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Managing Deep Vein Thrombosis Risk in Oncology Patients

Office and Outpatient Settings

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ABSTRACT

Thrombosis remains one of the leading causes of death in hospitalized cancer patients, and deep vein thrombosis (DVT) continues to cause multiple patient complications. Understanding the relationship between DVT and cancer may help prevent and manage these events. Recently, new low molecular weight heparin therapies (LMWH) have attracted much attention as an alternative to the standard DVT treatment protocols of inpatient intravenous heparin and oral warfarin anticoagulation therapy. LMWH therapies have shown economic and therapeutic advantages compared to unfractionated heparin in cancer patients, and are currently being studied for their use in DVT prevention, treatment, and survival enhancement.

While we are making great advances in understanding the correlations between DVT and cancer, many questions still remain unanswered, and we are still far from our diagnostic and therapeutic goals.

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Low Molecular Weight Heparin vs Unfractionated Heparin

The economic benefits of using low molecular weight heparin (LMWH) have been proven. Unfractionated heparin requires an inpatient hospital stay and all of the direct and indirect costs of treating a patient that inevitably ensue. The use of LMWH in the outpatient management of deep vein thrombosis (DVT) has shown true economic benefits—even allowing for the fact that the initial cost of the drug is higher. Hull and colleagues have shown that treating patients with LMWH results in a savings of $40,000 per 100 patients. Further, their work goes to show that if 37% of patients in the study were treated as outpatients, the total cost per 100 patients who received LMWH would have been about $284,000, as opposed to $375,000 with unfractionated heparin—a savings of approximately $95,700 per 100 patients.

The cancer patient is ideal for an outpatient treatment protocol because many are already accustomed to injecting themselves with growth factors. For those patients who have never injected themselves, a nurse can teach the patient proper subcutaneous injection technique prior to release. A videotaped subcutaneous injection teaching program may also reinforce injection technique. Patients that receive home care nursing may also benefit from teaching reinforcement by the home care nurse.

Treatment Protocol

There are several clinical and social factors to consider when selecting a patient for an outpatient DVT treatment protocol. Clinically, one must be sure that there is no overriding reason to admit the patient to the hospital, such as suspicion of pulmonary embolism, recent history of surgery or bleeding, a history of multiple recurrent DVTs or pulmonary emboli, or any other acute comorbidity. From a social standpoint, the patient must be available for a reasonable amount of follow-up. The patient must have a telephone, must not live too far away from the hospital, and must understand, or have a caregiver that understands, the symptoms of pulmonary embolism or worsening DVT. Most importantly, there must be no resistance on the part of the patient or the caregivers to embark upon this treatment regimen.

Several administrative factors require consideration as well. The patient must have acceptable coverage for drug costs, as the LMWH preparations are somewhat expensive. Some patients may also require home care visits. Not only must one be sure that the patient is eligible for these resources, but one must also have the ability to activate these resources without too much extra hassle or paperwork. In this instance, an active case management team in the hospital can be extremely helpful. When choosing a LMWH product, important factors to consider are ease of obtaining the drug, volume of injectate, and frequency of dosing.

Our outpatient DVT treatment protocol begins with same-day administration of the first dose of LMWH and the first dose of warfarin. The LMWH is dosed according to weight-based normograms and the warfarin is dosed at mg to start (less if the patient is severely cachectic). On day 1, we will obtain a baseline platelet count, send the patient home, and have the patient come back on day 3 for the first check of his INR. We aim for a target international normalized ratio (INR) between days 2 and 3 before discontinuing the LMWH. We anticoagulate our patients for as long as they have the "irreversible" thromboembolic risk factor of malignancy. Our "warfarin failures" are placed back on low molecular weight heparin at the initial weight-based treatment dose. How many patients are continuing on heparin in this regard? What are the recurrence rates and bleeding rates in those patients? Is the full treatment dose the correct approach? These are the questions that we hope to answer when we begin our prospective look at our DVT outpatients.

Limitations of LMWH Therapy

Renal insufficiency is a relative contraindication to LMWH therapy. LMWH and unfractionated heparin are both metabolized by the kidneys. If we elect to use LMWH in a patient with renal compromise, we will follow anti-Xa levels to make sure that we are not overly aggressive in our anticoagulation efforts.

Some people may ask about how to dose LMWH in the obese patient. In most cases, we are dealing with the opposite situation in the cancer patient—cachexia. We tend to feel more comfortable tailoring our dose of LMWH from a multi-dose vial in our cachectic patients. This allows us to provide the most accurate weight-based dose for our patients with minimal risk of both over-anticoagulation and wastage of drug product.

We are also very wary of treating patients with known spinal metastases and patients that have epidural spinal catheters for pain management. We do not treat any patients that have any manipulation of the spinal column with low molecular weight heparin. While there is little data to support or refute the use of LMWH in patients with brain metastases, we tend to feel comfortable using these drugs in patients who have not had evidence of hemorrhagic brain metastases or any form of brain surgery.

Leo R. Zacharski, MD, MS, is currently the associate chief of staff for research at the VA Hospital in White River Junction, VT, and professor of medicine at Dartmouth Medical School in Hanover, NH. In addition to his active role in research, Dr. Zacharski serves as area consultant in blood coagulation for the Dartmouth Hitchcock Medical Center, and maintains a referral coagulation clinic for the diagnosis and treatment of bleeding and thrombosing disorders. Currently, he is co-chairman of the Subcommittee on Haemostasis and Malignancy of the International Society on Thrombosis and Haemostasis, and is a frequent conference speaker at home and abroad.

The History of Deep Vein Thrombosis and Cancer

The clinical link between thrombosis and cancer was established well over 100 years ago. In the 1870s, Trousseau described deep venous thrombosis (DVT) with malignancy and Bilroth observed microscopic clots associated with tumor deposits within blood vessels. A half century later, blood coagulation test abnormalities referred to first as "consumptive coagulopathy" and subsequently as disseminated intravascular coagulation (DIC), were identified in patients with cancer.

Early clinical observations provided a starting point for numerous studies in experimental systems dating from about mid-century. These showed that tumor cells activate blood coagulation both in vitro and in vivo in experimental animals. However, animal models provided an insight not obvious from clinical observations, such as that the inhibition of the coagulation mechanism by various means altered tumor growth and dissemination. The problem was that variability existed in both the responses among types of animal tumors and the effects of various clot-inhibitory drugs. No unifying concept explained these findings although this approach was generally regarded as "anti-metastatic." Nonetheless, the coagulation–cancer interaction was undeniably a "two-way street." Not only did cancer activate clotting, but clotting also influenced tumor growth.

Understanding the Significance of DVT and Cancer

Recently, progress has been made on the clinical front in understanding Trousseau's syndrome. For example, DVT not only complicates the course of cancer but also may reveal an undiagnosed cancer. Patients with identifiable environmental risk factors for thrombosis or an hereditary thrombophilic defect have a relatively low risk for subsequent malignancy. In 1992, Prandoni and colleagues reported in the *New England Journal of Medicine* that DVT with a thrombophilic defect had under a 2% risk of malignancy within 2 years. But with idiopathic and especially recurrent DVT, the risk of malignancy was about 10%. The common thrombophilic defects, factor V Leiden and mutant prothrombin, had not yet been identified and diagnosing these would presumably enhance identification of patients at risk for malignancy. More studies are needed to determine whether acquired laboratory markers for thrombosis risk, including antiphospholipid antibody, homocysteine, and factor VIII levels will contribute to risk assessment.

It was once thought that patients with cancer diagnosed subsequent to an episode of DVT had a poor prognosis. This may not be the case, and guidelines exist for diagnosing such occult malignancies. Most important is a thorough history, physical examination, and basic laboratory evaluation. In other instances, an abdomino-pelvic CT scan, CEA, and PSA (in males) may be helpful.

Evidence indicates that coagulation activation and coagulation-reactive drugs influence the natural history of cancer. Both thrombosis and the severity of abnormal tests for DIC portend poor patient outcome. Reports indicate that anticoagulant therapy with either warfarin or heparin may either delay onset of some cancers or prolong survival of others.

Treatment

Observations that anticoagulants may improve cancer outcome have brought clinical studies of coagulation and cancer full circle. The first clinical trials performed by Thornes in Ireland in the early 1960s attracted little interest, primarily because of the concurrent development of chemotherapy. Our early prospective randomized trials of warfarin likewise attracted little attention because favorable effects were restricted to small cell lung cancer but were not found in other major tumor types. Subsequent mechanistic studies have suggested that thrombin inhibition, eg, with warfarin, effects relatively few malignancies because the presumed mechanism of interaction (tumor cell-induced thrombin generation in situ) exists in only a handful of human tumor types. The heterogeneity in mechanisms that plagued work in experimental animal models, evidently applies to human malignancy as well. It will be interesting to see whether more potent and specific thrombin inhibitors available today will influence the course of these particular tumor types.

Evidence from the past few years showing effects of heparin on cancer seem more promising. Heparin not only inhibits thrombin generation but, as a glycosaminoglycan, also binds tumor angiogenic and growth factors. It is surprising how many case reports, cohort studies, retrospective meta-analyses, and even prospective randomized trials have shown an effect of heparin on cancer. Beneficial effects seem to be greater for LMWH than for unfractionated heparin, with sometimes rather dramatic effects on patient outcome.

This form of experimental cancer therapy is feasible and scientifically sound, but a paradigm shift will be required for the coagulation hypothesis to be tested convincingly. For example, the concept of aiming for a maximally tolerated dose (following the "search and destroy" concept dominating the field for the past half century), may not apply to trials of heparin and related drugs. Rather, with such "growth-regulatory therapy," gains short of cure obtained with safe and effective doses can be combined with treatments of other agents selected through our knowledge of basic tumor biology. Elimination of a tumor by reducing the tumor cell birth rate to a level below the death rate achieves the goal of cytotoxic chemotherapy but without the toxicity. Well-designed, controlled clinical trials in progress and in planning should answer questions that have remained unaddressed for a century.

Steven R. Deitcher, MD, is head of the Section of Clinical Thrombosis, the director of research in the Department of Vascular Medicine, and staff physician in the Department of Hematology/Oncology at the Cleveland Clinic Foundation. Dr. Deitcher's laboratory and clinical research focuses on the relationships between cancer and thrombosis. He is the lead investigator of several clinical trials related to the treatment of venous thrombosis in cancer patients and the survival enhancing effects of antithrombotic agents.

Clinically relevant thrombosis has been detected in approximately 15% of cancer patients, while anatomical thrombosis has been found post-mortem in 20–50% of patients with metastatic carcinoma. Thrombosis may be the presenting feature of occult malignancy, a life-threatening component of advanced cancer, and a sequelae of a patient's antineoplastic therapy itself. Thrombosis in cancer may manifest in many ways, including DVT, superficial thrombophlebitis, and warfarin failure. Thrombosis is the second most common cause of death in hospitalized cancer patients, and may be the leading proximate cause of death in patients with nonhematologic cancers.

Cancer-associated thrombosis is associated with adenocarcinoma, advanced age and disease stage, combination hormonal and cytotoxic therapy, venous stasis, central venous catheters, and immobilization. The impact of inherited, acquired, and situational thrombosis risk factors cannot be overlooked. Laboratory hypercoagulable state testing is rarely helpful in patients with thrombosis in the setting of advanced malignancy. Malignant tumors can promote hypercoagulability by a multitude of mechanisms. Differences in tumor type, stage, histology, and location may invoke unique sets of coagulation derangements, all inducing hypercoagulability. Some mechanisms of tumor-induced hypercoagulability include hyperviscosity, vascular endothelial damage, tissue factor production, platelet activation and accumulation, along with several others. Coagulation activation can often be confirmed by quantification of several coagulation-related activation peptides and enzyme inhibitor complexes. The variability between different cancer patients makes the use of a single diagnostic assay for the detection and quantification of cancer associated hypercoagulability difficult.

We may underestimate the magnitude of thrombosis in cancer due to the nonspecific symptoms associated with acute thrombosis, inadequate physician index of suspicion, and limitations of standard DVT diagnostic methodologies. The presence of pelvic, inguinal, and mediastinal masses may mimic extremity DVT secondary to extrinsic vessel compression. Inconclusive or negative duplex ultrasound in a cancer patient suspected to have DVT should prompt performance of additional vascular imaging. Because patients with cancer have both a greater risk of thrombosis recurrence and bleeding during warfarin-based anticoagulation, the morbidity and mortality related to an incorrect diagnosis and unnecessary treatment are also likely to be greater. Accurate diagnosis is imperative.

Cancer patients with suspected pulmonary thromboembolism (PE) are initially evaluated by perfusion lung scintigraphy (V/Q scanning) or helical CT scanning. The presence of any pulmonary process such as infection, fibrosis, emphysema, and metastases, confounds the results of a V/Q scan reading. In fact, 73% of V/Q scans are neither high probability nor normal and must be viewed as indeterminate, thus warranting further imaging such as pulmonary angiography. An advantage of helical CT scanning is the ability to diagnose and characterize nonthrombotic pulmonary pathology while evaluating for central PE. Up to 40% of the time an alternative diagnosis for the patient's presenting symptoms is identified and 26% of the time an alternative diagnosis is confirmed. Helical CT scanning is favored by many for the evaluation of PE in cancer patients.

Assessment of cross-linked fibrin degradation product (D-dimer) levels has become popular as an adjunct to DVT diagnosis. The negative predictive values (NPV) for D-dimer assays have ranged from 83% to 99% and are dependent on methodology. When combined with a negative venous duplex ultrasound, a normal D-dimer level eliminates the need for serial ultrasound and venography. The performance characteristics of at least one D-dimer assay are less clinically useful in cancer patients with suspected DVT, with an NPV of 78.9% in cancer patients vs 96.5% in noncancer patients. A negative D-dimer study does not necessarily rule out acute thrombosis in cancer patients.

The thrombosis "challenges" in cancer patients include diagnosis and treatment. Cancer patients with DVT have an increased recurrence rate, increased bleeding rate on warfarin, perceived increased likelihood of anticoagulation failure, and spend less time within the target INR when compared to noncancer patients. The optimal intensity of anticoagulation in cancer patients may differ from those without such potent prothrombotic states. The prothrombin time and derived INR may not even accurately reflect the intensity of oral warfarin anticoagulation in many cancer patients. While cancer patients have been included in most contemporary, randomized prospective DVT treatment trials, cancer patient-specific treatment guidelines are lacking.

While intravenous heparin and oral warfarin anticoagulation remain the traditional standard of care for DVT in the cancer setting, LMWH is emerging as the preferred agent. LMWH has performed favorably in acute DVT settings and is actively being studied as an alternative to warfarin for the chronic phase of anticoagulant therapy. Benefits of LMWH in comparison to unfractionated heparin include subcutaneous weight-based dosing, lack of need for therapeutic monitoring in most patients, better bioavailability especially at low doses, less heparin-induced thrombocytopenia in heparin-naïve patients, and less nonspecific binding to acute phase proteins. LMWH has also been shown to improve cancer patient survival in meta-analyses and subgroup analyses. The results of prospective, randomized trials addressing the use of LMWH for DVT prevention, DVT treatment, and survival enhancement in cancer patients are awaited.

Question & Answer Forum

Q: The cancer data show that there is a significant difference in mortality when comparing unfractionated to low molecular weight heparin. Can that be reproduced or will that be something reproducible in the future?

LZ: Excellent question, and it seems to be something that actually has been seen in most clinical trials where low molecular weight heparin and unfractionated heparin have been compared for efficacy in terms of DVT treatment. When we look at the subset of patients with malignancy in detail, this difference seems to emerge. This has been recognized since 1992, and is quite consistent between meta-analyses. There have been about four large meta-analyses that have looked at this issue. The reduction in mortality seems to be specific for the subset of patients with malignancy and is not evident in this comparative group. I believe there is a likelihood that there will be a difference, but we need a cancer study in order to define whether heparin modifies the natural history of malignancy. This has not been done to date.

Q: What cancer-related trials are being conducted using direct thrombin inhibitors, pentasaccharide, and oral heparin?

SD: The major focus of clinical trials using direct thrombin inhibitors, pentasaccharide, and orally administered heparins has been on venous thromboprophylaxis in the setting of orthapedic surgery. It is safe to assume that DVT and PE treatment trials are not far behind. Pentasaccharide is likely to be the first to be approved for prophylaxis. The MATISSE series of clinical trials are evaluating pentasaccharide for treatment. The THRIVE V trial is specifically looking at AstraZeneca's investigational oral direct thrombin inhibitor. Parenteral agents are particularly important for the treatment of our cancer patients with oral intake limitations and significant nausea with vomiting. Oral agents offer a particular advantage in patients with thrombocytopenia who are more susceptible to significant injection-related bruising. Use of the newer agents to improve the treatment of cancer patients and/or enhance cancer patient survival has not been studied.

Q: Are stockings useful when treating your patients? It has been shown that custom-fitted stockings with a 30–40 millimeter of mercury pressure gradient reduces the postphlebitic syndrome by about 50% in patients.

SD: I prescribe below knee 20–30 mmHg or 30–40 mmHg fitted graduated compression stockings in most of my cancer patients with lower extremity DVT. Use of compression stockings starting 3 weeks after an acute DVT has been associated with a relative risk reduction of mild to moderate post thrombotic syndrome (PTS) and severe PTS of 58% and 51% respectively (Brandjes DP et al. *Lancet.* 1997;349:759-62). I favor the below knee stockings over thigh-high stockings because they are easier to put on and less likely to roll-down and act as a tourniquet. I also do not limit activity or ambulation in this setting.

Q: In cachexia patients, do you find that you are able to get away with a standard weight-based dose?

BM: We are currently creating a chart review of the work we have done for the past $2^1/_2$ years by creating a prospective look at our patients. We are following them for a year and seeing what happens to them. Anecdotally, just being the front door to the emergency room for these cancer patients coming in, we are seeing very little bleeding, including in our cachectic patients.

Q: In your warfarin failures, you revert to treatment doses of low molecular weight heparin. What do you do for long-term maintenance?

BM: We continue giving patients the acute treatment dose, though there is little literature to support that. Future clinical trials will delineate what dose of low molecular weight heparin can be used safely and efficaciously over the long term.

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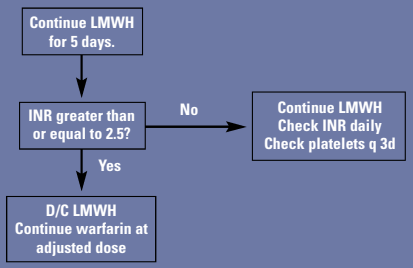
Treatment Pathway for Outpatient LMWH Protocol

01.5.01



LMWH=low molecular weight heparin; INR=international normalized ratio; D/C=discontinue.
Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

Eligibility Questions: Clinical Criteria

01.5.02

- No coexisting condition requiring hospitalization?
- No history of multiply recurrent DVT or PE?
- No signs or symptoms of pulmonary embolism?
- No active bleeding or recent surgery?

DVT=deep vein thrombosis; PE=pulmonary thromboembolism.
Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

LMWH VS UFH in Cancer

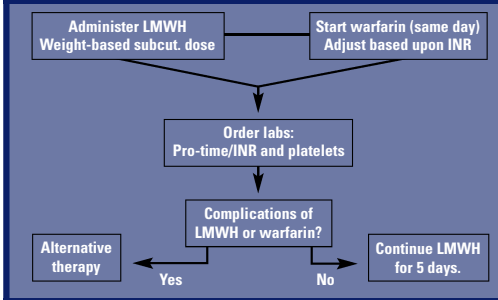
01.5.03

- Greater inhibition of angiogenesis
- Greater inhibition of heparin-binding growth factors
- Reduced direct activation of platelets
- Greater inhibition of platelet activation on vascular endothelium and by soluble agonists
- Improved inhibition of thrombin generation

UFH=unfractionated heparin; LMWH=low molecular weight heparin.
Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

Treatment Pathway for Outpatient LMWH Protocol

01.5.04



LMWH=low molecular weight heparin; INR=international normalized ratio.
Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

Heparin in Cancer Patients With DVT

01.5.05

Meta-analyses of Trials Comparing LMWH to UH

Author	Number of trials analyzed	Reduction in relative risk of death with LMWH
Lensing (1995)	10	64%
Siragusa (1996)	13	67%
Gould (1999)	11	43%
Hettiarachchi (1999)	9	39%

LMWH=low molecular weight heparin; UH=unfractionated heparin.
Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

The Coagulation-Cancer Time Line

01.5.06

1865 - Trousseau described association between malignancy and deep vein thrombosis
1878 - Bilroth observed microscopic association of thrombi with intravascular tumor deposits
1913 - Loeb and Fleischer demonstrated regression of tumors in animals with injection of leech extract
1925 - Fischer observed lysis of fibrin clots by cultured tumor cells
1930 - Goerner showed inhibition of tumor growth with heparin in experimental animals
1930 - Jurgens and Trautwein described "consumptive coagulopathy" (disseminated intravascular coagulation) associated with malignancy
1952 - Terranova and Chiossoni found inhibition of tumor dissemination (metastasis) with anticoagulant therapy in animal models
1961 - Thornes first performed clinical trials of anticoagulants in an attempt to modify the course of human malignancy

Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

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Eligibility Questions: Administrative Criteria

01.5.07

- Patient or caregiver able to give injectable LMWH?
- Able to sign consent form for treatment?
- Acceptable reimbursement available?
- Eligible for home care resources?

LMWH=low molecular weight heparin.
Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

Heparin Treatment in Oncology

01.5.08

- Thrombosis prophylaxis
- Thrombosis treatment
- Venous access catheter thrombosis (prevention and treatment)
- Thrombotic complications of bone marrow transplantation
- Disseminated intravascular coagulation
- Inhibition of tumor growth and dissemination (?)

Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

Background: Cancer and Thrombosis

01.5.09

- Clinically relevant thrombosis detected in up to 15% of cancer patients
- Thrombosis found postmortem in 20–50% of patients with metastatic cancer
- Thrombosis
  - Presenting feature of occult malignancy
  - Life-threatening component of advanced cancer
  - Sequelae of antineoplastic therapy itself
- Second most common cause of death in hospitalized cancer patients

Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

Malignant Tumor

01.5.10

- Tumor-associated hyperviscosity, vascular endothelial damage, and extrinsic vessel occlusion
- Tumor-derived tissue factor
- Tumor-derived cancer procoagulant a 68-kilodalton cysteine proteinase which activates factor X to Xa
- Mucinous adenocarcinoma-derived sialic acid which supports the nonenzymatic activation of factor X
- Tumor-mediated platelet activation and accumulation
- Tumor-induced acute-phase protein release including factor VIII, fibrinogen, vWf, and PAI-1
- Tumor cell expression of surface phospholipid species which can support prothrombin activation
- Tumor-stimulated release of monocyte procoagulants

vWf=von Willebrand factor; PAI-1=plasminogen activator inhibitor-1.
Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

Cancer Patients With VTE VS Noncancer Patients With VTE

01.5.11

- Higher rate of VTE in the first place
- Higher rate of VTE following surgery
- Increased VTE recurrence rate
- Increased bleeding rate on warfarin
- Increased likelihood of warfarin "failure"
- Less time spent between INR of 2–3 on warfarin

INR=international normalized ratio; VTE=venous thromboembolic events.
Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

Incidence of Recurrent Thrombosis in Patients With VTE

01.5.12

Number of Events per 100 Patient-Years

	Malignancy N=261	No Malignancy N=1038	Total N=1299
INR 2.0	54	15.9	23.7
2.0<INR 3.0	18.9	7.2	9.2
INR 3.0	18.4	6.4	8.7
Overall	27.1	9.0	12.3
	5.4% @ 3M	2.0% @ 3M	2.7% @ 3M

Hutten BA et al. *J Clin Onc.* 2000;18:3078-3083.
INR=international normalized ratio; N=number of patients; M=months; VTE=venous thromboembolic events.
Meltzer BA, Zacharski LR, Deitcher SR. *Oncology Spectrums.* Vol 2. No 5. 2001.

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