View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Elsevier - Publisher Connector

CLINICAL STUDY

The DENALI Trial: An Interim Analysis of a Prospective, Multicenter Study of the Denali Retrievable Inferior Vena Cava Filter

S. William Stavropoulos, MD, Ronald F. Sing, DO, Fakhir Elmasri, MD, Mitchell J. Silver, DO, Alex Powell, MD, Frank C. Lynch, MD, Ahmed Kamel Abdel Aal, MD, Alexandra J. Lansky, MD, Richard A. Settlage, MS, and Bart E. Muhs, MD, PhD, for the DENALI Trial Investigators

ABSTRACT

Purpose: To assess safety and effectiveness of a nitinol retrievable inferior vena cava (IVC) filter in patients who require caval interruption to protect against pulmonary embolism (PE).

Materials and Methods: Two hundred patients with temporary indications for an IVC filter were enrolled in this prospective, multicenter clinical study. Patients undergoing filter implantation were to be followed for 2 years or for 30 days after filter retrieval. At the time of the present interim report, all 200 patients had been enrolled in the study, and 160 had undergone a retrieval attempt or been followed to 6 months with their filter in place. Primary study endpoints included technical and clinical success of filter placement and retrieval. Patients were also evaluated for recurrent PE, new or worsening deep vein thrombosis, and filter migration, fracture, penetration, and tilt.

Results: Clinical success of placement was achieved in 94.5% of patients (172 of 182), with a one-sided lower limit of the 95% confidence interval of 90.1%. Technical success rate of filter placement was 99.5%. Technical success rate of retrieval was 97.3%; 108 filters were retrieved in 111 attempts. In two cases, the filter apex could not be engaged with a snare, and one device was engaged but could not be removed. Filter retrievals occurred at a mean indwell time of 165 days (range, 5–632 d). There were no instances of filter fracture, migration, or tilt greater than 15° at the time of retrieval or 6-month follow-up.

Conclusions: In this interim report, the nitinol retrievable IVC filter provided protection against pulmonary embolism, and the device could be retrieved with a low rate of complications.

ABBREVIATIONS

AE = adverse event, AP = anterior–posterior, CEC = clinical events committee, CI = confidence interval, CSP = clinical success of filter placement, DVT = deep vein thrombosis, FDA = Food and Drug Administration, ITT = intent to treat, IVC = inferior vena cava, PE = pulmonary embolism

From the Division of Interventional Radiology, Department of Radiology (S.W.S.), Perelman School of Medicine at the University of Pennsylvania, 1 Silverstein, 3400 Spruce St., Philadelphia, PA 19104; Division Surgical Critical Care (R.F.S.), Carolina's Medical Center, Charlotte, North Carolina; Division of Interventional Radiology (F.E.), Lakeland Regional Medical Center, Lakeland, Florida; Division of Interventional Cardiology and Peripheral Vascular Disease (M.J.S.), Ohio Health Heart and Vascular, Riverside Methodist Hospital, Columbus, Ohio; Department of Radiology, Division of Interventional Radiology (A.P.), Baptist Cardiac and Vascular Institute, Miami, Florida; Division of Interventional Radiology (F.C.L.), Penn State Milton S. Hershey Medical Center, Hershey, Pennsylvania; Division of Interventional Radiology, Department of Radiology (A.K.A.A.), University of Alabama at Birmingham Medical Center, Birmingham, Alabama; Division of Cardiovascular Medicine (A.L.) and Section of Vascular Surgery, Department of Surgery (B.M.), Yale University School of Medicine, New Haven, Connecticut; and C.R. Bard (R.A.S.), Murray Hill, New Jersey. Received May 1, 2014; final revision received and accepted July 1, 2014. **Address correspondence to** S.W.S.; E-mail: william.stavropoulos@uphs.upenn.edu

This study was funded by C.R. Bard (Murray Hill, New Jersey). S.W.S. is a paid consultant for C.R. Bard and Cook (Bloomington, Indiana) and has received research funding from W.L. Gore and Associates (Flagstaff, Arizona). R.F.S. is a paid consultant for C.R. Bard. A.K.A.A. is a paid consultant for St. Jude Medical (Saint Paul, Minnesota), Bard Peripheral Vascular (Tempe, Arizona), and Baxter (Deerfield, Illinois). R.A.S. is a salaried employee of C.R. Bard. B.M. is a paid consultant for Aptus (Sunnyvale, California), Cook, Medtronic (Minneapolis, Minnesota), Endologix (Irvine, California), and C.R. Bard. None of the other authors have identified a conflict of interest.

Table E1 is available online at *www.jvir.org*.

© SIR, 2014. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

J Vasc Interv Radiol 2014; 25:1497–1505

http://dx.doi.org/10.1016/j.jvir.2014.07.001

Management of venous thromboembolic disease, including deep vein thrombosis (DVT) and pulmonary embolism (PE), creates a burden to the health care system that results in significant patient morbidity and mortality rates approaching 300,000 per year from PE. The associated costs of treating venous thromboembolic disease have increased to more than $7.5 billion per year in the United States (1,2). Pharmacologic management with anticoagulant agents such as low molecular weight heparin or vitamin K antagonists (eg, warfarin) is standard therapy for venous thromboembolic disease. However, for some patients, anticoagulation may be contraindicated or ineffective or can result in bleeding complications that require discontinuation of therapy. Permanent IVC filters have been shown to reduce the initial risk of PE and provide long-term protection, but the effects of long indwell times increase the risk of DVT and other complications, including caval obstruction, filter fracture, or migration (3–7).

Retrievable IVC filters were developed to provide protection from PE for patients who temporarily need an IVC filter because they can be removed when no longer needed, potentially eliminating the long-term risks of a permanent filter. The United States Food and Drug Administration (FDA) initially changed the indications for use of three previously approved permanent filters to allow for retrieval (8,9), which was followed by the development of a new generation of optional vena cava filters designed with the option for retrieval when the period of increased risk for PE has passed or contraindications to anticoagulation are resolved (10–17).

The present study was designed to evaluate placement and retrieval of a new retrievable IVC filter in patients with documented DVT, PE, or temporary increased risk of PE requiring filter placement.

MATERIALS AND METHODS

The DENALI trial is a prospective, multicenter, nonrandomized, single-arm study conducted at 21 centers in the United States. The protocol was approved by the institutional review board or ethics committee at each enrolling institution, and all study procedures were conducted in accordance with the guidelines of good clinical practice and applicable FDA regulations. The DENALI trial was registered on clinicaltrials.gov (ID code NCT01305564) before the start of the study.

Patients eligible for inclusion were at least 21 years old, had documented evidence of DVT or PE at placement, or were at risk of PE with a clinical indication for IVC filter placement as a result of contraindication to or failure of anticoagulation (18). In addition, patients had an IVC diameter of no more than 28 mm and had adequate venous anatomy to allow placement and retrieval of an IVC filter. Women were required to have a negative pregnancy test, be surgically sterile, or be postmenopausal before enrollment. Patients were excluded from the trial if they had previously received an IVC filter; had a duplicated or left-sided IVC; or had an anatomic anomaly that the operator believed might impact the insertion, indwell stability, or retrieval of the filter. In addition, patients were excluded if they exhibited signs of renal failure (serum creatinine level $>$ 2.0 mg/dL) and were undergoing dialysis, had an uncorrectable bleeding diathesis, had a life expectancy of less than 25 months, or had a known allergy or sensitivity to study materials (eg, nickel or titanium) or iodinated contrast media that was not amenable to treatment with steroid agents, antihistamine agents, or other medications before device implantation.

Study Endpoints

The primary objectives of the study were to assess the technical and clinical success of filter placement and retrieval. Technical success of filter placement was defined as placement of a filter that provided sufficient mechanical interruption in the vena cava to prevent PE. Technical success of filter retrieval was achieved if the filter was retrieved completely intact without immediate complications. Clinical success of filter placement (CSP) was defined as freedom from subsequent PE, filter migration, vena cava occlusion, filter- or procedure-related death, adverse events associated with filter placement, or failure of filter placement. As per Society of Interventional Radiology (SIR) guidelines, clinical success was achieved if the lower bound of the 95% confidence interval (CI) was greater than 80%. Clinical success of filter retrieval was achieved if the filter was retrieved without complications that required intervention (18,19).

In addition, the overall clinical experience was evaluated by assessing recurrent PE to 6 months after filter placement or 1 month following filter retrieval, new or worsening DVT to 6 months, and the rate of filter complications such as migration, fracture, penetration, or tilt. Recurrent PE was defined as any PE occurring after filter placement documented by pulmonary arteriography, cross-sectional imaging, altered ventilation/perfusion lung scan, or autopsy. Worsening DVT was defined as an extension of DVT to a new venous segment in patients with documented evidence of DVT at baseline. Filter migration was defined as a change in filter position of more than 2 cm (cranial or caudal direction) compared with the baseline deployed position assessed by plain-film radiography, computed tomography (CT), or venography. Filter fracture was defined as a loss of structural integrity of the filter (ie, breakage or separation of filter components) documented by imaging or autopsy. Filter penetration was defined as penetration of a filter leg or arm more than 3 mm outside the vena cava wall as measured by CT, ultrasound (US), or venography, or noted during autopsy. Filter tilt was defined as greater than 15° tilt of the filter off the IVC axis. All

adverse events, defined as any untoward medical occurrence, were reported by the study investigators and reviewed and adjudicated by an independent clinical events committee (CEC).

Study Device

Patients who met the criteria for study enrollment received a retrievable vena cava filter (Denali Retrievable Vena Cava Filter, Bard Peripheral Vascular, Tempe, AZ) designed to mechanically prevent PE (Fig 1). The nitinol IVC filter consisted of 12 shape-memory struts laser-cut from a single piece of nitinol (nickel-titanium alloy). The struts were designed to form two levels of embolic filtration: six filter legs provided the lower level of filtration and six filter arms provided the upper level. The filter legs were designed with cranial and caudal anchors to resist superior and inferior migration and, if needed, provide permanent attachment to the vena cava wall; however, the legs were also designed to limit penetration through the wall of the vena cava, allowing percutaneous removal if the filter was no longer needed. The filter was implanted percutaneously through a femoral or jugular vein approach, and the device was intended for use in an IVC as large as 28 mm in diameter. The delivery system was composed of an introducer sheath, dilator, and preloaded filter with pusher. The sheath was 55 cm long with an 8.4-F inner diameter, and the dilator was compatible with an 0.035-inch wire.

Filter Placement, Filter Retrieval, and Imaging Analyses

Patients referred for retrievable vena cava filter placement were screened for inclusion in the study, completed written informed consent to participate in the trial, and received preprocedural imaging assessments. US screening of the internal jugular veins was performed before filter placement to assess potential pathways for filter retrieval. In addition, bilateral lower-extremity US examinations were performed to assess the presence of lower-extremity DVT.

A patient was considered enrolled in the study when the filter introducer sheath was inserted. An angiogram of the vena cava was obtained before filter deployment, with a known reference marker in the field of view to assess the vena cava diameter. The filter was advanced through the sheath by using the pusher, and then the pusher was used to fix the filter in place while it was unsheathed and deployed into the IVC. After device placement, anterior–posterior (AP) and lateral digital subtraction angiograms of the vena cava were obtained.

Phone consultations were performed at 3, 12, 18, and 24 months after the procedure to assess whether the filter should be retrieved, to document the recurrence of PE or DVT, and to determine whether the patient experienced filter-related complications. At 6 months after placement, a follow-up clinic visit was required. A physical examination, a lower-extremity US examination to assess the presence or change in lower-extremity DVT versus baseline, and plain radiographic film imaging of the abdomen to evaluate IVC filter position were performed.

If a patient was no longer at risk of PE requiring IVC filtration or could tolerate anticoagulation, the patient was referred for filter removal. Before attempted filter retrieval, AP and lateral digital subtraction angiograms of the vena cava were obtained. The filter retrievals were performed by using a dual-sheath technique with a 9-F, 70-cm Flexor sheath (Cook, Bloomington, Indiana) inside a 12-F, 40-cm Flexor sheath (Cook). A loop snare was used to engage the filter hook and remove the filter. An angiogram of the vena cava was obtained after retrieval. Patients were evaluated in the clinic at 30 days after retrieval to assess overall health status, the recurrence of PE or DVT, and filter-related complications based on SIR clinical practice guidelines (20). All IVC filter insertion, 6-month follow-up, and retrieval images were submitted to the Yale Angiographic Core Laboratory (Yale University, New Haven, Connecticut) for independent review and analysis. Each image set was reviewed by the staff radiologist and the laboratory director.

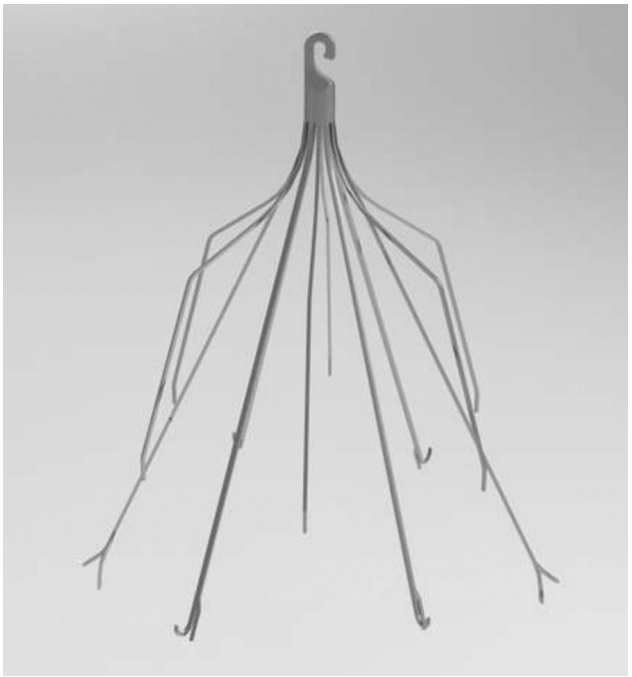

Figure 1. Image of the Denali IVC filter.

Statistical Analysis

SIR reporting standards were used to evaluate the IVC filters (21,22). This study included 200 patients implanted with a Denali filter. The sample size was based on plans to analyze data on the first 65 patients followed to 6 months after filter placement and 50 patients completing the 30-day postretrieval visit. The inclusion of 65 patients ensured that, if the observed rate of CSP was a minimum of 89%, the lower, one-sided

95% confidence bound would be no lower than 80%. All subjects enrolled in the study will be followed to 24 months or 30 days after retrieval. All endpoints were analyzed per patient and on an intent-to-treat (ITT) basis. The ITT population included all patients followed for at least 6 months or followed for at least 30 days after filter retrieval. Demographic and baseline characteristics (eg, sex and age) were summarized, summary statistics for categoric variables include frequency counts and percentages, and means and standard deviations are provided for continuous variables. Primary endpoints were summarized descriptively and reported as estimated proportions with associated 95% CIs. The composite coprimary endpoint of CSP was reported as the proportion of the ITT population with CSP with a one-sided lower 95% CI. If the lower 95% CI for the observed clinical success rate was greater than or equal to 80%, it was concluded that the endpoint was successfully achieved. The rate was selected based on a combined total of 20% representing the five elements suggested by SIR that contribute to clinical failure: technical failure (3%), recurrent PE (5%), filter embolization (< 1%), IVC occlusion (10%), insertion-related complications (1%), and death (< 1%) (18,19).

RESULTS

Pretreatment Demographics and Patient Characteristics

Between June 23, 2011, and May 14, 2013, 200 patients underwent IVC filter placement: 63% (n = 126) were male and 37% (n = 74) female, with an overall mean age of 56.6 years (range, 18–89 y). One hundred twenty patients (60%) were diagnosed with DVT or PE at the time of IVC filter placement, and 80 (40%) were at temporarily increased risk of PE but did not have active thromboembolic disease at the time of filter placement. Primary thromboembolic risk factors for temporary filter placement included surgery (43.5%), trauma (20.5%), and hypercoagulopathy (22%; Table 1).

Table 1. Baseline Patient Characteristics, Medications, History, and Disease Status

Variable	All Patients (N = 200)	Retrieved Filter (n = 108)
Sex, M/F (%)		
Male	126 (63)	69 (63.9)
Female	74 (37)	39 (36.1)
Mean age (y)	56.6 ± 15.63	56.4 ± 14.88
Weight (kg)	97.4 ± 26.00	99.2 ± 26.05
BMI (kg/m^2)	32.9 ± 9.07	33.8 ± 9.44
BMI > 30	119 (59.5)	68 (63.0)
Race, n (%)		
White	164 (82.0)	93 (86.1)
Black	31 (15.5)	12 (11.1)
Native American	1 (0.5)	0
Other	4 (2.0)	3 (2.8)
TED status		
Contraindication of anticoagulation	66 (33.0)	35 (32.4)
Complication of anticoagulation	9 (4.5)	2 (1.9)
Failure of anticoagulation	20 (10.0)	4 (3.7)
TED in the absence of the above	23 (11.0)	9 (8.3)
No TED (prophylactic)	80 (40.0)	58 (53.7)
Primary thrombotic risk factor for filter placement		
Surgery	87 (43.5)	–
Trauma	41 (20.5)	–
Hypercoagulopathy	44 (22.0)	–
Cancer	10 (5.0)	–
Stroke (past 6 mo)	3 (1.5)	–
Other	15 (7.5)	–

Values presented as means ± SD where applicable. Values in parentheses are percentages.
BMI = body mass index, TED = thrombotic disease.

Filter Placement

The mean procedure time for filter placement was 17.8 minutes ± 10.3 (range, 3–90 min), and the mean fluoroscopy time was 3.6 minutes ± 3.1 (range, 1–32 min; Table 2). The most common vascular access site used for placement was the right common femoral vein (55%), followed by the right internal jugular vein (35%). The mean IVC diameter at the site of placement was 22.2 mm ± 3.1 (range, 12.7–27.8 mm).

Postprocedure Follow-up

The disposition of the 200 patients in the DENALI study is outlined in Figure 2. Filters were retrieved in 108 patients, and 24 patients were removed from the study before completion; of these, 14 patients died from causes unrelated to the IVC filter, one withdrew consent to participate in the study, seven were lost to follow-up, and two were discontinued from the study at the discretion of the investigator. Forty-nine patients still had an indication for the filter to remain in situ during their 6-month follow-up clinic visit. Filters remained implanted in 92 patients.

Technical and Clinical Success of Placement

Technical success of filter placement was achieved in 99.5% (n = 199) of the patients enrolled in the trial (Table 2). One filter was introduced but could not be deployed, and a second filter was successfully deployed in the patient without clinical sequelae. In addition, a successfully deployed device was moved inadvertently with a guide wire during postprocedural imaging; this was not considered a technical failure, and the filter was immediately retrieved and replaced with a second filter at

Table 2. Filter Placement and Retrieval Technical Success and Procedural Data

Variable	All Patients (N = 200)	Retrieved Filters (n = 108)
Placement procedural data		
Technical success of placement*	199 (99.5)	–
95% CI	97.2–100	–
Placement time (min)		
Mean ± SD	17.8 ± 10.32	–
Median	17	–
Range	3–90	–
Fluoroscopy time (min)		
Mean ± SD	3.6 ± 3.14	–
Median	3.0	–
Range	1–32	–
IVC diameter (mm)†		
Mean ± SD	22.2 ± 3.10	–
Median	22.5	–
Range	12.7–27.8	–
Vascular access sites		
Right common femoral vein	110 (55.0)	–
Right jugular vein	70 (35.0)	–
Left common femoral vein	18 (9.0)	–
Left jugular vein	2 (1.0)	–
Hospitalization status		
Inpatient	160 (80.0)	–
Outpatient	40 (20.0)	–
Retrieval procedural data		
Technical success of retrieval‡	–	108 (97.3)
95% CI	–	92.3–99.4
Indwell time (d)		
Mean ± SD	–	165 ± 113.9
Median	–	147
Range	–	5–632
Retrieval time (min)§		
Mean ± SD	–	21.3 ± 15.65
Median	–	20
Range	–	4–118
Fluoroscopy time (min)		
Mean ± SD	–	6.4 ± 8.61
Median	–	4.0
Range	–	1–69
IVC diameter (mm)‖		
Mean ± SD	–	22.0 ± 2.98
Median	–	21.9
Range	–	15.6–27.4
Filter retrieval access site		
Right jugular vein	–	108 (100)

Values in parentheses are percentages.
CI = confidence interval, IVC = inferior vena cava, SD = standard deviation.
*One filter was introduced but could not be deployed. A second filter was successfully deployed in the patient without clinical sequelae.
†Quantitatively measured by the core laboratory after filter placement.
‡One hundred eight of 111 retrieval attempts were successfully completed. In two cases, the operator was unable to engage the filter apex with a snare. One device was engaged with a snare, but could not be removed.
§For all successful retrievals (N = 108).
‖Quantitatively measured by the core laboratory after retrieval.

the discretion of the operator. CSP—ie, freedom from placement failure, complications associated with filter placement, subsequent PE, filter embolization, vena cava occlusion, or filter- or procedure-related death—was achieved in 94.5% of patients (172 of 182; 95% CI, 90.1%–97.3%) in the ITT population (Table 3). There were 11 events reported in 10 patients that impacted CSP, including three in patients with access-site pain and discomfort that did not lead to clinical sequelae (two with pain at the access site; one with a bruise and discomfort), six in patients with recurrent PE (one of whom also experienced caval occlusion), and one technical deployment failure (described earlier). There were no reported filter embolizations or filter- or procedure-related deaths. Per SIR guidelines, CSP was achieved if the lower bound of the 95% CI was greater than 80%. The lower bound of the 95% CI for the ITT group was 90.1%.

Filter Retrieval

Sixteen sites performed 114 screenings for possible filter retrieval in 111 patients. Vena cava angiograms revealed thrombus in three filters. These three patients were administered anticoagulation and returned for a second screening venogram that revealed no thrombus. Their filters were then removed successfully. One hundred eight of 111 retrieval attempts were successfully completed and three retrievals failed, resulting in a technical success rate of filter retrieval of 97.3%. In two cases, the investigator was unable to engage the filter apex with a snare; core laboratory measurements revealed that neither device tilted, migrated, or penetrated the caval wall. One additional device was engaged with a snare but could not be completely collapsed in to the sheath as a result of thrombus in the IVC, so the filter could not be removed. In these three cases, the filter was left in place as a permanent device. The clinical success rate of retrieval—ie, successful retrieval without complications—was 99.1% (107 of 108). Of the 108 successful retrievals, filters were retrieved intact in all cases. In one case, retrieval of the filter resulted in intimal injury with caval narrowing. The filter was removed intact, but the patient was hospitalized overnight for observation and required no further intervention. No DVT or IVC thrombus has developed in this patient.

The mean filter indwell time for the 108 successfully retrieved filters was 165.0 days ± 113.9 (median, 147 d; range, 5–632 d), with 39.8% of filters retrieved at later than 6 months (Fig 3). The mean retrieval procedure time was 21.3 minutes ± 15.7 (range, 4–118 min), and the mean fluoroscopy time for successful retrieval was 6.4 minutes ± 8.61 (range, 1–69 min; Table 2). The right internal jugular vein was used for all retrieval procedures. Fifty patients (46.3%) who underwent filter retrieval had an indication for filter placement involving active thromboembolic disease (ie, DVT and/or PE at the time of placement); 58 patients (53.7%) who had

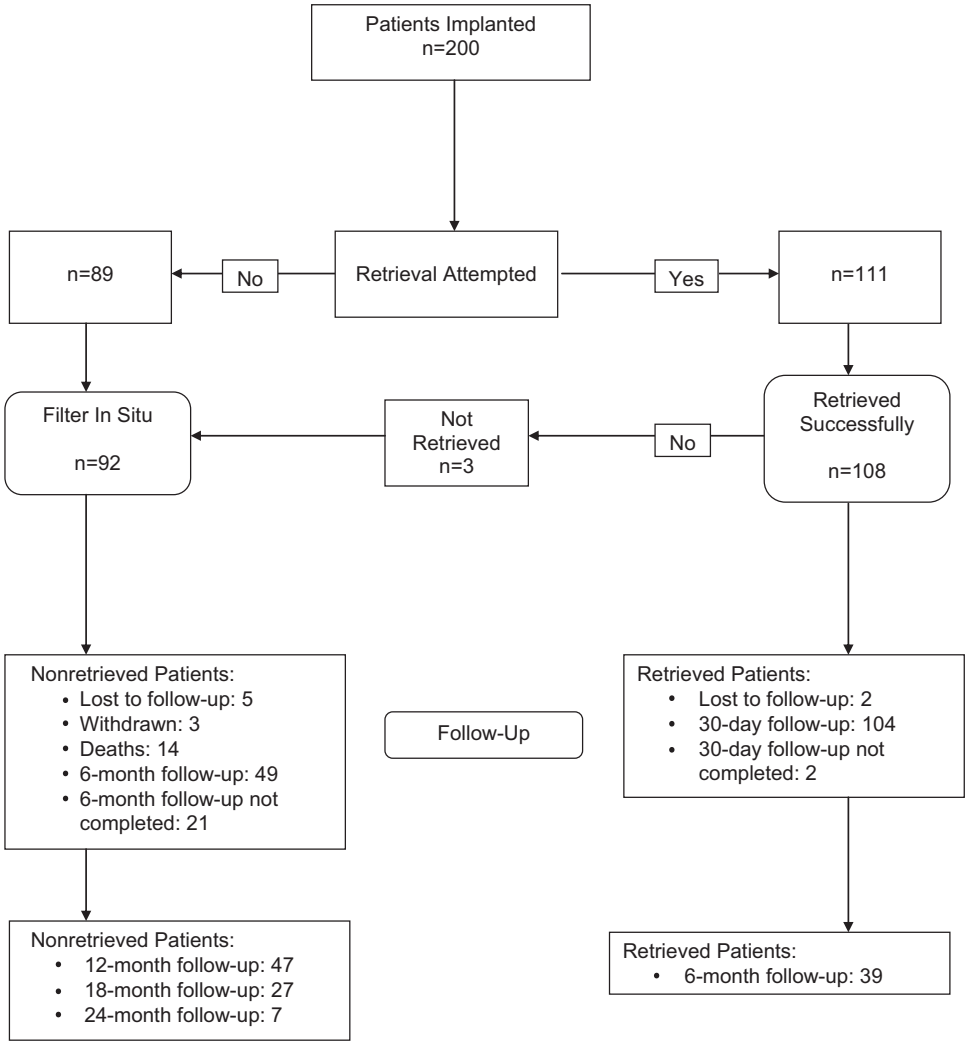

Figure 2. Disposition of the 200 patients in the Denali IVC filter trial.

filters retrieved were at risk of PE at the time of placement but had no active thromboembolic disease.

Overall Clinical Experience

The rates of recurrent PE, new or worsening DVT, filter fracture, migration (> 2 cm), penetration (> 3 mm), and tilt (> 15°) were evaluated and are presented in Table 4. The rate of recurrent PE was 3.0% (six of 200; 95% CI, 1.1%–6.4%). Five patients presented with small PEs located in the segmental and/or subsegmental vasculature; symptoms were not consistent with higher-risk PEs (eg, no signs of hypotension and/or signs of right ventricular dysfunction). One patient had PE associated with hypotension as well as right ventricular dysfunction along with an intractable hypercoagulable state possibly as a result of advanced malignancy; the patient subsequently died. New or worsening DVT was defined as an extension of existing DVT to a new venous segment in patients who had DVT at baseline, or new DVT in patients who did not exhibit signs at baseline (both determined by follow-up imaging). The rate of new or worsening DVT was 12.8% (95% CI, 8.3%–18.7%), including 26 instances of DVT in 23 patients, with 19 instances of new DVT and seven instances of worsening DVT. All reports of new DVT occurred in patients who had active thromboembolic disease at baseline, were considered to be in a hypercoagulable state, had experienced multiple-trauma injuries, or had lower-extremity orthopedic procedures.

There were no instances of IVC filter fracture, filter migration, or filter tilt greater than 15° in the DENALI trial. There were five instances (2.5%) of penetration of filter arms or legs more than 3 mm beyond the vena cava wall seen on venography (core laboratory–adjudicated): three instances noted at implantation and two at the time of filter retrieval. None of the reported penetrations were symptomatic, and the filter was subsequently retrieved or continued to be followed with no reported clinical sequelae.

Safety

A total of 148 patients had one or more adverse events (AEs) reported during the course of the study. An AE

was defined as an untoward medical occurrence regardless of the relationship to the study device or procedure. The independent CEC adjudicated all AEs and determined that 13 (6.5%) were possibly or definitely related to the procedure and nine (4.5%) were possibly or definitely related to the filter (**Table E1**, available online at *www.jvir.org*). Seventy-nine patients experienced serious AEs requiring inpatient medical care. The CEC determined that four (2.0%) were possibly or definitely related to the procedure and seven (3.5%) were possibly or definitely related to the filter. Fourteen patients died during the course of the study from

Table 3. Clinical Success of Filter Placement and Retrieval

Variable	Value
Placement success*	
Clinical success of placement†	172 (94.5)
95% CI	90.1–97.3
Recurrence of PE	6 (3.0)
Filter embolization	0
Vena cava occlusion‡	1 (1.0)
Filter/procedure-related death	0
Insertion adverse event	3 (1.5)
Technical failure	1 (1.0)
Retrieval success§	
Clinical success of retrieval	107 (99.1)
95% CI	94.9–100
Retrieval complications	
Required intervention	1 (1.0)

Values in parentheses are percentages.
CI = confidence interval, PE = pulmonary embolism.
*Clinical success of filter placement was defined as freedom from subsequent PE, filter embolization, vena cava occlusion, filter- or procedure-related death, adverse events associated with filter placement, or failure of filter placement.
†Interim intent-to-treat population consisted of 182 patients; 172 patients had clinical success of filter placement.
‡This patient was reported as a recurrent PE. There were 11 events in 10 patients.
§Successful technical retrieval of the filter without retrieval complications.

Table 4. Overall Clinical Experience

Variable	Incidence	95% CI
Recurrent PE*	6/200 (3.0)	1.1–6.4
DVT	23/179† (12.8)	8.3–18.7
New DVT‡	19/179 (10.6)	–
Worsening DVT§	7/179 (3.9)	–
Filter complications‖		
Filter fracture	0/179	0.0–2.0
Filter migration (> 2 cm)	0/179	0.0–2.0
Filter penetration (> 3 mm)	5/200 (2.5)	0.8–5.7
Penetration at placement	3/200 (1.5)	0.3–4.3
Penetration at retrieval¶	2/113 (1.8)	0.2–6.2
Tilt > 15°	0/200	0.0–1.8

CI = confidence interval, DVT = deep vein thrombosis, PE = pulmonary embolism.
*Clinical diagnosis of recurrent PE was confirmed by pulmonary arteriography, cross-sectional imaging, altered ventilation/perfusion lung scan, or at autopsy.
†All patients with imaging after baseline (n = 179).
‡New DVT, based on imaging, in patients who had no DVT at baseline.
§Extension of existing DVT, based on imaging, to a new venous segment in patients who had DVT at baseline.
‖Core laboratory evaluated all implant, retrieval, and 6-month images.
¶Rate of penetration based on 111 attempted retrievals and two cases in which the filter was screened for retrieval but an attempt was not made.

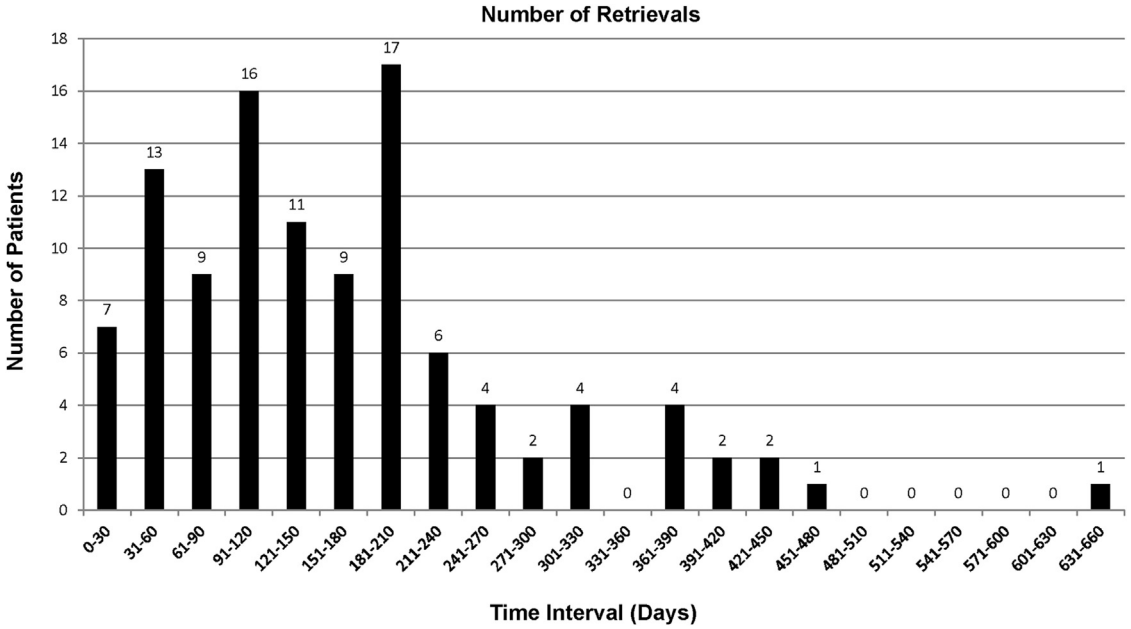

Figure 3. Dwell time for retrieved IVC filters.

preexisting or concomitant medical conditions adjudicated by the CEC as unrelated to the device or procedure.

DISCUSSION

In the present interim analysis of the 200 patients enrolled in the DENALI IVC filter trial, clinical success of filter placement was achieved in 94.5% of patients. The definition of clinical success in this trial was conservative, as three cases were classified as clinical failures based on the patients having self-limited pain at the access site after filter placement. The pain resolved in all three patients without treatment, and there was no access-site DVT in any of the three patients. Without these three patients included as cases of clinical failure, clinical success would have been achieved in 96.2% of patients. Six of the clinical failures were caused by PE. The PE rate of 3% in the DENALI trial was within the established threshold value of 5% (19). PE rates from 1% to 6% have been reported in similar IVC filter trials (11,14,15,17). Significantly, there were no instances of IVC filter fracture, migration, or filter tilt greater than 15°. There were 19 instances of new DVT (9.5%), which this also compares favorably with the findings of recent similar IVC filter clinical trials (11,14,15,17). The five instances of filter penetration in the trial (2.5%) were defined as penetration greater than 3 mm on venography. This definition was similar to those of other IVC filter trials, but can result in IVC wall "tenting" being overestimated as penetration or perforation. The more accurate CT-based grading system for IVC penetration, described by Oh et al (23), for filter penetration and perforation was not used in the present study. There were no instances of symptomatic filter strut penetration or perforation.

Of the 111 patients who underwent a filter retrieval attempt, 108 (97.3%) had their filter successfully retrieved. Two of the filters could not be retrieved because the investigator was unable to negotiate a snare around the hook of the filter. Other nonstandard filter retrieval techniques such as forceps retrieval or the loop-snare technique were not used. Review of the retrieval images by the core laboratory revealed that these two filters were not significantly tilted and the filter tips were not embedded in the wall of the IVC. The failure to engage the hook was believed by the investigator to be a result of AP angulation of the IVC. This AP angulation did not allow the hook of the filter to be snared, and both of these filters were left in place as permanent devices. There was one patient who had asymptomatic IVC narrowing after filter retrieval. The patient remained asymptomatic but was admitted overnight for observation. No other complications occurred as a result of filter retrieval.

A potentially clinically relevant finding of the DENALI trial was the long dwell times after which filters were retrieved. Mean indwell time of the retrieved filters was 165 days, and the maximum dwell time for a filter that was retrieved was 632 days. There were no retrieval failures related to incorporation of the filter struts in the wall of the IVC or the filter hook being embedded in the IVC. These are two of the most common causes of filter retrieval failures in currently used devices, and can increase in frequency the longer the filters are in place (24). The ability to retrieve IVC filters after long dwell times is a desirable quality for retrievable filters because it could potentially allow for a higher percentage of filters to be removed. An FDA communication in August 2010 (25) warned of the adverse events that could occur to patients with retrievable filters that are not removed. Implanting physicians were encouraged by the FDA to follow their patients closely and remove the filters when they are no longer needed for PE protection. Filters that can be removed after a prolonged period of time will potentially have the advantage of increasing the number of filters that can ultimately be removed. Although a retrievable filter with a long potential dwell time is advantageous, this is no substitute for close follow-up of all patients with IVC filters and removal of filters as soon as PE protection is no longer required.

Limitations to the present study exist. Although the DENALI trial was a prospective multicenter study, the nonrandomized single-arm design introduces some limitations. A potential for bias exists in any manufacturer-sponsored device trial. This is an interim analysis, and not all patients have been followed for 2 years, as will be the case when the study is concluded. However, the study was designed to enroll 200 patients, and all of them have been included in the present analysis. In addition, the follow-up is longer, and the number of patients included is greater, in this interim analysis than in many similar trials (11,14,15,17). As with other IVC filter studies, the PE rate could be underestimated in the present trial. This is because imaging for PE was done in only patients who had clinical symptoms that were suggestive of PE. PE imaging was not done in every patient, and additional patients with asymptomatic PEs may have gone undetected.

In the present interim analysis of the DENALI trial data, the Denali IVC filter has shown a high rate of clinical success with a low complication rate within the thresholds suggested by SIR, which compare favorably to data from similar clinical IVC filter trials (11,14,15,17,19). The ability to remove the filter after relatively prolonged dwell times shown in the present trial has the potential to increase filter retrieval rates as clinical use of this device increases.

ACKNOWLEDGMENTS

The following investigators and institutions participated in the DENALI trial: S. William Stavropoulos, MD

(principal investigator of the trial) and Mandeep Dagli, MD, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; Michael Darcy, MD, Washington University School of Medicine, St. Louis, Missouri; Bart Muhs, MD, Yale University School of Medicine, New Haven, Connecticut; Bruce Zwiebel, MD, Tampa General Hospital, Tampa, Florida; Pilar Bayona, MD, Cleveland Clinic Foundation, Cleveland, Ohio; Howard Cohen, MD, Doctors Hospital of Augusta, Augusta, Georgia; Scott Schultz, MD, North Memorial Hospital, Robbinsdale, Minnesota; Scott Resnick, MD, Northwestern Memorial Hospital, Chicago, Illinois; Ronald Sing, DO, Carolina HealthCare System, Charlotte, North Carolina; Fakhir Elmasri, MD, Lakeland Regional Medical Center, Lakeland, Florida; Alex Powell, MD, Baptist Cardiac and Vascular Institute, Miami, Florida; Frank Lynch, MD, Pennsylvania State Milton S. Hershey Medical Center, Hershey, Pennsylvania; Mitchell Silver, DO, MidOhio Cardiology and Vascular Consultants, Columbus, Ohio; Thuong Van Ha, MD, University of Chicago Medical Center, Chicago, Illinois; Nabeel Rana, MD, Heart Care Midwest/OSF Saint Francis Medical Center, Peoria, Illinois; Robert Spillane, MD, Hartford Hospital, Hartford, Connecticut; Danielle Bajakian, MD, Columbia University Medical Center, New York, New York; David Kay, MD, and Neil Goldstein, MD, St. Joseph's Hospital and Medical Center, Phoenix, Arizona; John Pigott, MD, Toledo Hospital, Toledo, Ohio; Alan Wladis, MD, Florida Hospital, Orlando, Florida; Ahmed Kamel Adel Aal, MD, University of Alabama at Birmingham Medical Center, Birmingham, Alabama; Daniel Komorowski, MD, Virginia Commonwealth University, Richmond, Virginia; and Zachary Collins, MD, University of Kansas Medical Center, Kansas City, Kansas.

REFERENCES

1. Raskob GE, Silverstein R, Bratzler DW, et al. Surveillance for deep vein thrombosis and pulmonary embolism. Recommendations from a national workshop. Am J Prevent Med 2010; 38(suppl):S502–S509.
2. Heit J. The epidemiology of venous thromboembolism in the community. Arterioscler Thromb Vasc Biol 2008; 28:370.
3. Hann CL, Streiff MB. The role of vena caval filters in the management of venous thromboembolism. Blood Rev 2005; 19:179–202.
4. The PREPIC Study Group. Eight-year follow-up of patients with permanent vena cava filters in the prevention of pulmonary embolism: the PREPIC (Prévention du Risque d'Embolie Pulmonaire par Interruption Cave) randomized study. Circulation 2005; 112:416–422.
5. Decousus H, Leizorovicz A, Parent F, et al, for the Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. New Engl J Med 1998; 338:409–415.
6. Williams R, Schenk W. A removable intracaval filter for prevention of pulmonary embolism: early experience with the use of the Eichelter catheter in patients. Surgery 1970; 68:999–1008.
7. Lynch FC. A method for following patients with retrievable inferior vena cava filters: results and lessons learned from the first 1,100 patient. J Vasc Interv Radiol 2011; 22:1507–1512.
8. Kaufman JA. Retrievable vena cava filters. Tech Vasc Interv Radiol 2004; 7:96–104.
9. Kaufman JA, Kinney TB, Streiff MB, et al. Guidelines for the use of retrievable and convertible vena cava filters: report from the Society of Interventional Radiology multidisciplinary consensus conference. J Vasc Interv Radiol 2006; 17:449–459.
10. Ziegler JW, Dietrich GJ, Cohen SA, et al. PROOF trial: protection from pulmonary embolism with the OptEase filter. J Vasc Interv Radiol 2008; 19:1165–1170.
11. Binkert CA, Drooz AT, Caridi JG, et al. Technical success and safety of retrieval of the G2 filter in a prospective, multicenter study. J Vasc Interv Radiol 2009; 20:1449–1453.
12. Charles HW, Black M, Kovacs S, et al. G2 inferior vena cava filter: retrievability and safety. J Vasc Interv Radiol 2009; 20:1046–1051.
13. Smouse HB, Rosenthal D, Van Ha T, et al. Long-term retrieval success rate profile for the Günter Tulip vena cava filter. J Vasc Interv Radiol 2009; 20:871–877.
14. Lyon SM, Riojas GE, Uberoi R, et al. Short- and long-term retrievability of the Celect vena cava filter: results from a multi-institutional registry. J Vasc Interv Radiol 2009; 20:1441–1448.
15. Johnson MS, Nemcek AA, Benenati JF, et al. The safety and effectiveness of the retrievable Option inferior vena cava filter: a United States prospective multicenter clinical study. J Vasc Interv Radiol 2010; 21:1173–1184.
16. Iqbal SI, Elmi A, Hedgire S, et al. Preliminary experience with Option inferior vena cava filter. Vasc Endovasc Surg 2012; 47:24–29.
17. Smouse HB, Mendes R, Bosiers M, et al. The RETRIEVE trial: safety and effectiveness of the retrievable Crux vena cava filter. J Vasc Interv Radiol 2013; 24:609–621.
18. Caplin DM, Nikolic B, Kalva S, et al. Quality improvement guidelines for the performance of inferior vena cava filter placement for the prevention of pulmonary embolism. J Vasc Interv Radiol 2011; 22:1499–1506.
19. Grassi CJ, Swan TL, Cardella JF, et al. Quality improvement guidelines for percutaneous permanent inferior vena cava filter placement for the prevention of pulmonary embolism. J Vasc Interv Radiol 2003; 14(suppl):S271–S275.
20. Sacks D, McClenny TE, Cardella JF, Lewis CA. Society of Interventional Radiology clinical practice guidelines. J Vasc Interv Radiol 2003; 14(suppl):S199–S202.
21. Participants in the Vena Caval Filter Consensus Conference. Recommended reporting standards for vena caval filter placement and patient follow-up. J Vasc Interv Radiol 2003; 14(suppl):S427–S432.
22. Millward SF, Grassi CJ, Kinney TB, et al. Reporting standards for inferior vena caval filter placement and patient follow-up: supplement for temporary and retrievable/optional filters. J Vasc Interv Radiol 2009; 20(suppl):S374–S376.
23. Oh JC, Trerotola SO, Dagli M, et al. Removal of retrievable inferior vena cava filters with computed tomography findings indicating tenting or penetration of the inferior vena cava wall. J Vasc Interv Radiol 2011; 22:70–74.
24. Kuo WT, Robertson SW, Odegaard JI, Hofmann LV. Complex retrieval of fractured, embedded, and penetrating inferior vena cava filters: a prospective study with histologic and electron microscopic analysis. J Vasc Interv Radiol 2013; 24:622–630.
25. Inferior Vena Cava (IVC) Filters: Initial Communication. Risk of adverse events with long term use. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Available at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm221707.htm. Accessed March 15, 2014.

Table E1. Adverse Events by System Organ Class

Category	Patients with ≥ 1 AE	Device-Related AEs*	Procedure-Related AEs*
All patients, all adverse events†	148 (74.0)	9 (4.5)	13 (6.5)
Blood and lymphatic system disorders	31 (15.5)	0	0
Cardiac disorders	30 (15.0)	0	0
Congenital, familial, and genetic disorders	1 (0.5)	0	0
Ear and labyrinth disorders	1 (0.5)	0	0
Gastrointestinal disorders	61 (30.5)	1 (0.5)	0
Eye disorders	6 (3.0)	0	0
General disorders and administration site conditions	44 (22.0)	2 (1.0)	2 (1.0)
Hepatobiliary disorders	6 (3.0)	0	0
Immune system disorders	3 (1.5)	0	0
Infections and infestations	58 (29.0)	0	0
Injury, poisoning, and procedural complications	27 (13.5)	1 (0.5)	3 (1.5)
Investigations	15 (7.5)	0	0
Metabolism and nutrition disorders	24 (12.0)	0	0
Musculoskeletal and connective tissue disorders	53 (26.5)	2 (1.0)	6 (3.0)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	12 (6.0)	0	0
Nervous system disorders	32 (16.0)	0	0
Psychiatric disorders	8 (4.0)	0	0
Renal and urinary disorders	25 (12.5)	0	0
Reproductive system and breast disorders	5 (2.5)	0	0
Respiratory, thoracic, and mediastinal disorders	30 (15.0)	1 (0.5)	0
Skin and subcutaneous tissue disorders	16 (8.0)	0	1 (0.5)
Surgical and medical procedures	1 (0.5)	0	0
Vascular disorders	42 (21.0)	3 (1.5)	1 (0.5)

The table lists AEs by *Medical Dictionary for Regulatory Activities* preferred terms.
Values in parentheses are percentages.
AE = adverse event.
*AEs were adjudicated and classified by the independent clinical events committee.
†The denominator is 200 enrolled patients. Some patients had adverse events in one or more category.