

Development of a Research Agenda for Inferior Vena Cava Filters: Proceedings from a Multidisciplinary Research Consensus Panel



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J Vasc Interv Radiol 2009; 20:697-707

Abbreviations: DVT = deep vein thrombosis, IVC = inferior vena cava, LMWH = low molecular weight heparin, PE = pulmonary embolism, PREPIC = Prevention du Risque d'Embolie Pulmonaire par Interruption Cave (trial), PTS = postthrombotic syndrome, RCT = randomized controlled trial, VTE = venous thromboembolism

VENA caval interruption is an important therapeutic option in the management of selected patients with venous thromboembolism (VTE). Currently, caval interruption is accomplished by percutaneous image-guided insertion of a filtering device into the vena cava. This widely available procedure is employed in as many as 15% of patients with a diagnosis of deep vein thrombosis (DVT) (1). However, vena cava filter placement has not been studied with the same methodologic rigor that has been applied to the most common treatment of VTE, anticoagulation (2,3). The majority of scientific publica-

tions on filter use have reported retrospective, noncontrolled studies, often from single institutions. To address the lack of level I data for inferior vena cava (IVC) filters, the Society of Interventional Radiology (SIR) Foundation convened a multidisciplinary research consensus panel to develop an agenda for vena cava filter research in June 2007. This report summarizes the proceedings from that meeting.

MEETING ORGANIZATION

A meeting of a multidisciplinary group of physicians and researchers

with expertise in IVC filters was convened in June 2007 by the Cooperative Alliance for Interventional Radiology Research (CAIRR), the clinical trials network of the SIR Foundation. The purpose of the meeting was to establish and prioritize a research agenda for IVC filters that included preclinical and health technology research, pilot clinical studies, and pivotal multicenter clinical trials.

An 11-member research consensus panel was created from a list of leading scientists developed by the Chair and the CAIRR Advisory Committee. The session was moderated by the CAIRR Network Chair. The panel included members from the fields of interventional radiology, surgery, and medicine. Representatives from industry and the federal government were also present as observers, as were other interested physicians and researchers.

Before the meeting, the panelists were given an agenda describing the structure and objectives of the session. The meeting was divided into four parts in accordance with the standard SIR Foundation process: (i) introductory presentations; (ii) moderated roundtable panel discussion followed by comments from industry and governmental representatives; (iii) research topic prioritization; and (iv) preliminary discussion regarding the development of a clinical research protocol.

Nine of the panel participants (M.S., S.R.K., W.G., D.G., F.B.R., J.A.K., S.W.S.,

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The SIR Foundation received financial support for the research meeting discussed herein from the following companies: Bard Peripheral Vascular (Covington, Georgia), B. Braun (Melsungen, Germany), Boston Scientific (Natick, Massachusetts), Cook (Bloomington, Indiana), and Cordis (Warren, New Jersey). None of the authors have identified a conflict of interest. The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Navy, Department of Defense, nor the U.S. Government.

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DOI: 10.1016/j.jvir.2009.03.007

J.H.R., S.V.) made presentations of background material before the roundtable discussion. The intent was to provide a common basis for dialogue about current and investigational IVC filter therapies and directions for future research.

The panel was presented with a summary of the reported outcomes from key IVC filter studies and additional information regarding IVC filter therapies. These formal presentations included Natural History of Venous Thromboembolism (M.S.), Current Status of Therapy of VTE (S.K.), Prevention of VTE (W.G.), How Vena Cava Filters Are Used Today (D.G.), The Outcomes of Vena Cava Filters (F.B.R.), The Filter as a Risk Factor for VTE (J.A.K.), Variability in Devices (S.W.S.), The IVC as a Dynamic Environment (J.H.R.), and Designing VTE Trials—A New Paradigm (S.V.). The key aspects of these presentations are summarized in the Results section.

Data Collection and Analysis

The panel began a dialogue of research priorities for IVC filters. Each panelist was solicited for opinions regarding knowledge gaps and opportunities for research related to IVC filters. To determine the research priorities, each panelist and audience member recorded one or two clinical priorities and one basic science priority, with the option to also include one organizational priority. The list of proposed priorities was then reviewed by the panel and similar suggestions were consolidated/combined when possible. After discussing the advantages and disadvantages of the different proposals, the panelists voted on the final list of priorities, and scores were tallied, ranked, and viewed by panelists and audience. After the pivotal clinical topic had been chosen (a randomized controlled clinical trial of prophylactic IVC filters in trauma patients), the discussion focused on key questions such as why this area was identified as the top priority, what the public health significance of further research in this area may be, and what the basic structure of the study should be.

PANEL PRESENTATIONS

The Natural History of VTE

Venous thromboembolism is estimated to affect one to two individuals

per 1,000 annually (4,5). DVT is diagnosed approximately twice as often as pulmonary embolism (PE). However, the 30-day case fatality rate of PE is twice that of DVT (5). Demographic characteristics such as age and race influence the incidence of VTE. In the entire population, VTE occurs with approximately equal frequency in men and women (6).

An increasing number of risk factors for initial VTE have been identified. Such factors include major surgery, trauma, acute medical illnesses, cancer and cancer therapy, immobility, pregnancy and the postpartum state, estrogen therapy, obesity, atherosclerosis, and thrombophilic disorders. The most common inherited thrombophilic disorder is factor V Leiden, which is found in its heterozygous form in 5% of white subjects, 2% of Hispanic subjects, and 1% of black subjects. Homozygosity is identified in 0.05% of healthy subjects. Heterozygotes have a three- to eightfold higher risk of VTE whereas homozygotes have an 80-fold increased risk (7,8). However, the annual incidence of VTE associated with factor V Leiden is only 0.2%–0.7% (9). The prothrombin gene mutation G20210A is found in 2.7% of healthy white subjects. This mutation increases the risk of VTE by two to three fold in heterozygotes but has been associated with an annual incidence of VTE of only 0.12% (7,8,10). Increased levels of several coagulation factors have also been associated with an increased risk of VTE (11). Factor VIII activity greater than 150 IU/dL, factor IX activity greater than 129 IU/dL, and factor XI antigen levels greater than 121 IU/dL are associated with 4.8-fold, 2.5-fold, and 2.2-fold increased risks of VTE, respectively (12–14).

Antithrombin deficiency affects only one in 5,000 in the general population, but has been associated with an increased risk of VTE of as much as 50 fold (7). Although protein C deficiency occurs in only 0.2% of the general population and 4% of unselected patients with VTE, it increases the risk of VTE by 6.5-fold (7,10). Protein S deficiency affects 2.3% of unselected patients with VTE. In case-control studies it is associated with a modest 1.7-fold increase in VTE, although family studies estimate an annual incidence of VTE of 1%–2% (8,9,10). Non-O ABO blood groups have long been associated with a two- to fourfold increased relative risk of VTE

that likely results in part from the influence of ABO blood group on factor VIII and von Willebrand factor levels (7). Increased levels of D-dimer, the end product of fibrinolytic digestion of fibrin clot and a marker of activated coagulation, has been linked in several studies to a two- to threefold increased risk of VTE (15,16).

Although inherited disorders are common causes of thrombophilia, acquired risk factors are far more common and are often more potent risk factors for VTE. Conditions among hospitalized medical patients associated with an increased risk of VTE include congestive heart failure, placement of a central venous catheter or pacemaker, neurologic disease with paresis, a history of VTE, and an acute infectious illness (17,18). Major surgery is associated with a substantial risk of DVT. The risk of VTE is influenced by the surgical procedure, its duration, patient age, a history of VTE, active cancer, and the duration of postoperative immobility (19–21). Major trauma is associated with an overall VTE incidence of 58%, with 50% of cases of PE occurring in the first 7 days (20,22). Cancer is associated with a four- to sevenfold increased risk of VTE, and this risk is further heightened by cancer therapies such as chemotherapy, hormonal therapy, and angiogenesis inhibitors (17,23). Patients with cancer account for 20% of patients with VTE, and 15% of patients with cancer develop VTE during their illness (24). Pregnancy and the postpartum period are associated with a four- to 14-fold increased risk of VTE, with an estimated incidence of 1.7 events per 1,000 pregnancies (25). Approximately half the thromboembolic events occur in the prepartum period and half in the 6-week postpartum period (25). Factors associated with an increased risk of VTE related to pregnancy include age greater than 35 years, black race, previous VTE, and thrombophilia (25).

Oral contraceptives are associated with a three- to sixfold increase in the risk of VTE, with third-generation combined estrogen/progesterone preparations posing greater risks than second-generation therapies. Hormone replacement therapy has also been associated with a two- to fourfold increased risk of VTE (26). The risks posed by these medications are further increased in the presence of inherited thrombophilic defects (26). Immobility is a common risk factor associated with VTE,

although usually in combination with other overt or silent thrombogenic risk factors. In the Leiden Thrombophilia Study (27), immobilization was identified in 17% of patients with VTE and was associated with a relative risk of VTE of 9.0. Obesity has been associated with a two- to threefold higher risk of VTE. The precise etiology of this association remains to be determined but is likely multifactorial, including reduced mobility, stasis, and blood alterations associated with the metabolic syndrome (28).

Atherosclerosis and VTE have traditionally been considered diseases of distinct and separate pathogenesis. However, several case-control and prospective cohort studies (29,30) have suggested an association between atherosclerosis and VTE. This link is further supported by two recent case-control studies (31,32) demonstrating an association between the metabolic syndrome and VTE. However, another recent prospective study (33) found no association between VTE and subclinical atherosclerosis on carotid ultrasound (US). Acquired blood disorders associated with a heightened risk of VTE include hyperhomocysteinemia and antiphospholipid antibodies. Elevated levels of homocysteine have been identified as a risk factor for VTE and atherosclerosis (odds ratio, 3.0), although treatment of the increased homocysteine level does not reduce the risk of thrombosis (34). Antiphospholipid antibodies have been identified in 2% of healthy blood donors and in 5%–15% of patients with VTE and are associated with a 2.4- to 10-fold increased risk of DVT (35). Although VTE risk factors are often presented individually, most patients who develop VTE have more than one identifiable risk factor present at the time of their thrombotic event (4).

Risk Factors for Recurrent VTE

Patients who present with an initial DVT are more likely to suffer a recurrent DVT, whereas patients with PE are more likely to have a recurrence of PE (7,27,36). Consequently, the mortality rate associated with an initial episode of PE is substantially higher than that associated with DVT (36). Among patients with PE, factors that place them at higher risk for adverse outcomes during treatment include age greater than 70

years, cancer, history of VTE or a coexisting DVT at the time of PE, hypotension, hypoxemia, heart failure, and right ventricular dysfunction (37,38).

The risk of recurrent VTE is greatest during the first 6–12 months after discontinuation of anticoagulant therapy (39). Patients who have had idiopathic thromboembolic events have substantially greater risk of recurrent events than those whose VTE occurred in association with a major transient risk factor. The presence of a moderate reversible risk factor, such as use of birth control pills, is associated with an intermediate risk of recurrence (39–42). The presence of active cancer is associated with a high risk of recurrent VTE both during and after discontinuation of anticoagulant therapy (23,42). Although thrombophilic conditions contribute to the risk of initial VTE, their influence on recurrent event is less clear (39,41,43,44). The presence of antiphospholipid syndrome is a strong risk factor for recurrent VTE (45,46).

Postthrombotic Syndrome and Chronic Thromboembolic Pulmonary Hypertension

In addition to recurrent VTE and bleeding, the course of VTE can also be complicated by the development of postthrombotic syndrome (PTS) and chronic thromboembolic pulmonary hypertension. The PTS occurs in approximately one third of patients within the first 2 years after a proximal DVT (47,48). Risk factors for development of PTS include recurrent ipsilateral DVT (sixfold), increased body mass index (3.5-fold), and poor quality anticoagulation (threefold), and use of compression stockings is protective (odds ratio, 0.5) (48–50). Risk factors for chronic thromboembolic pulmonary hypertension include idiopathic PE, recurrent PE, and large perfusion defects (51).

The Current Status of VTE Therapy

The principles of VTE therapy include (i) rapid initial anticoagulation to reduce the risk of clot extension and embolization, (ii) long-term anticoagulation to reduce the risk of VTE recurrence, and (iii) discontinuation of anticoagulation when the risk of treatment exceeds the risk of recurrent VTE (52).

Rapid initial anticoagulation is achieved with the administration of 5–7 days of subcutaneous low molecular weight heparin (LMWH), usually delivered entirely in the outpatient setting (53). Anticoagulant alternatives to subcutaneous LMWH include subcutaneous fondaparinux, intravenous unfractionated heparin with activated partial thromboplastin time monitoring, or unmonitored, weight-based subcutaneous unfractionated heparin (52). In patients with hemodynamically significant PE or severely symptomatic iliofemoral DVT, thrombolysis (intravenous or catheter-directed, respectively) should be considered if contraindications to lysis are absent.

An oral vitamin K antagonist (usually warfarin) is initiated concurrently with LMWH. The heparin is continued (usually 5–7 d) until the International Normalized Ratio is greater than 2.0 for 2 days. Warfarin (target International Normalized Ratio, 2.0–3.0) is highly effective at preventing recurrent VTE (>90% risk reduction) (52). Because of its superior protection, LMWH is recommended over warfarin for cancer-associated VTE for the first 3–6 months of treatment and possibly indefinitely for patients with active cancer (54). Predictors of bleeding on warfarin include age greater than 75 years, previous gastrointestinal bleeding, previous stroke, previous bleeding during warfarin treatment, renal or hepatic failure, low platelet count, widespread cancer, and concomitant antiplatelet therapy (55).

The duration of warfarin therapy for VTE is guided by the patient's risk group for recurrence (42,52). In patients with unprovoked VTE, the risks of recurrent VTE after treatment is stopped are approximately 10% in the first year and 30% after 5 years (42,46,56). The duration of anticoagulation in such patients is controversial, but indefinite anticoagulation with periodic reassessment is increasingly recommended (52,56). Further research is required to determine the optimal duration of anticoagulation in individual patients, especially those with unprovoked and cancer-associated VTE. In addition, trials to evaluate the precise role of catheter directed-thrombolysis for DVT and for PE and of IVC filters are warranted.

Prevention of VTE

Most hospitalized patients are at risk for VTE and warrant thromboprophylaxis. There are several hundred randomized trials unequivocally proving that thromboprophylaxis can improve patient safety by reducing DVT, PE, and fatal PE (20).

Every 3–4 years since 1986, the American College of Chest Physicians has sponsored and published evidence-based guidelines for the prevention of VTE (20). For most hospitalized patients, LMWH, low-dose heparin, or fondaparinux are the recommended options. Mechanical prophylaxis is recommended primarily for patients at very high risk of bleeding. The American College of Chest Physicians guidelines do not recommend the use of IVC filters as primary prophylaxis for any patient group.

Despite the overwhelming evidence, compliance with thromboprophylaxis continues to be underused in most centers (57). The greatest priority for thromboprophylaxis research is the development of effective strategies for the implementation of routine prophylaxis for every patient at risk.

How Vena Cava Filters Are Used Today

The indications for filters have not been derived from or studied in randomized prospective clinical trials (Table 1). IVC filter placement is not required in addition to anticoagulation for the treatment of most patients with DVT or PE (52,58). Vena cava filter placement is performed in three clinical situations: in patients with VTE and classical indications, in patients with VTE and extended indications, and in patients without VTE for primary prophylaxis against PE (59).

The classical indications for IVC filter placement include documented DVT and/or PE and an absolute contraindication to anticoagulation, documented progression of DVT or recurrent PE while in a fully anticoagulated state, and a complication of anticoagulation necessitating termination of therapy (60). The other traditional indication for filter insertion is massive PE that puts the patient at risk of death from further pulmonary emboli regardless of anticoagulation status (61).

Extended indications for filters in pa-

Table 1
Reported Indications for Vena Cava Filters*

Classic indications (proven VTE)
Contraindication to AC
Complication of AC
Inability to achieve/maintain therapeutic AC
Extended indications (proven VTE)
Recurrent VTE (acute or chronic) despite adequate AC
Iliocaval DVT
Large, free-floating proximal DVT
Difficulty establishing therapeutic AC
Massive PE treated with thrombolysis/thrombectomy
Chronic PE treated with thromboendarterectomy
Thrombolysis for ilio caval DVT
VTE with limited cardiopulmonary reserve
Recurrent PE with filter in place
Poor compliance with AC medications
High risk of complication of AC (eg, ataxia, frequent falls)
Prophylactic indications (no VTE†)
Trauma patient with high risk of VTE
Surgical procedure in patient at high risk of VTE
Medical condition with high risk of VTE

Note.—AC = anticoagulation.

* There was not uniform agreement on the panel for all these indications.

† Primary prophylaxis not feasible, eg, as a result of high bleeding risk, inability to monitor the patient for VTE.

tients with VTE are generally based on specific risks for complications from the VTE itself or from anticoagulation. These other possible indications, which have been introduced gradually into clinical practice as filters have become more available and easier to place, include documented DVT and/or PE and a large free-floating IVC or iliac vein thrombus, poor patient compliance with anticoagulation or follow-up, and risk for falls (61,62).

Prophylactic indications for IVC filter placement are those in which a patient does not have VTE, but is at risk of developing it and cannot receive effective prophylaxis or be monitored for the development of VTE. Although retrospective case series have suggested that the place-

ment of prophylactic IVC filters in trauma may reduce symptomatic and fatal PE, there are no randomized trials of prophylactic IVC filter use in any patient group (63).

There are two basic classes of filters available in the United States, permanent and retrievable (or optional). Retrievable filters are designed to be removed or left in place after the risk of PE has resolved. In clinical practice, 50% or fewer of retrievable filters are ever removed (64,65). The availability of retrievable filters has altered practice patterns for vena cava filters, with a shift to these devices and the perception of relaxation of thresholds for filter placement (63,64). However, there is currently no evidence directly comparing routine filter removal with permanent IVC filtration.

The number of filter placements in the United States increases steadily each year (66,67). Prophylactic indications for vena cava filter placement now account more than half of all filter placements. A large proportion of the prophylactic filters placed are retrievable (68,69).

Outcomes of Vena Cava Filters

Vena cava filters have been used since the early 1970s. Only one level I clinical trial has been conducted on their effectiveness in preventing pulmonary embolism (70). The PREPIC (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave) trial (70) was a randomized controlled trial (RCT) in 400 patients with proximal DVT who were believed to be at high risk for PE. Patients were randomized to receive anticoagulation plus an IVC filter versus anticoagulation alone. Four different permanent filters were used in this study. Within the first 12 days, two patients in the filter group and nine patients in the anticoagulation group developed PE. Although four of the emboli in the nonfilter group were believed to be fatal, there was no mortality difference, with five patients dying in each group. After 2 years, symptomatic PEs had occurred in six patients in the filter group and 12 patients in the nonfilter group, but the difference did not achieve statistical significance. However, there were significantly more symptomatic DVTs in

the filter recipients (20.8% vs 11.6%). In follow-up data reported at 8 years, there were significantly fewer occurrences of symptomatic PE (6.2% vs 15.1%) in the filter group, whereas there were significantly more occurrences of symptomatic DVT (35.7% vs 27.5%) in the filter group compared with the nonfilter group; the overall incidences of VTE were 36.4% in the patients with filters and 35.4% in those without filters ($P = .54$) (71). The incidence of PTS was identical in both groups. There was no survival difference between patients with or without filters at 12 days, 2 years, or 8 years.

There are data of modest quality on the long-term experience with the use of vena cava filters in the treatment of established VTE. Greenfield and Proctor (61) reported on their 20 years of experience with use of the Greenfield filter (Boston Scientific, Natick, Massachusetts) in 642 patients, with a rate of recurrent PE of 4% and a caval patency rate of 96% at a mean follow-up of almost 5 years. Of concern, there are the occasional case reports of vena caval filters that have embolized to the heart or the pulmonary artery—or perforated the aorta, ureter, or bowel—occasionally with fatal results. The short- and long-term complications associated with vena cava filters are presented in **Tables 2 and 3**.

In 2003, the US Food and Drug Administration first gave approval for a retrieval indication for a vena cava filter (72). Since then, other filters have been approved for retrieval in the United States. Nevertheless, there is a paucity of published literature on their efficacy or long-term outcomes of these filters.

The Filter as a Risk Factor for VTE

IVC filters have been associated with an increased incidence of DVT, even when the patient is concomitantly receiving anticoagulation, compared with patients treated with anticoagulation alone (67,70,71). Reviews of the filter literature cite widely varying rates of recurrent DVT, as high as 40% in some series (73). White et al (67) reviewed discharge data from 1991 to 1995 in California for patients with VTE treated with filters and compared readmissions and mortality versus patients with VTE who did not receive a filter. The anticoagulant treatment de-

Table 2
Short-term Complications

Contrast agent reaction
Arrhythmia
Air embolism (especially with jugular insertion)
Pneumothorax/hemothorax
Extravascular penetration of guide wire
Incomplete opening
Tilting/angulation
Misplacement (eg, iliac vein, renal vein, aorta, heart)
Guide wire entrapment
Filter migration
Embolization of filter (eg, to heart, pulmonary artery)
Filter fracture
Insertion site bleeding/hematoma
Infection at insertion site
Contrast agent–induced renal dysfunction
Arteriovenous fistula
Insertion site thrombosis (appears to be greater with femoral route)
PE
Fatal PE (rare)
Death (very rare)

Note.—Adapted from Oliva V, Geerts W. The Thrombosis Interest Group of Canada. Clinical guide—inferior vena cava filters, November 2004; 1–6.

Table 3
Long-term Complications

Increased risk of subsequent DVT
Migration: proximal or distal within IVC or iliac veins
Filter embolization
Symptomatic penetration outside IVC (eg, aorta, ureter, bowel, nerve, pancreas)
Filter fracture
IVC occlusion (symptomatic)
Vena caval stenosis
PE
Fatal PE (rare)
Guide wire entrapment

Note.—Adapted from Oliva V, Geerts W. The Thrombosis Interest Group of Canada. Clinical guide—inferior vena cava filters, November 2004; 1–6.

tails of the patients in both groups were unknown. Patients with PE who had a filter inserted had a twofold increased risk of subsequent readmission for DVT compared with patients who had received the filter for DVT only. At the same time, the presence of a filter did

not reduce the risk of readmission for PE. This study (67) concluded that filters did not offer a protective advantage for PE, and actually increased the risk of DVT, especially in patients with an initial diagnosis of PE.

Greenfield and Proctor (74) published results from a prospective registry of filter patients in Michigan and showed a similar rate of IVC occlusion and recurrent DVT in patients with filters regardless of the use of anticoagulation. This study suggested that patients with permanent filters may not require indefinite anticoagulation after completion of an appropriate duration of anticoagulant therapy for the thromboembolic event that prompted filter insertion.

The reason for the increased risk of DVT in patients with filters observed in some studies is unknown. IVC occlusion caused by de novo thrombosis or trapped emboli is suspected as the most likely etiology (67,71). In addition, filters have been shown to stimulate smooth muscle cell migration in the wall of the IVC at the points of contact, which could implicate caval stenosis in some cases of IVC occlusion (75). Assessment of this risk is one of the major considerations in designing a trial of vena cava filters.

Variability in Devices

Although IVC filters have been used for several decades, there are no level I RCTs comparing the safety and/or efficacy of different IVC filters. IVC filters appear to be associated with low rates of symptomatic PE (71). Attempts to compare filters have failed because of the retrospective nature of the data, most of which have been derived from single centers.

There are substantial differences among filters, including their shape, diameter, length, and materials. In addition, some filters are meant to be retrievable whereas others are permanent. Although the clinical significance of these differences has not been determined, the design of any prospective study must consider the differences among IVC filters.

Variability in the IVC

The IVC is a structurally dynamic vessel subject to great variations in anatomy and rapid and extreme

changes in vessel wall dynamics. Anatomically, the most common variant of the IVC is a duplicated infrarenal IVC that occurs in approximately 1%–2% of the population (66). In this instance, the infrarenal left IVC drains into the normally situated left renal vein, which then joins the right-sided IVC to form a common suprarenal cava. A single left-sided IVC occurs in 0.5% of individuals. In this case, the right and left iliac veins drain into a left IVC that enters the left renal vein and crosses to the right side anterior or posterior to the aorta to join the normal suprarenal IVC. Congenital absence of the suprarenal IVC results in drainage through the azygous system to the superior vena cava. In this situation, the hepatic veins drain directly into the right atrium. These anatomic variants must be carefully assessed during placement of an infrarenal IVC filter.

The IVC itself is a compliant vessel that is subject to constantly varying transmural pressures influenced by body posture and activity. Placement of IVC filters into this complex, constantly changing environment can alter hemodynamic flow in the IVC and potentiate venous intimal hyperplasia and fibrin deposition. Computational flow-dynamic models have recently been used to determine alterations in IVC flow and shear stress after IVC filter placement (76). Filter design alone appears to directly impact caval flow to varying degrees; areas of relatively stagnant venous blood flow are significantly more marked when thrombus is captured within the filter (77).

Designing VTE Trials: A New Paradigm

Clinical trials in VTE generally focus on defining rates of symptomatic recurrent VTE versus major bleeding. Adoption of this basic template for VTE trials has certain advantages: it facilitates comparison among different VTE studies and interventions, ensures use of endpoints generally considered important to physicians, and is helpful in initiating trial design. However, this structure can also be limiting if relied on without a careful assessment of potential modifications: (i) it can be slow to react to evolution in our understand-

ing of the disease process being examined and (ii) it can be slow to incorporate technological advances that widen the dynamic range of potential treatment effects.

PTS, which occurs in 25%–50% of patients with proximal DVT, is considered to be an important endpoint in VTE trials (50,78). However, assessment of PTS often reflects an incomplete understanding of this disease process. In addition, findings purported to be objective indicators of PTS (e.g., valvular reflux on duplex US) actually show weaker correlations with health impairment (ie, venous disease-specific quality of life) than validated clinical PTS scales that incorporate patient-reported symptom assessments (78). Therefore, some new VTE trials should incorporate measurements of PTS that actually indicate health impairment.

The dynamic range of different treatments is also an important factor to consider in trial design. It is important for clinical trialists to address key controversies directly in trial design. In summary, investigators should challenge existing VTE clinical paradigms with creative, contemporary methods to answer critical VTE questions.

PANEL DISCUSSION

Rank Order Prioritization of Panel Responses

On the basis of the earlier discussion in the present publication, a total of 32 clinical research topics (Table 4), eight basic science topics, and six organizational research topics were initially proposed. After further discussion, the panel voted to determine the research priorities (Table 5). The highest total score was for an RCT of prophylactic vena cava filters in trauma patients. The next three clinical topics selected by the expert panelists were, in order of decreasing priority, an RCT of prophylactic filters in a wide range of patient populations with retrieval, an RCT of filters in high-risk PE patient populations, and a multicenter prospective PREPIC-like trial of filters in anticoagulation candidates. The basic science and organization priorities are listed in Tables 6 and 7.

Discussion

Research on vena cava filters presents several challenges. The actual devices are changing rapidly, so that, by the time that a long-term study yields results, the study devices may no longer be available. Differences among devices are poorly understood, such that device selection may influence results when comparing filters as a group versus alternative therapies. Technical aspects of clinical practice, such as the location of filter placement in the IVC (eg, just at the renal veins, 1 cm caudal to the veins, above the renal veins), are based on opinion and anecdotal experience rather than objective data. Compounding the device-related challenges are the lack of validated *in vitro*, *in vivo*, and virtual models for testing devices.

The IVC has long been presumed to be a rather simple, stable environment for a device. In reality, the IVC is complex and poorly understood. Flow in the IVC varies dramatically with volume status, cardiac output, and patient position. The size and cross-sectional shape of the IVC change constantly, partially as a result of these factors. The IVC is also subject to external axial compression by the peritoneal contents, longitudinal compression by the movement of the diaphragm, and likely by additional yet unappreciated external forces. The unexpected fractures of filter elements may be partially explained by this complex environment.

The indications for filter placement have never been studied in a prospective, let alone a randomized, manner. The distinctions among “classic” and “extended” and “prophylactic” indications are based on historical or local standards of practice, not on science (Table 1). Further compounding the challenge of selecting appropriate filter indications is the constant evolution of these indications. As new devices become available, or clinicians become more familiar with filters, existing indications change and new indications are introduced.

Vena cava filters are not a treatment for a disease, but a prophylactic measure against a potentially morbid or even lethal event, PE. PE is only one manifestation of a much more complicated condition, VTE. The patient population with VTE is heterogeneous, and venous thrombo-

Table 4
Clinical Research Topics

1	IVC filter use in trauma patients with objective endpoints including survival and clot burden in pulmonary arteries
2	Short-term outcome trial in trauma patients
3	Prophylactic filter trial, evaluate retrieval, all patient populations, multiple endpoints
4	Retrievable filter trial: in whom do you place them, what filters do you use?
5	Repeat the PREPIC study or use this study design in new trial
6	RCT studying specific populations with high anticipated rate of filter retrieval
7	Registry of retrieval filter implantation in trauma, bariatric patients
8	Study evaluating clinically relevant endpoints following IVC filtration rather than surrogate events
9	Trauma filter RCT or registry: identify benefited populations, clinical and intermediary endpoints, stratify permanent vs (actually) retrieved filters
10	Trial evaluating coagulation profile and risk factor impact on clinical endpoints in filter recipients
11	Perform trial that will influence practice and have clinically relevant endpoints: hard endpoints, best alternative prophylaxis with/without IVC filter in trauma patients
12	Pattern-of-care study: what's being done now, filter use, costs, anticoagulation strategies
13	Study of patients with massive PE using different diagnostic criteria (eg, O ₂ saturation, cardiac echo, CT angiography, pulmonary artery pressures, and other hemodynamic measures) comparing anticoagulation with/without filter
15	Evaluate benefit of retrieving a filter in either the trauma population or patients with transient PE risk ("time limited" classic indications for filters) to determine if removing the filter is a "valid concept"
16	RCT with clinically relevant practice changing endpoints: study prophylactic IVC filter in a population who are at high risk of VTE and have early contraindication for anticoagulation; may compare permanent vs retrieved filters, need long-term follow-up including PTS, PE
17	RCT looking at retrieval filters in patients with massive and submassive PE high-event rate patient cohort (eg, congestive heart failure, elevated troponin levels)
18	Perform PREPIC-like study evaluating filters in anticoagulated patients, looking at health-consequential VTE outcomes
19	Upper-extremity DVT trial: role for vena cava filters in patients with contraindications to anticoagulation
20	Cancer filter trial: evaluating outcomes of IVC filters and other treatment strategies in patients with malignancy
21	Orthopedic surgery retrievable filter trial
22	Study evaluating "real-world" caval thrombosis and filter retrieval rates among different populations and filter designs
23	Long-term caval injury trial in patients with IVC filters
24	Filter thrombosis treatment trial
25	Initiate IVC filter registry, then use data to determine best trial
26	Bariatric retrievable filter population study
27	Prospective/retrospective time to filter removal trial, including filters not removed, looking at caval injury and clinical events
28	Prophylactic filter trial in wide-range of patient populations including bariatric, trauma, orthopedic, and other groups of patients: consider "community consent"
29	A national filter registry is essential
30	RCT of optional vs permanent filters
31	Massive PE thrombolysis trial, with or without IVC filters
32	RCT of filter use vs no filter use during thrombolysis of ilio caval venous thrombosis
33	Study worldwide use of IVC filters and create a "global" trial that evaluated PREPIC-eligible population

Table 5
Clinical Priority Topics

Rank	Topic	Score
1	RCT of prophylactic filters in trauma patients	67
2	RCT of prophylactic filters in a wide range of patients, evaluate retrieval	47
3	RCT of filters in high risk PE populations	46
4	Multicenter prospective PREPIC like trial of IVC filters in anticoagulation candidates	41
5	RCT of permanent vs retrievable filters	39
6	Long-term follow-up study of retrievable filters	39
7	RCT with clinically relevant practice changing endpoints: study prophylactic IVC filter in a population who are at high risk of VTE and have early contraindication for anticoagulation; may compare permanent vs retrieved filters, need long-term follow-up including PTS, PE	38
8	Registry of IVC filter outcomes	30
9	Filter comparison trial	26
10	Survey of practice patterns/preferences	24
11	RCT studying specific populations with high anticipated rate of filter retrieval	22
12	Risk factor stratification trial	19
13	RCT of IVC filters in high risk VTE cases and bleeding	18

Table 6
Basic Science Research Priorities

- 1 Study long-term changes in devices implanted in younger patients
- 2 Evaluate metallurgy, thrombogenicity and impact on risk of caval thrombosis
- 3 Computerized flow dynamics study evaluating multiple filters, correlated with clinical trial experience
- 4 IVC filter flow trial
- 5 Rheological study of coagulation after IVC filter placement in an animal model
- 6 Create hypercoagulable animal model to test IVC filter performance
- 7 Study IVC in patients who have retrieved filters
- 8 Find safe oral anticoagulant that does not require ongoing hematologic monitoring

Table 7
Organizational Research Priorities

- 1 Trial should be collaborative across organizations and specialties, for example with SIR Foundation and American Venous Forum
- 2 Industry participation in trial design and implementation
- 3 Work with hematologic societies, other national organizations concerned with venous thromboembolism
- 4 SIR should develop conservative recommendations for IVC filter use
- 5 Engage participation of broad based constituency of multiple organizations; consider discussing with Agency for Healthcare Research and Quality
- 6 Community consent for certain patient populations

sis is the end result of a complicated sequence of events (79). Patient outcomes are determined by the diverse underlying conditions that triggered the VTE, as well as the filter.

The outcomes of filters have not been systematically studied in accordance with rigorous definitions, robust study design, or hypothesis-based investigation. Large numbers of retrospective series and anecdotal reports have resulted in generally accepted types of outcomes and approximate rates of occurrence. However, the ranges of events are broad and precise rates are difficult to determine (59,73).

In clinical research, the presence of a filter in the IVC is often viewed as binary; either a filter is present or it is not. All filters are assumed to be the same, all filter placements presumed equivalent, all patients considered to have identical IVCs, and all thrombi assumed to have similar consequences. These assumptions are likely incorrect and require further study.

The panel considered the existing challenges to clinical research in vena cava filters in the context of current practice. The panel endeavored to develop research topics that could address the fundamental gaps in knowledge about filters while answering a pressing clinical question.

The primary gap in knowledge on which the panel focused was the indications for filters, specifically for VTE prophylaxis (ie, placement before development of VTE). The trauma population provides the best opportunity in which to study this indication. By a large margin, the top research priority for vena cava filters is to design and execute a prospective RCT of prophylactic filters in trauma patients.

This topic has several advantages. The study endpoint—assessment of prevention of clinically important PE—can be evaluated in a high-risk, easily identified population with a short duration of risk. The existing networks of trauma centers will allow multiple centers to participate. There is substantial controversy regarding the use of filters for this indication, yet it represents one of the largest groups of patients currently receiving filters (61,63,78,80–84). Finally, there have not been any randomized controlled studies of filters in this group.

Optional filters (retrievable or convertible) have been the subject of the majority of recent filter publications, as they have the potential to be removed when their short-term benefit has resolved. Notably, the panel's focus was on prophylactic indications independent of the type of filter—per-

manent or optional. Although there was much discussion about optional filters, and recognition of the pressing need for research on these devices, the panel decided that the first priority of research should be the evaluation of the most common prophylactic indication for vena cava filters. The concern of the panel about filter indications is reflected in the second most highly ranked topic, which was a study of prophylactic filters in an expanded population that would include patients at high surgical and medical risk.

The highest basic science research priority was the study of filters in the IVC over time. The long-term integrity of the filter, interaction with the IVC wall, and interaction with blood components were areas of major concern. The average age of patients receiving filters has decreased with time, probably reflecting the increase in prophylactic indications (66). The long-term behavior of these devices in the complex environment of the IVC requires further study and may lead to changes in filter design.

The filter is not a passive or inert structure in the IVC as previously believed. Specific interactions between the filter and the IVC have been found at a cellular level (75). Our current understanding of the relationship between the filter and the IVC is primitive and worthy of investigation.

There has been little investigation of the interaction between filters and the blood. Malignant cells have been recovered from retrieved filters (85). Elemental particles that were clearly ingested, such as barium, have also been detected on retrieved IVC filters (86). Further study of the relationship between blood and the filter is warranted.

The panelists recognized the importance of a multidisciplinary effort in the development of research initiatives. Vena cava filters are placed in many types of patients by several different types of physicians. Most of the physicians who place filters do not have primary responsibility for the long-term management of the patient's VTE. The panelists selected the engagement of all the major stakeholders in VTE treatment as the top organizational priority for research. To this end, formal collabora-

tion among the stakeholder groups such as the SIR, the American Venous Forum, trauma organizations, and hematology organizations should be sought.

SUMMARY

The body of knowledge about vena cava filters remains embarrassingly deficient. Most of what we do with filters is based on "expert opinion," personal experience, and uncontrolled case series. The goal of the panel was to use these opinions to begin the process of generating level I data on filters. The prophylactic use of filters in trauma patients was considered the leading clinical research topic by a wide margin. Accordingly, this prioritized research project will be the subject of multidisciplinary grant development efforts supported by the SIR Foundation's CAIRR network.

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