8-15-2009

Anticoagulation Treatment For Prevention Of Recurrent Thromboembolism In Patients With Cancer

Carissa Honeycutt
Pacific University

Follow this and additional works at: http://commons.pacificu.edu/pa

Part of the Medicine and Health Sciences Commons

Recommended Citation
Honeycutt, Carissa, "Anticoagulation Treatment For Prevention Of Recurrent Thromboembolism In Patients With Cancer" (2009). School of Physician Assistant Studies. Paper 166.
Anticoagulation Treatment For Prevention Of Recurrent Thromboembolism In Patients With Cancer

**Abstract**

Background: A comparison of Low-Molecular Weight Heparin (LMWH) and oral anticoagulants is necessary in order to find the most effective prophylaxis for venous thromboembolism (VTE) and pulmonary embolism (PE) in cancer patients. The hypercoagulability state of cancer patients poses several risk factors and makes treatment and the potential complications more difficult to manage than in patients without cancer. By using the most effective treatment for anticoagulation in cancer patients, health care professionals can help reduce the risk of recurrent venous thromboembolism and/or pulmonary embolism while improving the quality of life.

Hypothesis: Low Molecular Weight Heparin will be the most effective and safest method of anticoagulation for prevention of recurrent venous thromboembolism and/or pulmonary embolism in cancer patients.

Study Design: Search of the most up to date medical literature to formulate a systematic review using 4 electronic databases and citations from other relevant articles.

Methods: The following databases were used to find the best research available: OVID-MEDLINE, CINAHL, and PubMed in addition to reference lists from the included articles.

Results: Four randomized, controlled clinical trials of various sample sizes which addressed this specific issue were reviewed; none of the studies were double-blinded and 2 out of 4 were terminated early due to poor recruitment of subjects.

Conclusion: LMWH is the preferred anticoagulation for cancer patients because Warfarin shows higher rates of recurrent VTE and higher risk for hemorrhage. More research is needed to solidify the evidence comparing anticoagulation in cancer patients.

**Degree Type**

Capstone Project

**Degree Name**

Master of Science in Physician Assistant Studies

**First Advisor**

Mary Von, MS, PA-C

**Second Advisor**

Rob Rosenow PharmD, OD

**Third Advisor**

Anjanette Sommers MS, PA-C

This capstone project is available at CommonKnowledge: [http://commons.pacificu.edu/pa/166](http://commons.pacificu.edu/pa/166)
Keywords
Anticoagulation, Neoplasms, Cancer patients, Thromboembolism

Subject Categories
Medicine and Health Sciences

Rights
Terms of use for work posted in CommonKnowledge.

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/166
Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu

This capstone project is available at CommonKnowledge: http://commons.pacificu.edu/pa/166
NOTICE TO READERS

This work is not a peer-reviewed publication. The Master’s Candidate author(s) of this work have made every effort to provide accurate information and to rely on authoritative sources in the completion of this work. However, neither the author(s) nor the faculty advisor(s) warrants the completeness, accuracy or usefulness of the information provided in this work. This work should not be considered authoritative or comprehensive in and of itself and the author(s) and advisor(s) disclaim all responsibility for the results obtained from use of the information contained in this work. Knowledge and practice change constantly, and readers are advised to confirm the information found in this work with other more current and/or comprehensive sources.

The student authors attest that this work is completely their original authorship and that no material in this work has been plagiarized, fabricated or incorrectly attributed.
Anticoagulation Treatment For Prevention Of Recurrent Thromboembolism In Patients With Cancer

Carissa Honeycutt

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies
Pacific University
Hillsboro, OR
For the Masters of Science Degree, August 15, 2009

Faculty Advisor: Mary Von, MS, PA-C
Clinical Graduate Project Coordinators: Rob Rosenow PharmD, OD & Annjanette Sommers MS, PAC
Biography

Carissa Honeycutt has lived in many states but grew up North Carolina where she majored in Psychology at University of North Carolina-Asheville. After completion of her undergraduate degree and working in an inpatient psychiatric hospital for five years, she pursued her dream of becoming a Physician Assistant. Once accepted to her first choice Physician Assistant program, she moved over 3,000 miles away from all friends and family to Oregon to begin her graduate education in Physician Assistant studies at Pacific University. She is grateful for all of the support from her parents and has made some great friends here in Oregon.
Abstract

**Background:** A comparison of Low-Molecular Weight Heparin (LMWH) and oral anticoagulants is necessary in order to find the most effective prophylaxis for venous thromboembolism (VTE) and pulmonary embolism (PE) in cancer patients. The hypercoagulability state of cancer patients poses several risk factors and makes treatment and the potential complications more difficult to manage than in patients without cancer. By using the most effective treatment for anticoagulation in cancer patients, health care professionals can help reduce the risk of recurrent venous thromboembolism and/or pulmonary embolism while improving the quality of life.

**Hypothesis:** Low Molecular Weight Heparin will be the most effective and safest method of anticoagulation for prevention of recurrent venous thromboembolism and/or pulmonary embolism in cancer patients.

**Study Design:** Search of the most up to date medical literature to formulate a systematic review using 4 electronic databases and citations from other relevant articles

**Methods:** The following databases were used to find the best research available: OVID-MEDLINE, CINAHL, and PubMed in addition to reference lists from the included articles.

**Results:** Four randomized, controlled clinical trials of various sample sizes which addressed this specific issue were reviewed; none of the studies were double-blinded and 2 out of 4 were terminated early due to poor recruitment of subjects.

**Conclusion:** LMWH is the preferred anticoagulation for cancer patients because Warfarin shows higher rates of recurrent VTE and higher risk for hemorrhage. More research is needed to solidify the evidence comparing anticoagulation in cancer patients.

**Keywords:** Anticoagulation, Neoplasms, Cancer patients, and Thromboembolism
Acknowledgements

To my parents: Thank you for your ongoing love, understanding, and support. I never could have done the hardest thing in my life without you. Your dedication to my success is what helped me stay strong.
Table of Contents

Biography .................................................................................................................. 2
Abstract ..................................................................................................................... 3
Acknowledgements ................................................................................................. 4
Table of Contents ...................................................................................................... 5
List of Tables ............................................................................................................ 6
List of Abbreviations ............................................................................................... 6
Introduction ............................................................................................................... 7
Purpose of the Study ................................................................................................. 9
Methods .................................................................................................................... 10
Results ...................................................................................................................... 11
Discussion ............................................................................................................... 19
Conclusion/Recommendations .................................................................................. 21
Table 1 ..................................................................................................................... 23
Table 2 ..................................................................................................................... 24
Tables 3 and 4 .......................................................................................................... 25
Tables 5 and 6 .......................................................................................................... 26
References ............................................................................................................... 27
List of Tables

Table 1: Current Recommended guidelines for use of LMWH in cancer patients with VTE

Table 2: Summary of the four reviewed articles

Table 3: Primary Efficacy Outcome Events in the Lee et al Study

Table 4: Primary Efficacy Outcome Events in the Hull et al Study

Table 5: Primary Efficacy Outcome Events in the Meyer et al Study

Table 6: Summary of Adverse Events in the Deitcher et al Study

List of Abbreviations

DVT.................................................................Deep Vein Thrombosis

INR..............................................................International Normalized Ratio

IV.................................................................Intravenous

LMWH.........................................................Low-Molecular-Weight Heparin

PE.................................................................Pulmonary Embolism

UFH.............................................................Unfractionated Heparin

VTE..............................................................Venous Thromboembolic Event
Anticoagulation Treatment For Prevention Of Recurrent Thromboembolism In Patients With Cancer

Introduction

Thrombosis in cancer patients is considered to be the second leading cause of mortality.\(^1,2\) The risk of cancer-associated thrombosis can be increased by chemotherapy, which can cause endothelial cell damage and is a predisposing factor for clotting.\(^2,3\) Cancer patients also have a higher rate of recurrent venous thromboembolic event (VTE), with the potential for a fatal pulmonary embolism (PE).\(^4\) These adverse events can be prevented with adequate anticoagulation, but the risks of treatment and prophylaxis can include hemorrhage and death. Cancer patients with venous thromboembolic events are also shown to have a poorer rate of survival when compared to cancer patients without thrombosis.\(^3\)

Patients with cancer are in a state of hypercoagulability which predisposes them to fatal complications such as venous thromboembolism and pulmonary embolism.\(^2,3\) The exact mechanism for the hypercoagulability state of cancer patients is not fully understood, however, there are several proposed mechanisms to explain the increased risk of thromboembolism.\(^5\)

One specific mechanism that explains the increased coagulability involves the production of cytokines by the tumor, which stimulate monocytes to express tissue factor.\(^2\) Tissue factor and cancer procoagulant can activate the coagulation process.\(^3\) Previous research suggests that the tissue factor molecule, serves as a receptor for the activation of a specific coagulase factor (factor IIa), which stimulates activation of a
series of other coagulation factors. Tumor cells may also contribute to hypercoagulability because of their intrinsic production of procoagulant factors.3

Other non-specific explanations for the increased risk of thromboembolism in cancer patients include, the basic inflammatory response to tissue damage caused by the tumor, which leads to expression of tissue factor and activation of the coagulation process.2 The coagulation process also stimulates inflammation, which contributes to the state of hypercoagulability.

Extrinsic influences such as immobility, surgical procedures, insertion of vena caval filters, and chemotherapy also increase the risk of cancer-associated thrombosis.2 Cancer patients, in general, tend to be more debilitated, which interferes with their mobility and ultimately contributes to venous stasis.

Although there are currently no specific guidelines for treatment of thrombosis associated with cancer patients, there are a variety of recommendations with different levels of supporting evidence (See Table 1).5, 6 The current treatment options include: Unfractionated Heparin (UFH), Low-Molecular-Weight Heparin (LMWH), and oral anticoagulation. Unfractionated heparin requires frequent monitoring and dosing adjustment because of its narrow therapeutic window and unpredictable dose responses. LMWH has shown less recurrence of venous thromboembolic events and bleeding events, but it is quite expensive and requires patients to do subcutaneous injections at least once daily. Other reasons why LMWH is preferred over other anticoagulation treatment is that it is not known to cause potentially hazardous drug interactions.6 The anticoagulation effect of LMWH is much more stable and does not require strict laboratory monitoring. Oral anticoagulants, like Warfarin, have the potential for drug
interactions and alterations of the anticoagulant effects. Antiemetics, steroids, and analgesics decrease Warfarin’s effects by weakening it, which alters the effectiveness of the medication.\textsuperscript{3,6} The INR is a lab value that measures the effectiveness of the oral anticoagulants. Use of Warfarin and other oral anticoagulants require frequent INR measurement through a venous blood sample and often numerous dosing adjustments. The frequent INR monitoring requires venous access which has a severe impact on the quality of life of cancer patients. A low INR indicates an increased risk of clotting, and the Warfarin dose should be increased. If the INR is high, there is an increased risk for bleeding and the dose of Warfarin should be lowered. The variation of INR can last for up to two weeks, which poses a particular difficulty in maintaining a therapeutic level of Warfarin. Azole antifungals and quinolone antibiotics can also disturb the concentration of Warfarin and change the INR, which has the potential to increase the bleeding risk.\textsuperscript{6} Bleeding risk is also increased when using Warfarin with Cephalosporins, salicylates, and corticosteroids because of their ability to inhibit platelet aggregation factors.\textsuperscript{6} Another reason why Warfarin is suboptimal in the treatment of VTE in cancer patients is that treatment is sometimes interrupted due to thrombocytopenia that is induced by chemotherapy. The interruption in treatment results in INRs that are not within the therapeutic range, which increases risk of clotting or bleeding. Studies also reveal that cancer patients fall within a therapeutic INR range only 50% of the time.\textsuperscript{6}

How can healthcare providers improve the quality of life for cancer patients by preventing the recurrence of venous thromboembolism without causing death from hemorrhage?
**Purpose of the Study**

The determination of the safest and most effective method of anticoagulation for cancer patients will help improve the quality of life and aid in reducing mortality from embolism. By reducing complications from venous stasis and minimizing the risk for bleeding, cancer patients can be freed from some of the concern regarding their cancer treatment, instead of having to deal with thromboembolism or PE while struggling to manage their cancer treatment.

The mechanism for the hypercoagulability state of cancer patients is poorly understood and there seem to be minimal definitive treatment strategies which would allow patients with cancer the chance for reduced complications and improvement in their quality of life.

**Methods**

A comprehensive search for the best literature available was conducted on the following databases: OVID-MEDLINE, CINAHL, and PubMed. The search terms were a combination of: anticoagulation, anticoagulants, cancer patients, neoplasms, and thromboembolism. Data was limited to the last 9 years, English language, human subjects, and an additional search filter for randomized control trials. The interlibrary loan service was also utilized in order to gather more information that applies to the search terms. The reference list from the included articles was also used to glean additional information, with a limitation of beyond the year 2000.

The inclusion criteria were adults with cancer (any kind, any stage), anticoagulation comparisons, Low-Molecular-Weight Heparin (LMWH), oral anticoagulants, DVT (deep vein thrombosis) prophylaxis, 2001-2009, diagnosis with
current DVT and/or PE (pulmonary embolism). The exclusion criteria were adults without cancer, pediatrics with cancer, the use of aspirin, and data earlier than 2001.

Results

A total of four articles were applicable to the question and search criteria (See Table 2). All four of the articles addressed the use of Low-Molecular-Weight Heparin in comparison with oral anticoagulation. One of the articles compared LMWH and Unfractionated Heparin with a Vitamin K antagonist. The remaining three articles compared various LMWH such as Enoxaparin or Dalteparin and Warfarin. The majority of the studies had small sample sizes, with the exception of the Lee et al study which had a sample size of 676 patients.

Lee et al compared LMWH with an oral anticoagulant for 6 months duration in cancer patients for prevention of recurrent thrombosis. Funding and the study drug were supplied by Pharmacia. 338 cancer patients with symptomatic proximal DVT, PE, or both were randomized to receive subcutaneous Dalteparin 200 IU/kg once daily for month 1. The remaining 5 months of Dalteparin were administered subcutaneously at a dose of approximately 150 IU/kg and dosing was based on the patient’s weight. Patients and/or family members were instructed to self-administer the subcutaneous injection from prefilled syringes once daily. Home care was arranged “if necessary.”

The other 338 cancer patients received an initial dose of Dalteparin 200 IU/kg subcutaneously which was continued for five to seven days, until the INR was in therapeutic range. One of the oral anticoagulants, Warfarin or Acenocoumarol, was also started on day 1. Once INR was in therapeutic range, Dalteparin was discontinued and INR was monitored at least once every two weeks for the study duration.
Lee et al were able to obtain a large sample size and complete their study (See Table 3). 27 patients in the Dalteparin group experienced DVT, PE, or both, compared to 53 patients in the oral anticoagulant group. 20 of the patients in the oral anticoagulant group who experienced some kind of thrombotic event had an INR that was below 2.0 at the time of the event. 14 patients had DVT in the Dalteparin group and 37 had DVT in the oral anticoagulant group. In the Dalteparin group, there were a total of 13 patients who had PE, 5 of which were fatal. There were 16 patients in the oral anticoagulant group with pulmonary embolism; 7 were fatal PEs. Bleeding episodes occurred in 19 patients from the Dalteparin group. 2 of these patients had thrombocytopenia at the time. In the oral anticoagulant group, 12 patients experienced bleeding episodes with 6 having an INR greater than 3.0 at the time of the bleeding episode. A total of 130 patients in the Dalteparin group died and 136 patients in the oral anticoagulant group died during the six month study period. Progressive cancer was responsible for 90% of the deaths. One patient from the Dalteparin group died from hemoptysis secondary to metastatic lung cancer. Another patient with brain cancer from the Dalteparin group died from an intracranial bleed. A patient with prostate cancer in this group died from retroperitoneal bleeding. Another patient with lung cancer in the Dalteparin group died from pericardial bleeding. There were no fatal bleeding events in the oral anticoagulant group, however, two patients had intracranial bleeding, and two had retroperitoneal bleeding. They concluded that the recurrence of VTE in cancer patients was reduced when using long-term LMWH. The difference in bleeding episodes among both groups was not statistically significant. There was no difference in mortality between the groups but the
researchers did suggest a survival benefit from using long-term LMWH compared to oral anticoagulation treatment.

Hull et al examined long-term subcutaneous LMWH in comparison to initial IV heparin and long-term Warfarin for a total duration of three months. The study was funded by the Canadian Institutes of Health Research. All patients had cancer and proximal vein thrombosis. Hull et al were careful in their inclusion criteria to make sure none of the enrolled patients had any contraindications to treatment, a life-expectancy of less than three months, which would terminate prior to the end of the trial, and current treatment with anticoagulants. Risk factors for bleeding were also considered in the patient population. 100 patients were randomly assigned to receive subcutaneous Tinzaparin 175 IU/kg once daily. Patients and/or family members were instructed on proper administration techniques for the subcutaneous injection. The patients in this group had platelet counts at 14 and 21 days to screen for thrombocytopenia. The other 100 patients were assigned to receive a bolus of 5000 units or 80 units/kg of IV Unfractionated Heparin and then a continuous infusion, which was based on the hospital protocol for Heparin administration. The patients randomized to this group were required to be hospitalized to ensure proper administration of the IV Heparin. Laboratory monitoring of activated partial thromboplastin time was also used to adjust the heparin dosing. Warfarin was started along with the heparin regimen at 5-10 mg daily and adjusted based on the therapeutic INR range of 2.0-3.0. UFH was discontinued on day 6 as long as the INR was in therapeutic range and Warfarin was continued and titrated based on regular INR monitoring every 1-2 weeks until treatment was discontinued. Therapy was discontinued at 12 weeks, unless the primary care physician felt like
prolonged treatment was indicated. Use of acetylsalicylic acid was not allowed and drugs that inhibit platelet aggregation, specifically ticlopidine, sulfinpyrazone, dipyridamole, and nonsteroidal anti-inflammatory drugs, were “strongly discouraged.”

Patients were instructed to return to clinic at 12 weeks to determine which patients had suffered from recurrent VTE and/or death (See Table 4). A separate committee that was not involved in patient care and unaware of the treatment interpreted all events “independently without knowledge of the other findings.” During the trial period of 3 months, none of the patients in the Enoxaparin group were lost to follow-up or withdrew consent. One patient withdrew consent at 3 months in the Heparin/Warfarin group but no patients were lost to follow-up or withdrew consent at one year. After one year from the start of the treatment, the patients or the primary care physicians were contacted to determine whether or not the subjects had recurrent venous thromboembolism and also to see if they were alive. One patient in the Enoxaparin group withdrew consent after one year. After 12 months of evaluation, 16 out of 100 from the Heparin/Warfarin group and 7 from the LMWH group experienced recurrent VTE. One patient had a subtherapeutic INR when they were diagnosed with the recurrent VTE. Bleeding episodes happened in 27 of the LMWH patients and 24 in the other group. Out of the 24 patients in the Warfarin group with bleeding episodes, 2 patients with major hemorrhage and 2 patients with minor bleeding episodes had elevated INR on the day of bleeding. 47 patients in the LMWH group and 47 patients in the Warfarin group died after one year and mortality was thought to be secondary to progression of cancer in the majority of the cases. 2 patients in the LMWH group and 7 patients in the Warfarin group
died suddenly; 3 of those deaths were confirmed pulmonary embolism and were all from the Warfarin group.

The Hull et al study determined that long term LMWH offered improved efficacy in cancer patients for prevention of recurrent VTE without increased harm from bleeding episodes. The conclusion of Hull et al was that the cancer patients in the trial supported the outcome of improved efficacy with LMWH in prevention of recurrent VTE.

Meyer et al compared long-term Enoxaparin with Warfarin for a trial period of three months. The study was funded by Aventis. All 146 patients received an initial fixed dose of Enoxaparin 1.5mg/kg subcutaneously. 71 patients were randomized to receive Enoxaparin 1.5mg/kg subcutaneously for three months. Platelet count was also done twice per week for the first month, and then once per week until day 90. 75 patients were started on Enoxaparin 1.5 mg/kg subcutaneously and Warfarin 6-10 mg orally each day. At the point that the INR was within the therapeutic range the Enoxaparin was discontinued and the Warfarin was continued for the remainder of the three month period. The Warfarin dosage was adjusted based on INR monitoring with a therapeutic range of 2.0-3.0. INR monitoring took place on a daily basis until a therapeutic level was maintained for two days then the INR was monitored on a weekly basis until day 90. If the physician felt like the INR needed closer monitoring, INR was measured more frequently in order to establish a therapeutic level. Once the trial period of three months was reached, the attending physician determined whether or not anticoagulation treatment was needed for each patient.

Meyer et al recruited 146 patients over a four year period to participate in the trial. The trial was terminated at the four year point by the data management committee
because the number of subjects was “not compatible with continuation of the study.”

Out of the 146 study participants, eight patients were not able to be evaluated by the data committee because two of them were lost to follow-up, three withdrew consent, and three died. One patient who died was believed to have septic shock and another had acute onset of dyspnea and fever, which could have been related to a pulmonary embolism; neither patient had an autopsy. The other patient that died was believed to have a DVT, but the venous ultrasound was inconclusive.

Among the remainder of patients that completed the Meyer et al study, 15 patients in the Warfarin group had major bleeding episodes or recurrent thromboembolism, compared to 7 patients in the Enoxaparin group (See Table 5). In the Warfarin group, 17 patients died. Eight patients died in the Enoxaparin group. The six deaths that resulted from major hemorrhage were all assigned to the Warfarin group. The patients assigned to the Warfarin group had an INR within therapeutic range 41% of the time during treatment. There were no fatal bleeding events in the Enoxaparin group. Fourteen of the deaths were related to progression of cancer. Four patients died of sepsis and one died from aspiration pneumonia. Ten patients in the Warfarin group and 12 in the Enoxaparin group had progression of cancer (but did not die). At six month follow up, 121 patients were still alive. 29 patients in the Warfarin group died and 22 patients in the Enoxaparin group died. Progression of cancer was seen in 27 patients receiving Warfarin, compared to 24 patients in the Enoxaparin group. Minor bleeding episodes occurred in 9 patients receiving Warfarin and 5 patients who received Enoxaparin. Thrombocytopenia took place in 18 of the Warfarin patients and 16 of the Enoxaparin patients. The study
concluded that less patients in the Enoxaparin group experienced episodes of major hemorrhage, recurrent thromboembolism, and death.

Deitcher et al compared long-term Enoxaparin (in two different dosages) with initial Enoxaparin and Warfarin for 180 days in cancer patients with acute, symptomatic venous thromboembolic events. The trial was sponsored by Aventis Pharmaceuticals. 31 patients were randomized to receive Enoxaparin 1.0 mg/kg subcutaneously, twice per day for five days, then Enoxaparin 1.0 mg/kg daily for 175 days. The other group that received Enoxaparin alone consisted of 36 patients who took 1.0 mg/kg subcutaneously twice per day for five days, then 1.5 mg/kg subcutaneously daily for the remaining 175 days. 34 patients were randomized to the Warfarin group and initially received Enoxaparin 1.0 mg/kg twice per day for a minimum of five days until a therapeutic INR was established. Oral Warfarin was started within 24 hours of the initial dose of Enoxaparin and continued for 180 days.

In the group that received Enoxaparin 1.5 mg/kg, 63.9% of the patients were female and 58.3% were 51 years or older. In the Enoxaparin 1.0 mg/kg group, 51.6% were female and 41.9% were 51 years or older. 47.1% of the Warfarin group was female and were younger, on average, than both of the Enoxaparin groups.

Thirteen patients in the Warfarin group had DVT and PE, compared to 7 patients in the Enoxaparin 1.0 mg/kg group and 10 patients in the 1.5 mg/kg group (See Table 6). Three patients in the Warfarin group had VTE during treatment, compared to 2 patients in each of the Enoxaparin groups. The number of non-fatal adverse events were distributed among the three groups, and occurred in 87.1% of patients overall. Among the Enoxaparin 1.0 mg/kg group and the Warfarin group, there were similarities between the
incidence of serious adverse events, with 51.6% in the Enoxaparin group and 50.0% in the Warfarin group. The highest number of serious adverse events was in the Enoxaparin 1.5 mg/kg group with 63.9% of the group having at least one event.

There were other differences among groups with specific cardiovascular events. The subjects with the highest rate of cardiovascular events were in the Enoxaparin groups; the Warfarin group had no patients who experienced any cardiovascular adverse events. Among those who experienced a serious adverse effect in other body systems, there were 2 patients in the Warfarin group and 1 patient in the Enoxaparin 1.0 mg/kg group whose events were considered “possibly or probably related to the study drug.”

Major hemorrhagic events happened in 4 patients in the Enoxaparin 1.5 mg/kg group, 2 in the Enoxaparin 1.0 mg/kg group, and 1 patient in the Warfarin group. There were a total of 33 deaths during 7 months of observation and follow up. 29 deaths were linked to progression of cancer, 1 in the Enoxaparin 1.0 mg/kg group died of presumed PE, 1 in the Enoxaparin 1.0 mg/kg group died of VTE, 1 in the Enoxaparin 1.5 mg/kg group died of heart failure, and 1 died of cardiac arrest in the Warfarin group.

There were 12 patients eliminated from the study because of death prior to the end of the study period; the remainder of the patients that died completed 180 days of treatment. The highest rate of withdrawal was 58.3% of patients from the Enoxaparin 1.5 mg/kg group and was primarily due to death or adverse events. The lowest rate of discontinuation was in the Enoxaparin 1.0 mg/kg group at 41.9% and was because these patients reached the study end point and had recurrent VTE or major hemorrhage.

Compliance rates among the groups were an overall average of 95%. Overall compliance was lowest in the Warfarin group at an average of 90.1% compared to 97.9%
in the Enoxaparin 1.0 mg/kg group and 97.0% in the Enoxaparin 1.5 mg/kg group. Among all groups, 91.1% of the patients took 81-100% of the study medication and 6 patients (5.9%) were compliant with less than 81% of the study drug. The patients in the Warfarin group had the lowest rate of medication compliance with a rate of 50-100%. The Enoxaparin 1.0 mg/kg group had the best compliance rate of 82-100%.

Despite early termination of the Deitcher et al study due to poor recruitment of patients, the researchers were able to conclude that Enoxaparin was more effective than Warfarin at decreasing the incidence of recurrent venous thromboembolism in cancer patients. There were no differences among the groups for significant bleeding events. Deitcher et al concluded that 180 days of treatment with LMWH is at least as effective and safe as using Warfarin for long-term treatment of recurrent VTE in cancer patients.

**Discussion**

All four studies concluded that LMWH, in comparison with oral anticoagulants, was the most effective treatment for prevention of recurrent VTE, PE, or both, while also being more effective at decreasing the risk of bleeding, including fatal hemorrhage. Lack of power in the studies conducted by Meyer et al, Hull et al, and Deitcher et al was obvious in the small sample sizes and unclear, poorly defined results and discussion.

There were no dietary restrictions in the studies, which has the potential to interfere with INR measurement and skew Warfarin treatment. Certain medications could also alter the therapeutic range of INR and are important considerations in these trials. The Hull et al study was the only study to mention their restriction of acetylsalicylic acid for all of the patients in the study. They also discouraged the use of certain other medications which could alter the effect of the anticoagulants.
In addition to the small sample size and early termination, Meyer et al had other weaknesses that impacted their data. First of all, all of the patients included in the trial (except two) received anticoagulation prior to randomization, which seems to contradict the idea of randomization. Although the INR measurement was done regularly, the INR for the majority of the study participants was only in the therapeutic range for 41% of the treatment time. If the INR is not in therapeutic range, this could be at least partially responsible for the higher bleeding rate noted in the Warfarin group. Also, the dosing of Warfarin was managed by the investigator of the trial or the primary care provider, instead of being managed by a coagulation clinic, which tends to have more consistency. Other possibilities for the skewed outcome of the Meyer et al study is that their patients had poor hepatic functioning due to chemotherapy and/or were taking a medication which caused a drug interaction and inaccurate INR measurements.

There are minimal large trials with the latest and most up to date information. Results of the current trials can often overlap within the same trial, which distracts the reader from the lack of power in the study. Percentages also seem to demonstrate lack of power in the current available studies and take away from statistically significant data. It is extremely important to recruit as many candidates for collecting data as possible to account for drop-out rates, poor medication compliance, and inconclusive follow-up.

The previous systematic review that was conducted by Akl et al, published in 2008 investigated patients with and without cancer, whereas this systematic review includes patients with cancer. The Akl et al systematic review also contains older research. Despite differences in articles used for the reviews, the conclusions are the same. There is need for more trials with better design and a higher patient recruitment in
order to confirm that LMWH is superior to oral anticoagulation for prevention of recurrent VTE in cancer patients.

Further study on anticoagulation in cancer patients is important in order to establish clear guidelines. Recommendations for stronger research include only investigating patients with cancer and comparing LMWH and oral anticoagulants. Although cost of the study drugs may be a limiting factor, the cost of complications related to recurrent VTE in cancer patients is far more of a concern and should not limit further research or proper treatment. LMWH may be more expensive to use, but definitive results in its effectiveness may outweigh the cost of treatment, especially in cases where it can prevent a fatal outcome. Dietary and medication restrictions are also important parts of the investigation in order to accurately account for any potential medication or food interactions which may skew data. Larger study groups are perhaps one of the most important factors in the data collection as demonstrated by the early termination in 2 of the 4 studies because of poor recruitment of subjects.

**Conclusion/Recommendations**

The most current available data on anticoagulation in cancer patients for prevention of recurrent VTE indicates that LMWH is more effective and efficient in comparison to oral anticoagulation therapy. The benefits of using LMWH outweigh the risks but cost is also a factor. LMWH is significantly more expensive and requires daily subcutaneous injections but does not require the strict monitoring of INR and variable dosing that Warfarin requires. The quality of life for cancer patients is an important concern and LMWH seems to be the best option because there is no need for frequent venous access to measure INR.
Many other medications also alter the INR values and metabolism of Warfarin, which poses more of a challenge when using Warfarin for long-term treatment of VTE. Although the data lacks strength, LMWH is suggested to have benefit in survival of cancer patients, especially when compared to Warfarin, whether it is because of prevention of recurrent VTE or simply has less incidence of fatal hemorrhage.
TABLE 1. Current Recommended guidelines for use of LMWH in cancer patients with VTE

<table>
<thead>
<tr>
<th>Group</th>
<th>Recommendation for use of a LMWH</th>
<th>Definition of the category of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCP</td>
<td>Use during the first 3 to 6 months of long-term anticoagulant therapy (grade 1A). Anticoagulant therapy should continue indefinitely or until the cancer is resolved (grade 1C).</td>
<td>1A: strong recommendation; can apply to most patients in most circumstances without reservation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1C: intermediate-strength recommendation; may change when stronger evidence is available</td>
</tr>
<tr>
<td>ASHP</td>
<td>LMWH therapy for the treatment of acute DVT is as safe and effective as traditional therapy with unfractionated heparin in appropriate adult outpatients.</td>
<td>Positions statement; level of evidence is not applicable</td>
</tr>
<tr>
<td>AIOM</td>
<td>Initial treatment with weight-adjusted dose LMWH. In patients with severe renal failure (creatinine clearance &lt;25-30 mL), suggest IV UFH or LMWH with anti-Xa monitoring (grade 3B). In patients with active cancer, long-term LMWH until cancer disease is resolved (grade 3C).</td>
<td>3B: evidence is obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single group, prepost, cohort, time, or matched case-control studies; findings are generally consistent</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3C: evidence is obtained from well-designed, quasi-experimental studies such as non-randomized, controlled single group, prepost, cohort, time, or matched case-control studies; findings are inconsistent</td>
</tr>
<tr>
<td>NCCN</td>
<td>Monotherapy (without Warfarin) is recommended (up to 6 months) treatment of proximal DVT or PE, and prevention of recurrent VTE in patients with advanced or metastatic cancer who do not have contraindications to anticoagulation. (grade 2A)</td>
<td>2A: There is uniform NCCN consensus, based on lower level evidence including clinical experience, that the recommendation is appropriate.</td>
</tr>
</tbody>
</table>

ACCP, American College of Chest Physicians; AIOM, Italian Association of Medical Oncology; ASHP, American Society of Health-System Pharmacists; NCCN, National Comprehensive Cancer Network
TABLE 2. Summary of the four reviewed articles

<table>
<thead>
<tr>
<th>Reference</th>
<th>Methods</th>
<th>Intervention</th>
<th>Participants</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee 2003</td>
<td>Randomized, open-label, multicenter trial</td>
<td>LMWH vs coumarin derivative</td>
<td>Cancer patients with acute, symptomatic DVT, PE, or both</td>
<td>Higher probability of recurrent VTE in the oral anticoagulant group</td>
<td>Funding provided by Pharmacia</td>
</tr>
<tr>
<td>Hull 2006</td>
<td>Randomized, open-label multi-center trial</td>
<td>LMWH vs Vitamin K antagonists</td>
<td>Cancer patients with acute, symptomatic proximal vein thrombosis</td>
<td>LMWH is more effective than Vitamin K antagonists for prevention of recurrent VTE</td>
<td>Funded by Canadian Institutes of Health Research</td>
</tr>
<tr>
<td>Meyer 2002</td>
<td>Randomized, open-label multicentral trial</td>
<td>Enoxaparin vs Warfarin</td>
<td>Cancer patients with either PE or VTE</td>
<td>Warfarin is associated with high bleeding rate; LMWH may be as effective for anti-coagulation and safer</td>
<td>Funded by Aventis pharmaceuticals</td>
</tr>
<tr>
<td>Deitcher 2006</td>
<td>Randomized, open-label multidose active comparator parallel trial</td>
<td>Enoxaparin vs Warfarin</td>
<td>Adults with active malignancy</td>
<td>Lower incidence of VTE with Enoxaparin alone than with Warfarin</td>
<td>Sponsored by Aventis pharmaceuticals</td>
</tr>
</tbody>
</table>
TABLE 3. Primary Efficacy Outcome Events in the Lee et al study\textsuperscript{7}

<table>
<thead>
<tr>
<th>Event</th>
<th>Dalteparin (N=336)</th>
<th>Oral Anticoagulation (N=336)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep-vein thrombosis alone</td>
<td>14</td>
<td>37</td>
</tr>
<tr>
<td>Nonfatal pulmonary embolism</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Fatal pulmonary embolism</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>53</td>
</tr>
</tbody>
</table>

TABLE 4. Primary Efficacy Outcome Events at 3 and 12 months in the Hull et al study\textsuperscript{8}

<table>
<thead>
<tr>
<th>Event</th>
<th>Tinzaparin N=100 n</th>
<th>UFH and vitamin K antagonist N=100 n</th>
<th>Difference, (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>New episodes of venous thromboembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 3 months</td>
<td>6</td>
<td>10</td>
<td>-4.0 (-12.0 to 4.1)</td>
<td></td>
</tr>
<tr>
<td>At 12 months</td>
<td>7</td>
<td>16</td>
<td>-9.0 (-21.7 to -0.7)</td>
<td>.044</td>
</tr>
</tbody>
</table>

| Bleeding complications during 3 months treatment interval | | | | |
|----------------------------------------------------------| | | | |
| All                                                      | 27                | 24                                | -3.0 (-9.1 to 15.1)  |         |
| Major                                                    | 7                 | 7                                 | 0.0 (-7.1 to 7.1)    |         |
| Minor                                                    | 20                | 17                                | 3.0 (-7.8 to 13.8)   |         |

| Death                                                  | | | | |
|--------------------------------------------------------| | | | |
| At 3 months                                           | 20                | 19                                | 1.0 (-10.2 to 11.9)  |         |
| At 12 months                                          | 47                | 47                                | 0.0 (-14.6 to 13.2)  |         |
**TABLE 5. Primary Efficacy Outcome Events in the Meyer et al study**

<table>
<thead>
<tr>
<th>Event (at 3 months)</th>
<th>Enoxaparin group n=75 (%)</th>
<th>Warfarin group n=71 (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major outcome event (major bleeding or VTE)</td>
<td>7 (10.5)</td>
<td>15 (21.1)</td>
<td>P=.09</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>5</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Fatal hemorrhage</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>8 (11.3)</td>
<td>17 (22.7)</td>
<td>P=.07</td>
</tr>
</tbody>
</table>

**TABLE 6. Summary of Adverse Events in the Deitcher et al study**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Enoxaparin 1.0 mg/kg, n=31 (%)</th>
<th>Enoxaparin 1.5 mg/kg, n=36 (%)</th>
<th>Warfarin, n=34 (%)</th>
<th>Total, n = 101 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonserious</td>
<td>27 (87.1)</td>
<td>32 (88.9)</td>
<td>29 (85.3)</td>
<td>88 (87.1)</td>
</tr>
<tr>
<td>Treatment-related, nonserious</td>
<td>3 (9.7)</td>
<td>6 (16.7)</td>
<td>8 (23.5)</td>
<td>17 (16.8)</td>
</tr>
<tr>
<td>Discontinued due to nonserious adverse event</td>
<td>1 (3.2)</td>
<td>0 (0.0)</td>
<td>2 (5.9)</td>
<td>3 (3.0)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>16 (51.6)</td>
<td>23 (63.9)</td>
<td>17 (50.0)</td>
<td>56 (55.4)</td>
</tr>
<tr>
<td>Minor hemorrhage event</td>
<td>19 (61.3)</td>
<td>20 (55.6)</td>
<td>17 (50.0)</td>
<td>56 (55.4)</td>
</tr>
<tr>
<td>Major hemorrhage event</td>
<td>2 (6.5)</td>
<td>4 (11.1)</td>
<td>1 (2.9)</td>
<td>7 (6.9)</td>
</tr>
<tr>
<td>Died</td>
<td>7 (22.6)</td>
<td>15 (41.7)</td>
<td>11 (32.4)</td>
<td>33 (32.7)</td>
</tr>
</tbody>
</table>
References


