



Prevention and Treatment of Cancer-associated Thrombosis: Improving Patient Outcomes

Webinar

Planned and conducted by ASHP Advantage.
Supported by educational grants from Eisai Inc. and sanofi-aventis U.S.



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Webinar Information

How do I register?

Go to the educational initiative website at www.ashpadvantage.com/CaThrombosis. Click on the appropriate date in the “Register Now” box on the right side of your screen and complete the fields on the registration page. You will be e-mailed computer and phone connection information.

What is a live webinar?

A live webinar brings the presentation to you – at your desk, in your home, through a staff in-service. You listen to the speaker presentation in “real time” as you watch the slides on the computer screen. You will have the opportunity to ask questions related to the topic at the end of the activity. In fact, continuing pharmacy education (CPE) credits earned through participation in webinars qualify as **live CPE credit** and may be counted toward live CPE requirements when renewing your license. Please join the conference at least 5 minutes prior to the scheduled start time for important activity announcements.

How do I process my CPE?

After completion of this live webinar, you will process your CPE online and print your statement of credit at the ASHP Learning Center found at <http://ce.ashp.org>. To process your CPE, you will need the **Activity and Session Codes** that will be announced at the end of the webinar. Complete CPE processing instructions are available on the last page of this handout.

If you have questions about processing your CPE online, please contact ASHP Advantage at support@ashpadvantage.com.

What do I need in order to participate in the webinar?

1. Telephone to dial the toll-free number and listen to the presentation.
2. Computer with internet access and basic system requirements. When you register, the webinar system will assess your system to ensure compatibility.

What if I would like to arrange for my colleagues to participate in this webinar as a group?

One person should register for the webinar. That person will receive the webinar computer linking and telephone dial-in instructions via email. Groups may participate using one phone line (speaker phone). Each participant processes his or her individual continuing pharmacy education statement online at the conclusion of the CPE activity.

How do I ask a question of the presenter?

Follow the instructions provided at the beginning of the activity for submitting text questions. The speaker will answer as many questions as possible at the conclusion of the activity.

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Faculty

Ann K. Wittkowsky, Pharm.D., CACP, FASHP, FCCP

Clinical Professor
University of Washington School of Pharmacy
Director, Anticoagulation Services
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Seattle, Washington

Ann K. Wittkowsky, Pharm.D., CACP, FASHP, FCCP, is Clinical Professor of Pharmacy at the University of Washington School of Pharmacy and Director of Anticoagulation Services at the University of Washington Medical Center. As a clinician and educator in the field of antithrombotic pharmacotherapy, she has contributed extensively to the care of patients and the education of health care providers regarding antithrombotic pharmacotherapy. She is the author of over 100 scientific papers, book chapters and abstracts, and co-editor of the textbook *Managing Oral Anticoagulation Therapy: Clinical and Operational Guidelines*. She has lectured widely throughout the United States and Canada, maintains an active clinical research program, and is board certified as an anticoagulation care provider.

Dr. Wittkowsky serves as an editorial board member for *Pharmacotherapy* and the *Journal of Thrombosis and Thrombolysis*, as a reviewer for numerous medical and scientific journals, and as a member of the board of directors of The Anticoagulation Forum, a multidisciplinary organization of anticoagulation care providers. She is the director of the Northwest Anticoagulation Consortium, a preceptor for the ASHP Research and Education Foundation's Antithrombotic Pharmacotherapy Traineeship, a member of the American College of Chest Physicians' 8th Conference on Antithrombotic and Thrombolytic Therapy, and was recently selected as a member of the 9th Conference. She is an elected member of the Board of Regents of the American College of Clinical Pharmacy.

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The faculty and planners report the following relationships:

Ann K. Wittkowsky, Pharm.D., CACP, FASHP, FCCP

Dr. Wittkowsky declares that she has served on the speaker's bureau for sanofi-aventis.

John Fanikos, M.B.A., R.Ph.

Mr. Fanikos declares that he has served on the speaker's bureau for Eisai Pharmaceuticals and sanofi-aventis. He has also served as a consultant for The Medicines Company.

Peggy S. Kraus, Pharm.D., CACP

Dr. Kraus declares that she has no relationships pertinent to this activity.

Edith A. Nutescu, Pharm.D., FCCP

Dr. Nutescu declares that she has served on the speaker's bureau for Eisai Pharmaceuticals, GlaxoSmithKline, and sanofi-aventis. She has also served as a consultant for Baxter, Eisai Pharmaceuticals, GlaxoSmithKline, and sanofi-aventis.

Kristi Hofer, Pharm.D.

Dr. Hofer declares that she has no relationships pertinent to this activity.

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Continuing Education Information



The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1 hour (0.1 CEU) of continuing pharmacy education credit (ACPE activity #204-000-09-425-L01P).

Attendees must complete a Continuing Pharmacy Education Request online and may print their official ASHP statements at the ASHP Learning Center at <http://ce.ashp.org> after the activity.

Methods and Format

This is a live online activity consisting of audio, online presentation slides, and an activity evaluation tool. Participants must participate in the entire presentation and complete the course evaluation to receive continuing pharmacy education credit. Participants may print their official statements of continuing pharmacy education credit immediately. This activity is provided free of charge.

Target Audience

This continuing pharmacy education webinar was planned to meet the needs of all pharmacists, especially those who manage anticoagulation therapy and/or care for patients with cancer.

Prevention and Treatment of Cancer-associated Thrombosis: Improving Patient Outcomes

Activity Description

Patients with cancer face many challenges associated with their disease and treatment. One potential complication is cancer-associated thrombosis which has a negative impact on patient outcomes and may even result in death. Central to managing these patients is the ongoing need to assess each patient for the risk of developing venous thromboembolism, and then to tailor supportive care throughout the cancer treatment period such that the complication can be avoided, when possible, and appropriately treated, when necessary.

This activity will focus on preventing and managing cancer-associated thrombosis. Using patient case examples, the faculty will engage participants in the clinical decision-making process involved when assessing a patient's risk of venous thromboembolism, selecting preventative therapy, and then—after the prophylaxis fails—choosing a treatment regimen.

Learning Objectives

At the conclusion of this knowledge-based CPE activity, participants should be able to

- Explain the rationale for a proactive approach to risk assessment and prevention of thrombosis in patients with cancer.
- Summarize current literature and clinical guidelines regarding prevention and treatment of cancer-associated thrombosis.
- Select an appropriate anticoagulant strategy and duration of therapy for treatment of venous thromboembolism in patients with malignancy.

Prevention and Treatment of Cancer-associated Thrombosis: Improving Patient Outcomes



Prevention and Treatment of Cancer-associated Thrombosis: Improving Patient Outcomes

Ann K. Wittkowsky, Pharm.D., CACP, FASHP, FCCP
 Clinical Professor
 University of Washington School of Pharmacy
 Director, Anticoagulation Services
 University of Washington Medical Center
 Seattle, Washington

Learning Objectives

1. Explain the rationale for a proactive approach to risk assessment and prevention of thrombosis in patients with cancer
2. Summarize current literature and clinical guidelines regarding prevention and treatment of cancer-associated thrombosis
3. Select an appropriate anticoagulant strategy and duration of therapy for treatment of venous thromboembolism (VTE) in patients with malignancy

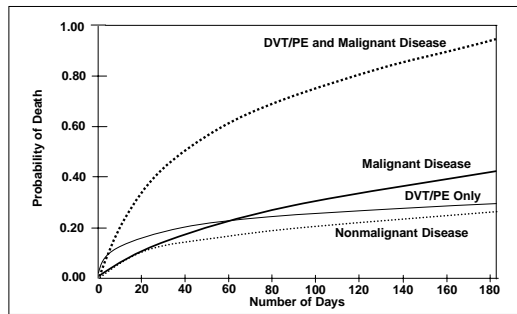
Cancer, Mortality and VTE

- Annual incidence of VTE in all patients: 117 in 100,000
- Cancer increases risk of thrombosis 4.1-fold
- Recurrence of VTE 3-fold higher in patient with cancer
- Chemotherapy increases risk of thrombosis 6.5-fold
- Death rate from cancer 4-fold higher if concurrent VTE
- Additive risk factors: surgery, radiation therapy, central venous catheters, other antitumor and supportive therapies

Silverstein MD et al. *Arch Intern Med*. 1998;158:585-93. Sorensen et al. *N Engl J Med* 2000;343:1846-50.
 Heit JA et al. *Arch Intern Med*. 2000;160:809-15. Levitan et al. *Medicine* 1999;78:284-91.
 Prandoni et al. *Blood* 2002;100:3484-8. Khorana et al. *J Thromb Haemost* 2007;5:632-4.
 White et al. *Thromb Haemost* 2003;90:445-55.

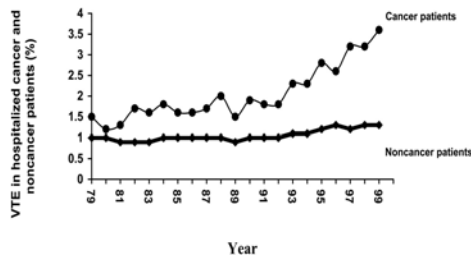
VTE, Cancer and Survival

N = 1,211,944 Medicare admissions with cancer vs 8,177,634 without cancer



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

Increasing Incidence of VTE in Patients with Cancer



Stein PD et al. *Am J Med* 2006; 119:60-8.

Presumed Causes for Increasing Incidence of VTE in Cancer

- Improved imaging techniques that detect incidental VTE
- Greater awareness of VTE
- Improved survival of cancer patients
- Use of more thrombogenic cancer treatments

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Outcomes and Cost of Deep Vein Thrombosis in Patients with Cancer

N = 529 consecutive cancer patients with DVT

COMPLICATIONS		
Hemorrhage		12%
- Minor hemorrhage		4%
- Major hemorrhage		8%
Pulmonary embolism		4%
DVT-related death		1%
Treatment-related death		1%
HOSPITALIZATIONS		
Mean length of stay		11 days
Mean cost per patient		\$20,065 (2002)

Elting LS et al. *Arch Intern Med.* 2004; 164:1653-61.

KK is a 44-year-old woman with a new diagnosis of ovarian cancer. She is admitted to the hospital for cytoreductive surgery and placement of a central venous catheter for administration of cisplatin-based chemotherapy.

Which of the following places KK at risk for VTE?

- Cancer
- Surgery
- Central venous catheter
- Chemotherapy
- All of the above

Pathogenesis of Thrombosis in Cancer – A Modification of Virchow's Triad

1. Stasis

- Prolonged bed rest
- Extrinsic compression of blood vessels by tumor

2. Vascular Injury

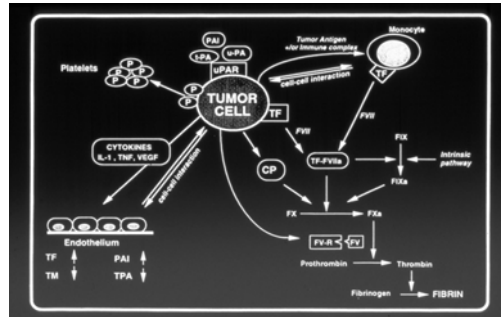
- Direct invasion by tumor
- Prolonged use of central venous catheters
- Endothelial damage by chemotherapy drugs
- Effect of tumor cytokines on vascular endothelium

3. Hypercoagulability

- Tumor-associated procoagulants and cytokines (tissue factor, CP, TNF α , IL-1 β , VEGF, etc.)
- Impaired endothelial cell defense mechanisms (APC resistance; deficiencies of AT, Protein C and S)
- Enhanced selectin/integrin-mediated, adhesive interactions between tumor cells, vascular endothelial cells, platelets, and host macrophages

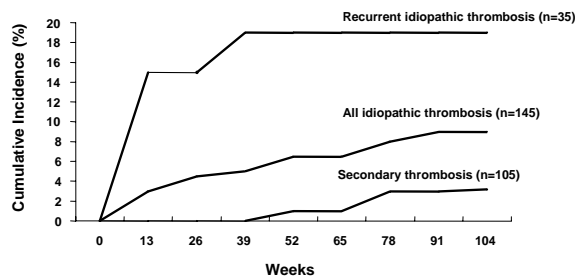


Procoagulant Tumor Cell Activities



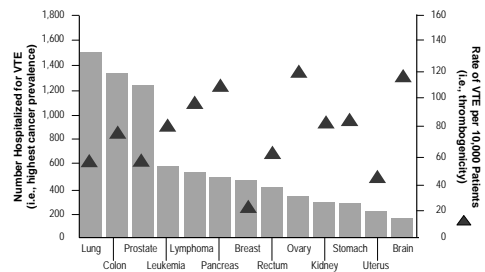
Falanga A, Rickles FR. *Semin Thromb Hemost.* 1999; 25:173-82.

Cumulative Incidence of Subsequent Cancer in Patients with Initial Diagnosis of VTE



Prandoni P, et al. *N Engl J Med.* 1992;327:1128-33.

Tumor Types Associated with VTE



Linenberger ML, Wittkowsky AK. *Oncology (Williston Park).* 2005; 19:853-61.
Levitan N et al. *Medicine (Baltimore).* 1999; 78:285-91.

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Additional Risk Factors for VTE in Malignancy

- Surgery
- Central venous catheters
- Radiation therapy
- Antitumor agents (chemotherapy, hormone therapy, targeted antibodies)
- Supportive agents (growth factors, heparins, immune globulin IV)

Linenberger ML, Wittkowsky AK. *Oncology (Williston Park)*. 2005; 19:853-61.

Anticancer Agents Associated with Increased Risk of VTE

L-asparaginase
 Bevacizumab
 Bleomycin
 Carmustine
 Cisplatin
 5-fluorouracil
 Mitomycin C
 Tamoxifen
 Thalidomide and derivatives
 (in association with chemotherapy or high-dose dexamethasone)*
 Vinca alkaloids

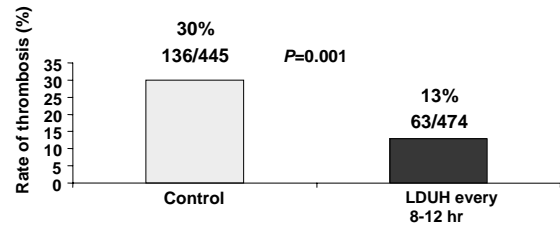
Lee AY. *Hematology Am Soc Hematol Educ Program*. 2006; 438-43.
 * Bennett CL et al. *JAMA*. 2006; 296:2558-60.

Which of the following is likely to be the most effective method for preventing VTE in KK?

- Enoxaparin 40 mg subcutaneously once daily
- Dalteparin 2500 units subcutaneously once daily
- Unfractionated heparin 5000 units subcutaneously every 8 hr
- Unfractionated heparin 5000 units subcutaneously every 12 hr
- All of the above are equally effective

Pharmacologic Prophylaxis in General Surgery Patients with Cancer

Meta-analysis of 29 surgical prophylaxis studies of low-dose unfractionated heparin (LDUH) vs. control with cancer patients analyzed separately



Ciaggett GP, Reisch JS. *Ann Surg*. 1988; 208:227-40.

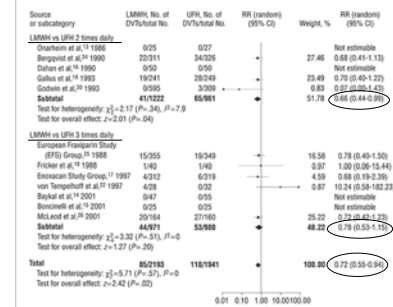
LDUH vs. LMWH for VTE Prophylaxis in Cancer Surgery

N: 1115 (631 evaluable venograms)
 Treatment: Abdominal/pelvic surgery for cancer
 Initiation: 2 hours preoperatively
 Duration: 10 days of prophylaxis

	UFH 5000 units q 8 hr	Enoxaparin 40 mg once daily	P-Value
3-month outcomes			
VTE	18.2%	14.7%	NS
Death	0	0.3%	NS
Major bleeding	2.9%	4.1%	NS
Total bleeding	17.1%	18.7%	NS

ENOXCAN Study Group. *Br J Surg*. 1997; 84:1099-103.

LDUH vs. LMWH for VTE Prophylaxis in Cancer Surgery: Meta-Analysis



Aki EA et al. *Arch Intern Med*. 2008; 168:1261-9.

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Incidence and Economic Implications of HIT in Patients Receiving VTE Prophylaxis

N = 10,121 adult medical patients receiving LDUH tid or enoxaparin 40 mg daily

Incidence of HIT UFH: 0.51%
LMWH: 0.084%

Admission cost with HIT: \$56,364
without HIT: \$15,231

Cost of LMWH is \$13.88 less than UFH per patient

Creekmore FM et al. *Pharmacotherapy*. 2006; 26:1438-45.

VTE Prophylaxis in Acute Medical Illness Drug Therapy vs. Placebo

Study	RRR (%)	Thromboprophylaxis	Patients with VTE (%)
MEDENOX <i>P</i> <0.001	63	Placebo	14.9
		Enoxaparin 40 mg	5.5
PREVENT <i>P</i> =0.0015	45	Placebo	5.0
		Dalteparin	2.8
ARTEMIS <i>P</i> =0.029	47	Placebo	10.5
		Fondaparinux	5.6

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

Routine Prophylaxis for Medical Patients with Malignancy

Unresolved Issues:

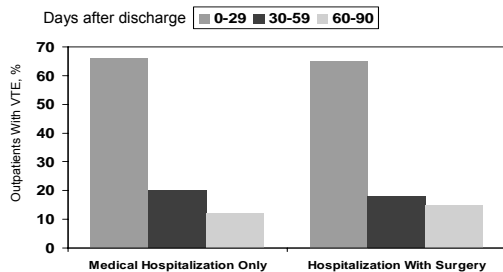
1. Relative efficacy of UFH q 8 hr vs. LMWH
2. Role of ambulatory status on VTE risk
2. Role of chemo- or radiation-induced thrombocytopenia on bleeding risk
4. Appropriate duration of therapy

For how long should KK receive VTE prophylaxis?

- a. Until hospital discharge
- b. 6-10 days
- c. 30 days
- d. 3 months
- e. Chronic prevention is necessary

Timing of VTE Diagnosis After Hospital Discharge

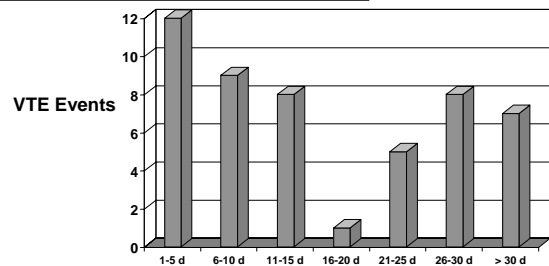
N=1897 patients discharged from hospital with subsequent VTE



Spencer FA et al. *Arch Intern Med*. 2007; 167:1471-5.

Time Distribution of VTE After Cancer Surgery

@RISTOS Registry: prospective cohort N=2373



Agnelli G et al. *Ann Surg*. 2006; 243:89-95.

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Extended Prophylaxis After Cancer Surgery

N: 501 (332 evaluable venograms) Duration: 21 days after initial
Tx: abdominal surgery for cancer 6-10 days of routine enoxaparin

90-day Outcomes:

	Placebo	Enoxaparin 40 mg once daily	
All VTE			<i>P</i> = 0.01
Proximal DVT	13.8%	5.5%	
PE	2.4%	1.2%	
	0.6%	0	
Major bleeding	0.4%	1.2%	<i>P</i> = 0.62
Total bleeding	4.4%	7.1%	<i>P</i> = 0.2

Bergqvist D et al for the ENOXACAN II investigators. *N Engl J Med.* 2002; 346:975-80.

Guidelines for VTE Prevention in Malignancy

	NCCN	ASCO	ACCP
VTE Prophylaxis in Hospitalized Cancer Patients	Anticoagulation for all inpatients with a diagnosis of cancer or clinical suspicion of cancer who do not have a contraindication (LMWH/fondaparinux/UFH tid)	Should be considered candidates for VTE prophylaxis in the absence of bleeding or other contraindications to anticoagulation (LMWH/fondaparinux/UFH tid)	1. Routine thromboprophylaxis appropriate for the type of surgery (Grade 1A) 2. Routine prophylaxis as for other high-risk medical patients (Grade 1A) (LMWH/fondaparinux/UFH tid)
Cancer Surgery Patients following Hospital Discharge	LMWH/fondaparinux/UFH tid for up to 4 weeks post-op particularly for high-risk abdominal or pelvic cancer surgery patients	LMWH for up to 4 weeks may be considered after major abdominal/pelvic surgery with residual malignant disease, obesity or a previous history of VTE	Consider extended prophylaxis up to 28 days in selected high risk patients, including cancer surgery and previous history of VTE (Grade 2A)
Medical Oncology Patients Following Hospital Discharge	Recommended in high risk settings	Not addressed	Optimal duration is unclear

1. J NCCN. 2006;4:839-69 (www.nccn.org)
2. J Clin Oncol. 2007;25:5490-5505
3. Chest. 2008;133:381S-453S

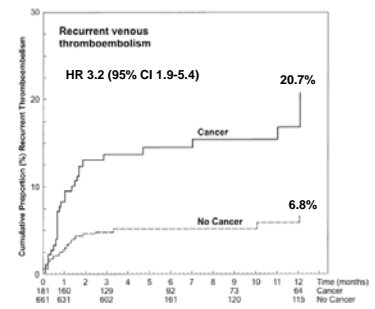
Six weeks after hospital discharge, KK returns to the hospital with left lower extremity pain, swelling, and tenderness. A duplex ultrasound is positive for DVT.

How should KK's DVT initially be treated?

- Dalteparin SC for 3 months
- Enoxaparin SC and warfarin overlapped until INR 2 to 3, then warfarin for 3 months
- Unfractionated heparin IV for 5-7 days, then warfarin for 3 months
- Fondaparinux SC for 1 month, then warfarin for 3 months

Recurrent VTE During Oral Anticoagulation

With Cancer Without Cancer
N: 181 661
Course: chronic 3-6 mo
Tx: initial UFH/LMWH, then warfarin (INR 2-3)

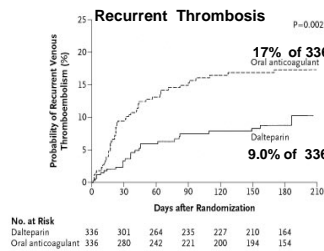


Prandoni P et al. *Blood.* 2002; 100:3484-8.

Warfarin vs. Dalteparin for VTE Treatment in Malignancy

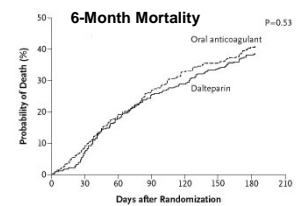
Tx: dalteparin 200 units/kg once daily x 1 mo, then 150 U/kg/day vs. dalteparin 200 units/kg/day, then coumarin derivative (goal INR 2-3)

Duration: 6 months



Lee AY et al. *N Engl J Med.* 2003; 349:146-53.

Warfarin vs. Dalteparin for VTE Treatment in Malignancy



Lee AY et al. *N Engl J Med.* 2003; 349:146-53.

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Subgroup Analysis

12-month cumulative mortality rate:

	<u>Dalteparin</u>	<u>Warfarin</u>	
Metastatic disease (n = 452)	72%	69%	P = 0.46
Non-metastatic disease (N = 150)	20%	36%	P = 0.03

Lee AY et al. *J Clin Oncol.* 2005; 23:2123-9.

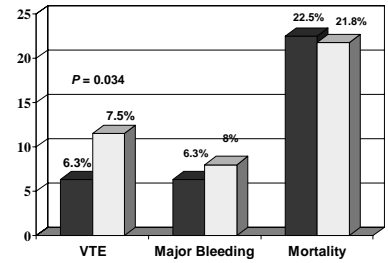
Warfarin vs. Tinzaparin for VTE Treatment in Malignancy

Subgroup of cancer patients from the LITE Study

■ Tinzaparin: n=80 (175 units/kg/day)
□ UFH/warfarin: n=87

Duration: 3 months

Follow-up: 3 months



Hull RD et al. *J Thromb Haemost.* 2003; 1(Suppl 1):OC395 (abstract) (LITE study)
Hull RD et al. *J Thromb Haemost.* 2003; 1(Suppl 1):P1373a (abstract) (Cancer subgroup)

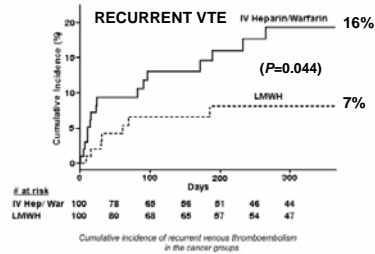
Warfarin vs. Tinzaparin for VTE Treatment in Malignancy

Tinzaparin: n=100 (175 units/kg/day)

UFH/warfarin: n=100

Duration: 3 months

Follow-up: 3 months & 12 months



Hull RD et al. *Am J Med.* 2006; 119:1062-72 (Main-LITE Study)

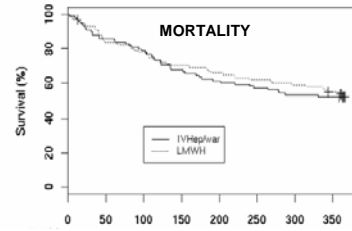
Warfarin vs. Tinzaparin for VTE Treatment in Malignancy

Tinzaparin: n=100 (175 units/kg/day)

UFH/warfarin: n=100

Duration: 3 months

Follow-up: 3 months & 12 months



Hull RD et al. *Am J Med.* 2006; 119:1062-72 (Main-LITE Study)

Warfarin vs. Enoxaparin for VTE Treatment in Malignancy

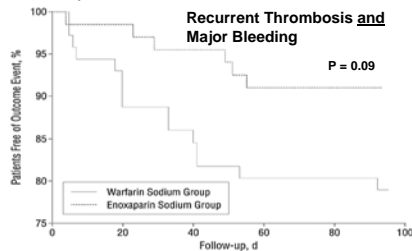
Tx: enoxaparin 1.5 mg/kg SC once daily vs. enoxaparin 1.5 mg/kg SC followed by warfarin to INR 2-3

Duration: 3 mo

Incidence of recurrent thrombosis and major bleeding:

Enoxaparin: 10.5% of 67

Warfarin: 21.1% of 71

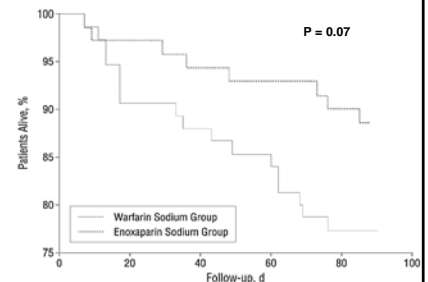


Meyer G et al. *Arch Intern Med.* 2002; 162:1729-35.

Warfarin vs. Enoxaparin for VTE Treatment in Malignancy

90-Day Mortality

Enoxaparin: 11.3%
Warfarin: 22.7%



Meyer G et al. *Arch Intern Med.* 2002; 162:1729-35.

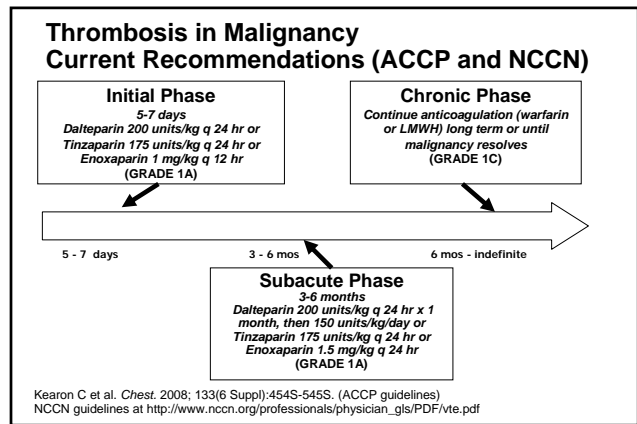
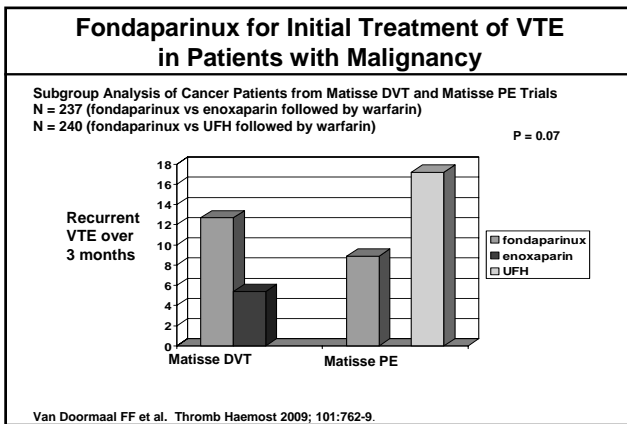
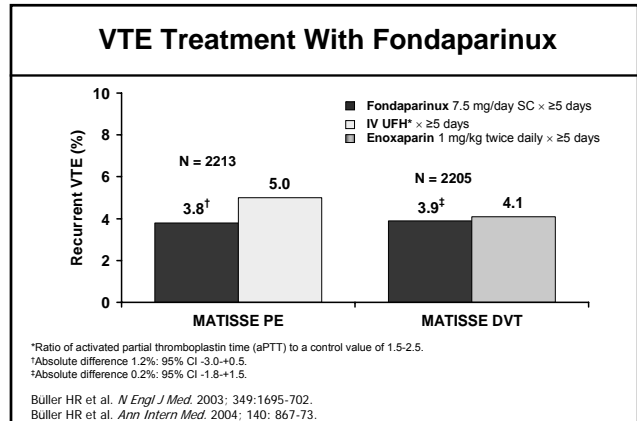
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Once- vs. Twice-Daily Enoxaparin for Treatment of VTE

N = 900

	UFH	1.5 mg/kg every 24 hr	1 mg/kg every 12 hr
Mortality	3.1%	3.7%	2.2%
Major hemorrhage	2.1%	1.7%	1.3%
Recurrent VTE			
All patients	4.1%	4.4%	2.9%
Obesity (BMI >27)	2.5%	7.3%	3.4%
Malignancy	6.7%	12.2%	6.4%

Merli G et al. *Ann Intern Med.* 2001; 134:191-202.



Guidelines for VTE Treatment in Malignancy

	NCCN	ASCO	ACCP
Treatment of established VTE	Immediate treatment with LMWH, fondaparinux or UFH	LMWH is the preferred approach for the first 5-10 days	Initial treatment with LMWH, fondaparinux or UFH (Grade 1A)
Long term treatment with LMWH (preferred) or warfarin	Long term treatment with LMWH (preferred) or warfarin	LMWH, given for at least 6 months, is preferred for long term anticoagulant therapy	LMWH for 3-6 months (Grade 1A)
Recommend indefinite treatment	Recommend indefinite treatment	After the first 6 months, indefinite anticoagulation should be considered	Subsequent anticoagulation with VKA or LMWH indefinitely or until cancer is resolved (Grade 1C)

- J NCCN. 2006;4:839-69 (www.nccn.org).
- J Clin Oncol. 2007;25:5490-5505.
- Chest. 2008;133:454S-545S.

Barriers to Long-Term use of LMWH for Treatment of Cancer-Associated VTE

Initial treatment	
LMWH for 3-6 months	19%
UFH/LMWH for 5-7 days followed by warfarin	81%
Reasons LMWH not used long term	
Not covered by medical insurance	49.4%
Physician preference	32.0%
Patient refused long-term injections	13.6%
History of HIT	2.5%
Severe renal insufficiency	2.5%

Witkowsky AK. *J Thromb Haemost.* 2006; 4:2090-1.

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Cost Considerations: LMWH vs. Warfarin for VTE Treatment

<i>Estimated VTE cost in malignancy¹</i>	\$20,065
Cost of VTE in 8 of 100 patients treated with dalteparin	\$ 160,520
Cost of VTE in 16 of 100 patients treated with warfarin	<u>\$ 321,040</u>
	SAVED \$160,520
Cost of dalteparin x 6 months x 100 patients (AWP)	\$1,140,000
Cost of warfarin x 6 months x 100 patients (AWP)	<u>\$16,080</u>
	SPENT \$1,123,920

DIFFERENCE: \$9,634 per patient²

1. Elting LS et al. *Arch Intern Med.* 2004; 164:1653-61.
 2. Linenberger ML, Witkowsky AK. *Oncology (Williston Park).* 2005; 19:1077-84.
- AWP = average wholesale price

Summary

- Patients with cancer are at increased risk of venous thromboembolism
- Cancer and cancer treatments promote hypercoagulability
- VTE prophylaxis is recommended in high-risk patients with cancer
- VTE should be appropriately and aggressively treated

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