Complications vasculaires

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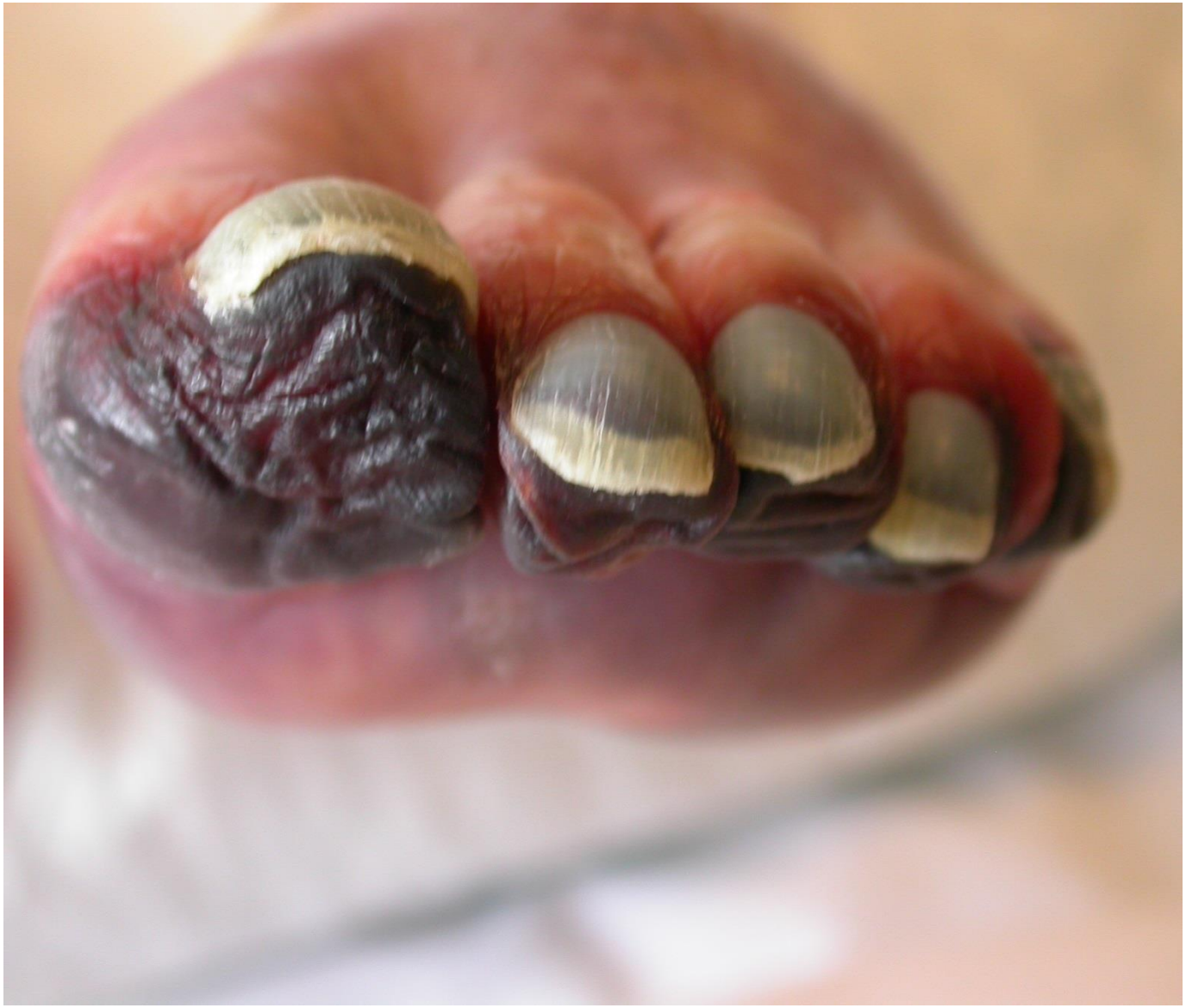
Déclaration

Absence de conflits d'intérêts avec le sujet abordé



Rev Méd Brux 16 : 65-67, 1995

TOXICITÉ CARDIOVASCULAIRE DE LA CHIMIO-THÉRAPIE ANTICANCÉREUSE : CINQ OBSERVATIONS RÉALISÉES EN SOINS INTENSIFS

CARDIOVASCULAR TOXICITY OF CANCER CHEMOTHERAPY : FIVE CASES TREATED IN AN INTENSIVE CARE UNIT

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Tableau 1. Caractéristiques des patients ayant présenté une toxicité cardiovasculaire de la chimiothérapie

Patient	*Âge, sexe*	*Néoplasie*	*Agent anticancéreux*	*Manifestation clinique*	*Mécanisme physio-pathologique supposé*
1	71 M	cancer bronchique	ifosfamide	choc cardiogénique	CMI
2	71 M	cancer ORL	cisplatine	infarctus myocardique	CMI
3	70 M	cancer vésical	cisplatine	AVC	?
4	43 F	cancer anal	5-FU	ischémie myocardique	CMI
5	55 F	cancer mammaire	cisplatine 5-FU	ischémie myocardique	CMI

M : masculin ; F : féminin ; 5-FU : 5-fluorouracile ; CMI : cardiomyopathie ischémique ; AVC : accident vasculaire cérébral.

Annals of Oncology 5: 641–643, 1994.

Short report

A four-drug combination chemotherapy with cisplatin, mitomycin, vindesine and 5-fluorouracil

A regimen associated with major toxicity in patients with advanced non-small cell lung cancer

Table 1. Overall response rate.

	Eligible patients	Evaluable patients
Total number of patients	182	164
Inevaluable	18 (10%)	–
Complete response	4 (2%)	4 (2%)
Partial response	52 (29%)	52 (32%)
No change	35 (19%)	35 (21%)
Progression	38 (21%)	38 (23%)
Early death due to cancer	8 (4%)	8 (5%)
Toxic death	20 (11%)	20 (12%)
Treatment discontinued for excessive toxicity	7 (4%)	7 (4%)

Table 2. Toxicity.

	O	I	II	III	IV	Inevaluable
Nausea - Vomiting	15	24	74	46	3	17
Diarrhea	143	13	7	1	0	18
Mucositis	127	19	13	5	0	18
Skin toxicity	156	6	2	0	0	18
Infection	146	4	12	3	4	13
Hemorrhage	148	9	2	3	2	18
Neurological	130	14	14	5	1	18
Cystitis	162	1	1	0	0	18
Alopecia	48	14	47	51	–	22
Respiratory	152	7	4	0	1	18
Ototoxicity	154	4	4	1	0	19
Cardiovascular	143	3	2	2	18	14
Nephrotoxicity	133	23	4	4	0	18
Leucopenia	18	15	40	46	16	47
Thrombopenia	43	18	22	21	32	46

During the entire treatment, most severe toxicity was observed in the 182 eligible patients (WHO grade).

Tableau clinique

- Thrombophlébites superficielles (migrantes)
- Thromboses veineuses profondes avec embolies pulmonaire et paradoxale
- Thrombose artérielle
- Endocardite thrombotique non bactérienne
- Thrombose cardiaque
- Embolie néoplasique
- Aggravation pathologie vasculaire préexistante
- Vasculites paranéoplasiques
- Auto-anticorps paranéoplasiques

Angor et infarctus myocardique

- Agents anticancéreux
- CIVD
- Endocardite thrombosante non bactérienne (marastique)
- Complication paranéoplasique : syndrome carcinoïde, phéochromocytome
- Embolies tumorales
- Artérites radiques
- Accidents ischémiques des syndromes myéloprolifératifs

Accidents vasculaires cérébraux

- Accidents ischémiques
  - CIVD
  - Endocardite thrombosante non bactérienne (marastique)
  - Embolies tumorales, lymphome malin endovasculaire
  - Artérites fungiques et bactériennes
  - Artérites granulomateuses et zostériennes
  - Artérites radiques (carotide)
  - Rupture artère carotide (ligature)
  - Accidents ischémiques des syndromes myéloprolifératifs
- Accidents hémorragiques

Autres atteintes

- Infarctus rénaux
- Infarctus mésentérique
- Artériopathie périphérique avec ischémie distale (membres):
  - chimiothérapie à base de cisplatine

État hypercoagulable du cancéreux

- Expression anormale de facteur tissulaire par les cellules néoplasiques : sarcome, mélanome, cancer pancréas, lymphome, leucémie aiguë promyélocytaire
- Facteur procoagulant du cancer (cystéine-protéase activant directement le facteur X): leucémie aiguë promyélocytaire, mélanome, cancers du colon, du poumon, du sein et du rein
- Stimulation de cellules normales à avoir une activité procoagulante: monocytes (facteur tissulaire), plaquettes, cellules endothéliales (TNF, IL-1)
- Syndrome d'hyperviscosité: par nombre accru de cellules (érythrocytes, leucocytes, plaquettes) ou par protéines plasmatiques anormales (myélome multiple, macroglobulinémie de Waldenström, cryoglobulinémie, dysfibrinogénémie)
- Auto-anticorps: anticardiolipine (anti-phospholipides), anti-IL8
- Facteurs de comorbidité : compression vasculaire, immobilisation, dysfonction hépatique, sepsis, pathologies vasculaires sous-jacentes, agents anticancéreux
- Toxicité endothéliale des traitements

Fréquence relative des comorbidités dans le cancer bronchique

	Pays-Bas	**Espagne**
n	3864	2993
période	1993-95	1993-97
BPCO	22%	50%
HTA	12%	16,5%
Cancer antérieur	15%	15,5%
Maladie cardiaque	23%	23,5%
Artériopathie périphérique	23%	23,5%
Diabète	7%	9%

Lung Cancer, 35: 263; 2002

Chimiothérapie (et hormonothérapie)

Cancer du sein

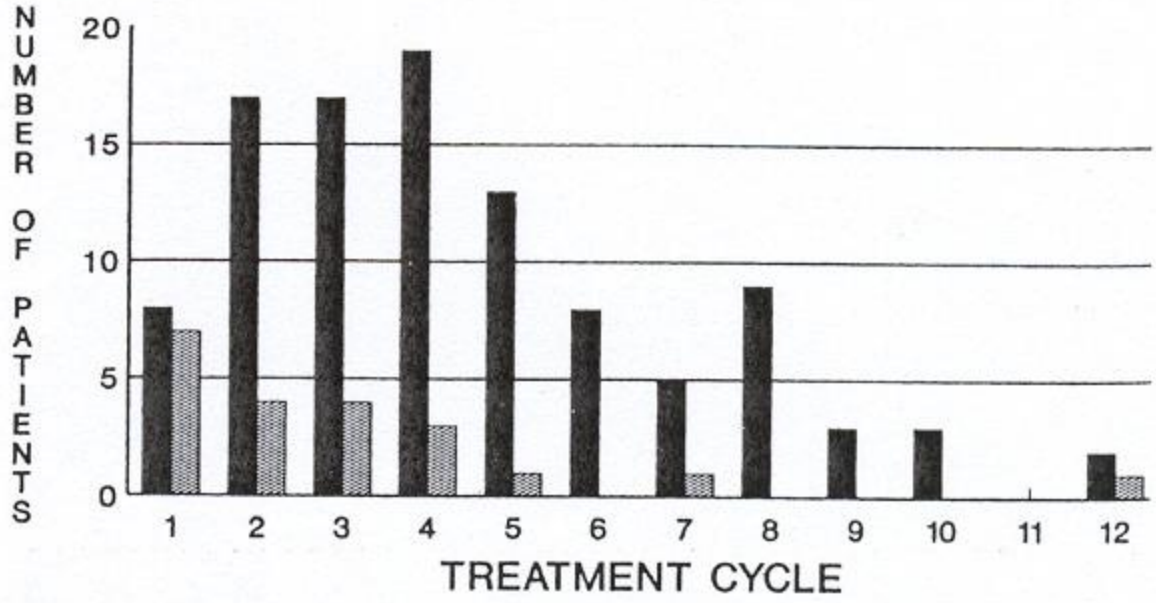

Fig 1. The 125 vascular complications that occurred during cyclic therapy. Complications on tamoxifen (three) or observation (five) were not included. (■) Venous, (▨) arterial.

Table 5. Vascular Complications Observed

	Adjuvant Therapy Patients (n = 2,352)	Observation Patients (n = 321)	Total
Venous events			
Deep venous thrombosis	73	1	74
Pulmonary emboli	31	0	31
Retinal vein thrombosis	1	0	1
Mesenteric vein thrombosis	1	0	1
Total venous events	106	1	107
Arterial events			
Cerebral vascular accidents	10	4	14
Emboli/thrombi to an extremity	11	0	11
Mesenteric artery thrombosis	1	0	1
Total arterial events	22	4	26
Total thrombotic events	128	5	133

Chimiothérapie et thromboses artérielles « Associations à risque »

- 5-FU: 1,6 à 2,3% toxicité cardiovasculaire
- Cisplatine, gemcitabine,
- ITK
- Bévacuzimab
- …

Prospective Evaluation of Major Vascular Events in Patients with Nonsmall Cell Lung Carcinoma Treated with Cisplatin and Gemcitabine

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BACKGROUND. Cancer and cisplatin-based chemotherapy both are well recognized risk factors for coagulation disorders and thrombosis. However, vascular events (VEs) seldom are considered adverse effects of treatment and may not even be taken into account in reports of chemotherapy trials.

METHODS. VEs were recorded prospectively in a population of patients with nonsmall-cell lung carcinoma (NSCLC) who were treated consecutively with cisplatin and gemcitabine using a diagnostic flow chart based on a thorough clinical examination, hematologic and coagulative parameters, and imaging assessments when appropriate.

RESULTS. From January, 2000 to January 2003, 108 patients with Stage III–IV NSCLC underwent chemotherapy and were evaluated. Overall, 22 VEs occurred in 19 patients (17.6%; 95% confidence interval [95% CI], 10.3–24.8%), including 10 arterial VEs (2 myocardial infarctions, 7 lower limb arterial thrombosis, and 1 ischemic stroke) and 12 venous VEs (3 catheter-related upper limb VEs, 6 venous thrombosis of the lower limb, and 3 pulmonary embolisms). The cumulative proportion of VEs at 1 year after the start of chemotherapy was 22.0% (95% CI, 12.7–31.3%). Four patients died due to the VE (overall mortality, 3.7%), and 3 patients needed surgical revascularization. In the other patients, conservative medical treatment was effective. Baseline patient-related and disease-related characteristics of the patients with VEs did not differ significantly from the characteristics of patients without VE; liver and brain metastases were more frequent in patients with VE, although the difference did not reach statistical significance. Response rates were similar in the two groups. A double VE was detected in three patients who were given further chemotherapy after resolution of the first event.

CONCLUSIONS. VEs were a common finding in chemotherapy-treated NSCLC patients. Chemotherapy itself seem to be a powerful risk factor for VE. Strategies to predict the occurrence of VEs should be developed to spare this life-threatening toxicity. ***Cancer* 2005;103:994–9.**

TABLE 2
Types of Vascular Events

Vascular event	No. of patients (%)
Arterial	10 (45.4%)
Myocardial infarction	2 (9.0)
Iliac artery embolism	7 (31.8)
Cerebral ischemic stroke	1 (4.5)
Venous	12 (54.6)
Deep venous thrombosis (upper limb)	3 (13.6)
Deep venous thrombosis (lower limb)	6 (27.2)
Pulmonary embolism	3 (13.6)

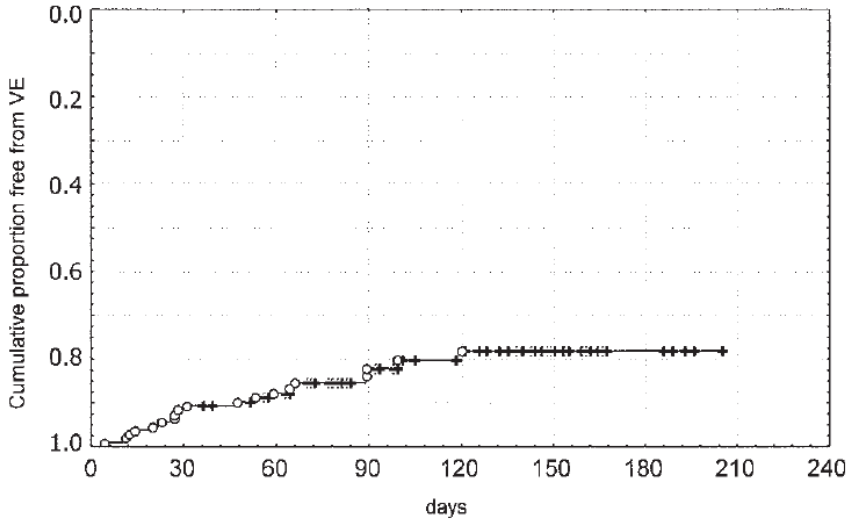

FIGURE 1. Kaplan–Meier plot of the time to first vascular event (VE). Time 0 corresponds to the day of treatment start.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

High Incidence of Thromboembolic Events in Patients Treated With Cisplatin-Based Chemotherapy: A Large Retrospective Analysis

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/11/2925-3466/$20.00

DOI: 10.1200/JCO.2011.35.5669

ABSTRACT

Purpose
This study was designed to determine the incidence of venous and arterial thromboembolic events (TEEs) in patients treated with cisplatin-based chemotherapy and to analyze the prognostic value of patients' baseline and treatment characteristics in predicting TEE occurrence.

Patients and Methods
We performed a large retrospective analysis of all patients treated with cisplatin-based chemotherapy for any type of malignancy at Memorial Sloan-Kettering Cancer Center in 2008. A TEE was cisplatin-associated if it occurred between the time of the first dose of cisplatin and 4 weeks after the last dose.

Results
Among 932 patients, 169 (18.1%) experienced a TEE during treatment or within 4 weeks of the last dose. TEEs included deep vein thrombosis (DVT) alone in 49.7%, pulmonary embolus (PE) alone in 25.4%, DVT plus PE in 13.6%, arterial TEE alone in 8.3%, or DVT plus arterial TEE in 3.0%. TEEs occurred within 100 days of initiation of treatment in 88% of patients. By univariate analysis, sex, age, race, Karnofsky performance status (KPS), exposure to erythropoiesis-stimulating agents, presence of central venous catheter (CVC), site of cancer, stage of cancer, leukocyte and hemoglobin levels, and Khorana score were all identified as risk factors. However, by multivariate analysis, only age, KPS, presence of CVC, and Khorana score retained significance.

Conclusion
This large retrospective analysis confirms the unacceptable incidence of TEEs in patients receiving cisplatin-based chemotherapy. In view of the controversy associated with prophylactic anticoagulation in patients with cancer treated with chemotherapy, randomized studies are urgently needed in this specific cancer population treated with cisplatin-based regimens.

J Clin Oncol 29:3466-3473. © 2011 by American Society of Clinical Oncology

Table 2. Overall Incidence of Thromboembolic Events (N = 932)

Thromboembolic Event	No. of Patients	%
Thrombosis	169	18.1
Types of thromboses (n = 169)		
DVT alone	84	49.7
PE alone	43	25.4
DVT + PE	23	13.6
Arterial thrombosis alone	14	8.3
DVT + arterial thrombosis	5	3.0
Subtypes of DVTs (n = 112)		
Proximal lower extremity	22	19.6
Proximal lower and distal lower extremity	18	16.1
Proximal lower extremity and central*	5	4.4
Proximal lower extremity and central* and distal lower extremity	1	0.9
Proximal upper extremity	2	1.8
Proximal upper and distal upper extremity	3	2.7
Proximal upper and internal jugular vein and distal upper extremity	4	3.6
Internal jugular vein	5	4.4
Internal jugular vein and distal upper extremity	1	0.9
Central*	27	24.1
Distal lower extremity	20	17.9
Distal lower and distal upper extremity	1	0.9
Distal upper extremity	3	2.7
Subtypes of arterial events (n = 19)		
Central†	6	31.6
Myocardial infarction	2	10.5
Cerebrovascular accident	10	52.6
Transient ischemic attack	1	5.3
Symptomatic or incidental event (n = 169)		
Symptomatic	95	56.2
Incidental	74	43.8

Abbreviations: DVT, deep venous thrombosis; PE, pulmonary embolus.

*Central venous thromboses sites include brachiocephalic vein (n = 1), gonadal vein (n = 7), hepatic vein (n = 1), inferior vena cava (n = 5), pelvic vein (n = 4), portal vein (n = 6), renal vein (n = 4), splenic vein (n = 3), superior mesenteric vein (n = 6), and superior vena cava (n = 3).

†Central arterial thromboses sites include aortic arch (n = 1), infrarenal aorta (n = 3), internal carotid (n = 1), splenic artery (n = 1), and superior mesenteric artery (n = 1).

Arterial Thromboembolism in Cancer Patients Treated With Cisplatin: A Systematic Review and Meta-analysis

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Cisplatin has been associated with an increased risk of arterial thromboembolic events (ATEs). However, because this association is mostly based on case reports and retrospective studies, we conducted a systemic review and meta-analysis of randomized controlled trials evaluating the incidence and risk of ATEs associated with cisplatin. Eligible studies included prospective randomized phase II and III trials evaluating cisplatin-based vs non-cisplatin-based chemotherapy in patients with solid tumors, which were identified from PubMed articles published between 1990 and 2010. Incidence rates, relative risks (RRs), and 95% confidence intervals (CIs) were calculated using a random effects model. A total of 8216 patients from 38 trials were included. Among patients treated with cisplatin-based chemotherapy, the summary incidence of ATEs was 0.67% (95% CI = 0.40% to 0.95%), and the RR of ATEs was 1.36 (95% CI = 0.86 to 2.17; *P* = .19). No increase in ATEs was detected in any prespecified subgroup.

J Natl Cancer Inst 2012:104;1837–1840

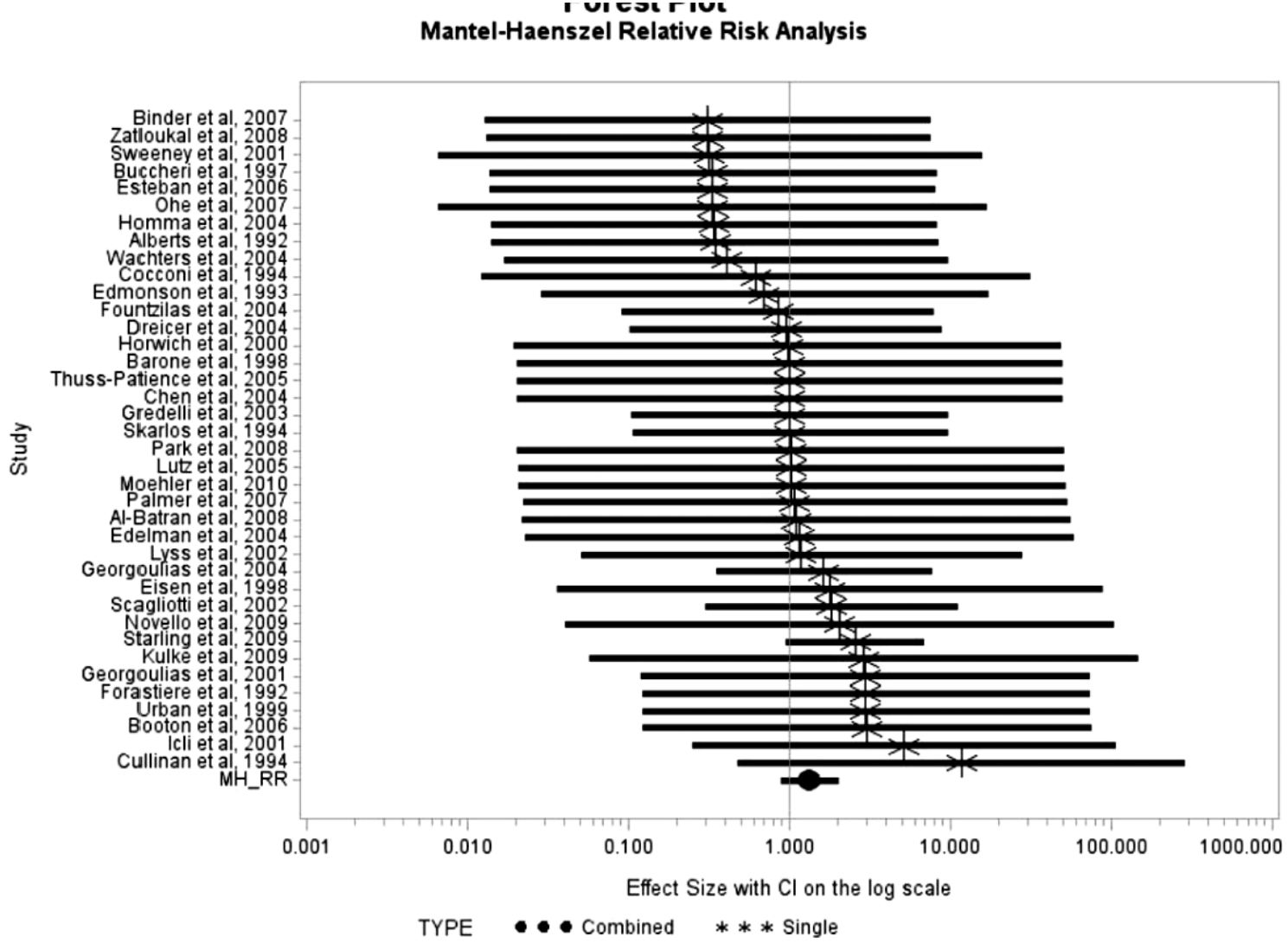

Figure 1. Relative risk of arterial thromboembolism associated with cisplatin-based vs non-cisplatin-based chemotherapy.

Table 1. Incidence and relative risk of arterial thromboembolism based on prespecified subgroups*

Group	Subgroup	No. of trials	Arterial thromboembolism, No./total No./incidence		I^2, %	Relative risk (95% CI)	*P* for relative risk	*P* for group difference
			Cisplatin	Non-cisplatin				
Overall		38	34/4154/0.67%	21/4062/0.47%	0.00	1.36 (0.86 to 2.17)	.19	NA
Tumor type	NSCLC	15	12/2167/0.57%	9/1686/0.43%	0.00	1.00 (0.47 to 2.13)	.99	
	Gastric/esophageal	8	15/909/1.26%	5/1023/0.59%	0.00	2.25 (0.99 to 5.14)	.054	
	Pancreas	3	0/134/N.A.	0/264/N.A.	0.00	1.47 (0.15 to 13.94)	.74	.97
	Head and neck	3	2/191/1.15%	2/184/0.92%	0.00	0.93 (0.16 to 5.32)	.94	
	Small cell lung	3	2/314/0.74%	2/347/0.44%	0.00	1.45 (0.86 to 2.44)	.16	
Weekly equivalent cisplatin dose	10–20 mg/m^2	13	17/1233/1.15%	9/1487/0.53%	0.00	1.74 (0.86 to 3.54)	.12	.64
	>20–30 mg/m^2	17	12/2378/0.52%	9/1970/0.40%	0.00	1.06 (0.51 to 2.22)	.16	
	>30 mg/m^2	8	5/543/1.02%	3/605/0.68%	0.00	1.31 (0.42 to 4.11)	.64	
Non-cisplatin chemotherapy	Non-platinum	24	10/1856/0.69%	10/2296/0.43%	0.00	1.20 (0.62 to 2.32)	.59	.59
	"Other" platinum	14	24/2298/0.79%	11/1766/0.55%	0.00	1.55 (0.80 to 2.99)	.19	
Publication year	1990–1999	10	4/893/0.57%	4/1130/0.40%	0.00	1.26 (0.45 to 3.59)	.66	.87
	2000–2010	28	30/3261/0.83%	17/2932/0.51%	0.00	1.39 (0.83 to 2.34)	.22	

* CI = confidence interval; NA = not applicable; NSCLC = non–small cell lung cancer.

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journal homepage: www.elsevier.com/locate/lungcan

Retrospective evaluation of thromboembolic events in patients with non-small cell lung cancer treated with platinum-based chemotherapy

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1/2000 – 12/2012 : 784 patients

Table 1
Baseline characteristics among patients with non-small cell lung carcinoma receiving platinum chemotherapy.

Variable	No. of patients (%)
Mean age in years (SD)[a]	59.5 (±10.6)
Sex	
Male	504 (64.3)
Female	280 (35.7)
Histology	
Adenocarcinoma	350 (44.6)
Large cell	238 (30.4)
Squamous cell	192 (24.5)
Smoking habits (missing = 49)	
Current	367 (46.8)
Former	312 (39.8)
Never	56 (7.1)
ECOG performance score (missing = 57)	
0	364 (46.4)
1	312 (39.8)
2	46 (5.9)
3	3 (0.4)
4	2 (0.3)
Disease stage	
I–IIb	42 (5.4)
IIIa	197 (25.1)
IIIb	199 (25.4)
IV	346 (44.1)

[a] Standard deviation.

Table 3
Characteristics of occurred thromboembolic events (TE).

	Events during chemotherapy
Arterial TE	**24**
Cerebral ischemic stroke	13
Myocardial infarction	6
Lower limb	5
Venous TE	**45**
Pulmonary embolism	25
Lower limb DVT[a]	11
Upper limb DVT	7
Superior vena cava	1
Kidney vein	1
Total	69

[a] Deep venous thrombosis.

3.4. Treatment of TE

Patients were treated with LMWH ($n = 20$), coumarine derivate ($n = 12$) or a platelet aggregation inhibitor ($n = 4$). In 5 patients no treatment was initiated, 10 patients died short after TE and in 12 patients data was missing. In the acute phase, 2 patients were treated with urokinase and 6 patients underwent surgery.

original article

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Bevacizumab increases the risk of arterial ischemia: a large study in cancer patients with a focus on different subgroup outcomes

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Background: Bevacizumab, a humanized monoclonal antibody targeting the vascular endothelial growth factor, is a therapeutic agent used in a variety of neoplasms. We did a meta-analysis of randomized controlled trials to fully characterize the arterial thromboembolic events (ATEs) risk with bevacizumab in certain patients' subgroups.
Materials and Methods: We carried out a literature search on Medline for randomized trial reported from January 1966 to December 2009. Abstracts presented at the American Society of Clinical Oncology held between 2004 and 2009 were also searched for relevant clinical trials. Summary incidence, relative risks (RRs) and 95% confidence intervals (CIs) were calculated using random-effects or fixed-effects models based on the heterogeneity of included studies.
Results: A total of 13 026 patients from 20 randomized trials were included in the meta-analysis. Overall RR for ATE with bevacizumab-based therapy versus controls was 1.46 (95% CI 1.11–1.93, $P = 0.007$). On subgroup analysis, no significant risk differences were found based on the type of malignancy, type of clinical trial (phase II or III trials), type of publication (full papers versus presentations), high- versus low-dose bevacizumab and early versus advanced disease trials. When stratified by concomitant therapies, we found that gemcitabine-based regimens had a significant lower ATE risk compared with non-gemcitabine regimens ($P = 0.01$).
Conclusions: Bevacizumab treatment is associated with a significant increase in the risk of arterial thrombosis. Our results seem to be generalizable to the vast majority of patients receiving bevacizumab in multiple settings.
Key words: arterial thromboembolic events, bevacizumab, ischemia, meta-analysis, monoclonal antibody, myocardial infarction

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Risk of Arterial Thromboembolic Events With Sunitinib and Sorafenib: A Systematic Review and Meta-Analysis of Clinical Trials

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0732-183X/10/2813-2280/$20.00

DOI: 10.1200/JCO.2009.27.2757

ABSTRACT

Purpose

Sunitinib and sorafenib are oral vascular endothelial growth factor receptor (VEGFR) tyrosine kinase inhibitors (TKIs) used in a vast range of cancers. Arterial thromboembolic events (ATE) have been described with these agents, although the overall risk remains unclear. We did a systematic review and meta-analysis to determine the incidence and the relative risk (RR) associated with the use of sunitinib and sorafenib.

Patients and Methods

PubMed databases were searched for articles published from January 1966 to July 2009, and abstracts presented at the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) meetings held between 2004 and 2009 were searched for relevant clinical trials. Eligible studies included phase II and III trials and expanded access programs. Statistical analyses were conducted to calculate the summary incidence, RRs, and 95% CIs, using random-effects or fixed-effects models based on the heterogeneity of included studies.

Results

A total of 10,255 patients were selected for this meta-analysis. The incidence for ATE was 1.4% (95% CI, 1.2% to 1.6%). The RR of ATEs associated with sorafenib and sunitinib was 3.03 (95% CI, 1.25 to 7.37; $P = .015$) compared with control patients. The analysis was also stratified for the underlying malignancy (renal cell cancer *v* non-renal cell cancer) and TKI (sunitinib *v* sorafenib), but no significant differences in incidence or RR were observed.

Conclusion

Treatment with VEGFR TKIs sunitinib and sorafenib is associated with a significant increase in the risk of ATEs.

J Clin Oncol 28:2280-2285. © 2010 by American Society of Clinical Oncology

Radiothérapie

- Atteinte coronaire:
  - Cas cliniques: prédominance sténose coronaire gauche
  - Étude norvégienne (1115 patientes avec néo sein) : stade I : 10 IDM si RT vs 1 si contrôle
  - Maladie de Hodgkin: atteinte myocardique à long terme (dysfonction ventriculaire à l'échocardiographie)
- Atteinte artère périphérique
  - Artériopathie MS cancer du sein avec RT postopératoire: 22 % côté ipsilatéral vs 4% côté controlatéral
- Atteinte carotide
  - Irradiation du cou: sténose ou occlusion: AIT, infarctus, amaurose fugace, convulsions
- Mécanisme: fibrose intimale intense avec sténose (et non athéromatose)
- Traitement: angioplastie (percutanée)

Embolie artérielle tumorale

- Rare
- Tumeurs les plus fréquemment en cause : poumon, sarcomes
- Vaisseaux atteints par ordre de fréquence décroissant : aorte, artères cérébrales, fémorales, iliaques, mésentériques, distales des MI, carotides, coronaires ….
- Conséquence: ischémie ou infarctus de l'organe irrigué
- Mécanismes:
  - Invasion veines pulmonaires et oreillette gauche
  - Manipulation chirurgicale de la tumeur (y penser en cas d'accident vasculaire en postopératoire)
- Traitement: embolectomie (le diagnostic n'est jamais posé avant l'intervention)
  - De mauvais pronostic en cas d'artère viscérale
  - De bon pronostic en cas d'artère périphérique

Traitement

- Attitude préventive
  - Bilan vasculaire avant traitement du cancer et traitement des lésions significatives
  - Si facteurs de risque : héparine (aspirine ?)
- Traitement
  - Interventionnel ou anticoagulation si thrombose
  - Vasodilatateurs si spasme

Eur Respir J 2009; 34: 17–41
DOI: 10.1183/09031936.00184308

ERS/ESTS TASK FORCE

ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy)

A. Brunelli*, A. Charloux*, C.T. Bolliger, G. Rocco, J-P. Sculier, G. Varela, M. Licker, M.K. Ferguson, C. Faivre-Finn, R.M. Huber, E.M. Clini, T. Win, D. De Ruysscher and L. Goldman on behalf of the European Respiratory Society and European Society of Thoracic Surgeons joint task force on fitness for radical therapy

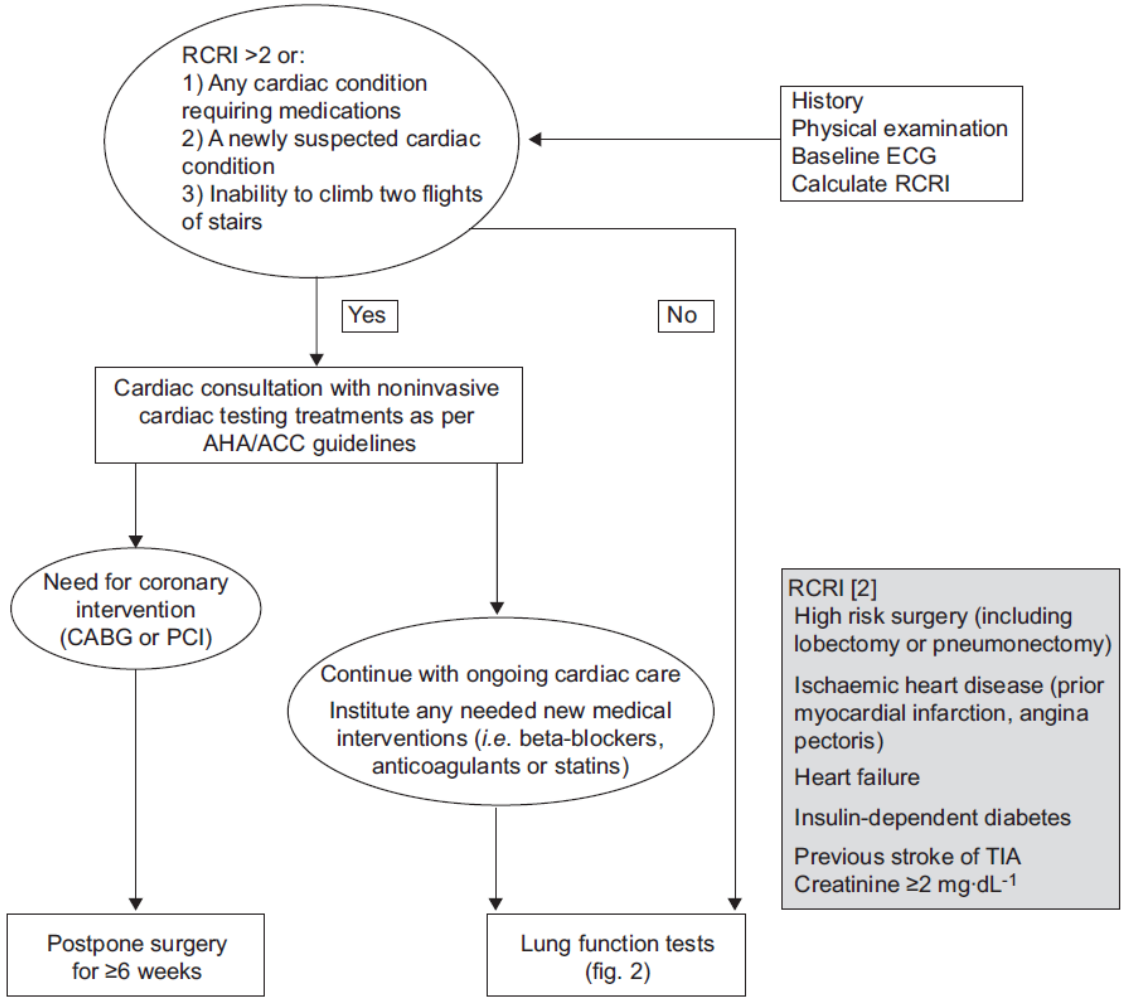


FIGURE 1. Algorithm for cardiac assessment before lung resection in lung cancer patients. For American College of Cardiology Foundation/American Heart Association (AHA/ACC) guidelines see [2–6]. CABG: coronary artery bypass graft; PCI: primary coronary intervention; TIA: transient ischaemic attack.

En cas d'antécédents

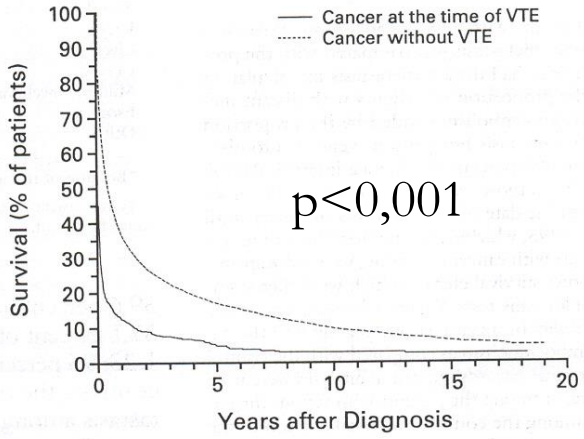
Conserver la prévention secondaire, voire l'optimaliser:

- **Infarctus du myocarde**
  - statine
  - arrêt du tabagisme
  - aspirine (75 mg/j)
  - β-bloquant
  - IEC
- **AVC**
  - arrêt du tabac
  - aspirine : 75 à 325 mg/jour
  - en cas de fibrillation auriculaire ou de cardiopathie embolique : anti-vitamine K avec INR entre 2 et 3
  - traitement anti-hypertenseur (diurétiques) si TA >140/80 mm Hg
  - simvastatine si cholestérol >140 mg/dl et LDL-cholestérol > 90mg/dl

La maladie thrombo-embolique

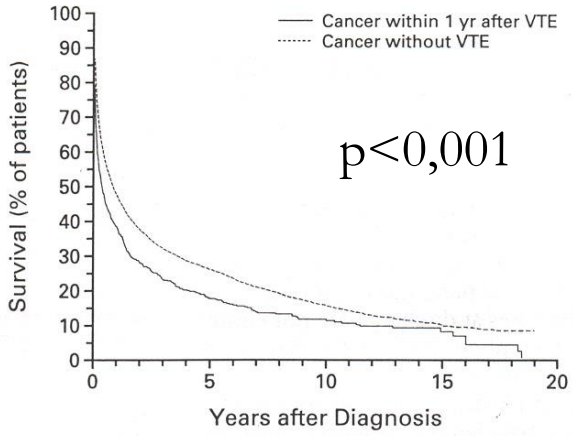
De mauvais pronostic

Sorensen, NEJM, 2000; 343: 1846-1850.



p<0,001

No. at Risk				
Cancer at the time of VTE	668	23	10	3
Cancer without VTE	6668	913	338	87



p<0,001

No. at Risk				
Cancer within 1 yr after VTE	560	72	37	7
Cancer without VTE	5586	1181	419	106

Il faut garder à l'esprit des causes spécifiques d'embolie pulmonaire.

- Il s'agit de l'embolie de cellules tumorales qui peut mimer initialement la maladie thromboembolique veineuse
- à l'origine de la lymphangite pulmonaire
- tableau de détresse respiratoire avec HTP aiguë
- diagnostic : biopsie bronchique ou pulmonaire, analyse cytologique de sang capillaire (prélevé par cathétérisme de l'artère pulmonaire)

Bassiri et al, Am J Respir Crit Care Med 155, 2089-2095; 1997

Les études randomisées disponibles

Table 3. Studies of venous thromboembolism treatment in patients with cancer

Study	*n*	Follow-up	Population	Agents	VTE	Major bleeding	Mortality
Charbonnier et al. (FRAXODI) [71]	–	3 months	Proximal DVT	Nadroparin b.i.d., nadroparin q.d.	7.2%[a], 4.1%[a]	1.2%, 1.3%	NR
Merli et al. [72]	141[b]	3 months	Symptomatic DVT	Enoxaparin b.i.d., enoxaparin q.d., UFH	6.4%, 12.2%, 6.7%	1.3%, 1.7%, 2.1%	NR
Meyer et al. (CANTANOX) [73]	146	3 months	PE or DVT	Enoxaparin, warfarin	10.5%[c], 21.1%[c]; $P = 0.09$	7%, 16%[d]; $P = 0.09$	11.3%, 22.7%; $P = 0.07$
Lee et al. (CLOT) [47]	672	6 months	Symptomatic acute DVT and/or PE	Dalteparin q.d. × 5–7 days + warfarin[e] × 6 months, dalteparin q.d. × 6 months	15.8%, 8.0%; $P = 0.002$	6%, 4%; $P = 0.27$	41%, 39%; $P = 0.53$
Hull et al. (LITE) [74]	200	3 months, 12 months	Symptomatic acute proximal vein thrombosis	Tinzaparin; UFH + warfarin × 6 days, then warfarin	T 6%, W 10%; T 7%, W 16%; $P = 0.04$	T 7%, W 7%	T 20%, W 19%; T 47%, W 47%
Deitcher et al. (ONCENOX) [75]	122	3 months	Symptomatic VTE	Enoxaparin × 5 days, then; LD enoxaparin; HD enoxaparin; warfarin	LD 6.9%; HD 6.3%; W 10%	LD 6.5%; HD 11.1%; W 2.9%	LD 22.6%; HD 41.7%; W 32.4%

[a]Recurrent VTE or death possibly related to pulmonary embolism.
[b]Subgroup analysis of the overall trial population.
[c]Composite of major bleeding or recurrent VTE.
[d]Six patients died of bleeding complications.
[e]Except in Spain and The Netherlands, where acenocoumarol was used.
b.i.d., twice daily; DVT, deep vein thrombosis; HD, high dose; LD, low dose; NR, not reported; PE, pulmonary embolism; q.d., each day; T, tinzaparin; UFH, unfractionated heparin; VTE, venous thromboembolism; W, warfarin.

Annals of Oncology

review

Annals of Oncology 20: 1619–1630, 2009
doi:10.1093/annonc/mdp068
Published online 26 June 2009

Cancer and thrombosis: implications of published guidelines for clinical practice

A. A. Khorana*

Étude de Meyer
(Arch Intern Med 2002; 162: 1729-35)

Table 1. Baseline Clinical and Biological Characteristics of Study Patients*

Characteristic	Warfarin Sodium Group (n = 75)	Enoxaparin Sodium Group (n = 71)
Male, No. (%)	37 (49.3)	28 (39.4)
Age, y		
Mean ± SD	66 ± 11	65 ± 13
Range	39-86	25-91
Weight, kg		
Mean ± SD	68 ± 14	70 ± 15
Range	40-100	40-106
Venous thromboembolism, No. (%)		
Isolated DVT	25 (33.3)	19 (26.8)
Isolated PE	11 (14.7)	8 (11.3)
DVT and PE	39 (52.0)	44 (62.0)
Risk factors, No. (%)		
Immobilization	20 (26.7)	21 (29.6)
Previous VTE	23 (30.7)	13 (18.7)
Recent surgery	12 (16.0)	18 (25.4)
Varicose veins	13 (17.3)	11 (15.7)
Congestive heart failure	4 (5.3)	5 (7.0)
BMI >30 kg/m², No. (%)	8 (10.7)	8 (11.3)
Blood urea nitrogen, mean ± SD, mg/dL (mmol/L)	17 ± 8 (6.0 ± 3.0)	16 ± 9 (5.6 ± 3.2)
Platelet count, mean ± SD, ×10³/μL	218 ± 101	225 ± 83
Creatinine, mean ± SD, mg/dL (μmol/L)	0.99 ± 0.26 (87.2 ± 23.1)	0.95 ± 0.26 (84.4 ± 22.9)
Hemoglobin, mean ± SD, g/dL	11.4 ± 2.1	10.9 ± 1.7

*DVT indicates deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; and BMI, body mass index.

Table 2. Characteristics of the Underlying Cancer at Inclusion in 146 Patients With Venous Thromboembolism*

Characteristic	Warfarin Sodium Group (n = 75)	Enoxaparin Sodium Group (n = 71)
Cancer localization		
Breast	13 (17.3)	19 (26.8)
Digestive tract	11 (14.7)	11 (15.5)
Bronchial	8 (10.7)	8 (11.3)
Hematologic	7 (9.3)	9 (12.7)
Urologic	15 (20.0)	9 (12.7)
Genital	8 (10.7)	8 (11.3)
Unknown origin	7 (9.3)	3 (4.2)
Other	6 (8.0)	4 (5.6)
Cancer duration, mean ± SD, mo	30.3 ± 38.3	25.9 ± 37.6
Metastatic cancer	39 (52.0)	38 (53.5)
Ongoing cancer treatment	52 (69.3)	54 (76.0)

*Data are presented as number (percentage) of patients unless otherwise indicated. No significant difference was observed between the groups.

Résultats

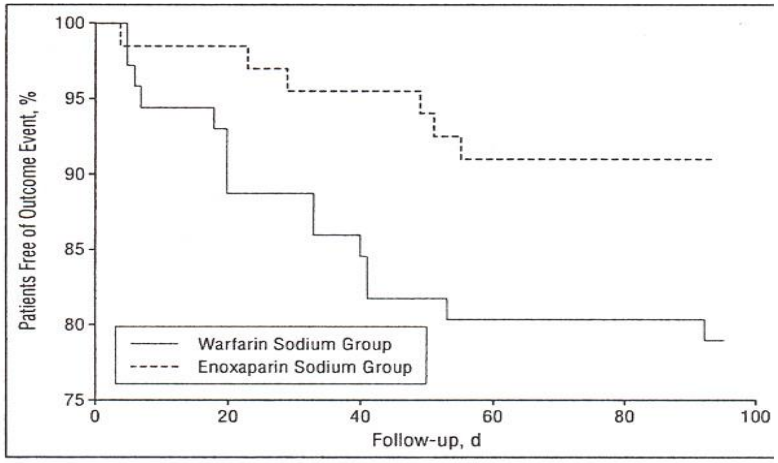


Figure 1. Recurrent venous thromboembolism or major hemorrhage during the 3-month treatment period in 138 patients with cancer and venous thromboembolism treated with warfarin and enoxaparin. *P*=.04 by the log-rank test.

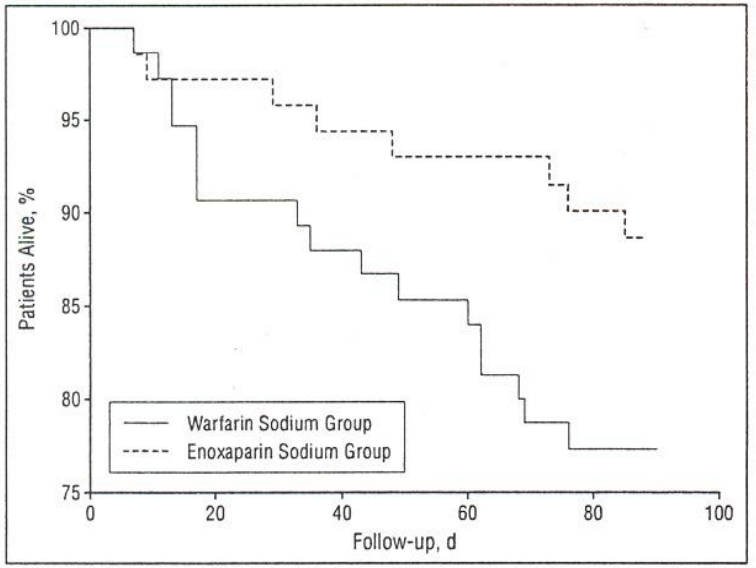


Figure 2. Overall mortality during the 3-month treatment period in 146 patients with cancer and venous thromboembolism treated with warfarin and enoxaparin. *P*=.07 by the log-rank test.

Résultats

Table 3. Major Bleeding During the 3-Month Treatment Period With Warfarin (n = 75) or Enoxaparin Sodium (n = 71) in 146 Patients With Cancer and Venous Thromboembolism*

Site of Bleeding	Time of Bleeding	Last INR or Anti–Factor Xa Value Before Bleeding, IU/mL (Date)
Warfarin sodium group		
Cerebral metastases	D 17	1.0 (D 16)
Upper gastrointestinal tract	D 41	6.5 (D 41)
Epistaxis (tumor)	D 31	4.0 (D 31)
Hematuria†	D 13	3.0 (D 13)
Hematuria (tumor)†	D 4	4.5 (D 4)
Upper gastrointestinal tract†	D 6	4.0 (D 4)
Rectal tumor†	D 2	1.4 (D 2)
Rectal tumor	D 19	3.7 (D 16)
Subdural hematoma	D 74	1.2 (D 74)
Upper gastrointestinal tract†	D 47	2.7 (D 47)
Upper gastrointestinal tract (tumor)†	D 18	4.0 (D 18)
Upper gastrointestinal tract	D 53	8.0 (D 53)
Enoxaparin sodium group		
Pancreatic tumor	D 23	ND
Lower gastrointestinal tract	D 55	0.34 (D 38)
Hematuria	D 48	0.97 (D 4)
Postoperative wound hematoma	D 13	ND
Upper gastrointestinal tract	D 68	0.59 (D 57)

*INR indicates international normalized ratio; D, day after inclusion; and ND, not done.
†Fatal bleeding occurred.

Conclusions : HBPM :
- aussi efficace et plus sûr que que antivitamines K

Étude de Lee
(NEJM 2003; 349:146-53)

Table 1. Base-Line Characteristics of the Patients.*

Characteristic	Dalteparin (N=338)	Oral Anticoagulant (N=338)
Mean age (yr)	62±12	63±13
Female sex (no. of patients)	179	169
ECOG performance score (no. of patients)		
0	80	63
1	135	150
2	118	122
3†	5	3
Hospitalization status (no. of patients)		
Outpatient	169	156
Inpatient	169	182
Hematologic cancer (no. of patients)	40	30
Solid tumor (no. of patients)		
No clinical evidence of disease	36	33
Localized disease	39	43
Metastatic disease	223	232
Antineoplastic treatment (no. of patients)‡	266	259
Current smoker (no. of patients)	33	42
History of DVT or PE (no. of patients)	39	36
Recent major surgery (no. of patients)	62	67
Central venous catheter (no. of patients)	46	40
Qualifying thrombotic event (no. of patients)		
DVT alone	235	230
PE, with or without DVT	103	108

* Plus–minus values are means ±SD. ECOG denotes Eastern Cooperative Oncology Group, DVT deep-vein thrombosis, and PE pulmonary embolism.
† Eight patients were included in the study before the protocol was amended to exclude patients with an ECOG score of 3 or 4.
‡ Antineoplastic treatment included chemotherapy, radiation, and surgery.

Table 2. Sites of Solid Tumors.

Tumor Site	Dalteparin (N=298)	Oral Anticoagulant (N=308)
	no. of patients	
Breast	59	49
Colorectal area	54	54
Lung	40	50
Genitourinary tract	39	47
Gynecologic system	38	30
Pancreas	13	16
Brain	14	13
Other	41	49

Résultats

Table 3. Primary Efficacy Outcome Events.

Event	Dalteparin (N=336)	Oral Anticoagulant (N=336)
	no. of patients	
Deep-vein thrombosis alone	14	37
Nonfatal pulmonary embolism	8	9
Fatal pulmonary embolism	5	7
Total	27	53

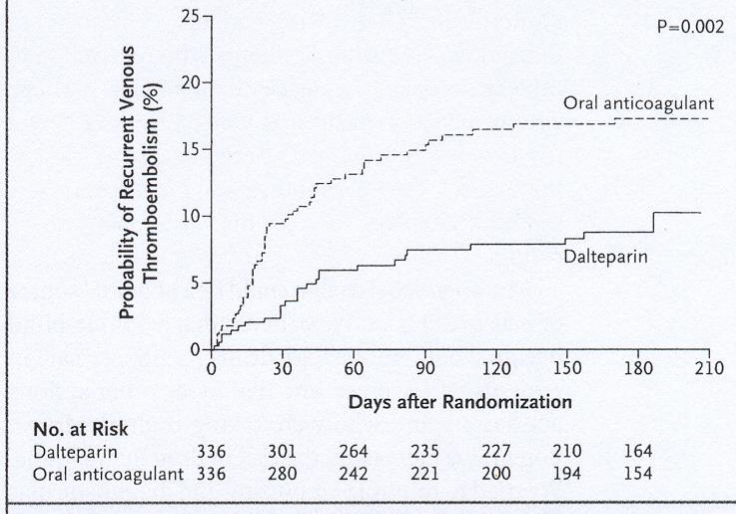


Figure 1. Kaplan–Meier Estimates of the Probability of Symptomatic Recurrent Venous Thromboembolism among Patients with Cancer, According to Whether They Received Secondary Prophylaxis with Dalteparin or Oral Anticoagulant Therapy for Acute Venous Thromboembolism.

An event was defined as an objectively verified, symptomatic episode of recurrent deep-vein thrombosis, pulmonary embolism, or both during the six-month study period. The hazard ratio for recurrent thromboembolism in the dalteparin group as compared with the oral-anticoagulant group was 0.48 (95 percent confidence interval, 0.30 to 0.77; P=0.002 by the log-rank test).

Résultats

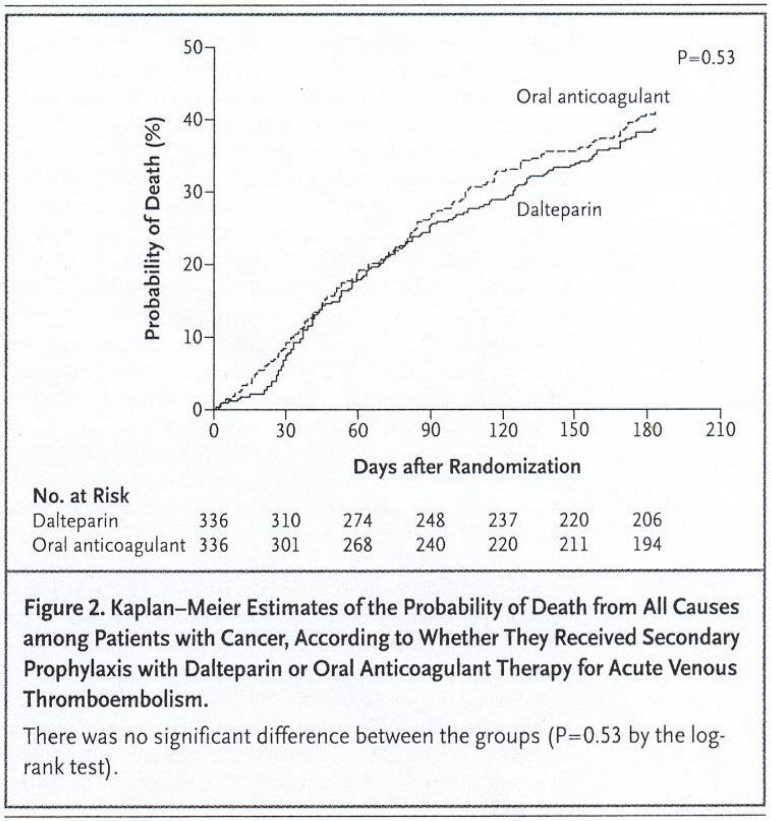


Figure 2. Kaplan–Meier Estimates of the Probability of Death from All Causes among Patients with Cancer, According to Whether They Received Secondary Prophylaxis with Dalteparin or Oral Anticoagulant Therapy for Acute Venous Thromboembolism.

There was no significant difference between the groups (P=0.53 by the log-rank test).

Conclusions : HBPM plus efficace que antivitamine K pour réduire le risque de récidive sans augmenter le risque hémorragique

En résumé

	Meyer 2002			Lee 2003		
	HBPM	**AVK**	**p**	**HBPM**	**AVK**	**p**
N pts	71	75		338	338	
TVP				4,1 %	10,9 %	0,002
Embolie non fatale			0,04	2,4 %	2,7 %	
Embolie fatale				1,5 %	2,1 %	
Hh majeure	7 %	16 %	0,09	6 %	4 %	0,27
Hh fatale	0	8 %	0,03	0,2 %	0	
Mortalité à 6 mois	31 %	38,7 %	0,25	39 %	41 %	0,53

Traitement recommandé

Table 4. Recommended anticoagulant regimens for venous thromboembolism prophylaxis and treatment in patients with cancer

Management phase	Dosage	Considerations
Prophylaxis[a]		
UFH	5000 U s.c. every 8 h	
Dalteparin	5000 U s.c. daily	
Enoxaparin	40 mg s.c. daily	
Fondaparinux	2.5 mg s.c. daily[b]	
Tinzaparin	4500 U s.c. or 75 U/kg s.c. daily	
Treatment: initial[c]		
UFH	80 U/kg i.v. bolus, then 18 U/kg/h i.v.[d]	
Dalteparin	100 U/kg s.c. every 12 h; 200 U/kg s.c. daily[e]	Significant renal clearance; avoid in patients with creatinine clearance <35 ml/min or adjust dose based on antifactor Xa levels
Enoxaparin	1 mg/kg s.c. every 12 h; 1.5 mg/kg s.c. daily[e]	Significant renal clearance; avoid in patients with creatinine clearance <35 ml/min or adjust dose based on antifactor Xa levels
Fondaparinux	<50 kg: 2.5–5 mg s.c. daily; 50–100 kg: 5–7.5 mg s.c. daily; >100 kg: 7.5–10 mg s.c. daily	Significant renal clearance; avoid in patients with creatinine clearance <35 ml/min or adjust dose based on antifactor Xa levels
Tinzaparin	175 U/kg s.c. daily	
Treatment: long term[f]		
Dalteparin	200 U/kg s.c. daily × 1 month, then 150 U/kg s.c. daily	
Warfarin	5–10 mg p.o. daily[g]	

Adapted from NCCN [16] and Lyman 2007 [14].

[a]Duration: until ambulatory or until hospital discharge.

[b]Not approved by the U.S. Food and Drug Administration for this indication.

[c]For 5–7 days minimum and until the INR is in the therapeutic range for two consecutive days if changing to warfarin.

[d]Adjust to achieve PTT of 2–2.9 times control value.

[e]Optimal dosing unclear in patients >120 kg.

[f]Duration: minimum 3–6 months for DVT and 6–12 months for PE. LMWH monotherapy is preferred for treatment of proximal DVT or PE and prevention of recurrent VTE in patients with advanced or metastatic cancer.

[g]Adjust dose to achieve INR of 2.0–3.0.

DVT, deep vein thrombosis; INR, international normalized ratio; i.v., intravenously; LMWH, low-molecular weight heparin; PE, pulmonary embolism; p.o., per os (by mouth); PTT, partial thromboplastin time; s.c., subcutaneously; UFH, unfractionated heparin; VTE, venous thromboembolism.

HBPM aussi pour des raisons de facilité

Table 1. Problems with the use of VKAs in cancer patients

- Treatment with VKAs is often difficult to manage and monitor (e.g. problems with venous access, potential interactions with a range of other drugs and foods)
- Frequent interruptions of anticoagulant therapy may be necessary due to thrombocytopenia or invasive procedures
- Resistance to VKAs can develop and lead to risk of recurrent thrombosis despite adequate levels of anticoagulation, increased risk of bleeding complications

Table 2. Advantages of LMWH over VKAs

- Body weight-adjusted dose without need for laboratory monitoring
- Predictable anticoagulant response that is not affected by concomitant medications or diet
- Rapid onset of action and predictable clearance, which minimises difficulties of treatment interruptions

Faut-il mettre sous HBPM les patients sous chimiothérapie à titre préventif?

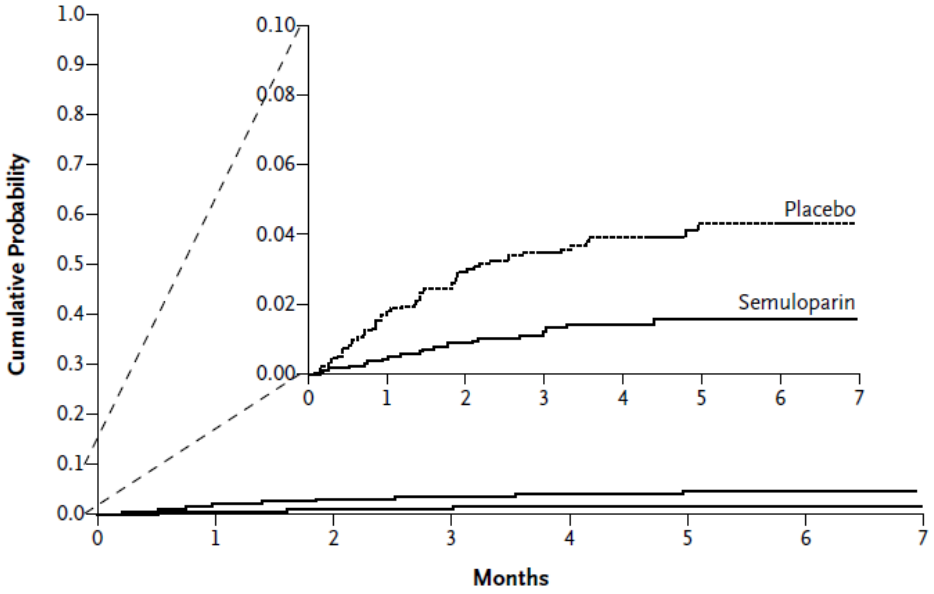
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Semuloparin for Thromboprophylaxis in Patients Receiving Chemotherapy for Cancer

Giancarlo Agnelli, M.D., Daniel J. George, M.D., Ajay K. Kakkar, M.B., B.S., Ph.D., William Fisher, M.D., Michael R. Lassen, M.D., Patrick Mismetti, M.D., Patrick Mouret, M.D., Umesh Chaudhari, M.D., Francesca Lawson, M.D., and Alexander G.G. Turpie, M.D., for the SAVE-ONCO Investigators*

N Engl J Med 2012;366:601-9.



No. at Risk								
Semuloparin	1608	1410	1227	986	681	384	197	77
Placebo	1604	1375	1212	985	689	403	201	92
No. of Events								
Semuloparin	0	7	13	17	19	20	20	20
Placebo	0	26	42	49	53	55	55	55

Figure 1. Kaplan–Meier Curves for the Primary Efficacy Outcome in the Intention-to-Treat Population, According to Study Group.

The primary efficacy outcome was the composite of any symptomatic deep-vein thrombosis in lower or upper limbs, any nonfatal pulmonary embolism, or death related to venous thromboembolism (fatal pulmonary embolism or unexplained death) occurring between randomization and 3 days after the last injection of the study drug. The inset shows the same data on an enlarged y axis.

Table 1. Primary Efficacy Outcome, According to Treatment Group.*

Outcome	Semuloparin (N=1608)	Placebo (N=1604)	Hazard Ratio (95% CI)†
Any VTE or VTE-related death — no. (%)	20 (1.2)	55 (3.4)	0.36 (0.21–0.60)
Symptomatic deep-vein thrombosis	11 (0.7)	34 (2.1)	0.32 (0.15–0.62)
Upper limbs	3 (0.2)	9 (0.6)	0.33 (0.07–1.18)
Lower limbs	8 (0.5)	25 (1.6)	0.32 (0.13–0.69)
Proximal	4 (0.2)	19 (1.2)	0.21 (0.06–0.58)
Distal	4 (0.2)	12 (0.7)	0.33 (0.09–0.99)
Pulmonary embolism	10 (0.6)	24 (1.5)	0.41 (0.19–0.85)
Nonfatal	3 (0.2)	15 (0.9)	0.20 (0.05–0.63)
Symptomatic	3 (0.2)	12 (0.7)	0.25 (0.06–0.83)
Detected during tumor evaluation	0	3 (0.2)	NE
Any VTE-related death	7 (0.4)	9 (0.6)	0.77 (0.27–2.13)
Outcome according to primary cancer site — no./total no. (%)			
Lung	9/591 (1.5)	25/589 (4.2)	0.36 (0.17–0.77)
Pancreas	3/126 (2.4)	14/128 (10.9)	0.22 (0.06–0.76)
Stomach	1/204 (0.5)	4/207 (1.9)	0.25 (0.03–2.20)
Colon or rectum	5/464 (1.1)	9/461 (2.0)	0.54 (0.18–1.60)
Bladder	1/32 (3.1)	3/31 (9.7)	0.30 (0.03–2.95)
Ovary	1/191 (0.5)	0/188	NE
Outcome according to stage of cancer — no./total no. (%)			
Metastatic	16/1097 (1.5)	38/1095 (3.5)	0.42 (0.23–0.75)
Locally advanced	4/511 (0.8)	17/509 (3.3)	0.23 (0.08–0.68)
Outcome according to no. of risk factors for VTE			
0	9/923 (1.0)	23/932 (2.5)	0.39 (0.18–0.84)
1 or 2	9/652 (1.4)	27/632 (4.3)	0.32 (0.15–0.68)
≥3	2/33 (6.1)	5/40 (12.5)	0.56 (0.11–2.93)

* Data are for the 3212 patients in the intention-to-treat population. Multiple outcomes occurred in individual patients. CI denotes confidence interval, NE not estimable, and VTE venous thromboembolism.

† Odds ratios are reported for the individual components of the composite primary outcome. Hazard ratios were not calculated for these values, owing to the low number of events.

Table 2. Clinically Relevant Bleeding Events during Treatment.*

Bleeding Events	Semuloparin (N=1589)	Placebo (N=1583)	Odds Ratio (95% CI)
	no. (%)		
Clinically relevant bleeding	45 (2.8)	32 (2.0)	1.41 (0.89–2.25)
Major bleeding†	19 (1.2)	18 (1.1)	1.05 (0.55–2.04)
Clinically relevant nonmajor bleeding‡	26 (1.6)	14 (0.9)	1.86 (0.98–3.68)

* Data are for the 3172 patients included in the safety analysis.

Routine Heparin for Patients with Cancer? One Answer, More Questions

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Table 1. Summary of Findings Table Showing the Relative Risks and Absolute Effects over 12 Months for Each Important Outcome after Treatment with a Low-Molecular-Weight Heparin in Patients Receiving Chemotherapy for Cancer.*

Outcome after 12 Months	Participants	Relative Risk (95% CI)	Anticipated Absolute Effect		Quality of Evidence (GRADE) and Comments†
			Risk without LMWH	Risk Difference with LMWH (95% CI)	
	no. (no. of studies)		*no. of events per 1000 patients*		
Death	6245 (10)	0.94 (0.88–1.00)	501	30 fewer (60 fewer to 0 more)	Moderate-quality evidence owing to imprecision and concern about publication bias; a survival analysis based on data from 9 studies shows a hazard ratio of 0.83 (95% CI, 0.72–0.95)
Symptomatic VTE	5979 (9)	0.57 (0.40–0.81)	46	20 fewer (27 fewer to 9 fewer)	High-quality evidence; the data are combined for pulmonary embolism and symptomatic deep venous thrombosis
Major bleeding	6518 (11)	1.06 (0.71–1.57)	16	1 more (5 fewer to 9 more)	Moderate-quality evidence owing to imprecision; the increase may be acceptable to patients, given that VTE, which occurs more frequently, may be equally unpleasant
Minor bleeding	6020 (9)	1.18 (0.89–1.55)	27	5 more (3 fewer to 15 more)	Moderate-quality evidence owing to imprecision; however, this outcome is unlikely to be critical for decision making

* These estimates of the effects of treatment with low-molecular-weight heparin (LMWH) were compared with no LMWH in patients with cancer who had no other therapeutic or prophylactic indication for anticoagulation. These pooled data are from the studies in our review (2857 patients),[3] the SAVE-ONCO trial (3212),[2] and one other study (503).[4] CI denotes confidence interval, GRADE Grading of Recommendations Assessment, Development and Evaluation, and VTE venous thromboembolism.

† We used the GRADE methodology to assess the quality of evidence. With high-quality evidence, further research is very unlikely to change our confidence in the estimate of effect. With moderate-quality evidence, further research is likely to influence our confidence in the estimate of effect and may change the estimate.

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ASCO SPECIAL ARTICLE

Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update 2014

Gary H. Lyman, Kari Bohlke, Alok A. Khorana, Nicole M. Kuderer, Agnes Y. Lee, Juan Ignacio Arcelus, Edward P. Balaban, Jeffrey M. Clarke, Christopher R. Flowers, Charles W. Francis, Leigh E. Gates, Ajay K. Kakkar, Nigel S. Key, Mark N. Levine, Howard A. Liebman, Margaret A. Tempero, Sandra L. Wong, Mark R. Somerfield, and Anna Falanga

Key Recommendations

- Most hospitalized patients with active cancer require thromboprophylaxis throughout hospitalization. Data are inadequate to support routine thromboprophylaxis in patients admitted for minor procedures or short chemotherapy infusion.
- Routine thromboprophylaxis is not recommended for ambulatory patients with cancer. It may be considered for highly select high-risk patients.
- Patients with multiple myeloma receiving antiangiogenesis agents with chemotherapy and/or dexamethasone should receive prophylaxis with either low–molecular weight heparin (LMWH) or low-dose aspirin to prevent venous thromboembolism (VTE).
- Patients undergoing major cancer surgery should receive prophylaxis starting before surgery and continuing for at least 7 to 10 days.
- Extending postoperative prophylaxis up to 4 weeks should be considered in those undergoing major abdominal or pelvic surgery with high-risk features.
- LMWH is recommended for the initial 5 to 10 days of treatment of established deep vein thrombosis and pulmonary embolism as well as for long-term secondary prophylaxis for at least 6 months.
- Use of novel oral anticoagulants is not currently recommended for patients with malignancy and VTE.
- Anticoagulation should not be used to extend survival of patients with cancer in the absence of other indications.
- Patients with cancer should be periodically assessed for VTE risk.
- Oncology professionals should educate patients about the signs and symptoms of VTE.

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ORIGINAL ARTICLE

International clinical practice guidelines for the treatment and prophylaxis of venous thromboembolism in patients with cancer

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3 In patients receiving chemotherapy, prophylaxis is not recommended routinely [Grade 1B].
Values and preferences: subcutaneous injections.