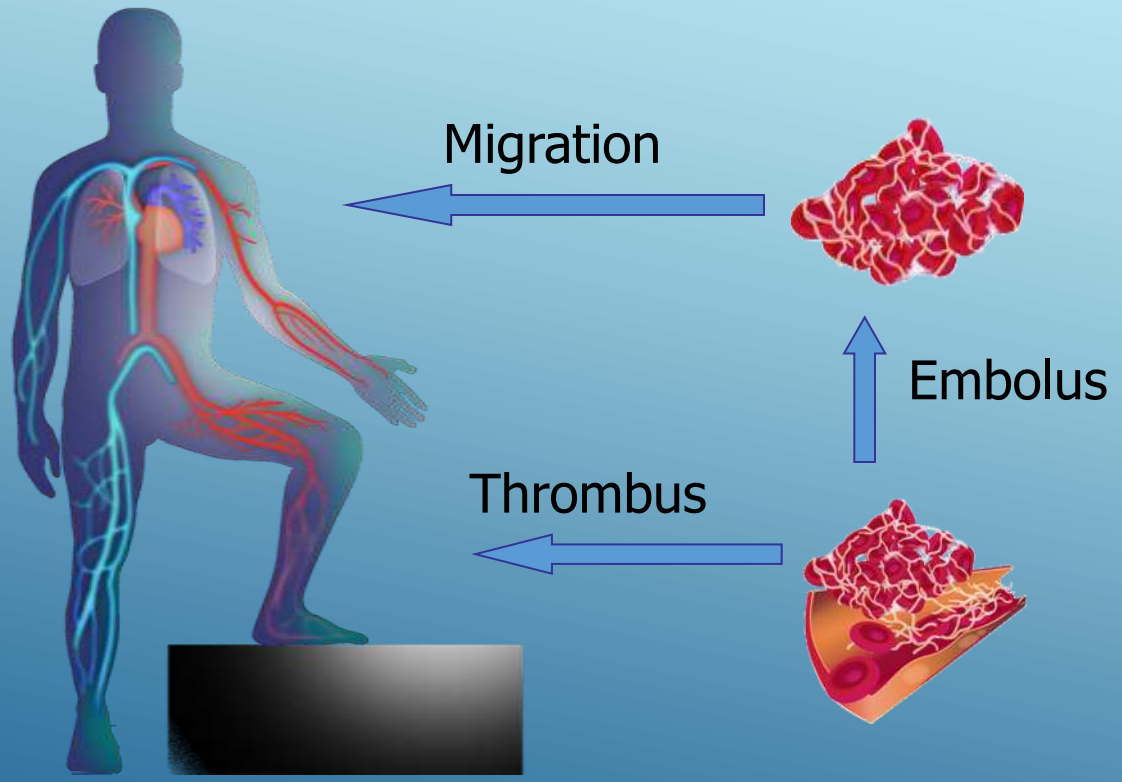
CANCER ASSOCIATED THROMBOSIS

Clot Meeting 2015

Dr Peter Rose

VENOUS THROMBOEMBOLISM (VTE) COMMONLY CONSIDERED AS A SINGLE DISORDER



DVT and PE represent distinct, albeit overlapping, clinical entities having similar treatment strategies

[1]Bates SM, et al. Thromb Haemost 1999. [2]Murin S, et al. Thromb Haemost 2002.

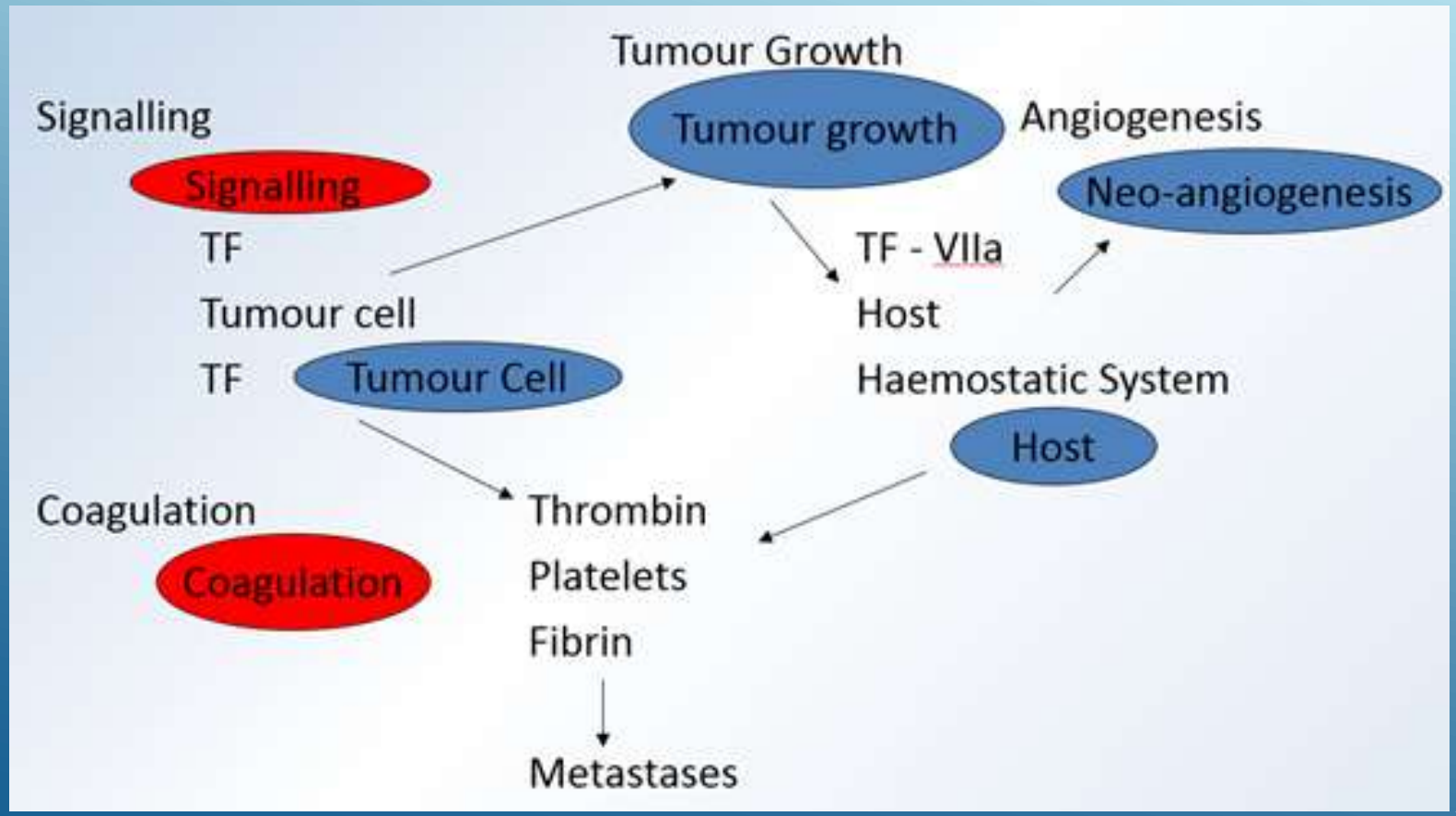
MECHANISMS OF THROMBOSIS IN CANCER

- Cancer cell activities
  - Procoagulant
  - Fibrinolytic
  - Interaction with platelets
  - Interaction with phagocytes
  - Interaction with endothelial cells
- Abnormalities of blood flow
- Treatment related

ABNORMALITIES OF FLOW

- External Compression
- Viscosity
- Immobilisation
- IV Access

TISSUE FACTOR COAGULATION AND TUMOUR SIGNALLING PATHWAYS



FACTORS TO PREDICT VTE IN CANCER PATIENTS

1. General risk factors for all VTE patients
2. Site of tumour
3. Metastatic disease
4. Surgery
5. Cancer therapy
6. Intravenous catheters
7. Biological markers

RISK FACTORS FOR VTE

Patient Related	Additional factors
Increasing age	Surgery within 90 days
Previous history VTE	Lower limb cast
Family history 1st degree relative	Hospital stay > 3 days
Thrombophilia	Cancer in past 6 months/ ongoing disease
Pregnancy	Medical comorbidities
Obesity > 30kg/m^2	Extended travel
Smoking/ Alcohol/ Substance abuse	Medication related

CANCER FACTORS FOR VTE

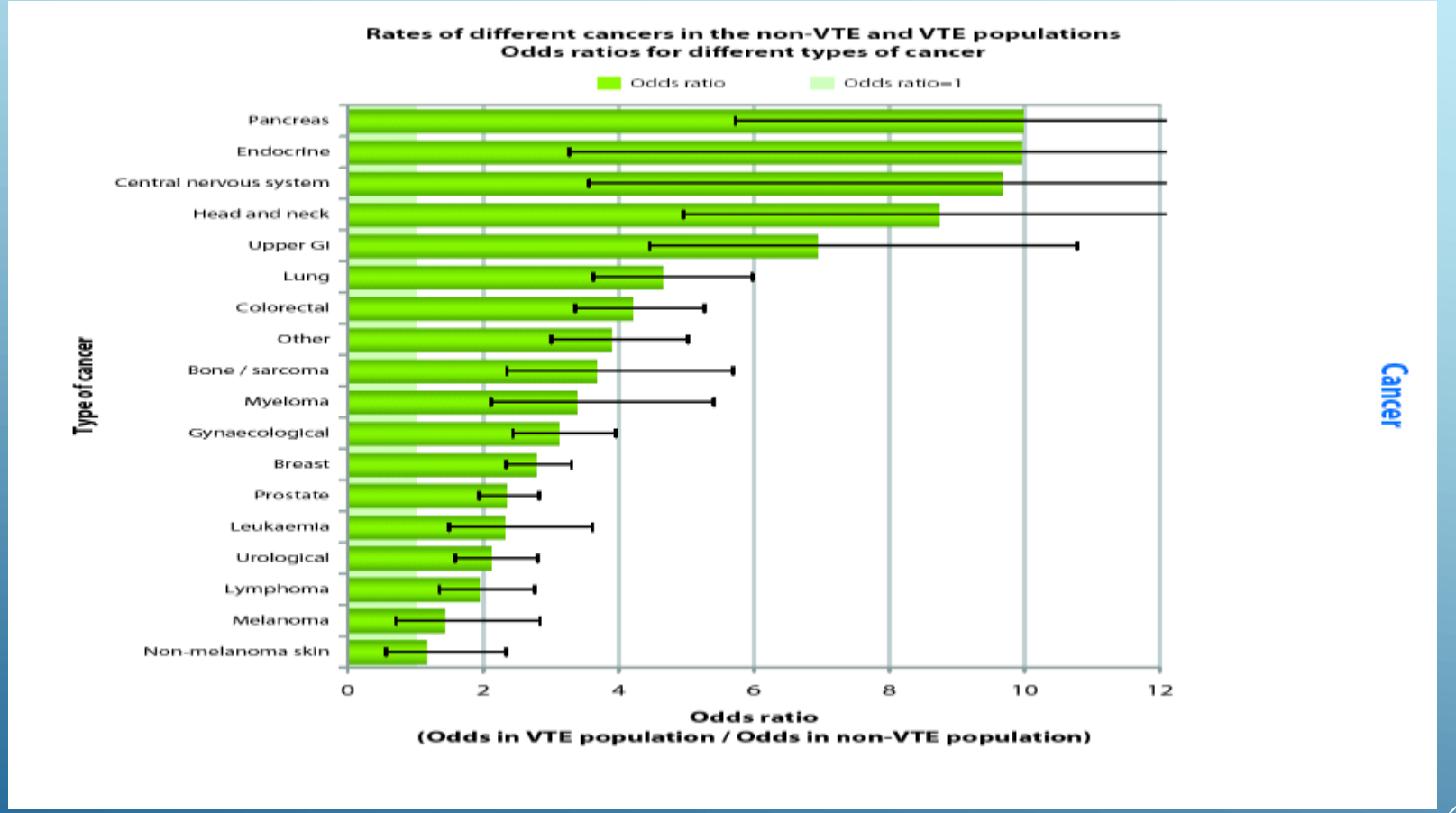
All Cancer patients	Cancer patients receiving Chemotherapy
Site of tumour High/ intermediate/ low risk	Platelets > 350 x 10^9/l
Metastatic disease	Haemoglobin 100g/l
Surgery	White blood count > 11 x 10^9/l
Chemotherapy	BMI > 35kg/m^2
Radiotherapy	High D-dimer
Hormone treatment	High serum P-selectin
Anti-angiogenic therapy	
Indwelling venous catheter	

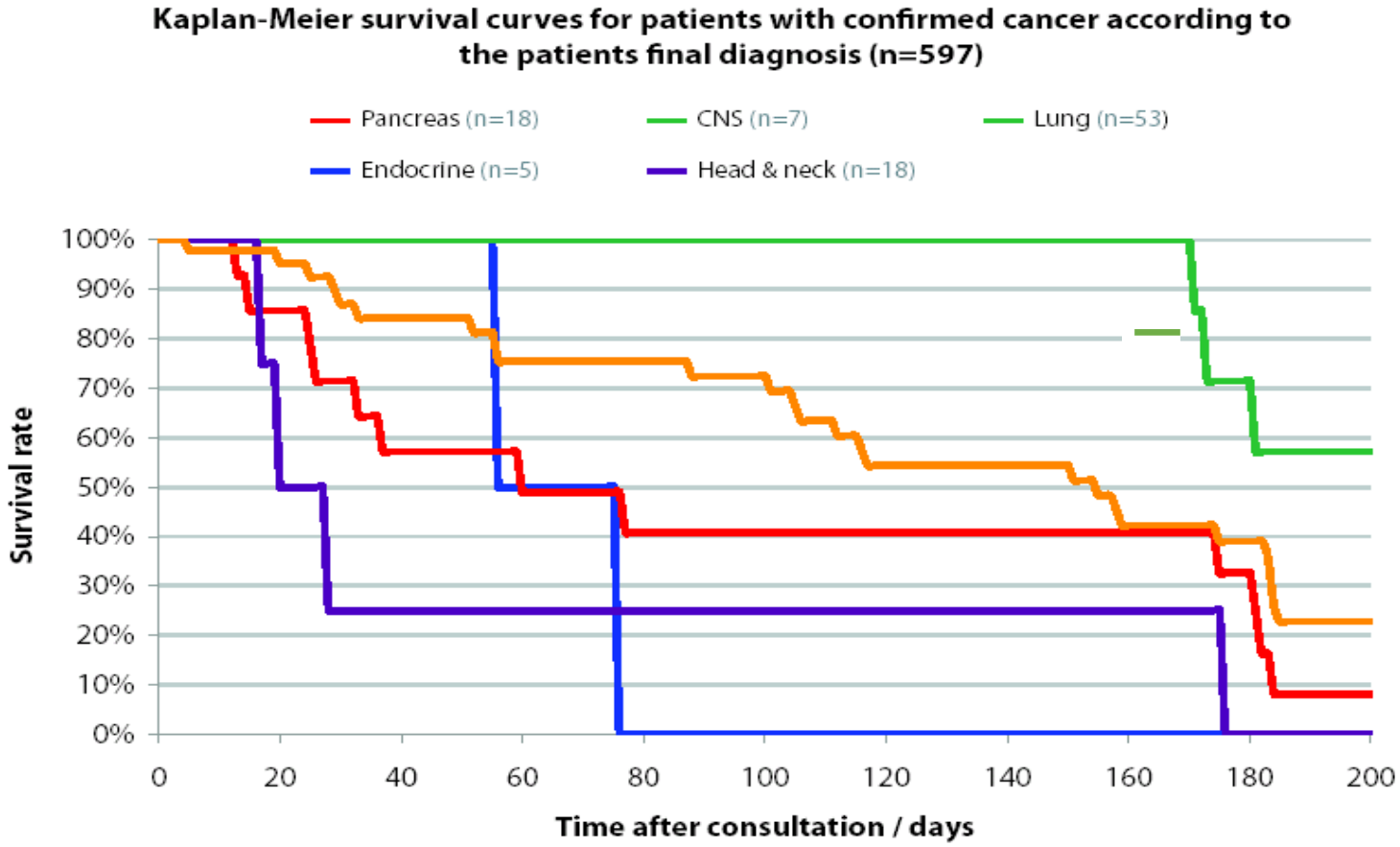
OUTPATIENT VTE PATIENTS (PUSH STUDY)

Risk Factor	More common in cancer patients	No difference		More common in non-cancer patients			
	Medical inpatient history / immobilisation >3-days within last 4 weeks	Major surgery in last 4 weeks	Hormonal risk*	Personal history of VTE	Thrombophilia	IV drug abuse	Current smoking
Patients, N	8730	9384	9103	9268	9019	9052	7807
Cancer Patients	14.8%	12.1%	6.7%	16.0%	0.7%	0.5%	14.5%
Non-cancer Patients	10.6%	10.5%	7.4%	25.6%	2.2%	7.7%	26.2%
X^2	17.7	2.86	0.67	51.3	10.8	80.3	61.9
DF	1	1	1	1	1	1	1
P	<0.001	<0.09	<0.42	<0.001	0.001	<0.001	<0.001

*Use of hormone replacement therapy or oral contraceptives; pregnant or post-partum

Are some cancers more thrombogenic?


Rates of different cancers in the non-VTE and VTE populations
Odds ratios for different types of cancer
Odds ratio
Odds ratio=1
Pancreas
Endocrine
Central nervous system
Head and neck
Upper GI
Lung
Colorectal
Other
Bone / sarcoma
Myeloma
Gynaecological
Breast
Prostate
Leukaemia
Urological
Lymphoma
Melanoma
Non-melanoma skin
Type of cancer
0
2
4
6
8
10
12
Odds ratio
(Odds in VTE population / Odds in non-VTE population)
Cancer


Kaplan-Meier survival curves for patients with confirmed cancer according to the patients final diagnosis (n=597)
Pancreas (n=18)
CNS (n=7)
Lung (n=53)
Endocrine (n=5)
Head & neck (n=18)
Survival rate
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
20
40
60
80
100
120
140
160
180
200
Time after consultation / days

Cancer

INCIDENCE OF VTE 1YEAR AFTER DIAGNOSIS OF CANCER

Cancer	N	VTE 1year Incidence	Deaths <1year
Pancreas	6,524	5.3%	85.3%
Brain	3,775	6.9%	56.3%
AML	2,292	3.7%	67.3%
Stomach	5,766	4.5%	57.6%
Renal Cell	4,897	3.5%	23.6%
Lung	44,497	2.4%	64.2%
Ovary	5,707	3.3%	28.1%
Colon	32,611	2.3%	23.8%
Uterus	8,721	1.6%	9.0%
Prostate	51,362	0.9%	6.2%
Breast	44,707	0.9%	5.7%
Melanoma	9,497	0.5%	6.5%

RH White. Thrombosis Research Suppl.2 (2007)

CANCER THERAPY

Cancer therapy

- Chemotherapy
- Hormone Therapy
- Anti-angiogenic Factors
- Cox-2 Inhibitors

Unusual thrombotic events secondary to therapy

- TTP
- Hepatic veno-occlusive Disease

AETIOLOGY OF HYPERCOAGULABILITY IN CANCER

Anti-tumour therapy

- Platinum compounds
- High-dose Fluorouracil
- Mitomycin
- Tamoxifen
- Growth factors*

} Induce vascular damage and increases risk of thrombosis

(*granulocyte colony-stimulating factor, granulocyte-monocyte colony-stimulating factor, erythropoietin)

Bick R. N Engl J Med 2003; 349(2): 109-111

INCIDENCE OF THROMBOEMBOLIC PHENOMENON OBSERVED IN VARIOUS MYELOMA TRIALS

REFERENCE	n	CHEMOTHERAPY	STAGE OF MYELOMA	VTE	%
Cavo	19	TD	Newly diagnosed	5	26
Zangari	192	D-PACE	Relapsed myeloma	31	16
Zangari	40	CDEP	Relapsed myeloma	1	3
Minnema	20	TC	Relapsed myeloma	7	35
Osman	45	TD	Newly diagnosed	5	11
Osman	15	TD	Newly diagnosed	4	27
Zangari	50	VAD	Newly diagnosed	14	28
Camba	18	TC	Relapsed myeloma	5	27.8
Rajkumar	50	TD	New diagnosed	6	12
Urbauer	14	CDEP + T	Refractory myeloma	3	21
Moehler	95	CTED	Refractory myeloma	4	4.2
Rodeghiero	58	Thalidomide	Relapsed myeloma	8	13.8

ANTI-ANGIOGENIC AGENT BEVACIZUMAB

2-fold increase in arterial thrombosis

VTE rate 12% in colon cancer

Hurwitz N, Eng J Med 2004;350:2335-42

VTE rate 25% in metastatic gastric cancer

Shah J, Clin Oncol 2005; 23:2574-6

A SYSTEMATIC REVIEW OF DVT PROPHYLAXIS IN CANCER PATIENTS UNDERGOING SURGERY

26 randomised control studies (7,639 cancer patients)

	Pharmaceutical Prophylaxis	Control
DVT Rate	12.7%	35.2%

	High-dose LMWH	Low-dose LMWH
	7.9%	14.5% (P< 0.01)

3% Bleeding complications

Leonardi MJ et al. Ann Surg Oncol 2007; 14(2):929-36

CATHETER RELATED THROMBOSIS IN CANCER PATIENTS

2-4%	clinically overt
18%	venography (absence of A/C's)
15-25%	UL-DVT+cancer clinically overt PE
50%	autopsy proven PE

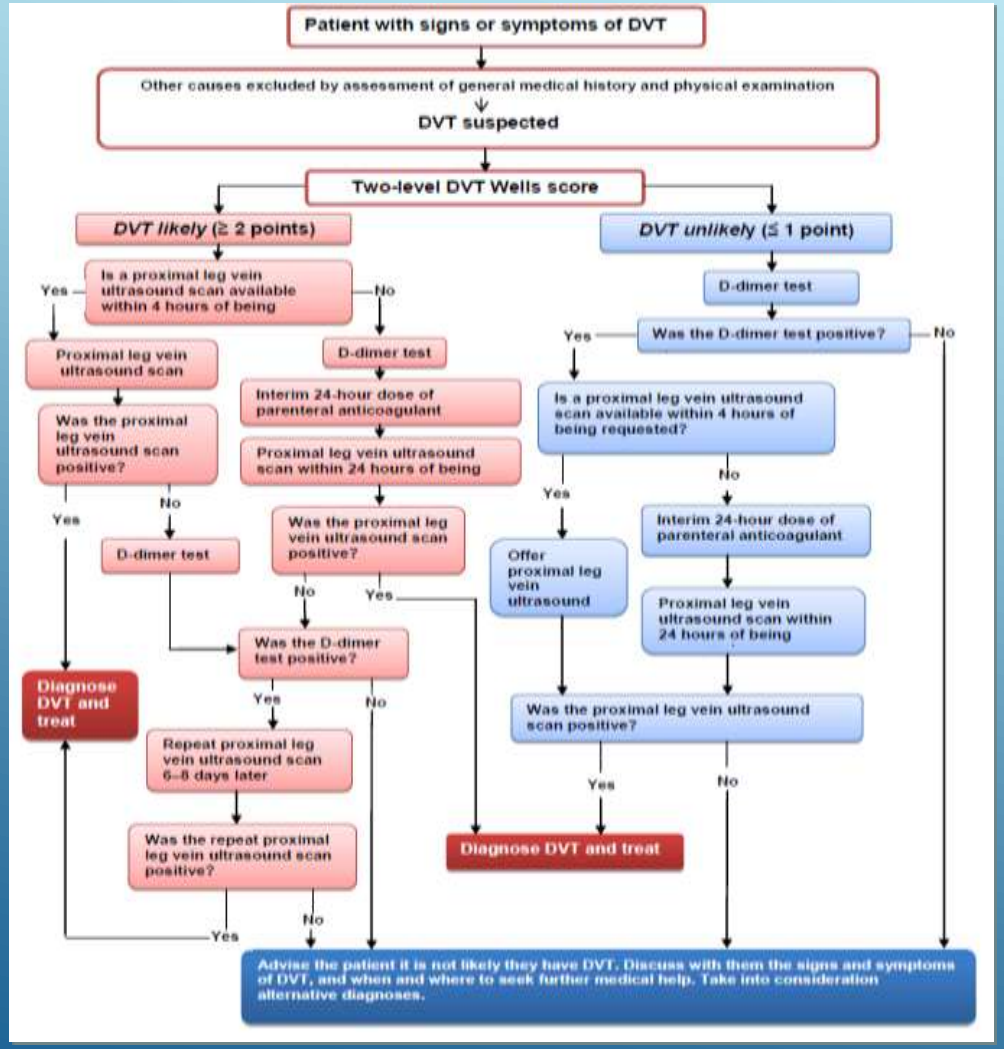
Agnelli et al, Nat Clin Pract Oncol 2006; 3 (4): 214-22

VTE AS A COMPLICATION IN BREAST CANCER

Stage of disease	Thrombosis Rate%	Treatment
I	0.1	Nil
	1.0	Tamoxifen
	4.5	Tam + Chemo
II	0 - 1.6	Tamoxifen
	1.3 - 10	Chemotherapy
	31. - 9.6	Tam + Chemo
III / IV	15 - 17	Chemotherapy

INVESTIGATION FOR VTE IN CANCER PATIENTS

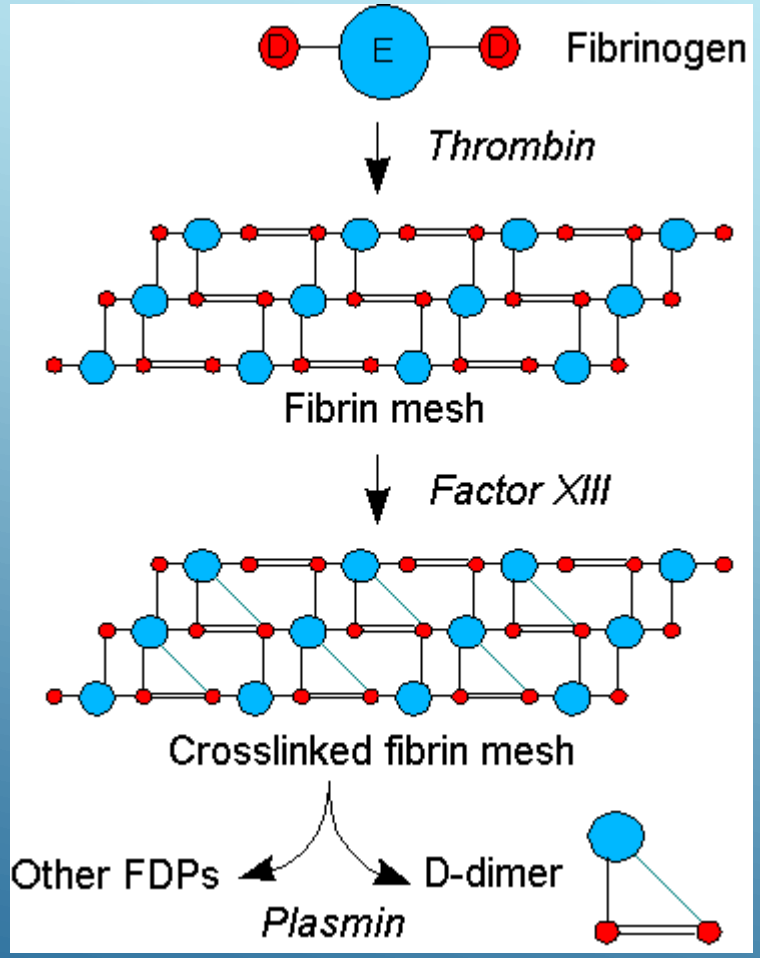
NICE CG 144 DIAGNOSIS OF DVT ALGORITHM



NICE Clinical Guidance 144. Appendix C:Venous thromboembolic diseases http://guidance.nice.org.uk/CG144. Last Accessed 06.08.2012

D-DIMER

D-dimer is an end product derived from the plasmin-mediated degradation of cross linked fibrin clots



- D-dimer is unhelpful in screening cancer patients with suspected VTE
- Well score is unhelpful in screening cancer patients with suspected VTE
- Only 9% of patients negative for both

G Geersing et al BMJ 2014; 348: g 1340

- How many patients with VTE go on to be diagnosed with cancer?
- How can unnecessary investigations for underlying cancer be avoided in VTE patients?

REQUIREMENTS OF A SCREENING PROGRAMME

1. High prevalence of adverse event
2. Minimal false positive results
3. Early diagnosis of benefit
4. Avoid patient harm
5. Cost effective

INVESTIGATIONS FOR CANCER (1)

Offer all patients with unprovoked DVT or PE, who are not known to have cancer:

- physical examination (guided by patient's full history) **and**
- chest X-ray **and**
- blood tests (full blood count, serum calcium and liver function tests) **and**
- urinalysis

INVESTIGATIONS FOR CANCER (2)

- First unprovoked DVT or PE?
- No signs or symptoms of cancer based on initial investigation?
- Over 40?
- Consider further investigations for cancer:
  - abdomino-pelvic CT scan
  - mammogram for women

PATIENT CHARACTERISTICS

No of patients	696
Female/ Male	358 / 338
Age at diagnosis (median/ range)	65 (16 - 96 yrs.)
Age>60yrs	438 patients (59.3%)
D-dimer (ng FEU/ ml) (median/range)	2300 (100-46300)
D-dimer >8000ng FEU/ ml	115 (17.2%)
Site of thrombosis	
Above knee VTE	412 (55.9%)
Below knee VTE	308 (41.8%)
Upper limb	17 (2.3%)
Presence of Malignancy	188 (25.4%)
Subsequent malignancy	29 (4.15%)
Time for subsequent malignancy (median / range)	1.6 (0 - 18mths)
Recurrence of VTE	36 (5.2%)
Follow up (median/ range)	23.2 (0 - 59 mths)

DVT AND D-DIMER

Mrs EC.

- 82 years, newly diagnosed proximal DVT
- D-dimer 10.6mg/ml

What does this D-dimer tell us?

PREDICTIVE ROLE OF D-DIMER

Elevated D-dimer levels at presentation in VTE patients is a marker for overt or occult malignancy

Schutgens, RE, et al. Haematologica (2005)

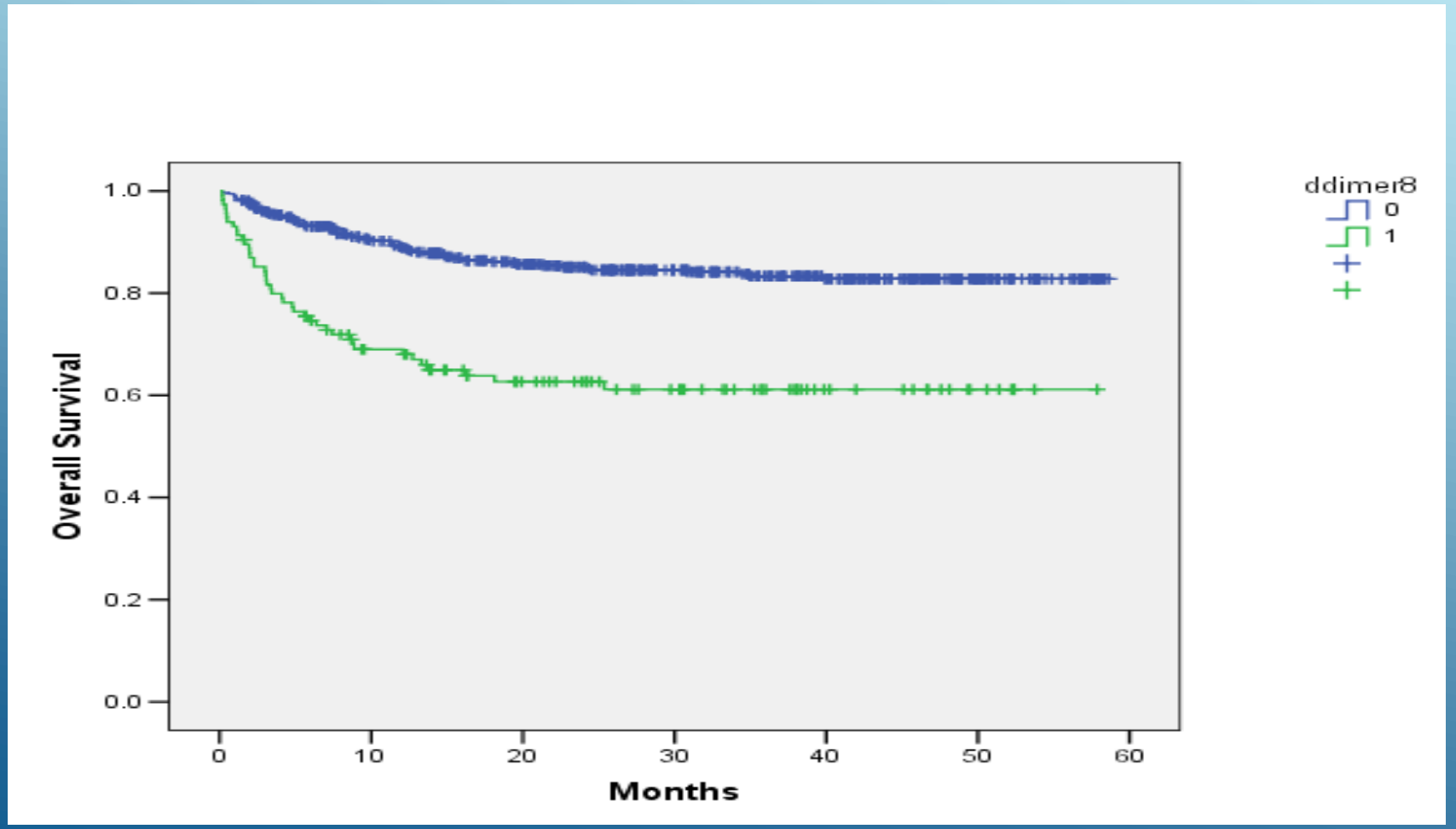
Paneesha, S, et al. Haematologica (2005)

Elevated D-dimer levels at presentation in VTE patients is a marker for shortened survival

Paneesha, S, et al. Br J Haematol (2006)

DO HIGH D-DIMER LEVELS PREDICT SURVIVAL?

Overall survival in VTE patients according to presentation D-dimer level



p value: <0.001

Paneesha, et al. BJH, 2006

RESIDUAL VEIN THROMBOSIS

- RVT at 3 months follow up higher in cancer patients
- OR 2.6 for cancer with RVT (95% CI, 1.1 - 6.1)

Prandoni, P., et al. ISTH, (2015) abstract 291.

CONCLUSION

- Proper clinical assessment for cancer at presentation with unprovoked VTE
- Consider cancer in patients with very high D-dimer at presentation
- (CT/ mammogram)
- Where RVT identified at 3 months, repeat clinical assessment if no other cause identified

CANCER AND VTE (CLOT TRIAL)

- 6 months Dalteparin 200iu/kg per day for 4 weeks 150iu/kg for 5 months vs Warfarin INR 2-3

- Dalteparin significantly less (recurrence rate) (8 vs 16%)

Bick N, et al, Eng J Med 2003; 349: 109

CLINICAL TRIALS OF INNOHEP® IN THE TREATMENT OF DVT AND PE IN CANCER PATIENTS

- Long-term innohep® Versus Usual Care in the Treatment of Proximal Vein Thrombosis Patients with Cancer

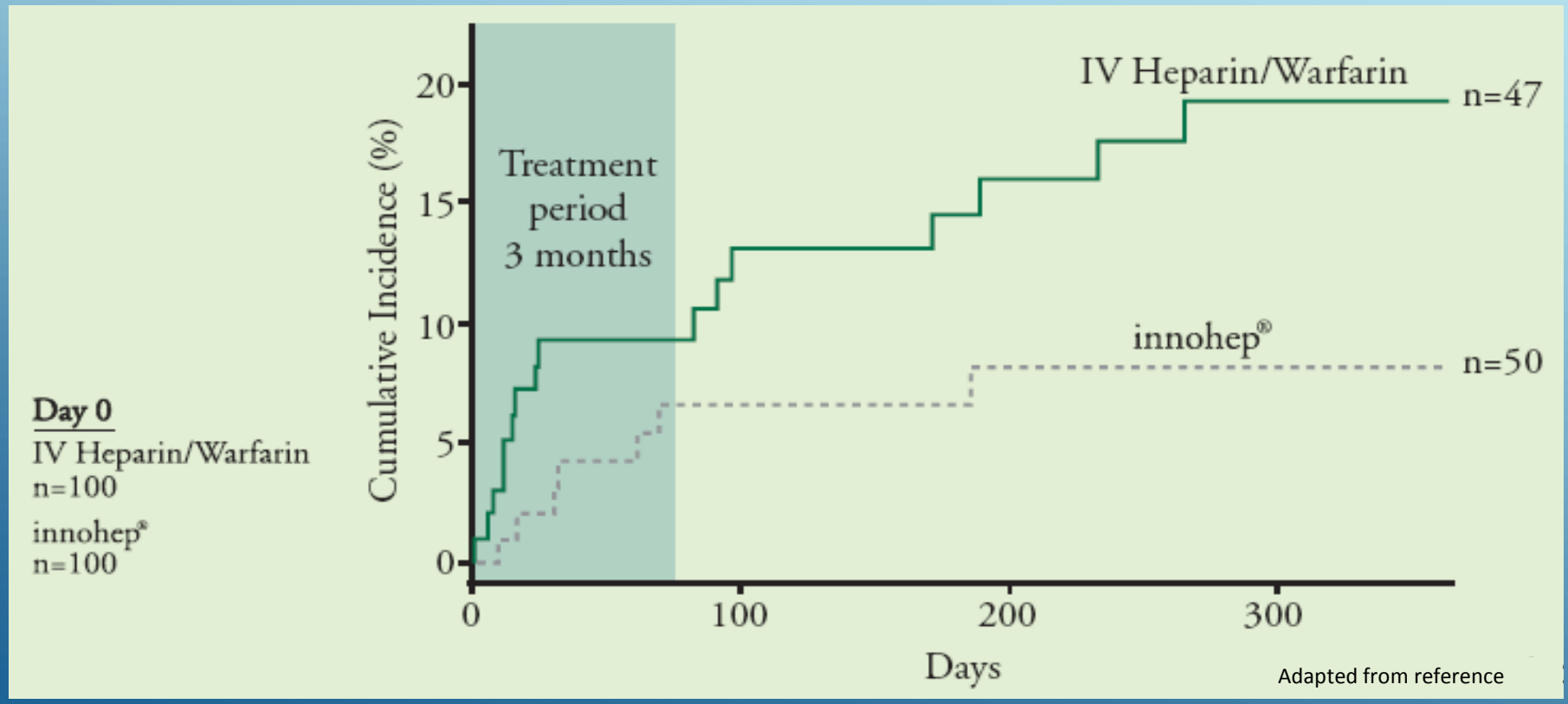
- A multi-centre randomised, open-label clinical trial compared long-term therapeutic innohep® subcutaneously once daily with usual care, initially IV heparin, followed by long-term warfarin therapy for 3 months

- At 12 months, the number of patients with recurrent venous thromboembolism was more than double in the group receiving warfarin (16/100), compared with those on innohep® (7/100) (P= 0.044)

- This benefit was reassuringly not compromised by any increased harm due to increased bleeding

Hull R et al. The American Journal of Medicine 2006; 119: 1062-1072.

TIME TO EVENT ANALYSIS FOR PATIENTS WHO HAD RECURRENT VENOUS THROMBOEMBOLISM



Adapted from reference

Hull R et al. The American Journal of Medicine 2006; 119: 1062-1072.

CATCH STUDY

Standard anticoagulant management

vs 6 month treatment Tinzaparin

DEMOGRAPHICS

Patients – 900

Mean age – 59

Female – 59%

TTR 47%

Above 27%

Below 26%

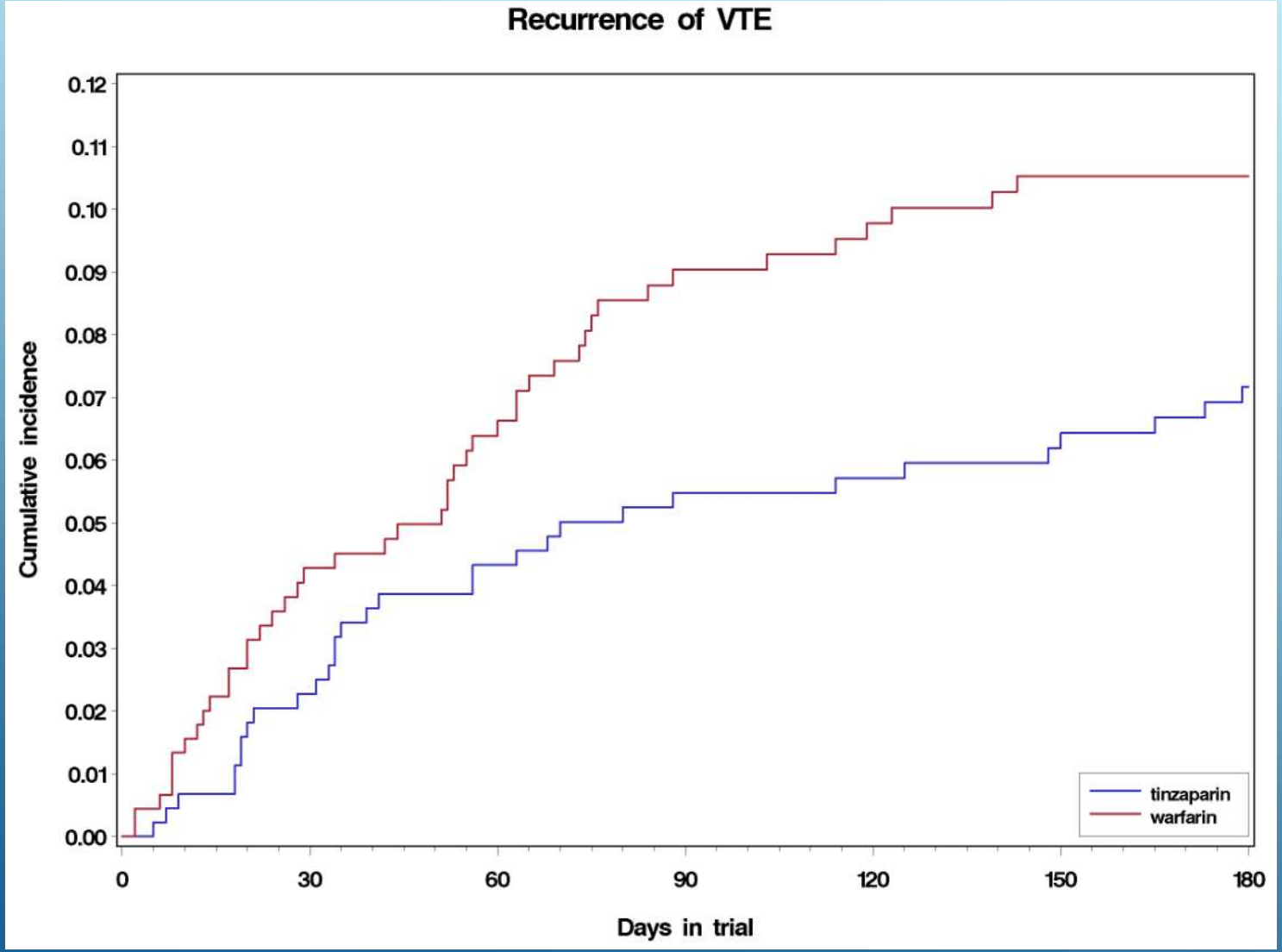
Lee, A., et al. Ash Dec 2014 abstract

CATCH STUDY RESULTS

- Standard treatment VTE recurrence (45) 10%
- Extended Tinzaparin (31) 6.9%
- Fatal PE 3.8%
- Major haemorrhage no difference
- Significantly less non-major haemorrhage with Tinzaparin.

Lee, A., et al. Ash Dec 2014 abstract

RECURRENCE OF VTE



CLINICALLY RELEVANT BLEEDING

- 16% of patients had CRB
- 4.7% died within 30 days
- 38% GI, 2% ICH
- Metastatic disease/ Age>75/Intracranial malignancy
- INR poor predictor of bleeding 42% INR

NOVEL ORAL ANTICOAGULANTS (NOACS) – DESIRABLE FOR PATIENTS WITH CAT OR NOT?

Interaction effect*	Dabigatran P-glycoprotein	Rivaroxaban P-glycoprotein CYP3A4	Apixaban P-glycoprotein 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 Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine	Dexamethasone Doxorubicin Vinblastine

Interactions with anticancer therapies based on known metabolic pathway activity

CYP34A: *cytochrome* P450 34A + inhibitors of pgp transport and CYP34A pathway
± inducers - lower NOAC levels

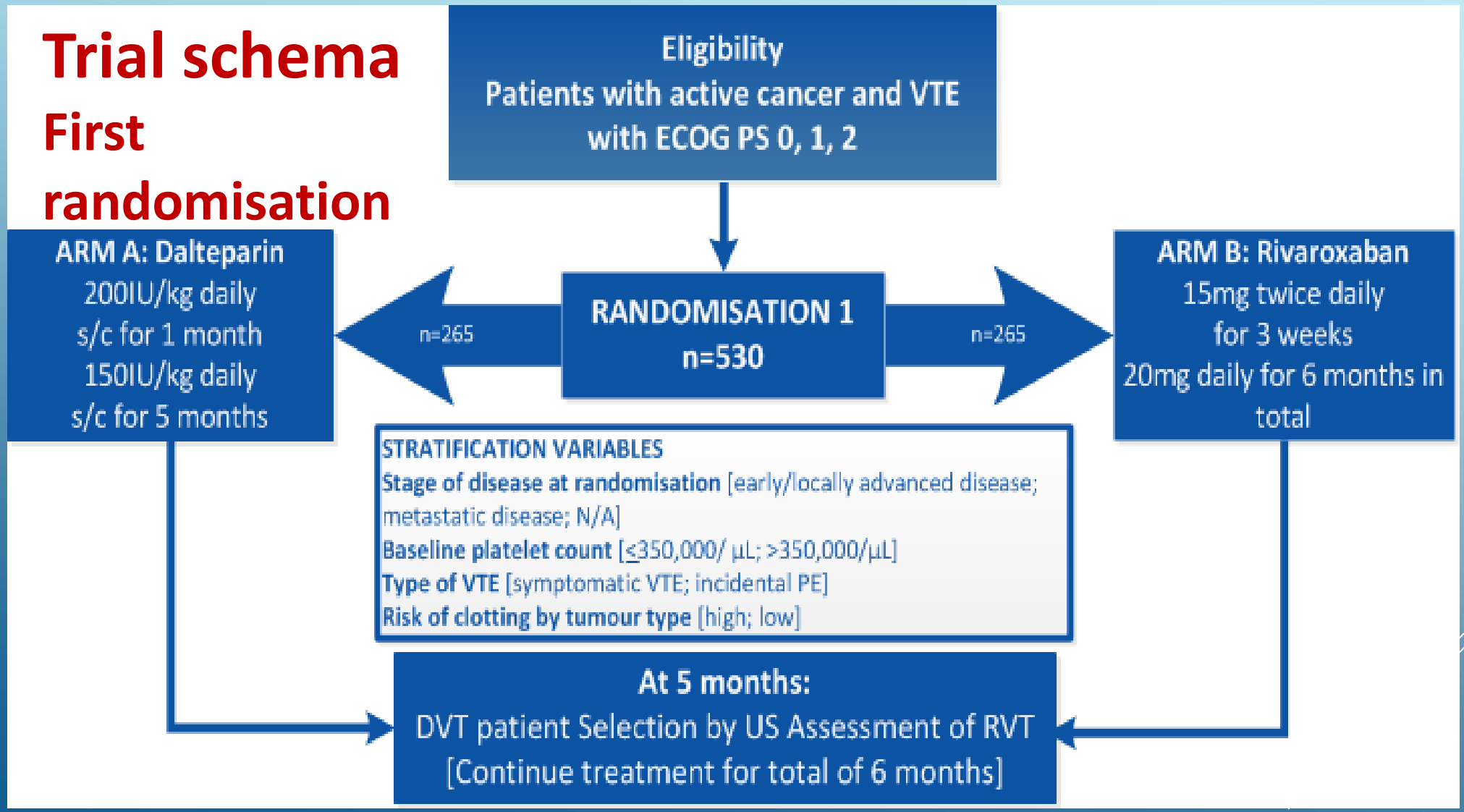
CANCER IN VTE TREATMENT STUDIES OF NOVEL ORAL ANTICOAGULANT (NOAC)

Study	NOAC control	Non-cancer patients n/N (%)	Cancer patients n/N (%)
RECOVER	Dabigatran control	28/1210 (2.3%) 24/1208 (2.0%)	2/64 (3.1%) 3/57 (5.3%)
EINSTEIN DVT	Rivaroxaban control	32/1613 (2.0%) 46/1629 (2.8%)	4/118 (3.4%) 5/89 (5.6%)
EINSTEIN PE	Rivaroxaban control	48/2305 (2.1%) 41/2304 (1.8%)	2/114 (1.8%) 3/109 (2.8%)
AMPLIFY	Apixaban control	Not available Not available	Not available Not available
HOKUSAI	Edoxaban Control	103/3658 (2.8%) 99/3629 (2.7%)	14/378 (3.7%) 28/393 (7.1%)

A.Y.Y. Lee and M.Carrier / Thrombosis Research 133 S2 (2014) S167-S171

Trial schema

First randomisation



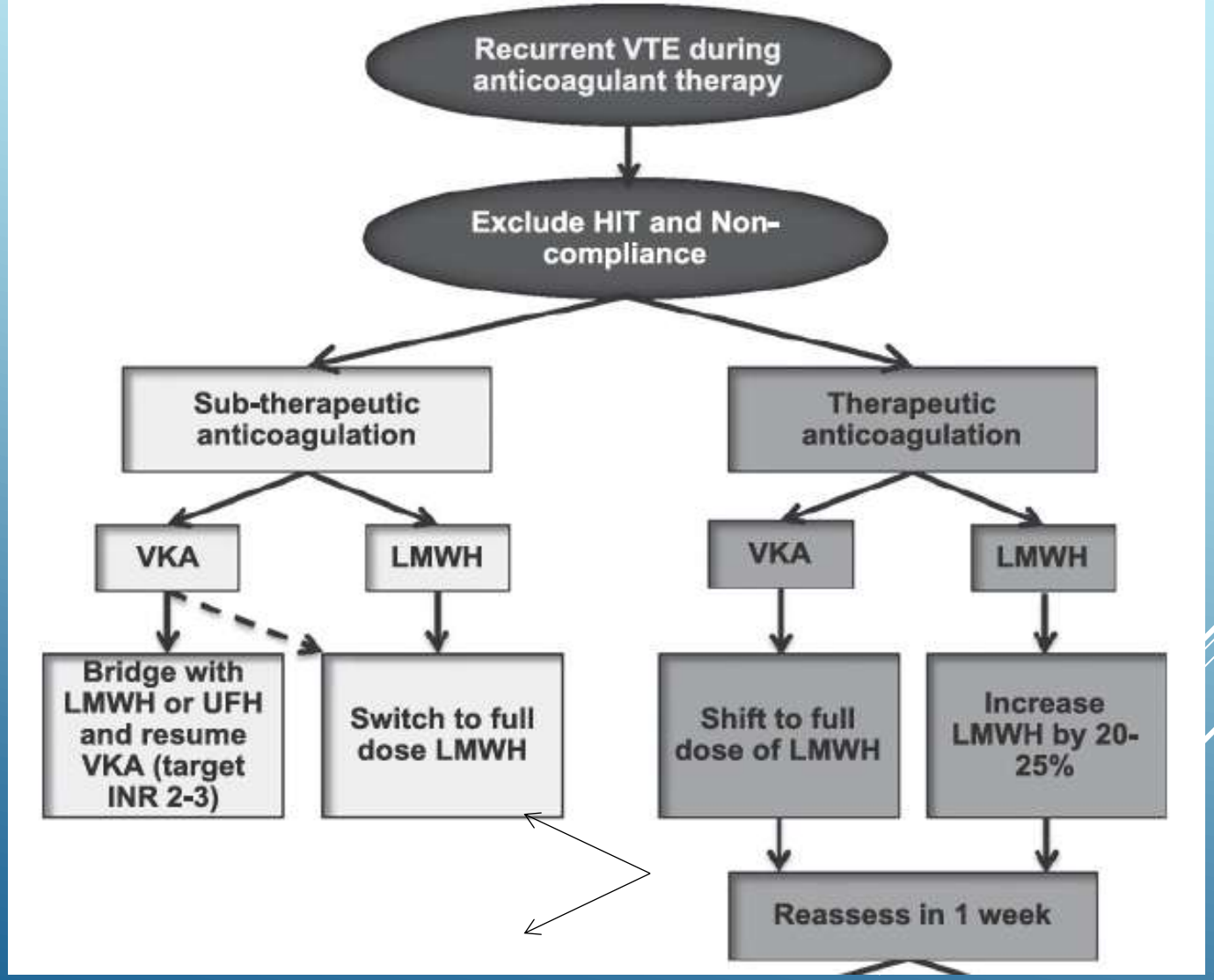
Levine ML et al. 2012 *JTH* **10**: 807-814

Treatment of Recurrent VTE[1]

Cancer patients have a three-fold risk of recurrent VTE in comparison with the general population[2]

Patients with symptomatic improvement – continue

Patients without symptomatic improvement, use peak anti-Xa levels to estimate dose of next esclalation



1. Lee AY et al. 2013 *Blood* **122**: 2310-2317
2. Prandoni P et al. *Blood* 2002, **100** (10): 3484-3488

THROMBOPROPHYLAXIS IN CANCER PATIENTS

- Cancer MDT meeting should include VTE risk assessment
- Currently no evidence to support widespread thromboprophylaxis
- No universally agreed clinical risk score

RISK FACTORS FOR CHEMOTHERAPY ASSOCIATED VTE

Patient characteristic (site of cancer)	Risk score*
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynaecological, bladder, testicular)	1
Prechemotherapy platelet count 350×10^9/l or more	1
Haemoglobin level less than 110 g/l or use of red cell growth factors	1
Prechemotherapy leucocyte count more than 11×10^9/l	1
BMI 35 kg/m^2 or more	1

*0 points = low risk; 1–2 points = intermediate risk and ≥3 points = high risk. Abbreviation: VTE, venous thromboembolism. Permission obtained from American Society of Hematology © Khorana, A. K. *et al.* Blood **111**, 4902–4907 (2008).

Addition of p-selectin and d-dimer[1]

VALIDATION Austrian - Cancer and Thrombosis Study (CATS)[1]

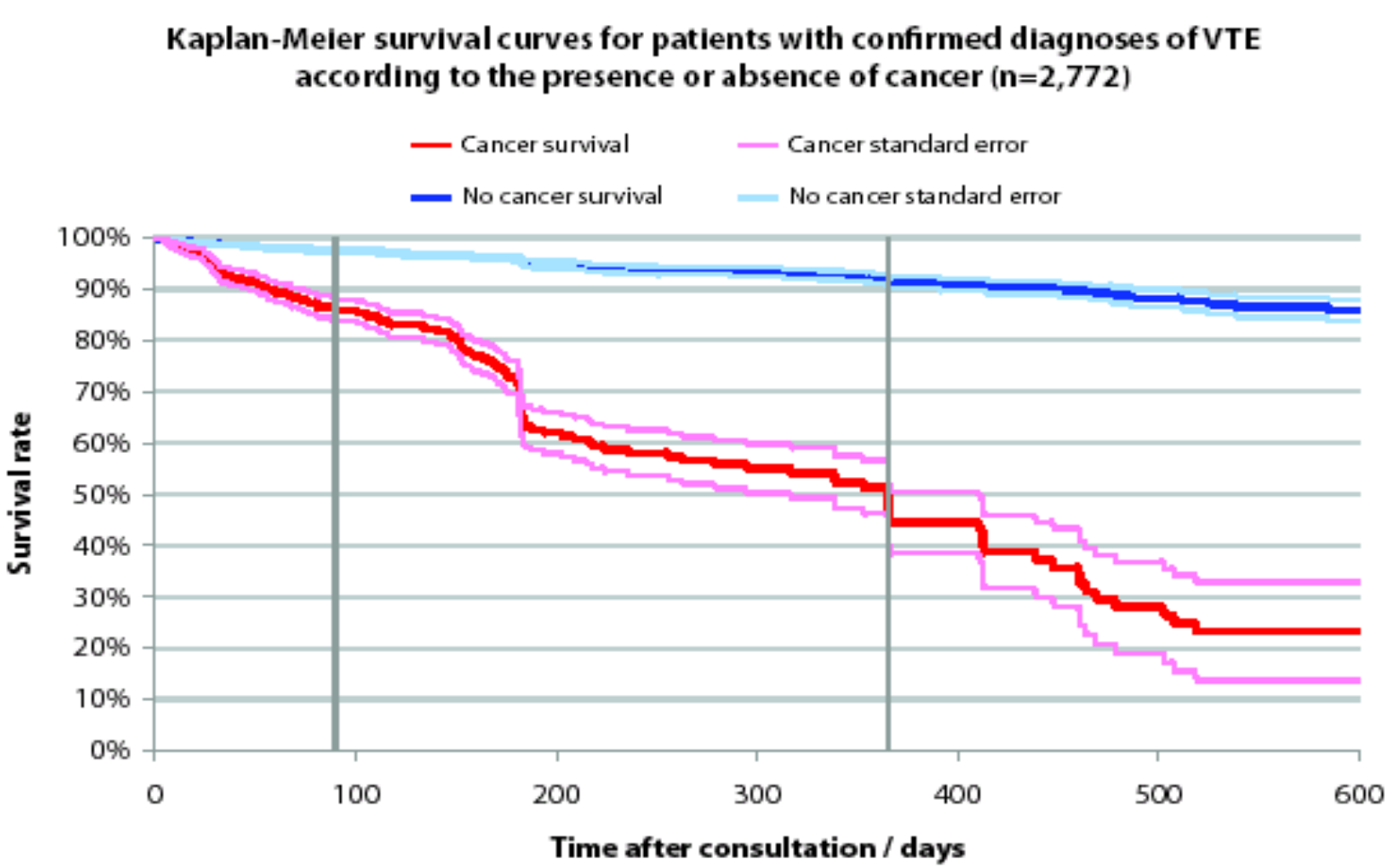
Italian-led (SENDO) in Phase I studies[2]

1. Ay C et al. 2010 Blood 116, 5377-5382
2. Mandala M et al. 2012 Ann Oncol 23: 1416-1421

VTE RISK BASED ON THE FOLLOWING

- Cancer type/staging
- Metastatic disease
- Chemotherapy
- Radiotherapy
- Other medication/ ERP, GCSF, Hormone,Anti-angiogenic therapy
- Surgery
- Indwelling catheter

What is the prognosis for different cancers in association with VTE?


Kaplan-Meier survival curves for patients with confirmed diagnoses of VTE according to the presence or absence of cancer (n=2,772)
Cancer survival
Cancer standard error
No cancer survival
No cancer standard error
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Survival rate
0
100
200
300
400
500
600
Time after consultation / days

South Warwickshire NHS
NHS Foundation Trust

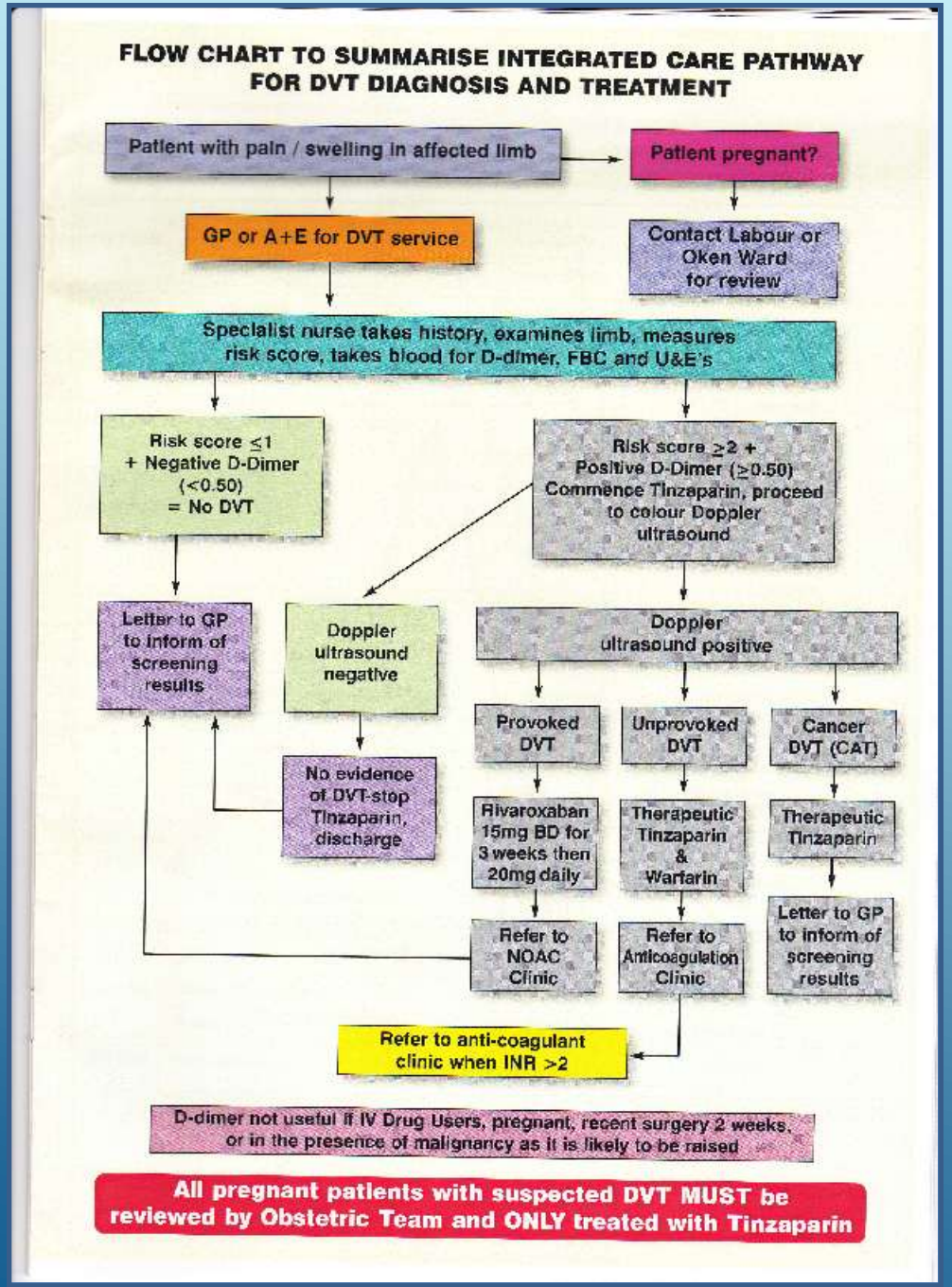
Integrated care pathway for ambulatory adult patients with suspected DVT

NHS No: Patient ID (UR) Name: Address: Post code: Date of birth: Telephone:	Date: Time: GP & Practice: Referred by: Seen by: DVT CNS / DVT support S/N/ A&E / RMO Print name:
Calf measurement (R) (L) Affected leg ☐ ☐ Other limb LMP__ / __/__ urine HCG done? Y / N Result neg / pos SaO_2 ___% Respirations _____ BP ___/___ Pulse _____ bpm	Allergies: Current medication:
History of presenting complaint: Previous medical history:	

	Yes	No	Comments
Hospital admission in last 90 days			
Surgery in last six months			
Smoker			
OCP / HRT			
Pregnant			Refer to Flow Chart
Malignancy			
Long haul travel (>2 hours)			
Previous thrombotic episode			
Family history of thrombosis			

Clinical model for predicting pre-test probability for DVT (Two-level DVT Wells score)

Clinical feature	Points	Patient Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1	
Paralysis, paresis or recent plaster immobilisation of the lower extremities	1	
Recently bedridden for more than 3 days or major surgery within 12 weeks requiring general regional anaesthesia	1	
Localised tenderness along the distribution of the deep venous system	1	
Entire leg swollen	1	
Calf swelling at least 3cm larger than asymptomatic side	1	
Pitting oedema confined to the symptomatic leg	1	
Collateral superficial veins (non varicose)	1	
Previously documented DVT	1	
Alternative diagnosis is at least as likely as DVT	-2	
Clinical probability simplified score		
DVT *likely*	2 points or more	
DVT *unlikely*	1 point or less	


FLOW CHART TO SUMMARISE INTEGRATED CARE PATHWAY FOR DVT DIAGNOSIS AND TREATMENT
Patient with pain / swelling in affected limb
Patient pregnant?
GP or A+E for DVT service
Contact Labour or Oken Ward for review
Specialist nurse takes history, examines limb, measures risk score, takes blood for D-dimer, FBC and U&E's
Risk score ≤1 + Negative D-Dimer (<0.50) = No DVT
Risk score ≥2 + Positive D-Dimer (≥0.50) Commence Tinzaparin, proceed to colour Doppler ultrasound
Letter to GP to inform of screening results
Doppler ultrasound negative
Doppler ultrasound positive
Provoked DVT
Unprovoked DVT
Cancer DVT (CAT)
No evidence of DVT-stop Tinzaparin, discharge
Rivaroxaban 15mg BD for 3 weeks then 20mg daily
Therapeutic Tinzaparin & Warfarin
Therapeutic Tinzaparin
Refer to NOAC Clinic
Refer to Anticoagulation Clinic
Letter to GP to inform of screening results
Refer to anti-coagulant clinic when INR >2
D-dimer not useful if IV Drug Users, pregnant, recent surgery 2 weeks, or in the presence of malignancy as it is likely to be raised
All pregnant patients with suspected DVT MUST be reviewed by Obstetric Team and ONLY treated with Tinzaparin