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Predicting the Safety and Effectiveness of Inferior Vena Cava Filters (PRESERVE): Outcomes at 12 months

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ABSTRACT

Objective: To determine the safety and effectiveness of vena cava filters (VCFs).

Methods: A total of 1429 participants (62.7 ± 14.7 years old; 762 [53.3% male]) consented to enroll in this prospective, nonrandomized study at 54 sites in the United States between October 10, 2015, and March 31, 2019. They were evaluated at baseline and at 3, 6, 12, 18, and 24 months following VCF implantation. Participants whose VCFs were removed were followed for 1 month after retrieval. Follow-up was performed at 3, 12, and 24 months. Predetermined composite primary safety (freedom from perioperative serious adverse events [AEs] and from clinically significant perforation, VCF embolization, caval thrombotic occlusion, and/or new deep vein thrombosis [DVT] within 12-months) and effectiveness (composite comprising procedural and technical success and freedom from new symptomatic pulmonary embolism [PE] confirmed by imaging at 12-months in situ or 1 month postretrieval) end points were assessed.

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Results: VCFs were implanted in 1421 patients. Of these, 1019 (71.7%) had current DVT and/or PE. Anticoagulation therapy was contraindicated or had failed in 1159 (81.6%). One hundred twenty-six (8.9%) VCFs were prophylactic. Mean and median follow-up for the entire population and for those whose VCFs were not removed was 243.5 ± 243.3 days and 138 days and 332.6 ± 290 days and 235 days, respectively. VCFs were removed from 632 (44.5%) patients at a mean of 101.5 ± 72.2 days and median 86.3 days following implantation. The primary safety end point and primary effectiveness end point were both achieved. Procedural AEs were uncommon and usually minor, but one patient died during attempted VCF removal. Excluding strut perforation greater than 5 mm, which was demonstrated on 31 of 201 (15.4%) patients' computed tomography scans available to the core laboratory, and of which only 3 (0.2%) were deemed clinically significant by the site investigators, VCF-related AEs were rare (7 of 1421, 0.5%). Postfilter, venous thromboembolic events (none fatal) occurred in 93 patients (6.5%), including DVT (80 events in 74 patients [5.2%]), PE (23 events in 23 patients [1.6%]), and/or caval thrombotic occlusions (15 events in 15 patients [1.1%]). No PE occurred in patients following prophylactic placement.

Conclusions: Implantation of VCFs in patients with venous thromboembolism was associated with few AEs and with a low incidence of clinically significant PEs. (J Vasc Surg Venous Lymphat Disord 2023;11:573-85.)

Keywords: Deep vein thrombosis; Pulmonary embolus; Vena cava filter; Venous thromboembolism

Anticoagulation (AC) therapy is the standard of care of treatment for patients with deep vein thrombosis (DVT) and/or pulmonary embolism (PE). A minority of people with venous thromboembolism (VTE) cannot undergo AC therapy. Vena cava filter (VCF) use in those persons is supported by current guidelines.[1,2] VCFs are also placed in those who have neither a history of VTE nor current VTE but who are at risk for PE (ie, "prophylactic" VCF placement). The appropriateness of VCFs in those populations is uncertain. Randomized controlled trials (RCTs) of VCF placement in anticoagulated patients have demonstrated decreased PE but increased DVT[3,4] or no benefit,[5] and an RCT of prophylactic VCF placement in severely injured trauma patients[6] demonstrated no overall survival benefit.

While the results of many nonrandomized studies have concluded that the use of VCFs improved outcomes, including PE-free survival in cancer patients with DVT and bleeding risk factors,[7] decreased all-cause mortality in patients with PE and congestive heart failure,[8] and reduced risk for all-cause death or fatal bleeding,[9] others[10] have demonstrated mixed outcomes, such as improved PE-related survival outcomes but an increased incidence of DVT in patients with VCFs. Other studies have demonstrated little or no benefit[11] or worse outcomes[12] in patients with prophylactic VCFs than in cohort populations without VCFs, and still others have demonstrated worse outcomes for patients with VTE and VCFs.[13,14] The complexity of VTE, the variety of VCFs evaluated in disparate populations, the difficulty in studying appropriate populations in randomized trials, and the lack of standard end points and definition of terms, among other impediments, have confounded efforts to determine the actual safety and effectiveness of individual VCFs.

The purpose of this study was to characterize the current practice of VCF use in the United States, including the indications for VCF placement; safety of placement and of VCF use over time; frequency and success of VCF removal; and incidence of subsequent embolic events as measures of VCF effectiveness.

METHODS

The PREdicting the Safety and Effectiveness of InferioR VEna cava filters (PRESERVE) study design has been described previously.[15] Briefly, this institutional review board–approved, Health Insurance Portability and Accountability Act (HIPAA)-compliant study was a multicenter, prospective, open-label, nonrandomized investigation of commercially available VCFs from seven manufacturers (Argon Medical Devices, Inc; ALN, Ghisonaccia; B. Braun Medical, Inc; C.R. Bard/BD; Cordis/Cardinal; Cook Medical; Volcano, San Diego) that are placed in patients for the prevention of PE. Adults at least 18 years old deemed to require an inferior VCF were enrolled if they were willing to comply with the scheduled follow-up. The only exclusion criterion was contrast sensitivity unalleviated by premedication. Women who were or became pregnant during the study were excluded from study-mandated imaging requirements.

Between October 10, 2015, and March 31, 2019, 1429 participants (62.7 ± 14.7 years old; 762 male [53.3%]) were enrolled at 54 sites in the United States (Appendix 1, online only). The indication for VCF placement and plan for retrieval were obtained at the enrollment visit. Demographic and clinical data are presented in Table I. At presentation, 1019 (71.3%) had acute or chronic VTE, including 438 (30.7%) with PE and 851 (60%) with DVT; 488 (34.1%) had a history of VTE, including 279 (19.5%) with PE and 323 (22.6%) with lower extremity (LE) DVT. Neither current VTE nor a history of VTE was present in 127 (8.9%) patients. Table II describes VTE status at presentation.

All patients were scheduled for evaluation at the time of the procedure and at 3 months, 6 months (telephone), 12 months, 18 months (telephone), and 24 months following the VCF placement (Appendix 2, online only). Patients whose inferior VCFs were removed were followed for 1 month after retrieval. Mandated imaging was scheduled at 3 months (radiograph) and at 12 and 24 months (contrast-enhanced abdominal computed tomography [CT]) for patients who still had VCFs. Images

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were submitted to the core laboratory for independent assessment.

The primary safety end point (PSE) was a composite end point that included freedom from serious adverse events (AEs) within the perioperative period and freedom from clinically significant perforation, VCF embolization, caval thrombotic occlusion, and/or new DVT within the first 12 months following VCF placement. The primary effectiveness end point (PEE) was a composite end point that included procedural and technical success and freedom from new clinically significant PE (new symptomatic PE confirmed by imaging) at 12 months in-situ or 1 month postretrieval, whichever came first. The null (H_0) and alternative (H_A) hypotheses were as follows:

H_0: $P \leq 80\%$ vs H_A: $P > 80\%$ for PSE
H_0: $P \leq 90\%$ vs H_A: $P > 90\%$ for PEE

where P is the proportion of patients free from the relevant events. The exact binomial test was employed to compare the observed proportions against a preplanned performance goal for PSE and PEE, respectively. A poolability analysis was performed to assess the appropriateness of aggregating the data across different VCF brands, specifically to compare different VCF brands regarding primary safety. Logistic regression of the primary safety outcome (safety event rate) vs VCF brand was performed. The results showed that there were no statistically significant differences between primary safety event rates (at 12 months postprocedure) across the VCF types ($P = .45$). Site-reported AEs were adjudicated by a clinical events committee (CEC), as described in Appendix 3 (online only). Enrollment of 2100 patients was planned. The reasons for enrollment of only 1428 patients are included in the description of statistical methodology in Appendix 4 (online only).

Secondary end points included mechanical stability as defined by the absence of the following at the time of retrieval or at each follow-up: cephalad or caudal migration >20 mm, perforation >5 mm outside the cava wall, VCF fracture, VCF or VCF component embolization, procedure-related complications at 3 months, major AEs at each follow-up, VCF tilt >15°, and VCF retrieval data including attempts, success rate, retrieval-related complications, and reasons for failed retrieval. Freedom from PE was evaluated on a per-patient basis; it was not stratified to those who did or did not receive AC therapy in addition to a VCF.

RESULTS

Two patients died before VCF placement. Following study VCF deployment failure in one patient, a nonstudy VCF was implanted. Venographic findings led to the decision not to place a VCF in five patients. Thus, VCFs were placed in 1421 of 1429 enrolled patients, in the infrarenal inferior vena cava (IVC) in 1386, the suprarenal IVC in 27, both iliac veins in five, and one iliac vein in three. The majority of VCFs were retrievable (1282, 90.2%) or convertible (16, 1.1%). Filters cleared only for permanent use were placed in 123 (8.7%) patients.

Prophylaxis in the absence of current or prior VTE was cited as the indication in 126 (8.9%), contraindication to AC therapy in 1026 (72.2%, including 223 [15.7%] with complications of AC therapy), failure of AC therapy in 133 (9.4%), during thrombolysis in 90 (6.3%), and as additional protection in 46 (3.2%). Indications and their relationship to plan for retrieval are presented in Table III. Mean and median follow-up for the entire population and for those whose VCFs were not removed were 243.5 ± 243.3 days and 138 days and 332.6 ± 290 days and 235 days, respectively.

PSEs and PEEs. As demonstrated in Table IV, the PSE rate was 89.4% and the PEE rate was 96.4%, with lower limits of the 95% confidence intervals exceeding the preplanned performance goals in both cases. As such, each primary end point was achieved.

Procedure-related and 30-day AEs. Thirty implantation procedural AEs were reported in 28 patients (2%). One VCF could not be advanced through its delivery sheath; of 15 tilted VCFs, 5 were snared and readjusted, 1 was replaced, 1 was removed at the end of procedure, and 8 were left tilted. One of two suboptimally positioned VCFs was repositioned; two of four VCFs with incompletely expanded struts were replaced, another's struts opened after catheter manipulation, and the fourth was left in place. Two VCF migration reports are included in the "VCF-related AEs" section that follows. One of two

ARTICLE HIGHLIGHTS

- **Type of Research**: Multicenter, prospective, open-label, nonrandomized investigation.
- **Key Findings:** Only 23 clinically significant, nonfatal pulmonary emboli were diagnosed following vena cava filter (VCF) placement in 1421 patients, of whom 1019 (71.7%) had current venous thromboembolism at the time of placement. Clinically significant VCF-related adverse events were rare. Post-VCF placement deep vein thromboses (DVTs) were diagnosed in 74 (5.2%) and caval occlusions in 15 (1.1%) patients. VCFs were removed from 632 of 640 (98.8%) patients who underwent attempted removal, 620 (96.8%) at first attempt.
- **Take Home Message:** The PRESERVE (PREdicting the Safety and Effectiveness of inferioR VEna cava filters) protocol, including formulation of a plan for VCF retrieval at placement and frequent reevaluation of patients for possible VCF removal thereafter, resulted in a high rate of VCF removal.

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Table I. Demographic and clinical data at enrollment[a]

Variable	All patients (n = 1421)	Intended VCF placement duration		
		Permanent (n = 198)	Temporary (n = 934)	Undetermined (n = 289)
Demographics				
Age, years				
Patients, No.	1421	198	934	289
Mean ± SD	62.7 ± 14.7	68.5 ± 13.4	60.9 ± 14.8	64.5 ± 13.9
Range	18.5-98.4	26.8-98.4	18.5-98.3	22.5-98.4
Sex				
Male	759 (53.4)	102 (51.5)	518 (55.5)	139 (48.1)
Female	662 (46.6)	96 (48.5)	416 (44.5)	150 (51.9)
Race				
White	1102 (77.6)	154 (77.8)	713 (76.3)	235 (81.3)
Black	213 (15.0)	35 (17.7)	139 (14.9)	39 (13.5)
Other[b]	106 (7.5)	9 (4.5)	82 (8.8)	15 (5.2)
Weight, kg				
Patients, No.	1386	195	911	280
Mean ± SD	90.6 ± 28.8	81.7 ± 20.1	93.8 ± 30.6	86.5 ± 25.7
Range	39.0-230.0	40.0-150.0	39.5-230.0	39.0-200.0
Missing	35	3	23	9
Height, cm				
Patients, No.	1372	195	900	277
Mean ± SD	170.9 ± 11.2	170.0 ± 11.0	171.4 ± 11.1	169.8 ± 11.4
Range	121.0-203.0	139.7-193.0	121.0-203.0	132.0-195.6
Missing	49	3	34	12
BMI, kg/m^2				
Patients, No.	1369	194	899	276
Mean ± SD	31.0 ± 9.3	28.3 ± 6.7	31.9 ± 10.1	29.7 ± 7.8
Range	14.4-81.8	15.9-57.3	15.3-81.8	14.4-60.4
Missing	52	4	35	13
Baseline comorbidities				
Hypertension				
Unknown	20 (1.4)	1 (0.5)	14 (1.5)	5 (1.7)
Yes	772 (54.3)	128 (64.6)	487 (52.1)	157 (54.3)
No	629 (44.3)	69 (34.8)	433 (46.4)	127 (43.9)
Coronary artery disease				
Unknown	26 (1.8)	1 (0.5)	20 (2.1)	5 (1.7)
Yes	207 (14.6)	42 (21.2)	128 (13.7)	37 (12.8)
No	1188 (83.6)	155 (78.3)	786 (84.2)	247 (85.5)
Congestive heart failure				
Unknown	35 (2.5)	6 (3.0)	23 (2.5)	6 (2.1)
Yes	136 (9.6)	26 (13.1)	86 (9.2)	24 (8.3)
No	1250 (88.0)	166 (83.8)	825 (88.3)	259 (89.6)
Compromised pulmonary function				
Missing	3 (0.2)	0 (0.0)	3 (0.3)	0 (0.0)
No	1085 (76.4)	132 (66.7)	722 (77.3)	231 (79.9)
Yes	333 (23.4)	66 (33.3)	209 (22.4)	58 (20.1)

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Table I. Continued.

Variable	All patients (n = 1421)	Intended VCF placement duration		
		Permanent (n = 198)	Temporary (n = 934)	Undetermined (n = 289)
Diabetes mellitus				
Unknown	15 (1.1)	1 (0.5)	11 (1.2)	3 (1.0)
Yes	275 (19.4)	43 (21.7)	169 (18.1)	63 (21.8)
No	1131 (79.6)	154 (77.8)	754 (80.7)	223 (77.2)
Renal failure or insufficiency				
Missing	4 (0.3)	0 (0.0)	3 (0.3)	1 (0.3)
Yes[c]	280 (19.7)	50 (25.3)	153 (16.4)	77 (26.6)
No[d]	1137 (80.0)	148 (74.7)	778 (83.3)	211 (73.0)
Malignancy				
Unknown	32 (2.3)	3 (1.5)	20 (2.1)	9 (3.1)
Yes	627 (44.1)	125 (63.1)	358 (38.3)	144 (49.8)
No	762 (53.6)	70 (35.4)	556 (59.5)	136 (47.1)
If yes to malignancy				
Current	530 (37.3)	110 (55.6)	292 (31.3)	128 (44.3)
Prior, in remission	97 (6.8)	15 (7.6)	66 (7.1)	16 (5.5)
Hypercoagulable disorder				
Unknown	95 (6.7)	12 (6.1)	56 (6.0)	27 (9.3)
Yes	131 (9.2)	15 (7.6)	88 (9.4)	28 (9.7)
No	1195 (84.1)	171 (86.4)	790 (84.6)	234 (81.0)
Ambulatory status				
Missing	2 (0.1)	1 (0.5)	1 (0.1)	0 (0.0)
Mobile	1154 (81.2)	136 (68.7)	784 (83.9)	234 (81.0)
Not mobile	265 (18.6)	61 (30.8)	149 (16.0)	55 (19.0)
Major LE surgery				
Unknown	32 (2.3)	0 (0.0)	22 (2.4)	10 (3.5)
Yes	177 (12.5)	19 (9.6)	126 (13.5)	32 (11.1)
No	1212 (85.3)	179 (90.4)	786 (84.2)	247 (85.5)
Stroke within 30 days				
Unknown	27 (1.9)	3 (1.5)	14 (1.5)	10 (3.5)
Yes	46 (3.2)	8 (4.0)	23 (2.5)	15 (5.2)
No	1348 (94.9)	187 (94.4)	897 (96.0)	264 (91.3)
Multiple trauma within 30 days				
Unknown	32 (2.3)	1 (0.5)	19 (2.0)	12 (4.2)
Yes	81 (5.7)	10 (5.1)	58 (6.2)	13 (4.5)
No	1308 (92.0)	187 (94.4)	857 (91.8)	264 (91.3)

BMI, Body mass index; *LE,* lower extremity; *SD,* standard deviation; *VCF,* vena cava filter.
Data presented as number (%), unless noted otherwise.
[a]"Unknown" was an option on the case report form for the category; "missing" indicated the data were missing from the database.
[b]Included Asian (n = 11), Native American or Alaskan Native (n = 1), Native Hawaiian or Pacific Islander (n = 1), other (n = 70), more than one race (n = 2), and unknown (n = 21).
[c]Glomerular filtration rate <30 mL/min/1.73 m^2 (n = 57), glomerular filtration rate 30-60 mL/min/1.73 m^2 (n = 206), and chronic dialysis (n = 17).
[d]None (n = 686) and glomerular filtration rate >60 mL/min/1.73 m^2 (n = 451).

groin hematomas was due to a pseudoaneurysm and accompanied by a subsegmental PE. One patient had postprocedural groin pain. One developed tachycardia, which resolved with intraprocedural medications.

Of the 27 clinically significant AEs reported within 30 days after VCF placement, one patient died from unknown causes, another succumbed to "undifferentiated shock," and a third with PE at presentation died from continuing hypoxia 3 days later. One instance of caval occlusion was diagnosed 15 days after VCF placement, 20 days before successful VCF retrieval. New or worsened DVTs were reported in eight patients, six of whom had acute VTE at presentation. New or worsened PE was reported in seven patients, all of whom had acute VTE at

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Table II. Venous thromboembolism (VTE) status at presentation[a,b]

Variable	History of PE and/or DVT	History of PE and DVT	History of PE only	History of DVT only	No history of PE or DVT	Total[c]
Current PE and/or DVT	214	54	46	106	805	1019
Current PE and DVT	58	25	11	21	220	278
Current PE only	31	6	17	8	129	160
Current DVT only	121	23	15	77	452	573
No current PE or DVT	273	78	100	84	127	400
Total	488	133	146	190	933	

DVT, Deep vein thrombosis; *PE,* pulmonary embolism.
Data presented as number of patients.
[a]Site investigators were provided with categories from which to choose in determining the absence or presence of VTE: previous history of resolved PE and/or DVT and current VTE (comprising newly diagnosed VTE and VTE for which the patient was receiving current anticoagulation [AC] therapy); thus, current VTE did not include patients who were not receiving AC therapy for VTE but could include those treated for VTE diagnosed before presentation.
[b]DVT events also included caval thrombotic events.
[c]Total numbers for each category are correct, although subcategory totals do not sum exactly to those totals because incompleteness of data for a minority of patients precluded definite subcategorization (ie, no patient was missing all VTE history but one was completely missing current VTE status), another 11 patients were partially missing VTE history, and another 6 were partially missing current VTE status; 16 patients had partially missing VTE data, instead of 17, because 1 patient had partially missing data for both VTE history and current VTE status and was counted twice. A total of 126 patients had VCFs placed prophylactically (ie, no VTE history or current VTE reported); 127 patients were included in Table II with no history of PE or DVT and no current PE or DVT, because 1 patient had a history of VTE that included only dyspnea (no DVT or PE).

presentation. One pseudoaneurysm was noted earlier; one VCF strut perforation and one VCF embolization are discussed in the following section. All other reported events were minor and/or unrelated to the VCF or procedure.

VCF-related AEs. Migration >20 mm occurred in three patients, leading to immediate VCF replacement in one and without negative sequelae in the others.

Embolization of a VCF or part of a VCF occurred in four patients: (1) One embolized VCF was snared from the heart 3 days after placement; (2) A fractured strut embolized to the left pulmonary artery (LPA) was removed percutaneously with the VCF 3.4 months after placement; (3) A fractured strut that had embolized to the right atrium prior to percutaneous retrieval of the body of the VCF was removed surgically 1.3 months thereafter; and (4) A strut segment that had embolized to the LPA was demonstrated during an unsuccessful VCF retrieval attempt but could not be removed during percutaneous retrieval of the VCF 3 weeks later. It remained in the LPA at study completion 1 month later.

In addition to the three strut fractures with embolization described previously, one VCF had a fractured strut at its placement and was replaced with a different study VCF, and one pre-existent strut fracture was noted at its retrieval with the body of the VCF 2.8 months after VCF placement.

Of the 11 instances of perforation reported by sites prior to the 12-month CT scan, 3, demonstrated on CT at 1.4-7.8 months after placement, were deemed clinically significant: (1) 9-mm strut perforation; (2) perforation of struts into the duodenum and the aorta, maximum 8 mm; and (3) strut perforation at 1.4 months, extending to 8.2 mm 11.6 months after placement.

At the 12-month follow-up interval, 211 CT scans (for 201 patients) were available to the core laboratory, which did not consider clinical symptoms and which considered abutment of an adjacent organ penetration even if it was <5 mm outside the IVC. As such, perforation of the IVC ≥5 mm (5.2-16.2 mm) was demonstrated on the CT scans of 31 patients (15.4%). Penetration of one or more adjacent organs by struts was demonstrated in 10 of these patients 239-406 days after placement: aorta (6 patients), bowel (4), vertebral body (2), pancreas (1), common iliac artery (1), disc space (1), and gonadal vein (1). CT scans 27-422 days after placement demonstrated organ penetration in 5 patients without axial perforation >5 mm: bowel (3), aorta (1), and muscle (1).

VCF retrieval. Retrieval of the VCF was attempted in 634 of 647 patients who returned for VCF retrieval (mean, 3.3 ± 2.3 months after placement) and was successful in 614 (96.8%). Retrieval was not attempted in 13 patients at first presentation because venography showed a clot in the VCF with (n = 7) or without (n = 6) associated extra-VCF thrombus. VCF retrieval was successful in all 6 of the 13 who returned for attempted retrieval at a second visit and in all 12 who returned for an additional attempt after a failed attempt at first visit. As such, of 647 patients who presented for VCF retrieval, it was attempted in 640, successful in the first attempt in 620 of 640 (96.8%), and successful in the first or second attempt in 632 of 640 (98.8%) at a mean of 101.5 ± 72.2 days and median 86.3 days following implantation (Fig 1).

No attempt was made to retrieve a VCF cleared only for permanent use. Of 1282 potentially retrievable VCFs, 632 (49.3%) were removed within 12 months of placement as follows: Of the 198 patients for whom VCFs were planned to be permanent, 83 (42%) died without

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Table III. Indication for vena cava filter (VCF) placement vs plan for filtration duration

Variable	All patients	Intended VCF placement duration		
		Permanent	Temporary	Undetermined
Current VTE with contraindication to AC	593 (41.7)	90 (45.5)	383 (41.0)	120 (41.5)
Bleeding unrelated to AC	150 (10.6)	39 (19.7)	78 (8.4)	33 (11.4)
Postoperative	57 (4.0)	4 (2.0)	49 (5.2)	4 (1.4)
Preoperative	262 (18.4)	15 (7.6)	195 (20.9)	52 (18.0)
Risk of bleeding unrelated to AC	121 (8.5)	31 (15.7)	60 (6.4)	30 (10.4)
Other	3 (0.2)	1 (0.5)	1 (0.1)	1 (0.3)
History of VTE with contraindication to AC	201 (14.1)	11 (5.6)	159 (17.0)	31 (10.7)
Bleeding unrelated to AC	13 (0.9)	3 (1.5)	7 (0.7)	3 (1.0)
Postoperative	8 (0.6)	0 (0.0)	8 (0.9)	0 (0.0)
Preoperative	171 (12.0)	5 (2.5)	141 (15.1)	25 (8.7)
Risk of bleeding unrelated to AC	8 (0.6)	3 (1.5)	2 (0.2)	3 (1.0)
Other	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Complication of AC	223 (15.7)	42 (21.2)	126 (13.5)	55 (19.0)
Bleeding	218 (15.3)	42 (21.2)	121 (13.0)	55 (19.0)
Other[a]	5 (0.4)	0 (0.0)	5 (0.5)	0 (0.0)
Failure of AC	133 (9.4)	29 (14.6)	64 (6.9)	40 (13.8)
New or growing DVT or PE despite AC	125 (8.8)	28 (14.1)	60 (6.4)	37 (12.8)
Noncompliance	3 (0.2)	0 (0.0)	1 (0.1)	2 (0.7)
Other[b]	5 (0.4)	1 (0.5)	3 (0.3)	1 (0.3)
Additional protection for patient receiving AC	46 (3.2)	14 (7.1)	19 (2.0)	13 (4.5)
PE other than massive, residual DVT	27 (1.9)	6 (3.0)	13 (1.4)	8 (2.8)
Other[c]	19 (1.3)	8 (4.0)	6 (0.6)	5 (1.7)
Other indications	9 (0.6)	1 (0.5)	6 (0.6)	2 (0.7)
Bleeding, unknown relationship to AC	8 (0.6)	1 (0.5)	6 (0.6)	1 (0.3)
Inability to receive AC for other reason	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)
Placed as part of thrombolysis procedure	90 (6.3)	3 (1.5)	71 (7.6)	16 (5.5)
Prophylaxis in absence of DVT or PE	126 (8.9)	8 (4.0)	106 (11.3)	12 (4.2)

AC, Anticoagulation; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism; *VTE*, venous thromboembolism.
Data presented as number (%).
[a]Included thrombocytopenia.
[b]Included drug interaction preventing adequate AC.
[c]Included severe cardiopulmonary disease with DVT.

removal attempt, 12 were lost to follow-up (LTFU), and 20 withdrew; VCFs were removed from 3 (1.5%) 171 ± 117 days after placement, and 80 (40.4%) were alive with VCFs at 1 year. Of the 289 for whom a plan had not been determined at placement, 78 (27%) died without removal attempt, 13 were LTFU, and 19 withdrew; VCFs were removed from 92 (31.8%) 138 ± 77 days after placement. In addition, 2 patients died after successful removal, neither from PE, and 87 (30.1%) were alive with VCFs. Of the 934 for whom VCF removal was planned at the time of placement, 116 (12.4%) died without a removal attempt, 30 were LTFU, and 46 withdrew. VCFs were removed from 537 (57%) 95 ± 69 days after placement; 2 died after VCF removal, 1 from pneumonia, the other from unknown causes, and 205 (21.9%) were alive with VCFs (Fig 2).

AEs related to retrieval procedure. One (0.15%) of 652 retrieval procedures resulted in death from an innominate vein injury. Procedure-related AEs were reported for 12 (1.8%) other patients: six procedural complications comprised pain during retrieval, five moderate and one severe, with associated tachycardia and hypoxia resolving in the interventional radiology suite. Two patients with pain were also noted to have small intimal filling defects on venography after VCF removal. Minimal or small contrast extravasation (n = 3) or spasm (2) without sequelae was reported on completion venography. One unsuccessful retrieval attempt was complicated by a segmental PE.

New or worsened VTE after VCF placement. Including those episodes reported within 30 days, 80 DVTs, 23 PEs,

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Table IV. Primary safety and effectiveness results

End point event	Rate,[a] % (n/N)	95% CI,[a] %
Primary safety event rate at 12 months[b]	89.4 (262/293)	85.3-NA
Freedom from clinically significant perforation	98.6 (289/293)	96.5-99.6
Freedom from VCF embolization	100.0 (293/293)	98.8-100.0
Freedom from caval thrombotic occlusion	98.6 (289/293)	96.5-99.6
Freedom from new DVT	91.5 (268/293)	87.7-94.4
Freedom from SAEs related to VCF within perioperative period[c]	97.8 (1264/1292)	96.9-98.6
Primary effectiveness event rates at 12 months in situ or 1 month after retrieval[d]	96.4 (799/829)	94.9-NA
Procedural and technical success at procedure	98.0 (1393/1421)	97.2-98.7
Freedom from clinically significant PE	98.3 (815/829)	97.2-99.1

CI, Confidence interval; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism; *SAE*, serious adverse event; *VCF*, vena cava filter.
[a]The exact binomial test model was used for analyses, with the denominator the number of patients evaluable for the specific end point.
[b]Primary safety event rates were calculated for patients with the inferior VCFs in situ at 12 months (aggregate data); hence to be evaluable for primary safety end point, patients were required to still be in the study at 12 months after their index procedure, which was established by counting the patients with 12-, 18-, and/or 24-month follow-up visits (ie, had not withdrawn or died or been loss to follow-up before 335 days after their index procedure). This method was used to not exclude patients who had missed the 12-month visit but who were still in the study and able to provide adverse event and other relevant information at a later visit. Of the 1421 patients who had had a study filter placed, 293 were evaluable for the primary safety end point.
[c]Defined as 30 days after the procedure.
[d]Primary effectiveness event rates were calculated for patients with the inferior VCF in situ at 12 months or 1 month after retrieval (whichever came first). Hence, for patients to be assessed as evaluable for primary effectiveness, they were required to still be in the study at 12 months after their index procedure or to have had the VCF retrieved within 335 days after their index procedure. This was established by counting the patients who had a 12-, 18-, and/or 24-month follow-up visit or had a retrieval within 12 months after the index procedure and had completed the 1-month visit after retrieval (ie, had not withdrawn or died or been loss to follow-up before 335 days after their index procedure or had not missed the 1-month visit after retrieval). Of the 1421 patients with a study VCF placed, 829 were evaluable for the primary effectiveness end point.

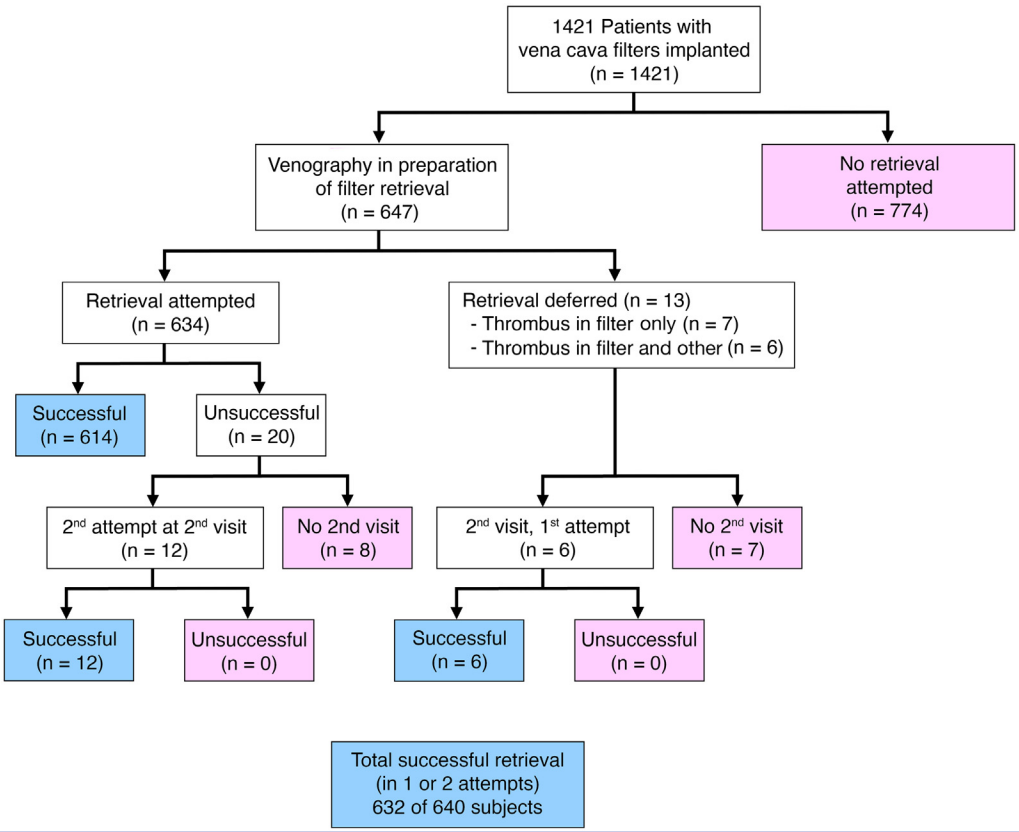

Fig 1. Study flowchart for vena cava filter (VCF) retrieval.

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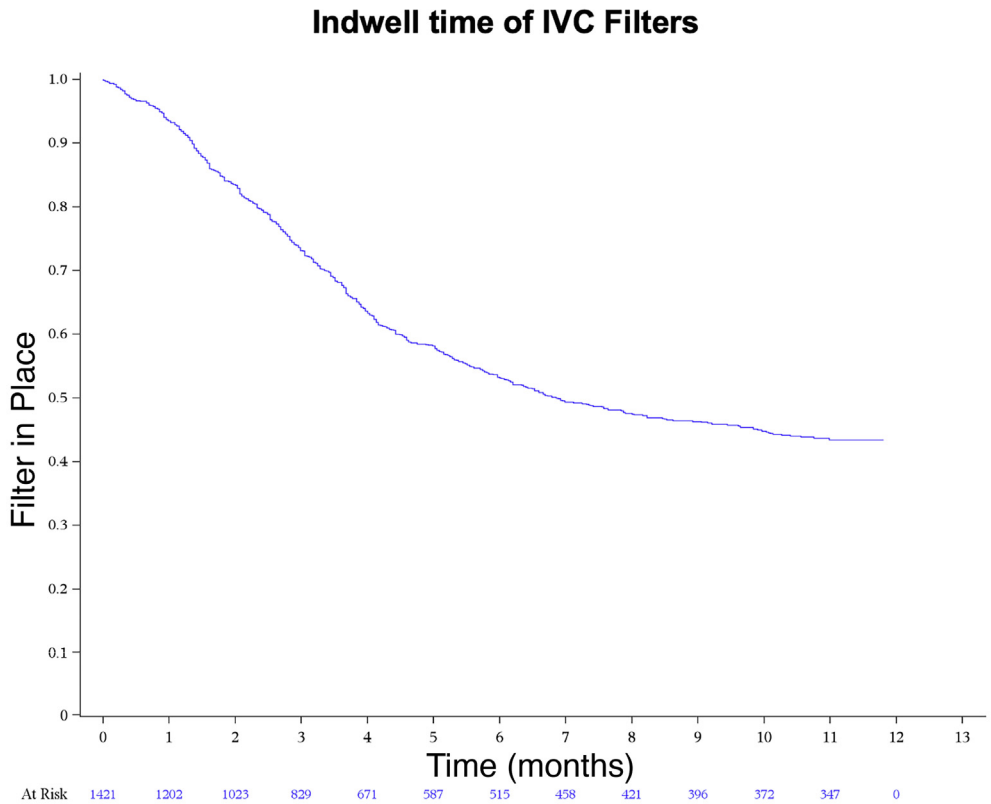

Fig 2. Kaplan-Meier curve for inferior vena cava (IVC) filter dwell time. At-risk numbers show patients who had not had their vena cava filter (VCF) retrieved and had not been censored (lost to follow-up [LTFU], died, or withdrawn from the study) before the time point. The curve is based on a maximum follow-up time of 12-months (ie, after 12 months all patients were censored). The median survival time was estimated as 6.85 months (ie, approximately 50% of the patients had not had a VCF retrieved 7 months after the procedure).

and 15 caval thrombotic occlusions in 93 (6.5%) patients were reported and confirmed by the CEC 73.1 ± 66.0 days, 65.7 ± 62.9 days, and 62.75 ± 46.19 days, respectively, after VCF placement. No event was fatal. Six DVTs, three PEs, and two caval occlusions were second events in patients with previous VTE AEs. Sixteen episodes comprised more than one VTE-related AE. There was one PE within 30 days after VCF removal (Fig 3).

Four DVTs extended to the IVC without obstructing it; most DVTs (65 episodes in 60 patients) were in or peripheral to the external iliac veins and not associated with a PE. Fourteen DVTs extended to the external iliac, 25 to the common femoral, 11 to the femoral, and 3 to popliteal veins. Twelve DVTs were limited to calf veins.

Eighteen cases of PE were reported without concurrent DVT. Two PEs were reported as concurrent events with DVTs, two with DVT and caval thrombus, and one with caval occlusion. Nineteen episodes of caval thrombus with (13) or without (6) concurrent DVTs were reported.

In addition to the confirmed cases, one patient who underwent thrombectomy at an outside hospital for confirmed DVT and caval thrombosis also reportedly had segmental PE, not confirmed by the CEC; three other patients with unconfirmed PE (one lobar, one segmental, one subsegmental) did not require treatment beyond AC therapy. One site-reported femoral DVT and one caval thrombotic episode could not be confirmed by the CEC.

Only three patients with DVT alone underwent intervention beyond AC therapy: one thrombectomy, one thrombolysis, and one angioplasty; one patient with PE treated with AC had concomitant paradoxical embolization to a subclavian artery requiring embolectomy. Seven patients with confirmed caval thrombus underwent thrombectomy procedures.

Among the prophylaxis population, nine (7.1%) died within 12 months. VCFs were retrieved from 78 patients (62%) 87.3 days ± 60.4 days after placement. No PEs, five DVTs, and one caval thrombotic event were reported: the immobile multitrauma patient with caval thrombus was treated with thrombectomy, VCF removal, and stenting. All DVTs resolved without sequelae.

Selected parameters and their relationships to VTE AEs are presented in Table V.

DISCUSSION

Determination of the safety and effectiveness of VCFs has been limited by study design issues, notably

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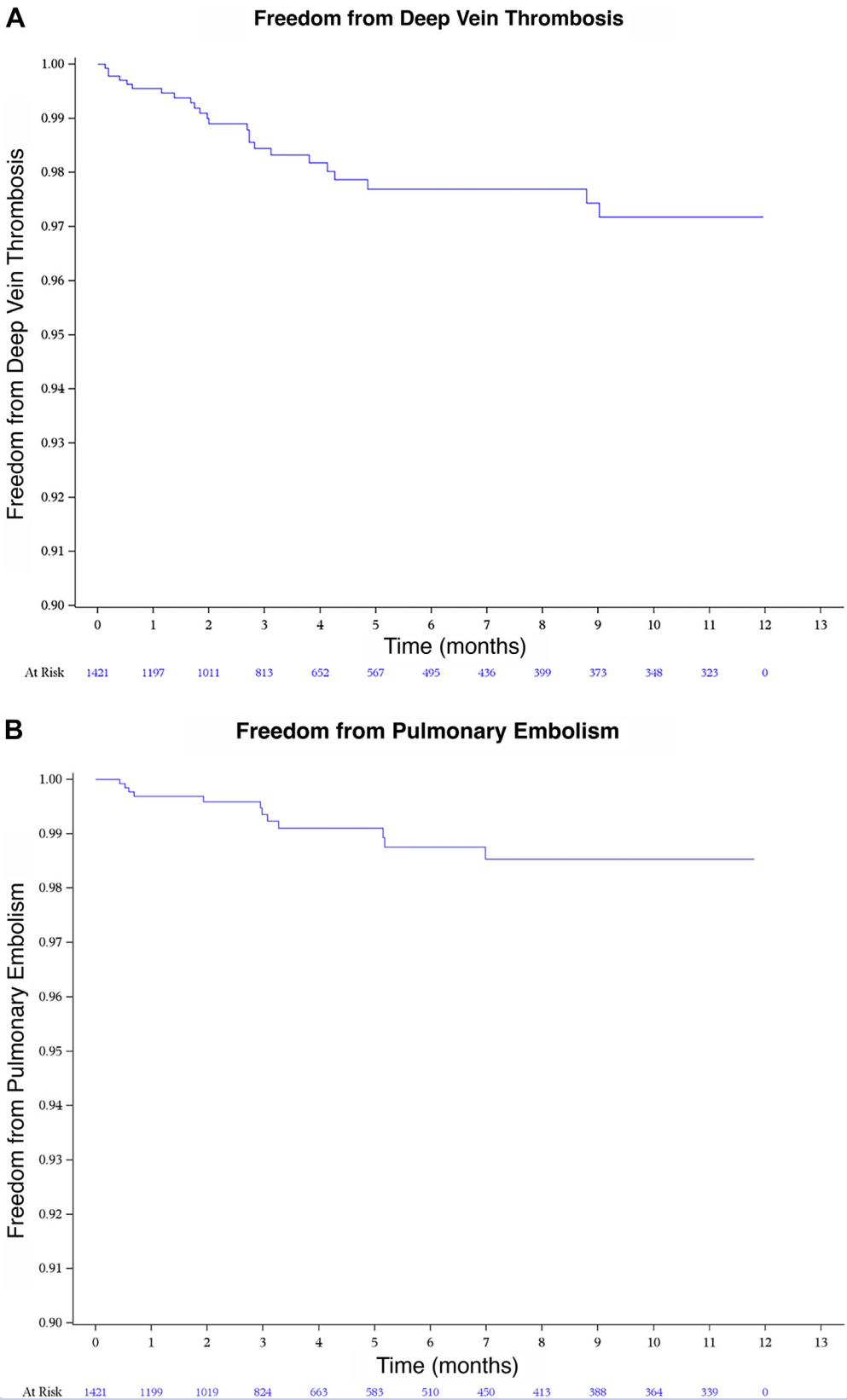

Fig 3. A, Kaplan-Meier curve for freedom from deep vein thrombosis (DVT). **B,** Kaplan-Meier curve for freedom from clinically significant pulmonary embolism (PE). For both **A** and **B**, at-risk numbers show patients who have not had an event and have not been censored (lost to follow-up [LTFU], died, or withdrawn from the study or had a vena cava filter [VCF] retrieved) prior to the time point. The Kaplan-Meier curve is based on a maximum follow-up time of 12 months (ie, after 12 months all patients were censored). Note that the y-axis represents 0.90 to 1.00.

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Table V. Selected parameters and their relationship to venous thromboembolism (VTE)-related adverse events (AEs)[a]

	PE (829 evaluable patients; 14 PE events)[b]			DVT (293 evaluable patients; 27 DVT or caval thrombotic events)[c]		
Parameter estimate	**OR**	***P* value**	**95% CI**	**OR**	***P* value**	**95% CI**
Intended VCF duration						
Permanent vs temporary	0.76	.79	0.10-5.93	0.80	.65	0.30-2.13
Undetermined vs temporary	0.81	.78	0.18-3.70	0.73	.56	0.26-2.08
Indication						
Prophylaxis vs all other	No events[d]			0.56	.58	0.07-4.41
Perioperative vs all other	0.67	.49	0.21-2.14	0.83	.70	0.32-2.15
Bleeding vs all other	1.08	.91	0.30-3.92	1.08	.85	0.47-2.51
Comorbidity						
Ambulatory status (immobile vs mobile)	0.52	.53	0.07-4.02	0.15	.07	0.02-1.14
Hypercoagulable disorder vs none	3.47	**.04**	1.06-11.30	1.43	.54	0.46-4.45
Current malignancy vs none	0.85	.78	0.26-2.73	1.01	.99	0.41-2.48
Stroke vs none	2.84	.33	0.35-22.74	1.17	.88	0.14-9.64

CI, Confidence interval; *DVT*, deep vein thrombosis; *OR*, odds ratio; *PE*, pulmonary embolism; *VCF*, vena cava filter.
Boldface *P* values represent statistical significance.
[a]Univariate logistic regression models were used to estimate the odds ratio for PE (yes vs no) and DVT (yes vs no) with each parameter as a covariate.
[b]For PE, the total number (n = 829) reflects patients who were evaluable for the primary effectiveness end point. For a patient to be evaluable for primary effectiveness, they needed to still be in the study 12 months after their index procedure or have had a VCF retrieved within 335 days after their index procedure. This was established by counting patients who had a 12-month, 18-month, or 24-month follow-up visit or who had a retrieval within 12 months from the index procedure and completed a 1-month postretrieval visit (ie, they had not withdrawn, died, or been lost to follow-up before 335 days after their index procedure or missed the 1-month postretrieval visit). Of the 1421 patients who had a PRESERVE study VCF placed, 829 were evaluable for the primary effectiveness end point.
[c]For DVT, the total number (n = 293) reflects patients who were evaluable for the primary safety end point. To be evaluable for the primary safety end point, the patient needed to still be in the study 12 months after their index procedure. This was established by counting patients who had a 12-month, 18-month, or 24-month follow-up visit (ie, they had not withdrawn, died, or been lost to follow-up before 335 days after their index procedure). This method was used in order not to exclude patients who missed the 12-month visit but who were still in the study and were able to provide adverse event and other relevant information at another time. Of the 1421 patients with a PRESERVE study VCF placed, 293 patients were evaluable for the primary safety end point.
[d]None of the patients in the prophylaxis group had experienced a PE event.

precluding appropriate control groups for RCTs, since those who can receive AC therapy generally do not require VCFs and withholding AC therapy from control groups with VTE is an unethical deviation from standard of care. That a minority of VCFs are placed in patients undergoing concomitant AC therapy or in other disparate scenarios, including as "prophylaxis," leads to additional difficulty in understanding the role of these devices. Further, what constitutes prophylaxis has not been clearly defined. Ambiguity of that and other terms related to VCFs, including "PE" and "DVT"—as both terms comprise events of varying extent and clinical significance—complicates that determination. The PRESERVE study was undertaken to evaluate VCF safety and effectiveness within existing constraints.

VCFs were placed in ill patients with few therapeutic alternatives. These patients frequently had often-severe comorbid conditions. The large majority had current VTE at presentation, and/or it had been determined that AC therapy was contraindicated, had caused bleeding, or had failed. While comparison of all outcomes to those of patients who could take advantage of AC therapy would be inappropriate, comparison of the incidence of recurrent VTE in both populations may be beneficial, as many have attributed an increased incidence of DVT to the use of VCFs: The 6.5% incidence of VTE events within the year following VCF placement in PRESERVE participants compares favorably to the 7.8% recurrence rate after first VTE presentation in a Danish registry[16] and to the 10.3% recurrence rate within a year of cessation of AC therapy in a recent meta-analysis of 7515 patients.[17]

The prespecified primary safety and effectiveness goals of the study were met. While data used in the calculation of those end points were limited to evaluable patients (eg, 293 patients with VCFs alive at 12 months for the majority of the safety end points), the safety and effectiveness of VCFs are further supported by very high technical success rates for implantation and retrieval, few procedural complications, and low rates of mostly minor VCF-related complications and thromboembolic AEs in patients with VCFs. Although high procedural technical success and low incidence of PE were not likely affected by the study design, the mandates for noting a plan for VCF removal at the time of placement and frequent post-VCF follow-up may have contributed to the high rate of VCF removal (49.3% of retrievable VCFs, 44.5% of all study VCFs) in the PRESERVE population and to the low rate of AEs that was demonstrated. We suggest that a physician implanting a VCF should consider *at placement* if and when that VCF will be

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removed and that patients with VCFs should be followed closely, with frequent re-evaluation for potential VCF removal when appropriate.

Except for perforation, clinically significant VCF-related and procedural complications were rare. Moreover, assessment of "clinical significance" of perforation was difficult. Sites identified several cases, including those with organ involvement, as clinically significant but considered insignificant or were unaware of others identified by the core laboratory. Although no relationship between perforation and other AEs was demonstrated, the potential for increasing penetration with involvement of surrounding structures suggests that a finding of perforation >5 mm and/or with organ involvement should lead to evaluation for VCF removal or replacement. Two-year PRESERVE results may strengthen that statement.

The PRESERVE study was not randomized, for reasons discussed earlier. The absence of a control population, while ethically mandated, limits direct comparison to participants without VCFs. Additionally, as determination of the nature and extent of VTE at presentation was not always complete (eg, a chest CT scan may not have been obtained in a patient with an LE DVT or an LE ultrasound [US] in a patient with a PE), VTE events that occurred within weeks of VCF placement that were counted as new may have represented pre-existing DVT or PE, artificially inflating their incidence. Another limitation was that patients whose filters were removed were followed for only one month after filter removal. As 45% of patients' VCFs were removed prior to 1 year, those patients were not evaluable for the primary safety outcomes.

Further, the contribution of concomitant AC therapy to the prevention of PE in the PRESERVE population cannot be determined. Many patients received AC therapy immediately before, during, and/or after VCF placement. Indeed, 9.5% of patients received VCFs during thrombolysis or for additional protection while undergoing AC therapy. Many others received AC therapy following cessation of a temporary contraindication such as an operation but prior to VCF removal. If AC therapy and filters are considered as complementary in prevention of PE throughout a patient's course, assignation of relative value in PE prevention while the VCF is in place is not appropriate; rather, in order to provide optimal protection against PE, patients should be reevaluated frequently following VCF placement for appropriateness of AC therapy and VCFs should be removed as soon as possible after sustainable therapeutic AC therapy is achievable or when the risk for PE is no longer elevated.

Pre-existing comorbidities and the infrequency of post-VCF DVT and PE precluded identification of single risk factors for their occurrence and significance in most cases. Only hypercoagulability was a significant risk factor for PE, and no predisposing factor proved significant for DVT. While limiting prediction, the infrequency of VTE-related AEs is compelling: in a population with a very high prevalence of current VTE and comorbid conditions at VCF placement, there were very few DVTs and fewer PEs, and none was fatal. Further, there were relatively fewer DVTs and no PEs in the prophylactic population (ie, those without current VTE or a history of VTE at VCF placement). To the extent possible without a control group, results of the PRESERVE study demonstrate that VCFs are safe and effective in preventing clinically significant PE.

Imaging core laboratory services for the present study were provided by the University of Virginia Clinical Overread Services, with James R. Stone, MD, PhD, serving as core director. Central imaging interpretation was performed by John F. Angle, MD, Saher S. Sabri, MD, Daniel P. Sheeran, MD, James R. Stone, MD, PhD, Andre B. Uflacker, MD, and Luke R. Wilkins, MD.

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Writing the article: MJ, JS, KS, BK, XM, JR, RW, RL, MK, DZ, TC, DG
Critical revision of the article: MJ, JS, KS, JR, RW, RL, MK, DZ, TC, DG
Final approval of the article: MJ, JS, KS, BK, XM, JR, RW, RL, MK, DZ, TC, DG
Statistical analysis: MJ, JS, KS, BK, XM, DG
Obtained funding: MJ, DG
Overall responsibility: MJ

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APPENDIX 1 (online only). Participating centers

Site name	Principal investigator	Patients enrolled, No.
Northwestern Memorial Hospital	Robert Lewandowski	155
University of Michigan	Minhaj Khaja	101
Washington University	Darryl Zuckerman	93
Indiana University	Thomas Casciani	86
Sarasota Memorial Hospital	Justin Lee	69
Holy Cross Hospital	Michael Rush	60
University of Colorado	Paul Rochon	58
Mayo Clinic, Rochester, MN	Haraldur Bjarnason	49
Rochester Regional	Donnette Dabydeen	48
Memorial Hermann Hospital	Rodrick Zvavanjanja	43
Southcoast	Richard Pin	38
University of California, San Francisco	K. Pallav Kolli	35
Memorial Sloan Kettering Cancer Center	Robert Siegelbaum	35
Miami Valley/Wright State	Shannon Kauffman	32
Hospital of the University of Pennsylvania	Benjamin Jackson	32
Duke Medical Center	Tony Smith	31
Medical College of Wisconsin	Eric Hohenwalter	29
Medstar Georgetown	James Spies	29
University of Pittsburgh Medical Center	Eric Hager	25
Ronald Reagan UCLA Medical Center	John Moriarty	25
Northshore University, Manhasset	Eric Gandras	23
Florida Hospital	Francisco Contreras	21
Spartanburg Regional Medical Center	Brian Baghdady	21
Albany Medical Center	Gary Siskin	20
Yale New Haven Hospital	C. Ochoa Chaar	20
Carle Heart and Vascular Institute	Jeremy Hogg	17
Overlook Medical Center	Clifford Sales	17
Rhode Island Hospital/Miriam	Gregory Soares	16
Carolinas Medical Center	Mark Lessne	16
Mount Sinai Hospital	Robert Lookstein	16
University of Minnesota	Michael Rosenberg	14
St. Mary's Medical Center	Lawrence Lottenberg	14
University of Miami, Jackson Health System	Issam Kably	13
Harbor–UCLA Medical Center	Anton Mlikotic	11
Massachusetts General Hospital	Omar Zurkiya	11
University Health/LSU	Chaitanya Ahuja	10
Tallahassee Memorial Hospital	Robert Brumberg	10
University Hospital/SUNY	Michael Costanza	9
Inova Fairfax Hospital	Alain Drooz	9
Cleveland Clinic	Karunakaravel Karuppasamy	8
Fairfield Medical Center	Krishna Mannava	8
Hackensack University Medical Center	Gregory Simonian	7
Oregon Health & Science University	John Kaufman	7
UT Southwestern Medical Center	Girish Kumar	6
New York– Presbyterian/Weill Cornell Medical Center	David Trost	5
University of Arkansas for Medical Sciences	Lewis Lyons	5
Atrium Health Wake Forest Baptist Health Medical Center	Michael Miller	5
University of Oklahoma-Tulsa	Rafael Malgor	5

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APPENDIX 1 (online only). Continued.

Site name	Principal investigator	Patients enrolled, No.
Boston Medical Center	Jeffrey Kalish	4
Palo Alto Veterans Affairs	Rajesh Shah	3
St. Louis University	Adam Fang	2
The Heart Institute Largo	Merrill Krolick	2
William Beaumont Hospital	Jeremy Handel	1
University of California, San Diego, Medical Center[a]	Jeet Minocha	0
Total	–	1429

[a]Enrollment closed before any patients were enrolled.

APPENDIX 2 (online only).

Protocol for evaluations at baseline and subsequent visits

The following tests and procedures are performed at time points shown.

Baseline visit.

- Demographic data
- Past medical history and comorbidities (eg, cancer, hypertension, known hypercoagulability, coronary disease, diabetes).
- Physical examination: body mass index as determined from height and weight measurements, blood pressure, heart rate, lower extremity (LE) swelling status, and clinical, etiologic, anatomic, and pathophysiologic (CEAP) class must be completed prior to index procedure.
- Concomitant medication: All anticoagulant and antiplatelet medications will be collected.
- Laboratory evaluations: hematology (eg, complete blood count and platelets), chemistry (eg, serum creatinine), and coagulation panel must be completed within 1 month (ie, 30 days) preprocedure.
- Radiological imaging:
  - Preplacement digital image(s), either (a) or (b)
    a. Inferior vena cavagram image(s) obtained during the implantation procedure before inferior vena cava (IVC) filter placement, optimally allowing a demonstration of the following:
       i. The location of renal vein(s)
       ii. The anteroposterior (AP) transverse diameter of the IVC (at the level of subsequently placed filter)
       iii. The presence or absence of IVC thrombus/embolus
    b. Correlative intravascular ultrasound (IVUS) image(s): Axial caval images at the level of renal veins, at the level of planned vena cava filter (VCF) placement, and at the level of clot (if applicable and appropriate).

Index procedure. The instructions for use, which contain the product safety, storage, design, deliverability, and sizing specifications, should be referenced before the use of any of the IVC filter brands included in the study and strict compliance must be maintained during this clinical investigation.

The procedure will be completed according to the operating physician's standard practice in an angiography suite or appropriately equipped operating room or intensive care unit. The procedure time will be recorded from the time the venotomy is started until the delivery sheath is ready for removal. Patients may have an IVC filter placed at bedside, in which case an IVUS may be performed instead of a venogram.

The following tests and procedures are performed during or immediately after the procedure:

- Radiographic imaging
  - Postplacement digital images, either (a) or (b)
    a. Either (i) or (ii):
       i. On-table digital radiographs of the abdomen, centered on VCF (maximum magnification that allows identification of the inferior endplate of the L1 lumbar vertebral body and VCF's relationship to it), AP and lateral projections, or
       ii. If digital subtraction angiography (DSA) runs are obtained following VCF placement, an unsubtracted early (noncontrast) image from each run (AP and lateral) may be submitted. If only an AP run is obtained, a lateral on-table digital radiograph as described previously should also be obtained.
    b. IVUS images
       i. An axial caval image at the cephalad aspect of the VCF.
       ii. An axial caval image at the level of the base of the VCF (point of contact of majority of legs/struts).
- Adverse event (AE) monitoring
- Clinical utility measures:
  - Procedure time (minutes).
  - Radiographic measures (fluoroscopic time, others if available [kerma (dose) area product, cumulative dose]).
  - Concomitant medication: All anticoagulant and antiplatelet medications will be collected.

Treatment failures. If a product malfunction occurs, detailed data on complications and their management will be collected and reported. Failure to implant the IVC filter will be recorded on the electronic case report form

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(eCRF) as a treatment failure. In the event of a failure to implant the IVC filter, each site will follow its standard of care procedures and/or use other commercially available products to ensure the safety of the patients. Patients will be followed by the study for 1 month after failure for AE monitoring. Treatment failures will be reported by the Contract Research Organization to the appropriate IVC filter brand manufacturer.

Postprocedure care. The procedure is considered completed once all the delivery material, including the catheter sheath introducer, has been removed. If thereafter a catheter sheath introducer is reinserted, it should be considered a repeat intervention. If the patient leaves the operating room or interventional suite with the catheter sheath introducer in place, the moment the patient is transferred from the procedure table after the procedure is considered the end of the procedure.

Laboratory evaluation. Postprocedure laboratory tests are not applicable to this trial.

Discharge. All patients will undergo a discharge assessment as defined by the schedule of measurements (Supplementary Table, online only) in addition to the standard of care procedures at each participating site and should include the following:

- Physical examination (weight, blood pressure, heart rate, LE swelling status, and CEAP class).
- Concomitant medication: all anticoagulant and antiplatelet medications will be collected.
- AE monitoring: If a new deep vein thrombosis (DVT) is diagnosed, LE US (and/or a contrast-enhanced chest computed tomography scan) will be collected, if obtained for clinical reasons.
- Clinical utility measures (eg, postindex procedural length of hospital stay [days] and length of intensive care unit stay [hours]).

Follow-up post discharge. Patients are followed until 1 month after successful retrieval of the VCF, or until study termination after 24 months of follow-up. Patients will have follow-up visits at 3 months, 6 months (telephone), 12 months, 18 months (telephone), and 24 months after the procedure. This should coincide with standard of care visits. Every effort should be made to ensure the required in-person visits are completed as designed, since imaging follow-up is so important to this study. However, if the alternative is that there would be no data for the follow-up visit, telephone follow-up is permitted for any visit to allow AE and other important data to be captured.

Follow-up assessments. The following postprocedure assessments will be performed at each in-person follow-up visit:

- Physical examination (blood pressure and heart rate).
- Concomitant medication: all anticoagulant and antiplatelet medications will be collected.
- AE monitoring (both in-person and telephone visits): if a diagnosis of new DVT is made, LE US (and/or contrast-enhanced chest CT scan) will be collected, if obtained for clinical reasons.
- Radiological imaging:
  - Three month (day 90) ± 15 days (images required by study), either (i) or (ii):
    i. Digital abdominal radiographs of the abdomen, centered on the VCF (maximum magnification that allows identification of the inferior endplate of the L1 lumbar vertebral body and the VCF's relationship to it), AP, and lateral projections, optimally correlating to those images obtained immediately after VCF placement, or
    ii. If the noncontrast images from the post-filter-placement DSA runs were submitted, images that correlate as closely as possible in magnification and centering to that of those images should be obtained.

12 months (day 365) ± 30 to 60 days (images required by study)

- CT tomogram from ≥5 cm above the IVC filter to ≥ 5 cm below the filter.
- Abdominal CT scan with intravenous contrast, with contiguous ≤5 mm axial sections obtained from ≥5 cm above the VCF to ≥5 cm below the VCF.
- Noncontrast imaging permitted if a CT scan with contrast is not possible.

24 months (day 730) ± 30 days (images required by study)

- CT tomogram from ≥5 cm above the IVC filter to ≥5 cm below the filter.
- Abdominal CT scan with intravenous contrast, with contiguous ≤5 mm axial sections obtained from ≥5 cm above the VCF to ≥5 cm below VCF.

Filter retrieval assessments. IVC filter retrieval can be attempted at any time during the course of the study. The following information will be collected regardless of success or failure of retrieval:

- Indication for retrieval
- Attempted retrieval
- Successful retrieval
- Failed retrieval
- Complications associated with filter retrieval
- Reasons for failed retrieval
- Method used for filter retrieval
- Images at filter retrieval
  - Preremoval digital images.
- AP and lateral vena cavagram DSA images should be obtained immediately before VCF removal. Care should be taken to use imaging factors (eg, centering and magnification) that correlate with those obtained immediately after VCF placement).
  - Postremoval digital images.

One month after vcf retrieval visit. If the IVC filter is removed, patients will be evaluated 1 month after retrieval. The following assessments will be performed:

- Physical examination (blood pressure and heart rate).
- Concomitant medication: All anticoagulant and antiplatelet medications will be collected.
- AE monitoring.

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Supplementary Table (online only). Time and event schedule of measurements

Variable	Baseline or procedure	Discharge	After discharge[a,b] 3 Months ± 15 days	6 Months ± 30 days	12 Months ± 30-60 days	18 Months ± 30 days	24 Months ± 30 days	Retrieval	1 Month ±15 days after retrieval[c]
Informed consent	X[d]	–	–	–	–	–	–	–	–
Eligibility	X[d]	–	–	–	–	–	–	–	–
Medical history	X[d]	–	–	–	–	–	–	–	–
Physical examination	X[d]	X	X	–	X	–	X	–	X
Procedure and filter information	X	–	–	–	–	–	–	X	–
Clinical utility measures	X[e]	–	–	–	–	–	–	–	–
Anticoagulant and antiplatelet medication	X[d]	X	X	X	X	X	X	X	X
Laboratory tests[f]	X[g]	–	–	–	–	–	–	–	–
Imaging									
Venography	X[h]	–	–	–	–	–	–	X	–
Contrast-enhanced abdominal CT scan[i]	–	–	–	–	X	–	X	–	–
Radiography (AP and lateral)	X	–	X	–	–	–	–	X	–
AE assessment[j]	–	X	X	X	X	X	X	X	X

AE, Adverse event; *AP*, anteroposterior; *CBC*, complete blood count; *CT*, computed tomography.
[a]Every effort should be made to ensure the required in-person visits were completed as designed because of the importance of imaging follow-up to the present study; however, if the alternative were the absence of data for that follow-up visit, telephone follow-up was permitted for any visit to allow for AE and other important data to be captured.
[b]The 6- and 18-month visits were scheduled as telephone visits.
[c]Patients without a VCF placed at the procedure were also to be followed up for 1 month after the procedure.
[d]Before any study-related procedure and within 6 weeks before the index procedure.
[e]Included length of hospital stay, length of intensive care unit stay, and index procedure time.
[f]Complete blood count, platelet count, serum creatinine, and coagulation panel.
[g]Laboratory tests must have been performed within 1 month before the procedure.
[h]For patients with an inferior VCF placed at bedside, intravascular ultrasound was allowed instead of venography.
[i]Non-contrast-enhanced imaging is permitted if contrast-enhanced CT is not possible.
[j]All device-related AEs were expected to have appropriate imaging studies available regardless of the imaging schedule.

APPENDIX 3 (online only).

End points

Primary safety end point. The primary safety end point is a composite end point that includes the following:

- Freedom from clinically significant perforation (confirmed by imaging; it is expected that the majority of clinically significant perforations will be confirmed by computed tomography [CT], although it may also be noted on abdominal radiography or during venography) after successful vena cava filter (VCF) placement (protrusion of filter legs through the wall of the IVC causing hemorrhage or hematoma or touching, impressing, or perforating another organ [eg, liver, bowel, aorta, psoas muscle, vertebral body, lymph nodes] or that triggers the decision to remove the filter, resulting in an attempt to remove the IVC filter or requiring other intervention) within first 12 months;
- Freedom from VCF embolization (movement of the filter or its components to a distant anatomic site completely out of the target zone after successful VCF placement, confirmed by imaging; it is expected the majority will be confirmed by CT, although it may also be noted on chest radiography or other modality) within the first 12 months;
- Freedom from caval thrombotic occlusion (presence of an occluding thrombus in the IVC filter after insertion

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and documented by ultrasound, CT, magnetic resonance [MR] imaging, venography, or autopsy; this may be symptomatic or asymptomatic after successful VCF placement) within the first 12 months;
- Freedom from new deep vein thrombosis (DVT; defined as lower extremity DVT that is confirmed present where it had not been present previously and that occurs after the placement of the VCF) within the first 12 months; and,
- Freedom from serious adverse events (AEs) within the perioperative period.

Primary effectiveness end point. The primary effectiveness end point was a composite end point at 12 months with the VCF filter in situ or 1-month post-retrieval (whichever comes first) that included the following:
- Procedural and technical success (deployment of the initial VCF such that the VCF is judged suitable for mechanical protection against pulmonary embolism [PE], and placement of a second VCF to address any anatomic variation without clinically significant perforation, VCF embolization, or insertion problems). Insertion problems are defined as (1) VCF or deployment system, such as incomplete filter opening; (2) clinically significant filter tilt >15° from the IVC axis (eg, non-self-centering filters); (3) misplacement of the filter outside the infrarenal IVC when the operator's intent is to place the VCF in the infrarenal IVC (eg, when a portion of the filter is within one iliac vein); (3) prolapse of VCF components; or (4) VCF malposition requiring surgical/endovascular removal.
- Freedom from clinically significant PE (ie, new symptomatic PE confirmed by appropriate imaging).

Secondary end points. Secondary end points include the following:
- Mechanical stability as defined by the absence of the following at the time of retrieval or at each follow-up:
  - Migration: evidence of cephalad movement of the VCF >20 mm relative to fixed anatomic landmarks compared with at placement, as determined by radiography.
  - Migration: evidence of caudal migration of the VCF >20 mm relative to fixed anatomic landmarks compared with at placement, as determined by radiography.
  - Perforation: >5 mm outside the apparent cava wall as determined by CT or perforation of adjacent viscera or a major vessel.
  - VCF fracture: any loss of a filter's structural integrity (ie, breakage or separation) documented by imaging or autopsy.
  - VCF embolization: postdeployment movement of the filter or its components to a distant anatomic site completely out of the target zone.
- Procedure-related complications, in the judgment of the principal investigator, at 3 months.
- Major AEs (composite and individual components) defined as death, PE, caval thrombotic occlusion, DVT, clinically significant perforation, retroperitoneal hematoma, or adjacent organ penetration (eg, bowel, spinal cord, aorta) at 3 months, 6 months, 12 months, 18 months, and 24 months.
- VCF tilting >15° at any time point as determined by appropriate imaging (note: this will not be considered an AE).
- Filter retrieval at any time.
  - Attempted retrieval
  - Successful retrieval
  - Failed retrieval
  - Percentage of retrieval success
  - Complications associated with filter retrieval
  - Reasons for failed retrieval

The analyses for the clinical assessment end points will be performed using the intent-to-treat population.

The clinical events committee adjudicated the following events: PE, caval thrombotic occlusion, DVT, clinically significant perforation, retroperitoneal hematoma, adjacent organ penetration (eg, bowel, spinal cord, aorta), and unanticipated adverse device effects.

APPENDIX 4 (online only).

Statistical methods

Demographics and comorbidities at enrollment were tabulated and summarized with descriptive statistics including counts, means, standard deviation (SD), minimum and maximum for continuous variables, and counts and relative frequencies for categorical data. The descriptive statistics were presented overall (for patients with a vena cava filter [VCF] placed) and by intended filter duration for 1421 patients who had a VCF placed. Incidence of venous thromboembolism at enrollment was summarized using counts of combinations of history and/or current pulmonary edema (PE), deep vein thrombosis, and caval thrombosis.

The null and alternative hypotheses for (composite) primary safety and primary effectiveness end points were as follows:

H_O: $P \leq 80\%$ vs H_A: $P > 80\%$ for primary safety

H_O: $P \leq 90$s H_A: $P > 90\%$ for primary effectiveness

where P is the proportion of patients free from the relevant events in the timeframes as described. The exact binomial test was employed to compare the observed proportions against a preplanned performance goal for primary safety and primary effectiveness, respectively. A lower limit of a one-sided 95% exact binomial confidence interval higher than 80% signified meeting the preplanned performance goal for primary safety; a lower limit of a one-sided 95% exact binomial confidence interval higher than 90% signified meeting the preplanned performance goal for primary effectiveness. The exact binomial method was employed to calculate the proportion of patients free from each of the component end

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points comprising the composite safety end point, the proportion of patients who were free from PE at 12 months postprocedure, and the proportion of patients with procedural/technical success. For each of the component end points, 95% confidence intervals for the proportions were also computed.

Univariate logistic regression models were used to assess the association between the incidence of outcomes (deep vein thrombosis and PE separately) at 12 months postprocedure and each of the following comorbidities: ambulatory status (mobile vs immobile), malignancy, stroke, and hypercoagulable disorder. The association between the incidence of the outcomes and the following was also assessed: intended VCF duration (permanent, temporary, undetermined), venous thromboembolism with contraindication to anticoagulation therapy (perioperative vs all other indications, prophylaxis vs all other indications, bleeding vs all other indications). There was no adjustment for multiple testing for primary safety and effectiveness end points.

Enrollment of 2100 patients (300 with VCFs from each of seven manufacturers) was planned. However, soon after study initiation, one filter was taken off the market. As such, only 7 of the planned 300 patients with those filters were enrolled. Also, as the study proceeded, it became clear that relatively few of two of the remaining six types of VCFs were being implanted. Despite extensive efforts by the investigators to enroll sites and physicians who placed those filters, relatively few (0-2 per month) of each were placed even months after the other four VCF-type groups had completed enrollment. Six months after enrollment with the other VCFs had been completed, analyses showed that had the enrollment trend for the other two filters continued, enrollment would have needed to remain open for another 8 years. Following the PRESERVE (Predicting the Safety and Effectiveness of Inferior Vena Cava Filters) Steering Committee and Data Safety Monitoring Board recommendations to close the trial for futility and discussion with the U.S. Food and Drug Administration, it was determined that the number of patients enrolled at study closure, while fewer than planned, was adequate to allow an acceptable power calculation, as described earlier.

All statistical analyses were conducted using SAS, version 9.4 (IBM Corp). A P value $<.05$ was considered statistically significant.

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