Cancer Associated thrombosis: 6 months and beyond

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National Thrombosis Week

5th May 2017

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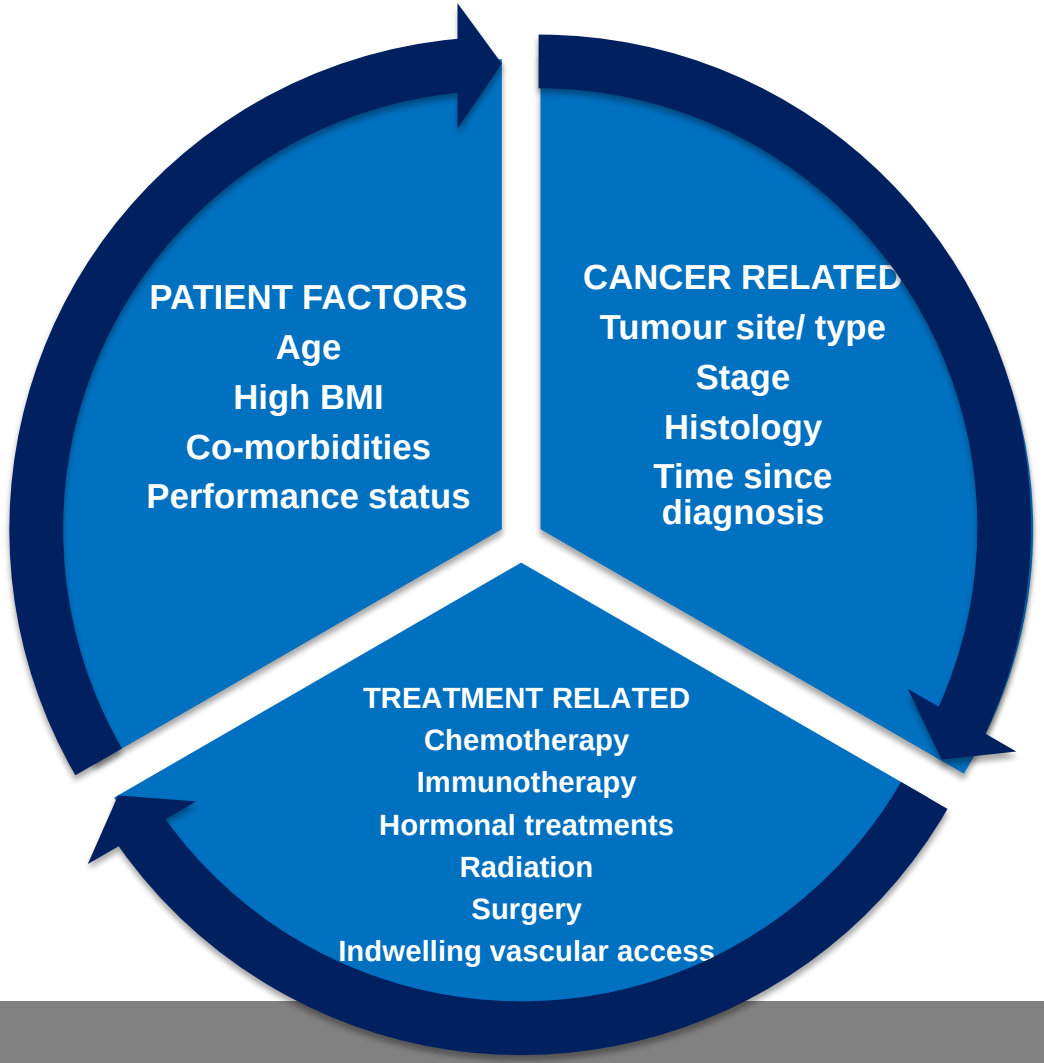
Risk Factors for cancer associated thrombosis



Guideline recommendations

	BCSH 2015	ASCO 2013	NICE CG144 2012	ESMO 2011
Initial/Acute Treatment	LMWH Consider oral agent if not tolerated	LMWH for initial 5-10 days if CrCl >30 mL/min	LMWH	LMWH for >5 days
Long-term Treatment	LMWH Consider oral agent if not tolerated	LMWH – 1st line VKA (INR 2-3) as alternative	LMWH	LMWH or oral agent
Duration of Treatment	Minimum 6 months Extend if active cancer Consider extend for some chemotherapy	Minimum 6 months Extend if metastatic disease or chemotherapy	6 months	Minimum 6 months Extend if metastatic disease or chemotherapy

Current recommendations

Guideline recommendations:

Standard of treatment for cancer-associated thrombosis is three to six months LMWH (Grade A)

In patients with ongoing active cancer, consideration should be given to indefinite anticoagulation but decision should be made on a case by case basis, taking into consideration bleeding risk and patient preference (Grade D)

Which patients?
Which agent?
What dose?
What drawbacks?

Patient AB

- 65 year old gentleman
- Oesophageal carcinoma with local node involvement
- Starts pre-operative chemotherapy: ECX
- Incidental PE diagnosed 1 month after starting chemotherapy: treated with Dalteparin 200 iu/kg for 1month then 150 iu/kg
- Has oesophagectomy, successful resection, good recovery
- Further ECX chemotherapy

- After 6 months Dalteparin, patient is receiving chemotherapy
- Subsequent scans have shown ‘complete resolution’ of the thrombus

- Patient wants to know whether to continue dalteparin?

Patient DE

- 45y female
- Breast carcinoma, with nodal involvement
- Treated with chemotherapy and surgery
- Patient had a proximal DVT during chemotherapy

- Has completed 6 months of dalteparin, cancer successfully resected
- Oncologists want to start tamoxifen

- Does she need secondary prevention?
- Which agent?

What evidence is there to guide management beyond 6 months?

Incidence of VTE recurrence

- **The risk of VTE recurrence after stopping anticoagulant therapy depends on the VTE risk factors associated with the initial thrombosis**

Risk factors (first VTE)	Annual rate of recurrence
Transient/reversible risk factors (eg, surgery)	~ 3%
Continuing risk factors (eg, cancer)	≥ 10%
Idiopathic (unprovoked)	≥ 10%

Kearon C. *Circulation* 2003;107:I22-I30.[9]

Prediction Models for VTE recurrence

Prediction models for recurrent venous thromboembolism

Model name	Vienna prediction model[16]	DASH score[19]	Rodger or men continue and HER DOO2 score[20]
Number of patients	929	1,818	646
Design	Prospective cohort study	Patient-level meta-analysis	Prospective cohort study
Predictive variables	Male > female. PE > proximal DVT > distal DVT. Elevated D-dimer after AC	D-dimer abnormal after cessation of AC (2 points). Age ≤50 years (1 point). Sex – male (1 point). Hormonal use at VTE onset (–2 points)	Men continue. Hyperpigmentation (1 point). Edema (1 point). Redness (1 point). D-dimer ≥250 µg/L during AC (1 point). Obesity (BMI ≥30 kg/m^2) (1 point). Old (age ≥65 years) (1 point)
Total score	0 to 350	−2 to 4	0 to 6
Annual risk of recurrence	2%–15% depending on total score (nomogram)	Score of ≤1: 3.1% Score of 2: 6.4% Score of ≥3: 12.3%	Women with score of ≤1: 1.6% Women with score of ≥2: 14.1% Men: 13.7%

Abbreviations: DVT, deep vein thrombosis; VTE, venous thromboembolism; AC, anticoagulation; BMI, body mass index; PE, pulmonary embolism.

BUT

Limited validation studies

Are these scores relavant to cancer patients?

Prediction models for VTE in cancer

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–

Only validated for initial VTE event and not recurrent events after 6 months of chemotherapy

What data can guide us?

CLOT Study: randomised LMWH vs warfarin in patients with CAT

subgroup analysis

Independent risk factors of VTE recurrence

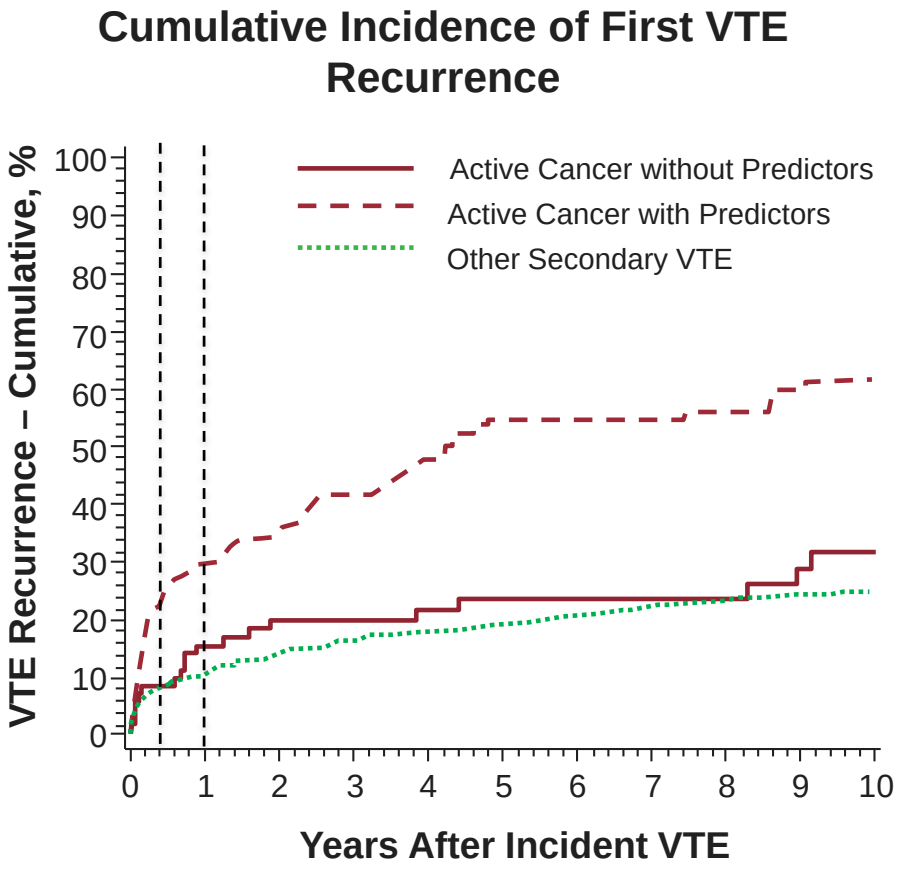
- Lung cancer (HR, 3.51; 95% CI, 1.62–7.62)
- Metastases (HR, 2.59; 95% CI, 1.29–5.60)

Lower risk

- Breast cancer (HR, 0.59; 95% CI, 1.62–7.62)

Lee AY *et al. J Clin Oncol* 27:499s 2009 (suppl abstract 9565)

Recurrent VTE Risk in Active Cancer
Population-based cohort Olmstead County



- 477 patients with active cancer and VTE (eligible between 1966 and 2000)
- Highest risk amongst panceratic cancer, CNS tumours, ovarian, lung and any metastatic tumour

- Warfarin reduced recurrence: Hazard ratio 0.43 (0.28-0.66)

Chee CE *et al. Blood* 2014.

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Risk Model for Recurrent VTE in CAT

The Ottawa score

Variable	Regression Coefficient	Point
Female	0.59	1
Lung cancer	0.94	1
Breast cancer	-0.76	-1
TNM Stage I	-1.74	-2
Previous VTE	0.4	1
Clinical probability: Low (≤0) Clinical probability: High (≥1)		-3 – 0 1 – 3

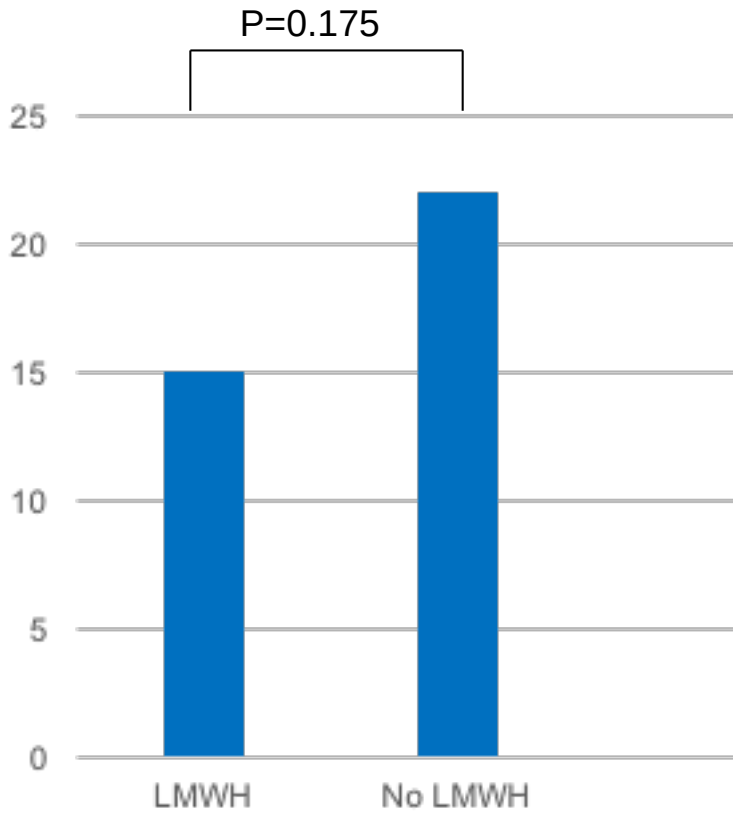
Outcome:

- Patients with a score <0 had a low risk of recurrence: **5.1%**
- Patients with a score of 0 had an intermediate risk of recurrence: **9.8%**
- Patients with a score ≥1 had a high risk of recurrence: **15.8%**

Results have not been fully validated

Louzada et al, Circulation 2012

Role of residual vein thrombosis



- 242 patients with residual vein thrombosis
  - (non-compressibility of 40% vein diameter)
- Randomly assigned to further 6 month LMWH
- 15% vs 22% recurrence in 12 month follow up
- Absence of residual vein thrombosis: 2.8% recurrence off anticoagulation

- Residual vein thrombosis NOT a useful tool for deciding to continue anticoagulation

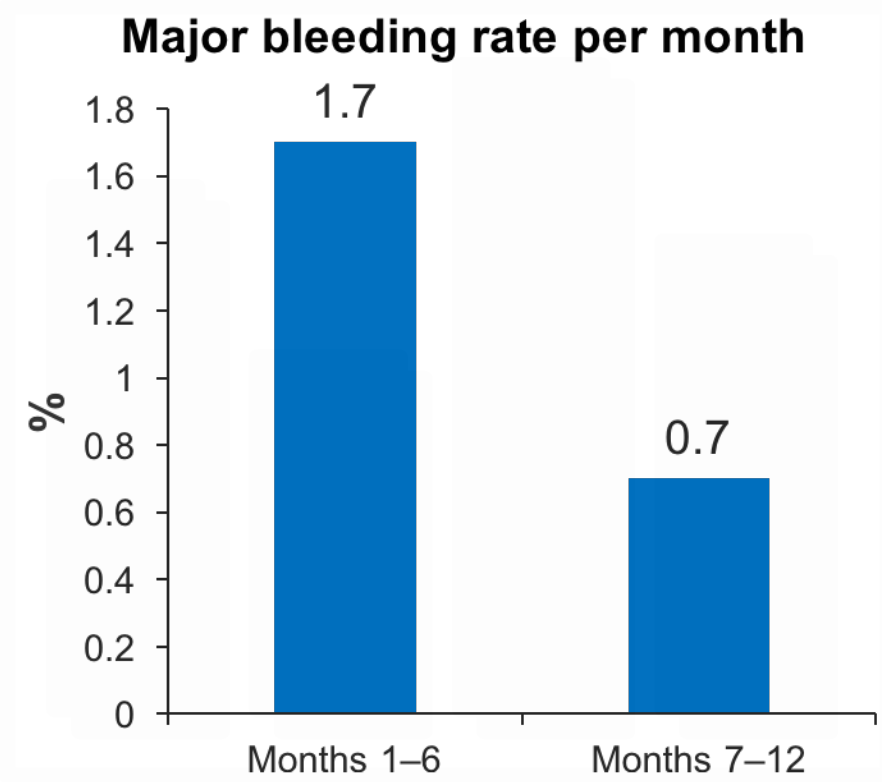
Napolitano et al, The Cancer DACUS study. JCO 2014

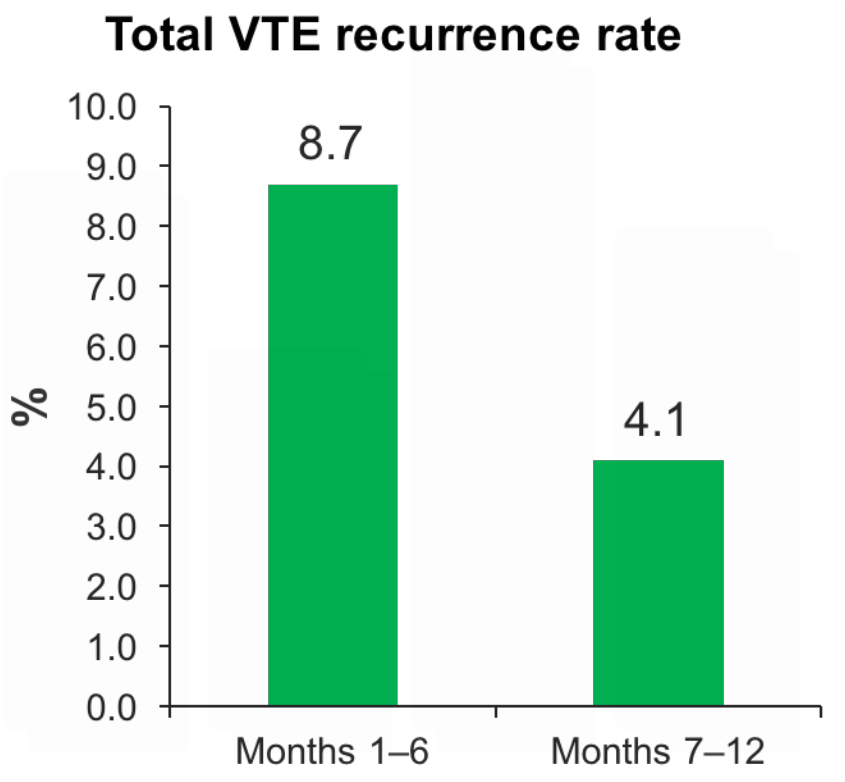
Cancer treatment and thrombosis

- Hormonal therapies:
  - oestrogen receptor modulators (tamoxifen)
  - Progestins
  - Aromatase inhibitors
- Thalidomide analogs
- Cisplatin
- Anti-angiogenic agents and growth factor inhibitors

DALTECAN: *Efficacy and safety of long-term therapy*

334 patients enrolled assessing dalteparin at 6 (55%) or 12 months (33%)





- 116 deaths: 105 cancer; 4 recurrent PE; 2 haemorrhage

Francis C *et al. J Thromb Haemost* 2015.

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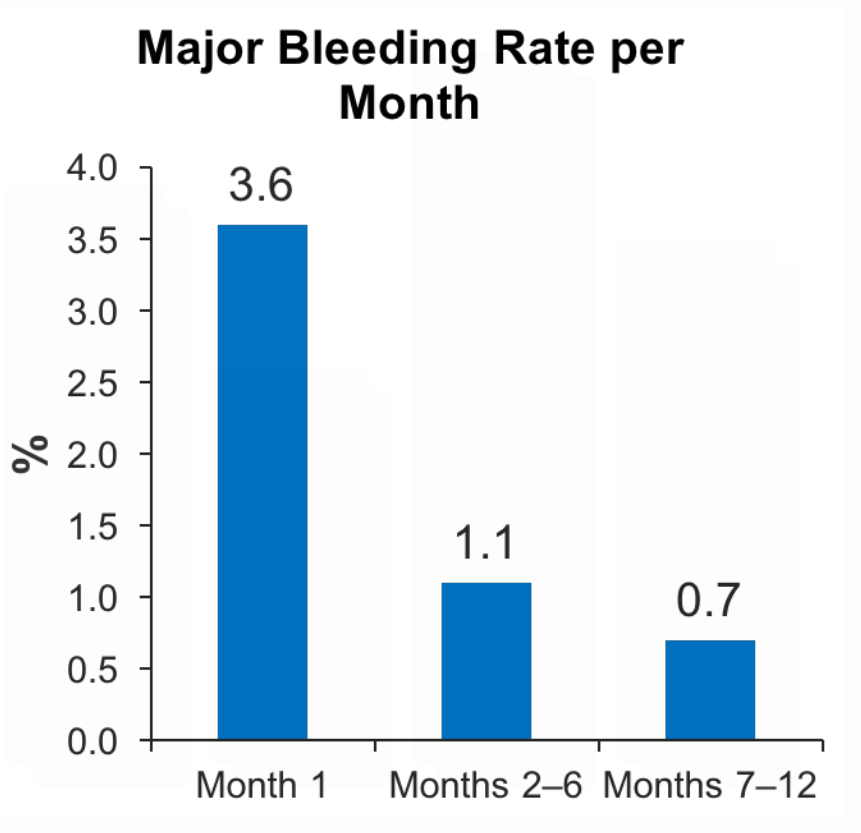
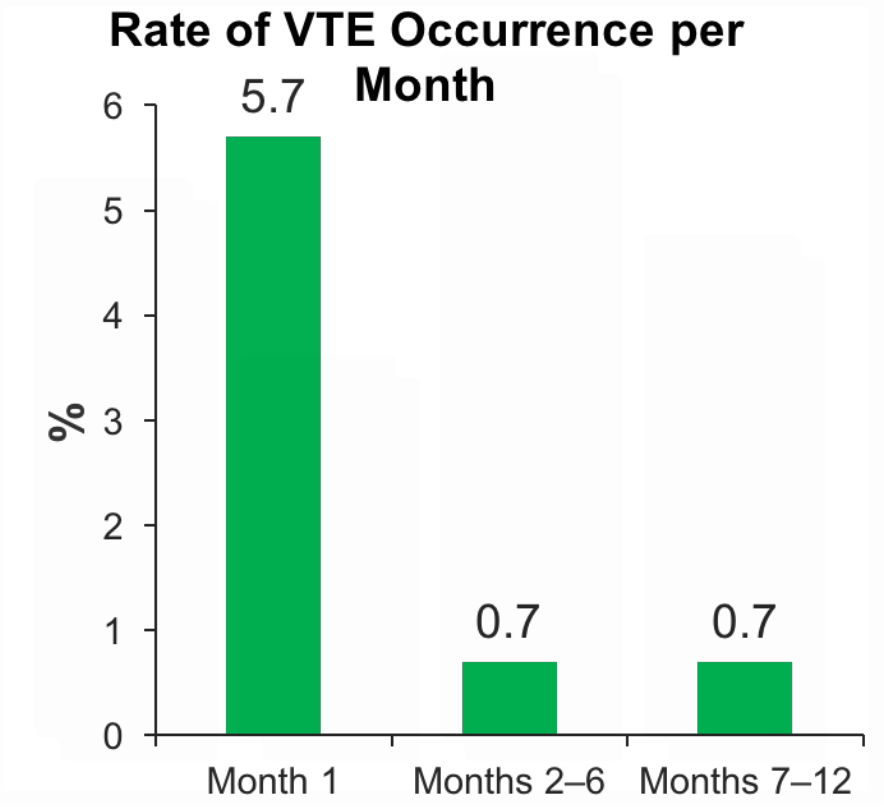
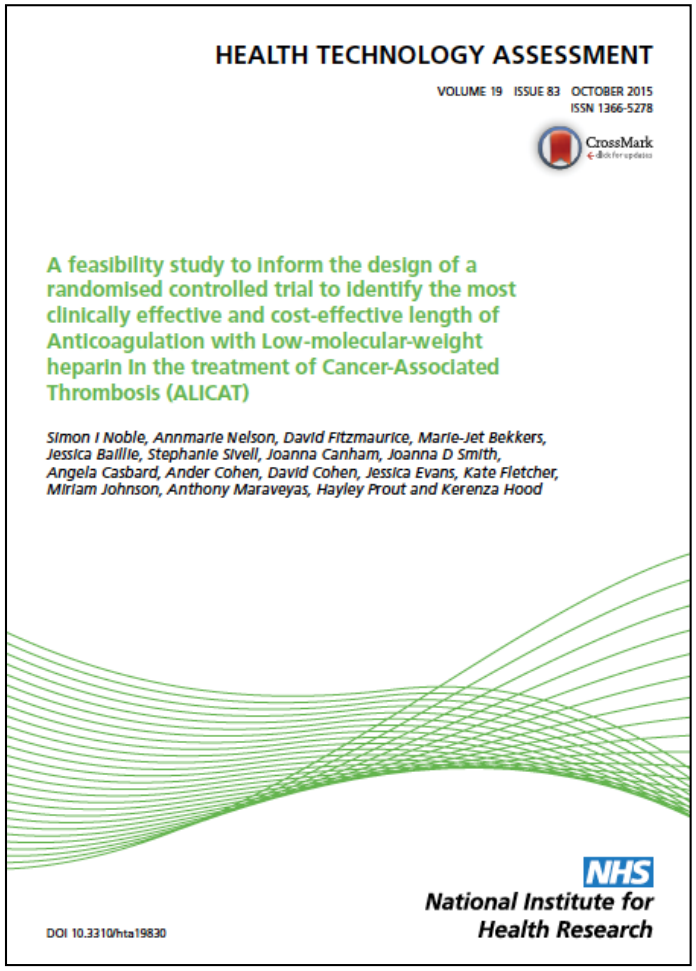
DALTECAN: *Efficacy and safety of long-term therapy*





- Bleeding was not increased in Months 6–12 compared to Months 2–6.

ALICAT



Feasibility study

RCT to explore anticoagulation > 6 months in those with ongoing cancer

Qualitative component

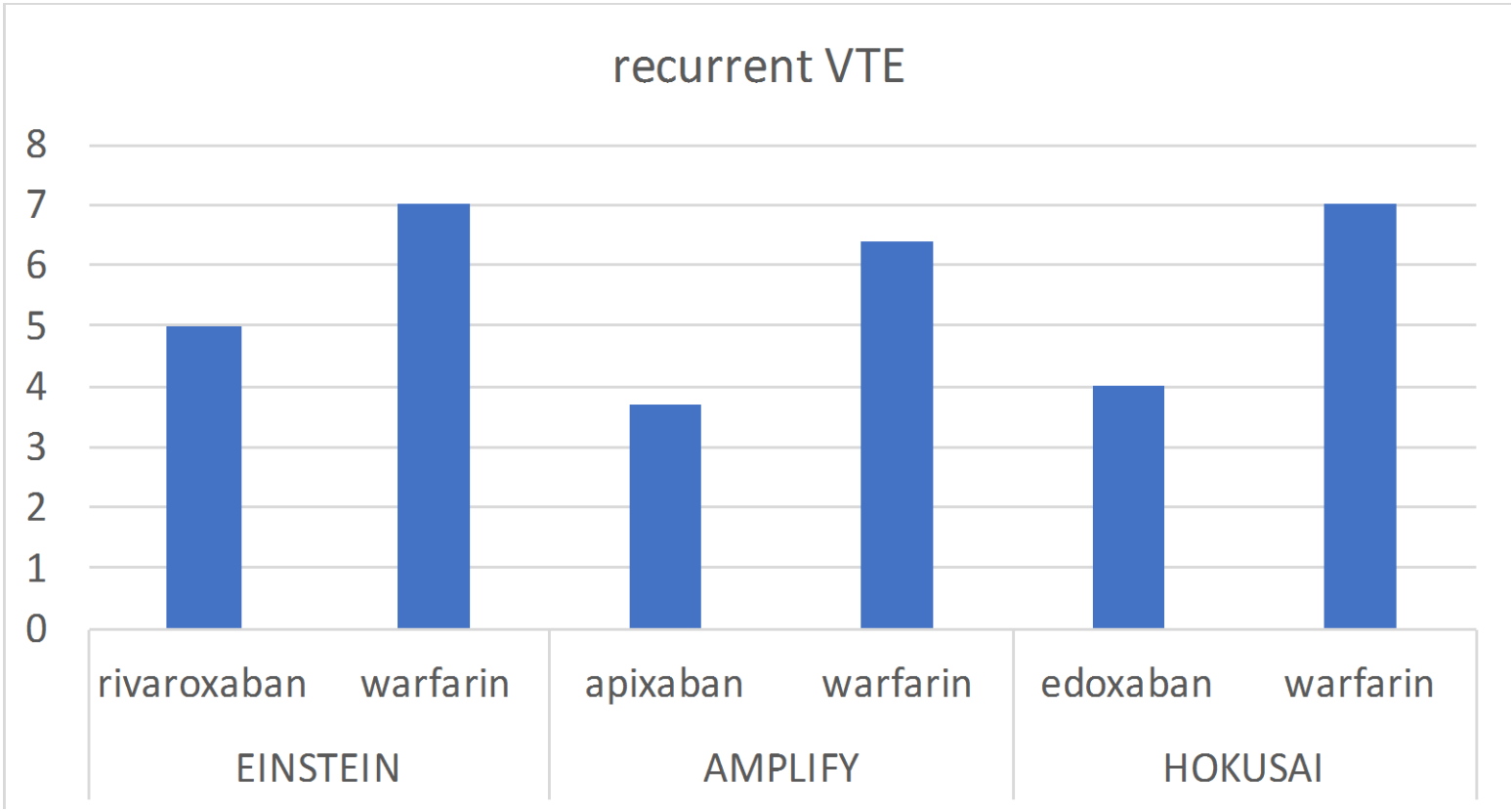
- Willingness of patients to be randomised
- Willingness of clinicians to recruit

Deemed not feasible

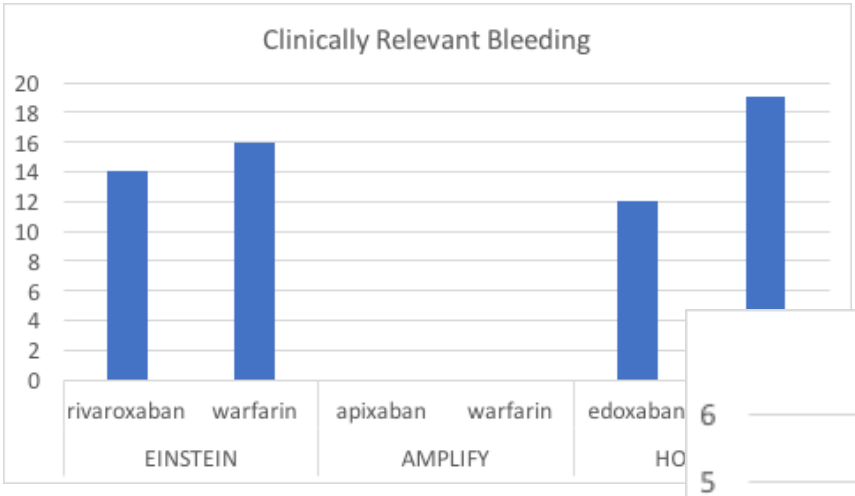
DATA STILL LACKING AND HARD TO OBTAIN…..

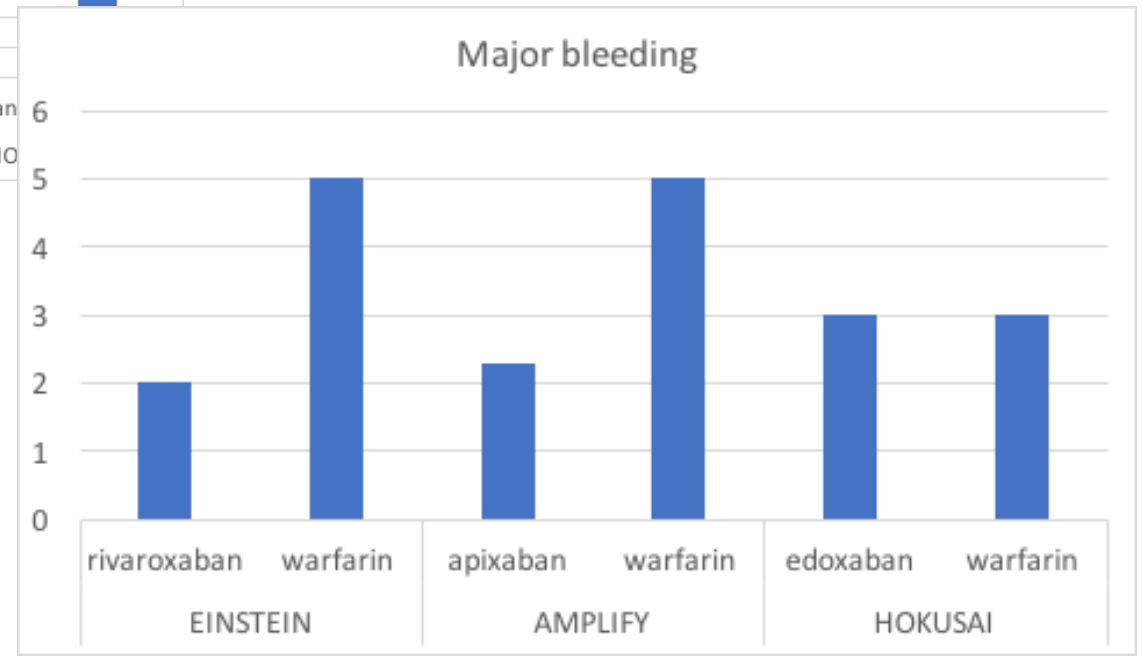
Direct Oral anticoagulants

Subgroup analysis: non-inferior to warfarin with respect to recurrent VTE



Direct oral anticoagulants: bleeding





What can we learn from our patients?

- Symptomatic CAT is a distressing experience[1]
- Patients are given insufficient information about risks of CAT during chemotherapy[2]
- LMWH injections acceptable within context of illness[1]
- Develop habits and rituals to normalize daily injections[2]

CAT = cancer-associated thrombosis; LMWH = low molecular weight heparin

1. Seaman S *et al. Pat Pref Adherence* 2014; 2. Noble S *et al. Pat Pref Adherence* 2015.

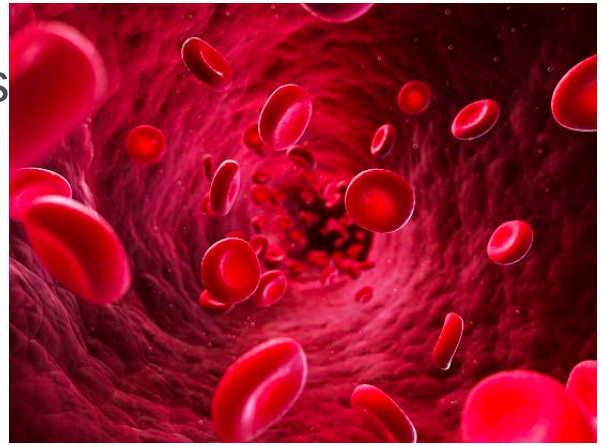
An ideal anticoagulant for patients in order of preference

1. Least interference with cancer treatments
2. Lowest thrombosis recurrence rate
3. Minimal bleeding risk
4. Oral
5. Once a day
6. No need for monitoring

Noble S *et al Haematologica* 2015.

There is limited evidence on which to make decisions

- Prior thrombosis, severity, recurrence on anticoagulation
- Thrombogenicity of cancer
- Thrombogenicity of treatments: chemotherapy, immunotherapy, hormone therapy
- Bleeding risks: tumour type; concurrent illnes
- **Patient views**



Factors influencing decision whether to extend anticoagulation in CAT

Factor	Favors continuing anticoagulation	Favors stopping anticoagulation
Patient preference	• 1^0 concern recurrence	• 1^0 concern hemorrhage
Malignancy specific	• Active malignancy • High risk cancer e.g., lung • Ongoing chemo or ESA	• No evidence of disease • Low risk cancer e.g., breast
Previous history of VTE	• Yes	• No
Nature of initial VTE	• Life-threatening PE • DVT with severe postphlebitic syndrome	• Non life-threatening PE • No residual symptoms
Risk of hemorrhage	• No	• Yes
Additional risk factors	• Obesity • Sex • Poor performance status • Central venous catheter	• Risk factors other than malignancy when diagnosed e.g., surgery

Zwicker JI, Bauer KA. *J Clin Oncol* 2014.32(32):3596–3600.

Patient AB

- 65 year old gentleman
- Oesophageal carcinoma with local node involvement
- Starts pre-operative chemotherapy: ECX
- Incidental PE diagnosed 1 month after starting chemotherapy: treated with Dalteparin 200 iu/kg for 1month then 150 iu/kg
- Has oesophagectomy, successful resection, good recovery
- Further ECX chemotherapy

- After 6 months Dalteparin, patient is receiving chemotherapy
- Subsequent scans have shown ‘complete resolution’ of the thrombus
- Patient wants to know whether to continue dalteparin?

Outcome: Patient continued with prophylactic dalteparin dose
Stopped once completed chemotherapy and confirmed cancer in remission
No further thrombosis

Patient BC

- 45y female
- Breast carcinoma, with nodal involvement
- Treated with chemotherapy and surgery
- Patient had an intracardiac thrombosis during chemotherapy, possibly due to line

- Has completed 6 months of dalteparin, cancer successfully resected
- Oncologists want to start tamoxifen

- Does she need secondary prevention?
- Which agent?

- **OUTCOME: Patient chose to take rivaroxaban 20mg as secondary prevention until tamoxifen complete**

Thanks for listening

- Questions and thoughts?