

Randomized Placebo-Controlled Study of Low-Dose Warfarin for the Prevention of Central Venous Catheter–Associated Thrombosis in Patients With Cancer

Stephen Couban, Michael Goodyear, Margot Burnell, Sean Dolan, Parveen Wasi, David Barnes, Darlene MacLeod, Erica Burton, Pantelis Andreou, and David R. Anderson

From the Departments of Medicine, Community Health and Epidemiology, and Radiology, Dalhousie University and Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia; Department of Oncology, Saint John Regional Hospital, Saint John, New Brunswick; and Department of Medicine, McMaster University, Hamilton, Ontario, Canada.

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Address reprint requests to Stephen Couban, MD, Department of Medicine, Queen Elizabeth II Health Sciences Centre, Room 417, Bethune Bldg, 1278 Tower Rd, Halifax, Nova Scotia B3H 2Y9, Canada; e-mail: stephen.couban@cpha.nshealth.ca.

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A B S T R A C T

Purpose

In this multicenter, randomized, placebo-controlled clinical trial, we studied whether warfarin 1 mg daily reduces the incidence of symptomatic central venous catheter (CVC)–associated thrombosis in patients with cancer.

Patients and Methods

Two hundred fifty-five patients with cancer who required a CVC for at least 7 days were randomly assigned to receive warfarin 1 mg or placebo.

Results

There were 11 (4.3%) symptomatic CVC-associated thromboses among 255 patients, with no difference in the incidence of symptomatic CVC-associated thrombosis between patients taking warfarin 1 mg daily (six of 130 patients; 4.6%) and patients taking placebo (five of 125 patients; 4.0%; hazard ratio, 1.20; 95% CI, 0.37 to 3.94). Warfarin had no effect on CVC life span (84 days v 63 days in control and warfarin groups, respectively; 95% confidence limit, –16 to 55 days; $P = .09$), and it did not affect the number of premature CVC removals (23.2% v 25.4% in control and warfarin groups, respectively; 95% confidence limit of difference –8.34 to 12.71; $P = .68$) or the frequency of major bleeding episodes (2% v 0% in control and warfarin groups, respectively; $P = .5$, Fisher's exact test).

Conclusion

Symptomatic CVC-associated thrombosis in patients with cancer, although significant, is less common than previously reported. In this study, the administration of warfarin 1 mg daily did not reduce the incidence of symptomatic CVC-associated thrombosis in patients with cancer. However, the low rate of symptomatic CVC-associated thrombosis means that a much larger trial is required to address this issue definitively.

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INTRODUCTION

Central venous catheters (CVC) are commonly used in patients with cancer to administer chemotherapy, facilitate antimicrobial, blood product, and fluid administration, and provide access for diagnostic phlebotomies. Two major long-term complications of CVC use in patients with cancer are thrombosis and infection. Both may lead to

significant morbidity and shorten the functional life span of the CVC. Patients with cancer are at increased risk of venous thrombosis in general,¹ and placement of a CVC further increases this risk. Increased venous stasis, direct endothelial injury, and prothrombotic effects of malignancy, chemotherapy, and other agents administered through the CVC are among the factors thought to cause CVC-associated thrombosis in patients with cancer.

CVC-associated thrombosis manifests itself either as thrombosis of the vein in which the CVC is situated or as an occlusion of a CVC lumen. CVC-associated venous thrombosis may be asymptomatic or present with ipsilateral arm or neck pain, swelling, and CVC lumen occlusion. Thrombotic occlusion of a CVC lumen may be partial (ball valve effect) or complete. Often resulting from the formation of a fibrin sheath at the CVC tip,² such CVC lumen occlusions compromise CVC utility and may be a nidus for infection.³

The incidence of CVC-associated thrombosis in patients with cancer has varied considerably among studies, reflecting variations in the population studied (patients with solid epithelial tumors *v* patients with hematologic malignancies) and whether only symptomatic patients were reported or if screening ultrasonography or venography were routinely performed. Four prospective studies⁴⁻⁷ of CVC-associated thrombosis in patients with solid tumors and hematologic malignancies have described rates of thrombosis between 3% and 37%. The incidence of CVC-associated thrombosis in retrospective studies has varied even more widely (2% to 67%).⁸⁻¹³

Previously, prophylactic low-dose warfarin (1 mg/d)⁴ and low molecular weight heparin⁷ were reported to reduce the incidence of CVC-associated thrombosis in patients with cancer in randomized controlled trials. However, neither warfarin nor low molecular weight heparin are widely used in clinical practice to prevent CVC-associated thrombosis.¹⁴

We undertook a randomized, placebo-controlled study to determine whether warfarin 1 mg daily reduced the incidence of symptomatic CVC-associated thrombosis in patients with cancer. We chose to study warfarin because it is a well-tolerated, inexpensive oral medication and because the efficacy of warfarin for this indication has not been evaluated in a large, placebo-controlled trial using symptomatic end points.

PATIENTS AND METHODS

Patient Eligibility

Patients who were 16 years of age or older with histologic or cytologic evidence of cancer who required an indwelling CVC for at least 7 days were eligible to participate. Patients were excluded if any of the following were present: the CVC had been in place for more than 72 hours, the patient had a known allergy to warfarin, there was a thrombosis of the vein in which the CVC was to be placed, the patient had experienced major bleeding within 6 weeks that would contraindicate anticoagulation, the patient's international normalized ratio (INR) was greater than 1.5 at screening and did not correct with vitamin K, the patient had a medical condition requiring long-term anticoagulation, or the patient was pregnant or had previously participated in this study. The trial was approved by the local institutional review board at each center, and all patients gave informed consent before randomization.

Study Design

This was a multicenter, randomized, placebo-controlled trial to evaluate the efficacy and safety of warfarin 1 mg daily for the

prevention of symptomatic CVC-associated thrombosis in patients with cancer. Patients at each center were randomized centrally in permuted blocks of up to six patients. Before randomization, patients were stratified by disease (disease stratum I: solid tumor, lymphoma, chronic leukemia, and myeloma *v* disease stratum II: acute leukemia and bone marrow or peripheral-blood transplantation) and by type of CVC (catheter stratum I: tunneled exteriorized catheter *v* catheter stratum II: implanted catheter).

Treatment Plan

Patients received either a capsule containing warfarin 1 mg or an identical placebo orally each day, starting within 72 hours after CVC insertion. Study medication was not administered when the platelet count was $20 \times 10^9/L$ or less. Study medication was continued until the CVC was removed, the patient died, or the patient developed a symptomatic, radiographically confirmed CVC-associated thrombosis.

CBC count and INR were measured monthly in all patients, weekly in hospitalized patients, and more frequently as clinically indicated. After CVC insertion, patients were observed until the development of a symptomatic CVC-associated thrombosis, until the patient died, or for 3 months after CVC removal. The use of antiplatelet medication or low-dose (≤ 100 U/kg/d) standard heparin or low molecular weight heparin as veno-occlusive disease prophylaxis in patients undergoing bone marrow or peripheral-blood transplantation was permitted. Patients who developed a medical condition requiring therapeutic anticoagulation after enrollment stopped the study medication and were analyzed according to their initial treatment assignment.

If the lumen of a CVC became occluded or blood could not be aspirated, a fibrinolytic agent (either streptokinase or tissue plasminogen activator) was instilled according to a standard protocol. If the occlusion or inability to withdraw blood did not resolve after administration of the fibrinolytic agent, a radiographic contrast study (line-*o*-gram) was undertaken.

Outcome Assessment

The primary outcome of this study was symptomatic, radiographically confirmed thrombosis of a CVC-associated vein. CVC-associated thrombosis was defined as thrombosis of either the vein or veins in which the CVC was placed or a contiguous vein. Patients in whom a CVC-associated thrombosis was suspected clinically were investigated first by compression ultrasonography. If the ultrasound was negative or equivocal in a patient in whom the clinical suspicion of CVC-associated thrombosis was high, then a venogram was also undertaken. No screening radiographic procedures were performed. Patients found to have a radiographically confirmed CVC-associated thrombosis were treated using standard or low molecular weight heparin followed by warfarin at the discretion of their attending physician.

Secondary outcomes of this study were CVC lumen occlusion, CVC life span, premature CVC removal, bleeding, non-CVC-associated venous thromboembolism, and death. CVC lumen occlusion was defined as the inability to instill fluid or withdraw blood from a CVC lumen. CVC life span was defined as the time from CVC insertion to CVC removal and was analyzed as a time-to-event variable. Premature CVC removal was defined as removal of the CVC for any reason other than completion of therapy. Bleeding was subclassified as either major bleeding or other bleeding. Major bleeding was present if any of the following occurred: CNS bleeding, bleeding with hypotension (systolic blood pressure < 80 mmHg or a > 30 -mmHg decrease in systolic

blood pressure), bleeding associated with the transfusion of more than 2 units of red cells in any 24-hour period, or a decrease in hemoglobin by 20 g/L or more in any 24-hour period. Deep venous thrombosis at sites other than the CVC-associated veins and pulmonary embolism confirmed by objective testing were also secondary outcomes. All suspected primary outcome events, bleeding episodes, and deaths were adjudicated centrally by two individuals blinded to the treatment assignments.

Statistical Analyses

The primary end point of the study was the incidence of symptomatic, radiographically confirmed CVC-associated thrombosis. The null hypothesis assumed no difference in the incidence of symptomatic CVC-associated thrombosis between the two treatment groups. We sought to reject this hypothesis in favor of the alternative hypothesis of a 50% risk reduction in the incidence of symptomatic CVC-associated thrombosis in patients randomly assigned to warfarin compared with patients randomly assigned to placebo. It was assumed that the incidence of symptomatic CVC-associated thrombosis in the placebo arm would be 32.5%, as has been previously reported.⁴ Furthermore, using a two-sided α of .05 with 0.80 power, a projected accrual period of 2 years, and a follow-up period of at least 3 months, 144 patients in each treatment arm allocated in a 1:1 ratio were required to detect this difference. After accrual of 250 (87%) of the planned 288 patients, the rate of symptomatic CVC-associated thrombosis in the overall blinded population was noted to be much lower than projected. A futility analysis was undertaken,¹⁵ and the study was closed early because continuing accrual to the originally planned sample size would not have yielded any additional information given the unexpectedly low primary event rate. In brief, at the time of the unplanned interim analysis, given the actual overall event rate of 5%, it was calculated that proceeding to accrual of the originally planned sample size of 288 would yield a result with a power of less than 0.25 to detect a difference if it were actually present. This report includes data of all 255 patients who were enrolled to July 2002 with follow-up to January 2003. Factors that might be asso-

ciated with CVC-associated thrombosis were examined in univariate analysis using the Fisher's exact test.

RESULTS

Patients

Two hundred fifty-five patients were randomized at three tertiary-care centers between March 1999 and July 2002. None of the randomized patients were ineligible, and all 255 patients were assessable and are the subject of this report. The median follow-up time of surviving patients who did not have a CVC-associated thrombosis was 25 weeks (range, 1 to 184 weeks). There were 125 patients randomly assigned to placebo and 130 assigned to warfarin. The treatment groups were well balanced for baseline patient (Table 1) and CVC (Table 2) characteristics.

Efficacy

There were 11 symptomatic CVC-associated thromboses (4.3%) among the 255 patients; five (4.0%; 95% CI, 1.3% to 9.1%) occurred in the placebo group, and six (4.6%; 95% CI, 1.7% to 9.8%) occurred in the warfarin group (hazard ratio, 1.20; 95% CI, 0.37 to 3.94). The median time from CVC insertion to CVC-associated thrombosis was 16 weeks (range, 1 to 20 weeks) and 5 weeks (range, 3 to 23 weeks) in the placebo and warfarin groups, respectively. The times to CVC-associated thrombosis were 10, 95, 110, 129, and 137 days in the placebo group and 19, 26, 33, 35, 153, and 161 days in the warfarin group. Among the five CVC-associated thromboses in the placebo group, four occurred in patients with solid tumors, and one occurred in a patient with acute leukemia. Similarly, of the six

Table 1. Patient Characteristics

Characteristic	Placebo (n = 125)		Warfarin (n = 130)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	51		52	
Range	17-84		14-82	
Sex				
Male	71	57	81	62
Female	54	43	49	38
Disease stratum I	80	64	84	65
Lymphoma	31	25	41	31
Myeloma	20	16	13	10
Chronic leukemia	6	5	1	1
Gastrointestinal cancer	13	10	12	9
Other solid tumor	10*	8	17†	13
Disease stratum II	45	36	46	35
Acute leukemia	29	23	32	25
Bone marrow or peripheral-blood transplantation	16	13	14	11

*Breast cancer (n = 3), lung cancer (n = 3), other solid tumor (n = 4).

†Breast cancer (n = 7), lung cancer (n = 2), genitourinary cancer (n = 2), other solid tumor (n = 6).

Table 2. Central Venous Catheter Characteristics

Characteristic	Placebo (n = 125)		Warfarin (n = 130)	
	No. of Patients	%	No. of Patients	%
Catheter type				
Catheter stratum I, tunnelled, exteriorized	102	82	104	80
Hickman type	78	62	62	48
PICC type	24	19	43*	33
Catheter stratum II, implanted	23	18	26	20
Portacath	23	18	23*	18
PAS-Port	0	0	2	1
Catheter location				
Right	80	64	81	62
Left	45	36	48	37
Not recorded	0	0	1	1
Catheter vein				
Subclavian	58	46	61	47
Jugular	39	31	26	20
Arm	27	22	41	31
Not recorded	1	1	2	1
Operator				
Radiologist	69	55	72	55
Surgeon	56	45	56	43
Not recorded	0	0	2	0

Abbreviations: PICC, peripherally inserted central catheter; PAS-Port, Peripheral Access System Port (Sims-Deltec Inc, St Paul, MN).
*One patient with a PICC type catheter was incorrectly assigned to catheter stratum II.

thromboses in the warfarin group, three occurred in patients with solid tumors, and three occurred in patients with acute leukemia or who were undergoing bone marrow or peripheral-blood transplantation. Of the 11 symptomatic catheter-associated thromboses, seven thromboses were diagnosed by ultrasound alone, and for four thromboses, an ultrasound was performed initially, and then the thrombosis was confirmed by venography.

There were no statistically significant differences between the placebo and warfarin groups in any of the secondary assessments of efficacy. Warfarin did not prolong CVC life span, reduce the number of premature CVC removals or the num-

ber of CVC lumen occlusions, or reduce the number of non-CVC-associated thromboembolic events (Table 3). There were three non-CVC-associated thromboses in the placebo group (three leg deep venous thromboses) and three in the warfarin group (two pulmonary emboli and one leg deep venous thrombosis). None of the deaths on study (21 in the placebo group and 22 in the warfarin group) were caused by pulmonary embolism.

Safety

There were no significant adverse effects associated with the use of warfarin 1 mg daily in this study. The

Table 3. Secondary Assessment of Efficacy

Factor	Placebo (n = 125)		Warfarin (n = 130)		P	95% Confidence Limits of the Difference Between the Two Arms
	No. of Patients	%	No. of Patients	%		
Catheter lifespan, days						
Median	84		63		.09	-16 to 55 days
Range	2-1209		1-762			
Premature catheter removals	29	23	33	25	.68	-8.3% to 12.7%
Administration of intracatheter fibrinolytic	11	9	8	6	.42	-9.1% to 3.8%
Non-CVC-associated deep venous thrombosis or pulmonary embolism	3	2	3	2	.96	-3.8% to 3.6%

Abbreviation: CVC, central venous catheter.

number of major bleeding events (three in the placebo group *v* none in the warfarin group), all bleeding events (six in the placebo group *v* five in the warfarin group), and deaths on study (21 in the placebo group *v* 22 in the warfarin group) were not significantly different between the placebo and warfarin groups (Table 4). There were 196 interruptions of study medication for at least 7 days occurring in 153 of the 255 study participants. Ninety-four interruptions occurred in the warfarin group, and 102 occurred in the placebo group. Many of the interruptions (102 of 196; 52.0%) were caused by thrombocytopenia (55 in the placebo group and 47 in the warfarin group). Study drug was held on four occasions because of a prolonged INR (INR > 2), once in the placebo group and three times in the warfarin group. None of the prolongations of INR above 2 were associated with bleeding. Some patients (23 of 255 patients; 9%) chose not to take the study medication after enrollment, and others (12 of 255 patients; 5%) withdrew from the study after enrollment. The median duration of study drug treatment was 9 weeks (range, 0 to 70 weeks) and 8 weeks (range, 0 to 48 weeks) in the placebo and warfarin arms, respectively.

DISCUSSION

Patients with cancer are at increased risk of venous thrombosis,¹ and placement of a CVC further increases this risk. Estimates of the incidence of CVC-associated thrombosis in patients with cancer have varied widely. Prospective studies of symptomatic CVC-associated thrombosis have described rates of 3% to 37% in patients not receiving prophylaxis.⁴⁻⁷

In this study, which is the largest prospective trial evaluating antithrombotic prophylaxis for CVC in patients with cancer, we confirm a clinically significant incidence of symptomatic CVC-associated thrombosis (11 of 255 patients; 4.3%). In our study, using a randomized, placebo-controlled, double-blind study design, we found that prophylaxis with warfarin 1 mg daily did not reduce the incidence of symptomatic CVC-associated thrombosis in this patient population. However, the unexpectedly low

rate of symptomatic CVC-associated thrombosis means that a much larger trial is required to address this issue definitively. This prophylactic strategy did not reduce the number of premature CVC removals, the number of CVC lumen occlusions, or the incidence of non-CVC-associated venous thromboembolism; this strategy also did not prolong CVC life span. In addition, we failed to confirm our previous observation from a retrospective study that CVC-associated thrombosis was more frequent when the CVC was inserted by an interventional radiologist rather than by a surgeon.¹⁶ However, the small number of primary events in this study (11 symptomatic CVC-associated thromboses) limits the statistical power to prove such associations even if they were present.

The strengths of this study are its relatively large size (255 assessable patients) and its prospective, placebo-controlled design. This study does not confirm the findings of Bern et al⁴ who first reported the efficacy of warfarin 1 mg daily in reducing the incidence of CVC-associated thromboses in patients with cancer. That study included 82 assessable patients and was not placebo controlled. The inclusion of patients with different types of cancers is unlikely to explain the different results of the two studies. Although our study included patients with hematologic cancers and patients undergoing bone marrow or peripheral-blood transplantation, it also included 58 patients with nonlymphoma solid tumors. The study of Bern et al⁴ included mostly patients with nonlymphoma solid tumors (78 of 82 assessable patients). Both studies included a similar absolute number of assessable patients with nonlymphoma solid tumors, and furthermore, we did not observe a difference in CVC-associated thrombosis among patients with different types of tumors. There were seven CVC-associated thromboses in disease stratum I (seven of 164 patients; 4.0%) and four in disease stratum II (four of 91 patients; 4.4%).

Three other studies have prospectively evaluated the efficacy of warfarin 1 mg daily in reducing the incidence of symptomatic CVC-associated thrombosis in patients with cancer. A recently reported prospective randomized trial of warfarin 1 mg daily in 88 patients with hematologic malignancies found no benefit of warfarin in reducing the incidence of

Table 4. Incidence of Adverse Events

Adverse Event	Placebo (n = 125)		Warfarin (n = 130)		P	95% Confidence Limits of the Difference Between the Two Arms (%)
	No. of Patients	%	No. of Patients	%		
Bleeding						
Major bleeding	3	2	0	0	.07	-5.1 to 0.3
Any bleeding	6	5	5	4	.74	-6.0 to 4.0
Deaths on study	21	17	22	17	.98	-9.1 to 9.3
Patient withdrawals	19	15	20	15	.97	-8.7 to 9.0

CVC-associated thrombosis or CVC lumen occlusion.⁵ The findings of that study were similar to our study; there was a 4.6% incidence (three of 65 patients) of CVC-associated thrombosis and a 15.4% incidence (10 of 65 patients) of CVC lumen occlusions, with no difference between the warfarin and control groups. A case-control study of 108 patients with hematologic malignancies⁶ reported a benefit of warfarin 1 mg daily in reducing the incidence of symptomatic CVC-associated thrombosis. However, the incidence of such symptomatic thromboses in the treatment group was 4.6% (five of 108 patients), which is similar to our findings (4.6%; six of 130 patients). The difference between that study⁶ and our study lies in the incidence of symptomatic CVC-associated thrombosis among control patients. In the study of Boraks et al⁶, the incidence of CVC-associated thrombosis in the control group was 13% (15 of 115 patients), but this is a less methodologically robust group for comparison compared with our prospective randomized control group.

There are several limitations of our study. The most important limitation of the study is its small sample size. In view of the unexpectedly low rate of symptomatic CVC-associated thrombosis, a much larger study is required to definitely address whether warfarin reduces the rate of CVC-associated thrombosis in patients with cancer. A second limitation is the frequency with which study medication was either never started or interrupted. We specified that the study drug not be administered when the platelet count was less than $20 \times 10^9/L$ or the INR was more than 2. There were 196 interruptions of 7 days or more occurring in 153 patients (60.0%), and study drug was never initiated in three patients (1.2%). There was no difference in the failure to start or interrupt the study drug between the two treatment groups, and all analyses were according to the intent-to-treat principle. Frequent interruptions of study drug may reflect the large number of other medications that patients with cancer are required to take. It may also reflect the burden of illness in these patients and a perception that the experimental and prophylactic nature of the study rendered this medication less important. Although interruption of study drug may have contributed to the lack of efficacy of warfarin observed in this study, it clearly did not affect the low incidence of symptomatic CVC-associated thrombosis observed in the control group. Similar considerations apply to the fact that patients were allowed to use aspirin and low-dose heparin in this study.

A third limitation of this study may lie in the time from CVC insertion to initiation of study drug. Study drug was always administered after CVC insertion and may have been started up to 72 hours later. Guidelines of postoperative venous thromboembolism prophylaxis recommend that prophylaxis should begin early, even before the operative procedure in orthopedics and general surgery. We may have not observed a benefit of warfarin in reducing the incidence of CVC-associated thrombosis because medica-

tion was started after initiation of the pathophysiologic events leading to thrombosis.

A key difference between our study and the prospective studies of Bern et al⁴ and Monreal et al⁷ was that our primary outcome was symptomatic CVC-associated thrombosis. Because we did not perform routine screening ultrasonography or venography, the incidence of CVC-associated thrombosis was lower than in studies that included both symptomatic and asymptomatic events. We believe that the use of symptomatic CVC-associated thrombosis as the primary end point of our study was important because it is symptomatic CVC-associated thromboses that lead to morbidity, utilization of resources for treatment, and costs of dealing with the complications of therapy, such as bleeding and CVC removal. The low rate of symptomatic pulmonary embolism in our study and the similar number of deaths in each treatment arm suggest that asymptomatic CVC-associated thrombosis is likely to be clinically unimportant in this patient population.

The use of warfarin 1 mg daily has not been associated with an increased risk of bleeding, and our study confirms this observation. We found no increased risk of bleeding or significant prolongation of the INR in the warfarin group compared with the placebo group. Although reassuring from a safety perspective, warfarin may have been ineffective in reducing the incidence of CVC-associated thrombosis because no clinically important impairment of hemostasis was consistently achieved with this dose of medication.

In conclusion, we have found that the incidence of symptomatic CVC-associated thrombosis in patients with solid tumors and hematologic malignancies, although clinically significant, is lower than previously reported. In this large, prospective study using a placebo-controlled, double-blind design with an intent-to-treat analysis, we found that warfarin 1 mg daily did not reduce the incidence of symptomatic CVC-associated thrombosis. The incidence of such thrombosis remains much more common in patients with cancer than in other populations, and further studies of prophylactic strategies are warranted.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Other Remuneration: Margot Burnell, OrthoBiotec. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section of Information for Contributors found in the front of every issue.

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