Commentary

Implications and limitations of the PREPIC2 study—the interventionist's perspective

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Inferior vena cava (IVC) filters have proven invaluable in the prevention algorithm for pulmonary embolism (PE), reflected in their increased use within the past decade (1). On the other hand, prolonged dwell time, overall low retrieval rates ranging from 1.0–40.5%, and lack of follow-up, have resulted in an increase incidence of filter-related adverse events (2). Permanent and retrievable filters are available expanding indications, and specifically prophylactic placement in patients with high risk of venous thromboembolic disease, have contributed to steady rise in retrievable IVC filter placements, without clear support of clinical consensus guidelines (3). The estimated amount of implanted IVC filters were 2,000 in 1979 and increased by a factor of approximately 83.5 in 2007 to almost 167,000 (1). Though there is lack of evidence based on randomized trials for the efficacy of IVC filters to positively impact patient outcome.

The PREPIC2 study (Prevention du Risque d'Embolie Pulmonaire par Interruption Cave 2)/(Prevention of Recurrent Pulmonary Embolism by Vena Cava Interruption) sought to address this uncertainty in a large, randomized, blinded, multi-center, end-point trial assessing the safety and benefit of retrievable IVC filter placement plus anticoagulation (AC) versus anticoagulation alone for the prevention of recurrent PE in high risk acute PE patients related to lower extremity venous thromboembolism (4).

The hypothesis of the PREPIC2 trial was based on results from the PREPIC1 study, which demonstrated a lower rate of PE in patients with implanted permanent IVC filters at 12 days (5), but an increase in delayed recurrent deep venous thrombosis (6) in the eight year follow-up data, despite a decrease in the non-fatal PE recurrence rate. Retrievable IVC filters may therefore prevent short-term PE, but avoid long-term complications. Based on this hypothesis, the PREPIC2 study enrolled 399 patients and assigned them to either the IVC filter placement plus AC or anticoagulation alone groups. At 3- and 6-month follow-up no significant differences were observed with regards to recurrence. The authors concluded there was no reduced risk of recurrent PE in patients with acute PE related to lower extremity venous thromboembolism when performing a combined treatment approach of retrievable IVC filter placement plus AC therapy as compared to AC alone (4).

In order to understand the clinical implications of this trial, it is important to focus on the patient population enrolled in PREPIC2. The recurrent PE rate in both study arms of PREPIC2 was well below the published and expected 8.0% rate. The low recurrent PE rate and lack of benefit of filter placement was observed in a patient population, where full AC therapy was possible and effective. However, in clinical practice, one of the more common indications for IVC filter placements are for those patients in whom either AC is not effective or cannot be pursued due to increased bleeding risk, or other contraindications to AC therapy (7). These patients may benefit the most from retrievable IVC filter placement, but the PREPIC2 study did not provide answers for this patient group commonly seen on our practice.

Another clinical parameter which needs to be considered when evaluating IVC filter effectiveness is the cardiopulmonary status of the patient. Patients who are

critically ill and hemodynamically unstable may not be able to compensate for even a small embolus traveling into the pulmonary vasculature, and may therefore benefit most from IVC filter placement (8,9). The lack of correlation between IVC filter efficacy and systemic clot burden is a further limitation of PREPIC2. Patients with large mobile lower extremity venous thromboembolism, such as a large free floating iliocaval thrombus and massive PE, may benefit from IVC filter placement (10). Thus, it remains unclear if patient populations not included in this clinical trial may benefit from a combined approach of AC plus retrievable IVC filter placement

IVC filter placement was technically successful in 99% of patients and IVC filter removal was achieved in 92% of patients (4). These findings demonstrate the safety and high technical success rate of IVC filter placement and retrieval when accomplished within 3 months of placement. With regard to timing of IVC filter removal, a decision analysis study was performed to analyze the benefit/risk ratio of retrievable IVC filter placement as a function of the duration of the IVC filter dwell time. Based on this analysis, the authors concluded that the benefit/risk ratio suggests IVC filter removal between 29 and 54 days post implantation in those patients with subsided PE risk (11). Outside clinical trials a more individualized approach may be considered.

In August 2010, and updated in May 2014, the United States Food and Drug Administration issued a safety report stating physicians should consider removal of retrievable IVC filters as soon as protection from PE was no longer necessary, and placed the onus on the clinician responsible for the long-term care of the patient, as well as on the physician who initially placed the retrievable device (12). This action was taken after the Food And Drug Administration (FDA) had received over 900 reports of adverse events associated with IVC filter implantation, with the two most frequent being device migration and embolization. Concern was raised that a portion of these reported events may have been associated with long-term placement. Retrievable filters, which can be safely removed with a high degree of success and low complication rate, should therefore be removed, once caval filtration is no longer needed. In addition to the adverse events listed above, long term IVC filter placement increases the risk for lower extremity deep venous thrombosis and IVC occlusion. This reinforces the principal that patients tolerating anticoagulation and who are not critically ill, should not need additional IVC filtration.

In general two types of IVC filters are available, retrievable or permanent ones. In particular if the indication for the IVC filter placement is temporary, a retrievable IVC filter should be implanted and can be removed once the risk factor has subsided (13). For example in a post trauma patient if the immobilization is limited to several weeks to a few months, this patient can benefit from retrievable IVC filters. Permanent IVC filters are associated with certain complications, such as post-thrombotic syndrome, recurrent deep venous thrombosis and even IVC occlusion (14,15).

Large prospective registry-style studies may eventually answer a number of open important questions related to IVC filter efficacy, not addressed by the PREPIC2 trial (15). One ongoing trial is the PRESERVE (Predicting the safety and effectiveness of inferior vena cava filters) study which is evaluating the use of IVC filters and the post-procedural follow-up algorithm (16). The PRESERVE trial is a prospective observational cohort study. Future studies also need to address to what extent IVC filters reduce the PE risk and if patients who are not candidates for anticoagulation may particularly benefit from IVC filter placement.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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