Evaluation of a Device Combining an Inferior Vena Cava Filter and a Central Venous Catheter for Preventing Pulmonary Embolism Among Critically Ill Trauma Patients

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ABSTRACT

Purpose: To evaluate efficacy and safety of a novel device that combines an inferior vena cava (IVC) filter and central venous catheter (CVC) for prevention of pulmonary embolism (PE) in critically ill patients.

Materials and Methods: In a multicenter, prospective, single-arm clinical trial, the device was inserted at the bedside without fluoroscopy and subsequently retrieved before transfer from the intensive care unit (ICU). The primary efficacy endpoint was freedom from clinically significant PE or fatal PE 72 hours after device removal or discharge, whichever occurred first. Secondary endpoints were incidence of acute proximal deep venous thrombosis (DVT), catheter-related thrombosis, catheter-related bloodstream infections, major bleeding events, and clinically significant thrombus (occupying > 25% of volume of filter) detected by cavography before retrieval.

Results: The device was placed in 163 critically ill patients with contraindications to anticoagulation; 151 (93%) were critically ill trauma patients, 129 (85%) had head or spine trauma, and 102 (79%) had intracranial bleeding. The primary efficacy endpoint was achieved for all 163 (100%) patients (95% confidence interval [CI], 97.8%–100%, $P < .01$). Diagnosis of new or worsening acute proximal DVT was time dependent with 11 (7%) occurring during the first 7 days. There were no (0%) catheter-related bloodstream infections. There were 5 (3.1%) major bleeding events. Significant thrombus in the IVC filter occurred in 14 (8.6%) patients. Prophylactic anticoagulation was not initiated for a mean of 5.5 days ± 4.3 after ICU admission.

Conclusions: This novel device prevented clinically significant and fatal PE among critically ill trauma patients with low risk of complications.

ABBREVIATIONS

CI = confidence interval, CVC = central venous catheter, DVT = deep vein thrombosis, FDA = US Food and Drug Administration, ICU = intensive care unit, IQR = interquartile range, ISS = Injury Severity Score, IVC = inferior vena cava, PE = pulmonary embolism, VTE = venous thromboembolism

Each year, nearly 200,000 Americans die as a result of major trauma (1). Critically ill patients with severe traumatic brain injury, spinal cord injury, visceral trauma, or pelvic or long bone fractures are at highest risk of fatal venous thromboembolism (VTE). Pulmonary embolism (PE) often occurs within the first 7 days after injury and is a leading cause of death for patients surviving > 24 hours (2,3). Prophylactic heparin and low-molecular-weight heparin

Please see Acknowledgments section at the end of this article for author affiliations and financial disclosures.

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J Vasc Interv Radiol 2017; 28:1248–1254

http://dx.doi.org/10.1016/j.jvir.2017.05.001

have not reduced the incidence of clinically significant PE among critically ill trauma patients (4,5). This result may be explained by a combination of marked immobility, hemodynamic instability, active or recent bleeding, low trough levels of anti–factor Xa, and a high rate of antithrombin III depletion (6–8). In addition, the risk of life-threatening bleeding reduces the use of pharmacologic prophylaxis in this patient population (6–8).

Inferior vena cava (IVC) filters are commonly used rather than pharmacologic VTE prophylaxis for patients at high risk of both major thrombosis and major bleeding, with the goal of preventing new or recurrent PE. However, the prophylactic use of filters for hospitalized patients with VTE (9–11) or with severe trauma (12–14) is supported by a low level of evidence. Placement of IVC filters in this setting is often delayed, when the risk of PE is highest, and most are not retrieved (15,16). Furthermore, the risk of complications, including dislodgment, migration, fracture, vena cava perforation, and chronic venous thrombosis, increases the longer the IVC filter remains in place (15–17). The Angel Catheter (Bio2 Medical, San Antonio, Texas) is an IVC filter combined with a triple-lumen central venous catheter (CVC). It is designed for nonfluoroscopic bedside insertion and for retrieval after performing cavography and before hospital discharge. The device received 510(k) clearance by the US Food and Drug Administration (FDA) on July 28, 2016, as a short-term intravascular IVC filter and CVC. We report the outcomes of a prospective, multicenter, single-arm clinical trial evaluating the efficacy and safety of this novel device in critically ill trauma patients in whom anticoagulation was contraindicated.

MATERIALS AND METHODS

Study Design and Oversight

The trial (ClinicalTrials.gov Identifier: NCT02186223) was designed by a steering committee with the participation of the sponsor (Bio2 Medical) and in consultation with the FDA and clinical investigators. The trial was conducted at 20 intensive care units (ICUs) in the United States and was supervised by the sponsor and an independent Clinical Events Committee and Data and Safety Monitoring Board. All data related to endpoints and adverse events were collected at the sites, and standardized assessments of all relevant imaging studies were completed by a core radiology laboratory (Intrinsic Imaging, Boston, Massachusetts), with final adjudication by the Clinical Events Committee. Two contract research organizations were involved in collecting, storing, monitoring, auditing (Novella Clinical, Morrisville, North Carolina), and analyzing (CardioMed Device Consultants, LLC, Catonsville, Maryland) the data. The first draft of the manuscript was prepared by the first 3 and the last 2 authors (V.F.T., J.P.H., J.M., G.P., S.Z.G.), with substantial review and comments by the other authors. The first author (V.F.T.), in consultation with the other authors, made the decision to submit the manuscript for publication. The authors had unrestricted access to the data and attest to the completeness and accuracy of the data and the final version of this manuscript. The FDA and institutional review board of each participating center approved the study.

The treatment period began with device insertion and ended 72 hours after device removal or discharge, whichever occurred first. During the treatment period, patients were evaluated daily for clinical suspicion of PE, lower extremity deep vein thrombosis (DVT) (including catheter-related thrombosis), catheter-related bloodstream infections, and major bleeding. Bilateral lower extremity compression ultrasound was performed within 24 hours of device insertion and again within 24 hours before device retrieval.

Inclusion and Exclusion

We enrolled critically ill patients at high risk of acute PE for whom pharmacologic thromboprophylaxis was contraindicated. Eligible subjects were at least 18 years old and expected to remain in the ICU at least 72 hours. Study subjects had to meet 1 or both of the following inclusion criteria: (*a*) recognized contraindications to standard pharmacologic thromboprophylaxis; (*b*) confirmed acute proximal lower extremity DVT or confirmed acute PE, with recognized contraindications to anticoagulation. Exclusion criteria were pregnancy, enrollment in a drug or device trial within 30 days before enrollment, use of pharmacologic thromboprophylaxis, IVC filter already in place, body mass index > 45, inability to place the device because of an anatomic issue, and hypersensitivity to nitinol (nickel titanium).

Primary and Secondary Endpoints

The primary efficacy endpoint was freedom from clinically significant PE or fatal PE at the time of hospital discharge or up to 72 hours after device removal, whichever occurred first. The diagnosis of PE was confirmed by the identification of $>$ 1 segmental or at least a single more proximal PE as detected by chest computed tomography (CT) angiography, unless the patient's condition was too unstable to allow transport to the scanner. Clinically significant PE was defined following the American Heart Association and European Society of Cardiology Guidelines as either (*a*) PE associated with systemic hypotension or (*b*) PE without hypotension but with right ventricular dysfunction confirmed by echocardiography or chest CT angiography and myocardial injury confirmed by an elevated troponin I or troponin T level (18). Fatal PE was defined as death caused by PE or unexpected death within 24 hours of onset of the acute event. Secondary safety endpoints were acute proximal DVT, catheter-related thrombosis, catheter-related bloodstream infections, severe bleeding events, and discovery of clinically significant thrombus in the IVC filter ($>$ 25% of the volume of the filter). The independent Clinical Events Committee adjudicated all primary and secondary endpoints and all serious adverse events.

Patients

Between February 2015 and December 2015, 172 patients provided informed consent for study participation at 20

clinical sites in the United States. Of these, 163 underwent successful placement of the device. Nine patients provided informed consent but were not enrolled in the study; 6 of these patients were deemed ineligible, and femoral access could not be obtained in 3 patients. For 160 of the 163 participants (98.2%), the device was used for primary PE prophylaxis (no previous diagnosis of PE).

Baseline characteristics of the study population are shown in Table 1. The mean (± SD) age was 44 years ± 19, and 122 (75%) patients were men. Mechanical ventilation was required for 127 (78%) patients, and vasopressors were required for 40 (24.5%) patients. For 117 (72%) patients, a different CVC had been placed before study enrollment. Active bleeding was present in 67 of 163 patients (41%) and was severe in 56 (84%) patients. The Injury Severity Score (ISS) was used to assess trauma severity. The ISS is an anatomically based scoring system that classifies each injury in various body regions according to its relative severity (19). Of the 151 patients with traumatic injuries, 92 (61%) presented with a critical injury (ISS $\geq$ 25), and 41 (27%) presented with a severe injury (ISS 16–24); 129 (85%) had head trauma, spinal injury, or both; and 102 (79%) had intracranial hemorrhage. At baseline, 18 (11%) patients had confirmed proximal lower extremity DVT.

Table 1. Baseline Characteristics of Study Population

Characteristic	Value
Number of patients	163
Age, years, mean ± SD	44.1 ± 18.7
Male sex, n (%)	122 (74.8)
BMI, kg/m^2, mean ± SD	28.2 ± 5.6
Primary diagnosis at admission to ICU	
Trauma, n (%)	151 (92.6)
Head/spine, n (%)	129 (85.4)
Intracranial hemorrhage, n (%)	102 (79.1)
Chest, n (%)	63 (41.7)
Abdomen, n (%)	41 (27.2)
Lower extremity, n (%)	54 (35.8)
> 1 area, n (%)	80 (53.0)
Surgical, n (%)	2 (1.2)
Medical, n (%)	6 (3.7)
Neurologic, n (%)	4 (2.5)
ISS, median (IQR)*	26 (21–34)
Minimal (1–9), n (%)	7 (4.6)
Moderate (10–15), n (%)	11 (7.3)
Severe (16–24), n (%)	41 (27.2)
Critical (≥ 25), n (%)	92 (60.9)
Active bleeding, n (%)	67 (41.1)
Minor, n (%)	11 (16.4)
Major, n (%)	56 (83.6)
History of bleeding, n (%)	13 (8.0)
At high risk of bleeding, n (%)	69 (42.3)
Baseline VTE†	
PE, n (%)	3 (1.8)
DVT, n (%)	18 (11.0)
Life support	
Mechanical ventilation, n (%)	127 (77.9)
Vasopressors, n (%)	40 (24.5)
Central venous catheterization, n (%)	117 (71.8)

BMI = body mass index; DVT = deep thrombosis; ICU = intensive care unit; IQR = interquartile range; ISS = Injury Severity Score; PE = pulmonary embolism; VTE = venous thromboembolism.
*Scores range from 0 to 75; higher scores indicate more severe trauma.
†Baseline VTE was the presence or diagnosis of VTE within 24 h of enrollment in study.

Device Design

The device consists of a self-expanding nitinol IVC filter permanently attached to a 9-F triple-lumen CVC (Fig 1). The CVC has the functions of a triple-lumen vascular catheter in critically ill patients for administration of medications and fluids and for blood withdrawals. The catheter is made of polyether block amide resins and is coil reinforced to provide flexibility and kink resistance and to allow limited patient mobility. The permanently attached IVC filter has a self-centering closed cell design without hooks anchoring it to the caval wall.

Placement, Maintenance, and Retrieval

The device was inserted with ultrasound guidance for accessing the femoral vein. Although neither CT nor magnetic resonance imaging was required by protocol, physicians reviewed existing images, when available, to identify the renal veins in relationship to the lumbar vertebral bodies and to detect any vascular anomalies or preexisting thrombus. After vascular access was obtained, a 0.035-inch J-tip 100-cm guide wire was advanced into the IVC. The catheter was advanced over the wire without fluoroscopy. Deployment of the filter was performed by retracting the 9-F outer sheath over the coaxial catheter until the hubs were securely locked together. After insertion of the device, portable abdominal radiography was performed to verify the position of the filter relative to the lumbar vertebral bodies. The catheter was sutured to the skin, and a 3M Tegaderm CHG Chlorhexidine Gluconate I.V. Securement Dressing (3M, St. Paul, Minnesota) was placed. The filter was positioned below the L1-2 intervertebral space (anatomic reference, below renal veins) and above the L4-5 intervertebral space (origin of the IVC). The device was maintained by daily assessments of the CVC access site and flushing techniques consistent with standard of care.

Before removal of the device, a cavogram was obtained through the catheter sheath to determine whether there was thrombus in the filter. If a significant thrombus (> 25% of the volume of the filter) was detected, the interventional radiologist determined the best therapeutic option (eg, thrombus aspiration, local thrombolysis, or placement of a commercial IVC filter). The device was retrieved by pulling the multilumen catheter back into the outer sheath

so that the filter collapsed over the inner multilumen catheter.

Statistical Analysis

Freedom from clinically significant PE was compared against a performance goal agreed by the FDA and the sponsor based on (*a*) published reports of clinical trials evaluating the use of pharmacologic thromboprophylaxis in patients at high risk of VTE and (*b*) historical control studies evaluating the risk of VTE and PE among patients not treated with pharmacologic thromboprophylaxis (20). With an evaluable sample size of 150 patients and a power of 80% to detect a type I error (α) of 0.05, this performance goal would be met if, at the end of the trial, freedom from clinically significant PE or fatal PE was $\geq$ 96.8% (meaning that $\leq$ 4 patients had a clinically significant or fatal PE). Categorical variables were presented as number (%), and continuous variables were presented as mean (SD) or median (with interquartile range [IQR]) to describe baseline characteristics and effects and timing of events. All 95% confidence intervals (CIs) were based on Fisher exact 2-sided approach. Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Device Insertion Results

Of 163 devices, 157 (96.3%) were inserted without fluoroscopy at the bedside in the ICU, 4 (2.5%) were inserted in the operating room, 1 (0.6%) was inserted in the interventional radiology suite, and 1 (0.6%) was inserted in another location. The median time from ICU admission to device insertion was 1.7 days (IQR, 1–2.8 d), and the median time required for insertion was 11 minutes (IQR, 7–17 min). Ultrasound guidance was used for 159 (97.5%) insertions. No serious adverse events were reported as a result of device insertion. Of 163 devices, 128 (79%) were placed via the right femoral vein with a catheter insertion depth of 27 cm, and the remaining 35 (21%) were placed via the left femoral vein with a catheter insertion depth of 29 cm. In 8 (5%) patients, it was necessary to reposition the filter after the procedure. The device was maintained in place after insertion for a mean of 7.2 days ± 3.8.

Device Efficacy

No patient experienced clinically significant PE or fatal PE (freedom from clinically significant PE or fatal PE was 100%; 95% CI, 97.8%–100%, $P < .01$) (Table 2). Before

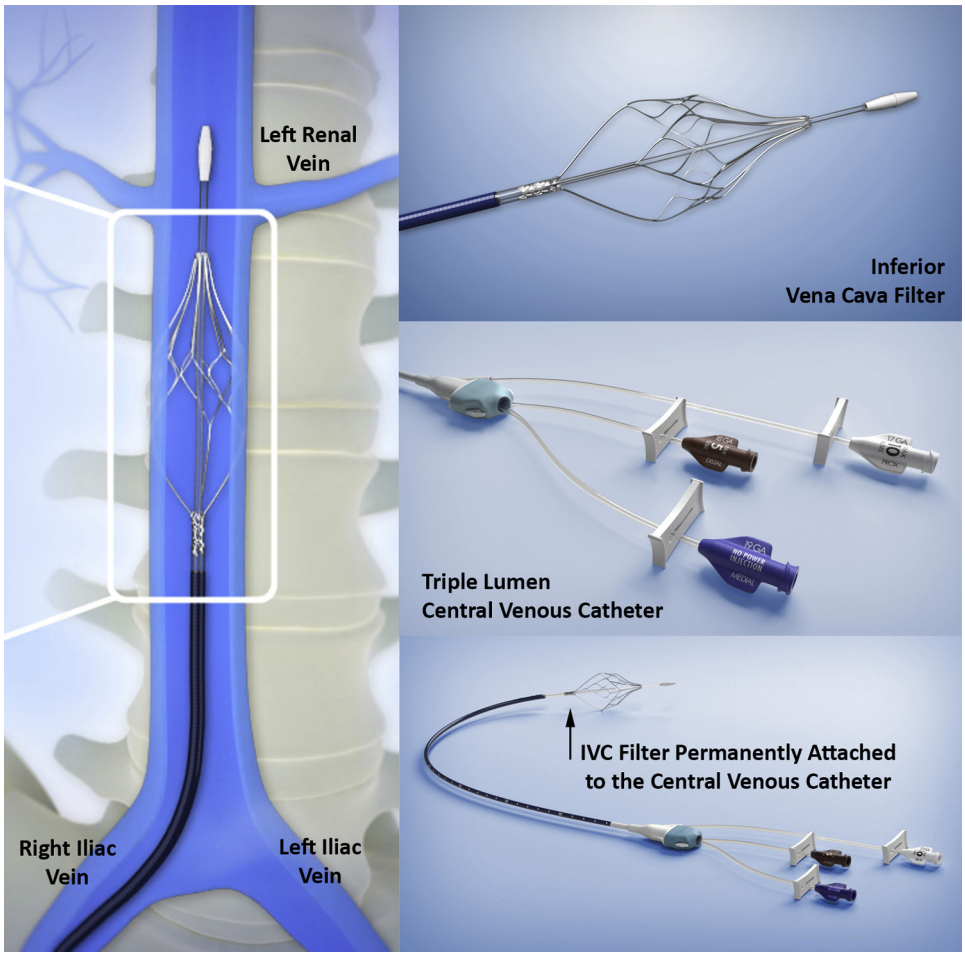


Figure 1. Angel Catheter. (Right bottom panel) Overview of Angel Catheter, a CVC with a permanently attached IVC filter. (Right middle panel) Triple-lumen CVC. (Right top panel) Detailed view of IVC filter. (Left panel) Angel Catheter placement in IVC.

retrieval of the device, 129 cavograms were obtained: 14 (8.6%) confirmed the presence of large thrombus in the IVC filter (> 25% of the filter volume), and 17 (10.4%) showed thrombus occupying < 25% of the filter volume (Table 2). Of the 14 patients with significant thrombus, 12 (86%) received anticoagulation an average of 4.1 days before the filter was removed, 5 of whom also had a traditional IVC filter placed. Of the 2 patients who did not receive anticoagulation, 1 had a traditional IVC filter placed, and 1 had the device removed without prior intervention. The median time after insertion of the device in these patients was 9.7 days ± 4.7. During retrieval of the filter, the larger thrombi were pulled back from the IVC and left into the iliac and femoral vein. There were no complications or acute embolic events after the retrieval of the device in patients with thrombus in the filter.

Device Safety

Major bleeding occurred in 5 (3.1%) of 163 patients. There were 12 (7.4%) catheters unintentionally removed with no evidence of venous injury or major bleeding, most often by patients who dislodged the device during an agitated or semiconscious state. During the study, 25 (15%) patients died; the median time to death after hospital admission was 6.8 days (IQR, 4.2–11.2 d). No deaths were associated with fatal PE; 20 deaths occurred while the catheter was still in place, 3 of which occurred within 48 hours of the catheter insertion, and 5 deaths occurred after the retrieval of the device. A new or worsening acute proximal DVT was diagnosed in 11 patients (7%) by day 7 and in 30 patients (18%) by the end of the study period. Freedom from new acute proximal lower extremity DVT is demonstrated in Figure 2. Prophylactic anticoagulation therapy was administered in 81 (50%) patients, and 40 (25%) patients received therapeutic anticoagulation therapy. In patients with a baseline DVT, anticoagulation was started an average of 5.87 days ± 6.53 after the ICU admission (median 4 d; range, 2–28 d) and maintained for an average duration of 5.43 days ± 4.70. In approximately 73% of patients without a baseline DVT (106 of 145), anticoagulation was started an average of 6.07 days ± 3.91 (median 5 d; range, 0–21 d) after admission to the ICU and an average of 3.64 days ± 3.41 (median 3 d; range, 1–6 d) before Angel Catheter removal; the average duration of use was 6.51 days ± 3.61. No anticoagulation was administered in 42 (25%) patients (Table 3).

Device Retrieval Results

The device was removed from 143 (88%) of 163 patients; 129 (79%) devices were retrieved according to protocol, and 12 (8%) were removed by the patient and 2 (1%) by treating physicians without a cavogram. The most common reasons for device retrieval were that the device was no longer clinically needed and that initiation of pharmacologic VTE prophylaxis was considered safe (55%). The median duration of the removal procedure, including cavogram, was 8 minutes (IQR, 4–18 min).

DISCUSSION

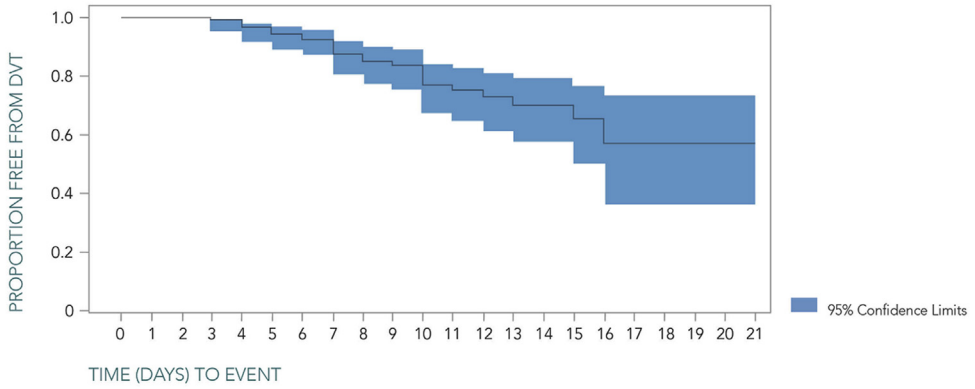
The Angel Catheter met the prespecified performance goal and the primary endpoint of freedom from clinically significant PE or fatal PE in all 163 critically ill patients in whom it was inserted. Most patients had head or spine trauma, with concomitant intracranial bleeding, other active bleeding, or a high risk of bleeding. Almost all devices (98%) were placed at the bedside without fluoroscopy.

A systematic review of 8 controlled nonrandomized studies in trauma patients found that compared with not placing an IVC filter, placement of an IVC filter was associated with an 80% lower rate of PE (relative risk, 0.20; 95% CI, 0.06–0.70) and a 91% lower rate of fatal PE (relative risk, 0.09; 95% CI, 0.01–0.81) (12). Neither the PROTECT (Prophylaxis of Thromboembolism in Critical Care Trial) (21,22) nor the PREPIC I and II (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) (9,23) trials included any critically ill trauma patients. In the PROTECT and PREPIC trials, all patients were eligible for full-dose anticoagulation.

Table 2. Primary and Secondary Endpoint Analysis

Endpoint	Devices Inserted (N = 163)	Exact 95% CI*
Freedom from clinically significant PE or fatal PE at time of discharge or up to 72 h after device removal, n (%)	163 (100)	97.8%–100%
Freedom from clinically significant PE, n (%)	163 (100)	97.8%–100%
Freedom from fatal PE, n (%)	163 (100)	97.8%–100%
Secondary endpoints		
Acute proximal DVT, n (%)	30 (18.4)	12.8%–25.2%
Catheter-related thrombosis, n (%)	20 (12.3)	7.7%–18.3%
Catheter-related bloodstream infections, n (%)	0 (0)	0%–2.2%
Major bleeding events, n (%)	5 (3.1)	1%–7%
Clinically significant thrombus in filter (> 25% of the volume), n (%)	14 (8.6)	4.8%–14.0%

CI = confidence interval; DVT = deep vein thrombosis; PE = pulmonary embolism.
*Two-sided Fisher exact 95% CI.



Angel® Catheter (N=163)	0 Days	1 Day	2 Days	3 Days	4 Days	5 Days	6 Days	7 Days	14 Days	21 Days
Number of Patients At Risk	163	163	161	157	150	138	124	111	93	15
Proportion Free From DVT	1.000	1.000	1.000	0.994	0.967	0.946	0.931	0.881	0.703	0.574

Figure 2. Kaplan-Meier curve showing time to new acute proximal DVT. Diagnosis of new or worsening acute proximal DVT from the time of Angel Catheter insertion through study exit. The median follow-up time was 8.93 days. The median time from catheter insertion to the development of a new or worsening acute proximal DVT was 7.4 days; the number of new or worsening DVT events was time dependent with DVT diagnosed in 11 patients (7%) by day 7 and in 30 patients (18%) by the end of the study period.

Table 3. Venous Thromboembolism Prophylaxis

Prophylaxis	Study Population	
	With IVC Filter in Place (N = 163)	After Removal of IVC Filter (n = 141)*
Medications		
Anticoagulants		
Therapeutic dose, n (%)	38 (23.3)	43 (30.5)
Prophylactic dose, n (%)	85 (52.2)	76 (53.9)
Antiplatelet agents, n (%)	4 (2.5)	5 (3.6)
Thrombolytics, n (%)	4 (2.5)	5 (3.6)
Mechanical prophylaxis		
Compression stockings, n (%)	17 (10.4)	6 (4.3)
Pneumatic compression, n (%)	123 (75.5)	92 (65.3)
Others, n (%)	36 (22.1)	32 (22.7)

IVC = inferior vena cava.
*The denominator in this group has been limited to subjects with at least 1 day of follow-up after removal.

Most IVC filters are inserted late after ICU admission and are retrieved from only a minority of patients (15,16). In contrast, in this clinical trial, the median insertion time was 1.7 days (IQR, 1–2.8 d) after ICU admission, and all filters were retrieved except for filters placed in the 20 (12%) patients who died with the device in place. Of the 129 cavograms obtained before device retrieval, 14 (11%) confirmed a significant thrombus in the IVC filter. These thrombi may represent averted PE and may explain the observed 100% freedom from clinically significant or fatal PE.

The rate of new or worsening acute proximal lower extremity DVT was time dependent; 11 (7%) occurred by day 7 and 30 (18%) occurred by the end of the study period as demonstrated in the Kaplan-Meier curve (Fig 2). This overall rate is similar to the rate reported by Geerts et al (24) in a prospective study of venous thromboembolism after major trauma. The 12% rate of catheter-related thrombosis is similar to that reported by Parienti et al (25) in a recent large randomized clinical study of central venous catheterization in critically ill patients.

This trial is the largest prospective study evaluating the use of IVC filters for prevention of clinically significant PE in critically ill, primarily trauma patients. Previous experience with this device was reported in the European Angel Catheter Registry (26), a "real-life" observational study involving 60 critically ill patients at high risk of PE with contraindications to anticoagulation. In this registry, 33 (55%) patients had major trauma, including 22 (67%) with head trauma. None of the patients in the European registry developed clinically significant PE.

This study has limitations. It was a single-arm clinical trial. It was not feasible to randomly assign these critically ill patients to the Angel Catheter versus no device or a placebo because the insertion of retrievable IVC filters is the standard of care for many critically ill trauma patients (27). In addition, the median duration of follow-up was relatively short.

In conclusion, this trial demonstrated that a novel device combining an IVC filter and CVC can be placed safely at the bedside without fluoroscopy and that the device can prevent clinically significant PE and fatal PE. Future studies in critically ill medical and surgical patients will build on these findings.

ACKNOWLEDGMENTS

The authors thank Vickie Arford, RN, for clinical trial management; Kristen Russell, for data analysis; and Flo Witte, for manuscript editing.

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V.F.T. received research support from Bio2 Medical (San Antonio, Texas), Bayer, EKOS/BTG, Daiichi-Sankyo, Inari, Janssen, and Portola and consulting fees from Bayer and Janssen. J.P.H., J.M., C.R., R.G., J.A.D., M.B., M.A.C., A.P., S.W., L.L., J.D., P.R.M., B.C., R.R.G., C.A.C., A.M., B.A.H., H.L., O.D.G., and V.N. received research support from Bio2 Medical. G.P. received research support from BTG/EKOS, Daiichi-Sankyo, Janssen, and Bristol-Myers Squibb. S.Z.G. received research support from Bio2 Medical, Boehringer-Ingelheim, Bristol-Myers Squibb, BTG/EKOS, Daiichi-Sankyo, Janssen, Thrombosis Research Institute (Boston, Massachusetts), and National Heart, Lung, and Blood Institute (Bethesda, Maryland) and is a paid consultant for Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi, Janssen, Portola, and Zafgen.

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