- TTR not reported for control groups
- duration of treatment and follow-up unknown
- “cancer” patients in DOAC trials are different from those in LMWH trials

Amplify: Subgroup analysis for CAT

	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	

CI, confidence interval; CRNMB, clinically relevant non-major bleeding; MB, major bleeding; *n*/*N*, number of patients with event/number of treated patients; RR, relative risk of event for apixaban versus enoxaparin/warfarin; VTE, venous thromboembolism. *This subgroup is based on the patients who have active cancer and/or cancer history (without active cancer). †*P*-values are for interaction of treatment by three cancer subgroups, which are defined as active cancer, cancer history (without active cancer), and no cancer history/no active cancer.

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 LMWH in these patients.

G. Agnelli et al. JTH 2015

Discussion

- The preliminary results of trials on long-term VTE treatment suggest that **DOAC could be an attractive alternative to conventional (warfarin) anticoagulation in patients with active cancer.**

- However, further studies in patients with active cancer should be performed to confirm these results.

- In particular, **studies should be performed with LMWH as comparator**, and should probably investigate different doses of DOAC to determine the best clinical benefit in the treatment of VTE in patients with cancer.

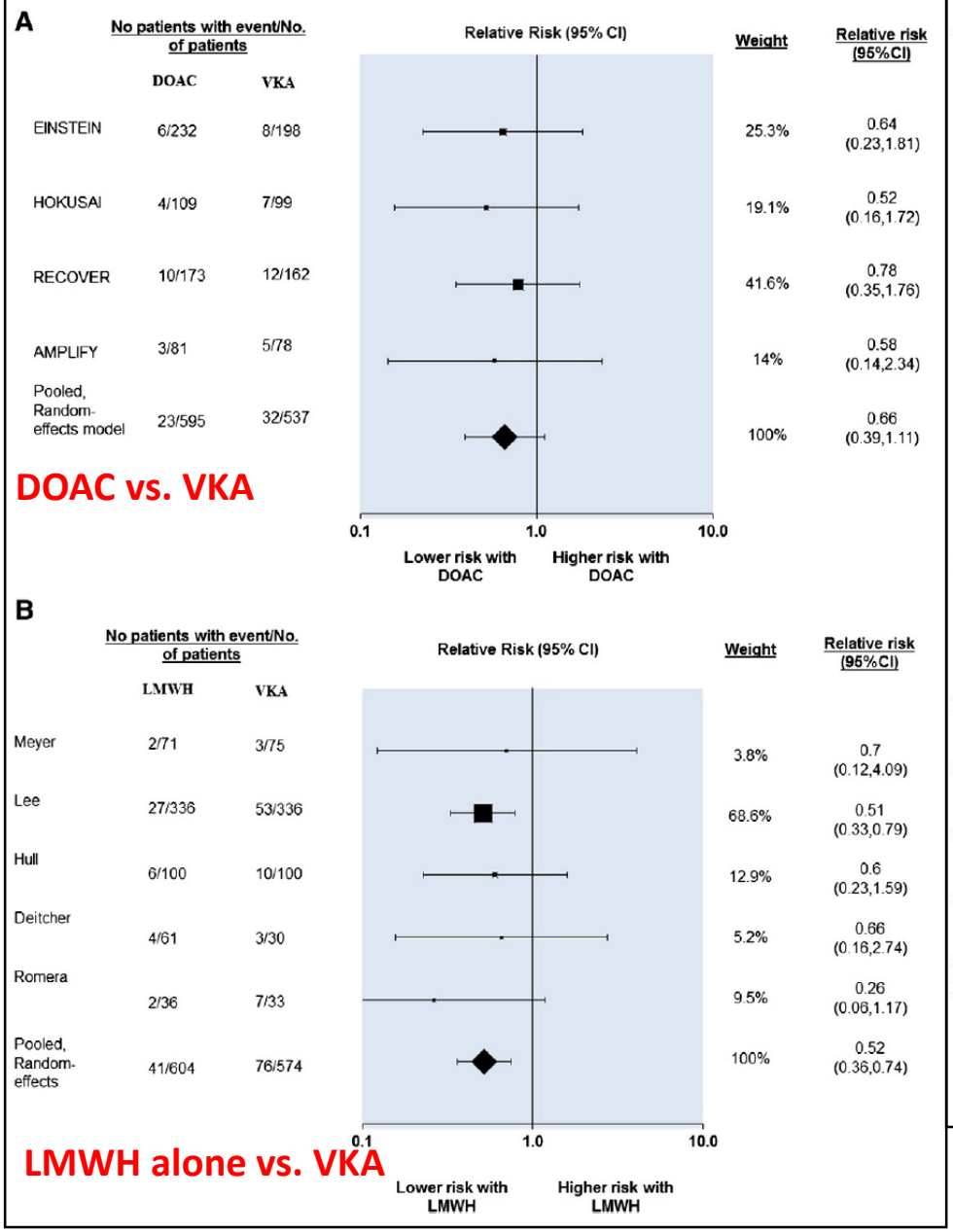
M. Verso, G. Agnelli, P. Prandoni. Intern Emerg Med 2015

Forest plot of relative risks across clinical trials comparing *DOAC vs VKA* and *LMWH alone vs VKA* for recurrent cancer-associated VTE.

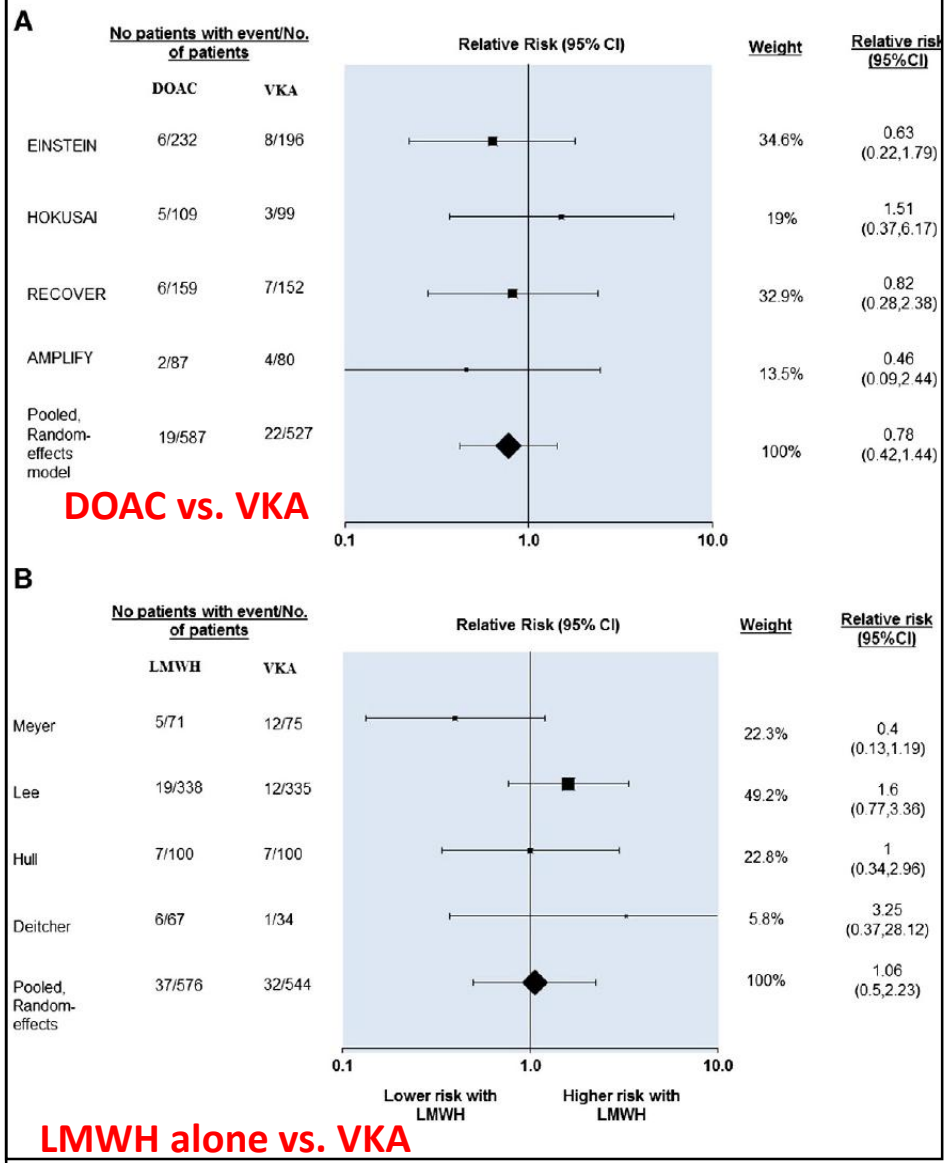
- This meta-analysis evaluated 9 randomized trials involving patients with cancer-associated thrombosis:
  - 4 with DOACs vs warfarin
  - 5 with LMWH vs warfarin

Carrier M. et al. Thromb Res 2014

Recurrent VTE



Major bleeding



M. Carrier et al. TR 2014

Results

- VTE recurrence: In comparison to VKA, LMWH showed a significant reduction in recurrent VTE events (RR: 0.52; 95 % CI 0.36–0.74) whereas DOACs did not (RR: 0.66; 95 % CI 0.39–1.11).

- Bleeding: LMWH was associated with a non-significant increase in the risk of major bleeding (RR: 1.06; 95 % CI 0.5–2.23) whereas DOACs showed a non-significant reduction (RR: 0.78; 95 % CI 0.42–1.44) compared to VKA.

- **In summary**, LMWH monotherapy should be used for the treatment of acute cancer-associated thrombosis. This is in-line with current clinical practice guidelines and further recommendations regarding the use of DOACs cannot be supported until trials comparing them to LMWH are conducted.

M. Carrier et al. TR 2014

Patients with cancer have multiple factors to consider:

- They are at high risk for hemorrhage for reasons including chemotherapy-induced **thrombocytopenia** or receipt of **antiangiogenic** therapy.

- DOAC may have a potential limitation in cancer patients who suffer abnormal liver function and severe **renal impairment** or have **poor attitude to oral intake**.

- DOAC may cause **drug interactions** with chemotherapeutic agents, which may result in less efficacy and higher bleeding than that observed in patients without cancer

Principal pharmacological charatteristics of DOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Target	IIa	Xa	Xa	Xa
Hours to Cmax	2	2-4	1-3	1-2
Prodrug	Yes	No	No	No
CYP metabolism	**No**	**Yes** (CYP3A4/A5, CYP2J2)	**Yes** (CYP3A4, CYP1A2, CYP2J2)	**Yes** (CYP3A4)
Efflux transporter P-gp	**Yes**	**Yes**	**Yes**	**Yes**
Bioavilability	7%	80%	66%	>45%
Protein binding	35%	>90%	87%	55%
Half-life (Hours)	12-14	9-13	8-15	8-10
Renal elimination	**80%**	**66%**	**25%**	**35%**
Dosing	Twice a day	Once a day	Twice a day	Once a day

Pengo V et al. JTH 2012.

Drug interactions

- Strong and moderate modulators of the CYP3A4 enzyme, especially those that also interact with P-glycoprotein, carry the highest relative risk for significant drug interactions with the DOACs.

- Two strong inhibitors of CYP3A4 were identified: **1. enzalutamide**, an androgen receptor antagonist used to treat castration-resistant prostate cancer, and **2. dexamethasone**, a glucocorticoid used for its antitumor effects in many lymphoid malignancies and for the treatment and palliation of various cancer-related complications, including nausea and vomiting.

- Use of these drugs in combination with any of the three DOACs could result in increased plasma concentrations of the DOAC.

J.M. Connors. The Oncologist 2014

Oncology drugs with CYP3A4 and P-glicoprotein interactions

	CYP3A4 interactions			P-glycoprotein interactions		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Antimitotic agents						
Vinca alkaloids						
Vinblastine	+++		+	*	*	
Vincristine	+++		+	*		
Vinorelbine	+++		+			
Taxanes						
Docetaxel	+++		+	*		
Paclitaxel	+++	++		*		
Topoisomerase inhibitors						
Topotecan						
Irinotecan	+++			*		
Etoposide	+++		+	*		

+++= strong interaction; ++= moderate interaction; += weak interaction; *= indicates that an interaction has been documented

Short & Connors. The Oncologist 2014

Oncology drugs with CYP3A4 and P-glicoprotein interactions

	CYP3A4 interactions			P-glycoprotein interactions		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Hormonal agents						
Tamoxifen	+++		+			*
Raloxifene						
Anastrozole			+			
Letrozole	+					
Fulvestrant	+					
Leuprolide						
Flutamide	+++					
Bicalutamide			++			
Enzalutamide	+++	+++				*
Abiraterone	+++		++			*
Mitotane						

+++= strong interaction; ++= moderate interaction; += weak interaction; *= indicates that an interaction has been documented

Short & Connors. The Oncologist 2014

Tyrosine Kinase inhibitors with CYP3A4 and P-glicoprotein interactions

	CYP3A4 interactions			P-glycoprotein interactions		
Oncology drugs	**Substrate**	**Inducer**	**Inhibitor**	**Substrate**	**Inducer**	**Inhibitor**
Imatinib	+++		++	*		*
Dasatinib	+++		+			
Nilotinib	+++		+++	*		*
Erlotinib	+++					
Gefitinib	+++					
Lapatinib	+++		+	*		*
Sunitinib	+++					*
Sorafenib	+					
Crizotinib	+++		++	*		*
Vermurafenib	+	++		*		
Vandetanib	+++					*

+++= strong interaction; ++= moderate interaction; += weak interaction; *= indicates that an interaction has been documented

Short & Connors. The Oncologist 2014

Guidance for treatment of cancer-associated VTE

- The efficacy and safety of DOACs in patients with cancer-associated VTE remains uncertain.
- Guidance Statement:
  - *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.*
- Ongoing and planned studies aim to determine the relative safety and efficacy of DOACs in cancer-associated VTE compared with LMWH.

Khorana A.A. et al. J Thromb Thrombolysis 2016

DOAC Clinical Trials for treatment of Cancer-associated VTE

- **SELECT-D TRIAL**
  - phase 3, 2-phase randomized, multicentre study in treatment
  - open label dalteparin vs rivaroxaban x 6 mos
  - placebo vs rivaroxaban in patients with residual vein DVT at 6-12 mos

- **RIVAROXABAN TRIAL**
  - phase 4 multicentre, open-label, study in treatment
  - single arm prospective cohort treated with rivaroxaban x 6 mos

- **EDOXABAN TRIAL (Hokusai VTE-Cancer Study)**
  - phase 3 multicentre trial in treatment of CAT
  - edoxaban vs dalteparin x 6 mos

- **APIXABAN TRIAL (Caravaggio Study)**
  - phase 3b multicentre trial in treatment of CAT
  - Apixaban vs dalteparin x 6-12 mos