

# CANCRO-TROMBOSI LINEE GUIDA TEV

Mario Mandalà

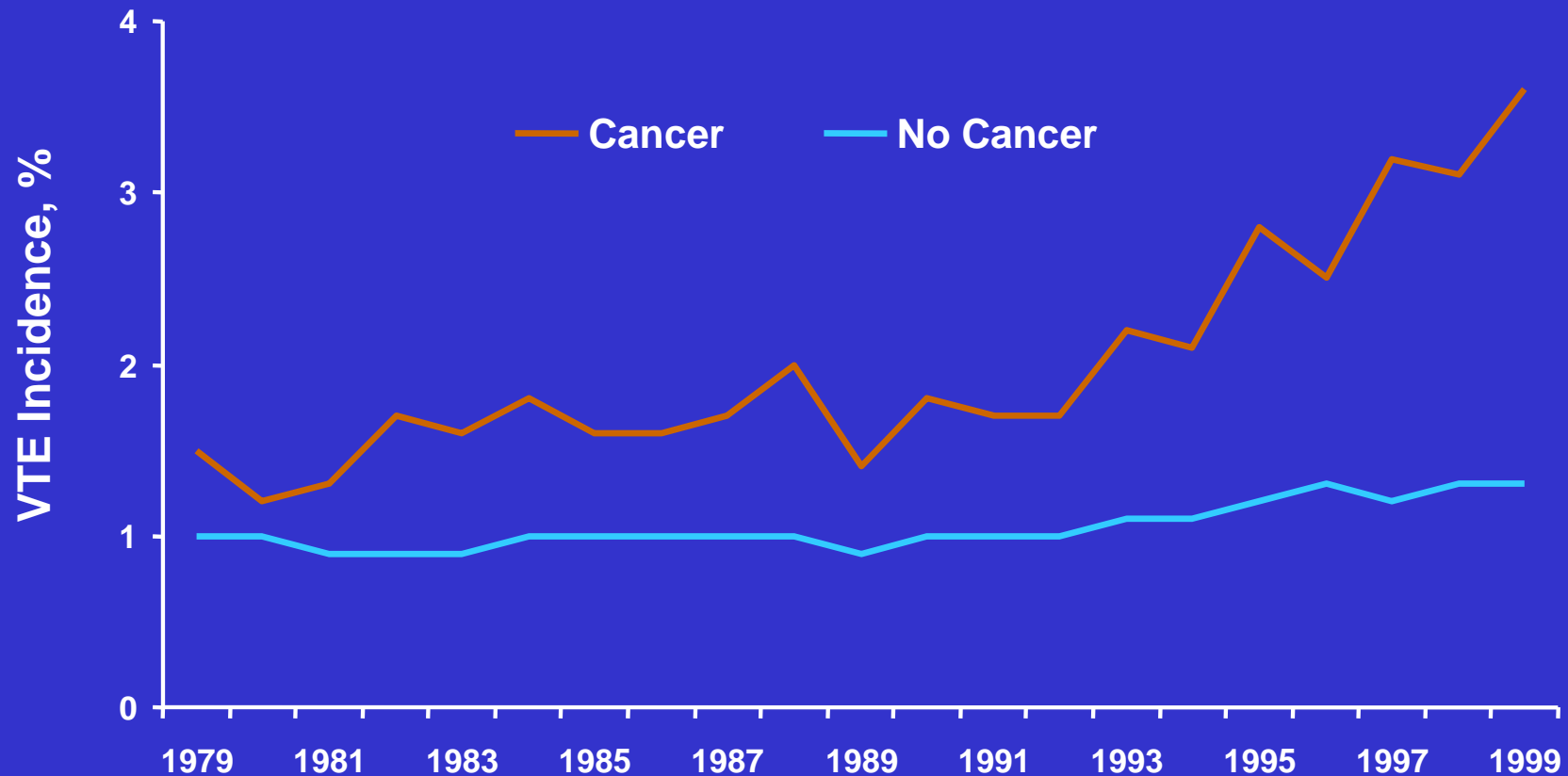
U.O. Oncologia

Ospedali Riuniti Bergamo,



*Torino, 10 Ottobre 2011*

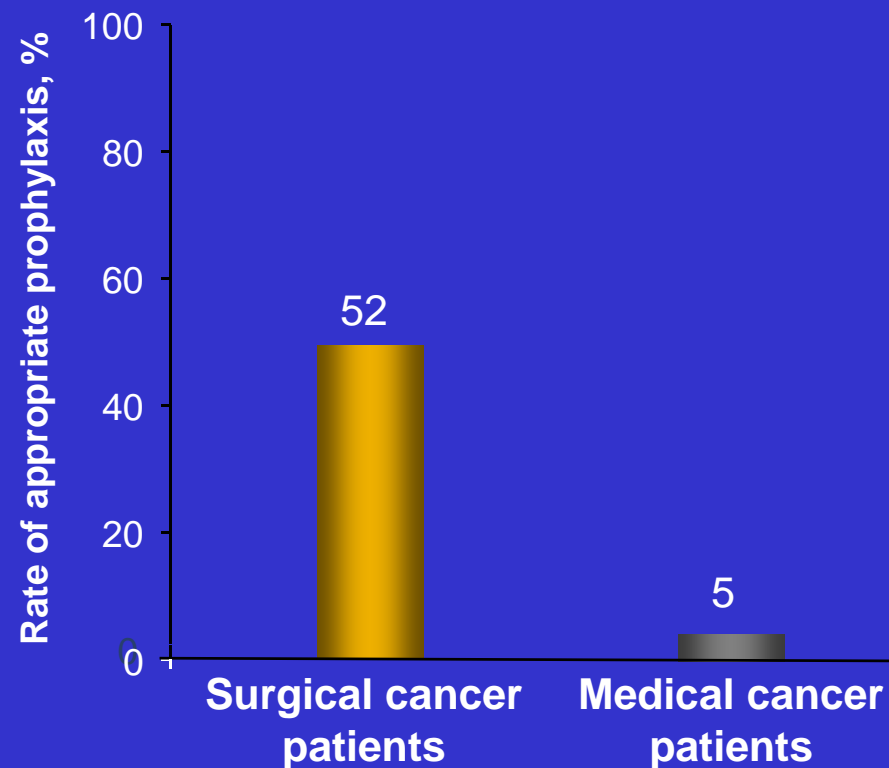
# Incidence of VTE in US Cancer Patients: 1979-1999



National Hospital Discharge Survey data.  
Stein PD et al. *Am J Med.* 2006;119:60-68.

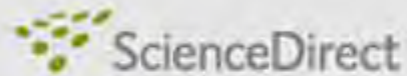
# FRONTLINE survey: rate of appropriate thromboprophylaxis in clinical practice

- A comprehensive global survey on thrombosis in cancer
- A questionnaire was distributed globally to clinicians involved in cancer care
- 3,891 completed questionnaires were available for analysis





available at [www.sciencedirect.com](http://www.sciencedirect.com)



journal homepage: [www.ejconline.com](http://www.ejconline.com)

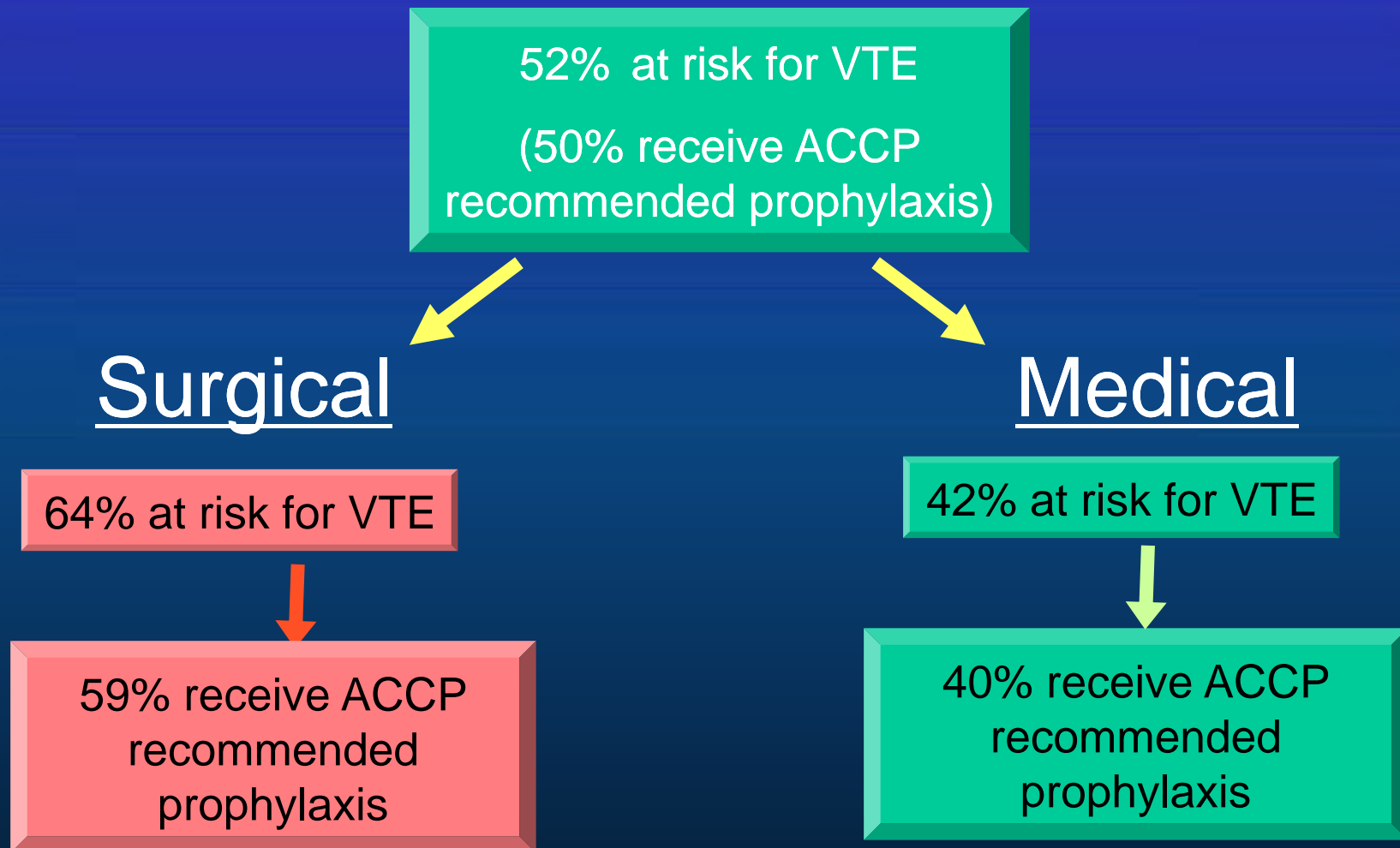


2 **Incidence and clinical implications of venous**  
3 **thromboembolism in advanced colorectal cancer patients: The**  
4 **'GISCAD-alternating schedule' study findings**

M. Mandalà on behalf of GISCAD Group

EUR J CANCER 2009

# ENDORSE: 68,183 Patients



**IN QUALI PAZIENTI E'  
PIU' FREQUENTE?**

# PER RICORDARSI

- DOVE: dove vediamo il paziente
- COME: Come è estesa la malattia
- QUANDO: storia naturale, CT o No



# DUE GRUPPI DI PAZIENTI

- **Ospedalizzati**

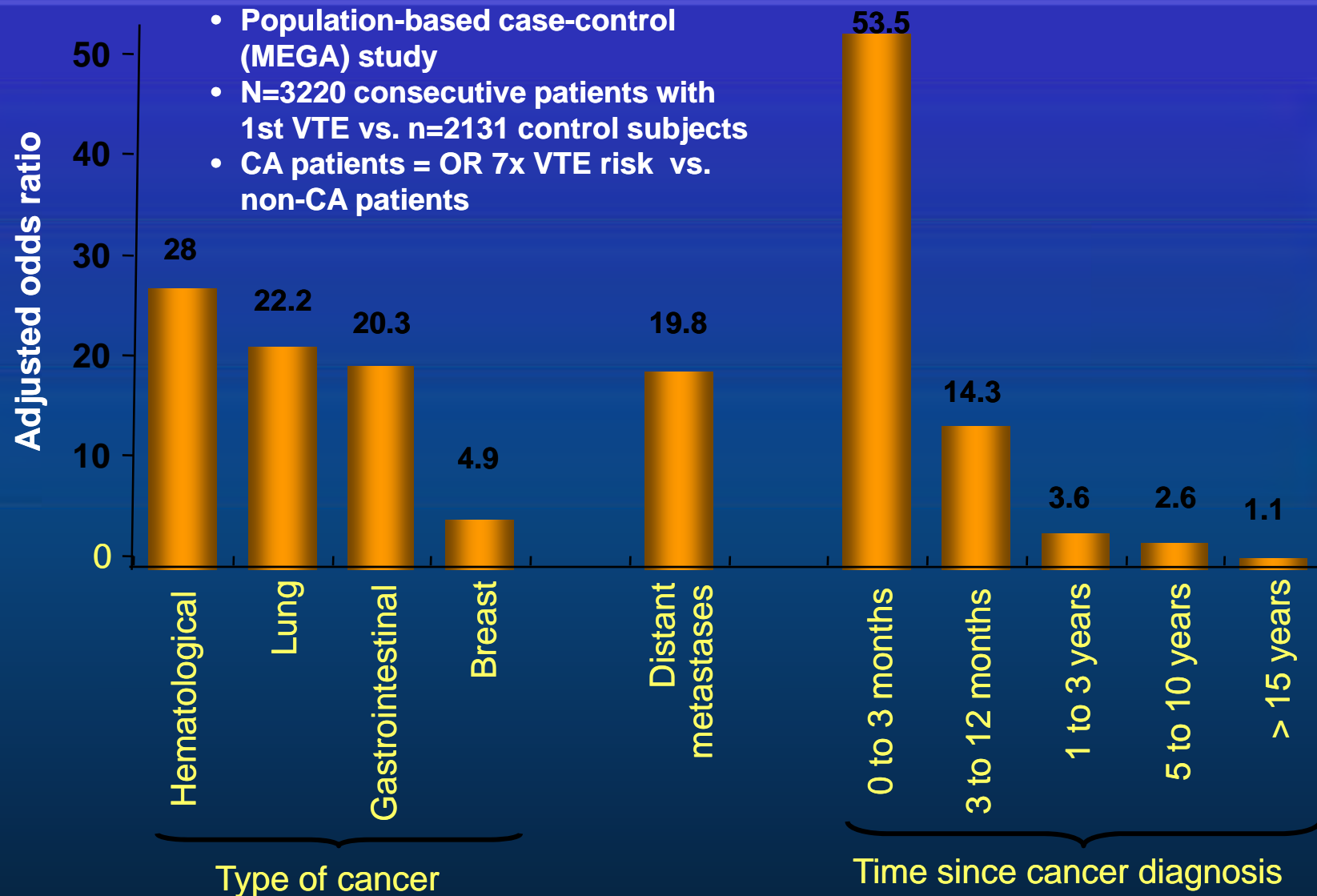
- Chemioterapia
- Allettamento
- Evento acuto
- Trasfusione
- G-CSF
- Polipatologie
- Malattia avanzata

- **Ambulatoriali**

- Chemioterapia
- Polipatologie

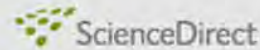


# Effect of Malignancy on Risk of Venous Thromboembolism (VTE)





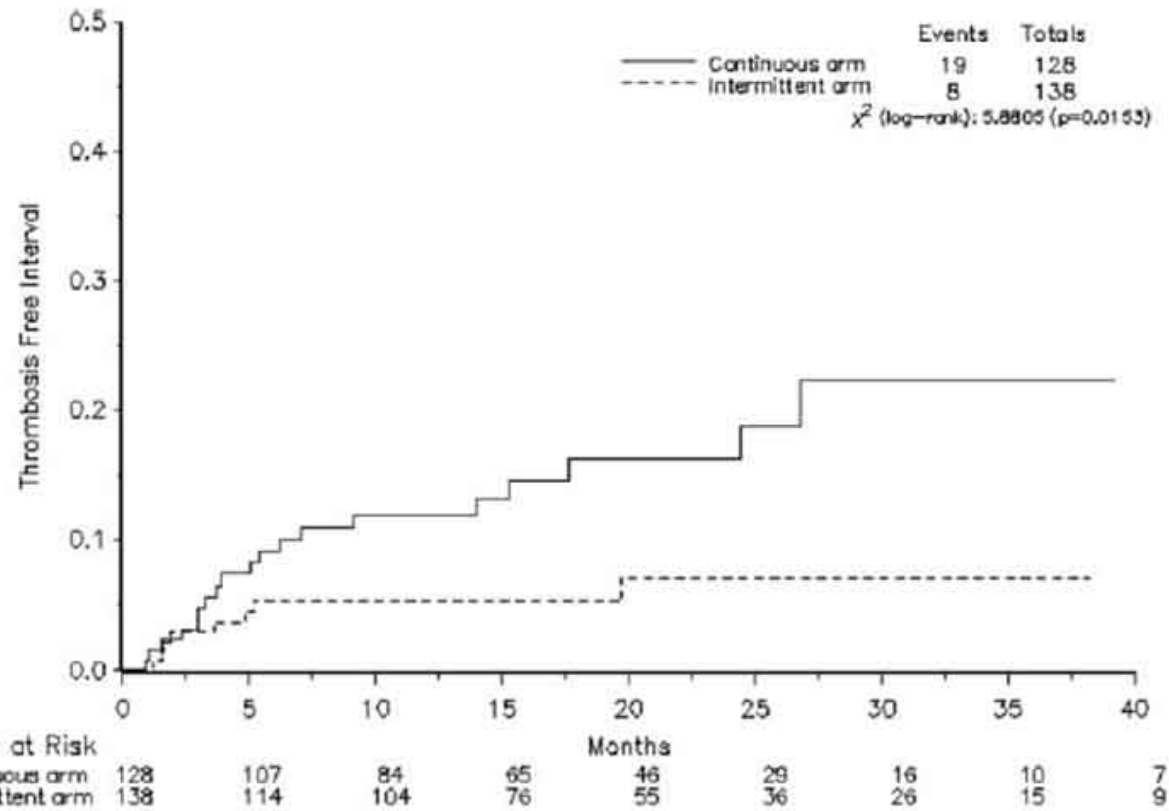
available at [www.sciencedirect.com](http://www.sciencedirect.com)



journal homepage: [www.ejconline.com](http://www.ejconline.com)



2 Incidence and clinical implications of venous  
3 thromboembolism in advanced colorectal cancer patients: The  
4 'GISCAD-alternating schedule' study findings



# CLINICAL SCORE PER TEV

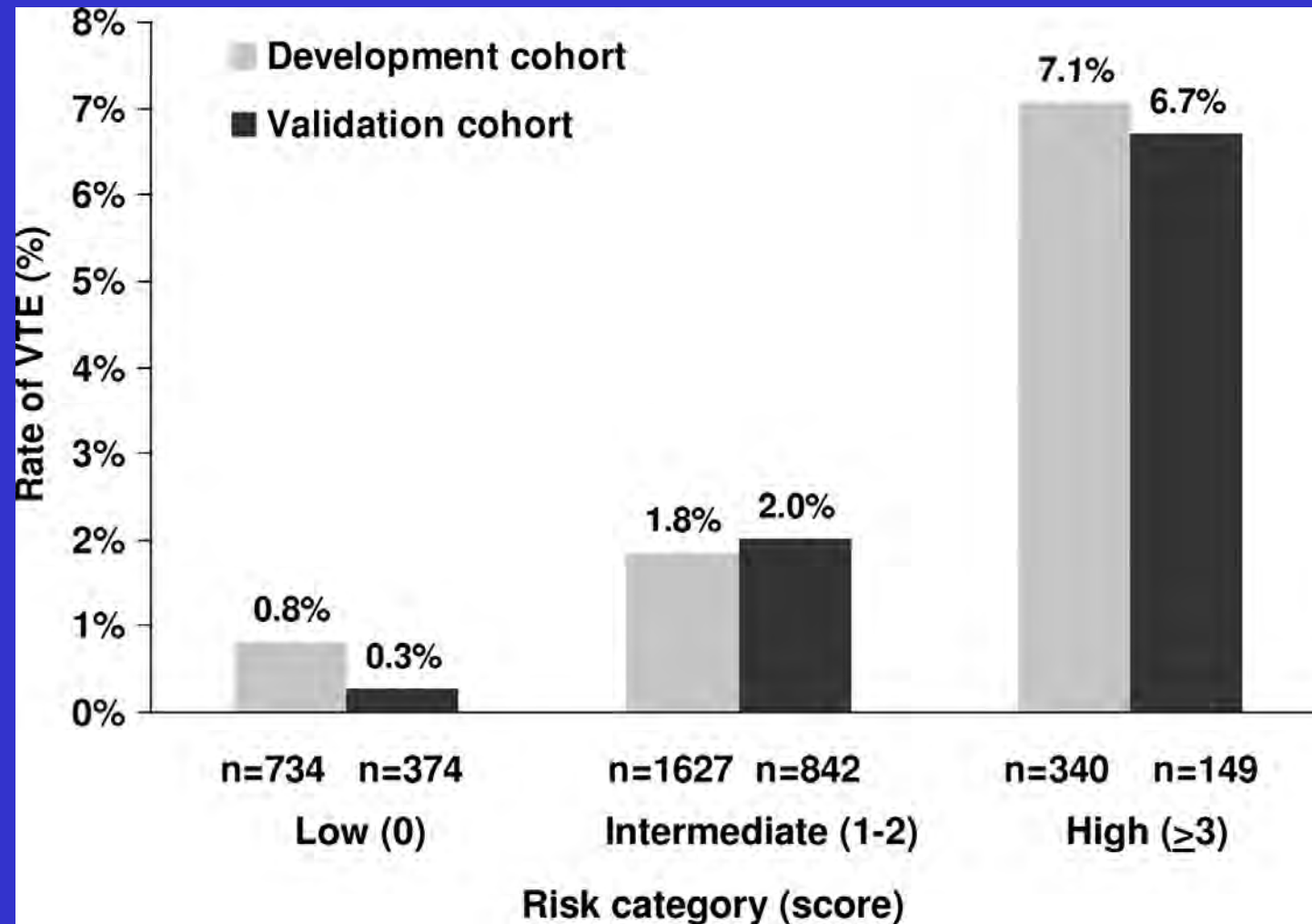
**Table 2. Predictors of venous thromboembolism in the derivation cohort by multivariate logistic regression analysis**

Patient characteristic	$\beta$	Odds ratio* (95% CI)
<b>Site of cancer</b>		
Very high risk (stomach, pancreas)	1.46	4.3 (1.2-15.6)
High risk (lung, lymphoma, gynecologic, genitourinary excluding prostate)	0.43	1.5 (0.9-2.7)
Low risk (breast, colorectal, head and neck)	0.0	1.0 (reference)
Prechemotherapy platelet count $350 \times 10^9/L$ or more	0.60	1.8 (1.1-3.2)
Hemoglobin level less than 100 g/L or use of red cell growth factors	0.89	2.4 (1.4-4.2)
Prechemotherapy leukocyte count more than $11 \times 10^9/L$	0.77	2.2 (1.2-4)
BMI $35 \text{ kg/m}^2$ or more	0.90	2.5 (1.3-4.7)

\*Odds ratios are adjusted for stage.

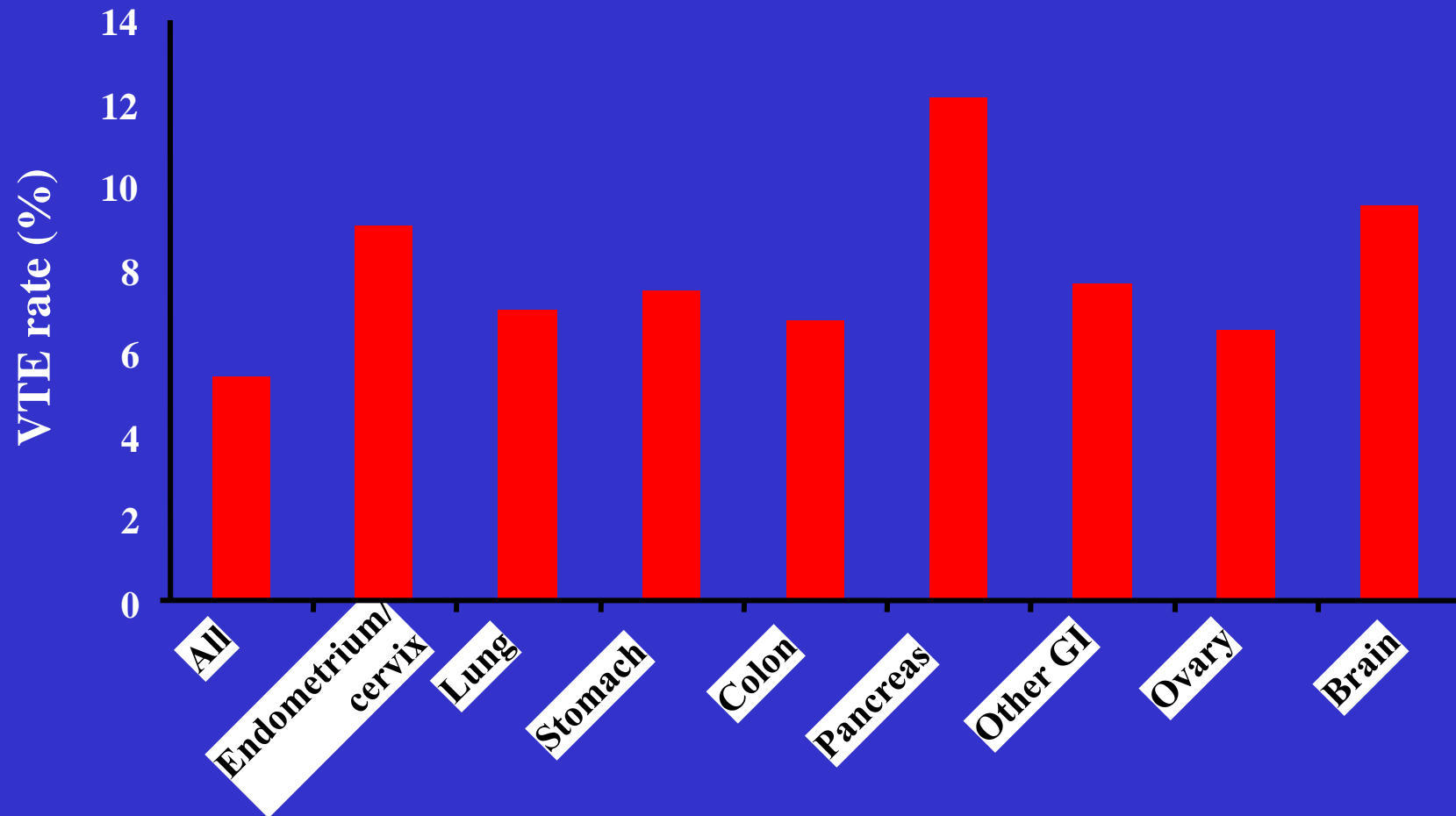
**Khorana, A. A. et al. Blood 2008;111:4902-4907**

# RATE OF VTE: CLINICAL SCORE



Khorana, A. A. et al. Blood 2008;111:4902-4907

# Risk in hospitalised patients



Khorana AA, et al. J Clin Oncol. 2006;24:484-90.

# VTE IN PHASE 1 STUDIES

# **VTE COMPLICATIONS IN PHASE 1 SENDO EXPERIENCE**

**Mandala et al. Ann Oncol in press**

- **Phase I trials are dose- and toxicity-defining studies to identify dose levels of novel drugs or combinations potentially worthy for further evaluation in phase II trials.**
- **The clinical benefits may be limited, whereas, potentially, the risks of toxicity may be considerable.**

# **VTE COMPLICATIONS IN PAHSE 1 SENDO EXPERIENCE**

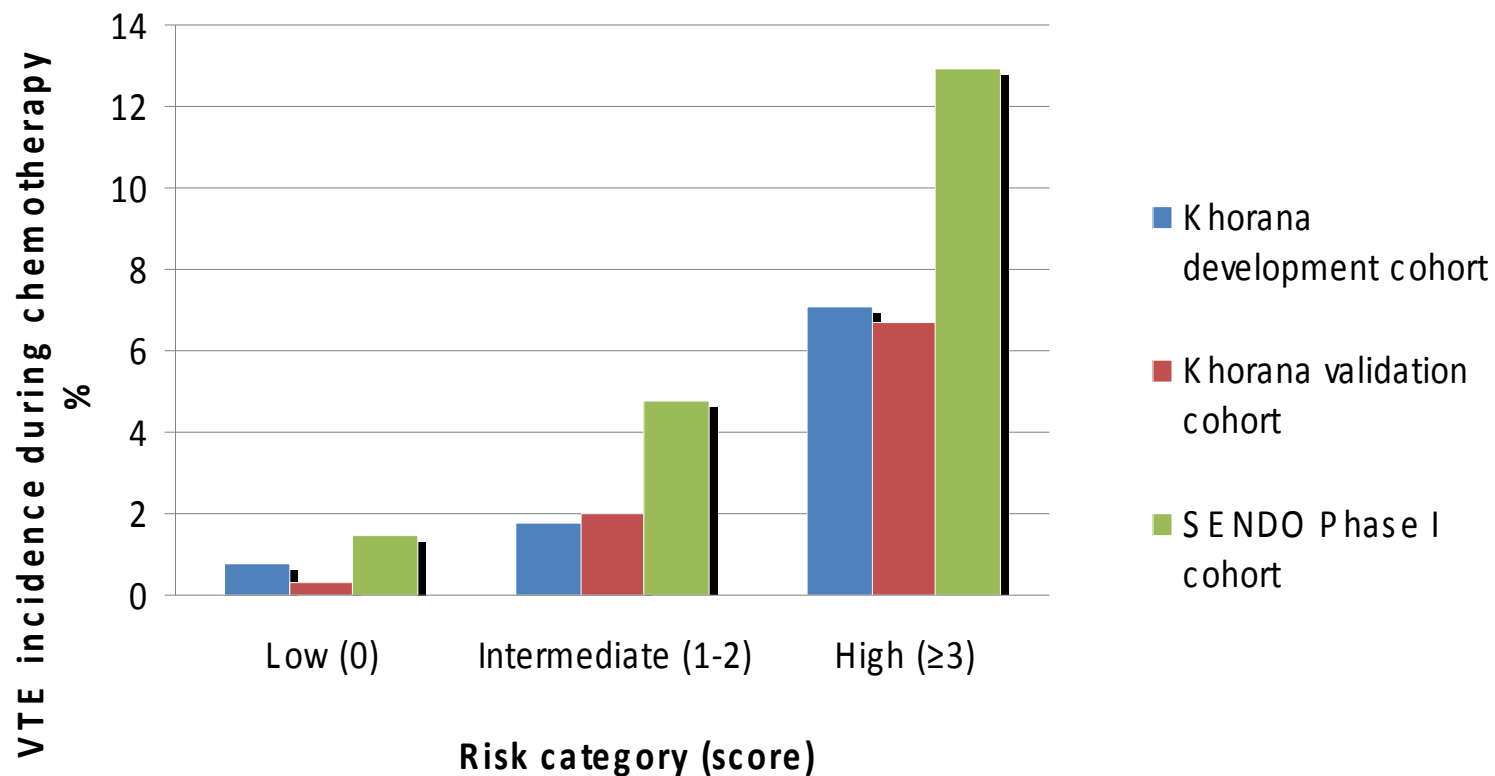
**Mandala et al. Ann Oncol in press**

- **25% of patients developing VTE complications cannot complete the planned clinical study.**

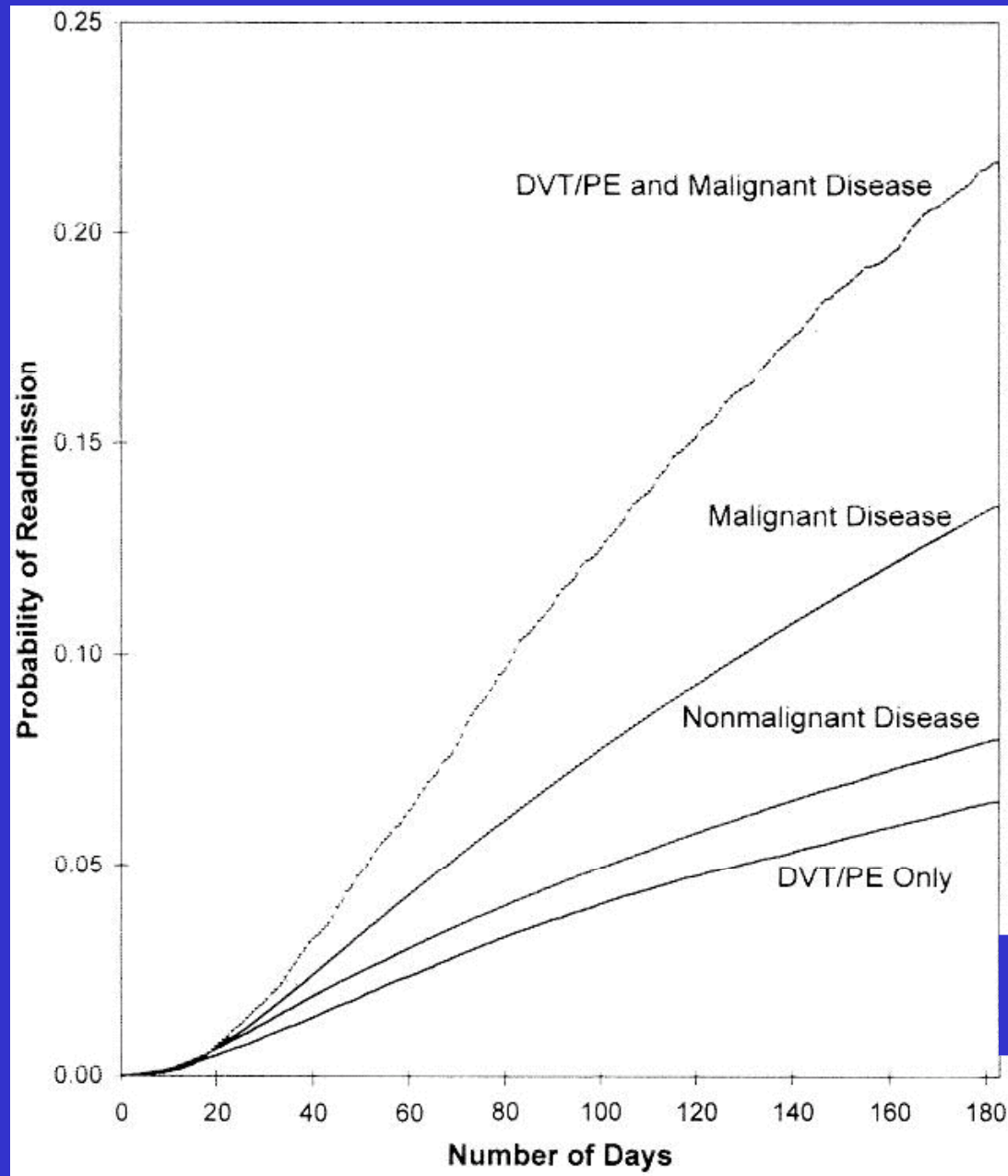


# VTE incidence according to scores from the risk model in the Khorana cohorts versus SENDO phase I cohort.

Mandala et al. Ann Oncol in press

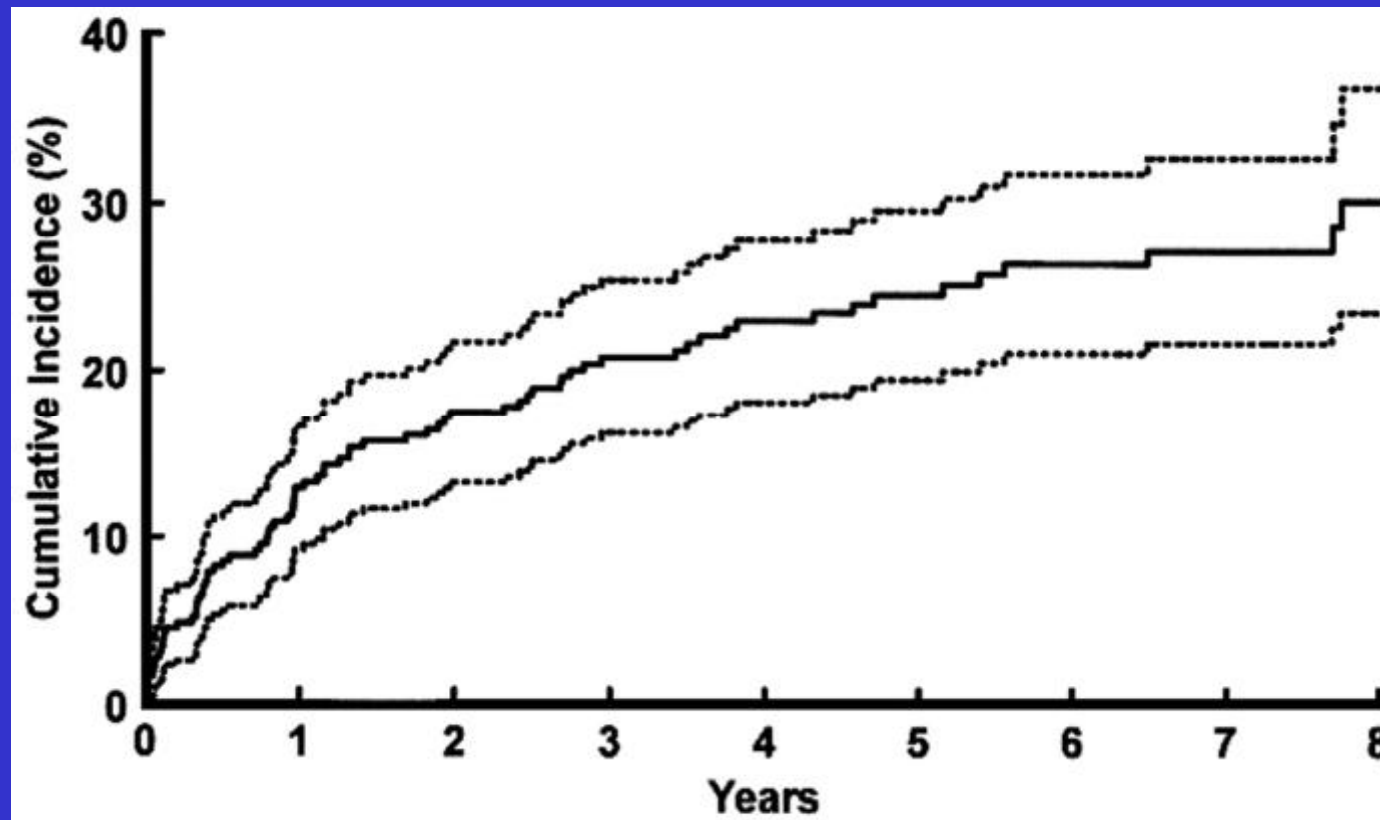


# BACK TO HOSPITAL



Levitan,  
Medicine 1999

## The cumulative incidence of recurrent venous thromboembolism in patients with a first episode of symptomatic deep venous thrombosis



Prandoni, P. et. al. Ann Intern Med 1996;125:1-7

# LINEE GUIDA TEV E CANCRO

ASCO<sup>1</sup>, <sup>2</sup>ESMO, <sup>3</sup>NCCN, Guidelines, ISTH  
in process

<sup>1</sup>LYMAN JCO

<sup>2</sup>MANDALA ANN ONCOL

<sup>3</sup>Streiff NCCN WS

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# **Primary Thromboprophylaxis**

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# Prophylaxis in Acutely Ill Hospitalised Medical Patients

- No randomized clinical trials designed *a priori* for hospitalized medical cancer patients
- Randomized, placebo-controlled trials in acutely ill hospitalized medical patients
  - MEDENOX<sup>1</sup> - enoxaparin 40 mg daily
  - PREVENT<sup>2</sup> - dalteparin 5000U daily
  - ARTEMIS<sup>3</sup> - fondaparinux 2.5 mg daily

1. Samama MM, et al. N Engl J Med 1999;341:793-800

2. Leizorovicz A, et al. Circulation 2004;110:874-879

3. Cohen AT, et al. Blood 2003; 102(11): 15a

# Thromboprophylaxis of Medical Patients: Clear Benefits Over Placebo

Study	RRR	NNT	Prophylaxis	Patients with VTE, %
MEDENOX <sup>1</sup> <i>P</i> <0.001	63%	10	Placebo	14.9* (n=288)
			Enoxaparin 40 mg	5.5 (n=291)
PREVENT <sup>2</sup> <i>P</i> =0.0015	45%	45	Placebo	5.0 (n=1,473) <sup>†</sup>
			Dalteparin	2.8 (n=1,518)
ARTEMIS <sup>3</sup> <i>P</i> =0.029	47%	20	Placebo	10.5 <sup>‡</sup> (n=323)
			Fondaparinux	5.6 (n=321)

\*VTE at day 14; <sup>†</sup>VTE at day 21; <sup>‡</sup>VTE at day 15.

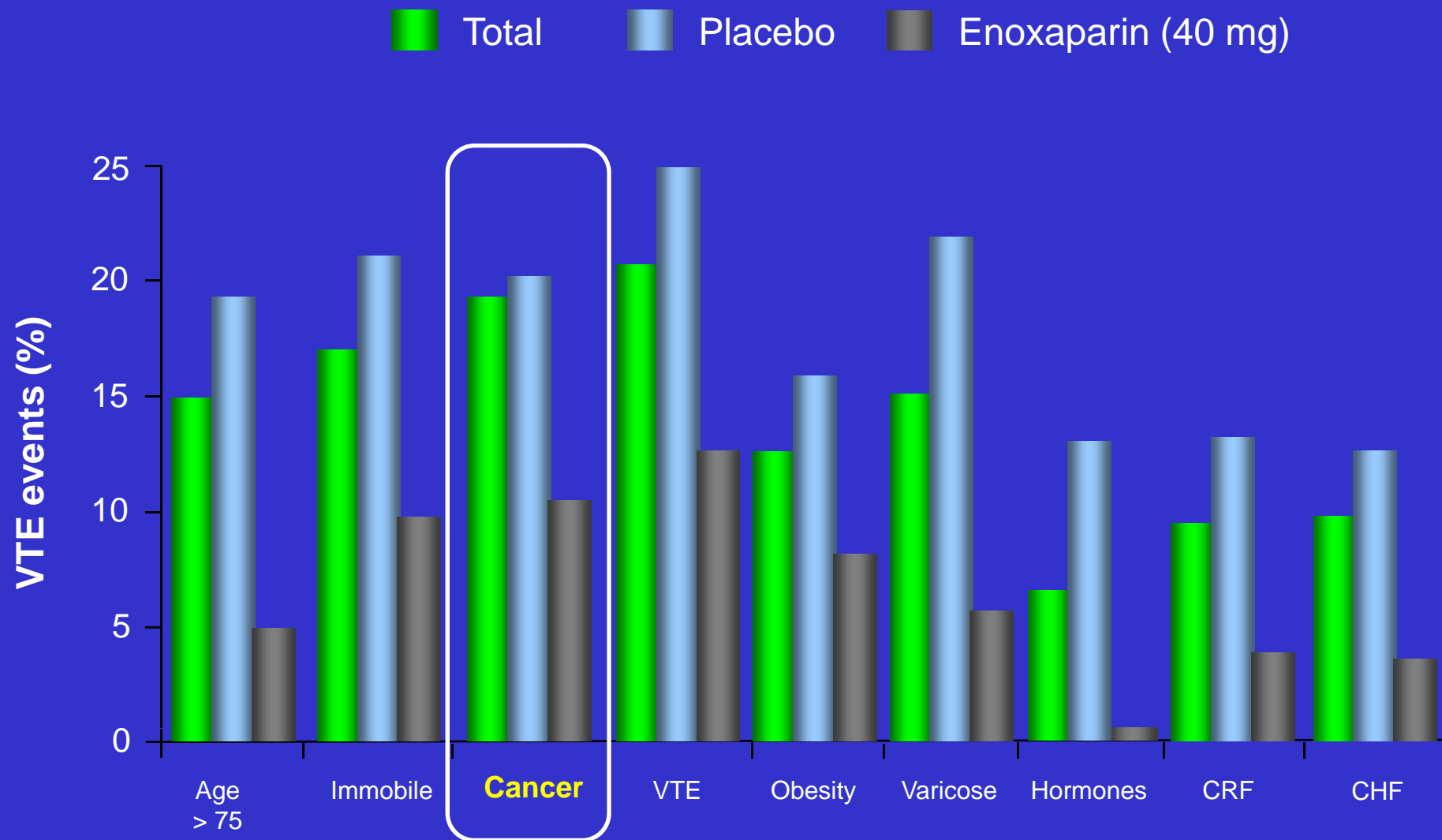
NNT = number needed to treat;  
RRR = relative risk reduction.

<sup>1</sup>Samama MM, et al. N Engl J Med. 1999;341:793-800.

<sup>2</sup>Leizorovicz A, et al. Circulation. 2004;110:874-9.

<sup>3</sup>Cohen AT, et al. Br Med J 2006; .....

# MEDENOX sub-analysis: VTE prophylaxis decreases the rate of VTE events also in cancer patients



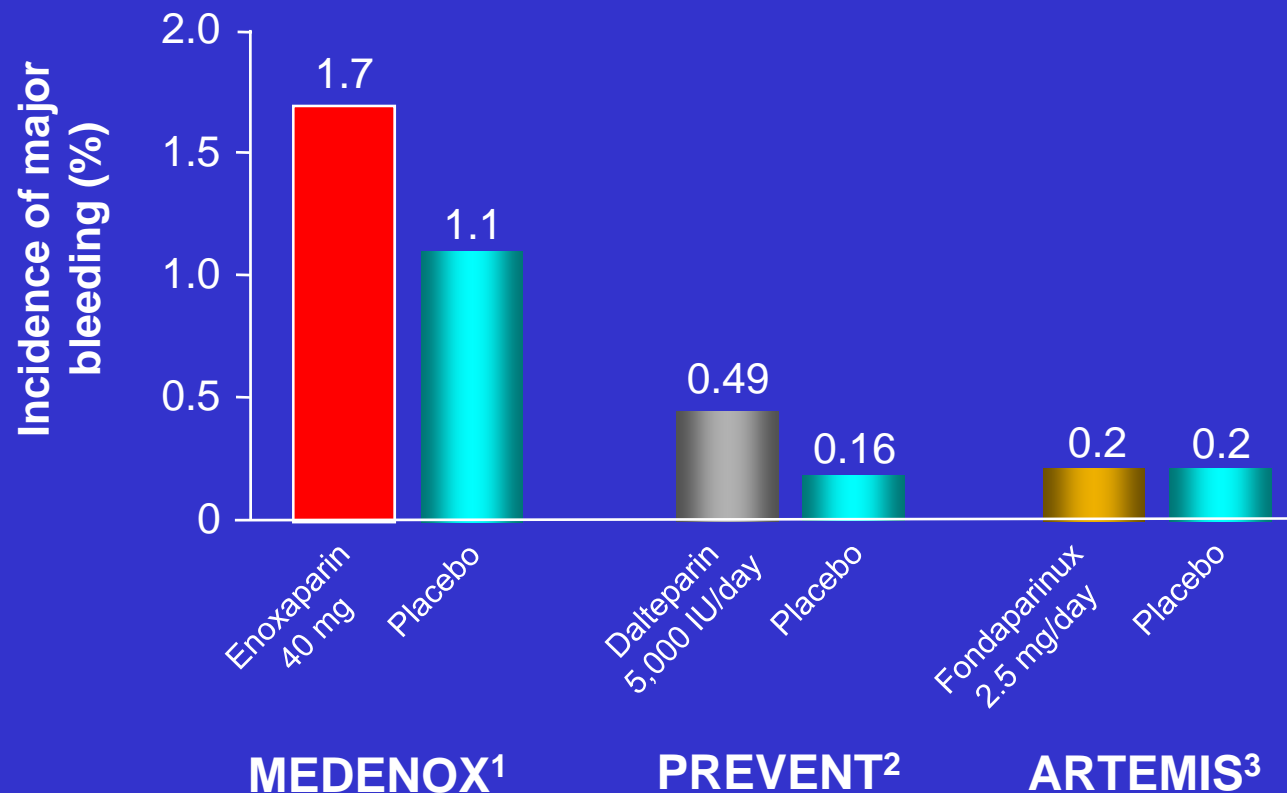


# Identification of patients at risk for VTE

Feature	Score
Cancer	3
Previous VTE	3
Hypercoagulability	3
Recent major surgery	2
Advanced age	1
Obesity	1
Bed rest	1
Hormonal treatment	1

Kucher N, et al. N Engl J Med. 2005;352:969-77.  
Prandoni P, Samama MM. Br J Haematol. 2008;141:587-97.

# MEDENOX, PREVENT, ARTEMIS: safety



1. Samama MM, et al. N Engl J Med. 1999;341:793-800.
2. Leizorovicz A, et al. Circulation. 2004;110:874-9.
3. Cohen AT, et al. Br Med J. 2006;332:325-9.

# Hospitalized medical cancer patients: guideline recommendations for VTE prophylaxis

	ASCO 2007 <sup>1</sup>	ACCP 2008 <sup>2</sup>	ESMO 2011 <sup>3</sup>	NCCN 2011 <sup>4</sup>
<b>Hospitalized medical cancer patients confined to bed with an acute medical illness</b>	<b>Should be considered candidates for VTE prophylaxis in the absence of bleeding or other contraindications to anticoagulation</b>	<b>Routine thromboprophylaxis is as for other high risk medical patients is recommended</b>	<b>Prophylaxis with UFH, LMWH or fondaparinux is recommended</b>	<b>Thromboprophylaxis recommended for all inpatients with active cancer who do not have a contraindication</b>

1. Lyman GH, et al. J Clin Oncol. 2007;25:5490-505.

2. Geerts WH, et al. Chest. 2008;133:381S-453S.

3. Mandala M, et al. Ann Oncol. 2011;21:274-6.

4. NCCN guidelines 2011: available from [www.nccn.org/professionals/physician\\_gls/pdf/vte.pdf](http://www.nccn.org/professionals/physician_gls/pdf/vte.pdf) . Accessed August 2011.

# **Double Blind Randomized Trial of Very-low-dose Warfarin (INR 1.3-1.9) for Prevention of Thromboembolism in Stage IV Ambulatory Breast Cancer**

<b>Patients *</b>	<b>Warfarin n=152</b>	<b>Placebo n=159</b>	<b>p=</b>
<b>Thromboembolic events</b>	<b>1</b>	<b>7</b>	<b>0.031</b>

**relative risk reduction = 85%**

**\* women receiving chemotherapy for metastatic breast cancer**

# Primary prophylaxis during chemotherapy: LMWH recent closed studies

Study	Cancer
TOPIC-1 <sup>1</sup>	Breast cancer
TOPIC-2 <sup>1</sup>	Non-small-cell lung cancer
PRODIGE <sup>2</sup>	Malignant glioma (Grade III or IV)
PROTECHT <sup>3</sup>	Lung, breast, gastrointestinal, ovarian, head/neck cancer
SAVE-ONCO <sup>4</sup>	Lung, colon-rectum, stomach, ovary, pancreas, or bladder

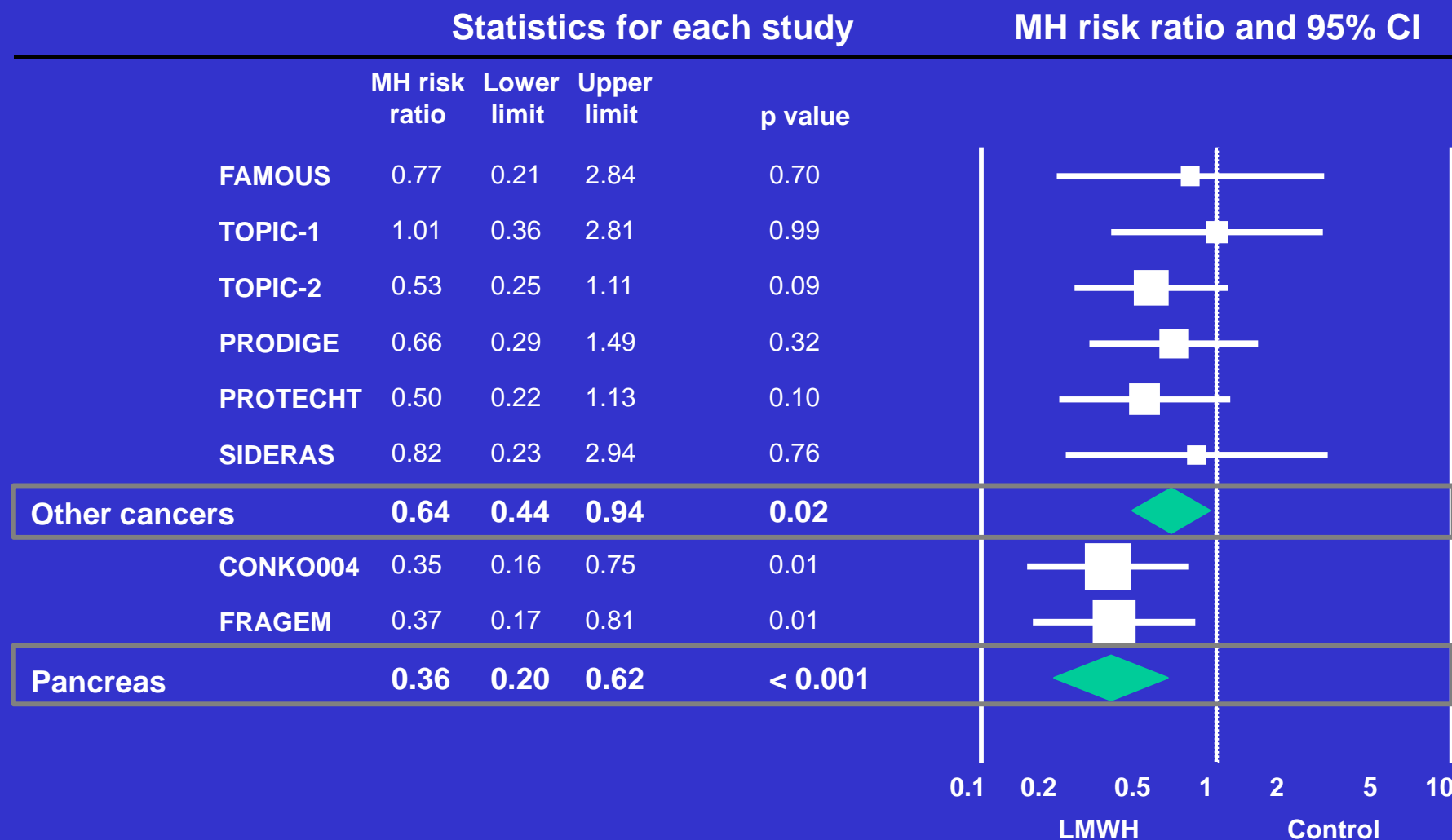
1. Haas SK, et al. J Thromb Haemost. 2005;3 Suppl 1:abstract OR059.

2. Perry JR, et al. J Thromb Haemost. 2010;8:1959-65.

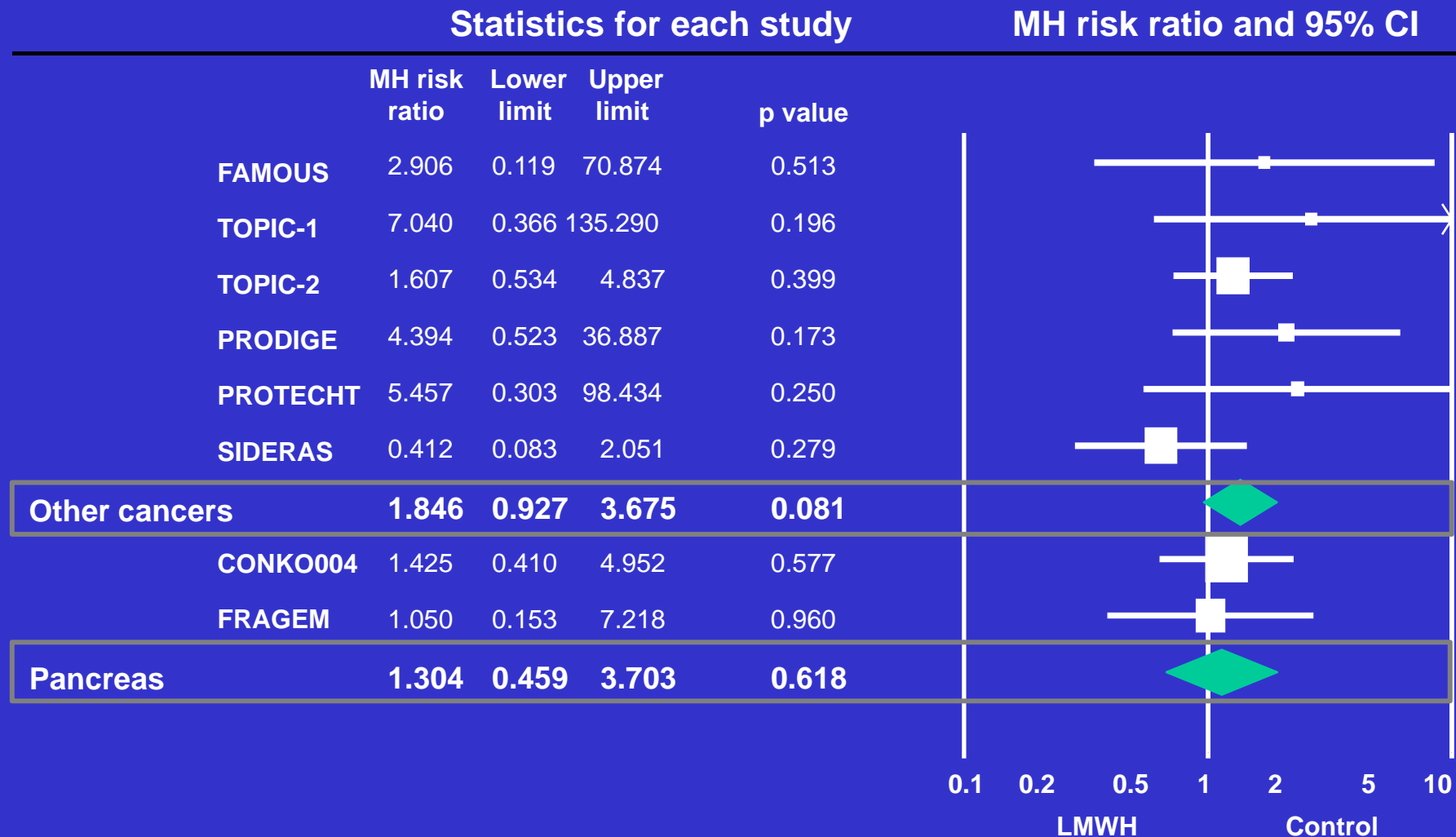
3. Agnelli G, et al. Lancet Oncol. 2009; 10: 943-9.

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

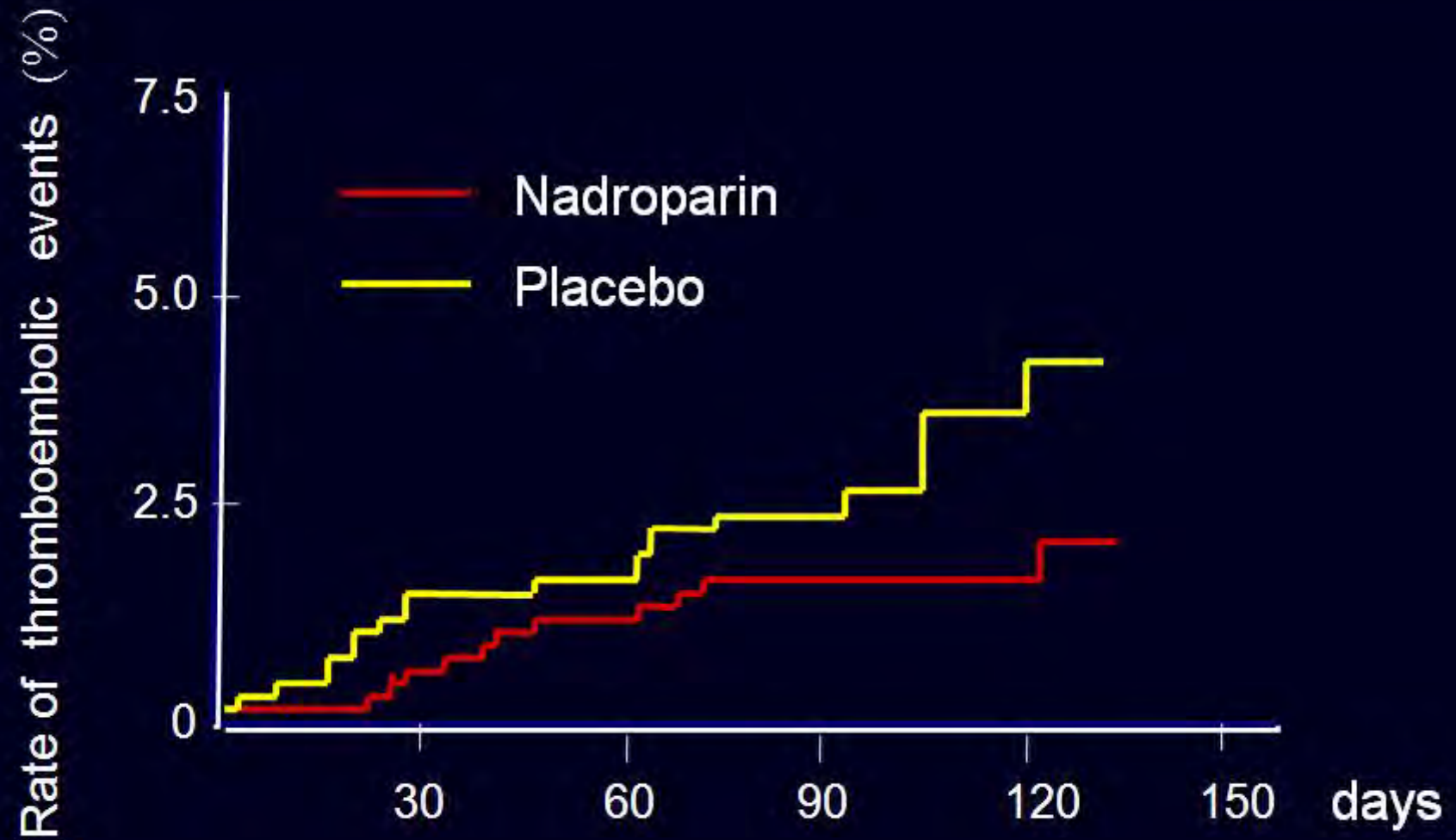
# Prophylaxis in medical outpatients: efficacy (VTE)



# Prophylaxis in medical outpatients: safety (major bleeding)



## Thromboembolic events: cumulative event rate





## Thromboembolic events by treatment and cancer site

	Nadroparin (15/769)	Placebo (15/381)	All (30/1150)
Lung *	7/199 (3.5%)	7/80 (8.8%)	14/279 (5.0%)
GI	4/272 (1.5%)	4/148 (2.7%)	8/420 (1.9%)
Pancreas	3/36 (8.3%)	1/17 (5.8%)	4/53 (7.5%)
Other	1/262 (0.4%)	3/136 (2.2%)	4/398 (1.0%)

\* NNT = 18.7

# Ambulatory Patients ESMO Guidelines 2011

Mandala et al. Ann Oncol in press

Role of VTE Prophylaxis	Evidence
Routine prophylaxis with an antithrombotic agents is not recommended except as noted below	<b>Extensive prophylaxis in ambulatory patients receiving chemotherapy is not recommended, but may be considered for high risk patients</b>
LMWH or adjusted dose warfarin (INR ~ 1.5) is recommended in myeloma patients on thalidomide or lenalidomide plus chemotherapy or dexamethasone	<b>This recommendation is based on 1 randomised and several nonrandomized trials</b>

# **Electronic and “Human” Prophylaxis Alerts**

## **Implications for Cancer Patients**

View PtLookup

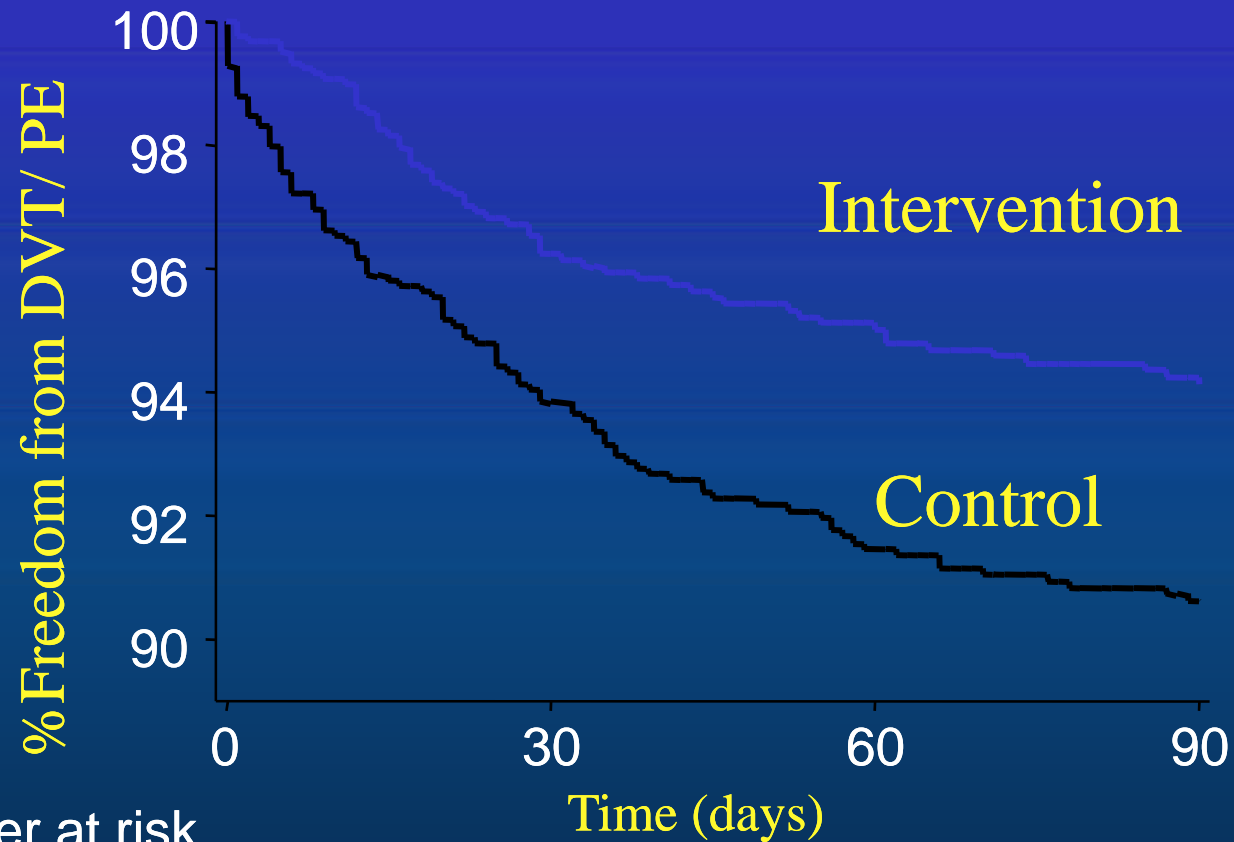
Patient: XXXXXXXX XXXX 76M 00000000 Adm: 09/02/2005 Room: 8B-312  
Time: 09:03 AM Mar 3, 2005 Alert #1681848 88 phone: x7725  
Alert: Patient is at high risk for deep vein thrombosis, according to BPH  
guidelines.  
Reason: Total DVT risk assessment score is 6.  
Patient does not have any active Anti-Embolic orders.  
Patient is currently NOT on a drug from ANTICOAGULANTS drug family.  
Relevant medications and lab results: <Alert Details>

Act- I 10 Order set: DVT Prophylaxis  
ions: I 10 Quick Ref: Prevention  
I 10 Exit to order entry

Covering M.D.: BPH  
<done>

<Not my patient> <Add M.D.> <Comments> <Logic>

# Primary End Point



Number at risk				
— Intervention	1255	977	900	853
— Control	1251	976	893	839

Kucher N, et al. NEJM 2005;352:969-977

# Electronic Alerts

## Halve Rate of PE and Maintain Effectiveness

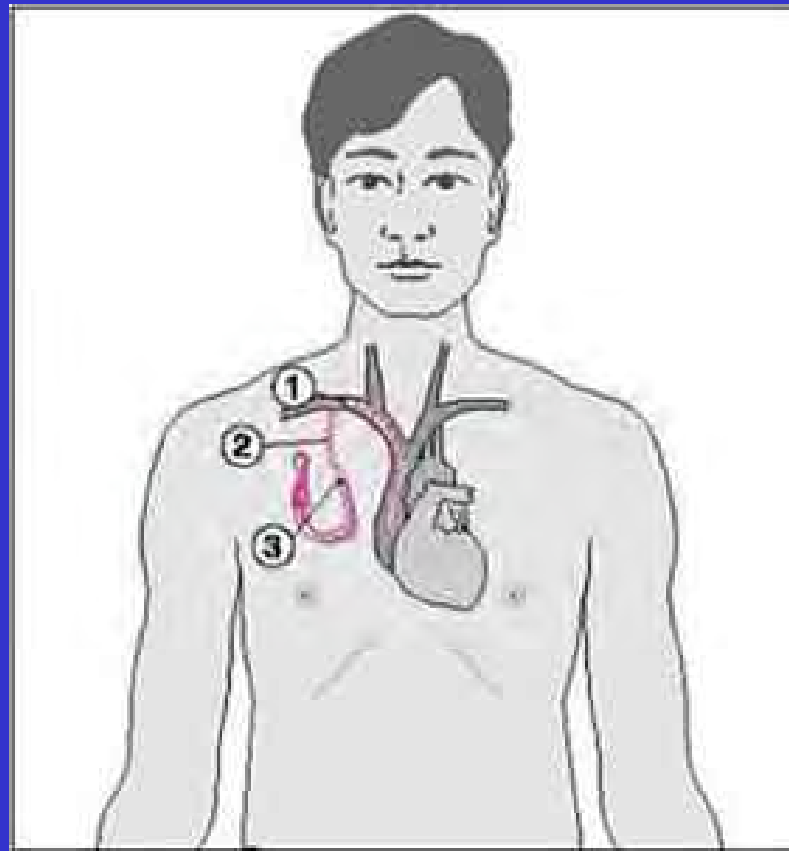
### VTE Rate:

Pre-Alert      2005—3.3/1000

Post-Alert      2006—1.7/1000

Post-Alert      2007—1.7/1000

# Central Venous Catheter (CVC) – Related Thrombosis



# Prophylaxis for CVC-related DVT: randomized trials

Author, year	Study design	N	Regimen	Duration	Endpoint assessment	DVT, %	p
Bern, 1990 <sup>1</sup>	P, open	82	Warfarin 1 mg No treatment	90 days	Mandatory venography	9.5 37.5	< 0.001
Monreal, 1996 <sup>2</sup>	P, open	29	Dalteparin 2,500 U No treatment	90 days	Mandatory venography	6 62	0.002
Couban, 2005 <sup>3</sup>	R, DB	255	Warfarin 1 mg Placebo	Variable	Symptomatic events	4.6 4.0	0.81
Verso, 2005 <sup>4</sup>	R, DB	385	Enoxaparin 40 mg Placebo	42 days	Mandatory venography	14.1 18.0	0.35
Karthus, 2006 <sup>5</sup>	R, DB	439	Dalteparin 5,000 U Placebo	16 weeks	Symptomatic events	3.7 3.4	0.88

1. Bern MM, et al. Ann Intern Med. 1990;112:423-8.
2. Monreal M, et al. Thromb Haemost. 1996;75:251-3.
3. Couban S, et al. J Clin Oncol. 2005;23:4063-9.
4. Verso M, et al. J Clin Oncol. 2005;23:4057-62.
5. Karthus M, et al. Ann Oncol. 2006;17:289-96.



# Prophylaxis of CVC - Related Thrombosis

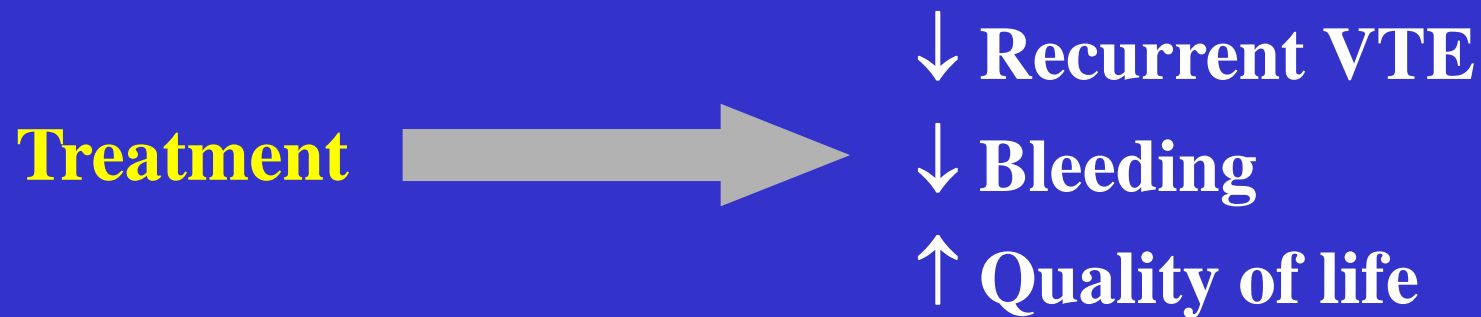
- The presence of CVC is a risk factor for VTE.
- Three recent clinical trials have assessed that the incidence of CVC-related symptomatic thrombosis is approximately 3% to 4%.
- These trials failed to show a significant effect of prophylaxis with 1 mg fixed dose warfarin, or LMWH dalteparin, or LMWH enoxaparin in reducing symptomatic and asymptomatic thrombosis in patients with cancer.

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# Therapy of established VTE in cancer patients

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# Optimising treatment of VTE in the cancer patient



# Standard Treatment of VTE

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**Initial treatment** (5 to 7 days)

**LMWH or UFH**

*Bridging*

**Long-term therapy** →  $\geq 3-6$  months

**Vitamin K antagonist (INR 2.0 - 3.0)**

# **Long-Term 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 invasive procedures**
- Venous access is difficult**
- There is increased risk of recurrence and bleeding**

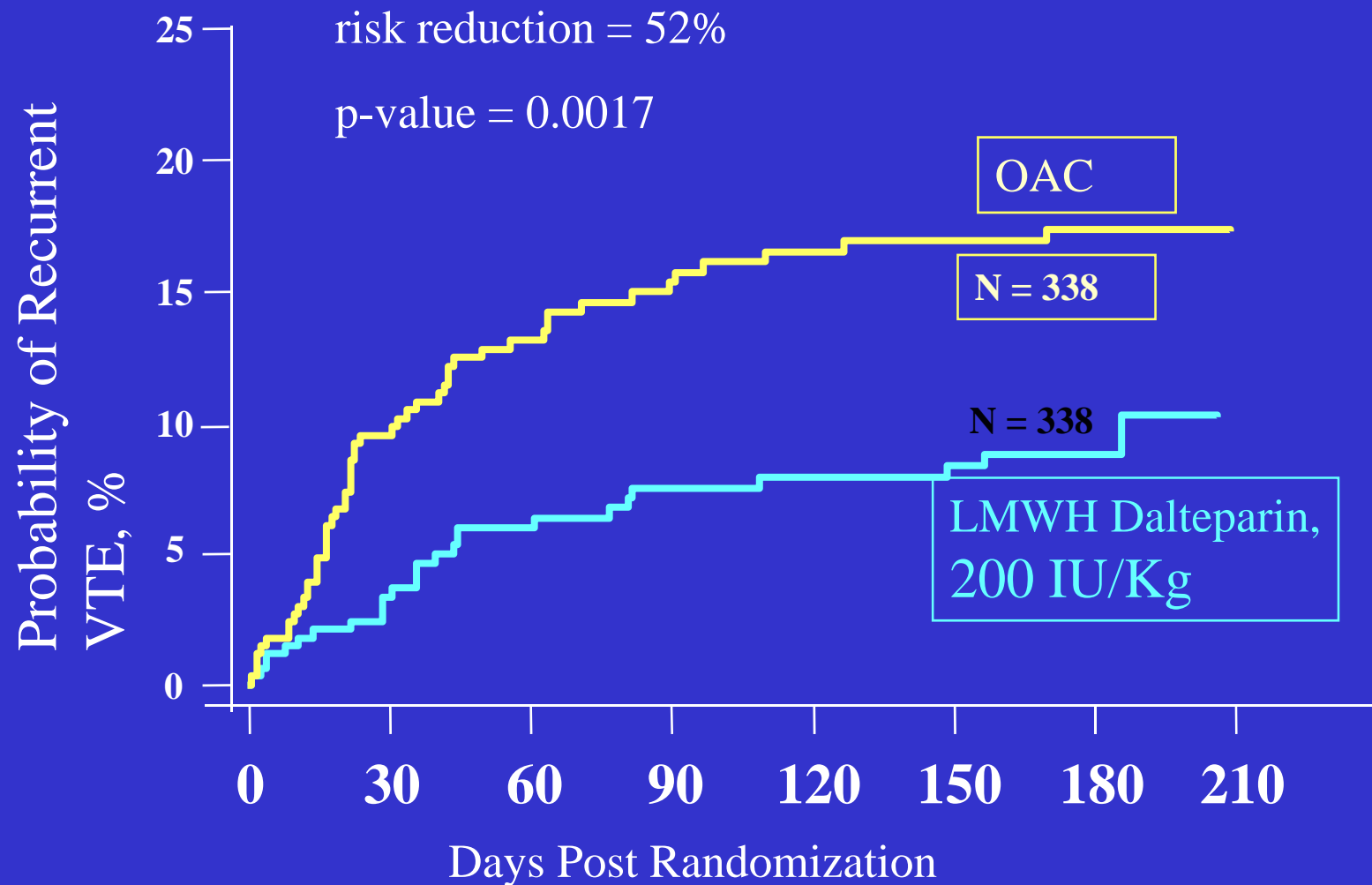
# VTE long term therapy in cancer patients

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Cancer patients with acute DVT and/or PE



# Clot trial: Recurrent VTE



Lee et al. *NEJM*, 2003

# Comparison between LMWH and warfarin for long-term treatment of VTE in cancer patients

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## Other prospective randomized clinical trials:

**CANTHANOX trial:** Comparison between long term therapeutic dose of LMWH Enoxaparin with Warfarin for VTE treatment in cancer (*Meyer G et al Arch Intern Med 2002*)

**LITE trial:** Comparison between long term therapeutic dose of LMWH Tinzaparin with Warfarin for VTE treatment in cancer (*Hull R et al, Am J Med 2006*)



# Comparison between LMWH and warfarin for long-term treatment of VTE in cancer patients

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## Other prospective randomized clinical trials:

**CANTHANOX trial:** Comparison between long term therapeutic dose of LMWH Enoxaparin with Warfarin for VTE treatment in cancer (*Meyer G et al Arch Intern Med 2002*)

**LITE trial:** Comparison between long term therapeutic dose of LMWH Tinzaparin with Warfarin for VTE treatment in cancer (*Hull R et al, Am J Med 2006*)

# Treatment of Cancer-Associated VTE

Study	Design	Length of Therapy (Months)	N	Recurrent VTE (%)	Major Bleeding (%)	Death (%)
CLOT Trial (Lee 2003)	Dalteparin OAC	6	336 336	9 17 0.002	6 4 NS	39 41 NS
CANTHENOX (Meyer 2002)	Enoxaparin OAC	3	67 71	11 21 0.09	7 16 0.09	11 23 0.03
LITE (Hull ISTH 2003)	Tinzaparin OAC	3	80 87	6 11 0.03	6 8 NS	23 22 NS
ONCENOX (Deitcher ISTH 2003)	Enox (Low) Enox (High) OAC	6	32 36 34	3.4 3.1 6.7 NS	NS	NR

# Treatment of Patients with Established VTE to Prevent Recurrence:

ASCO, ESMO, AIOM, NCCN

Role of VTE Prophylaxis	Evidence
LMWH is the preferred approach for the initial 5-10 days in cancer patient with established VTE.	LMWH for 3-6 months is more effective than vitamin K antagonists given for a similar duration for preventing recurrent VTE.
LMWH for at least 6 months is preferred for long-term anticoagulant therapy. The CLOT study demonstrated a relative risk reduction of 49% with LMWH vs. a vitamin K antagonist.	

# FILTRI CAVALI

# FILTRI CAVALI

- 1) Patients with recurrent pulmonary embolism despite adequate anticoagulant treatment or
- 2) With a contraindication to anticoagulant therapy (i.e. active bleeding and profound, prolonged thrombocytopenia).

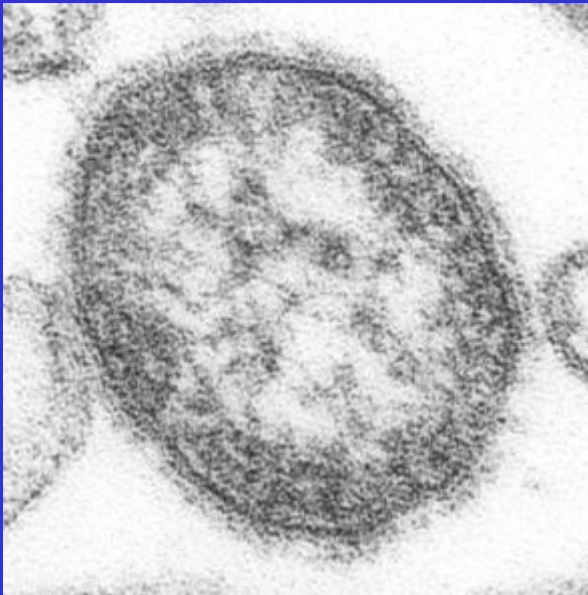


**Morbillo**

# Prevenzione – Vaccinazione

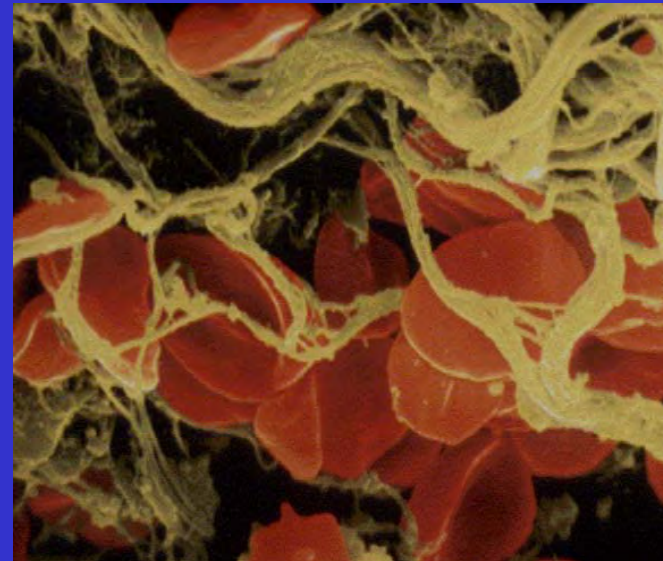
## Morbillo

- **Malattia virale altamente contagiosa che uccide circa 1 milione di bambini all'anno**



## TEV

- **Malattia cardiovascolare comune che uccide più di 2 milioni di persone all'anno**



# Morbillo

- Nonostante l'encefalopatia si verifica in 1/1000 le complicanze possono essere devastanti



# TEV

- Anche qui complicanze altrettanto fatali
- Pensa ogni volta che vedi un paziente ad alto rischio

