VENOUS THROMBOEMBOLISM IN CANCER

Prophylaxis and treatment Using LMWHs

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THROMBOSIS IN CANCER PATIENTS

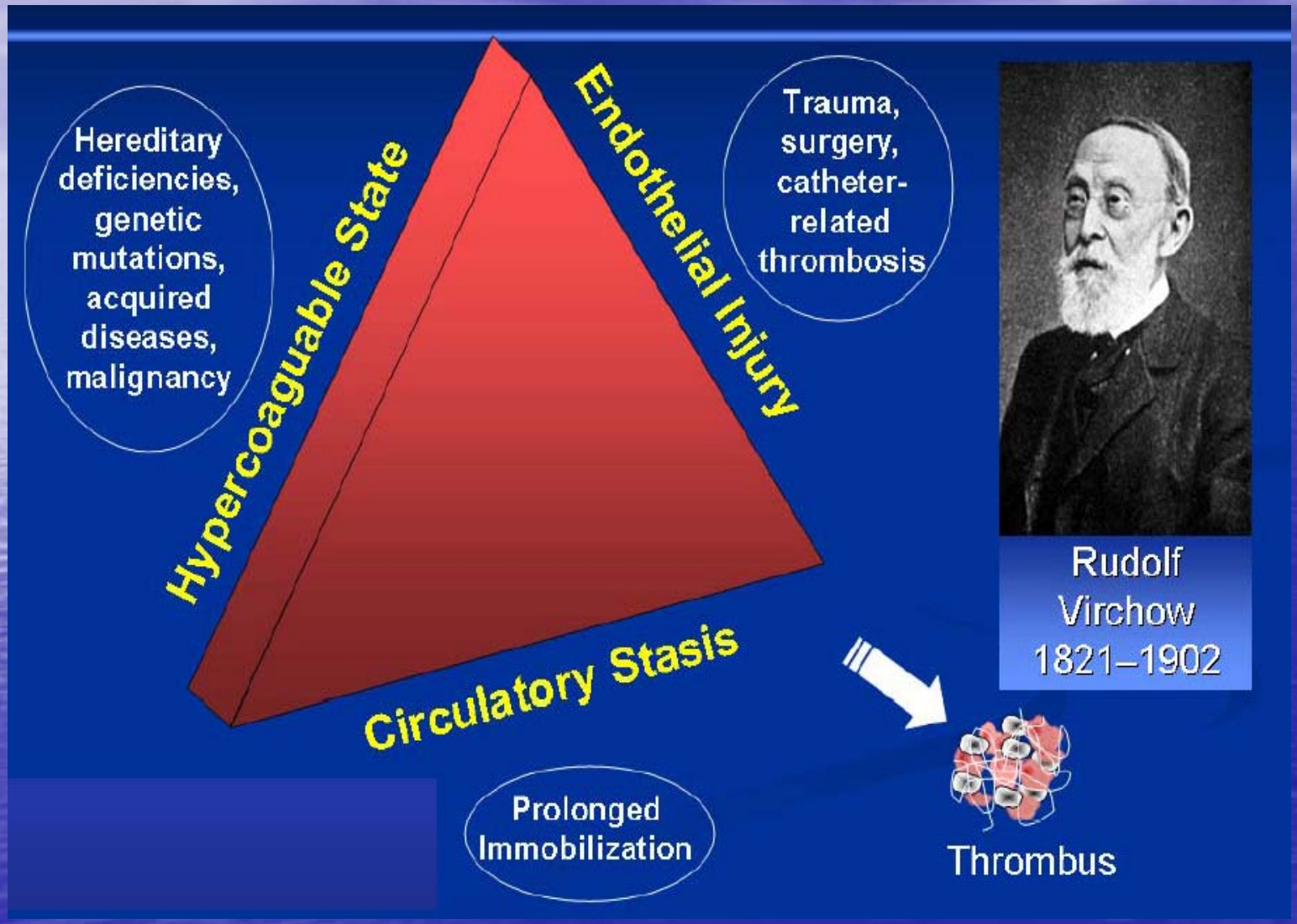
- Cancer patients with thrombosis are at increased risk of recurrent VTE compared with non-cancer patients
- Cancer patients with thrombosis are at increased risk of anticoagulant-associated bleeding compared with non-cancer patients
- Many cancer patients have a compromised quality of life, and the occurrence of thrombosis has an additional negative impact on quality of life

Health consequences of CAT

- The risk for recurrent VTE and death (from any cause) is at least 3 times higher in cancer patients with VTE than in patients with VTE but no cancer
- One in 7 hospitalized cancer patients die from PE
- Cancer patients who undergo abdominal surgery have 2 times the risk for postoperative lower extremity DVT and 4 times the risk for fatal postoperative PE, compared with surgical patients without cancer
- The cancer increases the risk of VTE (4-6 fold)

1. Paolo Prandoni et al., *Recurrent Thromboembolism in CancerPatients: Incidence and Risk Factors, SEMINARS IN THROMBOSIS AND HEMOSTASIS/VOLUME 29, SUPPLEMENT 1 2003*
2. Kakkar AK, Levine M et al*, Venous thrombosis in cancer patients: insights from the FRONTLINE Survey.* Oncologist. 2003;8:381-388
3. Kakkar VV et al, Deep vein thrombosis of the leg: Is there a 'high risk' group? Am J Surg 1970;120: 527–530.
3. Kakkar AK et al, Prevention of venous thromboembolism in cancer patients. Semin Thromb Haemost 1999;25:239–243.
3. Gallus AS et al, Prevention of post-operative deep leg vein thrombosis in patients with cancer. Thromb Haemost 1997;78:126–132.

Virchow's triad



Blood flow abnormalities

- Venous stasis increases the risk of VTE by
  - Reducing the dilution and clearance of factors that lead to coagulation
  - Limiting the presence of substances that inhibit coagulation
- Causes of venous stasis in cancer patients
  - Lack of activity
  - Compression of a vein
  - Increased blood viscosity

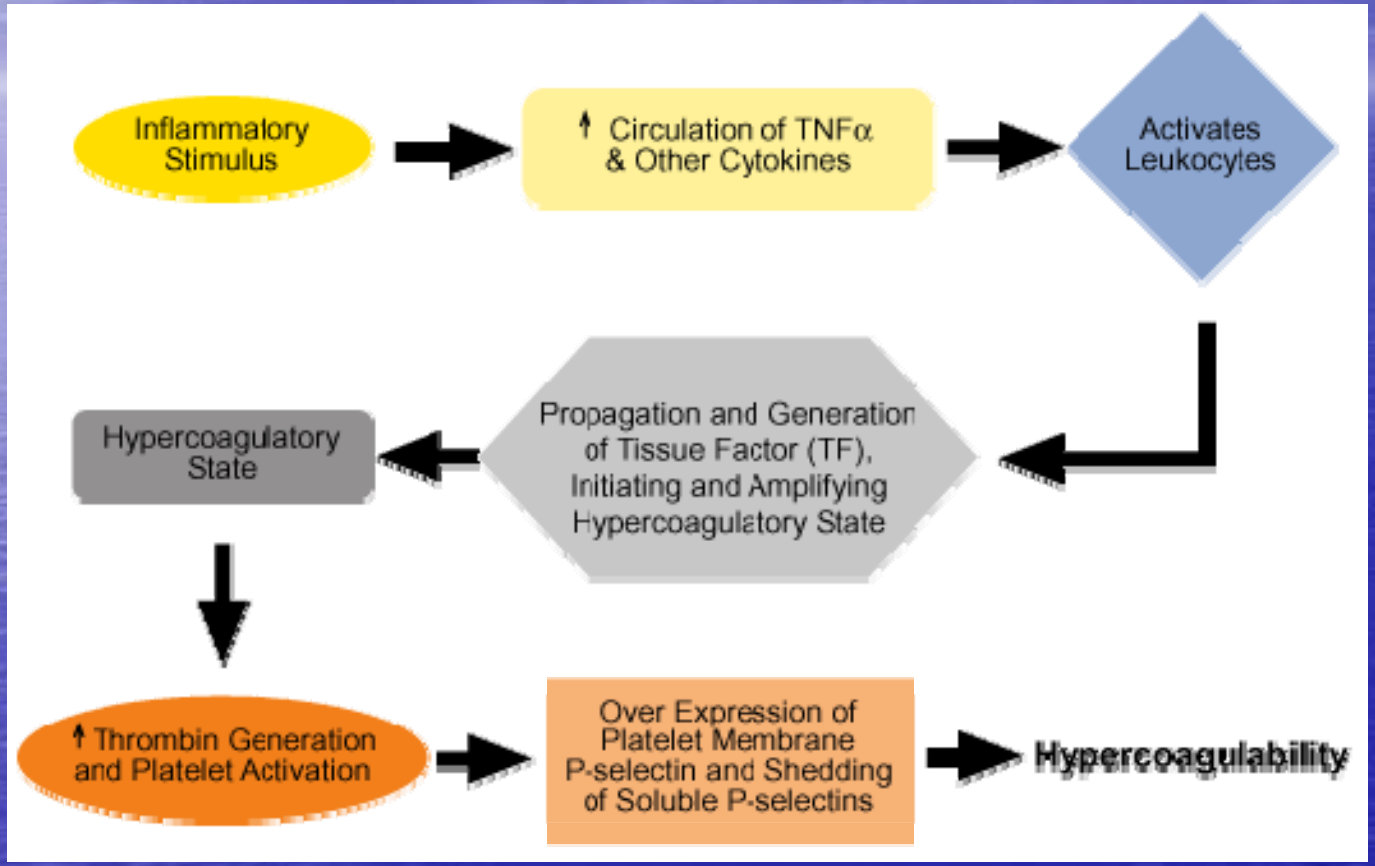
Blood vessel injury

- When a blood vessel is injured, a blood clot (thrombus) forms as a protective mechanism to slow blood loss
- Causes of blood vessel injury in cancer patients
  - Surgery
  - Central venous catheters
  - Chemotherapy agents
  - Invasion of cancer cells into the blood vessel
  - Secretions from the tumor that affect blood vessel permeability

Hypercoagulable state

- Hypercoagulable state : changes in the blood that promote coagulation
- Cancer patients are prone to a hypercoagulable state due to :
  - Secretion of procoagulant factors by tumor cells
  - Release of procoagulant factors from tumor cells damaged by cancer treatment
  - Chemotherapy or hormone therapy that leads to a decrease in naturally occurring anticoagulants
  - Increased activation and aggregation of platelets

VTE and Cancer Patients (5) : *Hemostatic Abnormalities in Patients with Cancer*



1. Lip GYH, Chin BSP, Blann AD. Cancer and the prothrombotic state. Lancet Oncol 2002;3:27-34

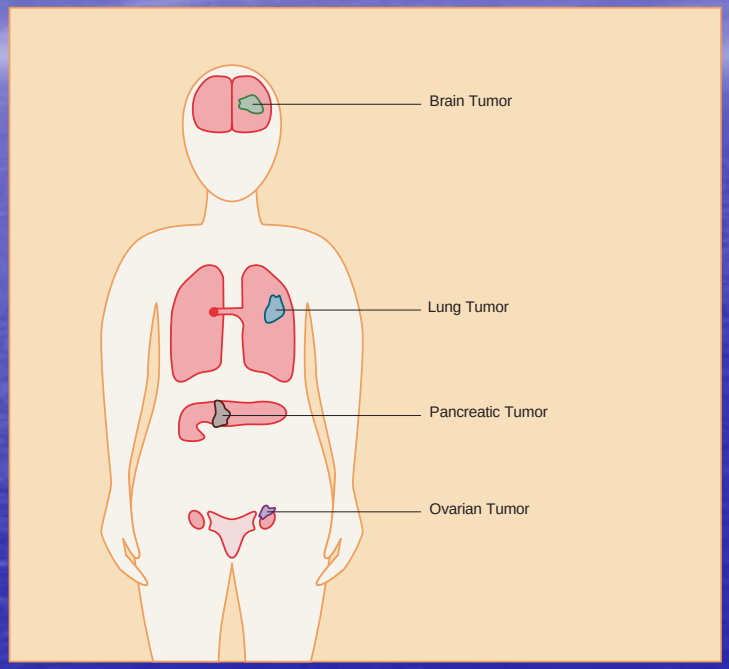
2. Mousa SA. Anticoagulants in thrombosis and cancer: the missing link. Semin Thromb Hemost 2002;28:45-52.

VTE : *risks of VTE in cancer patients*

Activation of coagulation	Tissue factor expression
Endothelial damage	Tumour invasion Chemotherapy Radiation Catheters
Platelet dysfunction	Activation Thrombocytosis
Venous stasis	Vein obstruction Immobilization Increased viscosity

Berqvist, 11th international symposium, Barcelona 2004

Risk factors for CAT



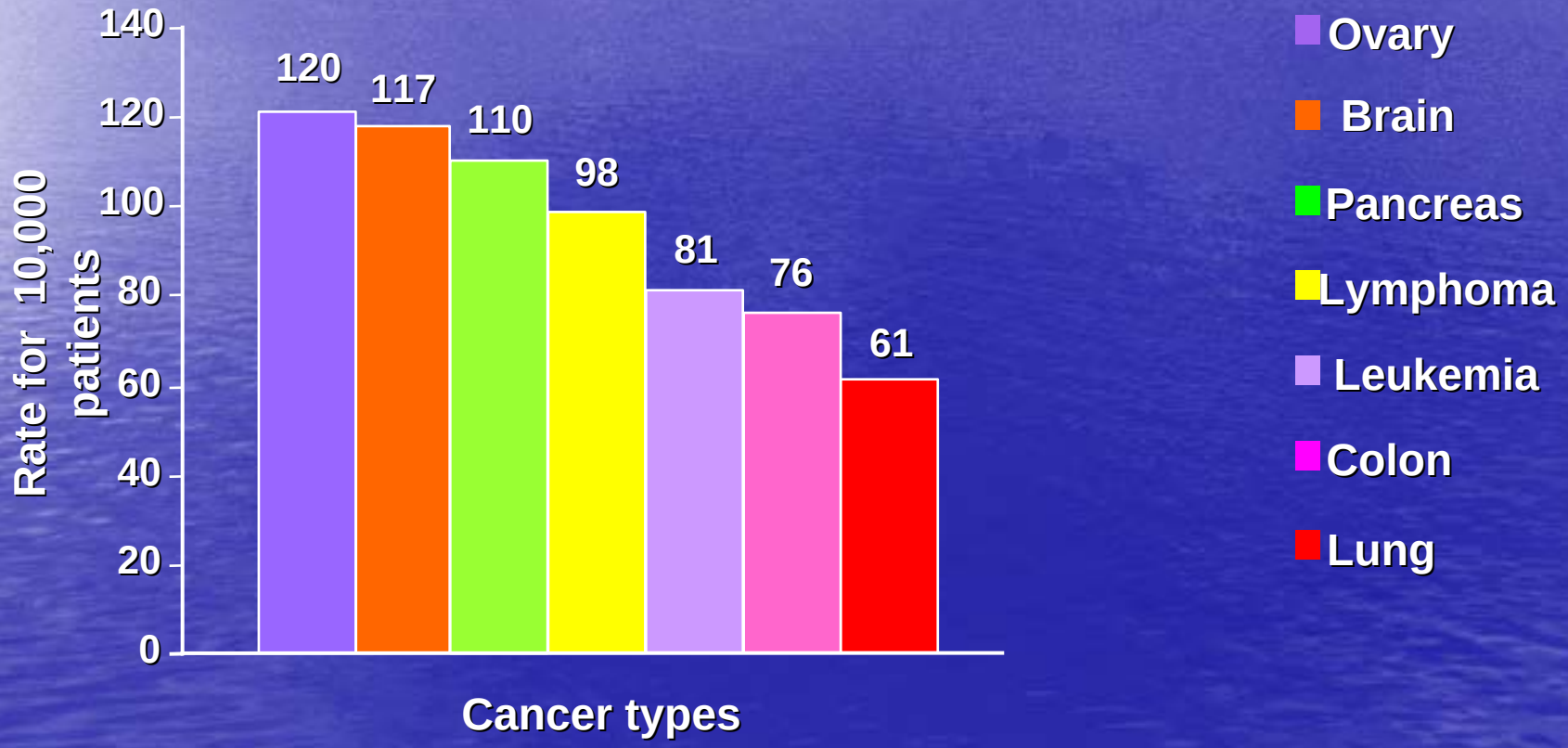
- Type of cancer. Tumors of the brain, lung, pancreas, and ovary are strongly associated with CAT

VTE Risk factors associated with cancer therapies

Cancer surgery	20-40 %
Central venous catheter	3-21 %
Immobilization	14 %
Chemotherapy	8-10 %
Hormonal treatment	2 %

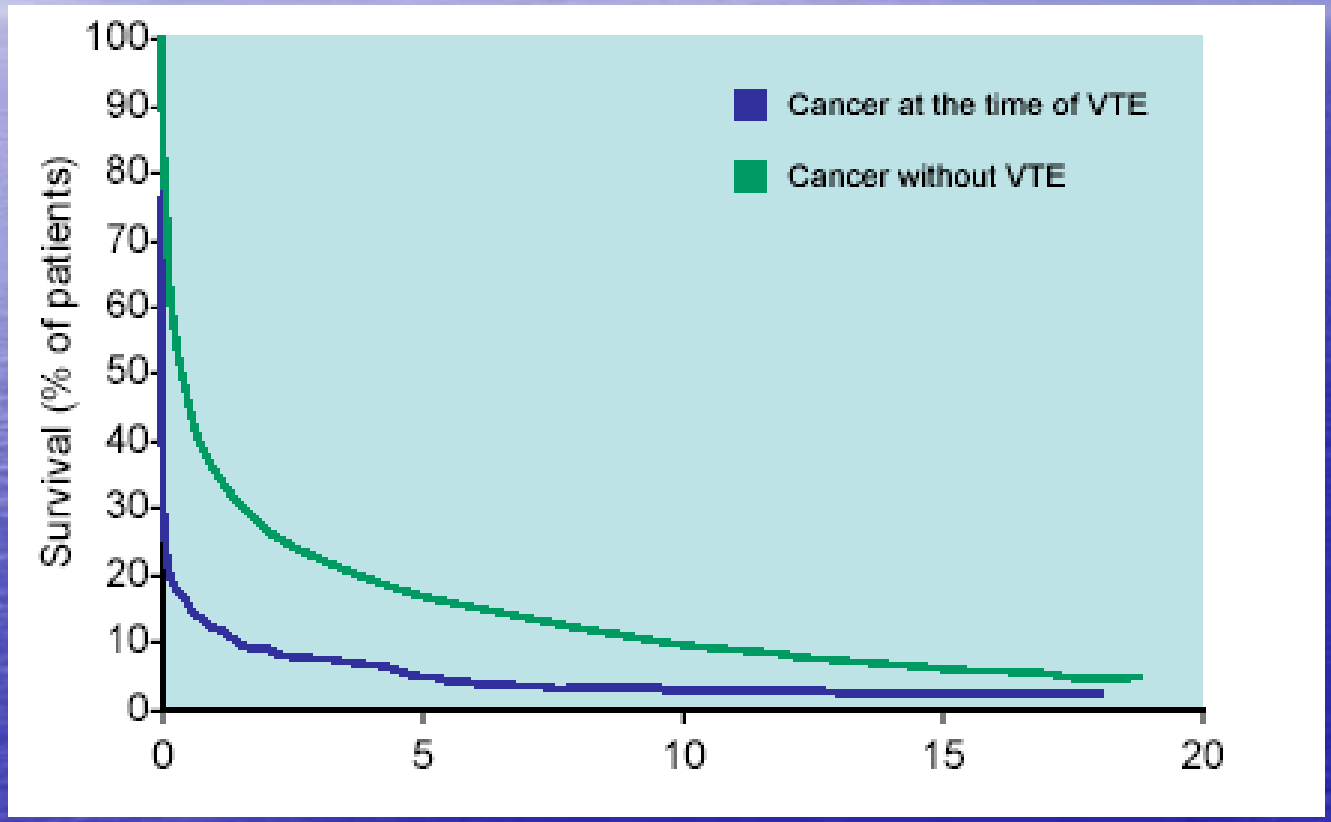
Hillen Ann of Oncol 2000

CAT (7) : *Risk factors per tumor type*



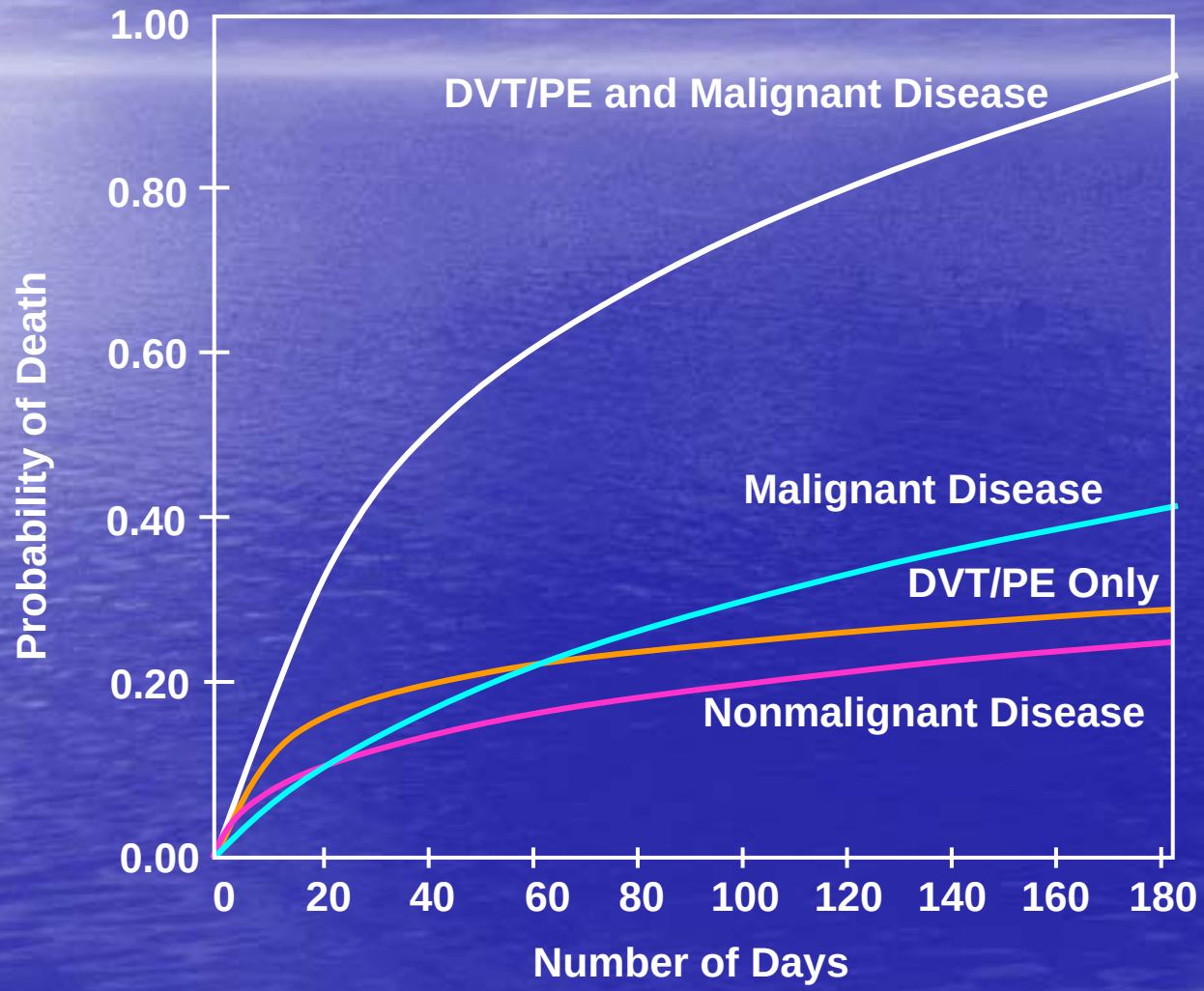
Levitan et al. *Medicine*. 1999

Impact of VTE on survival for cancer patients



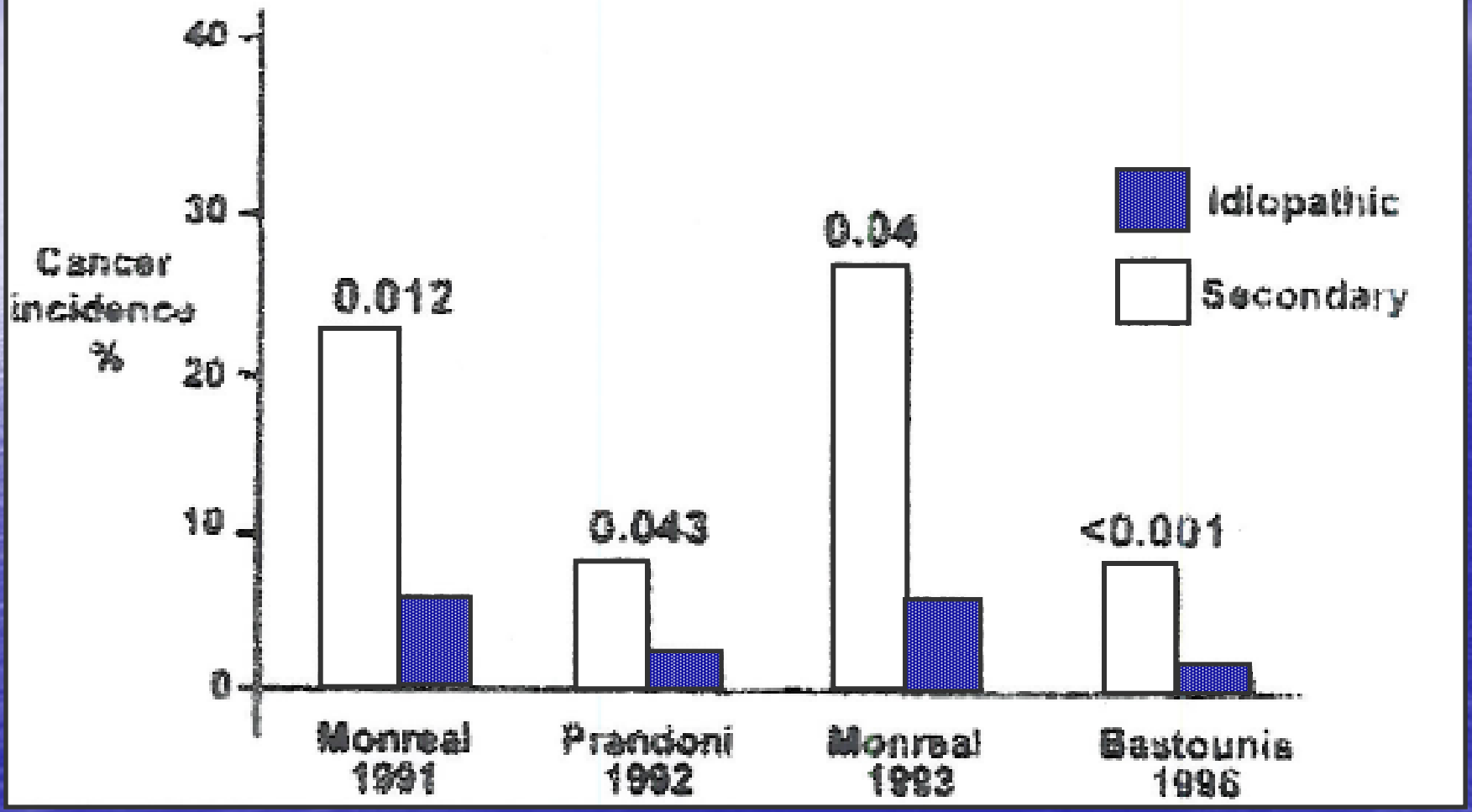
Sorensen et al., 2000

VTE, Cancer and Survival



Levitan N, et al. Medicine 1999;78:285-291.

Detection of malignancy in the patient presenting with thrombosis



OPTIMISING TREATMENT OF VTE IN THE CANCER PATIENT

Treatment ⟶

↓ Recurrent VTE

↓ Bleeding

↑ Quality of life

Héparine VS Héparine de bas poids moléculaire

Mécanisme responsable des avantages pharmacocinétiques de l'Héparine de bas poids moléculaire sur l'Héparine

AVANTAGE	MÉCANISME
• Meilleure réponse anticoagulante	• Se lie moins aux protéines plasmatiques sécrétées par les plaquettes activées et les cellules endothéliales
• Meilleure disponibilité à petite dose	• Se lie moins à l'endothélium
• Métabolisme + excrétion indépendante de la dose et ½ vie + longue	• Se lie moins aux macrophages

Mécanisme responsable des avantages biologiques de l'Héparine de bas poids moléculaire sur l'Héparine

AVANTAGE	MÉCANISME
• Plus faible incidence de thrombopénie reliée à l'Héparine	• Moins d'activation de plaquettes et de sécrétion de PF4; moins d'affinité pour le PF4, ce qui résulte en moins de complexe Héparine/PF4
• Plus faible incidence d'ostéoporose induite par l'Héparine.	• Moins d'affinité pour les ostéoclastes.

LMWH VS Anticoagulation orale

ORAL ANTICOAGULANT THERAPY IN CANCER PATIENTS

Warfarin therapy is complicated

- It is difficult to maintain tight therapeutic control (anorexia, vomiting, and drug interactions)
- There are frequent interruptions for thrombocytopenia and procedures
- Venous access is difficult
- There is increased risk of recurrence and bleeding

STUDY QUESTION

Is long-term LMWH therapy more effective and safer than oral anticoagulant therapy in treating cancer patients with VTE?

CLOT TRIAL

Randomized comparison of LMWH *vs.* oral anticoagulant therapy for long-term anticoagulation in cancer patients with VTE

New Engl J Med 2003;349:146-53.

CLOT TRIAL

Group	Initial Treatment (5-7 days)	Long-term therapy (6 months)
VKA	Dalteparin 200 IU/kg SC once-daily	Warfarin or acenocoumarol (target INR 2.5)
LMWH	Dalteparin 200 IU/kg SC once-daily	Month 1: Dalteparin 200 IU/kg Month 2-6: 75-80% of full-dose

New Engl J Med 2003;349:146-53.

STUDY POPULATION

Inclusion criteria

- Objectively documented, symptomatic proximal DVT and/or PE

- Active cancer
  - Cancer diagnosis within past 6 months
  - Recurrent or metastatic malignancy
  - Received cancer treatment within past 6 months

- 16 years or older

BASELINE CHARACTERISTICS

	LMWH n = 338	OAC n = 338
Female gender	179	169
Age, mean (years)	62	63
Out-patient	169	156
Qualifying VTE		
DVT only	235	230
PE ± DVT	103	108
ECOG score		
0	80	63
1	135	150
2	118	122

BASELINE CHARACTERISTICS

	LMWH n = 338	OAC n = 338
Solid tumour	298	308
No evidence	36	33
Localised	39	43
Metastatic	223	232
Haematological malignancy	40	30
Cancer treatment	266	259
Central venous catheter	46	40
Previous VTE	39	36

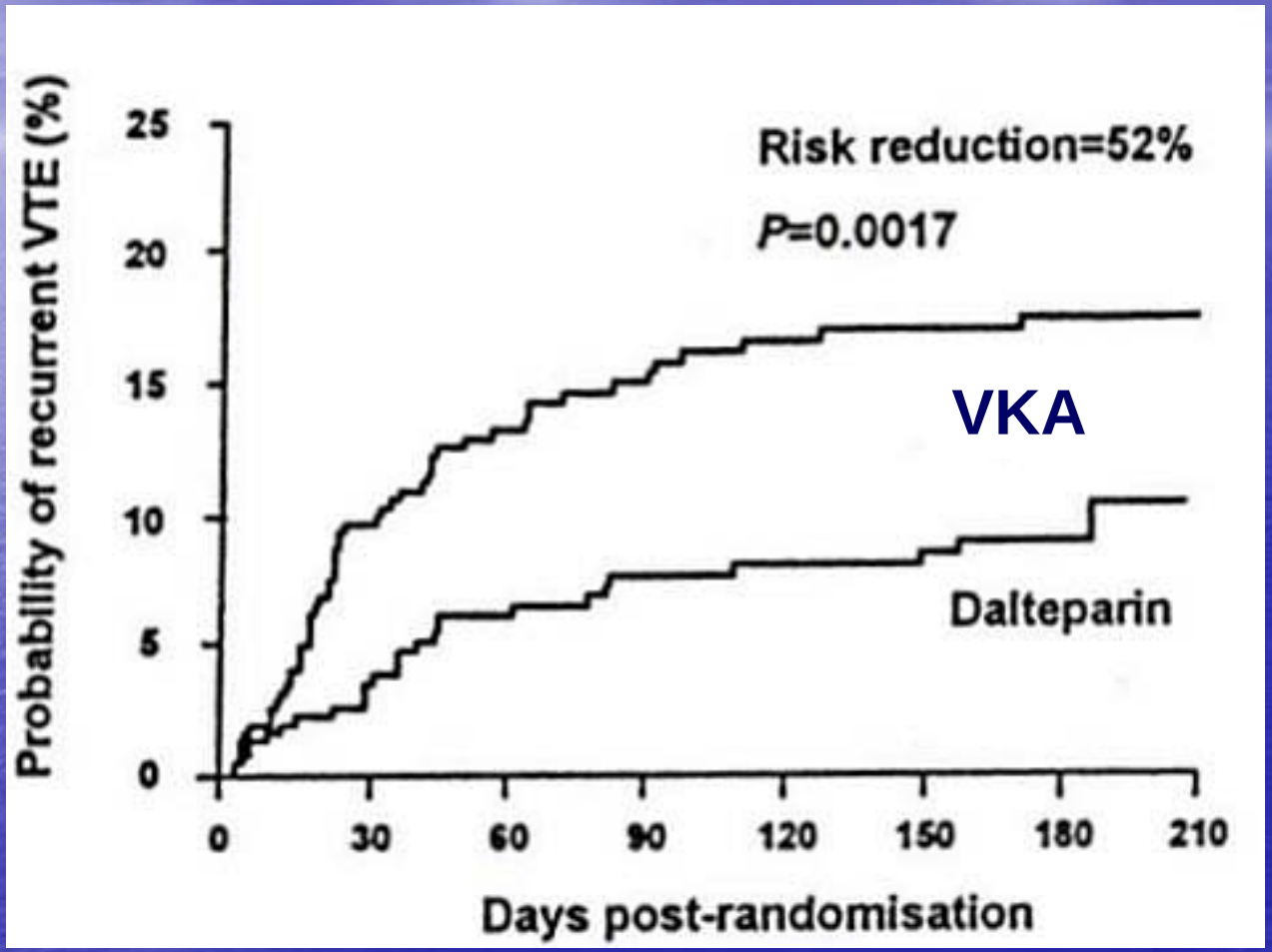
CANCER SITES

	LMWH n = 338	OAC n = 338
Colorectal	54	54
Breast	59	49
Lung	40	50
Genitourinary	35	41
Gynaecological	38	30
Pancreas	13	16
Brain	14	13
Other	87	87

RECURRENT VTE

	LMWH n = 336	OAC n = 336
Total VTE	27	53
DVT	14	37
Non-fatal PE	8	9
Fatal PE	5	7

CLOT TRIAL


Probability of recurrent VTE (%)
25
20
15
10
5
0
Risk reduction=52%
P=0.0017
VKA
Dalteparin
0
30
60
90
120
150
180
210
Days post-randomisation

CLOT TRIAL

Event	LMWH n=338 (%)	VKA n=335 (%)	P*
Major bleeding	19 (5.6)	12 (3.6)	0.27
Any bleeding	46 (13.6)	62 (18.5)	0.093

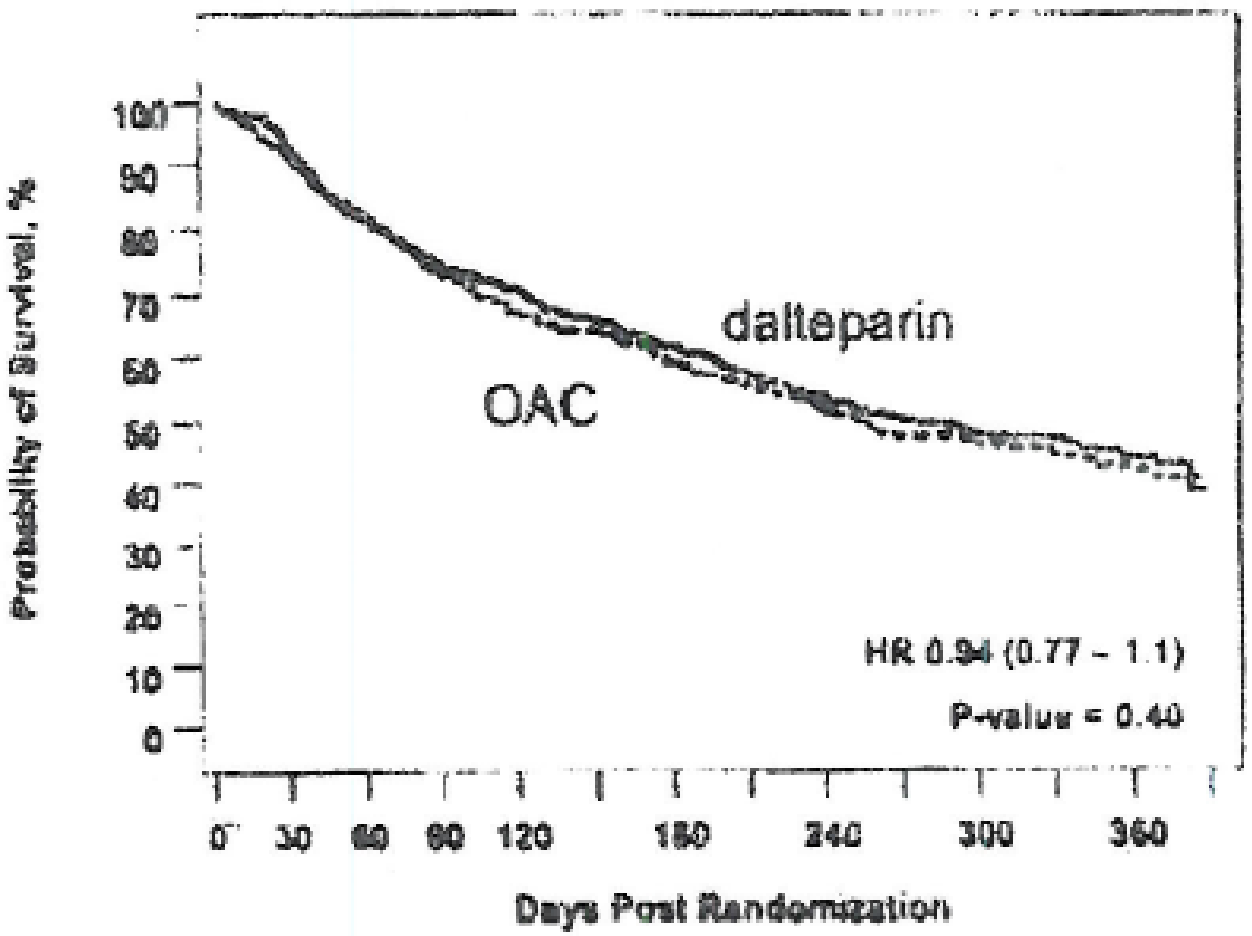
* Fisher's exact test

SITES OF MAJOR BLEEDS

	LMWH n = 338	OAC n = 335
Fatal	1	0
Critical sites:		
Intracranial	1	2
Retroperitoneal	1	2
Pericardial	1	0
Gastrointestinal	5	4
Genitourinary	5	2
Other	5	2

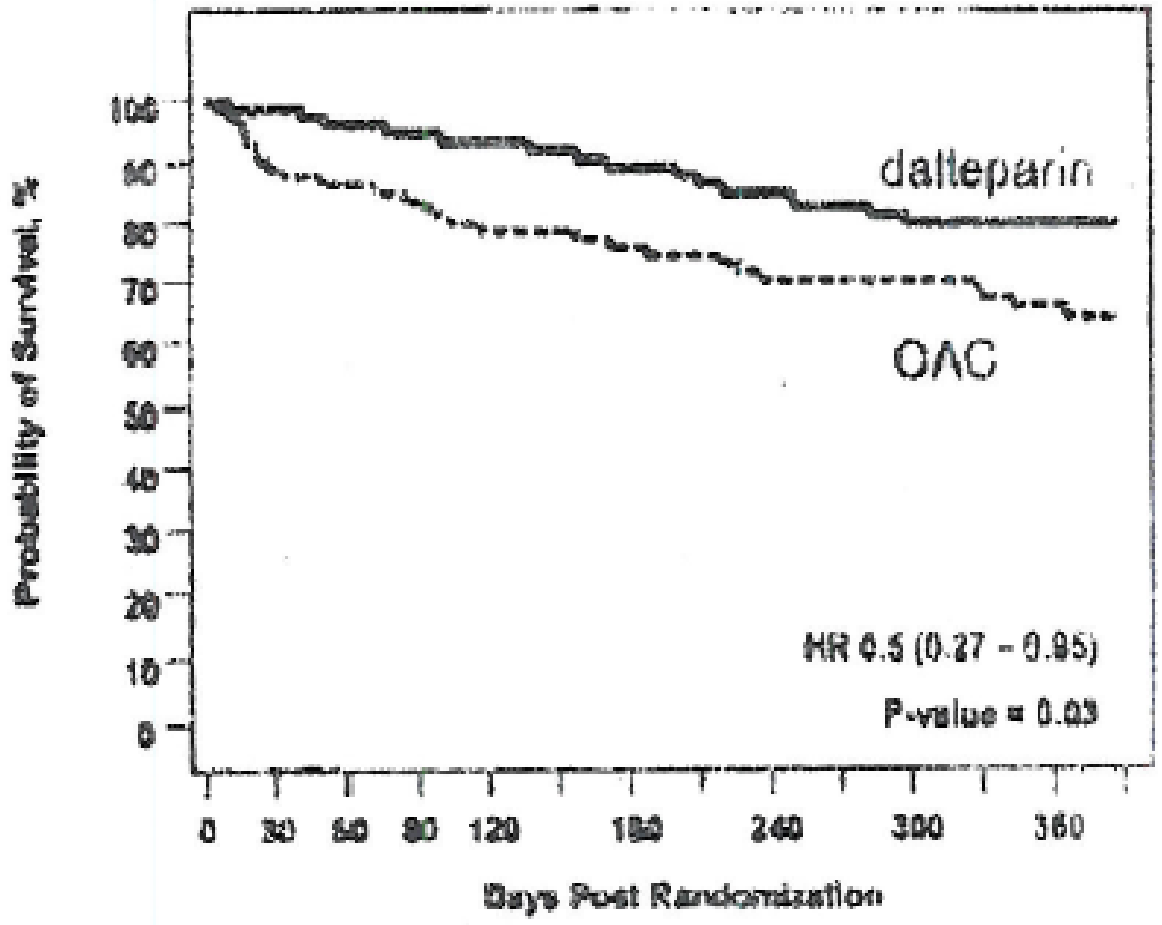
12-month Mortality

All patients

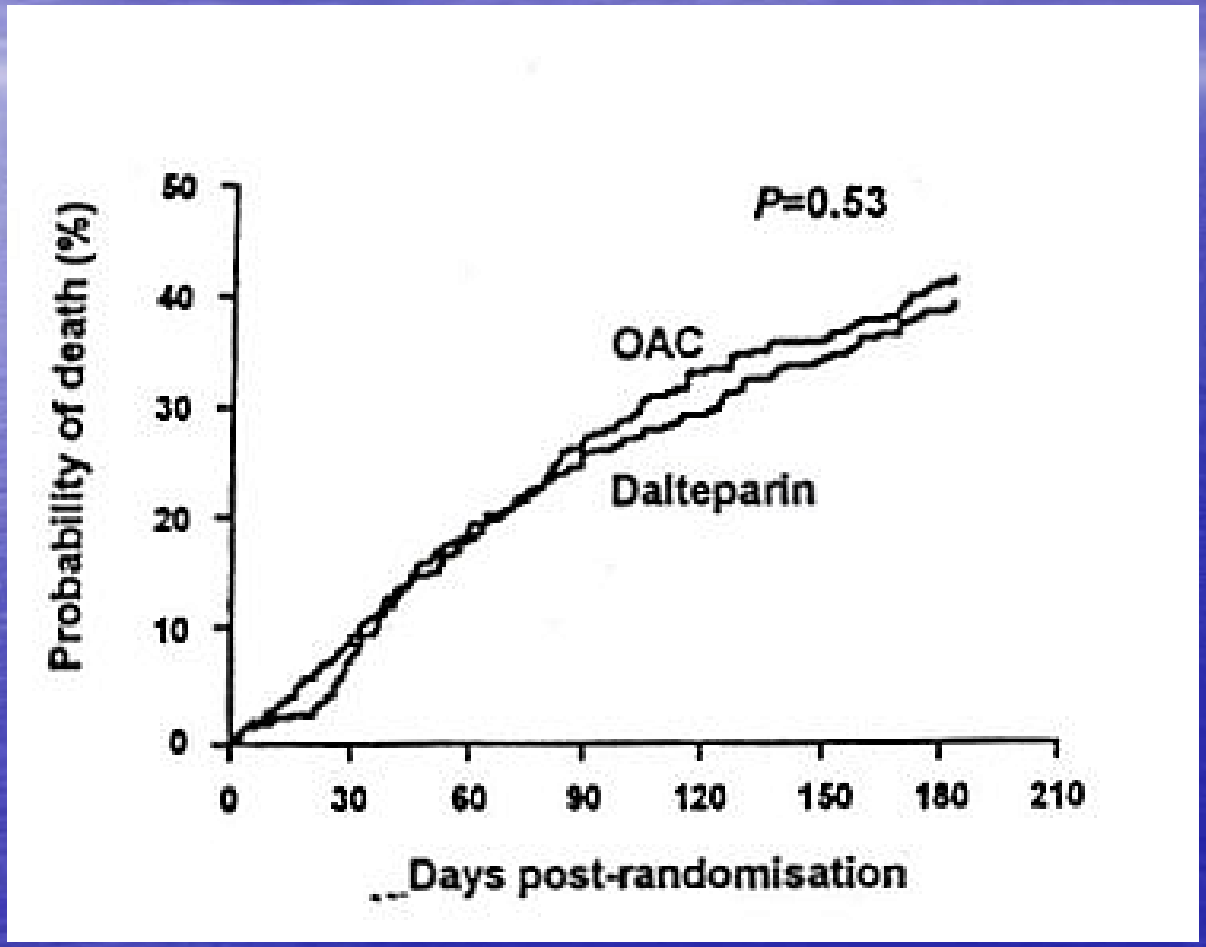


12-month Mortality

Patients without metastases



CLOT TRIAL


P=0.53
OAC
Dalteparin
Probability of death (%)
50
40
30
20
10
0
0
30
60
90
120
150
180
210
Days post-randomisation

CLOT TRIAL - CONCLUSIONS

In cancer patients with acute VTE:

- Long-term dalteparin therapy substantially reduced the risk of symptomatic, recurrent VTE compared with VKA therapy
- Long-term dalteparin therapy was not associated with an increase in bleeding
- No difference in mortality was detected between dalteparin and VKA therapy

CLOT TRIAL – CONCLUSIONS

- ~30% of patients treated with heparin followed by warfarin experience recurrent VTE or major bleeding despite warfarin therapy

- Monotherapy with Dalteparin is more effective than warfarin therapy for secondary prophylaxis

LMWH VS Fondaparinux (Anti-X A)

Fondaparinux

Anti-X A
- penta saccharide synthétique

Avantage
- ½ vie + longue
- pas de thrombopénie ou très très rare

Désavantage
- non neutralisé par sulfate de protamine
- s'accumule en insuff. rénale

Prévention

- LMWH < Fondaparinux

Traitement

- LMWH = Fondaparinux

Idraparinux

- Anti-X A
- S/C 1 sem.
- Antidote – Bioavidine
- Le problème ...

Anti-X A par voie orale

- 18 molécules dans le pipeline
- Semble aussi efficace
  - prévention
  - traitement
- Ximelagatran retiré du marché
  Toxicité hépatique

RÉSUMÉ

- Héparine de bas poids moléculaire bientôt le « standard of care » des thromboses associées au cancer.

7e conférence de consensus de l'ACCP sur le traitement antithrombotique, 2004

Recommandations pour le traitement *initial* de la TEV[1]

Patients atteints ou non de cancer

- Pour les patients qui ont une TVP objectivée, on recommande d'administrer une HFPM par voie s.c. ou une HNF par voie i.v. ou par voie s.c. pour le traitement à court terme [grade 1A].
- Pour les patients qui ont une EP non massive objectivée, on recommande d'administrer une HFPM par voie s.c. ou une HNF par voie i.v. pour le traitement à court terme [grade 1A].

TVP = thrombose veineuse profonde
HFPM = héparine de faible poids moléculaire
EP = embolie pulmonaire
TEV = thromboembolie veineuse
HNF = héparine non fractionnée
i.v. = intraveineuse
s.c. = sous-cutanée

1. Buller HR *et al. Chest* 2004.

7e conférence de consensus de l'ACCP sur le traitement antithrombotique (suite)

Recommandations pour le traitement *prolongé* de la TEV1

Patients non atteints de cancer

- Pour les patients ayant un 1er épisode de TVP attribuable à un facteur de risque transitoire, on recommande d'administrer un anti-vit. K pendant 3 mois [grade 1A]

- Pour les patients ayant un 1er épisode d'EP attribuable à un facteur de risque transitoire, on recommande d'administrer un anti-vit. K pendant au moins 3 mois [grade 1A]

Patients atteints de cancer

- Chez la plupart des patients ayant une TVP et un cancer, on recommande d'administrer une HFPM au moins pendant les 3 à 6 premiers mois d'un traitement de longue durée [grade 1A]

- Chez la plupart des patients ayant une EP et un cancer, on recommande d'administrer une HFPM au moins pendant les 3 à 6 premiers mois d'un traitement de longue durée [grade 1A]

TVP = thrombose veineuse profonde
HFPM = héparine de faible poids moléculaire
EP = embolie pulmonaire
TEV = thromboembolie veineuse
HNF = héparine non fractionnée
i.v. = intraveineuse
s.c. = sous-cutanée

TRAITEMENT

	I.D.	B.I.D.
Enoxaparine Lovenox	150 µi/kg/J	100 µi/kg/B.I.D.
Daltéparine Fragmin	200 µi/kg/J	100 µi/kg/B.I.D.
Tinzaparine Innohep	175 µi/kg/J	

Dosage Héparine de bas poids moléculaire par dosage Anti-X A

- 4 heures post-injection
- Dose thérapeutique 0,5 µ/ml à 1,3 µ/ml d'activité anti-X A

Combien de temps?

- Aussi longtemps que la maladie est active ou en traitement de chimiothérapie.

Recurrence rates by D-dimer, Prior VTE and Treatment (PREVENT)