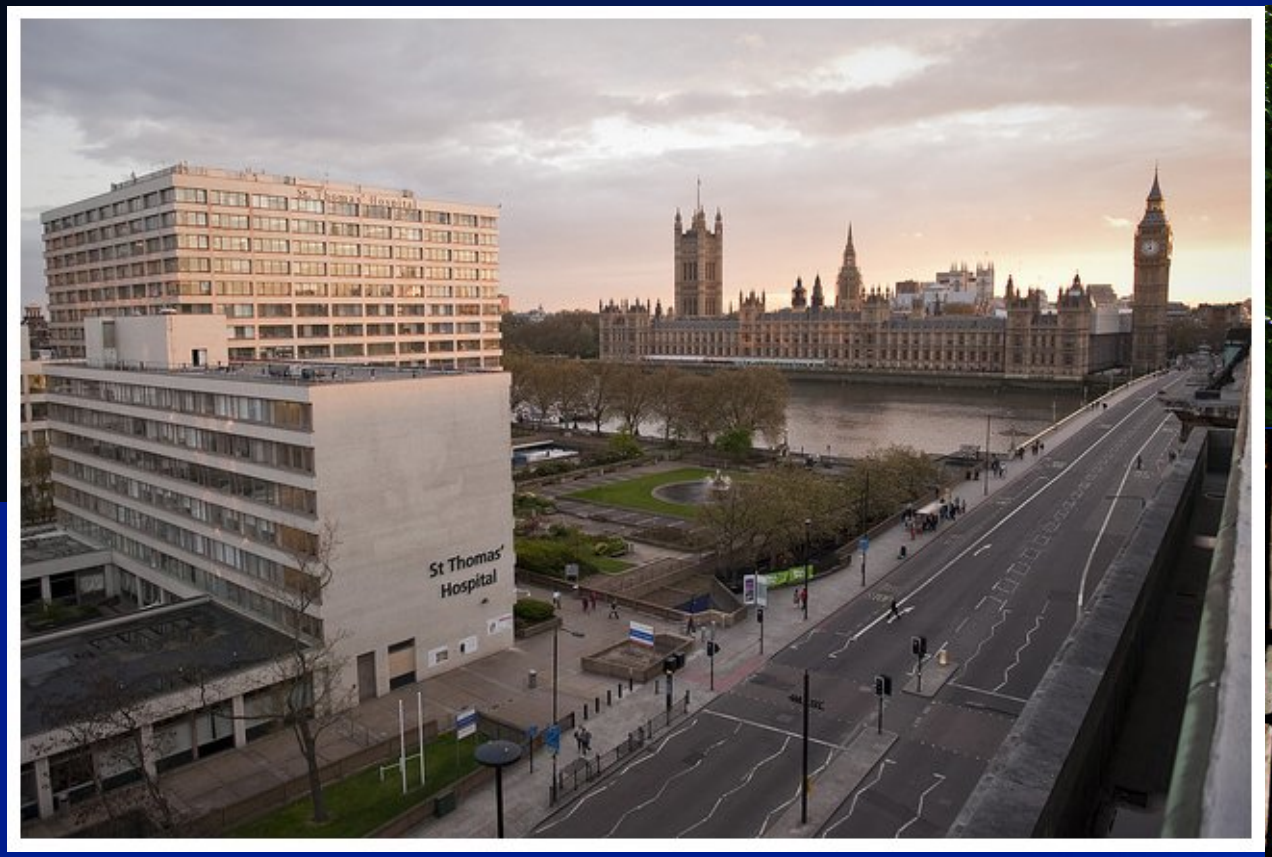
DOACs and CAT



Alexander (Ander) Cohen
Vascular Medicine / Haematology
Guy's and St Thomas' Hospitals,
King's College, London

05 May 2017 NTW St Thomas' Hospital

Disclosures for Dr. Alexander (Ander) T. Cohen

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Employee	No relevant conflicts of interest to declare
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Stockholder	No relevant conflicts of interest to declare
Speakers Bureau	Bayer, Boehringer Ingelheim, BMS, Daiichi Sankyo, Johnson and Johnson, Pfizer, Portola, Sanofi
Scientific Advisory Board	See consultant

Presentation includes discussion of off-label use of a drug or medical device

Some Take Home Messages

- LMWH more effective that VKA for CAT
- NOACs appear to be “as good as, or better than” VKA for CAT
- NOACs (or VKA) can be used to treated CAT if:
  - ✓ Lower risk of recurrence
  - ✓ Not, or no longer, “severely ill”
- Indefinite anticoagulation (usually) unless cancer becomes “in active”
- Treatment decisions should be influenced by patient preference for oral versus parenteral therapy


Thank you very much for your attention!

Limitations of LMWH and VKA Result in Poor Adherence to Guideline-Recommended Therapies for Treatment of CAT

LMWH limitations

- Parenteral administration
  - Perceived higher treatment burden
- Weight-adjusted dosing
- Some risk of heparin-induced thrombocytopenia
- Quality of life concerns, particularly in cancer patients

Oral VKA limitations

- Narrow therapeutic window
- Frequent monitoring and dose adjustment required
- Interaction with food and drugs including chemotherapy drugs, making INR control challenging
- Less effective than LMWH for treatment of CAT[1–3]

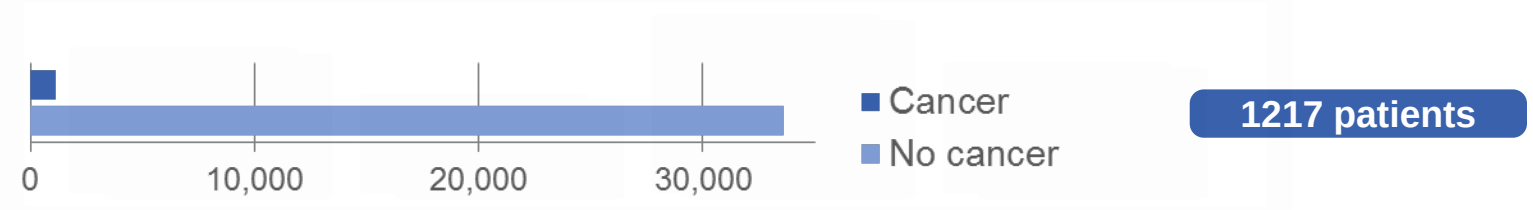
1. Lee AYY *et al*, *N Engl J Med* 2003;349:146–153; 2. Lee AYY *et al*, *Blood* 2014:124:Abstract LBA-2; 3. Alk EA *et al*, *Cochrane Database Rev* 2014;7:CD006650

Who has been studied?

- Answer – not all patients

Treatment of VTE in Patients with Cancer: NOACs

Phase III NOAC trials including more than 30,000 patients



Drug	Trial name	Patients with cancer (%)
Rivaroxaban[1]	EINSTEIN DVT	6.0
	EINSTEIN PE	4.6
	EINSTEIN Extension	4.5
Dabigatran[2]	RE-COVER	4.8
	RE-COVER II	3.9
	RE-MEDY	4.2
	RE-SONATE	N/A
Apixaban[1]	AMPLIFY	2.7
	AMPLIFY-EXT	1.7
Edoxaban[1]	Hokusai-VTE	2.5

1. Wharin C *et al. Blood Rev* 2014;28:1–4; 2. Vedovati M *et al. Chest* 2015;147:475–483

Broad Group of Active Cancer Types Included

Active cancer* type	Rivaroxaban (n)	Enoxaparin/VKA (n)	Total (n)
Genitourinary tract	89	96	185
Haematological	54	32	86
Lower gastrointestinal	42	28	70
Lung	34	30	64
Breast	32	30	62
Upper gastrointestinal	29	14	43
Squamous/basal cell carcinoma	8	6	14
Skin	10	3	13
Brain	5	5	10
Endocrine	4	5	9
Combinations	18	22	40
Other or unspecified	17	13	30
TOTAL			626

*At baseline or diagnosed during the study

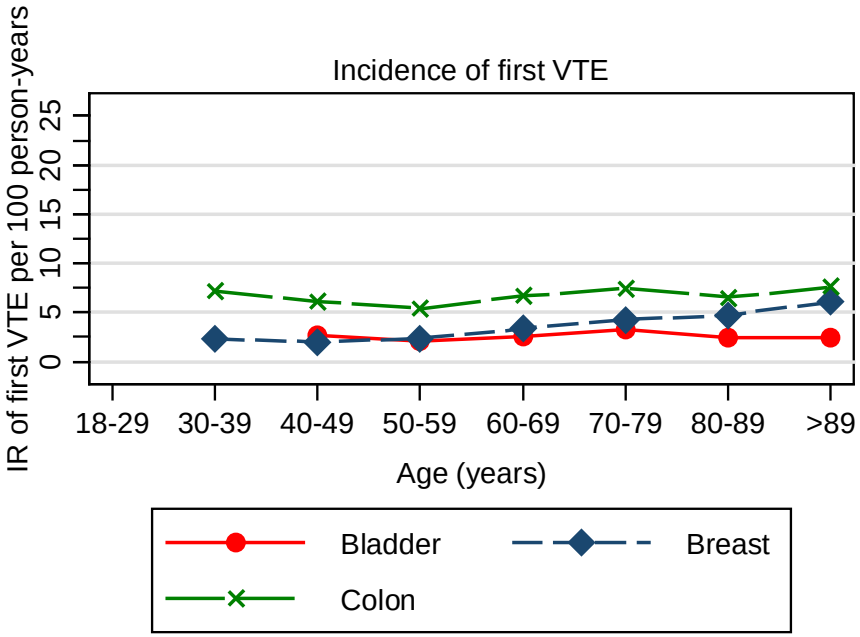
Prins MH *et al. Lancet Haematol* 2014;1:e37–e46

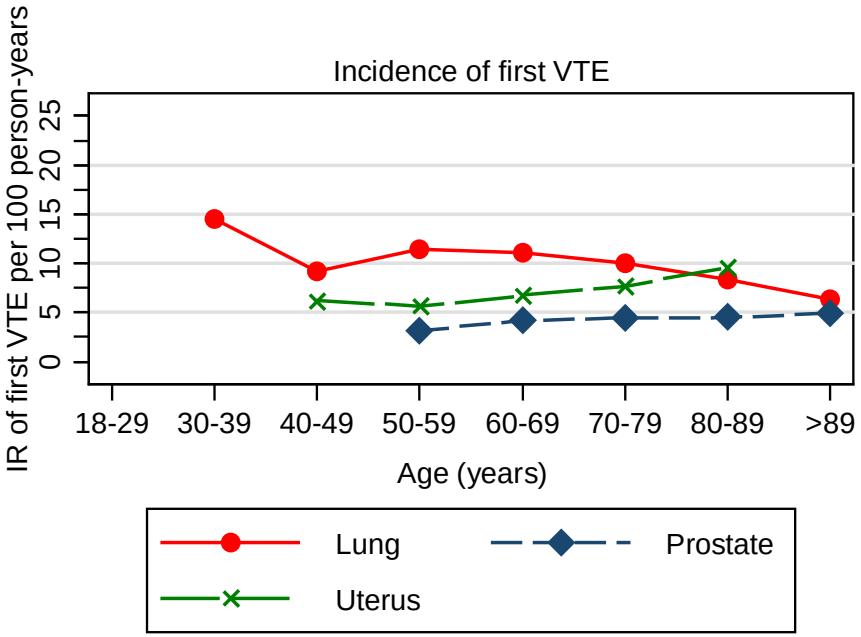
Patient Demographics

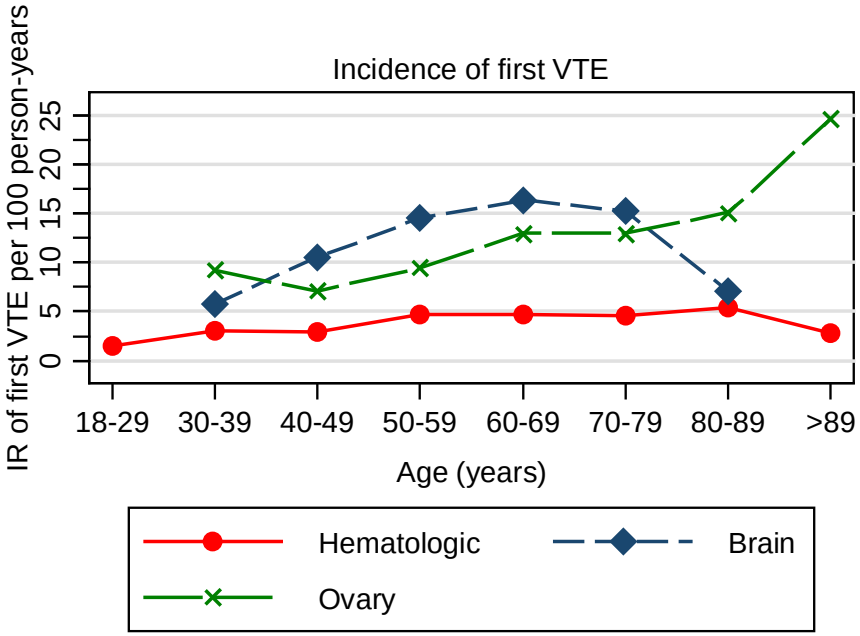
Patients with active cancer* and a first VTE (N=6592)

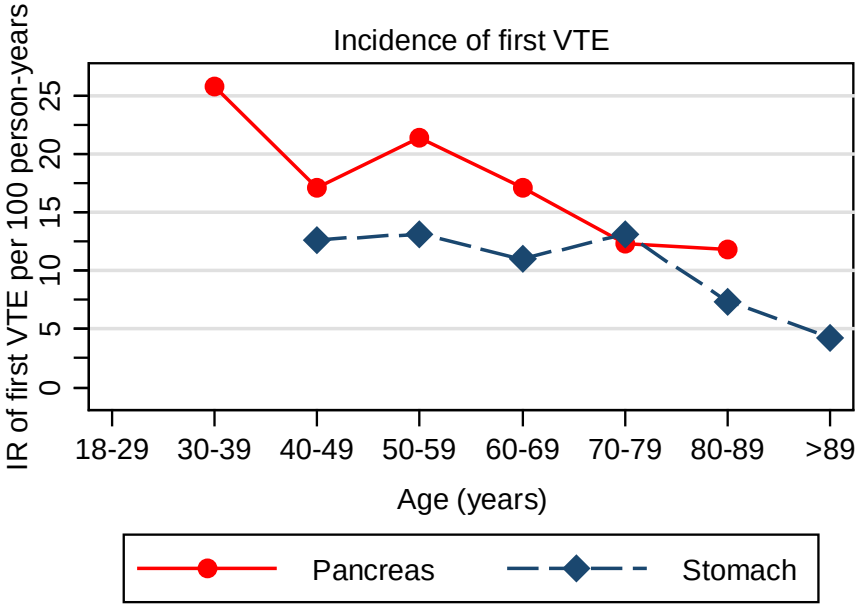
	DVT (n=3055)	PE (n=3537)	Total (N=6592)
Common cancer types, n (%)			
Prostate (males)	278 (19.1)	287 (16.1)	565 (17.5)
Breast (females)	225 (14.0)	281 (16.0)	506 (15.1)
Lung	315 (10.3)	603 (17.0)	918 (13.9)
Colon	384 (12.6)	443 (12.5)	827 (12.5)
Haematological	360 (11.8)	309 (8.7)	669 (10.1)
Ovarian (females)	136 (8.5)	182 (10.3)	318 (9.5)
Bladder	186 (6.1)	133 (3.8)	319 (4.8)
Uterus (females)	83 (5.2)	58 (3.3)	141 (4.2)
Pancreas	129 (4.2)	131 (3/7)	260 (3.9)
Stomach	104 (3.4)	133 (3.8)	237 (3.6)
Brain	79 (2.6)	87 (2.5)	166 (2.5)

Cohen AT *et al*, *Thromb Haemost* 2017;117:57–65





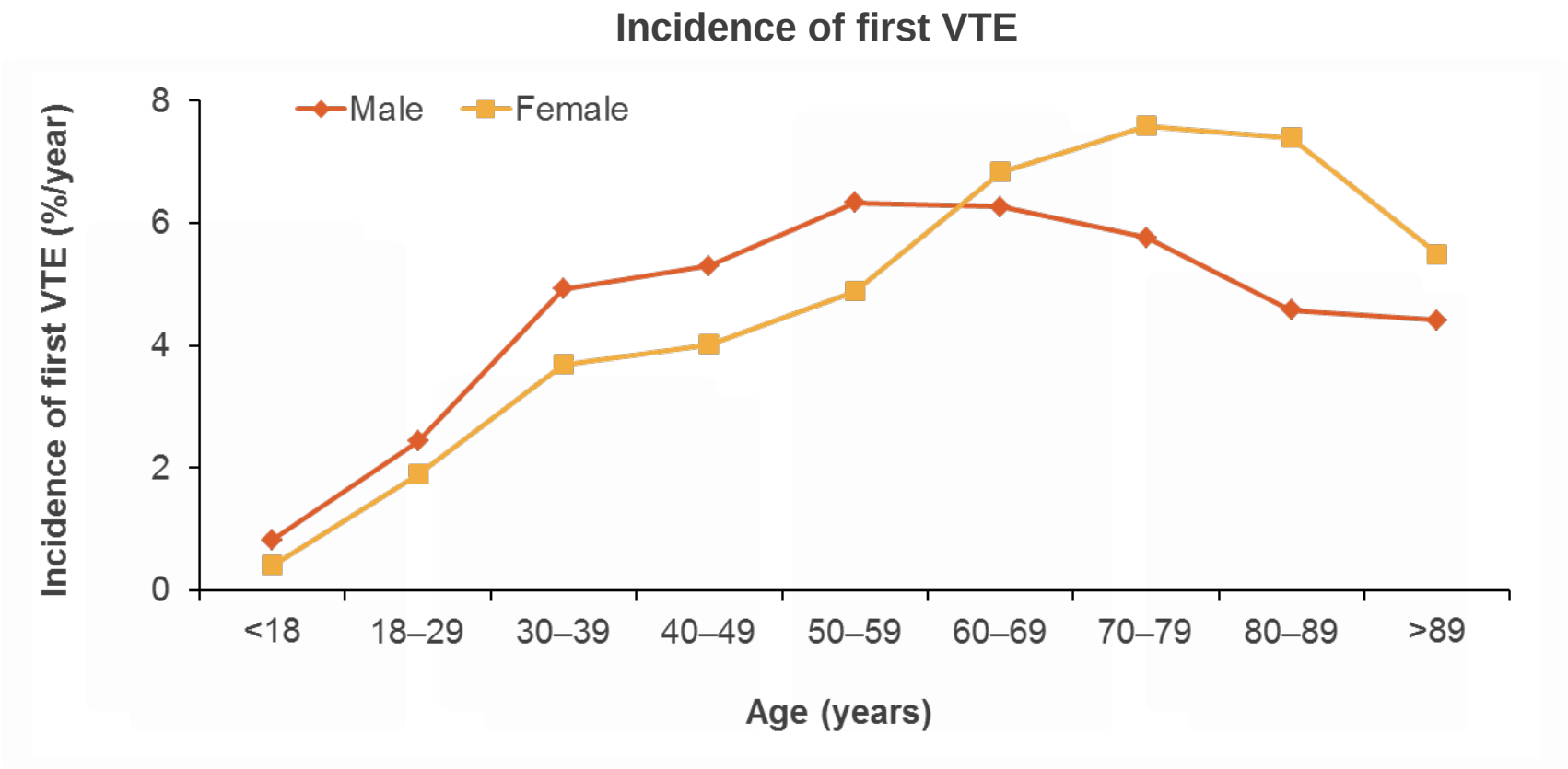




Derived from: Cohen AT *et al*, *Thromb Haemost* 2017;117:57–65

Results: First VTE

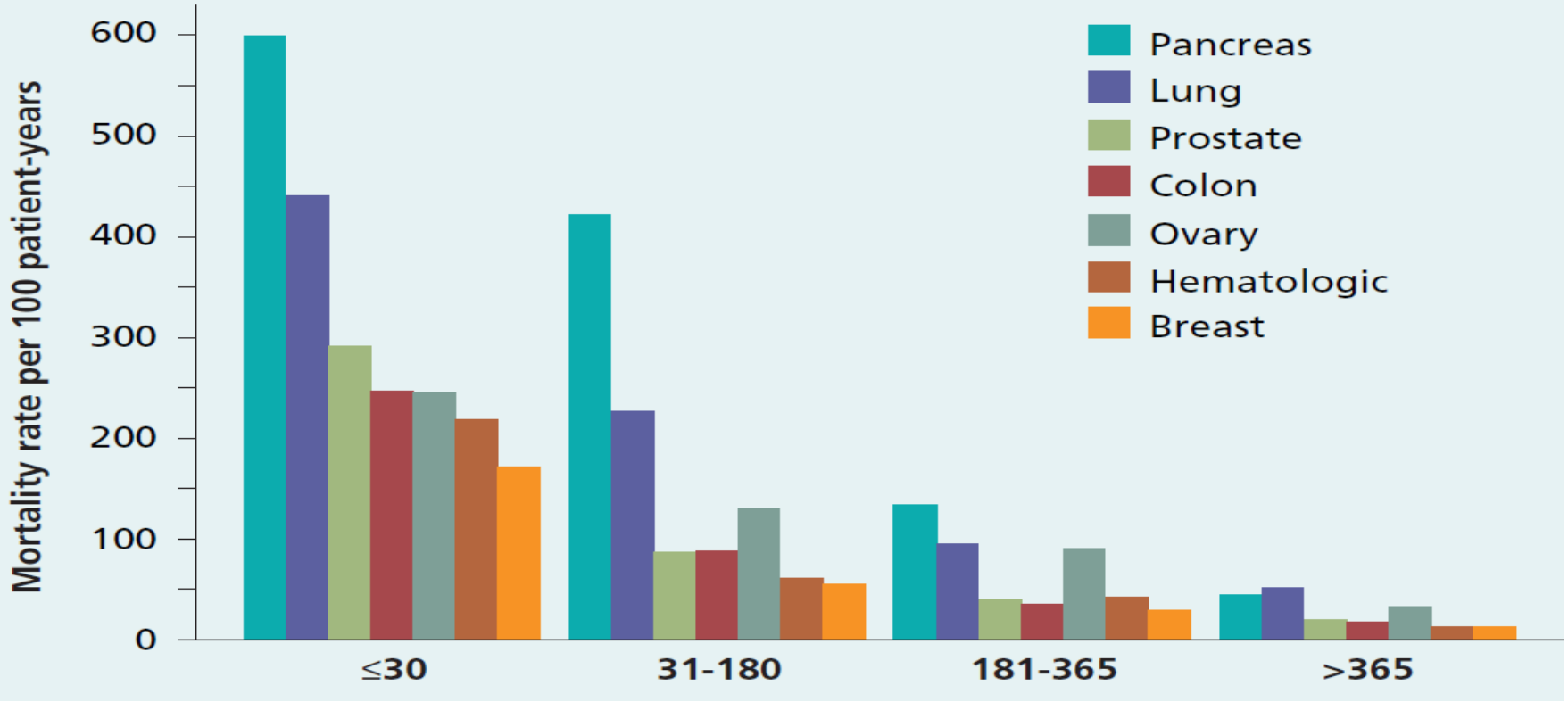
- IR of first VTE in patients with active cancer: 5.8 (95% CI 5.7–6.0) per 100 person-years
- Incidence of first VTE was highest in the elderly population



Cohen AT *et al*, *Thromb Haemost* 2017;117:57–65

Mortality Rates Following Active Cancer

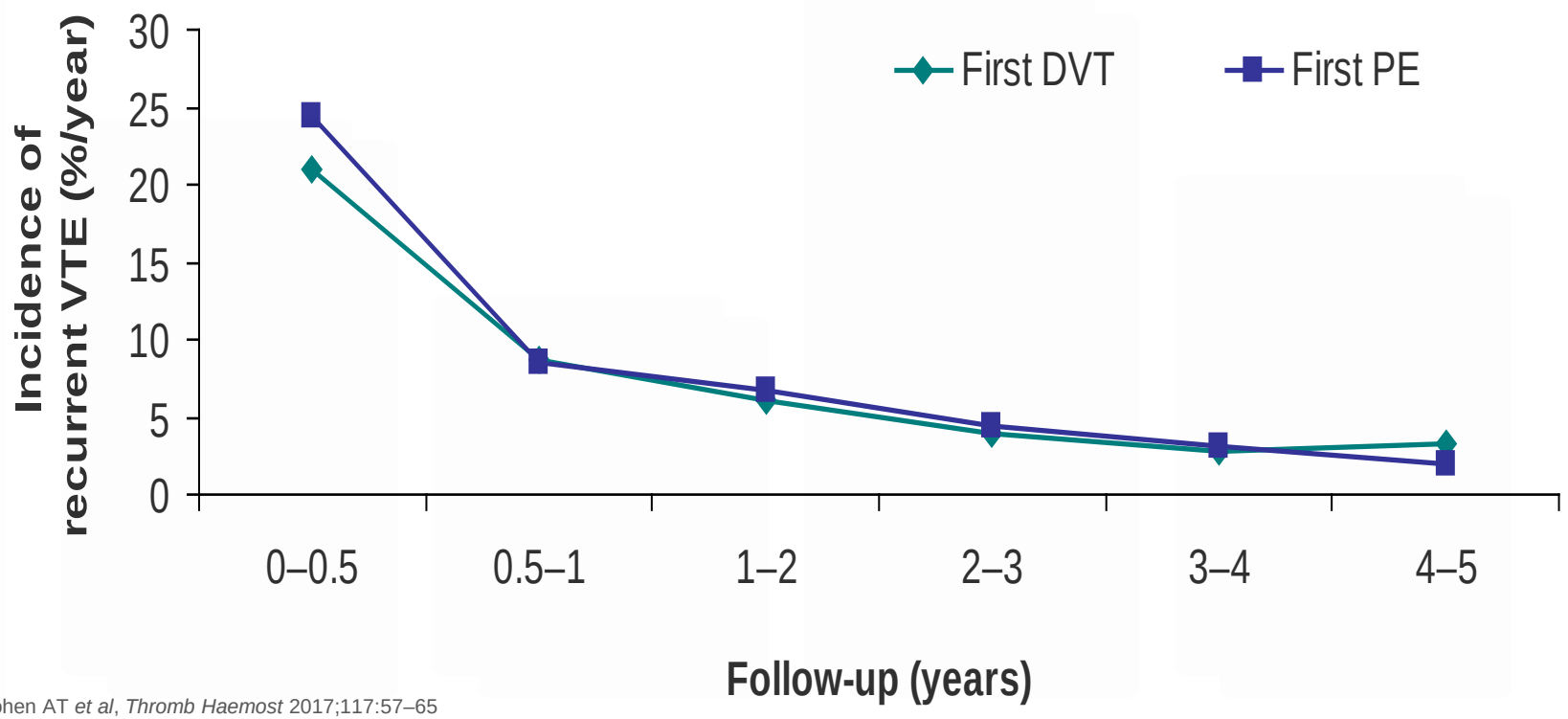
Mortality rates following active cancer VTE by time since VTE and cancer site



Martinez C *et al*, ITSH 2015;Poster PO124-TUE

Results: Recurrent VTE by Type of Index Event

- IR of VTE recurrence: 9.6 (95% CI 8.8–10.4) per 100 person-years
  - 8.8 per 100 person-years following first DVT
  - 10.5 per 100 person-years following first PE
- Peak recurrence in first 6 months



Cohen AT *et al*, *Thromb Haemost* 2017;117:57–65

Unmet Needs in CAT

- Significant knowledge gaps remain in the treatment of CAT, including:
  - Head-to-head trials comparing NOACs vs LMWH in CAT treatment
  - Extended anticoagulation to prevent recurrent VTE

- Significance of interactions between NOACs and cancer drugs
  - Dosing in patients with chemotherapy-induced side effects
  - Manage temporary interruptions of NOACs for invasive procedures

- Treatment satisfaction, treatment persistence and quality of life in cancer patients receiving NOACs

Ay C *et al, Thromb Haemost* 2016; doi:10.1160/TH16-08-0615

Patients with CAT who can be Treated with an Oral Anticoagulant?

Less severe DVT or PE (initially or follow-up)

- Popliteal and more distal DVT
- Segmental and subsegmental PE
- & Less severe symptoms and signs

Lower risk for recurrence (initially or follow-up)

- Localized cancer
- Resected cancer
- Less aggressive cancer (type, progression, systemic effects)
- Not on chemotherapy
- No previous VTE
- After initial LMWH therapy

“Cured” vs. “Active” cancer – 6M rule

Cured (or inactive) Cancer

- successful treatment completed (Sx, chemo)
- no known residual disease (no mets)
- cancer recurrence is unlikely
- ± disease-free interval (eg, 6 mo)

Active Cancer

- does not meet “inactive” criteria

New oral anticogulants for VTE treatment in cancer patients: pros

- Oral
- Fixed dose
- No lab monitoring
- No risk of HIT

Oral rivaroxaban versus enoxaparin with VKA for treating VTE in cancer patients: a pooled subgroup analysis of EINSTEIN-RCTs

	Rivaroxaban	Enoxaparin and vitamin K antagonist	HR (95% CI)	ARD (95% CI)	p value*
Intention-to-treat population	354	301	..	..	..
Safety population	353	298	..	..	..
Recurrent venous thromboembolism†	16 (5%)	20 (7%)	0·67 (0·35 to 1·30)	−1·7% (−5·2 to 1·8)	0·24
Major bleeding‡	8 (2%)	15 (5%)	0·42 (0·18 to 0·99)	−3·0% (−5·9 to 0·0)	0·047
Clinically relevant bleeding‡§	48 (14%)	49 (16%)	0·80 (0·54 to 1·20)	−2·7% (−8·3 to 3·0)	0·28
Mortality†	58 (16%)	53 (18%)	0·93 (0·64 to 1·35)	−1·6% (−7·4 to 4·2)	0·70
Net clinical benefit†	25 (7%)	38 (13%)	0·54 (0·33 to 0·90)	−5·3% (−9·9 to −0·7)	0·018

Data are n (%) or HR (95% CI). HR=hazard ratio. *Calculated from the Cox models. †Percentage based on intention-to-treat population. ‡Percentage based on safety population. §Composite of major bleeding and non-major clinically relevant bleeding.

***Table 3*: Recurrent venous thromboembolism, bleeding, mortality, and net clinical benefit in patients with active cancer**

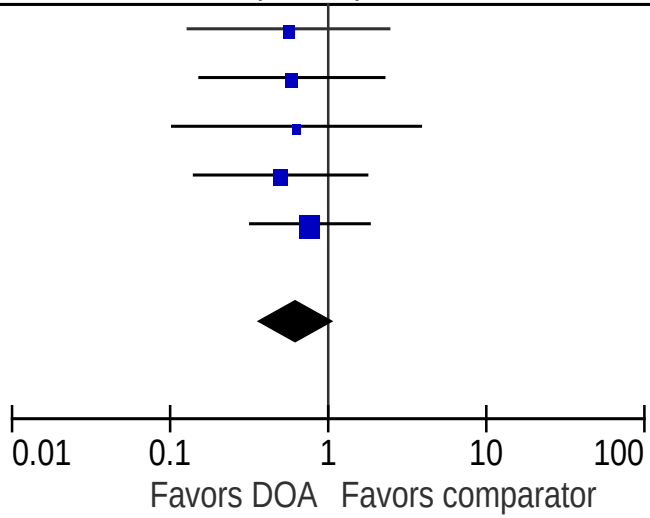
Prins M et al , Lancet Haematol, 2014

Long-term VTE treatment in cancer patients
Metanalysis: efficacy outcomes

NOACs: **23 / 595 (3.8%)**
Conventional treatment: **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: $Z = 1.62$ ($P = 0.10$)



Vedovati, Chest, 2014

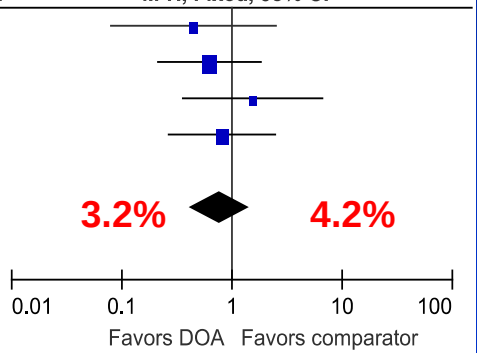
Long-term VTE treatment in cancer patients
Metanalysis: safety outcomes

Major bleeding

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)



CR non major bleeding

Vedovati, Chest, 2014

Conclusions of meta-analysis

- RCT suggest DOACs are as effective, and possibly more effective, than warfarin in cancer patients with VTE.
- In such patients, bleeding is appreciable during anticoagulation therapy and may potentially be reduced by DOAC therapy
- DOAC could be an alternative to standard therapy.


AND THEN THE STUDENT JUMPED STRAIGHT-IN AND ASSESSED CHEST EXPANSION....
BEFORE THEY HAD FULLY ADDRESSED THE PATIENT'S IDEAS, CONCERNS AND EXPECTATIONS!
imgflip.com

New oral anticogulants for VTE treatment in cancer patients: cons

- Few cancer patients enrolled in RCTs (5-6%)
- No RCTs comparing these new agents with LMWHs
- Oral route may be not ideal in cancer patients (vomiting, nausea, anorexia)
- Interactions with anticancer drugs unknown
- Limited experience in patients with liver and renal impairment
- Reducing the dose (i.e. for occurrence of thrombocytopenia) more challenging than with LMWHs
- No evidence about possible survival improvement effect (antitumoral activity)

Chemotherapeutic Agents and Immunosuppressants

	Dabigatran	Rivaroxaban	Apixaban
Interaction effect*	P-gp	P-gp CYP3A4	P-gp CYP3A4
Increases NOAC plasma levels#	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib	Cyclosporine Tacrolimus Tamoxifen Lapatinib Nilotinib Sunitinib Imatinib
Reduces NOAC plasma levels‡	Dexamethasone	Dexamethasone	Dexamethasone
	Doxorubicin	Doxorubicin	Doxorubicin
	Vinblastine	Vinblastine	Vinblastine

*Clinicians should consult pharmacist; #drugs that inhibit P-gp or CYP3A4 can increase NOAC levels; ‡drugs that induce P-gp or CYP3A4 can lower NOAC levels
P-gp, P-glycoprotein; CYP3A4, Cytochrome P450 3A4
Lee AYY *et al. Blood* 2013;122:2310–2317

Antithrombotic therapy for VTE disease: CHEST guidelines 2016

Summary of recommendations in cancer patients

Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date)

- *In patients **with DVT of the 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 2C), **apixaban** (Grade 2C) or **edoxaban** (Grade 2C).*

Kearon C, et al. CHEST 2016, doi: 10.1016/j.chest2015.11.026

Antithrombotic therapy for VTE disease: CHEST guidelines 2016

Summary of recommendations in cancer patients

Choice of Long-Term (First 3 Months) and Extended (No Scheduled Stop Date)

- In patients with VTE and cancer ("cancer-associated thrombosis"), 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 a 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.

Kearon C, et al. CHEST 2016, doi: 10.1016/j.chest2015.11.026

Cancer VTE treatment NOACs trials

Hokusai Cancer VTE study (EDOXABAN)

CALLISTO Programme (RIVAROXABAN)

- CARAVAGGIO Study (APIXABAN)

Some Take Home Messages

- LMWH more effective that VKA for CAT
- NOACs appear to be “as good as, or better than” VKA for CAT
- NOACs (or VKA) can be used to treated CAT if:
  - ✓ Lower risk of recurrence
  - ✓ Not, or no longer, “severely ill”
- Indefinite anticoagulation (usually) unless cancer becomes “in active”
- Treatment decisions should be influenced by patient preference for oral versus parenteral therapy

Say nothing more

Apixaban for the Treatment of Venous Thromboembolism in Patients with Cancer (CARAVAGGIO)

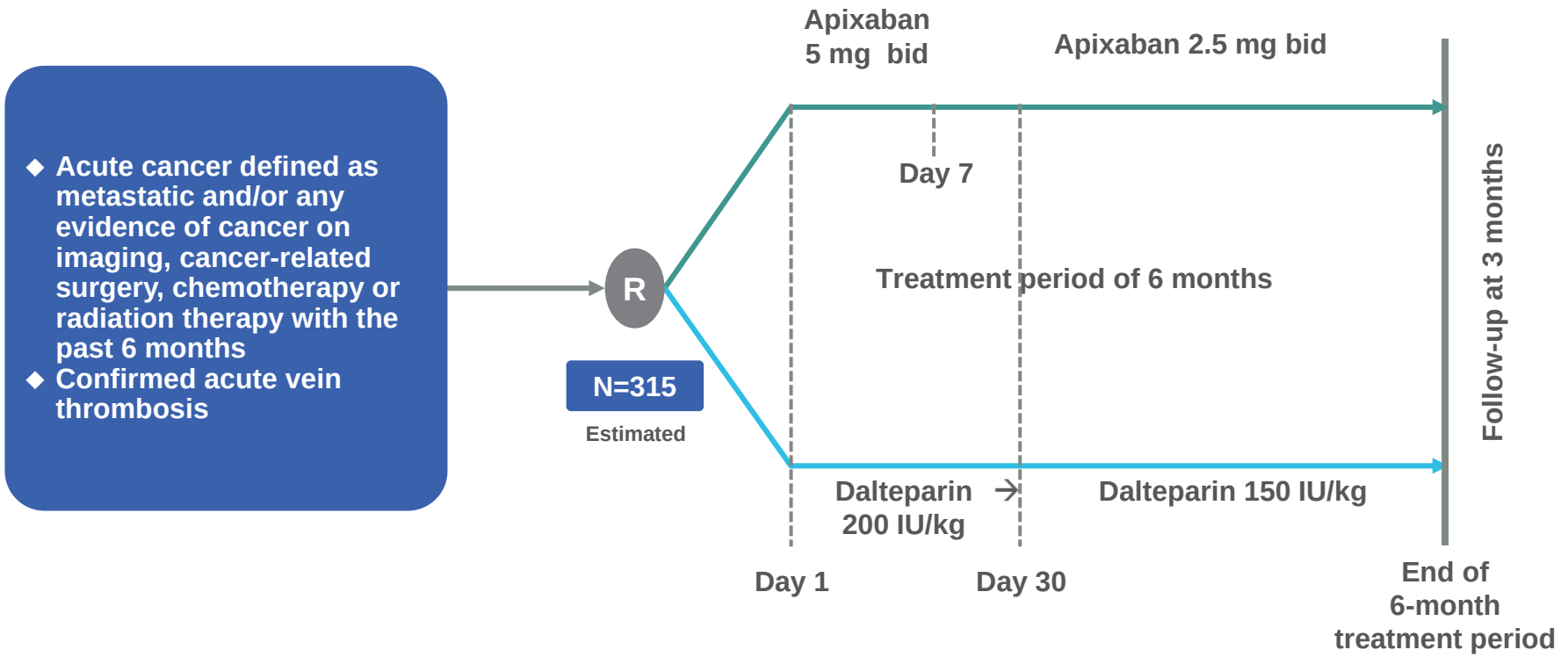
Phase IIIb European multicentre study

- Aim: to assess whether apixaban is non-inferior to the LMWH dalteparin for the treatment of newly diagnosed VTE in patients with cancer
- Eligibility: patients with cancer and newly diagnosed, proximal lower limb DVT, PE or both
- Primary efficacy outcome: recurrent DVT or PE occurring during the 6-month study treatment period
- Approximately 120 study sites in Europe are planned for the enrolment of ~1400 patients in this study

Exom Group. http://www.exomgroup.com/hilights/clinical-trial-news-3 [accessed 01 Dec 2016]

Apixaban Versus Dalteparin For Reducing Blood Clots in Patients with Cancer-Related Venous Thromboembolism

Phase III open-label, randomized study

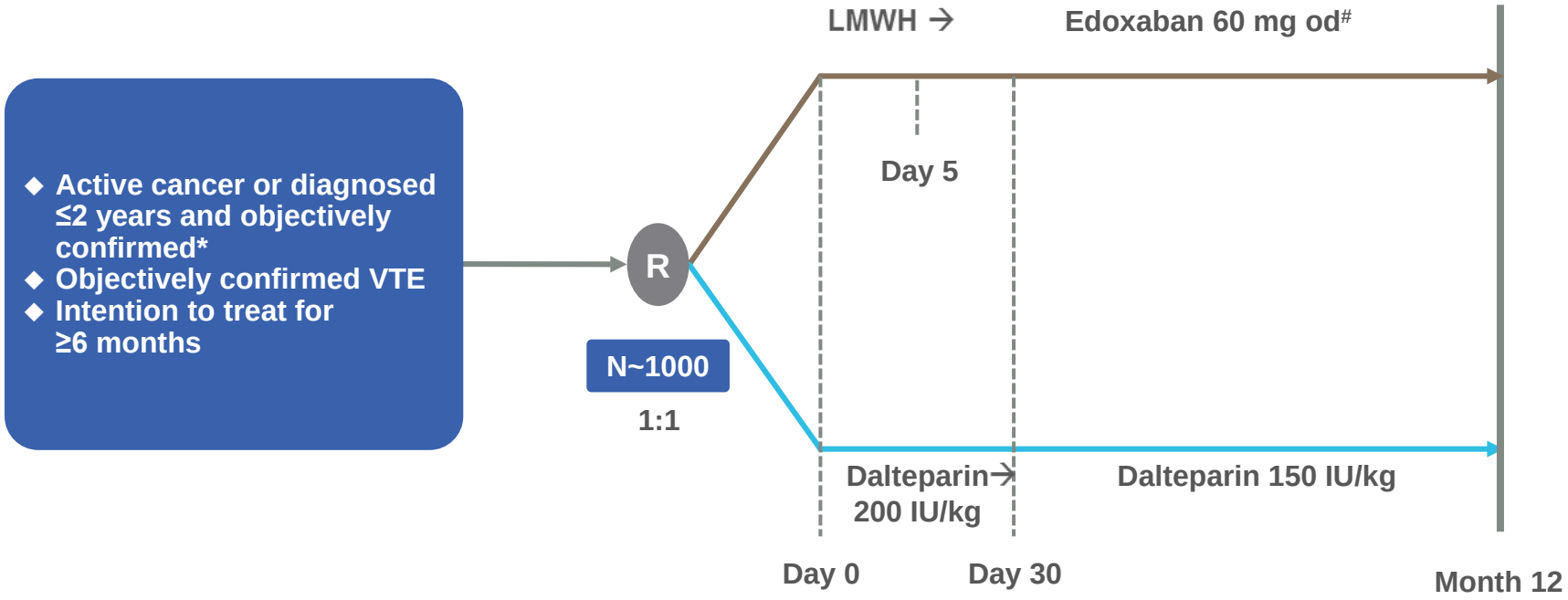


- Primary outcome: any episode of major bleeding including fatal bleeding
  - Secondary endpoint: VTE recurrence (up to 3 months post-treatment); any episode of major bleeding or clinical relevant non-major bleeding
- Estimated primary completion date: December 2020

National Cancer Institute. NCT02585713 (available at clinicaltrials.gov)

Edoxaban Versus Dalteparin for the Prevention of Venous Thromboembolism in Cancer Patients

Phase IV open-label, randomized, PROBE design study



- Primary outcomes: incidence of recurrent VTE at end of study; incidence of clinically relevant bleeding on treatment
- Estimated primary completion date: December 2017

Stratified randomization for bleeding risk and dose adjustment; *patients with basal-cell or squamous cell carcinoma were excluded; #dose adjustment to edoxaban 30 mg od in patients with body weight of 60 kg or less, a creatinine clearance 30–50 ml/min inclusive, or concomitant use of P-gp inhibitors

van Es N *et al*, *Thromb Haemost* 2015;114:1268–1276; Daiichi Sankyo. NCT02073682 (available at clinicaltrials.gov)