Thrombosis and Cancer

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Total VTE Mortality per Year. (Extrapolated to 25 EU Countries)

	EU 25
DVT	684,019
PE	434,723
Mortality following VTE	543,454

- **Deaths due to VTE : 543,454[1]**

- **More than double the combined deaths due to:**
  - **AIDS 5,860[2]**
  - **breast cancer 86,831[2]**
  - **prostate cancer 63,636[2]**
  - **transport accidents 53,599[2]**

[1]Cohen AT. Presented at the 5th Annual Congress of the European Federation of Internal Medicine; 2005.
[2]Eurostat statistics on health and safety 2001. Available from: http://epp.eurostat.cec.eu.int.

Adapted from Dr A.T. Cohen's presentation at the ISTH July 7,2007

VENOUS THROMBOEMBOLIC DISEASE (VTE) AND CANCER

- **VTE :**
  - **-- 2nd cause of death in hospitalised Ca patients (after infections)**
  - **– 4-20 %, leading cause of death in cancer patients**
- **Risks of VTE :**
  - **– factor 4,1 in cancer**
  - **– factor 6,5 chemotherapy**
- **VTE :**
  - **– autopsy rates of cancer patients : 50 %**
  - **– clinical rates in cancer patients : 4-20 %**
- **Fatal pulmonary embolus and VTE recurrence : cancer patients vs non cancer patients 3:1**

Risk of DVT in Hospitalized Patients

- No prophylaxis + routine objective screening for DVT

Patient group	DVT incidence
Medical patients	10 - 20 %
Major gyne/urol/gen surgery	15 - 40 %
Neurosurgery	15 - 40 %
Stroke	20 - 50 %
Hip/knee surgery	40 - 60 %
Major trauma	40 - 80 %
Spinal cord injury	60 - 80 %
Critical care patients	15 - 80 %

Risk Factors for VTE

- Previous venous thromboembolism
- Increased age
- Surgery
- Trauma - major, local leg
- Immobilization - bedrest, stroke, paralysis
- Malignancy and its treatment (CTX, hormonal..)
- Heart or respiratory failure
- Estrogen use, pregnancy, postpartum, SERMs
- Central venous lines
- Thrombophilic abnormalities

Risk Factors for VTE

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Most hospitalized patients have at least one risk factor for VTE

Risk Factors for VTE (1)

E. Previtali 2010

Strong Risk Factors (Odds Ratio >10)

- Trauma or fractures
- Major orthopedic surgery
- Oncological surgery

Moderate risk Factors (OR 2-9)

- Non-onco surgery
- Hormones, Pregnancy & Puerperium
- Hypercoagulability
- Previous VTE

Risk Factors for VTE (2)

Moderate risk Factors (OR 2-9)

- Non-onco surgery
- Hormones, Pregnancy & Puerperium
- Hypercoagulability
- Previous VTE:

8.6%/6mo, 17%/24mo, 30%/8y

Weak Risk Factors (OR <2)

- Age
- Bed Rest (>3 days)
- Prolonged Travel
- Metabolic Syndrome (Obesity (OR 2,33), DM, Hyperlipidemia, Hypertension (OR 1,5)

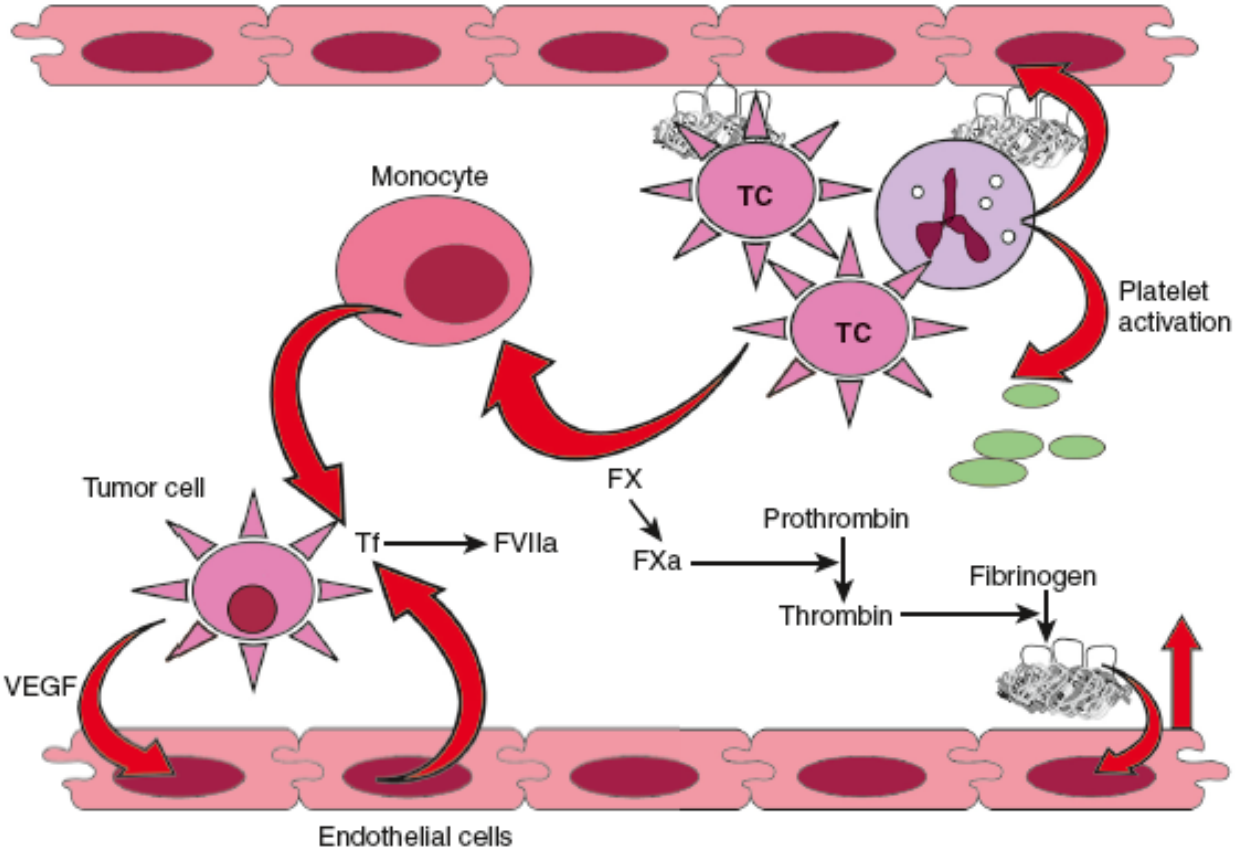
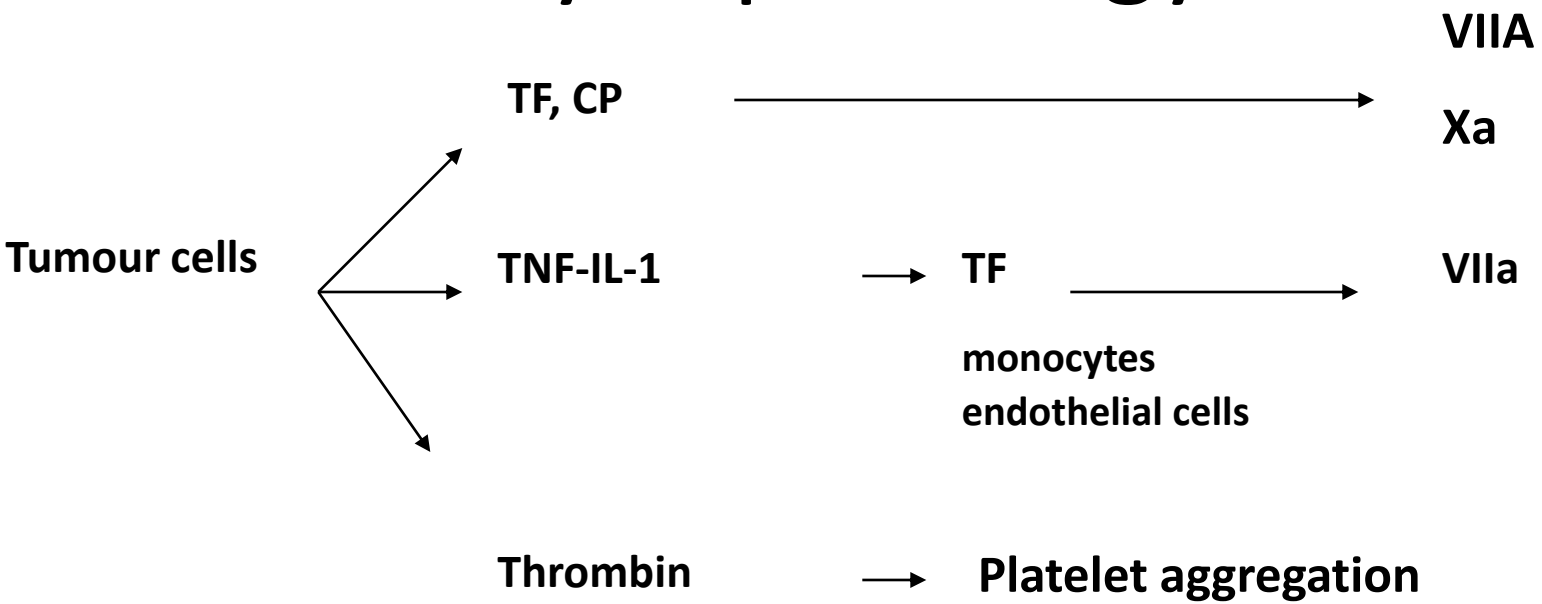


Fig. 26-1 Molecular mechanism underlying venous thromboembolism (VTE) in cancer. Tissue factor expressed on the surface of cancer cells activates factor VII, thereby triggering coagulation. Fibrin enhances angiogenic interleukin (IL)-8 expression by endothelial cells. Endothelial cells further express tissue factor, which will help to maintain activated coagulation. Vascular endothelial growth factor (VEGF) expression by tumor cells (TCs) will favor angiogenesis. Activation of neutrophils by tumor cells will activate the procoagulant and adhesive properties of platelets and endothelial cells. Activation of monocytes by cancer cells induces coagulation through the expression of tissue factor.

L. Plawny, M. Dicato: Thrombosis in Cancer in Mellar & Davis, p275-283

Physiopathology

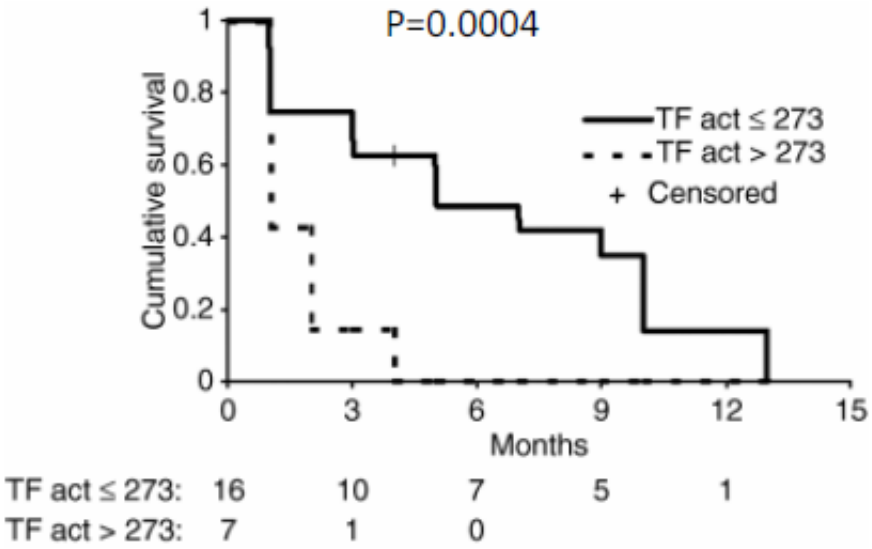


Pathways of activation of coagulation in cancer : TF (tissue factor) and CP (cancer procoagulant) activate factors VIIa and Xa. TNF (tumour necrosis factor), IL-1 (interleukin-1) induce TF expression on monocytes and on endothelial cells.

Why is Pancreatic Cancer so Thrombogenic?

- Location: retroperitoneal, bedridden..
- Thrombophilic state: **TF**, Thrombin, **GWAS**…
- Decrease in inhibitors: AT, Prot C&S, thrombomodulin..
- Platelet aggregation increase..**Mucin**
- Inflammation: TGF, TNF,…
- KRAS- mdm2/p53

Kaplan–Meier survival curve of patients with pancreatic carcinoma



Tesselaar MET et al, JTH 2006

Relative Risk of VTE in Cancer Patients

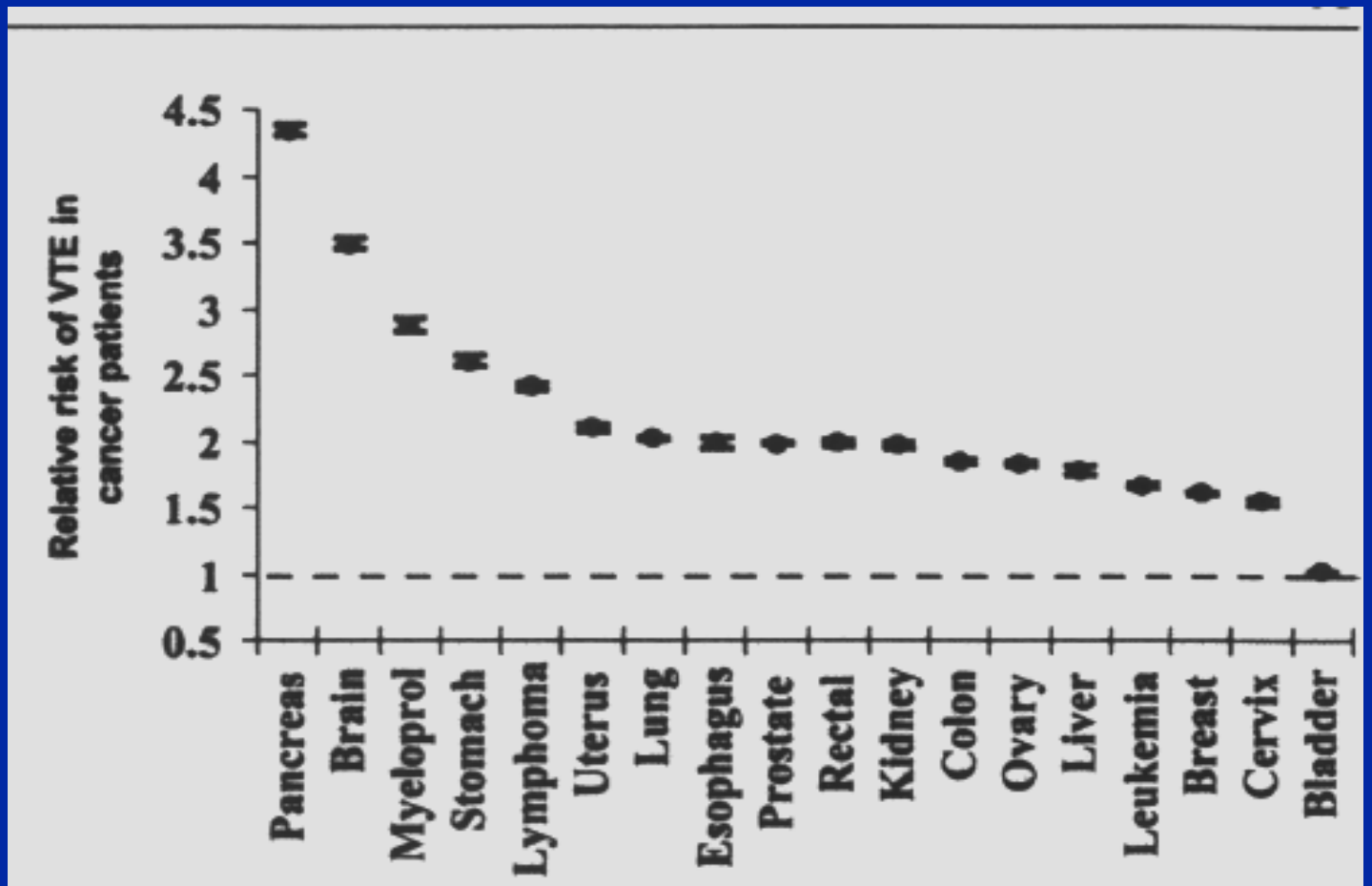


Figure 4 Relative risk of venous thromboembolism (VTE) ranged from 1.02 to 4.34.

Stein, Am J Med, 2006

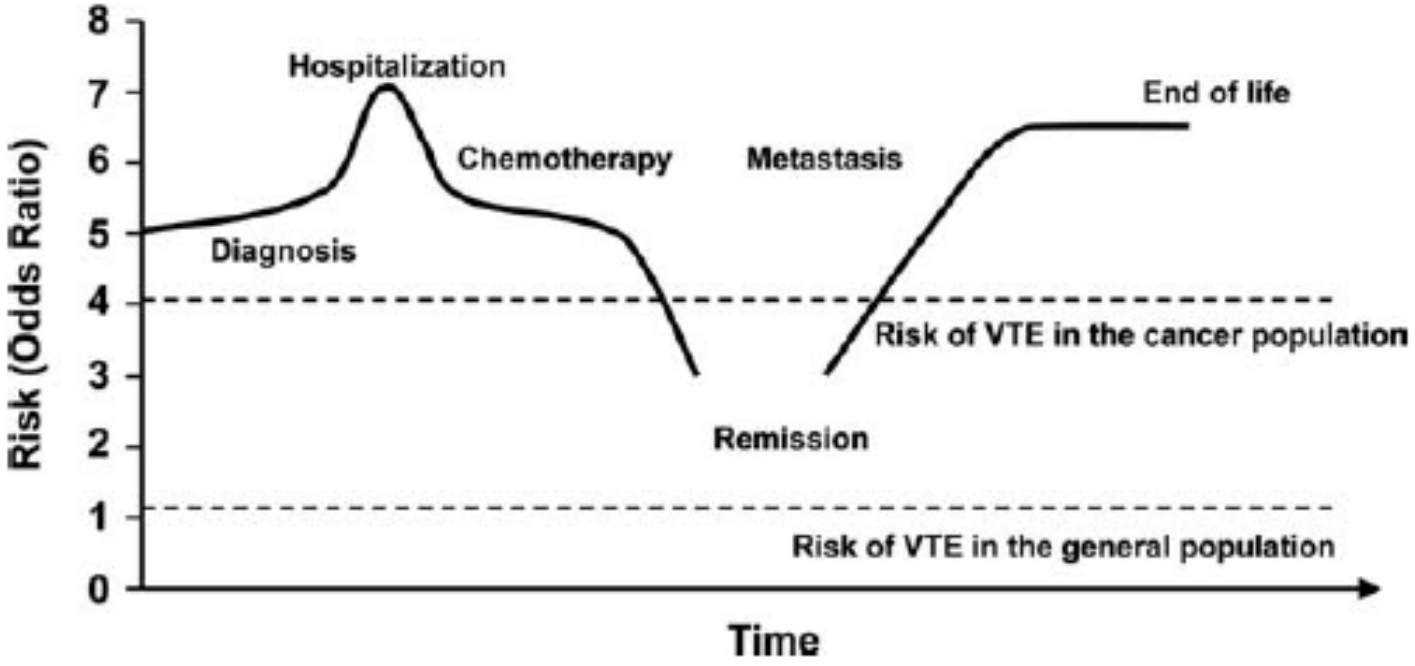


Figure 1. The risk of venous thromboembolism (VTE) varies over the natural history of cancer. Reproduced with permission from Rao MV, Francis CW, Khorana AA. Who's at risk for thrombosis? Approaches to risk stratifying cancer patients. In: Khorana AA, Francis CW, eds. Cancer-Associated Thrombosis: New Findings in Translational Science, Prevention, and Treatment. New York, New York: Informa Healthcare USA, Inc; 2007:169-192. ©2007 Informa Healthcare.[17]

Acquired APC Resistance (1/2)

ASCO 2006: # 8563 : adriamycin and epirubicin downregulate endothelial Protein C receptor and impair the APC (activated protein C) pathway. The conversion of Protein C to APC is hampered.

- After the treatment with these anthracyclins 25 % of patients had a low APC.

<u>Conclusion :</u> This might be one of the contributing factors of chemotherapy induced thrombophilia.

Acquired APC Resistance (2/2)

- -62 patients with MM (Blood Coag. Fibrinolys.:2002,13: 187)
  - 23% APC resistance at baseline: 50% developed VTE. Increase of VTE with thalidomide, ++ Dexa & ADR
- -1178 patients (Br. J. Haem. 2006, 134: 399)
  - 109 patients APC resistance, 36 V Leiden
  - 30/31 acquired APC resistance normalised after Rp

Thrombophilia Mutations

- **In cancer patients with VTE, testing for mutations (VLeiden, PT, MTHFR) is only useful if there is a previous personal or family history of VTE**

(M. Dicato et al. :Blood 2001,S1: 3984)

V LEIDEN, OESTROGENS AND DVT

V_L	OESTROGENS	DVT
-	-	0,8
-	+	3
+	-	5,7
+	+	28,5
HOMOZYGOSITY		> 100

(BMJ 1996, 313 : 1127)

GWA

- **ASCO 2011: Abstr. 1000**: Genome wide association (GWA) study in 2204 pts: identified a genetic predictive marker for paclitaxel induced neuropathy: several SNPs identified of which a missense SNP in gene RWDD3 (important in cellular response to stress).

  Concl.:Risk for neuropathy was 40% for heterozygosity and 60% for homozygosity

GWAS in VTE (www.genome.gov/gwastudies/)

- aPTT: decrease is risk of VTE: GWAS: Ile582Thr (in KNG1gene encoding HMWK)

  KNG1 Knock out mice have an increase aPTT and arterial thrombosis
- PS: any SNP contributing to plasma variability, C' and others; role of inflammation in VTE
- vWF increase
- Other GWAS data:

Prot C level interference

Plasminogen activator inhibitor-1 (PAI-1), MPV: SNPs variability on ABO: VTE, lipids, inflammatory markers, DM type 2 and CHD.

- **Overall these risk are 1- 1.5. Multiple SNPs with modest effect and rare variants with stronger impact; add DNA methylation modif, histone modifications…**

Predictive Model (modified from Khorana)

Cancer related risk factors:

- Very high risk: pancreas, stomach 2
- High risk: lung, lymphoma, Gynecology, bladder, brain 1

Laboratory:

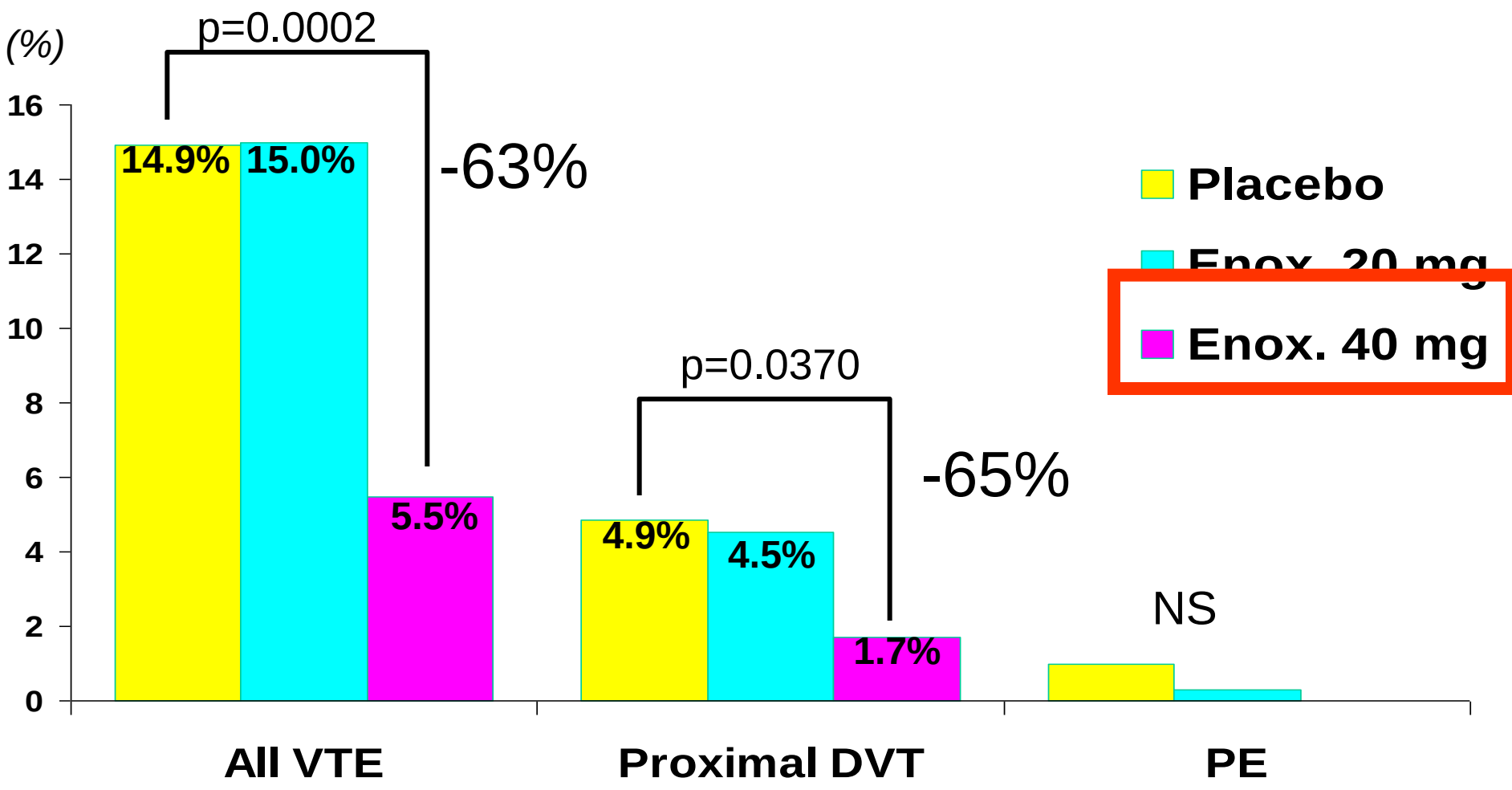
- Before Rp platelet count: > 349 000/ul, Hb <10g/dl, PMN > 11 000/ul, ESA use 1

Patient related risk factor: BMI >/= 35 kg/m2 1

Score: Low risk: 0, intermediate risk :1-2,

high risk >= 3

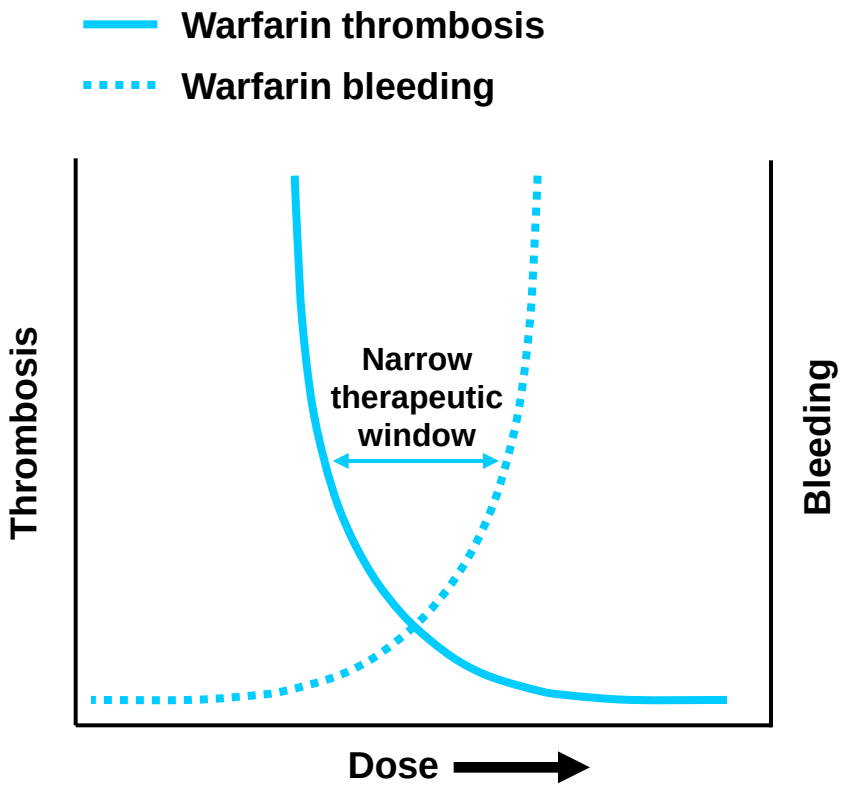
Reduction of Venous Thromboembolic Events in medical patients with Enoxaparin 40 mg/day



Medenox Study: Blood Coag Fibrinolysis, 2003

Limitations of vitamin K antagonists (VKAs)

- Unpredictable pharmacology
- Narrow therapeutic window
  - Difficult to keep within therapeutic range
- Multiple drug–drug and food–drug interactions
- Dosing problems in the initial phase of therapy
- Increased risk of major and minor bleeding



Ansell *et al*., *Chest* 2004; Hirsh *et al*., *Chest* 2004

Oral Anticoagulants:

- **Coumarinics:**

Pharmacogenetics: CYP2C9
VKORC1

- **Antithrombins:**

Ximelagatran: hepatotoxicity, off market EMEA 2008
Dabigatran: studies on-going, 2009-2010-2011

- **Anti Xa:**

Rivaroxaban (Xarelto)
Dabigatran (Pradaxa)
Apixaban: studies on-going

Recurrent VTE under adequate Treatment

- Progressive malignant disease
- Not weight adjusted LMWH
- Consider INR 3.0-3.5
- Inferior Vena Cava Filter (+ oral AVK ?)

Oral Rivaroxaban for Symptomatic Venous Thromboembolism (Einstein Investigators NEJM Dec 4. 2010)

1st non inferiority study: n= 3449 pts, Riv. 1731, Enox 1718.

VTE randomised into Rivaroxaban 15mg bid/3w then 20mg qd 12 mo

Enoxaparin 1mg/kg bid followed by AVK (INR 2-3) 12 mo

Efficacy outcome: recurrent VTE

Safety outcome: major bleeding & relevant non major bleeding

Riv vs Enox 36 vs 51 events p< 0.001

2nd superiority study: 2nd randomisation after the 12 mo (above)

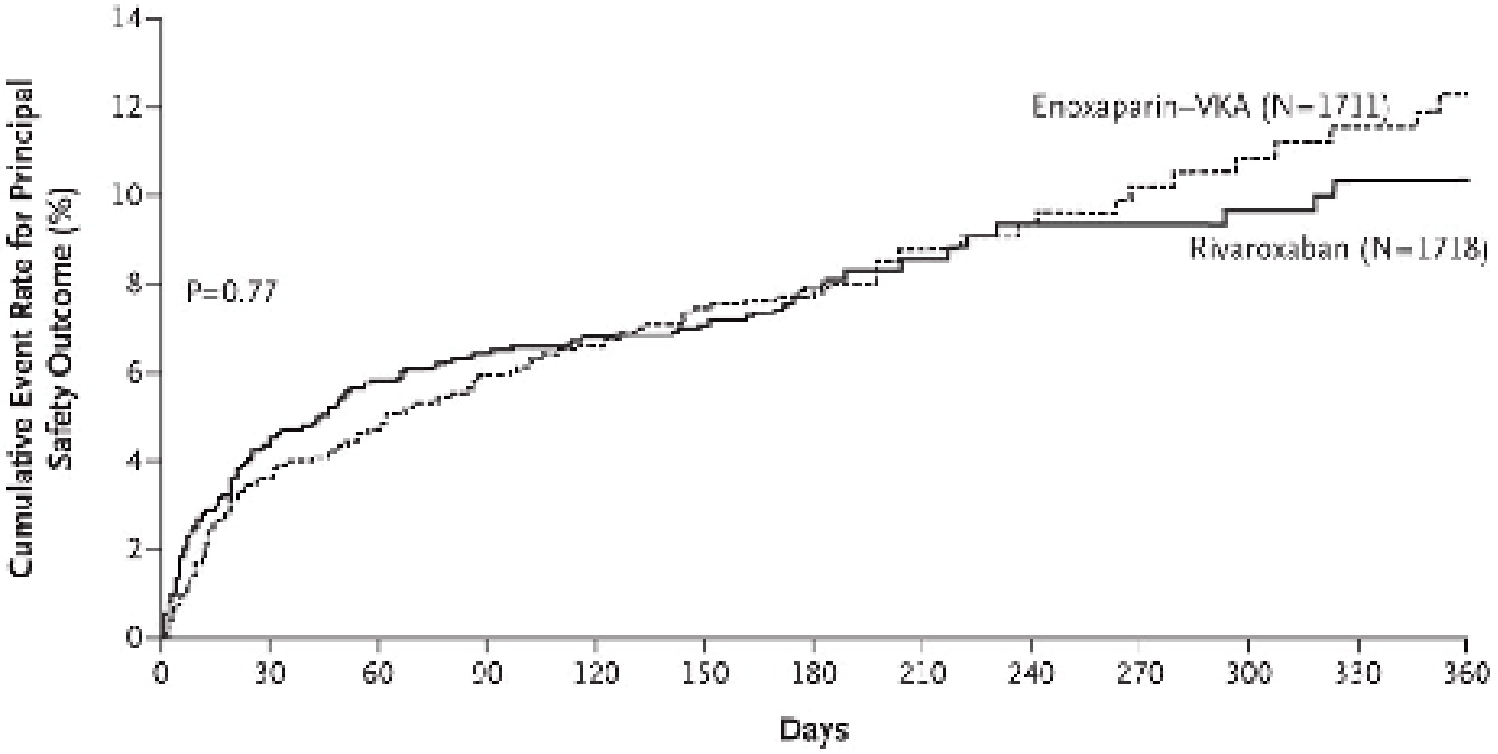
Rivaroxaban 20mg p.o qd vs Placebo

Efficacy: recurrent VTE; Safety outcome: major bleeding

N= 602 Riv, 594 placebo, 8 vs 42 events p< 0,001

3 studies total: 1 acute DVT, 2 acute PE, 3 continued TTT after acute TTT for DVT or PE. 1&3 above, 2 on-going

Figure 3 Kaplan–Meier Cumulative Event Rates for the Principal Safety Outcome in the Acute DVT Study. NEJM Dec 4, 2010



No. at Risk													
Rivaroxaban	1718	1585	1538	1382	1317	1297	715	355	338	304	278	265	140
Enoxaparin–VKA	1711	1554	1503	1340	1263	1238	619	338	321	287	268	249	118

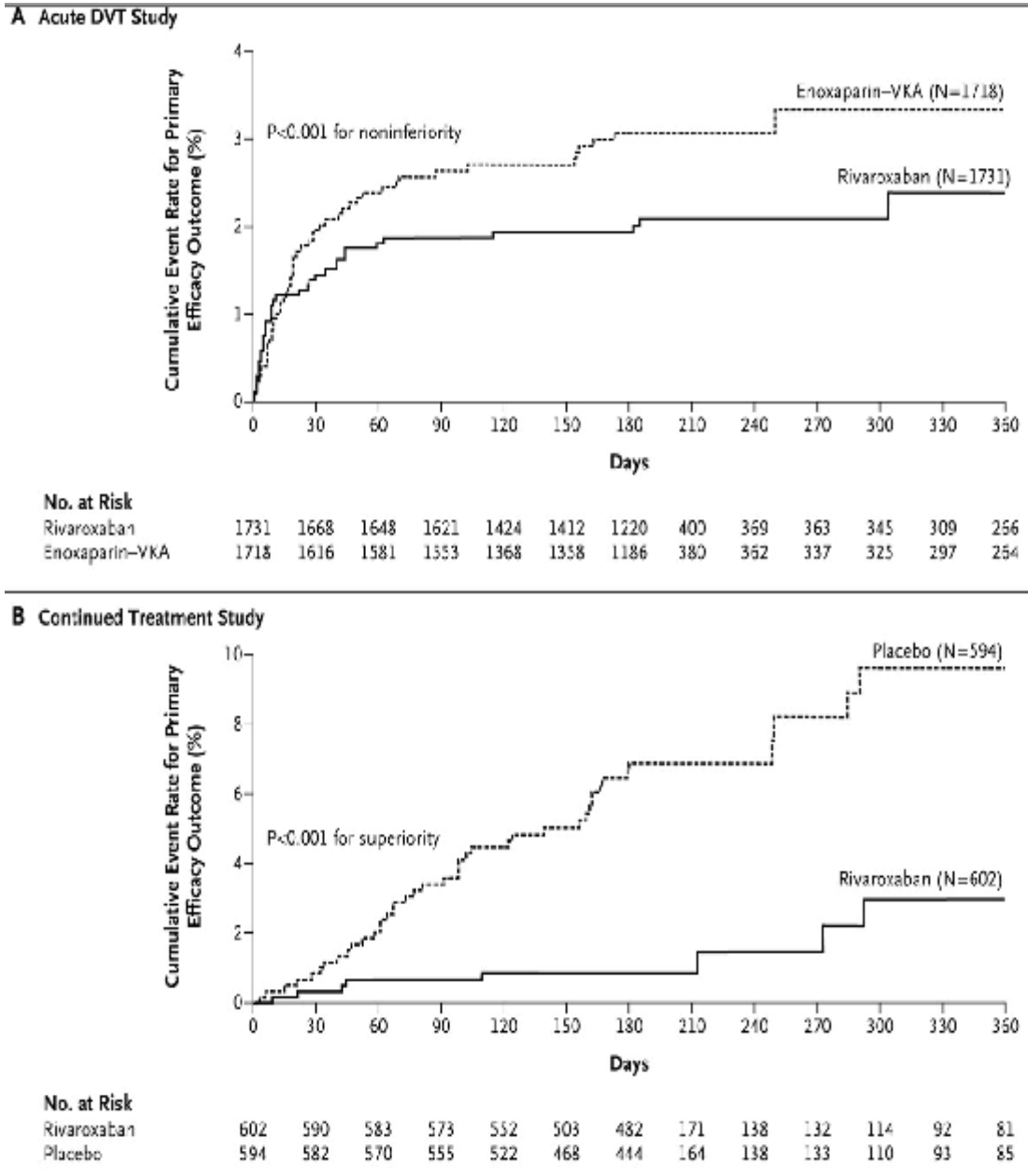
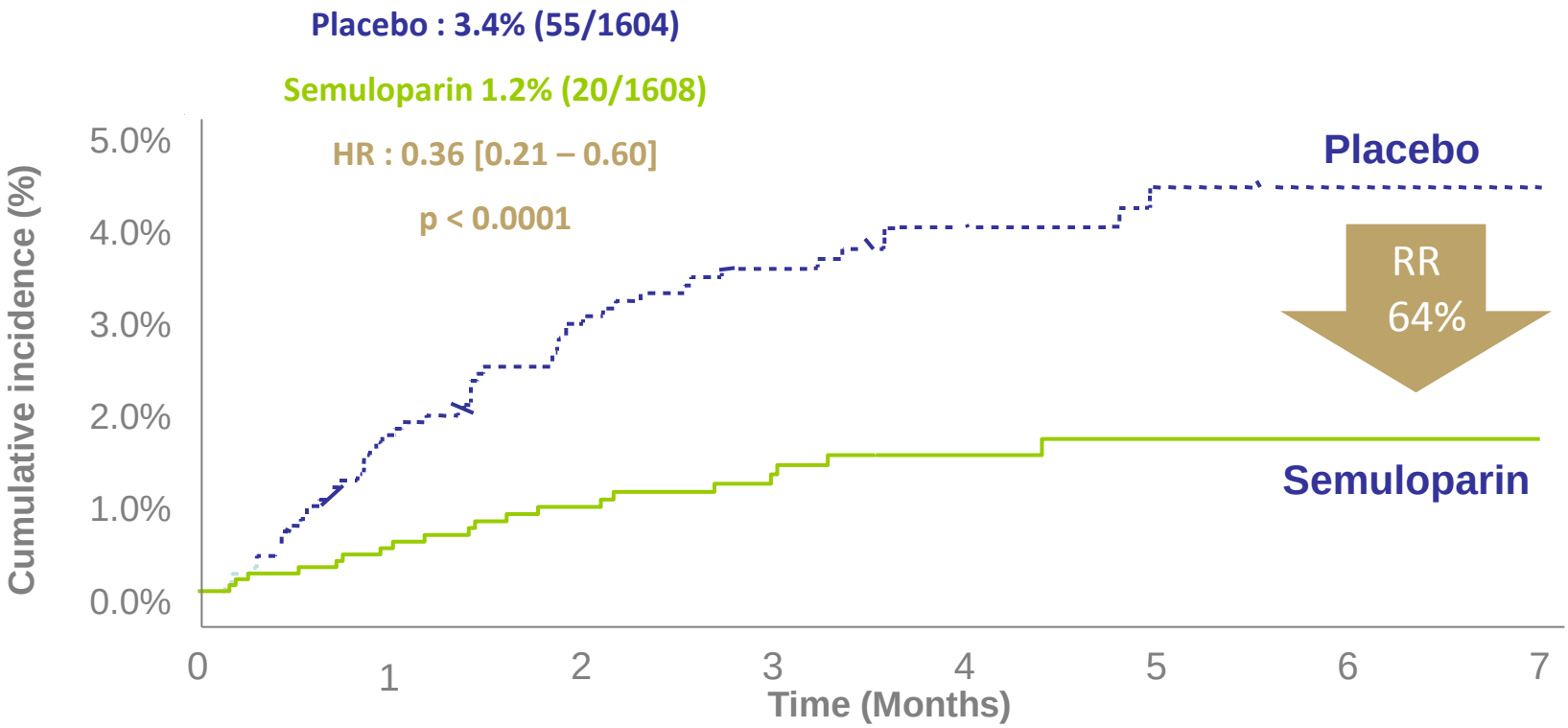


Figure 2 Kaplan–Meier Cumulative Event Rates for the Primary Efficacy Outcome in the Two Studies.

VKA denotes vitamin K antagonist.

Primary efficacy endpoint
Any symptomatic DVT, any non-fatal PE, or VTE-related deaths



Number at Risk

Placebo	1604	1375	1212	985	689	403	201	92
Semuloparin	1608	1410	1227	986	681	384	197	77

ECCO- ESMO Stockholm 2011, abstr. 3.001

HR = hazard ratio, CI = confidence interval

Anticoagulation Recommendations 1/3

	ACCP	ASCO	NCCN
Hospitalized patients (no contraindications to anticoagulation)	▪UFH ▪LMWH - Enoxaparin - Dalteparin ▪Fondaparinux	▪UFH ▪LMWH - Enoxaparin - Dalteparin ▪Fondaparinux	▪UFH ▪LMWH - Enoxaparin - Dalteparin - Tinzaparin† ▪Fondaparinux
Post-surgery	▪UFH ▪LMWH - Enoxaparin - Dalteparin ▪Fondaparinux ▪Mechanical compression devices (IPC, GCS) in combination with pharmacologic agents depending on the type of surgery	▪LMWH ▪Approved for treatment of DVT with or without PE ▪Mechanical compression devices (IPC, GCS) in combination with pharmacologic agents in high-risk patients‡	▪Caution with renal dysfunction, obesity, or weight < 50 kg ▪If CrCl < 30 mL/min, consider UFH ▪Contraindicated in HIT ▪Mechanical compression devices (IPC, GCS) in combination with pharmacologic agents in high-risk patients‡
Extended postsurgery prophylaxis	▪No specific recommendation	▪Up to 4 weeks post-surgery in high-risk patients‡	▪Up to 4 weeks post -surgery in high-risk patients‡

† Not approved for VTE prophylaxis by US FDA
‡ Age > 60 years, higher stage, increased duration of anesthesia (> 2 hours), prolonged postoperative immobilization, with bed rest > 3 days, and previous history of VTE
IPC: intermittent pneumatic calf compression devices; GCS: graduated compression stockings

Anticoagulation Recommendations (Cont'd)

	ACCP	ASCO	NCCN
Patients with central venous catheters	▪VTE thromboprophylaxis not recommended	▪VTE thromboprophylaxis not recommended	▪VTE thromboprophylaxis not recommended
Outpatients without VTE	▪VTE thromboprophylaxis not recommended	▪VTE thromboprophylaxis not recommended	▪VTE thromboprophylaxis not recommended
Patients with renal insufficiency	▪UFH is recommended as the safest option in these individuals ▪Recommend caution with LMWH and fondaparinux	▪UFH is recommended as the safest option in these individuals ▪Recommend caution with LMWH and fondaparinux	▪UFH is recommended as the safest option in these individuals ▪Severe renal insufficiency (CrCl < 30 mL/min): - Enoxaparin is the only LMWH with a manufacturer-recommended dose - Fondaparinux is contraindicated ▪Moderate renal insufficiency (CrCl 30-60 mL/min) - LMWH and fondaparinux should be used with caution

Anticoagulation Recommendations (Cont'd) 3/3

	ACCP	ASCO	NCCN
Weight (either obese or weight < 50 kg)	▪UFH is recommended as the safest option in these individuals ▪Recommend caution with LMWH and fondaparinux	▪UFH is recommended as the safest option in these individuals ▪Recommend caution with LMWH and fondaparinux	▪UFH is recommended as the safest option in these individuals ▪Recommend caution with LMWH and fondaparinux
Active chemotherapy	▪VTE thromboprophylaxis is not recommended	▪VTE thromboprophylaxis using LMWH or low-dose warfarin (dose adjusted to an INR ~ 1.5) in myeloma patients receiving thalidomide with dexamethasone or chemotherapy	▪VTE thromboprophylaxis should be considered in highly thrombogenic chemotherapy
Patients with contraindications to anticoagulant therapies	▪Mechanical compression devices (IPC, GCS)	▪Mechanical compression devices (IPC, GCS)	▪Mechanical compression devices (IPC, GCS)

Thank You