Evidence and Clinical Judgment*: Vena cava filters

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Introduction

Venous thromboembolism (VTE), including deep-vein thrombosis (DVT) and pulmonary embolism (PE), is a major cause of morbidity and mortality (1). Full-dose anticoagulant treatment with parenteral drugs (unfractionated heparin, low-molecular-weight-heparin or fondaparinux) followed by vitamin K antagonists is recommended for the majority of patients with VTE (2); novel oral anticoagulants, such as direct thrombin or factor Xa inhibitors, are potential alternative for both the acute phase and the long-term treatment. However, in the presence of major contraindications to anticoagulant treatment, including bleeding complications during antithrombotic treatment, interruption of the inferior vena cava (IVC) with a filter may prevent life-threatening PE (3-6). IVC filters are permanent or not-permanent devices. Permanent IVC filters are associated with a number of long-term complications, such as increased risk for lower limb DVT, thrombotic occlusion of the vena cava itself and mechanical failure with vascular perforation or embolisation (7). A prospective observational cohort study performed in long-term anticoagulated patients with permanent devices reported a high rate of recurrent DVT, symptomatic PE and filter thrombosis (20%, 5% and 30%, respectively) (8). Non-permanent filters represent an important alternative, especially in patients with a long life expectancy and in whom the period of contraindication to anticoagulant therapy is short (9). In particular, retrievable filters are an attractive option because they may be either left in place permanently or safely retrieved after quite a long period when they become unnecessary (10, 11); currently, retrievable IVC filters are the first choice of device, except for rare situations (for example permanent contraindication to anticoagulation) where permanent devices may be the optimal option. The insertion of an IVC filter is almost never a needed adjunct to anticoagulant therapy; the American College of Chest Physicians (ACCP) guidelines recommend the use of an IVC filter only in patients with acute PE or acute proximal DVT of the leg and contraindication to anticoagulation and suggest the implantation of a permanent IVC filter before or during pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension (2). On the contrary, the ACCP guidelines suggest against the implantation of a filter for primary prevention of VTE in high risk patients (e.g. in patients with major trauma) (12). Because limited evidence from clinical studies is available to support recommendations, clinical guidelines do not address a number of practical issues that clinicians encounter in everyday clinical practice.

The Italian Society for Thrombosis and Haemostasis (SISET) has proposed a new format for its guidelines, named “Evidence and Clinical Judgment” (13). The aim of these documents is not to provide a traditional guideline based on graded recommendations derived from higher quality published evidence. Rather the documents are meant to address specific and clinically relevant questions that cannot be addressed in evidence-based guidelines. In this paper, we will provide evidence and clinical judgments describing the management of patients with IVC filters.

Methods

A working group (DI, FD and WA) was nominated by SISET and invited to define clinical questions on the role of vena cava filters in the management of VTE. The working group performed systematic reviews of the literature using the following data sources: electronic databases (MEDLINE, from 1966 to March 2013 and EMBASE, from 1980 to March 2013), reference lists of selected papers and narrative reviews, editorials, guidelines and direct consultation with experts. Two reviewers performed study selection independently, with disagreements resolved through discussion and by the opinion of a third reviewer, if necessary. Detailed information on search strategies and results are available upon request. Selected articles were ranked according to a hierarchy of evidence levels (14-20), including systematic reviews, controlled clinical trials, uncontrolled clinical trials and case series. Finally, all available evidence was summarised in evidence tables (Table 1). It was anticipated that very low quality evidence would be available and thus the clinical questions were also subsequently addressed by internationally recognised experts in the field (MC, DG, MH) in order to obtain an “evidence-based clinical judgment”. Inter-
national experts were three internists/hematologists with considerable experience in the management of VTE and use of anticoagulant drugs. To avoid intellectual bias, we selected experts who were not directly involved in any of the main studies retrieved in the literature.

We identified five clinical questions on the management and on the prognosis of patients with VTE treated with IVC filters. The first two questions were on the potential role of IVC filters in reducing mortality and PE recurrence in patients with VTE; the third question was on the potential risk of developing post-thrombotic syndrome (PTS) in patients with IVC filters; the fourth question was on the optimal duration of anticoagulation after the insertion of an IVC filter and the last question was on the optimal timing for the removal of optional IVC filters (Table 2). The experts were requested to review the summary of the evidences provided by the working group and to briefly answer each of the proposed questions. Experts were contacted via e-mail and were blinded to the answers provided by their peers. Based on the clinical judgment provided by the experts, we formulated practical suggestions aimed to assist practicing clinicians in their daily activity. No formal method for the grading of recommendations was applied.

### Table 1: Vena cava filters: principle available evidence.

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<tr>
<th>Reference</th>
<th>Study type</th>
<th>Treatment</th>
<th>Patients, N</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Endpoint</th>
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<tr>
<td>Decousous, NEJM 2003 (14)</td>
<td>RCT</td>
<td>Vena caval filter vs control.</td>
<td>400</td>
<td>Hospitalised patients over 18 years of age with acute proximal DVT confirmed by venography, with or without concomitant symptomatic PE considered at high risk for PE.</td>
<td>Placement of a previous filter, contraindication to or failure of anticoagulant therapy, curative anticoagulant therapy lasting more than 48 hours, an indication for thrombolysis, short life expectancy, allergy to iodine, hereditary thrombophilia, severe renal or hepatic failure, pregnancy, or likelihood of non-compliance.</td>
<td>- By day 12, 2 patients (1.1%) in the filter group and 9 patients (4.8%) in the no-filter group had PE (P 0.03). - After 2 years, symptomatic PE occurred in 6 patients (with 1 death) in the filter group and in 12 patients (with 5 deaths) in the no-filter group (P 0.16). - Recurrent DVT occurred in 37 patients (20.8%) in the filter group and in 21 patients (11.6%) in the no-filter group (OR, 1.87; 95% CI 1.10, 3.20; P 0.02). - Recurrent VTE occurred in 37 patients (20.8%) in the filter group and 29 patients (15.5%) in the no-filter group. - In the first 12 days, 5 patients in the filter group died, and 5 patients in the no-filter group died (4 from PE). After 2 years, 43 patients (21.6%) in the filter group had died, as compared with 40 patients (20.1%) in the no-filter group. Examination for filter patency was performed in the 37 patients who had symptomatic VTE within the two-year follow-up period. The examination found a thrombosis at the filter site in 16 patients.</td>
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<tr>
<td>The PREPIC study group, Circulation 2005 (15)</td>
<td>RCT</td>
<td>Eight years follow-up of the PREPIC study.</td>
<td>See study above</td>
<td>See study above.</td>
<td>See study above.</td>
<td>Symptomatic pulmonary embolism occurred in 9 patients in the filter group (cumulative rate 6.2%) and 24 patients (15.1%) in the no-filter group (p 0.008). DVT occurred in 57 patients (35.7%) in the filter group and 41 (27.5%) in the no-filter group (p 0.042). PTS was observed in 109 (70.3%) and 107 (69.7%) patients in the filter and no-filter groups, respectively. At 8 years, 201 (50.3%) patients died in the filter and no-filter groups, respectively.</td>
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Imberti et al. VTE and inferior vena cava filters

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<td>Fox, J Vasc Interv Radiol 2008 (16)</td>
<td>Systematic review</td>
<td>To evaluate the frequency of symptoms and signs of PTS in relation to IVC filter placement.</td>
<td>1552 (11 studies), mean follow-up 4.5 years.</td>
<td>Clinical studies that evaluated 10 or more patients who were followed and assessed for symptoms or signs of PTS at least 1 year after IVC filter placement.</td>
<td>Studies in which the authors did not explicitly state their definition of PTS, the duration of follow-up, the proportion of patients who completed follow-up.</td>
<td>- The weighted pooled incidence of oedema at follow-up was 42.9% (647 of 1,507; 95% CI, 40.4%–45.4%) and that of skin changes (including venous ulcers) was 12.0% (176 of 1,470; 95% CI, 10.3%–13.7%). - Among studies that reported the rate of venous ulcers separately from skin changes in general, the overall pooled incidence of ulcers was 3.4% (501 of 1,470; 95% CI, 2.5%–4.3%). - Among PTS who had IVC filter insertion for the secondary prevention of PE, 565 of 1,103 (51.2%; 95% CI, 48.3%–54.1%) developed chronic oedema, compared with 61 of 302 (20.2%; 95% CI, 15.7%–24.7%) of PTS who received an IVC filter for the primary prevention of PE. Similarly, the rate of chronic skin changes, including venous ulceration, was also higher among patients whose filters were inserted for secondary prevention (149 of 1,103; 13.5%; 95% CI, 11.5%–15.5%) versus primary prevention (25 of 302; 8.3%; 95% CI, 5.2%–11.4%). Of note, the average follow-up times differed considerably between the two groups; (5.6 years in the secondary prevention vs 2.1 years, in the primary prevention).</td>
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| Johnson, J Vasc Interv Radiol 2010 (17) | Prospective cohort study | Retrieval success | 39 | Subjects ≥18 years, with one or more of the following four conditions: PE when anticoagulant therapy was contraindicated; failure of anticoagulant therapy in thromboembolic disease; complication as a result of anticoagulant therapy in thromboembolic disease; or indication for temporary caval filtration (e.g. trauma or planned operation such as bariatric or pelvic surgery). | Subjects were excluded from enrollment if they already had a filter in place or had undergone filter retrieval within the previous 60 days. They were also excluded if they had confirmed bacteremia, a duplication of the IVC, a life expectancy of less than 6 months, a known sensitivity to radiographic contrast medium that could not be adequately premedicated prophylactically, a known hypersensitivity to nickel or titanium alloys, or any comorbid condition that the investigator deemed might compromise the study. | Retrieval was successful at a mean of 67.1 days after implantation (range, 1–175 days) for 36 of 39 subjects (92.3%). |
### Table 1: Continued

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<tr>
<td>Usoh, J Vasc Surg 2010 (18)</td>
<td>RCT</td>
<td>IVC thrombosis, filter migration, recurrent PE, overall mortality.</td>
<td>156</td>
<td>Contraindication to anticoagulation with DVT/PE. Failed anticoagulation with DVT/PE. Trauma patient at high risk for DVT/PE. High-risk procedure for PE with history of VTE.</td>
<td>Age ≥18 years. Preexisting filter. Uncontrollable coagulopathy. Vena cava diameter &gt;30 mm. Hypersensitivity to nickel, chromium, stainless steel. Pregnancy or planning pregnancy ≤6 months. Nonfemoral vein access for IVC filter placement. Suprarenal IVC filter placement.</td>
<td>IVC/IV thrombosis developed in five patients (6.94%) in the TrapEase group and none in the Greenfield group (p 0.019). No filter migration, access-site thrombosis, misplacement, or IVC perforation occurred. Recurrent PE was suspected in one of the five patients with IVC/IV thrombosis. Overall mortality was 42.3% (66 patients), and 30-day mortality was 13.5% (21 patients: 10 TrapEase, 11 Greenfield).</td>
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<tr>
<td>Oliva, J Vasc Interv Radiol 2005 (19)</td>
<td>Prospective cohort study</td>
<td>Efficacy of the retrieval of the Op- tEase Permanent/Retrievable Vena Cava Filter (Cordis, Warren, NJ, USA).</td>
<td>21</td>
<td>Age ≥18 years and indications for placement of an IVC filter according to the Society of Interventional Radiology Guidelines.</td>
<td>Filter was expected to remain in place for greater &gt;14 days; IVC diameter &gt;30 mm; septic status, presence of thrombus either at the site of venous access or in the IVC; life expectancy &lt;6 months; patients were currently enrolled in another device study or drug study; patients had another filter implanted or a history of a filter implanted in the past.</td>
<td>21 patients (77.8%) met the criteria for retrieval and all 21 patients (100%) had filters successfully retrieved with no associated adverse events. Time to retrieval ranged from 5 to 14 days with a mean implantation time of 11.1 days (SD ± 1.82).</td>
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<tr>
<td>Imberti, J Thromb Haemost 2005 (20)</td>
<td>Prospective cohort study</td>
<td>To evaluate the clinical efficacy and the likelihood to remove the retrievable IVC filter ALN.</td>
<td>18</td>
<td>Indications for implantation were acute VTE with a contraindication to anticoagulation, primary prophylaxis after major trauma or before surgery in patients with very high thromboembolic risk.</td>
<td>The ALN retrieval was attempted through right internal transjugular approach was successful in 14/18 patients (78%). When the decision of removal was taken within 3 months after the implantation, the retrieval was possible in 10 of 10 patients (100%); otherwise, when the attempt of retrieval was performed more than 3 months after the implantation, the retrieval was possible only in four of eight patients (50%).</td>
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CI, confidence interval; DVT, deep vein thrombosis; IVC, inferior vena cava; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; PTS, post-thrombotic syndrome; RCT, randomised controlled trial; UFH, unfractioned heparin; VTE, venous thromboembolism.

### Results of the review of the literature

Only one randomised controlled study (RCT) evaluated the efficacy of IVC in reducing the mortality and the rate of thromboembolic complication in patients with acute proximal DVT with or without concomitant PE (14). With a two-by-two factorial design, patients were also randomised to receive unfractionated or low-molecular-weight heparin followed by vitamin K antagonists for at least three months. At two-year follow-up, patients in the filter group had a significantly higher risk of DVT recurrence and a statistically non-significant trend toward a lower risk of PE. Mortality was similar irrespective of the use of an IVC filter. A second publication presenting eight-year follow up results of this study confirmed the results found at...
two years: patients randomised to receive IVC filters had a significantly increased risk of DVT recurrence, a statistically significant reduction in their risk of PE, and no difference in mortality (15). At eight-year follow-up the incidence of PTS was similar in patients with and without vena cava filters. To our knowledge, no data are available about the possibility of IVC filters to prevent chronic thromboembolic pulmonary hypertension, which may occur in about 1-4% of the patients after acute PE (21, 22).

A small, single RCT compared two different vena cava filters (Greenfield and TrapEase) in patients with VTE and a contraindication or a failure of anticoagulation and in patients undergoing procedures at high risk of VTE (18). In this study, 156 patients were enrolled and filter thrombosis developed in five patients (6.94%) in the TrapEase group and none in the Greenfield group (p=0.019), whereas all other outcomes, including recurrent PE and mortality, were similar between the two groups. A systematic review and a meta-analysis of the literature including 11 studies for a total of 1,552 patients evaluated the frequency of PTS after IVC filter placement with a mean follow-up of 4.5 years (16). PTS was very common in patients with IVC filter, with an incidence of 42.9% at follow-up (647 of 1,507; 95% confidence interval [CI], 40.4% - 45.4%). PTS incidence was higher when filters were inserted for secondary prevention of VTE (51.2%; 95% CI, 48.3% - 54.1%) compared to primary prevention of VTE (20.2%; 95% CI, 15.7%- 24.7%). Finally, we identified three observational cohort studies evaluating the rates of successful IVC filter retrieval (17, 19, 20). In these studies, filter retrieval was successful in almost all the patients when performed within three months after implantation, whereas it was unsuccessful in about 50% of patients when performed after three months.

Recently, the results of a RCT, PREPIC 2, comparing a retrievable IVC filter with no filter in high-risk patients with PE have been presented during the XXIV Congress of the International Society on Thrombosis and Haemostasis (ISTH) (23). Although all the authors acknowledge the importance of this study in this field, a decision was taken to not include the results of the PREPIC 2 study in our “evidence and clinical judgment” because the study is only available in the form of an abstract and currently available information is considered insufficient to be included in this consensus document.

Areas of agreement or controversy in clinical judgment

Based on available evidence and on the clinical judgments provided by international experts, we have addressed clinically relevant questions likely to be encountered by practicing clinicians dealing with patients with IVC filters. Some heterogeneity among expert opinions reflects current knowledge gaps, but may also reflect the different backgrounds of the interviewed clinicians.

All three experts agreed that IVC filters are not able to reduce mortality in patients with acute VTE. Support for this assumption is found in the results of a single RCT in which patients with acute DVT at high risk for PE were randomised to receive or not to receive a permanent IVC filter as an adjunct to anticoagulant therapy (14, 15). After two (14) or eight (15) years of follow-up there was no apparent mortality benefit from IVC filter placement compared to anticoagulation therapy alone. However, experts were inconsistent with respect to the lack of a mortality benefit in all cases where a filter might be used; one expert answered that IVC filter placement in patients with acute VTE who cannot be treated with anticoagulation may reduce death when compared with no treatment.

There was consensus among experts that IVC filters reduce PE in patients with acute DVT. One expert suggested that there is no evidence to support the utility of filter insertion in patients with PE who do not have a documented DVT. Of interest, among patients with PE and haemodynamic instability enrolled in an international registry (ICOPER) (24), the use of an IVC filter as an adjunct to anticoagulant therapy was associated with a reduction of early recurrent PE and mortality; this hypothesis is currently under investigation in a recently completed but still unpublished RCT (PREPIC 2) (23, 25).

There was no consensus about whether a permanent IVC filter increases the risk of developing PTS. This is despite the evidence from the PREPIC study that after eight years from the implantation of an IVC filter for acute DVT there was no significant difference in the occurrence of PTS between filter and no-filter group (15).

Summary of practical suggestions based on “evidence and clinical judgment”

The questions are listed in Table 2.

Question 1

Based on available evidence, IVC filters should not be used in adjunct to anticoagulation with the primary aim to reduce mortality.

Question 2

Compared to anticoagulant therapy alone, there is reasonable evidence to suggest that IVC filter placement reduces the short-and, to a lesser extent, the long-term risk of first or recurrent PE in patients with acute DVT.

Question 3

Although the available evidence is of low quality and inconsistent, IVC filters may be associated with an increased risk of PTS when used in patients with acute DVT.

Question 4

In the absence of RCTs supporting the optimal duration of anticoagulation after the insertion of an IVC filter, treatment should be prolonged as long as the filter remains in place and the therapy is safe (i.e. in absence of an ongoing contraindication to anticoagulation).

Question 5

Filters should be removed as soon as possible, when contraindications to anticoagulant treatment no longer exist; optimal timing for attempting filter retrieval is ideally within few weeks and not later than 90-120 days from insertion.
The lack of consensus may have occurred because patients in PREPIC were highly selected, while in general clinical practice many patients who receive filters do not receive therapeutic anticoagulation which may impact the frequency of subsequent development of PTS.

There was full agreement among experts about the need to prolong anticoagulation for the duration of filter placement. The experts partially disagreed about the selection of the subgroups of patients in whom anticoagulation should be stopped; these should either include patients with ongoing contraindications to anticoagulation only, or patients in whom VKA therapy is not well tolerated or in whom the proportion of time in the therapeutic range of the international normalized ratio (INR) is low. The expert opinion is in contrast to the recommendations of the most recent
ACCP guidelines (2) that do not consider a permanent IVC filter an indication for extended anticoagulation and suggest treating patients with filters for the same length of time as patients without an IVC filter.

Finally, there was consensus that all filters should be removed at the earliest possible time, when the contraindication to anticoagulation has resolved.

Conflicts of interest
None declared.

References