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It is not necessary to use both an IVC filter and anticoagulation therapy for severe pulmonary embolism

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ABSTRACT A critical appraisal and clinical application of Mismetti P, Laporte S, Pellerin O, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. *JAMA*. 2015;313(16):1627–1635. doi: [10.1001/jama.2015.3780](https://doi.org/10.1001/jama.2015.3780).

Keywords: *IVC filter, inferior vena cava filter, pulmonary embolism, deep vein thrombosis, anticoagulation*

Clinical Context

NS is a 72-year-old female who presented to the emergency department with a one-day history of severe shortness of breath and chest pressure. Symptoms began when the patient was sitting. We diagnosed a large saddle pulmonary embolism (PE) with right ventricular strain through CT, V/Q scan, positive troponin biomarkers, and an electrocardiogram. Additionally, Doppler study revealed multiple right lower extremity deep vein thrombi (DVTs). The patient recalled some calf pain in the past, but had no current swelling or redness. She denied any family history of clotting disorders, frequent miscarriages or abnormal bleeding. The patient was treated with a retrievable inferior vena cava (IVC) filter, EKOS (an ultrasound-enhanced catheter guided thrombolysis), and bridged to warfarin as prophylaxis against future events. The patient wondered if both the IVC filter and anticoagulation were necessary.

Clinical Question

Is there an additional benefit to having an IVC filter in a patient who is able to be anticoagulated?

Research Article

Mismetti P, Laporte S, Pellerin O, et al. Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: a randomized clinical trial. *JAMA*. 2015;313(16):1627–1635. doi: [10.1001/jama.2015.3780](https://doi.org/10.1001/jama.2015.3780)

Related Literature

PubMed database was used to search for articles that contained the keywords “inferior vena cava filter,” “anticoagulation,” and “pulmonary embolism.” Many of the resulting articles assessed the benefit and harm of IVC filters in patients that were contraindicated for anticoagulation; the patient in question is a candidate for anticoagulation and for this reason these studies did not help answer the clinical question.

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Randomized trials that reviewed the use of IVC filters for pulmonary embolism prevention, such as the 1998 study by Decousus et al., set the groundwork for future studies. The 1998 study limitations were the use of a permanent filter (our patient had a retrievable filter) and the focus of low-molecular-weight heparin in comparison with unfractionated heparin. Additionally the study did not focus on high-risk individuals, which is the population that are considered candidates for IVC filters.¹ This study propelled the discussion of retrievable IVC filters as a possible form of intervention, as the first 3-6 months were shown as the time when the filter has the optimal amount of benefit. Dr. Jack Ansell commented on these strengths and shortcomings in his editorial “Vena cava filters: do we know all that we need to know?”² He discussed the 8-year follow-up of the Decousus et al. study, and the trade-off that exists with placing an IVC filter, namely fewer PEs at the cost of more DVTs. Of note, there is no significant difference in long-term morbidity or mortality, establishing that permanent IVC filters do not add benefit to anticoagulation.² The Cochrane reviews addressed the use of IVC filters for pulmonary embolism as well as the use of anticoagulant treatment for subsegmental pulmonary embolism. In both reviews, there was insufficient evidence at the time to recommend the use of either therapy over no intervention. More research was needed before informed decisions could be made.^{3,4}

In 2015, Isogai et al. published a study evaluating the effectiveness of IVC filters on mortality as an adjuvant to antithrombotic therapy.⁵ Because the paper was a retrospective study, the risk of bias was high. The types of filters assessed were both retrievable and permanent; there is a potential for differences in outcome between the two types of filters.

The article chosen for this critical appraisal and clinical application was a randomized, open-label, blinded end-point clinical trial of 399 patients, and carried the additional benefit of solely using retrievable filters, which our patient received. This article used the ALN filter to standardize the therapy across all patients, whereas the patient in our scenario had a Gunther Tulip IVC filter placed. Further research revealed that IVC filters have comparable efficacy, and therefore this study by Mismetti et al. best fit our clinical question and context.⁶

Critical Appraisal

The article by Mismetti et al. was a randomized, open-label, blinded end-point trial conducted in 17 French centers from August 2006 to January 2013, with a 6 month follow-up, by the Prévention du Risque d’Embolie Pulmonaire par Interruption Cave 2 (PREPIC2) Study Group.⁷ The purpose of the study was to evaluate the risk of benefit and the risk of harm of adding inferior vena cava filters to anticoagulation in patients with a high risk for recurrent pulmonary embolism. This study follows the PREPIC study published in 2005 that analyzed the harms versus benefits of vena cava filters in patients at high risk for pulmonary embolisms. The 2005 study analyzed data collected over eight years and found that although there may be a benefit to high-risk patients. They were not able to recommend its use for the general population. Although the risk of pulmonary embolism was reduced, there was also an increase in deep vein thromboses at two years. Results at eight years showed no effect on survival.⁸ Additionally, as noted in the Cochrane reviews, though there were no adverse events of filters reported in the PREPIC study the numerical size of the trial was too small to even allow for detection.³

The PREPIC2 study randomly assigned patients to one of two groups: the first group was treatment with a retrievable inferior vena cava filter implantation plus anticoagulation therapy, and the second group was treatment with anticoagulation alone without a filter implantation. The anticoagulation therapy was prescribed for 6 months and the filters were scheduled for removal 3 months after implantation. Patients were chosen for this study if they were hospitalized with an acute symptomatic pulmonary embolism, with an associated lower extremity vein thrombosis, and at least one severe criteria (defined by this study as >75 years, active cancer, chronic cardiac or respiratory insufficiency, ischemic stroke with leg paralysis within the last 6 months, DVTs of the ilio caval segment, bilateral DVTs, at least one sign of right ventricular dysfunction or myocardial injury, or abnormal levels of biomarkers such as brain natriuretic peptide). Exclusion criteria were clearly defined. Our patient satisfied the criteria to be included in this study.

The main primary efficacy outcome of this study was symptomatic nonfatal or fatal recurrence of a PE within 3 months. Secondary outcomes were recurrent fatal or symptomatic nonfatal PEs at 6 months, symptomatic DVTs, major bleeding, death at 3 and 6 months, or complications with the IVC filter. Harms associated with patients who randomized to receive filters were access site hematomas (2.6%), filter thrombosis (1.6%), and retrieval failure due to mechanical reasons (5.7%).



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The analysis was performed using an intention-to-treat analysis, which led to a total of 399 patients. A concealed randomization system blinded the committee to treatment assignments. Follow up at 3 months showed a recurrent PE in 6 patients of the filter group (3%) and 3 patients in the control group (1.5%). At the 6-month follow up, one additional patient in each group developed a PE. These measures were much lower than the expected 8% and there was no additional benefit of significance ($p=0.5$ with a large range 95% CI 0.51 to 7.89) in the addition of an IVC filter to a patient that is anticoagulated to prevent recurrence of a PE. These results are not consistent with the PREPIC study.

Of concern is the possibility of publication bias, as the authors of the study have disclosed conflicts of interest due to receiving research grants, fees for board memberships, and consultancy activities, among other conflicts, from numerous pharmaceutical companies such as Bayer, Pfizer, Siemens Health Care, and many others. Authors that disclosed conflicts of interest contributed to study concept and design, acquisition or interpretation of data, drafting of the manuscript, critical revision of the manuscript, statistical analysis, obtained funding, administrative support, or supervised the study.

This paper did not provide details when defining the criteria to diagnose a patient with a pulmonary embolism. The paper simply stated the tests used to confirm DVTs or PEs. The authors did not provide any further detail on how the results were read, raising the issue of test reliability. There are also major inconsistencies, as published in commentary by Dr. Hoffer, between PREPIC and PREPIC2, as Mismetti et al. did not comment on the opposing 3-month rate of PE recurrence between the two studies. In PREPIC there was a higher recurrent PE rate in the no filter group (3.2% vs PREPIC2's 1.5%) whereas in PREPIC2 the filter group had a higher rate of PE recurrence (3% vs PREPIC's 1.1%).⁹ Limitations of the study included a lack of long-term follow-up and the occurrence of pulmonary embolus that was far lower (1.5%) than expected (8%) with the use of a high-risk population. The choice of anticoagulation therapy used was not fully standardized and therefore any injectable anticoagulant agent could be used as long as a Vitamin K antagonist was given shortly after. An additional limitation was inherent in the open-label nature of the study. Drs. Hoffer and Mismetti et al. exchanged comments and responses regarding the length of IVC and anticoagulation treatment. PREPIC2 was designed using 3 months of anticoagulation, although previous studies showed significant benefit after 1 year, due to the increased risk of lower-limb DVTs with long-term treatment.^{10,11} This is a strength of the PREPIC2 study as an attempt to balance the risk of benefit and the risk of harm of anticoagulation treatment. The use of a high-risk population can also be seen as a strength for this study.

Clinical Application

Current clinical guidelines cite Mismetti et al. and, in agreement with this critical appraisal, state: "In patients with acute DVT or PE who are treated with anticoagulants, we recommend against the use of an IVC filter (Grade 1B)."¹² Therefore in future patients we should refrain from using an IVC filter in patients receiving anticoagulation therapy.

The patient of interest fit within the criteria for the PREPIC2 study. She was a Caucasian female with right lower extremity DVTs diagnosed with a saddle pulmonary embolus, with the additional severity criteria of right ventricular dysfunction and myocardial injury. Taking into account the results from Mismetti et al., the patient did not receive any additional benefit from the placement of an IVC filter: treatment with anticoagulation alone was sufficient. The patient was scheduled for removal of her IVC filter 3 months after it was placed, and was discharged from the hospital on warfarin with follow up to evaluate the duration for which she will need to be on anticoagulation.

Lessons learned:

1. There is no an increased benefit of using both an IVC filter and anticoagulation.
2. I wonder if provider concerns rather than evidence influenced management. This might be a case of our misconception that more is better.



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