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Efficacy and safety of rivaroxaban in patients with inferior vena cava filter placement without anticoagulation contraindications (EPICT): a prospective randomised controlled trial study protocol

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ABSTRACT

Introduction Inferior vena cava (IVC) filters are commonly used in patients with venous thromboembolism to prevent fatal pulmonary embolism, but the thrombosis risk increases after filter placement. Warfarin is a widely anticoagulant, but long-term monitoring and dose adjustments are required. Anticoagulation with rivaroxaban is more straightforward as it dose not require laboratory monitoring. This study compares the efficacy and safety of rivaroxaban and warfarin as an in anticoagulation therapy for patients with IVC filter placement.

Methods and analysis This is a multicentre, randomised controlled trial. In total, 200 patients with deep vein thrombosis (DVT) with IVC filter implantation from 10 hospitals will be recruited. The patients will be randomised to the experimental group (rivaroxaban) or the control group (nadroparin overlapped with warfarin). The primary outcomes include death of any cause, pulmonary embolism (PE)-related death, bleeding and recurrent PE/DVT. The secondary outcomes include the percentage of other vascular events, IVC filter retrieval failure and net clinical benefits. This study aims to provide reliable, verification for the efficacy and safety of rivaroxaban antithrombotic therapy after IVC filter placement.

Ethics and dissemination The study was approved by the Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (approval number: (2019) 295). The results will be disseminated through presentations at scientific conferences and publications in peer-reviewed journals

Trial registration number NCT04066764.

Strengths and limitations of this study

- This study is a prospective, randomised, multicentre, controlled trial.
- This is the first trial to compare the safety and efficacy of rivaroxaban and vitamin K antagonists in patients with inferior vena cava filter placement.
- This is an open-label study, and researchers and competent physicians are aware of the patients' grouping information.
- Patients in the control (ie, warfarin) group require international normalised ratio and dose adjustment monitoring during the follow-up period, so they are not blinded to the treatment strategy, resulting in bias.
- The participating centres have different brands of retrieval inferior vena cava filters because of variable medical insurance policies, leading to potential errors in the results.

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a common and potentially fatal disease with an annual incidence of approximately one or two cases per 1000 persons in the general population, which is mostly observed in patients older than 55 years.[1 2] The standard VTE treatment is anticoagulation, which effectively stops the abnormal clotting process, preventing DVT, PE and recurrent VTE progression.[3] However, inferior vena cava (IVC) filter placement is considered for patients with a recent proximal DVT who show contraindication to therapeutic anticoagulation during acute treatment. Filters are also placed in patients with suspected recurrent VTE or progressive DVT despite therapeutic anticoagulation, extensive DVT (involving the vena cava or iliac veins) or DVT with a free-floating proximal end, proximal DVT in patients undergoing a catheter-directed thrombus reduction procedure or PE managed with thrombolysis or

surgical embolectomy[4–7] IVC filters also have prophylactic indications, such as when applied in trauma patients or before bariatric and pelvis surgeries.[4] Changes in the IVC haemodynamics after filter implantation may increase the risk of thrombosis in or around the filter, and the thrombosis risk significantly increases once the filter is tilted.[8] For patients with an IVC filter and without anticoagulation contraindications, adequate anticoagulation therapy inhibits the spread of thrombus and promotes autolysis, preventing filter-related thrombosis and PE recurrence.[6 9]

Until recently, the standard treatment for acute VTE was initial parenteral heparin (eg, low-molecular-weight heparin) administration with overlapping vitamin K antagonist (VKA) administration, with a target international normalised ratio (INR) of 2.0–3.0.[3 10] Studies have confirmed that low-molecular-weight heparin is safe and effective in the prophylaxis and initial treatment of VTE,[11 12] and is suitable for cancer and pregnant patients.[13–15] Warfarin is a standard oral anticoagulant with a sufficient anticoagulant effect and low price. The efficacy and safety of anticoagulation using low-molecular-weight heparin overlapped with adjusted doses of VKAs in patients with IVC filter implantation are widely recognised.[16] However, VKA treatment requires laboratory monitoring and dose adjustment and may be complicated by drug and food interactions, presenting a challenge for outpatient management. Altogether, follow-up management is more difficult, and there is more uncertainty regarding the treatment effect and potential for more severe bleeding complications.[17] The annual major bleeding risk associated with VKAs is 1%–2% after the first year.[3] Non-adherence to warfarin therapy during VTE treatment has also been associated with increased risk for recurrent VTE events.[18]

Rivaroxaban, an oral direct factor Xa inhibitor, has several advantages over VKAs, including rapid onset and predictable pharmacokinetic profile, allowing for simplified drug administration in a standardised dose, and avoiding the need for laboratory monitoring and dose adjustments. There are also no food interactions and only a few drug interactions.[1 19] Previous studies have shown that rivaroxaban prevents DVT after orthopaedic surgery,[19–21] offering an effective, safe, single-drug approach to the initial and continued treatment of DVT and PE,[19 22] even in patients with active cancer.[23 24]

There are limited clinical data on the safety and effectiveness of rivaroxaban as an anticoagulant in patients with an IVC filter. Therefore, we are conducting a prospective, randomised, multicentre, controlled trial to assess the efficacy and safety of rivaroxaban for preventing DVT in patients with an IVC filter. This study aims to provide the basis for VTE treatment guidelines and explore the clinical indications for rivaroxaban.

METHODS AND ANALYSIS

Study design and setting

The study is a randomised, multicentre, open-label, controlled trial comparing the efficacy and safety of rivaroxaban with standard therapy consisting of enoxaparin and a VKA in patients with IVC filter placement. The ethics committee approved the study at each participating hospital. Written informed consent was obtained from the patients before randomisation. The data will be collected and maintained by the sponsor. All suspected outcome events will be classified by a central adjudication committee whose members are unaware of the treatment assignments. An independent data and safety monitoring board will periodically review the outcomes. Patients are randomly allocated to either the experimental or control group after enrolment. Figure 1 illustrates the study design.

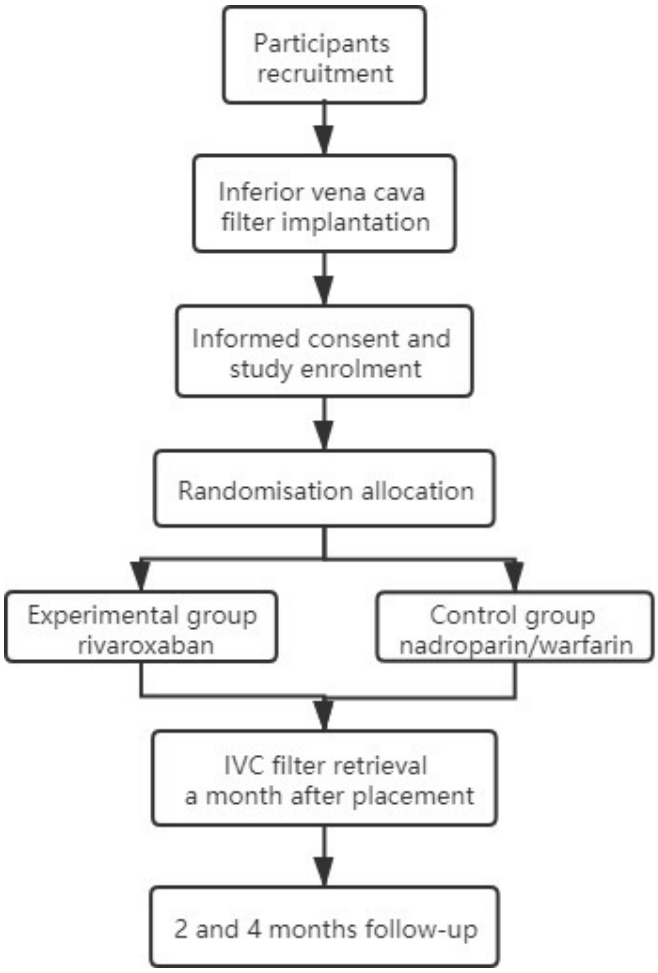

Figure 1 The flow of screening, randomisation, treatment and follow-up of patients in the trial. IVC, inferior vena cava

Sites and patients

In total, 10 hospitals attended the kick-off meeting and discussed the research protocol and details. All 10 hospitals fully communicated and discussed the DVT clinical diagnosis and treatment procedure, indications for IVC filter placement and the optimal retrieval window according to the existing clinical guidelines. Moreover, the anticoagulation treatment and monitoring programmes after IVC filter implantation were formulated. The diagnosis and treatment process, diagnostic

criteria and research protocols were approved according to the revised discussion results and the agreement of all participating units.

All patients aged 18–75 years, diagnosed with DVT of the lower extremity and implanted with an IVC filter from the 10 participating hospitals will be recruited. Patients with typical symptoms will be screened through D-dimer testing, colour Doppler ultrasound, CT venography, magnetic resonance venography or venography with digital subtraction angiography to objectively confirm DVT. The indications for IVC filter placement were:[3 5 25] (1) DVT or PE with contraindication to anticoagulation, (2) recurrent VTE or progressive DVT despite therapeutic anticoagulation, (3) large free-floating proximal DVT in the vena cava or iliac veins, (4) prior to catheter-directed thrombolysis, percutaneous mechanical thrombectomy or surgical embolectomy, (5) DVT of the lower limb with ipsilateral limb surgery and (6) prophylactic indications, such as in trauma patients or before bariatric, pelvis or lower limb surgeries.

Patients conforming to the inclusion and exclusion criteria will be randomised. The inclusion criteria were patients with a definite DVT diagnosis who will receive an IVC filter to prevent fatal PE. As some indications are not absolute for IVC filter implantation, those who refused to insert an IVC filter were not enrolled. Patients were excluded if they (1) aged <18 or >75 years, (2) had obvious contraindications for anticoagulation therapy, (3) were allergic to iodine contrast agents, (4) had concomitant diseases requiring high-intensity anticoagulation and the anticoagulation intensity is higher than that of the patients with only an IVC filter, (5) had a creatinine clearance below 30 mL/min, (6) had clinically significant liver disease (eg, acute hepatitis, chronic active hepatitis or cirrhosis) or an alanine aminotransferase level that was more than three times the upper limit of the normal range, (7) had bacterial endocarditis, (8) had active bleeding or a potential bleeding risk, (9) were pregnant or breast-feeding, (10) had a systolic blood pressure of more than 180 mm Hg or diastolic blood pressure of more than 110 mm Hg, (11) had malignant tumours and a life expectancy of <1 year or (12) taking CYP-450 3A4 inhibitors or inducers.

Randomisation and blinding

Blocked randomisation was performed. Central randomisation based on the Research Electronic Data Capture (REDCap) system will be conducted. The REDCap system was developed by Paul Harris of Vanderbilt University with a randomisation module.[26] Someone not involved in this study will generate the allocation sequence using the REDCap system to ensure allocation concealment. Patients will be randomly assigned to either the experimental or the control group. It is an open-label study, and the assessors will be blinded to the interventions after the assignment.

Therapy treatment and protocol

The DVT patients will receive retrieval IVC filter implantation, the filters will be retrieved 1 month after insertion. In all participating centres, filters will be placed and retrieved by experienced vascular and interventional radiologists following a standardised procedure based on the technical documentation provided by the manufacturer. All patients will undergo cavography before and after filter placement and conventional abdominal radiography between 24 and 48 hours after implantation. Before filter retrieval, ultrasonography or venography will be performed to detect filter thrombosis.

Participants assigned to the rivaroxaban group will receive 20 mg of rivaroxaban orally once daily for 4 months after the operation. Patients assigned to the standard therapy (ie, control) group will receive 1.0 mg/kg of body weight of nadroparin subcutaneously twice daily plus 3 mg of warfarin orally once daily after the IVC filter insertion. Enoxaparin will be discontinued when the INR is between 2.0 and 3.0 or more for two consecutive days; the patient will receive at least 5 days of enoxaparin treatment.

Discontinuaion or modification criteria

Participants should withdraw from this clinical trial when they have active bleeding after anticoagulant administration, diseases that cannot continue anticoagulation or surgery is needed to stop anticoagulation. The detailed definitions for bleeding have been systematically described.[27 28] Subjects may be withdrawn from this study at their request or the request of their legal representative. However, early permanent discontinuation of the study drug is discouraged wherever possible and we will purchase insurance for all participants to cover study-related adverse events.

Surveillance and follow-up

All participating hospitals will use the same electronic case report form (eCRF) available in the REDCap system to collect patient data. All centres participating in the trial, ethics committee and statisticians will have access to the system, and patients' identity information is encrypted to prevent leakage. An independent data monitoring committee is responsible for summarising and checking the data of each centre. Moreover, if they have any questions, they can contact the coinvestigators of each centre for review or revision. We will follow the patients for the intended treatment period and assess them at the time of IVC filter retrieval (after 1 month) and 2 and 4 months after the operation in both study groups, using the eCRF data to elicit information on the symptoms and signs of recurrent VTE, bleeding and adverse events. Patients are instructed to report to the study centre immediately if any symptoms or signs suggestive of VTE or bleeding occurred between visits.

Outcome measures

The primary outcomes of the study are death of any cause, PE-related death, bleeding and recurrent PE/DVT. Patients with suspected recurrent PE/DVT and bleeding will undergo objective testing and a clinical summary form. Suspected recurrent PE/DVT is defined as a composite of DVT or non-fatal or fatal PE based on the previously described diagnostic criteria.[29] Clinically relevant bleeding is defined as a composite of major or clinically relevant nonmajor bleeding, as also described previously.[30]

The secondary outcomes are vascular events (eg, acute coronary syndrome, ischaemic stroke, transient ischaemic attack or systemic embolism), IVC filter retrieval failure and net clinical benefits (defined as a composite of the primary efficacy outcome and major bleeding assessed in the intention-to-treat population). IVC filter retrieval failure is relevant to IVC filter complications (eg, IVC thrombosis, IVC perforation, IVC filter migration or tilting and IVC filter embolisation), system factors and technical factors.[31] We will also transform the retrieval IVC filters to permanent filters and prolong the duration of anticoagulant therapy. Bleeding will be defined as major if it is clinically overt and associated with a haemoglobin level decrease of 2.0 g/dL or more, if bleeding leads to the transfusion of two or more units of red cells or if bleeding is intracranial or retroperitoneal, occurs in another critical site or contributes to death.

Sample size calculation

Adverse clinical outcomes of IVC filters are defined as a composite of recurrent VTE, IVC thrombosis or death. Weinberg *et al*[32] reported that the adverse clinical outcomes rate for patients with IVC filters and without anticoagulants was 67.9%. However, the rate was only 30.5% and 29.1% for patients receiving prophylactic or therapeutic anticoagulation, respectively. For the group design non-inferiority test, 180 cases are sufficient under a power of 0.8, and the non-inferiority margin was –0.12. Thus, we will recruit 200 patients, considering a dropout rate of 10%, 100 patients per group.

Statistical analyses

Statistical analyses will be performed on an intention-to-treat basis. Descriptive data will be reported as either means±SD, medians (IQR) or numbers and percentages. Abnormally distributed data will be presented as medians (IQRs). The χ^2 will be used to compare categorical variables between the two groups. Continuous variables will be compared using the sample t-test for normally distributed data and the Mann-Whitney U test for abnormally distributed continuous variables. The binary classification outcome variables will first be compared using a non-corrected χ^2 test, and then the binary logistic regression analysis wil be established to correct for other confounding factors and calculate the ORs and 95% CIs. The survival differences between the two groups will be compared using the log-rank test, and the results will be described by Kaplan-Meier survival curves. Statistical analyses will be performed by using GraphPad Prism (V.X, Microsoft, San Diego, CA, USA), and R software (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance will be defined as a p-value of <0.05.

Patient and public involvement

Patients or the public were not involved in the study design, recruitment and conduct. The study results will be disseminated to study participants via a thank you letter at the end of the study.

ETHICS AND DISSEMINATION

Approval and consent to participate

The study was approved by the Human Research Ethics Committee of the Second Affiliated Hospital of Zhejiang University School of Medicine (approval number: (2019) 295). This trial was also approved by other centres' ethics committees, such as the Ethics Committee of Sir Run Run Shaw Hospital of Zhejiang University School of Medicine, the Ethics Committee of Zhongshan Hospital of Fudan University, the Ethics Committee of Huadong Hospital of Fudan University, the Ethics Committee of The Fifth People's Hospital of Shanghai, the Ethics Committee of Yantai Yuhuangding Hospital, the Ethics Committee of The First Affiliated Hospital of USTC, the Ethics Committee of Zhejiang Provincial People's Hospital, the Ethics Committee of Zhejiang Xiaoshan Hospital and the Ethics Committee of Hangzhou Third Hospital. An English translation of the ethical approval document is attached at online supplemental appendix 1. Written informed consent to participate (online supplemental appendix 2) will be obtained from all participants.

Dissemination

Study information will be prepared following the Good Clinical Practice Guidelines and is publicly available at www clinicaltrialsgov. The results of this trial will be submitted for publication in a peer-reviewed journal. The data will be used for publication and presentation at scientific meetings.

DISCUSSION

IVC filters are designed to trap venous emboli from the lower extremity and prevent clinically significant PE. The most common indication for IVC filter placement is an absolute contraindication to anticoagulation during the acute treatment of DVT or PE. The implantation of IVC filters for other indications, such as anticoagulation failure, massive clot burdens or reduced cardiopulmonary reserve, before thrombolysis or prophylaxis in high-risk patients has expanded.[6] The availability of retrievable IVC filters has likely contributed to the increasing filter use.[25] Vena cava filters are thrombogenic, and thrombi were macroscopically detected in the removed temporary filters in 75% of patients after a mean insertion duration

of only 5 days.[33] Haemodynamic changes in the IVC after filter placement may increase the risk of thrombosis,[8] and evidence suggests that IVC filters increase the DVT risk after filter placement.[34 35] Therefore, high-intensity anticoagulation should be performed as soon as the IVC filter is placed to prevent filter-related thrombosis and recurrent DVT or PE.

VKAs administration after initial parenteral heparin treatment is recommended for long-term oral treatment in patients with an IVC filter. However, treatment with a VKA requires laboratory monitoring and dose adjustment and may be complicated by drug and food interactions, presenting a challenge to outpatient management. Novel oral anticoagulants (NOACs) are an ideal alternative because they do not require laboratory monitoring and have fewer drug, disease and diet interactions.[1] However, there is no high-level evidence-based clinical verification for NOACs in anticoagulation regimens after implanting IVC filters. Therefore, it is necessary to conduct a randomised controlled trial to compare the anticoagulant effects of NOACs with warfarin. As a direct factor Xa inhibitor of NOACs, rivaroxaban has been demonstrated as effective and safe in the prophylaxis and treatment of VTE and as an antithrombotic therapy for atrial fibrillation,[36] and peripheral or carotid artery disease.[37] Therefore, rivaroxaban was chosen for this trial.

The study has some limitations. First, this is an open-label study. Researchers and competent physicians are aware of the patients' grouping information, so we will arrange for independent coordinators blinded to the allocation of groups to collect the outcome data to reduce bias. Second, as the patients in the control group require INR and dose adjustment monitoring of warfarin during the follow-up period, they are not blinded to the treatment strategy, bringing more bias. However, we will make every effort to ensure that outcome assessors, data managers and statisticians are unaware of the treatment allocations. Third, different brands of retrieval IVC filters have their own advantages, limitations and complications rates. Owing to the variable medical insurance policies of participating centres, the obtained filters are different, which may also lead to errors in the results. We will use a single filter model to ensure study homogeneity, unify the indwelling time and reduce the corresponding errors.

Altogether, this trial aims to provide more clinical basis for anticoagulation after IVC filter implantation and explore the clinical indications for rivaroxaban.

Trial status

Ethics approval was granted before submission. Recruiting patients for the trial has not started (scheduled date: 31 December 2020). We anticipate that recruitment will be completed on 31 December 2021. The current protocol is V.4.0, and any protocol amendments will be updated at clinicaltrials.gov.

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