

The Use of Low-Dose Warfarin as Prophylaxis for Central Venous Catheter Thrombosis in Patients With Cancer: A Meta-Analysis

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Purpose/Objectives: To determine whether the use of low-dose warfarin could reduce the incidence of thrombosis in patients with cancer who have a central venous catheter (CVC).

Data Sources: MEDLINE®, CINAHL®, CANCELIT®, EMBASE®, and the Cochrane Library.

Data Synthesis: Meta-analysis of four studies (N = 1,236 patients) revealed that 6.4% of warfarin-treated patients experienced a thrombotic event compared with 7.5% in the control (no treatment) group. The risk difference for thrombus formation was not significant (2.0%, confidence interval = -9.0% to 5.0%).

Conclusions: The administration of warfarin did not reduce the incidence of symptomatic or asymptomatic CVC-associated thrombosis in patients with cancer.

Implications for Nursing: Using research findings to inform clinical nursing practice is important in caring for patients and providing optimal and improved patient outcomes. Prophylactic use of low-dose warfarin may not prevent thrombus formation and is associated with potentially adverse patient outcomes.

One in 200 patients with cancer will experience venous thromboembolism (Lee & Levine, 2003), the second-leading cause of death in these patients (Agnelli, 1997; Sorensen, Mellemkjaer, Olsen, & Baron, 2000). Many factors contribute to the development of thrombus in the oncology population. For example, tumor cells and their products can activate the body's coagulation and fibrinolytic systems. In addition, comorbid states (e.g., bed rest, surgery, infection, chemotherapy) and the use of central venous catheters (CVCs) can stimulate coagulation and contribute to hypercoagulable states (Kakkar & Williamson, 1998; Lip, Chin, & Blann, 2002; Prandoni, Piccioli, & Girolami, 1999).

Because deep vein thrombosis, pulmonary embolism, and CVC thrombosis all can lead to complications, clinicians need effective prevention strategies. The standard treatment for thrombosis is the use of anticoagulants. However, the use of low-dose warfarin is unclear regarding prophylaxis for the prevention of thrombosis in patients with cancer who have CVCs because of the potential for complications. The development of complications from anticoagulants is associated with patient age and gender, the presence of malignancy, and the length of time on anticoagulant therapy. The most serious complication with anticoagulants is major hemorrhage. The risk is estimated to be as high as 1% for every month on therapy (Levine, Raskob, Landefeld, & Kearon, 2001) and

Key Points . . .

- Cancer is a chronic hypercoagulable state that increases the risk of thromboembolism.
- Central venous catheter-related thrombosis is a common complication and a significant cause of morbidity and mortality in patients with cancer.
- The routine use of low-dose warfarin as prophylaxis does not significantly reduce the incidence of thrombus formation and is associated with potentially adverse patient outcomes.

increases exponentially when the international normalized ratio (INR) rises to 4.5–5.0 (Hylek et al., 2001; Pineo & Hull, 2003).

Patients with cancer tend to experience greater difficulty maintaining INRs in the therapeutic value range, with INRs exceeding 4.5 for longer durations (Bona, Sivjee, Hickey, Wallace, & Wajcs, 1995; Hylek et al., 2001). This may result from the disease process, cancer medications, or the hypercoagulable state of many patients. Thus, the administration of anticoagulants to patients with cancer often requires frequent monitoring and dose modifications. Anticoagulant use has disadvantages, including adverse events, demands on patients' and clinicians' time, the number of interventions required, and costs to the healthcare system. A low-dose anticoagulant would be desirable if it did not require frequent monitoring and proved efficacious (Coccheri, Palareti, & Cosmi, 1999).

Research on low-dose anticoagulant therapy was conducted first on surgical patients (De Takats, 1950). By the late 1980s, researchers had concluded that warfarin caused no changes in prothrombin time or the levels of clotting factors II, VII, IX, and X (Bern et al., 1990). Because no blood test effectively measures the subtle changes in coagulation

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Digital Object Identifier: 10.1188/07.ONF.1037-1043

created by the use of low-dose warfarin, the end point of thrombus formation is critical to determine the effects of low-dose treatment.

Bern et al. (1990) conducted the first clinical trial using low-dose warfarin (1 mg daily) as primary preventive treatment for patients with cancer who have CVCs. They found that patients taking low-dose warfarin experienced fewer thrombotic events compared with those receiving no treatment ($p < 0.001$). Based on that research, the Consensus Conference on Antithrombotic Therapy published guidelines that all patients with long-term indwelling catheters receive low-dose warfarin (Clagett, Anderson, Levine, Salzman, & Wheeler, 1992). However, as treatments evolved and clinicians used low-dose warfarin, the authors were prompted to inquire into the current state of evidence 14 years after the initial trial. Although the risk associated with low-dose anticoagulants has decreased, questions of efficacy remain. To promote the use of evidence-based treatments by nurse-clinicians, a meta-analysis was proposed to determine the therapeutic value of low-dose warfarin. This review may help clinicians to better assess the risk-benefit ratio of using warfarin as a primary prophylactic agent.

The purpose of this meta-analysis was to determine whether low-dose warfarin prevents thrombus formation in adult patients with cancer who have CVCs, as compared to patients receiving a placebo or no treatment. Low-dose warfarin was defined as a daily oral dose of 1 mg, as a variable dose that maintains an INR less than 2.0, or any combination of these. Both dosing regimens are considered subtherapeutic when compared to standard dosing for anticoagulation (i.e., maintaining INR in the therapeutic range of 2.0–3.0) (Kuruvilla & Gurk-Turner, 2001).

If warfarin is an effective prophylactic treatment for patients with cancer who have CVCs, additional nursing education will be required regarding its benefits in reducing the risk of complications and providing optimal care. However, if the use of low-dose warfarin is ineffective, clinicians and researchers must search for new strategies to decrease the risk of thrombus formation.

Methods

Trial Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they were randomized controlled trials (RCTs), were published as a paper or an abstract in any language, and compared the incidence of thrombus formation in patients with cancer who had CVCs and were receiving low-dose warfarin (1 mg orally) or a variable dose of warfarin (maintaining INR less than 2.0) versus a control group receiving a placebo or no prophylaxis. Participants were adults (18 years or older) with cancer (hematologic or solid tumors) who had a semipermanent or permanent CVC and were randomized to receive low-dose warfarin or placebo (no treatment) within a week of CVC insertion. Trials were excluded if they used low-molecular-weight heparin, unfractionated heparin, or oral thrombin inhibitors because these treatments have different mechanisms of anticoagulation action.

Outcome Measures

Two primary outcomes were chosen for analysis. The first was the incidence of symptomatic or asymptomatic venous

thrombosis, pulmonary embolism, or catheter thrombosis confirmed by a Doppler ultrasound, ventilation perfusion scan, or spiral or dye contrast computed tomography scan. The second was the incidence of a major hemorrhage, defined as a fall in hemoglobin levels by greater than 20 g/l and requiring transfusion. One secondary outcome, correlation between the incidence of thrombus formation and the types of chemotherapeutic agents given (sclerosing or nonsclerosing), was included. Because sclerosing drugs damage the endothelial lining and any such damage can result in the body releasing thromboplastic substances and sending platelets to the site of injury (Bona, 1999; Wickham, Purl, & Welker, 1992), the researchers hypothesized that those drugs might influence the incidence of thrombus formation.

Search Strategies for Identifying Studies

Articles were selected for review from a comprehensive electronic search of MEDLINE® (1966–2007), EMBASE® (1988–2007), CANCERLIT® (1975–2007), CINAHL® (1982–2007), and the Cochrane Controlled Trials Register. Two Web sites, Current Controlled Trials (www.controlled-trials.com) and Clinical Trials.gov (www.clinicaltrials.gov/ct), which serve as metaregistries of current clinical trials, were used to track ongoing or recently completed but not published trials. Articles were retrieved using the following headings and key words: anticoagulants, warfarin, neoplasm, oncology, catheter, thrombus, and primary prevention. A sensitive search filter was used to enable identification of RCTs in MEDLINE and EMBASE. Abstracts from the American Society for Clinical Oncology (1999–2007) and the American Society for Hematology (2001–2007) also were reviewed. The researchers attempted to locate unpublished materials through first author contacts and discussions with a scientific advisor of Bristol-Myers Squibb, the manufacturer of warfarin. Contacting authors of selected studies resulted in six responses. Additional study information was obtained from an author who was not included in the published materials. The reference lists of all primary studies were reviewed to identify additional articles. Finally, the researchers personally contacted colleagues and medical oncologists to identify other studies or researchers in the field.

Methodologic Quality of Trials

Articles meeting the inclusion criteria were rated on methodologic quality. Two reviewers independently assessed the quality of the included trials using the Jadad scale (Jadad et al., 1996) and the Cochrane method for the assessment of allocation concealment (Schulz, Chalmers, Hayes, & Altman, 1995). Using the Jadad scale, the researchers assessed the internal validity of each trial against the randomization of study participants; blinding of patients, caregivers, and those assessing study outcomes; and a complete description of the withdrawals and dropouts to determine the number of patients in each treatment group entering and completing the trial. One point was given for each item present. If the randomization was concealed and the method used for double-blinding was appropriate, an additional point was given to each item, yielding an overall score of 0–5 points for each clinical trial. Higher scores indicated higher study quality. To be deemed high quality, a trial must have received a score of 3 or more. Studies also were scored according to the adequacy of allocation concealment: grade A (adequate concealment), grade B (uncertain), and grade C (clearly

inadequate concealment) (Clarke & Oxman, 2003). Inter-rater reliability was measured for both quality scales by calculating the kappa (K) statistic. Disagreements regarding inclusion and quality were resolved by discussion and consensus.

Statistical Analysis

The authors independently assessed the selected studies and extracted data on methodology, population, intervention, and outcome measures. The data then were entered using Comprehensive Meta-Analysis computer software version 2.0 (Biostat, Inc.), and an overall treatment effect was calculated across trials. As the specified outcomes were dichotomous (thrombosis versus no thrombosis), the pooled results for each study were expressed as a risk difference and 95% confidence intervals using the Mantel-Haenszel method of determining average treatment effect (Deeks, Altman, & Bradburn, 2001). Heterogeneity among pooled estimates was tested by means of a chi-square test; a significance level less than 0.10 was considered evidence of heterogeneity. Visual inspection of the forest plot for discrepancy in the confidence intervals and the chi-square test were used to further analyze the heterogeneity among pooled estimates. Where significant heterogeneity was found, a random effects model was used to assume that studies are a random sample from a hypothetical population of studies. The model weighs each study's effect size by its sample size and the between-study variance. Consequently, smaller studies are weighted more in the pooled summary statistics. Because it incorporates between-study differences, the model tends to mitigate discrepant results when significant study variation exists. Using a random effects model results in more conservative pooled estimates of effect, creating wider confidence intervals (Dickersin & Berlin, 1992). However, that may result in greater susceptibility to publication bias, which was evaluated using a funnel plot, which may have limited power in detecting bias if the number of studies in the meta-analysis is small (Clarke & Oxman, 2003).

Results

The researchers initially screened 2,680 titles and abstracts, excluding most because they were review articles or did not meet the inclusion criteria. The full texts of 115 articles were reviewed. Of 15 potential articles, four studies (N = 1,236 patients) were chosen that met the eligibility criteria. They were published from 1990–2005, three in peer-reviewed journals and one as an abstract. A coefficient of the included and excluded studies was measured. The agreement between the researchers was $r = 0.78$.

The characteristics of the studies selected for meta-analysis are outlined in Table 1. Trials were conducted in North America, New Zealand, and the United Kingdom. The study populations were heterogeneous as to types of cancer. The studies by Bern et al. (1990), Couban et al. (2005), and Young et al. (2005) assessed the effects of low-dose warfarin on patients with all types of malignancies, whereas Heaton, Han, and Inder (2002) selected only patients with hematologic disorders. In three of the studies (Bern et al.; Couban et al.; Heaton et al.), the treatment dosage of warfarin was 1 mg orally every day with no dosing variation. In Young et al.'s trial, patients were randomized according to physicians' prescribing practices to control (no warfarin) versus warfarin (1 mg daily or dose-adjusted warfarin to maintain INR from

1.5–2.0). Couban et al. used a placebo, and the other three studies used none. Bern et al. and Couban et al. started warfarin 72 hours prior to insertion of the CVC; participants in the Heaton et al. study began warfarin on the day of insertion. Timing of the intervention in Young et al.'s trial was not available in the published abstract.

Interruptions in the use of low-dose warfarin were common for periods of thrombocytopenia. Bern et al. (1990) and Young et al. (2005) did not state whether warfarin was withheld during periods of thrombocytopenia. Couban et al. (2005) used a platelet count of $20 \times 10^9/L$ or less as the critical stopping point. Heaton et al. (2002) required the first 65 participants to stop taking warfarin when the platelet count dropped to less than $10 \times 10^9/L$; subsequently, for the remaining participants, stoppages for thrombocytopenia were deemed unnecessary. All four studies used objective tests such as Doppler ultrasound or venography to confirm the diagnosis of thromboembolism. The Bern et al. and Heaton et al. trials were conducted over 90 days; the duration of the Couban et al. trial was 180 days. The median follow-up for patients in the Young et al. trial was eight months from time of randomization.

Overall, the methodologic quality of the included trials was poor. Bern et al. (1990) and Heaton et al. (2002) did not specify the randomization method used and did not include a blinded placebo control group. Consequently, they scored 1 out of 5 on the Jadad criteria. Only the Couban et al. trial (2005) was assessed as high quality, scoring 5 out of 5; it used an acceptable method of concealment, allocation by block randomization, and an adequately described placebo control. The information in the Young et al. (2005) abstract was insufficient to complete a Jadad assessment of the trial's quality. Young et al. informed this review's researchers that they are writing the study results for publication.

The Presence of Heterogeneity

Visual inspection of the forest plot and the results of the chi-square test for heterogeneity confirmed significant study variation ($p = 0.01$). Despite that result and the small number of trials included, the data were pooled because heterogeneity can be examined from clinical, methodologic, and statistical perspectives and from the results of any or all three factors. Researchers must consider the degree and source of heterogeneity prior to pooling data. Clinical heterogeneity, in particular, stems from differences across study participants, interventions, and outcomes; if the data are found, they should not be pooled. The researchers believed, however, that the studies were clinically homogeneous. Given that all patients with cancer can exhibit a hypercoagulable state, the population of mixed tumor types appears sufficiently similar to the pool. A consistent intervention was used in all studies: administration of 1 mg of warfarin daily or dose-adjusted warfarin to maintain an INR greater than 1.5. Finally, the outcome of thrombosis was chosen across all studies. Pooling of the data from a clinical standpoint was deemed justifiable.

To understand heterogeneity, the methodologic diversity of the trials was examined. Methodologic heterogeneity is defined as the difference between trial designs, as well as trial quality. All four trials in the meta-analysis were RCTs, but they varied significantly in quality. In general, if allocation concealment has not been reported, it has not been carried out (Egger, Ebrahim, & Smith, 2002). Inadequate concealment of allocation reportedly results in an overestimation of treatment

Table 1. Characteristics of Studies Included in the Meta-Analysis

Study	Design and Quality Rating	Setting and Participants	Interventions	Outcomes
Bern et al., 1990	Type: open RCT Randomization: yes or no code Outcome blinding: no Duration: 90 days Confounders: Whether the study drug was withheld for periods of thrombocytopenia is unknown. The study was conducted in the late 1980s, and PTT was the standard measure of coagulation rather than INR. Quality assessment score: Jadad = 1	Setting: United States, multicenter Inclusion criteria: survival > 3 months, need for indwelling CVC Exclusion criteria: Baseline platelet count < 125 × 10 ⁹ /L, acquired or congenital coagulopathies, previous CVC, obstructing mediastinal tumors, previous DVT, anatomic lesions that bleed (ulcers), serum creatinine > 140 mcmol/l Number recruited: 121 patients (59 men, 62 women) Withdrawals: 39 patients, including 26 patients who died because of disease progression Population: 82 had solid tumors and hematologic cancers.	Experimental group: warfarin 1 mg orally per day Control group: no treatment Timing of intervention: The drug commenced 72 hours prior to CVC line insertion. Type of line inserted: port or implanted vascular access device	Experimental group: 4 of 42 (10%) developed thrombosis. Control: 15 of 40 (38%) developed thrombosis (p < 0.001). Conclusions: Overall, the results favored the use of low-dose warfarin for prophylaxis of CVC thrombosis in patients with solid tumors and hematologic cancers. The authors recommended the daily use of minidose warfarin in patients with cancer who had CVCs. Mean time to thrombosis: 38 days
Heaton et al., 2002	Type: open RCT Randomization: unknown Outcome blinding: no Duration: 90 days Confounders: Warfarin was withheld in the first 65 patients if severe thrombocytopenia (platelet count < 10 × 10 ⁹ /L) was present. For the remainder of the study, warfarin was not stopped when the platelet count was < 10 × 10 ⁹ /L. Patients took warfarin for a mean of 41 days. Only the first 88 catheters were included in the final analysis because patients with two or three catheters had a high incidence of thrombus (5 of 14, 36%). Patients with previous CVC lines were not excluded. Quality assessment score: Jadad = 1	Setting: New Zealand, single center Inclusion criteria: hematologic malignancy; patients with previous CVC lines were allowed to participate. Exclusion criteria: not detailed Number recruited: 102 catheters initially registered in 88 patients; subsequent results showed a high incidence of thrombi in patients with second- or third-line insertions. Consequently, only first catheters (88 catheters in 88 patients) were included in the data analysis. Withdrawals: 14 patients Population: 88 patients (52 men, 36 women); all patients had hematologic cancers.	Experimental group: warfarin 1 mg orally per day Control group: no treatment Timing of intervention: Warfarin administration commenced on the day of catheter insertion and continued until 90 days had passed, a clot developed, the catheter was removed, or INR > 1.5. Type of line inserted: double-lumen central subclavian catheters	Experimental group: 8 of 45 (18%) developed thrombosis. Control group: 5 of 43 (12%) developed thrombosis (p > 0.05). Conclusion: No benefit was found from using minidose (1 mg daily) warfarin for the prevention of thrombosis in patients with hematologic cancers. Mean time to thrombosis: unknown
Couban et al., 2005	Type: double-blind RCT Randomization: A pharmacist at each site randomly assigned patients to intervention and control groups, using permuted blocks of up to six, after stratification. Outcome blinding: double-blind randomized Duration: 180 days Confounders: Warfarin was withheld when the platelet count was < 20 × 10 ⁹ /L. Low platelet counts occurred in 75% of participants for an unknown duration. Quality assessment score: Jadad = 5	Setting: Canada, multicenter Inclusion criteria: biopsy-confirmed cancer and need for indwelling CVC Exclusion criteria: previous CVC-associated thrombosis, baseline INR > 1.5, requirement for therapeutic anticoagulation Number recruited: 255 patients (152 men, 103 women) Withdrawals: none Population: 166 had solid tumors; 89 had hematologic cancers.	Experimental group: warfarin 1mg orally per day Control group: placebo Timing of intervention: Study drug commenced within 72 hours of CVC line insertion. Type of line inserted: port or implanted vascular access device	Experimental group: 6 of 130 (4.6%) developed thrombosis. Control group: 5 of 125 (4%) developed CVC-related thrombosis. Conclusion: no treatment effect (p > 0.05) Mean time to thrombosis: 92 days
Young et al., 2005	Type: prospective RCT Randomization: according to clinicians' prescribing practices Outcome blinding: no	Setting: United Kingdom, multicenter (68 sites) Inclusion criteria: all patients with cancer ≥ 16 years with a CVC inserted for	Experimental and control groups: randomized 408 patients to warfarin (20% dose-adjusted warfarin	Experimental group: 22 of 408 (5.4%) had CVC-related thrombosis. Control group: 21 of 403

(Continued on next page)

CVC—central venous catheter; DVT—deep vein thrombosis; INR—international normalized ratio; PTT—partial thromboplastin time; RCT—randomized controlled trial

Note. No study declared a conflicting interest except Bern et al. (1990), which received grants from Pharmacia-Nu Tech and DuPont Pharmacy.

Table 1. Characteristics of Studies Included in the Meta-Analysis (Continued)

Study	Design and Quality Rating	Setting and Participants	Interventions	Outcomes
	Duration: Median follow-up for surviving patients was eight months from the point of randomization. Confounders: Data were incomplete about thrombotic events for warfarin use (n = 53, 13%) and patients receiving no treatment (n = 65, 16%). Quality assessment score: inadequate data for Jadad assessment	chemotherapy; adequate hematologic, hepatic, and renal function; no contraindication to warfarin; not currently on warfarin Withdrawals: not stated Population: 811 had a colorectal, upper gastrointestinal, or breast tumor, and 170 had a tumor in another site.	[DAW]; 80% 1 mg warfarin versus no warfarin (n = 403 controls)]. The second arm of the RCT was not included (1 mg warfarin versus DAW to keep INR from 1.5–2.0). Timing of intervention: not stated Type of line inserted: not stated; central or peripheral insertion sites	(5.2%) developed thrombosis. Conclusion: No benefit was found in using low-dose warfarin for prophylaxis of symptomatic CVC-related thrombosis in patients with cancer. If clinicians chose to provide prophylaxis, DAW was recommended. Mean time to thrombosis: unknown

CVC—central venous catheter; DVT—deep vein thrombosis; INR—international normalized ratio; PTT—partial thromboplastin time; RCT—randomized controlled trial

Note. No study declared a conflicting interest except Bern et al. (1990), which received grants from Pharmacia-Nu Tech and DuPont Pharmacy.

effects by as much as 30% (Schulz et al., 1995). Of the studies that lacked allocation concealment, only the Bern et al. (1990) study showed a statistically significant benefit of low-dose warfarin, leading the researchers to conclude that the lack of concealment resulted in an overestimation of the benefit of low-dose warfarin. Heaton et al. (2002) lacked adequate allocation concealment but showed no treatment effect. Given the dichotomous result, the researchers questioned the impact of allocation concealment on the chi-square test that indicated significant heterogeneity, concluding that the lack of allocation concealment resulted in some methodologic diversity but did not provide enough justification for not pooling the data.

Two studies had small sample sizes. Because that often is associated with poorer quality, the methodologic strength of the research may be limited. Part of the heterogeneity shown in the meta-analysis can be explained by this diversity (Clarke & Oxman, 2003). An examination of the overlapping confidence intervals in the forest plot suggests that chance remains a probable and logical explanation for between-study differences and pooling remains an option. Research indicates that when confidence intervals in meta-analysis overlap, as they did with the current study, and clinical homogeneity exists, the heterogeneity may be present because of chance or random sampling (Montori, Swiontkowski, & Cook, 2003).

This study's meta-analysis indicated heterogeneity ($p = 0.01$). Statistical heterogeneity indicates that the true underlying treatment effects in the trials are not identical. Instead, the observed treatment effects are more different than should be expected from random error alone. In an effort to account for the significant heterogeneity, a random effects model was used when pooling the data. The model assumes each study represents one of several studies distributed around the true underlying treatment effect; it incorporates within-study and between-study variations, and the confidence interval is wider (Montori et al., 2003). As a result, a greater degree of uncertainty was incorporated into the statistical calculation and placed more weight on the findings of the smaller studies.

Clarke and Oxman (2003) cautioned against excessive interpretation of the causes of heterogeneity as the examination into its reasons is done post hoc. Nevertheless, all of the studies selected met the stringent inclusion criteria; thus, pooling of the data was deemed justifiable. The test for statistical het-

erogeneity perhaps is irrelevant because any studies included in a meta-analysis will possess some clinical heterogeneity. Hardy and Thompson (1998) suggested that researchers should instead examine the clinical differences among studies through narrative description, as opposed to relying on the overall statistical test for heterogeneity. That examination was provided in the meta-analysis and Table 1.

Outcomes of Interest

The individual studies showed varying efficacy of low-dose warfarin in preventing thrombus formation, the first primary outcome of interest. Bern et al. (1990) reported a statistically significant improvement in lowering the risk of thrombus formation. Of the 40 control patients who completed the study and did not receive warfarin, 15 had venogram-proven thrombosis, whereas only 4 of 42 patients on warfarin had thrombosis ($p < 0.001$). The other three studies failed to find a significant treatment effect; prophylactic use of low-dose warfarin in those trials did not decrease the risk of CVC-related thrombosis in patients with cancer.

Why the Bern et al. (1990) trial results differed significantly from the other three studies is unclear, but several possibilities exist. Bern et al. may have included patients with more advanced cancer in their study. Given that 82 of 121 patients (68%) who were enrolled in the trial completed it and that 26 of the patients who withdrew after randomization died, the research may have been conducted with a very ill population, despite the inclusion criterion of survival more than three months. The population may have differed from those selected by Couban et al. (2005), Heaton et al. (2002), and Young et al. (2005), considering that those with advanced cancer have a higher risk of venous stasis because of decreased mobility and often have increased platelet aggregation or activation along with greater tumor burden, resulting in larger release of procoagulant factors (Lip et al., 2002; Prandoni et al., 1999; Schwartz & Simantov, 1998; Solymoss, 2000). Perhaps the subtle difference in population contributed to low-dose warfarin appearing to be a statistically effective treatment.

Data regarding the second primary outcome, hemorrhage, were reported poorly in the trials. Bern et al. (1990) reported no incidence of hemorrhage in either group, whereas Couban et al. (2005) stated that no difference existed in major or minor

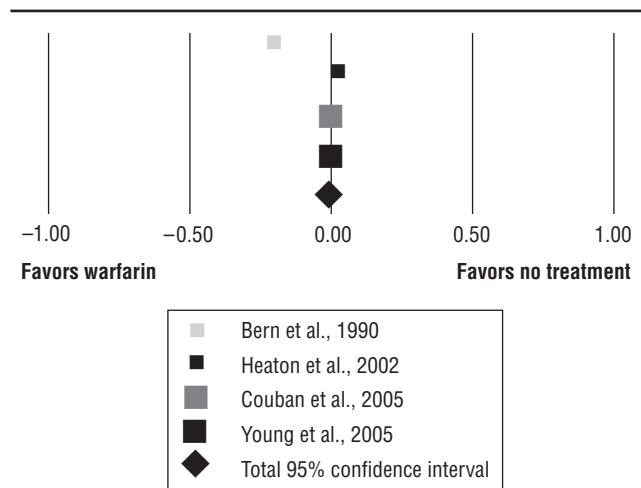
episodes of bleeding but failed to provide data on the actual rates of bleeding. Heaton et al. (2002) reported one case of hemorrhage in the treatment group, although the description provided suggests that the hemorrhage could have been related to the patient's cancer. Young et al. (2005) reported no difference in major bleeding incidence. Given the lack of data and the low incidence of hemorrhage, the planned statistical analysis could not be completed. No author reported hemorrhage using the definition that was set a priori (greater than a 20 g/l decrease in hemoglobin).

A statistical analysis could not be performed on the secondary outcome, specifically the incidence of thrombus formation as it relates to the types of chemotherapy drugs given. Only Bern et al. (1990) and Young et al. (2005) provided data, which were not statistically significant, on the effects of sclerosing chemotherapy and its relationship to the incidence of thrombus formation.

In the four studies, 40 of 625 patients (6%) in the low-dose warfarin groups developed proven thrombosis, versus 46 of 611 patients (8%) in the control groups. Meta-analysis of the four studies of warfarin versus placebo or no treatment yielded a pooled risk of difference of 2.0% (95% confidence interval = -9.0% to 5.0%, $p = 0.56$) (see Table 2 and Figure 1). Therefore, warfarin, as a prophylactic strategy, showed a nonsignificant reduction in the incidence of thrombus formation. Based on the results of the trials reviewed, the evidence is insufficient to support the use of low-dose warfarin as prophylaxis in patients with cancer who have CVCs. To the researchers' knowledge, this is the first meta-analysis examining the effects of low-dose warfarin on the incidence of thrombosis in patients with cancer who have CVCs. Thus, comparisons between this meta-analysis and other reviews are not possible.

Discussion

The meta-analysis found no evidence that prophylactic use of low-dose warfarin in patients with cancer who had CVCs resulted in a significant decrease in the risk of thrombosis; however, this meta-analysis had a number of limitations. A



Note. The forest plot shows the risk difference of central venous catheter-related thrombosis in patients with cancer treated with low-dose warfarin compared with patients with cancer treated with a placebo or nothing. The size of the squares represents the weight that the trial contributes to the meta-analysis. The combined (pooled) risk difference estimate is reported in the bottom row.

Figure 1. Mantel-Haenszel Risk Difference Forest Plot

small number of studies met the inclusion criteria. In addition, the researchers questioned whether a homogeneous population of patients with solid tumors would yield different results, given the high propensity of this group of patients to develop thrombosis. From the researchers' knowledge of pathophysiology, they hypothesized that patients with solid tumors might gain greater benefit from low-dose warfarin compared to patients with other tumor types. However, that theory lacks sufficient evidence. Patients with solid and hematologic tumors can develop thrombosis, and both groups possess numerous risk factors for the development of thrombus; thus, a mixed population was included in the meta-analysis. The a priori proposal to study a mixed population proved to be an appropriate reflection of the research conducted to date, given that two of the studies used a mixed tumor population. Unfortunately, insufficient data were provided to conduct a subgroup analysis of hematologic versus solid tumor thrombosis incidence.

Researchers may need better evidence about the factors influencing the incidence of thrombosis development. If clinicians knew more, perhaps select patients with cancer could be anticoagulated instead of all patients. A well-designed randomized trial involving low-dose warfarin and stratifying patients according to tumor type (solid versus hematologic) and stage might provide a better understanding of whether a particular group of patients with cancer should be anticoagulated.

Conclusion

Evidence-based nursing practice has become important in health care as a strategy to improve patient outcomes, and increasingly, oncology nurses are being asked to address relevant clinical questions that affect patient management. This meta-analysis examined the efficacy of low-dose warfarin for the prevention of thrombosis in patients with cancer who had CVCs. Based on the results of the meta-analysis,

Table 2. The Impact of Low-Dose Warfarin as Prophylaxis for Prevention of Central Venous Catheter Thrombosis in Patients With Cancer

Study	MH Risk Difference	Lower Limit	Upper Limit	p
Bern et al., 1990	-0.28	-0.45	-0.11	-
Heaton et al., 2002	0.06	-0.09	0.21	0.41
Couban et al., 2005	0.01	-0.04	0.06	0.81
Young et al., 2005	-	-0.03	0.03	0.91
Total 95% CI	-0.02	-0.09	0.05	0.56

CI—confidence interval; MH—Mantel-Haenszel

Note. The total number of thrombotic events was 40 of 625 (warfarin) and 46 of 611 (placebo). The test for heterogeneity was $\chi^2 = 11.27$, $df = 3$ ($p = 0.01$), $I^2 = 73.4\%$. The test for overall effect was $p = 0.56$.

the researchers concluded that the routine use of low-dose warfarin (1 mg daily or dose-adjusted warfarin to maintain an INR from 1.5–2.0) as prophylaxis does not reduce the risk of CVC-related thrombosis in patients with cancer. Young et al. (2005) recommended that if clinicians choose to offer prophylaxis, dose-adjusted warfarin would be superior; however, bleeding diathesis is increased. Oncology nurses need to be informed that prophylactic use of low-dose warfarin may not prevent thrombus formation and is associated with potentially adverse patient outcomes.

The authors gratefully acknowledge the guidance and technical support provided by Brian Rowe, MD, MSc, CCFP(EM), FCCP, Canadian research chair in emergency airway diseases at the University of Alberta, and Terry Klassen, MD, MSc, FRCPC, director of the Alberta Research Center for Child Health Evidence, in the development and implementation of this systematic review and meta-analysis. They also thank Natasha Wiebe, MMath, PStat, for her statistical assistance and guidance in the completion of this project.

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