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ORIGINAL ARTICLE

Investigating the benefit of adding a vena cava filter to anticoagulation with fondaparinux sodium in patients with cancer and venous thromboembolism in a prospective randomized clinical trial

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Abstract
Background The benefit of adding a vena cava filter to anticoagulation in treating cancer patients with venous thromboembolism remains controversial. We initiated this study as the first prospectively randomized trial to evaluate the addition of a vena cava filter placement to anticoagulation with the factor Xa inhibitor fondaparinux sodium in patients with cancer.
Methods Sixty-four patients with deep vein thrombosis (86%) and/or pulmonary embolism (55%) were randomly assigned to receive anticoagulation with fondaparinux sodium with or without a vena cava filter. Endpoints included rates of complications by treatment arm, recurrent thromboembolism, complete resolution of thromboembolism, and survival rates.
Results No patient had a recurrent deep vein thrombosis; two (3%) patients had new pulmonary emboli, one in each randomized cohort. Major bleeding occurred in three patients (5%). Two patients on the vena cava filter arm (7%) had complications from the filter. Median survivals were 493 days in the anticoagulation only arm and 266 days for anticoagulation+ vena cava filter ($p<0.57$). Complete resolution of venous thromboembolism occurred in 51% of patients within 8 weeks of initiating anticoagulation.
Conclusions No advantage was found for placement of a vena cava filter in addition to anticoagulation with fondaparinux sodium in terms of safety, recurrent thrombosis, recurrent pulmonary embolism, or survival in this prospective randomized trial evaluating anticoagulation plus a vena cava filter in cancer patients. Favorable complete resolution rates of thrombosis were observed on both study arms.

Keywords Vena cava filter · Fondaparinux sodium · Venous thromboembolism

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Introduction

Venous thromboembolism (VTE) represents one of the most common causes of morbidity and mortality in cancer patients [1]. Considerable advances have been made over the past decade in the treatment of VTE, specifically with the use of more effective and safe forms of anticoagulation [2, 3]. Anticoagulation is the cornerstone of VTE treatment; the anticoagulant of choice for patients with cancer who have an acute, symptomatic VTE, initially and long term, is a low molecular weight heparin (LMWH) [2, 4].

Even with LMWHs, more than 20% of distal VTEs propagate, extend into proximal veins, and may remain detectable after a year despite anticoagulant therapy [2, 5, 6]. In addition, up to half of cancer patients have a recurrent VTE within 5 years [7]. With these findings, it is clear that

more effective agents are needed to treat and prevent recurrent VTE in cancer patients. A promising approach is to inhibit thrombin generation through inhibition of the coagulation factor Xa [8]. Fondaparinux sodium is the first in a new class of synthetic factor Xa inhibitors that binds reversibly with high affinity to antithrombin III. Investigational use of fondaparinux sodium in this study falls outside the FDA approved indications.

The benefit of adding a vena cava filter (VCF) to anticoagulation in treating cancer patients with VTE remains controversial and untested, prospectively, in this specific patient population. According to several treatment guideline groups, the indications for insertion of a VCF in cancer patients are failure of anticoagulation therapy or a contraindication to anticoagulation, such as active bleeding [9, 10]. These indications are based on retrospective data and expert opinion (Table 1). Nevertheless, an increasing number of VCFs are being used in patients with VTE who present with less strictly defined indications, such as those with a large burden of clot, medically unstable patients, and patients deemed by their physicians to be at increased risk for recurrent VTE or anticoagulant-related bleeding [11, 12].

The ease of insertion of modern VCFs by the percutaneous route and the reportedly low complication rates have made these devices attractive for use. Between 1979 and 1999, the number of VCFs placed annually in the USA rose 25-fold, from 2,000 to 49,000 [13]. With the introduction of retrievable VCFs, the expansion in the clinical use of these devices have continued to increase [14].

A literature search using a *MedLine* database with an *Ovid* interface revealed over 2,500 publications on VCFs; yet, only one randomized controlled trial in a general medical population, followed by an 8-year follow-up report, has been conducted to evaluate outcomes [15, 16]. In this 1998 study, only 15% of the 400 patients had a diagnosis of cancer. Patients were randomized to a VCF or no VCF and anticoagulation with either a LMWH or unfractionated heparin. After 2 years, no significant difference in the incidence of symptomatic PE was found between the two treatment arms. However, a significant 9.2% increase in the incidence of recurrent DVT was found in the patients assigned to the VCF arm (p=0.02).

Additional studies evaluating the role of VCFs and anticoagulation in cancer patients with a VTE are chart reviews [17–21]. These retrospective studies report recurrent PE rates of up to 10% among patients treated with anticoagulation and up to 28% among patients treated with a VCF. Of note, the majority of patients receiving VCFs did not receive concomitant anticoagulation therapy.

We initiated this trial to prospectively determine, using a randomized study design, if the addition of a VCF to anticoagulation is advantageous in patients with cancer. We also sought to evaluate the safety and efficacy of fondaparinux sodium in cancer patients.

Materials and methods

Study design

In this randomized, single institution open trial, we compared the insertion of a permanent VCF with no VCF (Fig. 1). All patients received fixed doses of subcutaneous fondaparinux sodium (Glaxo Smith Kline Biologicals, King of Prussia, PA, USA). Subjects were randomly assigned in a 1:1 ratio, using a permuted block design, to either fondaparinux sodium or fondaparinux sodium with a VCF. The study was reviewed and approved by the institutional human subjects r\eview board; all participants gave written informed consent.

Table 1 Current recommendations for placement of a vena cava filter by professional society

	Vena cava filter indication	Level of recommendation
American Society of Clinical Oncology [10]	Contraindication to anticoagulation Recurrent thrombosis	Expert Opinion
National Comprehensive Cancer Network [9]	Contraindication to anticoagulation Failure of anticoagulation	Consensus
	Non-compliance	
	Cardiac or pulmonary dysfunction severe enough to make a recurrent PE life threatening	
	Multiple PE	
	Chronic pulmonary hypertension	
American College of Chest Physicians[a] [33]	Contraindication to anticoagulation Risk of bleeding	Observational studies
Society of Interventional Radiology[a] [34]	Contraindication to anticoagulation Complication to anticoagulation	Not listed
	Inability to achieve/maintain therapeutic anticoagulation	

[a]Not specific to cancer-associated venous thrombosis

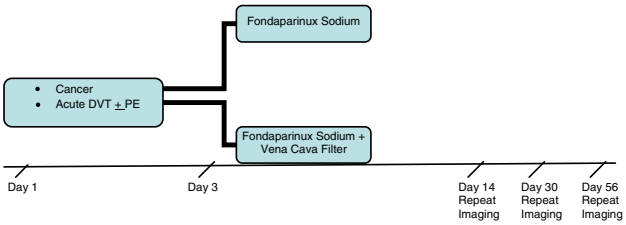

Fig. 1 Schema of the trial. Eligible patients were randomized within 72 h of enrollment to an age and weight-adjusted dose of subcutaneous fondaparinux sodium with or without a vena cava filter. Upon study entry, patients enrolled secondary to an acute DVT were evaluated for a PE and patients enrolled secondary to an acute PE were evaluated for a DVT. Repeat imaging to evaluate the clot burden as specified below

Patients

All patients over 18 years of age with a definitive diagnosis of cancer, hospitalized or ambulatory, were eligible if they had an acute DVT, confirmed by duplex/Doppler ultrasound, with or without a concomitant PE, confirmed by a ventilation/perfusion scan (V/Q) or computed tomography pulmonary angiogram (CTPA). Patients with any of the following factors were not eligible for this study: creatinine clearance <30 mL/min, placement of a previous VCF, active anticoagulant therapy lasting more than 72 h, indication for thrombolysis, allergy to iodine, hereditary thrombophilia, pregnancy, platelet count of <50,000/μL, bleeding requiring blood transfusion, intracranial bleeding, and/or brain metastasis secondary to melanoma, choriocarcinoma, renal cell carcinoma, or medullary thyroid carcinoma.

Treatments

Patients were anticoagulated with an age and weight-adjusted dose of subcutaneous fondaparinux sodium (5 mg for patients <50 kg or age >65 years, 7.5 mg for patients 50–100 kg and 10 mg for patients >100 kg) for 90 days. The study period of 90 days was established as a conservative approach to evaluate the specified endpoints while taking into account the lack of safety data with fondaparinux sodium in cancer patients (IND# 76,762). After 90 days, patients were given further anticoagulant therapy at the discretion of their physician. Patients may have received anticoagulation with unfractionated heparin or a LMWH for up to 72 h prior to randomization.

Permanent VCFs (Vena Tech Vena^{TM} LP, B. Braun Medical) were used. These percutaneous filters were inserted within 3 days of randomization, to patients assigned to a VCF, under fluoroscopic guidance.

Baseline evaluation of venous thromboembolism

All patients underwent baseline evaluation for a DVT and a PE. Patients enrolled secondary to an acute DVT, diagnosed by a bilateral duplex/doppler ultrasound of the lower extremities, were evaluated for a PE by V/Q scanning within 72 h of enrollment. A CTPA was performed if the V/Q scan was not available or strongly recommended secondary to an abnormal V/Q scan. Patients enrolled secondary to a new, acute PE were evaluated for a DVT within 72 h of enrollment by a bilateral duplex/doppler ultrasound of the lower extremities. The diagnosis of a DVT was made if there was a new intraluminal-filling defect on duplex/doppler ultrasonography [2]. A PE diagnosis required the finding of a high probability on a V/Q scan or an intraluminal filling defect or sudden arterial cutoff on CTPA [2].

Follow-up and surveillance

In patients with a confirmed PE at baseline, a CTPA was systematically performed on day 56 to evaluate the clot burden. The two-month time interval to reevaluate asymptomatic patients with a baseline PE was based on previous studies, indicating this time interval to be the most frequent period of recurrent PE [6, 22]. If a clinically suspected PE occurred before day 56 or at any time during the first 90 days after randomization, a V/Q scan was obtained. A CTPA was performed if the V/Q scan could not be obtained.

In patients with a confirmed DVT at baseline, a bilateral duplex/doppler ultrasound of the lower extremities was systematically performed on days 14, 30, and 56 to evaluate the VTE. Initially, bilateral duplex/doppler ultrasound of the lower extremities was performed on day 56 in all patients in whom a baseline DVT was confirmed to evaluate the clot burden. However, three out of the first five patients enrolled had repeated, off-study, bilateral duplex/Doppler ultrasounds of the lower extremities within the first 3–4 weeks of anticoagulation with fondaparinux sodium. The repeat studies revealed VTE stability and/or VTE regression. Subsequently, the protocol was modified to evaluate patients' VTE on days 14, 30, and 56 in all patients in whom a baseline DVT was confirmed.

Complete blood counts were obtained at baseline, monthly, and if any bleeding occurred. At study discharge, all patients and their physicians were asked to report any symptoms of recurrent VTE or bleeding. Follow-up visits were scheduled monthly during the 90-day treatment period, and follow-up communications with patients' physicians were conducted every 6 months for up to 3 years, or until death. All events, radiological, biologic, and clinical data, obtained at the time of occurrence, were recorded.

Assessment of outcome events

The primary outcome focused on adverse outcomes. This included rates of VCF complications, bleeding, and recurrent or residual DVTs or PEs. The therapy-specific endpoint represented a clinically relevant outcome. Major VCF complications were defined as thrombosis at the filter site, erosion into the wall of the vena cava, infection, prolonged

hospitalization, and/or migration of the filter. Major and minor bleeding was defined by the Common Terminology Criteria for Adverse Events, version 3.0 (CTCAE) [23]. CTCAE, version 3.0, is detailed in Appendix 1.

Diagnoses of recurrent or residual PEs or DVTs were based on a comparison between baseline findings and those obtained at previously specified follow up intervals. Recurrence of a DVT was defined as a lack of compressibility at a new site or an extension to a new venous segment of the thrombus on duplex/Doppler ultrasound [24]. The angiographic diagnosis of a recurrent PE required the visualization of a new intraluminal filling defect or a sudden new arterial cutoff. When CTPA was unavailable, the diagnosis based on the V/Q scan required the visualization of at least two new segmental mismatched perfusion defects, with no current improvement in other areas in cases of initial extensive perfusion defects [16]. In suspected VCF thrombosis, duplex ultrasonography or abdominal CT assessed patency of the filter. Secondary outcome events were survival and VTE resolution. All events were evaluated and validated by an independent Data Safety Monitoring Board.

Statistical analysis

Data were analyzed based on an intention-to-treat design, i.e., data on individual subjects were analyzed within the groups to which each subject was randomized. The chi-square test or Fisher's exact test, as deemed appropriate, was used to compare the two groups for categorical variables, and the two sample *t* test was used for continuous data.

Standard methods of survival analysis were applied [25]. An analysis of event-free survival, as defined above, was conducted. Kaplan–Meier/product-limit estimates and their corresponding 95% confidence intervals were computed, using Greenwood's formula to calculate the standard error [26]. Kaplan–Meier product limit curves were also computed, where the randomization group (fondaparinux sodium or fondaparinux sodium with a VCF) was used as the stratification variable. In cases where the endpoint event, "death," did not occur, the number of months until last follow-up was used and considered censored. The survival distributions of the two randomization groups were compared using the log-rank test. All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA). A result was considered statistically significant at the $p<0.05$ level of significance.

Results

Patient characteristics

Between May 2007 and May 2010, 64 patients were enrolled. Of the 64 patients, 31 were randomly assigned to receive a VCF with fondaparinux sodium, and 33 patients were randomly assigned to receive fondaparinux sodium only. Patient characteristics in the two treatment cohorts were similar; no statistically significant differences were found (Table 2). The performance status of patients at the time of randomization was lower than in many studies in patients with cancer, with an ECOG performance status of two or three in 56% of patients. The most frequent cancer diagnoses were lung (28%), breast (16%), pancreatic (14%), and colon cancers (11%), as seen in Table 2. Seventy-seven percent of patients had stage IV extent of disease, and 13% of patients had pre-existing stable brain metastases.

Venous thromboembolism and resolution

There were a total of 107 DVT and 43 PE sites that were confirmed by CTPA in 95% of patients and by V/Q scanning in 5% of patients (Table 3). Fifty-one percent of all patients enrolled (95% CI 40.6–60.3%) had DVT resolution by study day 56. A similar percentage of patients enrolled with a PE had resolution of the PE by study day 56 (47%, 95% CI 31.2–62.3%). No patient had a recurrent DVT. Two patients (3%) had new asymptomatic PEs, one in each treatment arm.

Anticoagulation complications

Major bleeding, CTCAE grades 3 and 4, occurred in three patients (4.7%, 95% CI <1–13.1%; Table 4) [23]. These occurred in two patients receiving fondaparinux sodium only and in one patient receiving fondaparinux sodium and a VCF. Minor bleeding (CTCAE grade 2), occurred in four patients (6.2%, 95% CI 1.7–15.2%); 2 patients in each treatment arm. The issues included petechiae, ecchymosis, and epistaxis. With the very similar complication rates on both study arms, no statistically significant differences were suggested. All four patients were receiving concomitant cytotoxic therapy, and minor complications were primarily seen when platelet counts were <50,000/μL. Fondaparinux sodium was temporarily withheld at this degree of thrombocytopenia and restarted in all patients when platelet counts were >50,000/μL.

Eighty-six percent of patients completed the planned fondaparinux sodium treatment for 90 days. At the completion of the 90-day study period, 85% of patients continued anticoagulation. At the discretion of the treating physician, 18% continued anticoagulation with fondaparinux sodium, 55% received anticoagulation with a LMWH, and 27% received anticoagulation with warfarin.

Vena cava filter complications

Among the 31 patients assigned to receive a VCF with fondaparinux sodium, 30 patients received a VCF within 72 h of randomization. One patient refused the VCF. Two (7%)

Table 2 Patient characteristics by randomized treatment arm

Characteristics	Cohorts			
		Fondaparinux sodium (n=33)	Fondaparinux sodium+vena cava filter (n=31)	p value
Gender	Female	24 (73 %)	16 (52 %)	0.0812
	Male	9 (27 %)	15 (48 %)	
Mean age[a]		67±14 years	63±12 years	0.2413
ECOG PS	0	2 (6 %)	2 (6.5 %)	0.6244
	1	14 (42 %)	10 (32 %)	
	2	13 (39 %)	17 (55 %)	
	3	4 (12 %)	2 (7 %)	
Treatment regimens[b]	Chemotherapy	31 (94 %)	28 (90 %)	0.6673
	Hormonal	3 (9 %)	2 (7 %)	1.0000
	Darbepoetin alpha or epoetin alpha	6 (18 %)	3 (10 %)	0.4764
	Anti-angiogenic	0 (0 %)	1 (3 %)	0.4844
Malignancy	Lung cancer	12 (37%)	6 (19%)	0.1825
	Breast cancer	5 (15%)	5 (16%)	
	Pancreatic cancer	3 (9%)	6 (19%)	
	Colon cancer	1 (3%)	6 (19%)	
	Lymphoma	4 (12%)	2 (7%)	
	Ovarian cancer	4 (12%)	1 (4%)	
	Other cancers	4 (12%)	5 (16%)	
TNM stage	II	3 (9%)	1 (3%)	0.7400
	III	5 (15%)	6 (19%)	
	IV	25 (75%)	24 (77%)	
	Brain metastases	5 (15%)	3 (9%)	0.7091

[a]Reported as mean±standard deviation

[b]Patient may have been on >1 treatment regimen

patients had complications from the VCF, which included thrombosis requiring a percutaneous thrombectomy and continued bleeding at the insertion site requiring prolonged hospitalization.

Survival

Patients were followed for 3 years or until death. Fourteen percent of patients died prior to the 90-day study period; four patients were in the fondaparinux sodium only arm, and five patients were in the VCF with fondaparinux sodium arm. One patient with brain metastases from lung cancer developed a cerebral hemorrhage; she had been randomized to the fondaparinux sodium only treatment cohort. The other eight patients died from progression of disease.

Patients randomized to the fondaparinux sodium only arm had a median survival of 493 days. The median survival of patients randomized to the fondaparinux sodium and a

Table 3 Thrombotic sites and resolution of venous thromboembolism across treatment cohorts: there were a total of 107 DVT and 43 PE sites

	Fondaparinux sodium	Fondaparinux sodium+vena cava filter	p value	Combined cohorts	95% CI
Sites of thrombosis					
DVT	59 (58.4%)	48 (64.0%)	0.6342	107 (60.8%)	53.2–68.1
PE	25 (24.8%)	18 (24.0%)		43 (24.4%)	18.3–31.5
DVT and PE	17 (16.8%)	9 (12.0%)		26 (14.8%)	9.9–20.9
Resolution of thrombosis					
Resolution DVT[a] (N=54/107 DVTs resolved)	36 (61.0 %)	18 (37.5 %)	0.0155	54 (51 %)	40.6–60.3
Resolution PE[a] (N=20/43 PEs resolved)	8 (32.0 %)	12 (66.7 %)	0.0246	20 (47 %)	31.2–62.3

[a] Resolution by day 56

Table 4 Complications by treatment cohort (patients may have had more than one complication)

	Fondaparinux sodium (n=33)	Fondaparinux sodium+ vena cava filter (n=31)
Recurrent PE N=2	1	1
Recurrent DVT N=0	0 (0.0 %)	0 (0.0 %)
VCF thrombosis N=1	0 (0.0 %)	1 (3.2 %)
Major Bleed N=3	2 (6.1 %)	1 (3.2 %)
Minor Bleed N=3	2 (6.1 %)	2 (6.5 %)

VCF was 266 days (p<0.57); the survival curves are seen in Fig. 2.

Discussion

Venous thrombosis remains a common and serious complication in patients with cancer. While there is consensus that anticoagulation is the basis of VTE treatment, the use of VCFs in patients with cancer has increased markedly. This increased use appears to exceed guideline-based recommendations. Additionally, there are few prospective randomized trials involving the use of VCFs in any patient population. The current study is the first prospective randomized clinical trial specifically addressing this issue in patients with cancer.

Vena cava interruption with a VCF can be safely performed, as occurred in the current trial. All VCFs were placed under fluoroscopic guidance in the angiography suite, and there was no VCF tilting, misplacement, fracture, or migration. We chose to use a permanent VCF in lieu of a retrievable VCF, as its placement is common practice in cancer patients and the current literature does not support the placement of one VCF category over the other. The complication rates of VCFs in our study were low at 7% and consistent with the previously reported complication rate of 7–10% for cancer patients [27]. Nonetheless, VCF placement involves additional patient inconvenience and discomfort, the risks of intravenous contrast agent use, added radiation exposure, and considerable additional cost. Based on these issues, it is clear that if VCF placement is to be recommended, it should have demonstrated advantages for cancer patients in terms of efficacy and safety. Otherwise, current restrictive guidelines should be followed.

Major bleeding complications were <5% and similar in both cohorts; major bleeding complications from prior studies report rates of up to 10% [2, 28, 29]. In addition, no significant differences in survival were observed in this trial according to treatment arm. Although a trend toward decreased survival was seen for patients assigned to the VCF plus fondaparinux sodium arm, some differences in patient characteristics were found between the two treatment groups and may explain this negative survival trend. For example, we noted that the number of colon and pancreatic tumors were higher in the VCF plus fondaparinux sodium arm. In general, advanced colon cancer and pancreatic cancer have more dismal survival rates than lymphoma, for example. Numerically, there were more lymphoma patients randomized to fondaparinux sodium only arm. However, these numerical differences were not statistically significant. The median survivals were brief in both arms of this study in patients with VTE with the majority having stage IV extent of disease and an ECOG performance status of 2 or 3.

An interesting finding in this trial was the higher than expected VTE resolution rates among all 64 patients anticoagulated with fondaparinux sodium. This is a higher VTE resolution rate than previously reported with fondaparinux sodium; however, one must note that this trial incorporated a much longer treatment period with fondaparinux sodium. In contrast to The Matisse Investigators' study and the recent meta-analysis by Akl and colleagues, patients were not initially treated with fondaparinux sodium for days then

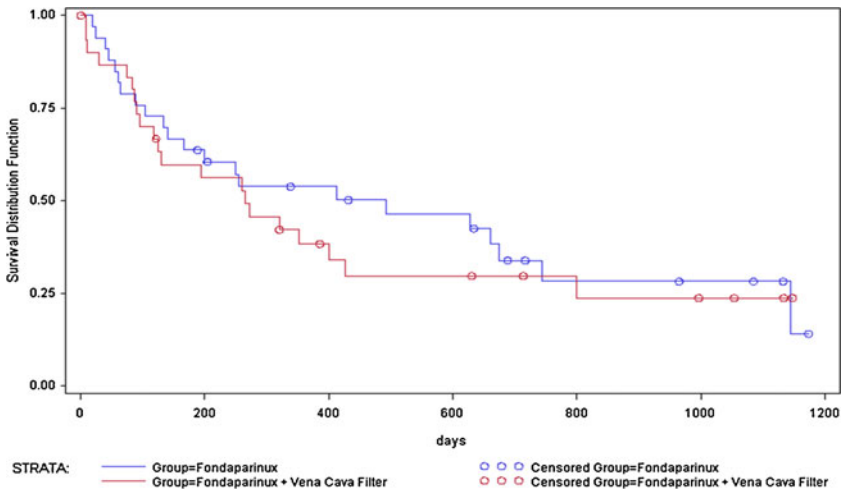

Fig. 2 Kaplan–Meier survival curve after a venous thrombotic event defined by treatment cohort (log-rank, p<0.5696). Patients received anticoagulation with fondaparinux sodium with or without a vena cava filter. Survival time listed in days after initial thrombotic event

switched to a vitamin k antagonist; patients were treated with therapeutic doses of fondaparinux sodium for the entire study period of 90 days [30, 31].

This experience is the largest with a subcutaneous factor Xa inhibitor in a trial designed for patients with cancer. The complete resolution rates, 51% for DVTs and 47% for PEs, occurred within 8 weeks of initiation of fondaparinux sodium and are among the highest reported VTE resolution rates in patients with cancer. These findings are surprising in that the literature to date reports VTE extension in the first few weeks of anticoagulant treatment as well as a 3-fold increase in the frequency of recurrent VTE during the first several weeks of treatment [5, 32].

It is possible that VTE resolution could be used as a criterion leading to an individualized approach in determining the duration of anticoagulant treatment. These favorable results support future randomized trials to compare resolution rates of fondaparinux sodium with other anticoagulants and to evaluate if the VTE resolution should affect the duration or intensity of anticoagulation in patients with active malignancy.

As the only prospective randomized controlled trial evaluating VCFs with anticoagulation in patients with cancer, the findings from this study lead to the following conclusions. First, based on these results, there is no efficacy or safety outcome supporting the routine use of VCFs in patients with VTE and cancer who receive anticoagulation with fondaparinux sodium. Second, the observed high complete resolution rates with fondaparinux sodium present an opportunity for comparison with other methods of anticoagulation and may indicate a basis for individualizing anticoagulation strategies.

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Conflict of interest There are no financial disclosures from any authors

Appendix 1

Table 5 Adapted from Common Terminology Criteria for Adverse Events (CTCAE), version 3.0

Adverse event	Short name	Grading				
		1	2	3	4	5
Hemorrhage/bleeding						
Hematoma	Hematoma	Minimal symptoms, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, interventional radiology, or operative intervention indicated	Life-threatening consequences; major urgent intervention indicated	Death
Hemorrhage, CNS	CNS hemorrhage	Asymptomatic, radiographic findings only	Medical intervention indicated	Ventriculostomy, ICP monitoring, or operative intervention indicated	Life-threatening consequences	Death
Coagulation						
DIC	DIC		Laboratory findings with no bleeding	Laboratory findings with and bleeding	Laboratory findings, life-threatening or disabling consequences (e.g., CNS hemorrhage, organ damage. Or hemodynamically significant blood loss	Death

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