Prevention and management of venous thromboembolism

M. AAPRO

Thromboprophylaxis of DVT and PE in Ambulatory Cancer Patients

Zurich, February 2017

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Based on a lesson in April 2016 by

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Relative Risk of VTE in Cancer Patients

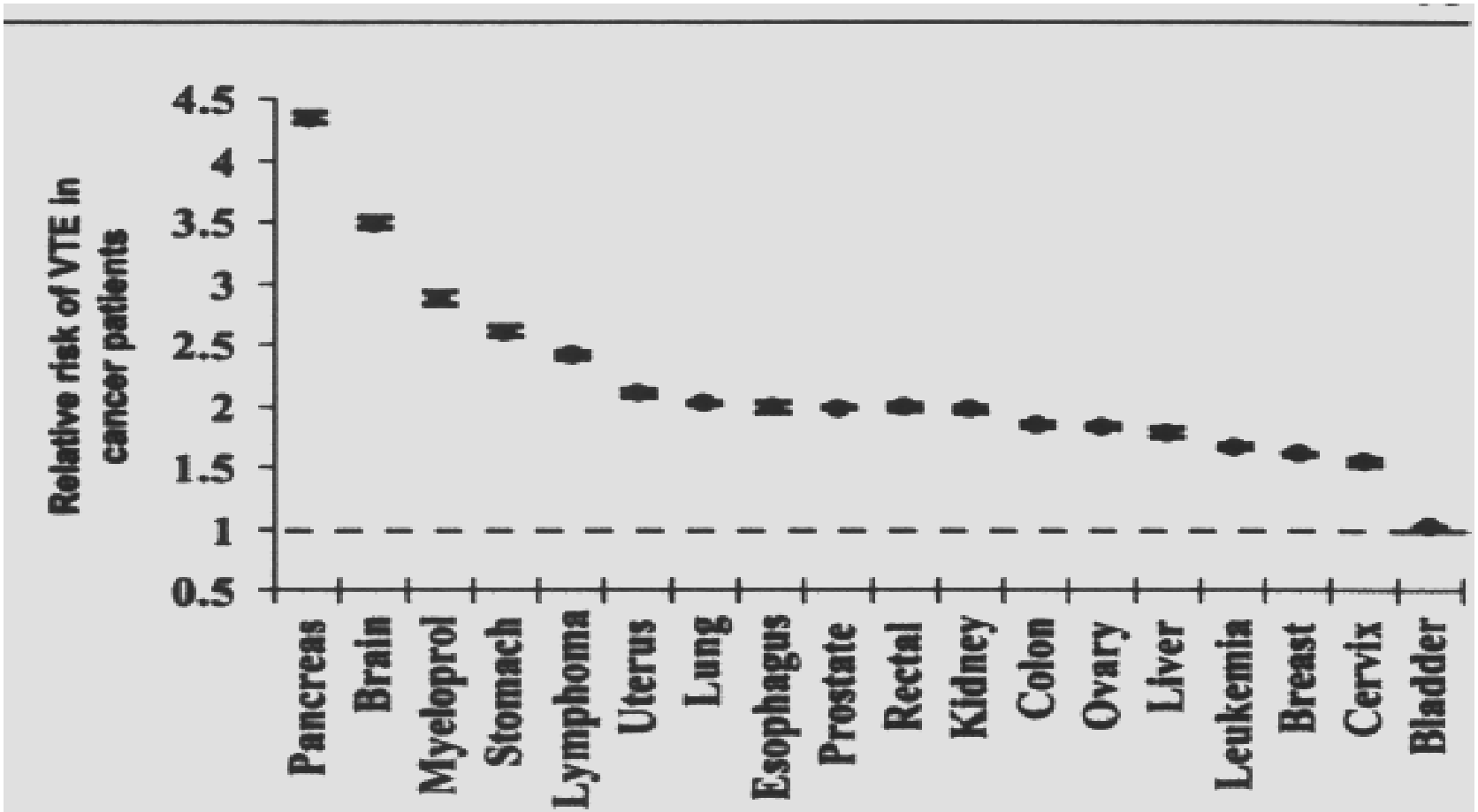
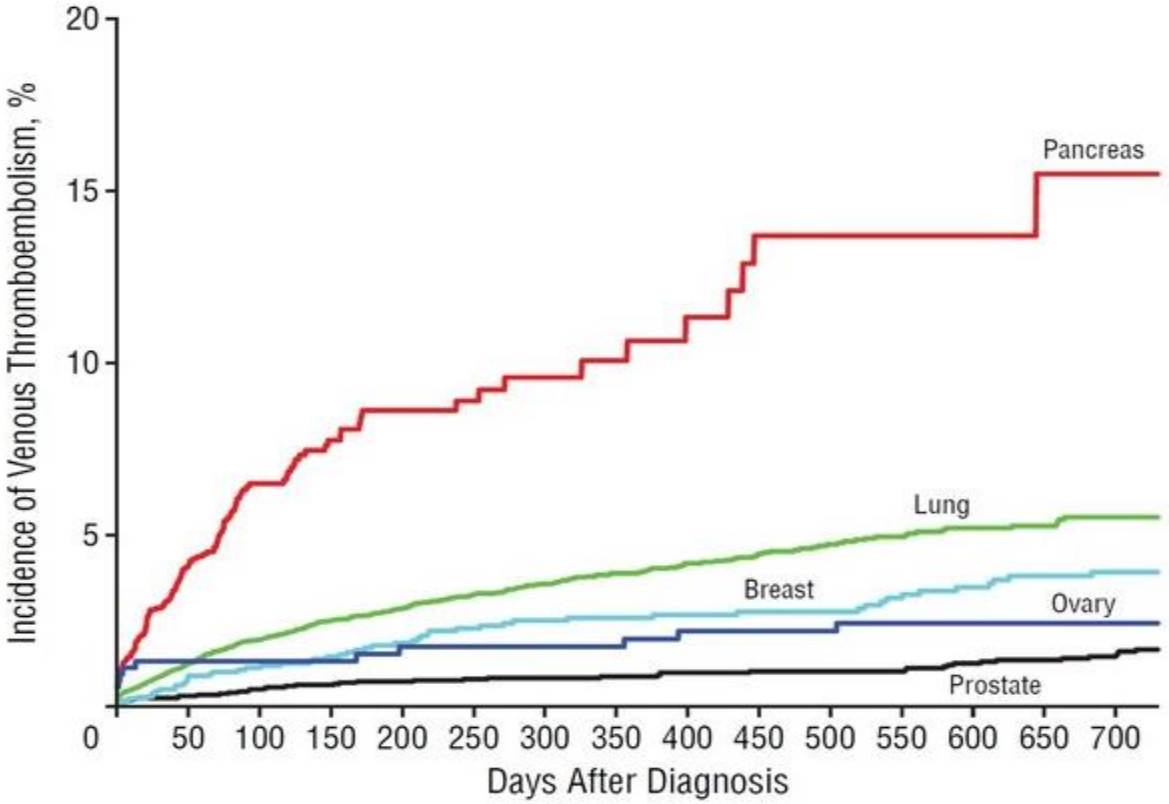


Figure 4 Relative risk of venous thromboembolism (VTE) ranged from 1.02 to 4.34.

Stein, Am J Med, 2006

Incidence of VTE
Cancer patients with metastatic-stage disease



Chew HK. Arch Intern Med 2006; 166: 458

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

- **Previous venous thromboembolism**
- **Increased age**
- **Surgery**
- **Trauma - major, local leg**
- **Immobilization - b**
- **Malignan** **, hormonal..)**
- **[illegible]** **are**
- **[illegible]** **pregnancy, postpartum, SERMs**
- **[illegible]** **venous lines**
- **Thrombophilic abnormalities**

Most hospitalized patients have at least one risk factor for VTE

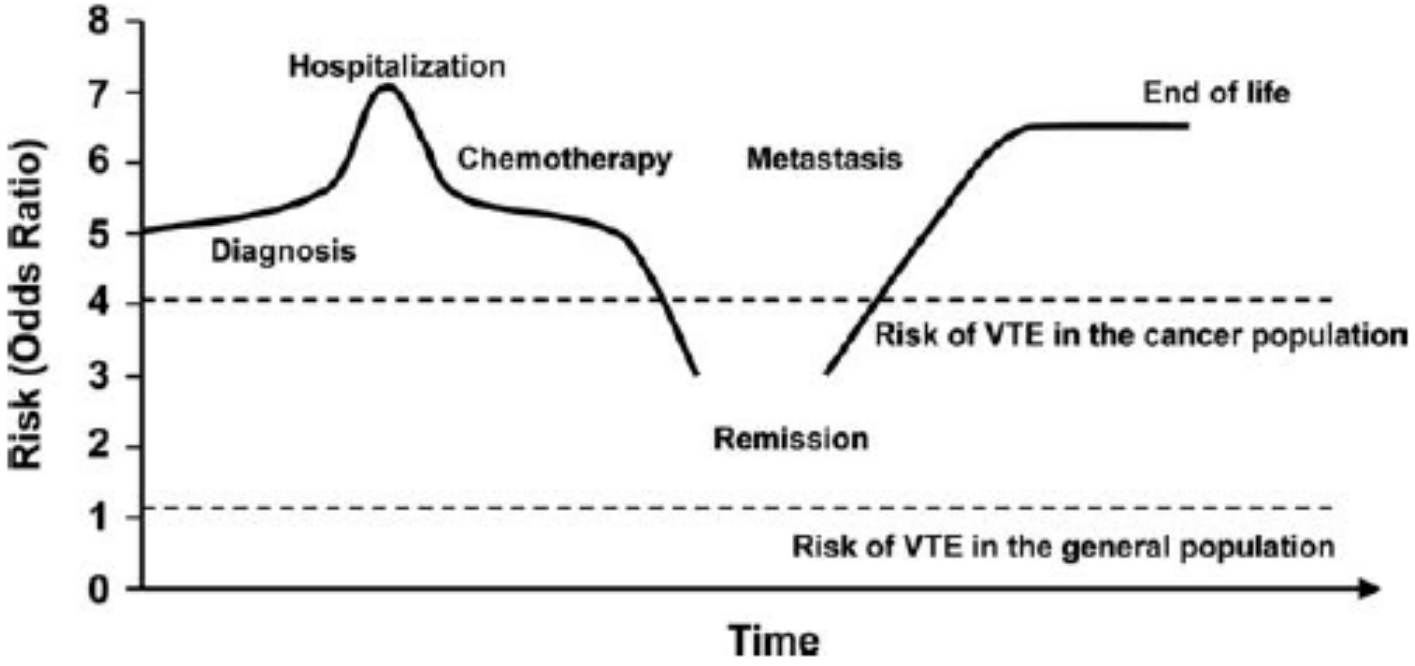


Figure 1. The risk of venous thromboembolism (VTE) varies over the natural history of cancer. Reproduced with permission from Rao MV, Francis CW, Khorana AA. Who's at risk for thrombosis? Approaches to risk stratifying cancer patients. In: Khorana AA, Francis CW, eds. Cancer-Associated Thrombosis: New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

V LEIDEN, OESTROGENS AND DVT

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

(BMJ 1996, 313 : 1127)

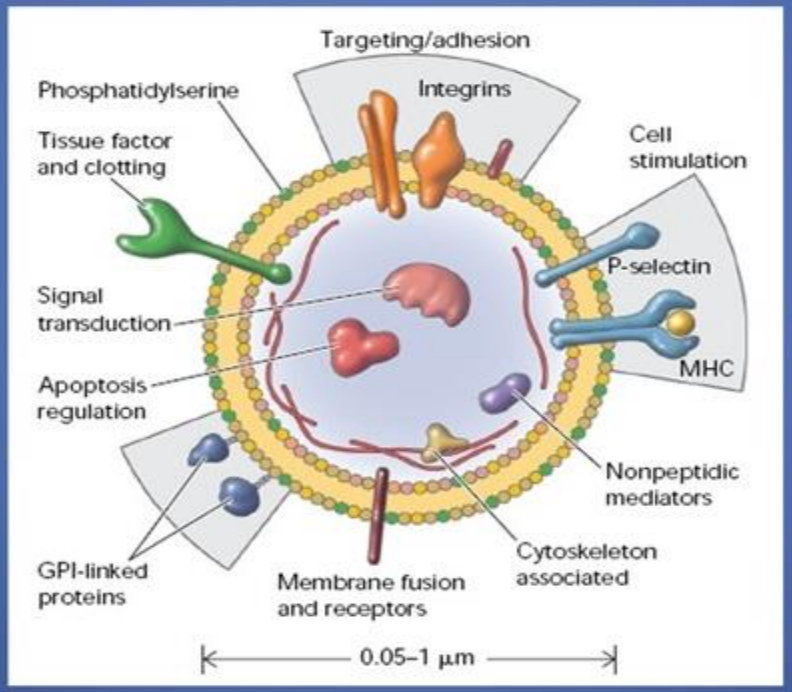
The Infernal Trio: Cancer- Inflammation- Thrombosis

Circulating microparticles (MPs)

cell-to-cell communication

small and heterogeneous membrane vesicles

express membrane antigens characteristic of their cell of origin



size: 0.1 - 1.0 μm

negatively charged phosphatidylserine-rich surface

released in response to apoptosis and cell activation

released from different cell types (including cancer cells

Elevated levels of circulating MPs have be found in inflammatory, metabolic, malignant and thrombotic diseases

Hugel et al. Physiology 2005

What is New?

Research:

- relations between cancer spread, hemostasis and inflammation

Clinic:

- VTE prevention in ambulatory Cancer Pts?
- Novel anticoagulants:
  - heparins
  - oral anticoagulants

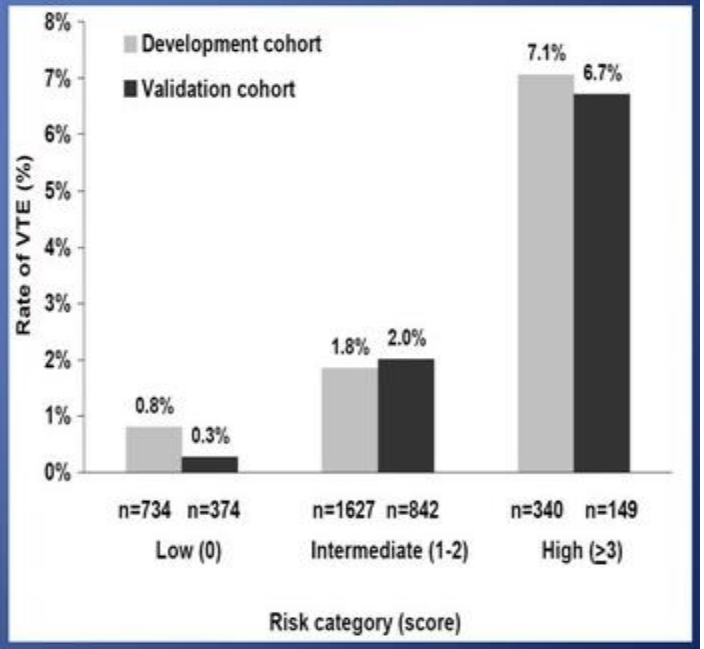
Prophylactic Anticoagulation

Risk scoring models
Prediction of cancer-associated VTE

- **Predictive Risk Scoring Model („Khorana-Score“)** for chemotherapy-associated thrombosis

- Follow-up time: 2.4 months

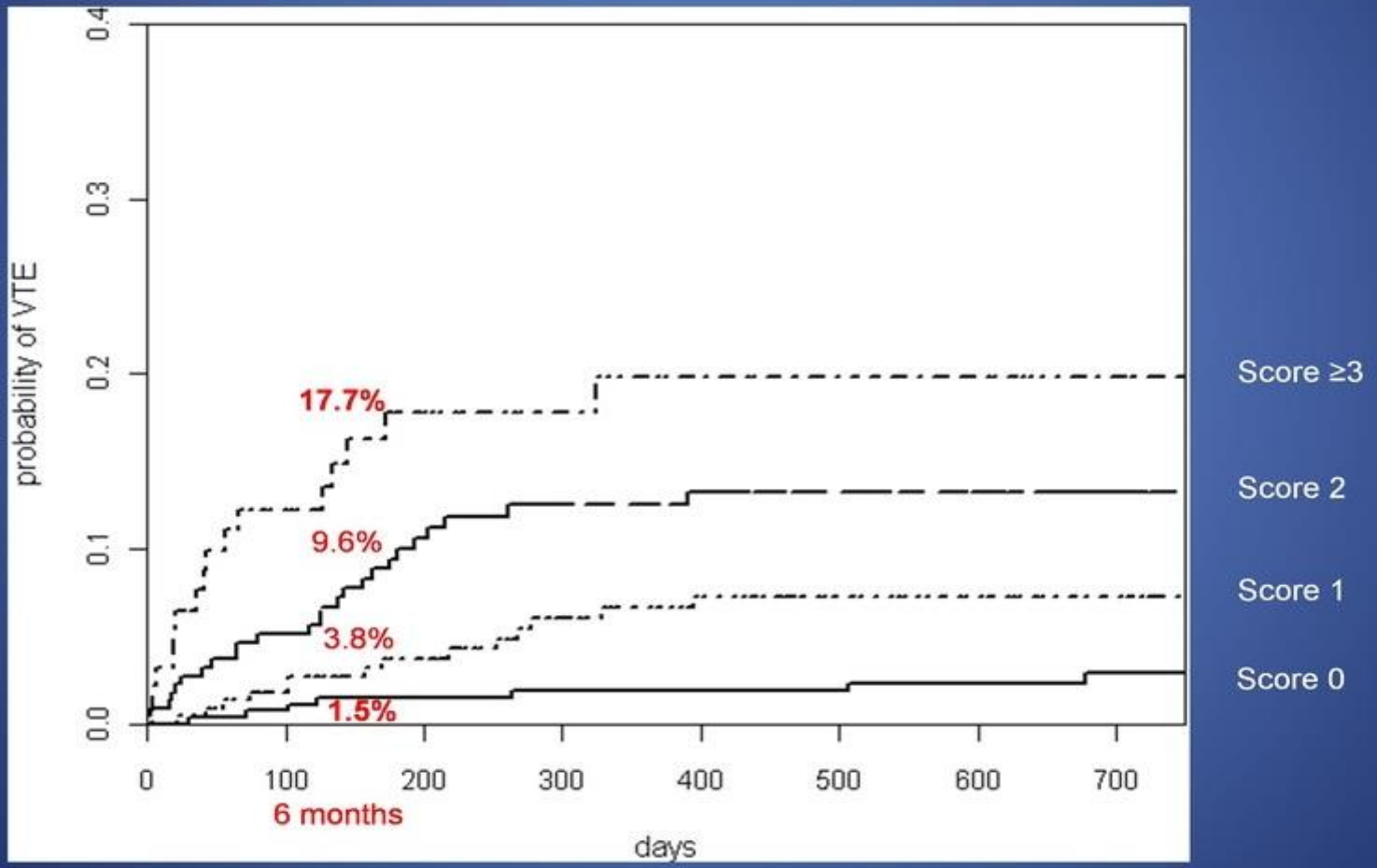
Patient characteristic	Risk score
Site of cancer	
Very high risk (stomach, pancreas)	2
High risk (lung, lymphoma, gynecologic, bladder, testicular)	1
Prechemotherapy platelet count 350 × 10^9/L or more	1
Hemoglobin level less than 100 g/L or use of red cell growth factors	1
Prechemotherapy leukocyte count more than 11 × 10^9/L	1
BMI 35 kg/m^2 or more	1



Khorana et al, Blood 2008

Vienna Cancer and Thrombosis Study (CATS)

Application of the predictive risk scoring model by Khorana et. al.

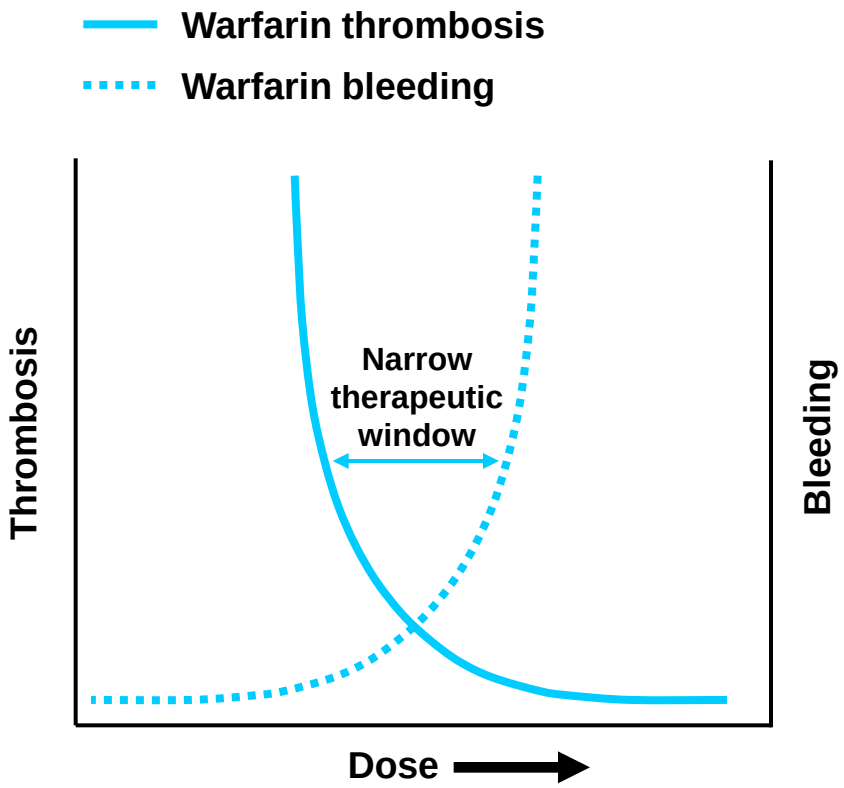


Ay C et al, Blood 2010; 116:5377-82

Novel Anticoagulants

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

Percentage of Patients in therapeutic range (INR 2.3) with Coumarins

- Warfarin ~ **45%** at 4 weeks (S.Kimmel NEJM 2013)
- Acenocoumarol & Phenprocoumon **~60%** at 10 weeks (T Verhoef NEJM 2013)

Novel Anticoagulants

- FXI-ASO: FXI antisense oligonucleotide
- Semuloparin
- Oral: Dabigatran
  Rivaroxaban
  Apixaban
  Edoxaban

N Engl J Med. 2015 Jan 15;372(3):232-40. doi: 10.1056/NEJMoa1405760. Epub 2014 Dec 7.

Factor XI antisense oligonucleotide for prevention of venous thrombosis.

Büller HR[1], Bethune C, Bhanot S, Gailani D, Monia BP, Raskob GE, Segers A, Verhamme P, Weitz JI; FXI-ASO TKA Investigators.

FXI-ASO (ISIS Pharmaceuticals) 2^{e} generation diminishes synthesis of FXI

N=300 pts. Knee replacement, Venography

FXI-ASO (200 vs 300mg) vs enoxaparine 40mg/j:

- Result similar for 200mg vs enoxaparine.
- For 300mg vs enoxaparine:
  - VTE 3/71pts (4%) vs 21/69 (30%), p<0.001.
  - Bleeding 3% vs 8%

➢ Antithrombotic with low risk of bleeding

The NEW ENGLAND JOURNAL of MEDICINE

Oral Rivaroxaban for Symptomatic Venous Thromboembolism

The EINSTEIN Investigators*

Characteristic	Acute DVT Study		Continued Treatment Study	
	Rivaroxaban (N=1731)	Standard Therapy† (N=1718)	Rivaroxaban (N=602)	Placebo (N=594)
Unprovoked	1055 (60.9)	1083 (63.0)	440 (73.1)	441(74.2)
Recent surgery or trauma	338 (19.5)	335 (19.5)	21 (3.5)	28 (4.7)
Immobilization	265 (15.3)	260 (15.1)	89 (14.8)	77 (13.0)
Estrogen therapy	140 (8.1)	115 (6.7)	23 (3.8)	22 (3.7)
Active cancer	118 (6.8)	89 (5.2)	28 (4.7)	26 (4.4)
Puerperium	6 (0.3)	11 (0.6)	1 (0.2)	0

Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism in patients with cancer

Martin H Prins

Maastricht University Medical Center, Maastricht, The Netherlands

ESMO Congress, 26–30 September 2014

Outcomes

	History of cancer		
	Rivaroxaban	**Enoxaparin/VKA**	**HR (95% CI)**
Recurrent VTE, n (%)	5/233 (2.1)	5/236 (2.1)	0.98 (0.28–3.43)
Major bleeding, n (%)	1/231 (0.4)	4/236 (1.7)	0.23 (0.03–2.06)
Mortality, n (%)	5/233 (2.1)	4/236 (1.7)	1.12 (0.30–4.22)

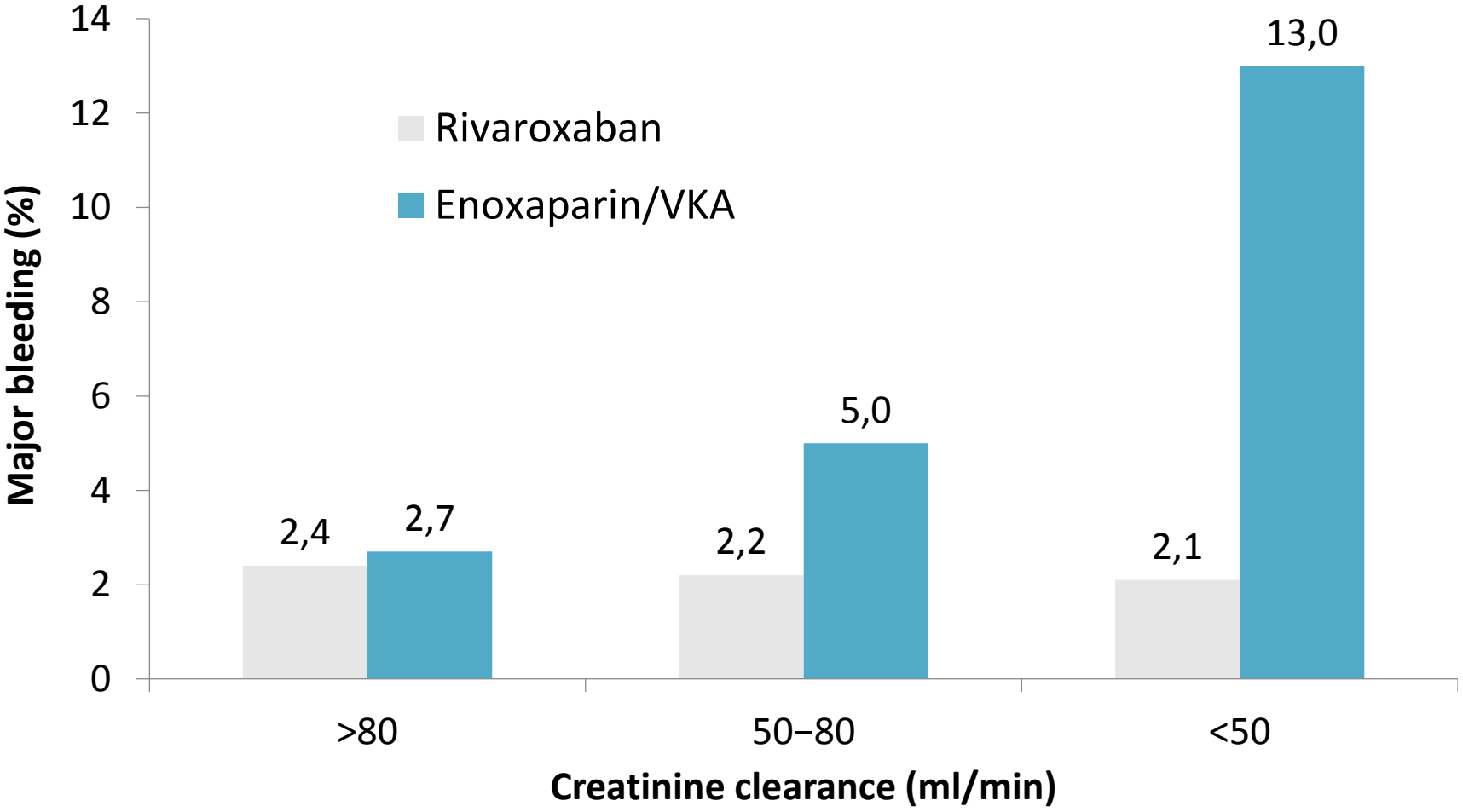
Outcomes

	Active cancer*		
	Rivaroxaban	**Enoxaparin/VKA**	**HR (95% CI)**
Recurrent VTE, n (%)	16/354 (4.5)	20/301 (6.6)	0.67 (0.35–1.30)
Major bleeding, n (%)	8/353 (2.3)	15/298 (5.0)	
Mortality, n (%)	58/354 (16.4)	53/301 (17.6)	0.93 (0.64–1.35)

*At baseline or diagnosed during the study

Major bleeding in patients with active cancer

Major bleeding in patients with active cancer



Novel oral anticoagulants

- Comparator non-inferiority studies on NOAC have been done with short initiation LMWH followed by AVK. No direct comparison

- All studies done so far, life- threatening bleeding NOAC < AVK. Some dosage problems?

- New product. Lack of experience.

- Idarucizumab, antidote of dabigatran. In October 2015 FDA approval. CMP to EMA approval.

- Specific Ca patient studies on-going vs LMWH

Ambulatory Prophylaxis of VTE in Cancer Patients

Ambulatory Chemotherapy and VTE prophylaxis

Patients:	311 with advanced (stage IV) breast cancer
Dosage:	Warfarin 1 mg daily for the first 6 weeks followed by INR-adjusted doses (INR 1.3–1.9) (double-blind)
End-point:	Objectively confirmed VTE
Results:	RRR of 85% without increase of bleeding: 8 (5.3%) bleeding events in warfarin-treated patients compared with 5 (3.1%) in placebo recipients (p = 0.4)

Levine M, et al. Lancet. 1994;343:886-9.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Efficacy of Prophylactic Low–Molecular Weight Heparin for Ambulatory Patients With Advanced Pancreatic Cancer: Outcomes From the CONKO-004 Trial

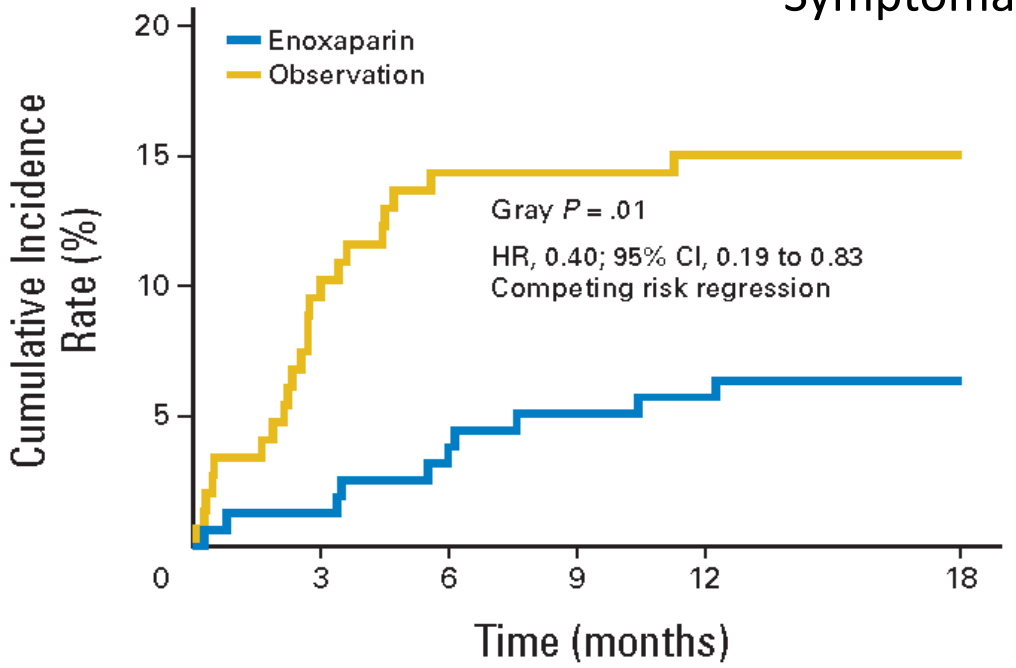
Uwe Pelzer, Bernhard Opitz, Gerd Deutschinoff, Martina Stauch, Peter C. Reitzig, Sabine Hahnfeld, Lothar Müller, Martina Grunewald, Jens M. Stieler, Marianne Sinn, Timm Denecke, Sven Bischoff, Helmut Oettle, Bernd Dörken, and Hanno Riess

- Open label unblinded randomized study
- No baseline screening at study entrance
- Pancreatic Ca: 43% of patients no other risk factor versus other with risk factors:

  - VTE: 2.6% if no other risk factor vs 6.3% if one or 10.5% >1 risk factor.

Enoxaparin in advanced pancreatic cancer

Symptomatic VTE

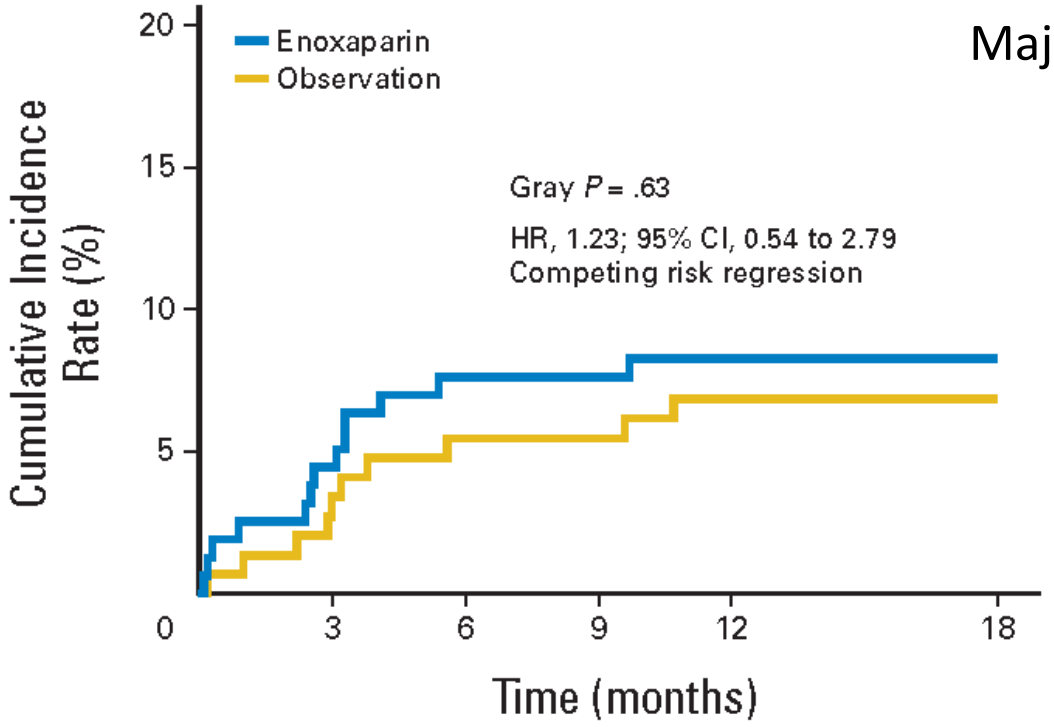


No. at risk						
Enoxaparin	160	102	55	26	12	4
Observation	152	87	47	27	14	5
Incidence rate, %						
Enoxaparin	0	1.3	3.8	5.1	5.7	6.4
Observation	0	10.2	14.4	14.4	15.1	15.1

Pelzer U. et al. *J Clin Oncol* 2015; 33:2028-2034

Enoxaparin in advanced pancreatic cancer

Major bleedings



No. at risk						
Enoxaparin	160	99	52	26	14	5
Observation	152	94	52	26	13	4
Incidence rate, %						
Enoxaparin	0	4.5	7.6	7.6	8.3	8.3
Observation	0	3.4	5.5	5.5	6.9	6.9

Pelzer U. et al. *J Clin Oncol* 2015; 33:2028-2034

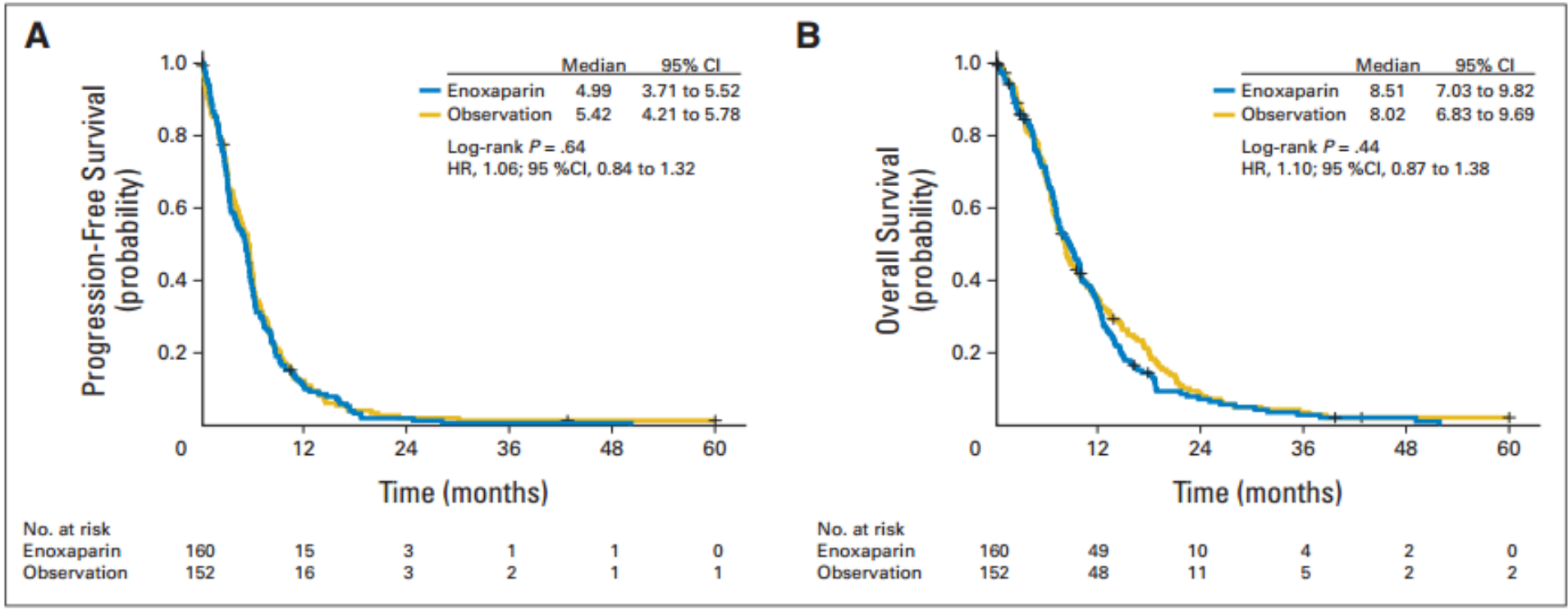
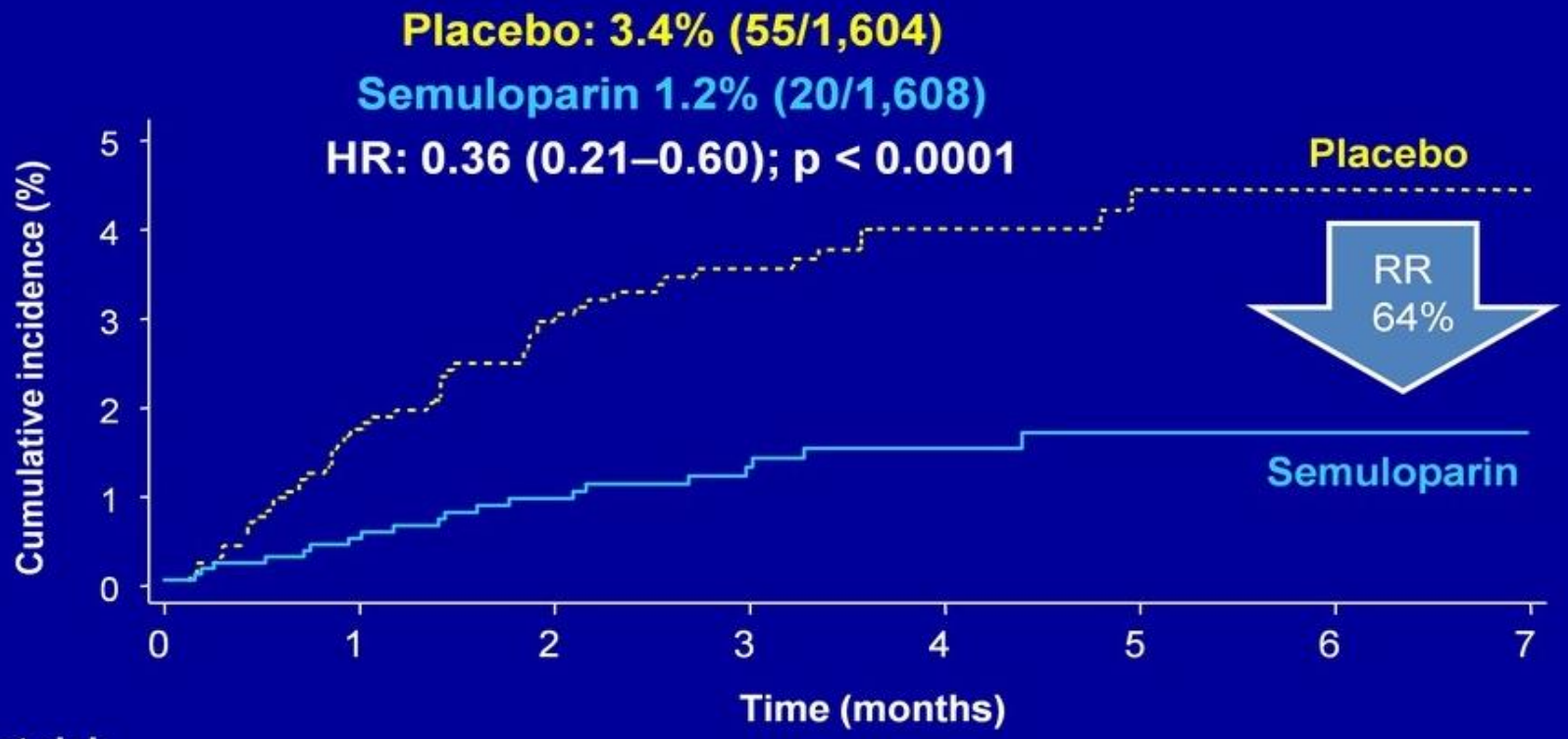


Fig 4. Kaplan-Meier curve for (A) progression-free and (B) overall survival. HR, hazard ratio.

SAVE-ONCO: primary efficacy end-point
Composite of symptomatic DVT and any PE



Number at risk

Placebo	1,604	1,375	1,212	985	689	403	201	92
Semuloparin	1,608	1,410	1,227	986	681	384	197	77

Agnelli G, et al. J Clin Oncol. 2011;29 Suppl:[abstract LBA9014].

Thromboprophylaxis of DVT and PE

SO WHAT DO GUIDELINES TELL US?

ESMO Clinical Practice Guidelines

Establishing the highest standards of clinical practice is a collective effort of the whole oncology community. The ESMO Clinical Practice Guidelines, prepared and reviewed by leading experts, help you provide patients with the best care options.

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clinical practice guidelines

Annals of Oncology 22 (Supplement 6): vi85–vi92, 2011
doi:10.1093/annonc/mdr392

Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines

M. Mandalà[1], A. Falanga[2] & F. Roila[3]

On behalf of the ESMO Guidelines Working Group*

[1]*Unit of Medical Oncology;* [2]*Division Immunohaematology and Transfusion Medicine, Haemostasis and Thrombosis Center, Department of Oncology and Haematology, Ospedali Riuniti, Bergamo;* [3]*Department of Medical Oncology, S. Maria Hospital, Terni, Italy*

Chemotherapy: guideline recommendations for VTE prophylaxis in ambulatory cancer patients

	ASCO 2015[1]	ACCP 2012[2]	ESMO 2012[3]	NCCN 2011[4]
Ambulatory cancer patients receiving outpatient chemotherapy	1) Routine thromboprophylaxis during systemic chemotherapy is not recommended 2) But should be discussed in high risk population 3) Prophylaxis is recommended in myeloma patients receiving thalidomide or lenalidomide	Routine thromboprophylaxis is not recommended But consider in high risk population	Routine thromboprophylaxis is not recommended, But may be considered in high risk patients	1) Routine thromboprophylaxis is recommended for: •multiple myeloma patients receiving thalidomide or lenalidomide in combination with high dose dexamethasone or doxirubicin or multi-agent chemotherapy •myeloma patients with 2 or more risk factors 2) Consider prophylaxis in other outpatients at risk

1. Lyman GH, et al. J Clin Oncol. 2013
2. Chest. 2012;133:381S-453S.
3. Mandala M, et al. Ann Oncol. 2012
4. NCCN guidelines 2011: available from www.nccn.org/professionals/physician_gls/pdf/vte.pdf. Accessed August 2011.

VTE RISK ASSESSMENT: ASCO AND ESMO GUIDELINES

- Cancer patients should be assessed for VTE risk at the time of chemotherapy initiation and periodically thereafter.
- Individual risk factors, including biomarkers or cancer site, do not reliably identify cancer patients at high risk of VTE.
- In the outpatient setting, risk assessment can be conducted based on a validated risk assessment tool.

ASCO AND ESMO GUIDELINES: MULTIPLE MYELOMA

Patients with multiple myeloma receiving thalidomide- or lenalidomide- based regimens with chemotherapy and/or dexamethasone should receive pharmacologic thromboprophylaxis with either aspirin or LMWH for lower-risk patients and LMWH for higher-risk patients.

Table 1. Predictive model for chemotherapy-associated VTE in ambulatory cancer patients

	Risk score
Cancer-related risk factors	
Site of cancer and tumour histotype	
Very high risk (stomach adenocarcinoma, pancreas adenocarcinoma)	2
High risk (lung, lymphoma, gynaecological, bladder, testicular)	1
Haematological risk factors	
Prechemotherapy platelet count ≥350 000/μl	1
Haemoglobin <10 g/dl or use of ESA growth factors	1
Prechemotherapy leukocyte count >11 000/μl	1
Patient-related risk factor	
Body mass index ≥35 kg/m^2	1

The rates of VTE were as follows: low-risk category (score = 0), 0.5%; intermediate-risk category (score = 1–2), 2%; high-risk category (score ≥3), 7%.
ESA, erythropoiesis-stimulating agents VTE, venous thromboembolism.

ESMO Guidelines

International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer

Dominique Farge, Henri Bounameaux, Benjamin Brenner, Francis Cajfinger, Philippe Debourdeau, Alok A Khorana, Ingrid Pabinger, Susan Solymoss, James Douketis, Ajay Kakkar

Venous thromboembolism (VTE) is the second leading cause of death in patients with cancer. These patients are at an increased risk of developing VTE and are more likely to have a recurrence of VTE and bleeding while taking anticoagulants. Management of VTE in patients with cancer is a major therapeutic challenge and remains suboptimal worldwide. In 2013, the International Initiative on Thrombosis and Cancer (ITAC-CME), established to reduce the global burden of VTE in patients with cancer, published international guidelines for the treatment and prophylaxis of VTE and central venous catheter-associated thrombosis. The rapid global adoption of direct oral anticoagulants for management of VTE in patients with cancer is an emerging treatment trend that needs to be addressed based on the current level of evidence. In this Review, we provide an update of the ITAC-CME consensus recommendations based on a systematic review of the literature ranked according to the Grading of Recommendations Assessment, Development, and Evaluation scale. These guidelines aim to address in-hospital and outpatient cancer-associated VTE in specific subgroups of patients with cancer.

Lancet Oncol 2016; 17: e452–66

Assistance Publique-Hôpitaux de Paris, Internal Medicine: Autoimmune and Vascular Disease Unit, Saint-Louis Hospital, Paris, France (Prof D Farge MD); **Sorbonne Paris Cité, Paris 7 Diderot University, Paris, France** (Prof D Farge); **Division of Angiology and Hemostasis, University Hospitals of Geneva and Faculty of Medicine, University of Geneva, Geneva, Switzerland** (Prof H Bounameaux MD);

Conclusion: ambulatory patients

- Does an absolute gain of 3-5% of VTE incidence justify the treatment of >90% of patients who shall not benefit but have to give themselves a daily injection for the rest of their life, without (?) improvement of OS?
- There is at present no final marker allowing to select out the high risk group within Ca patients.
- The clinician needs to discuss the situation with the high risk patient and may give prophylactic treatment


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Thank you