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Design of the FP-RESTORE study: a prospective, observational study of real-world treatments with endovascular therapy in patients with femoropopliteal artery Tosaka III in-stent restenosis.

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Design of the FP-RESTORE study: a prospective, observational study of real-world treatments with endovascular therapy in patients with femoropopliteal artery Tosaka III in-stent restenosis.

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Abstract

Introduction: Femoropopliteal artery in-stent restenosis(FP-ISR) has become one of the main blocks for stent implantation in PAD patients, especially Tosaka III FP-ISR, which is also called in-stent occlusion. The endovascular treatments of Tosaka III FP-ISR are diverse and the effects are also remained controversial and real-world data are scarce. This study aims to evaluate the efficacy, safety and health economics evaluation of various endovascular procedures in treating Tosaka III FP-ISR.

Method and analysis

This study is a prospective, multicenter, real-world, observational clinical study. Patients diagnosed with Tosaka III FP-ISR and treated with endovascular procedures in 9 centers from 1 April 2021 to 31 December 2022 will be recruited. The relevant clinical information, ankle-brachial index and CT angiography will be collected. All the participants will undergo follow-up at 1, 6, 12,18 and 24 months after operation. The primary outcome is freedom from target lesion revascularization at 24-month. The safety and health economics issues are also planned to be reported.

Ethics and dissemination

The FP-RESTORE clinical trial has been registered in ClinicalTrial (http://clinicaltrials.gov/). This study has also been approved by the Institutional review board and Human Research Ethics Committee of Zhongshan hospital, Fudan university(Approved number: B2021-427). Moreover, the written informed consent will be obtained at the time of recruitment. The study outcomes will be disseminated by publication in a peer-reviewed journal to provide information for further clinical

practice.

Trial registration number : Number: NCT04801004.

Protocol version and date : V.1.1, 1 April 2021.

Strengths and limitation of this study

1. This study is a prospective, multicenter, real-world, observational clinical study.
2. This study majors in the efficacy, safety and health economics evaluation of various endovascular operations in treating Tosaka III FP-ISR.
3. This is an observational study and no interference with endovascular treatments will take place.
4. The Tosaka III FP-ISR patients usually have poor prognosis and may withdraw due to adverse events in early stage.

Introduction:

Femoropopliteal artery is one of most common treated peripheral artery diseases (PAD).[1] The treatment modalities cover mainly conservative treatment, endovascular procedures and surgical operations, with endovascular treatment more widely applied. However, femoropopliteal artery in-stent restenosis(FP-ISR) has become one of the main blocks for stent implantation in PAD patients with high morbidity, especially Tosaka III in-stent restenosis which is also named in-stent obstruction.[2 3] Tosaka et al reported the freedom from recurrent ISR at 12-month is 22.7% of TOSAKA III

lesions compared with 72.5% and 65.6% in Tosaka I and II lesions, respectively.[4] Meanwhile, Armstrong et al reported the freedom from recurrent restenosis at 24-month was 28% of Tosaka III lesions compared with 61% and 34% in TOSAKA I and II lesions, respectively.[5] This indicated in-stent occlusion correlated with worse prognosis compared with in-stent restenosis.

The endovascular procedures employed to treat FP-ISR include balloon angioplasty(BA) alone, drug-coated balloon(DCB), cutting balloon, bare metal stent(BMS), covered stent, mechanical debulking devices, laser atherectomy(LA) or the combination of above.[6-13] Giannopoulos et al reported freedom from TLR in 12-month estimate to 88.9% in LA + DCB group compared with 54.2% in LA + BA group in treating Tosaka III FP-ISR.[14] Meanwhile, Zhang et al reported the results of DCB treating Tosaka III FP-ISR: primary patency and freedom from TLR estimate to 79.2% and 91.5% at 14-month follow-up.[15] Debulking devices(laser debulking or mechanical debulking devices) have also been widely used in treating FP-ISR. Our previously study has also demonstrated that the patients with long and occlusive ISR lesion benefit more from debulking devices compared with short and stenosis ISR lesions.[16] Previous studies have reported roles for mechanical atherothrombectomy in treating femoropopliteal artery Tosaka III in-stent restenosis, the freedom from TLR at 12-month ranged from 80.5% to 94.5%.[17] The outcomes for endovascular treated Tosaka III FP-ISR are varied. Thus, there is need for a real-world setting outcome to distinguish and evaluate the safety, efficacy and economic cost of different endovascular modalities in treating Tosaka III FP-ISR. In real-world setting, the trial

could recruit the patients with in-stent occlusion rather than mild in-stent restenosis lesions.

Although there have been clinical reports about the preliminary and midterm stage results of different endovascular treatments in treating Tosaka III FP-ISR patients, these results were still insufficient to reflect the real-world clinical practice. Thus, we initiated a clinical trial named FP-RESTORE study to examine the safety, effectiveness and economic cost of different endovascular therapies in treating Tosaka III FP-ISR patients in a real-world setting across China.

METHODS

Study design

FP-RESTORE is a prospective, multicenter, real-world, observational clinical study, which aims at evaluating the safety, efficacy and economic cost of different endovascular therapies in Tosaka III (totally occluded) in-stent restenosis. It is estimated that 300 subjects diagnosed with femoropopliteal artery Tosaka III in-stent restenosis and receiving endovascular treatments is being enrolled in nine centers from April 2021 to December 2022 nationwide in China. There was no restriction of the endovascular techniques used to make it easier to compare effects of different endovascular treatments in Tosaka III in-stent restenosis.

The main purpose is to observe the freedom from TLR(target lesion revascularization), primary patency, the improvement of quality-of-life score, and Health economics evaluation.

The study is designed and initiated by the Department of Vascular Surgery,

Zhongshan Hospital, Fudan University. Patient and public involvement No patient or public involvement.

Participants

To minimize bias in the selection of patients, investigators at participating sites are encouraged to enroll all eligible Tosaka III in-stent restenosis patients receiving endovascular treatments. The patients are being screened for enrollment from April 2021 to December 2022 in nine designated centers across China. A total number of 300 patients who had received stent implantation to treat PAD and developed Tosaka III FP-ISR will be recruited. Recruitment is non-competitive and will not affect clinical practice.

CRITERIA

Inclusion criteria

1.Tosaka III In-stent restenosis after stent implantation in PAD patients. (Including acute and subacute thrombotic lesions).

2.The length of occluded lesion is ≥ 5cm.

3. Rutherford grade 2-5, symptoms of claudication or resting pain or localized gangrenous ulcer.

4. Stents should be located in the femoralpopliteal artery.

5.The stenosis of iliac artery on the affected side is less than 30% or the residual stenosis after treatment is less than 30%.

6.Informed consent has been signed

Exclusion criteria

1.Tosaka I or II in-stent restenosis or stent occlusion lesion less than 5cm in length.

2.Stents are located in iliac artery, or artery below the knee, or the preoperative CTA showed type 3 or 4 stent fracture.

3.Rutherford Grade 6.

4.Thromboangiitis obliterans (TAO) based, arteritis-based or connective tissue disorder-based FP-ISR.

5.Intraoperative conversion to hybrid or open surgery.

6.Patients refusing to sign informed consent.

7.Life expectancy of patients is less than 12 months.

8.The pregnant or nursing patients.

9.The patients with severe ischemia of lower extremity who would receive major amputation in plan.

10.Patients in whom antiplatelet or anticoagulant therapy is contraindicated.

11.Myocardial infarction or stroke within 3 months prior to enrollment.

12.Patient with known allergy to contrast agents or medications used to perform endovascular intervention.

13.Patients participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint.

14.Patients who refuse to cooperate with long-term follow-up , or who have difficulty communicating.

Criteria for discontinuing

Subjects could discontinue participation in this trial at any time for any reason without any consequences. Besides, the investigators could decide whether to discontinue the patient or not depending on the following condition.

1. The patients are lost to follow-up.

2. The patients voluntarily withdraw their informed consent.

3. In case of serious violation of the study protocol by investigators or subjects.

4. The subject is necessary to discontinue form the study for other reasons.

Once the subject discontinues participation in the trial, his/her relevant primary outcomes and secondary outcomes would be eliminated.

Endovascular procedure

All enrolled patient will be treated with endovascular therapies. In general, endovascular approaches are established from the contralateral common femoral artery or the ipsilateral common femoral artery or a brachial approach. A retrograde puncture access via popliteal artery will be chosen once intervention with the antegrade approach is unsuccessful. Followed by angiography to assess the lesion severity, length and location, the guide wire will be passed through the in-stent occlusion lesion. Then multiple types of endovascular treatments will be applied according to the characteristics of the lesion and physician preferences. For instance: BA, DCB, DES implantation, BMS implantation, intravascular lithotripsy, directional atherectomy, laser debulking , stent-grafts implantation or combination of above.

Final angiography is performed to access the efficacy of endovascular treatment. The residual stenosis of less than 30% will be defined as technical success.

Recruitment

All suitable patients will receive a routine examination during admission, Patients will receive intraoperative angiography of lower extremity artery, the lesion length, stenosis degree, extent of lesion, collateral circulation will be assessed. Moreover, eligible patients will be enrolled after signing the informed consent.

Data collection

A standard case report form (CRF) has been established at the beginning of this study. This CRF will collect the patients' quality of life(QoL), systemic diseases history, perioperative risk factors assessment, clinical symptom classification, the location of lesion and Trans-Atlantic Inter-Society Consensus II (TASC) classification, endovascular procedure details, the treatment outcomes and complications as well as follow-up information. Two investigators perform the data input independently and the data input verification is conducted to lower the chance of error. The original CRF will be archived by sponsor, the copy of CRF is kept at center and transferred into electronic records in correlated data management system. This system covers preoperative assessment, intraoperative detail and follow-up information.

Surveillance and follow-up

Follow-up will be coordinated by each participating centers independently. The

follow-up information come from via telephone interviews and outpatients clinical visits. The telephone interview follow-up information covers ambulation improvements, current medication, smoking status, wound healing(if necessary), rehospitalization and quality of life. Outpatients clinical visits follow- up information covers ABI, Rutherford classification, vascular ultrasound, the need of reintervention and presence of new-onset lesions.

These relevant details will also be recorded in CRF and transferred into electronic records in the lower extremity artery data management system. All centers participating in this study have access to the data. The participant's personal information will be kept encrypted to prevent leakage. All the participants will undergo follow-up at 1, 6, 12,18 and 24 months after operation.

Outcome measures

The primary outcome of the study is freedom from TLR at 24-month. TLR is defined as any reintervention performed for more than 50% diameter stenosis at target lesion.[18] Freedom form TLR were defined as the rates of the number of patients who did not receive reintervention verse the number of patients during the follow-up period. The secondary outcomes cover 1)Primary patency, which defined as the percentage of stent patency examined by DUS or CTA examination during follow-up. 2)Technical success rate. 3)incidence of major adverse events. 4)freedom from TLR at 1, 6, 12 and 18 months. 5) Vascular quality of life questionnaire(VascuQol), which contains five domains: pain (4 items), symptoms (4 items), activities (8 items), social (2 items), and emotional (7 items) to evaluate Health related quality of life (HRQL).

6) health economics evaluation, which defined as all the cost related to the target vessel revascularization in the inpatient ward.

Adverse events

The adverse events will be categorized into minor and major adverse events and the frequency of minor and major adverse events during the treatment period and follow-up period will both be recorded. The minor adverse events cover arterial puncture complications, distal embolism without clinical manifestations, postoperative thrombosis without critical limb ischemia, reversible contrast induced nephropathy. Meanwhile, major adverse events cover major amputation related to endovascular treatment, cardio and cerebrovascular events arterial puncture complications requiring intervention, progressive decrease of hemoglobin, acute renal failure and death. Once adverse events are identified, the corresponding centers will deal with it positively. The adverse events and the process of treatment will be documented and report to the corresponding ethics committee. Once death events occur, the corresponding centers and the participating investigator should provide all necessary information to ethics committee immediately.

Sample size and statistical analysis

Taking into account a lost follow-up rate of 10% and a target enrollment of 300 patients, 270 patients will be accessible for effectiveness analysis.

Statistical analysis will be performed using Stata SE 15.1 software (Stata Corp, College Station, TX, USA). Continuous data are presented as the mean ± standard

deviation, and categorical data are presented as numbers (n) and percentages (%).

Normal distribution and homogeneous tests of variance will be performed in advance. For the data groups that have a normal distribution and homogeneous variances, comparisons between two groups will be made using unpaired Student's t-tests, and one-way ANOVA followed by Bonferroni tests for multiple groups comparisons. For the data groups that do not have a normal distribution or homogeneous variances, nonparametric tests will be used. Univariate and multivariate analyses will be performed by logistic analysis. Generally, a P value < 0.05 at the bilateral will be considered statistically significant unless otherwise stated.

Ethics and dissemination

The study protocol has been approved by the Institutional review board and Human Research Ethics Committee of Zhongshan hospital, Fudan university(B2021-427). All the patients will be informed their voluntary participation and given their written informed consent. The trial protocol complies with Declaration of Helsinki.

The medical record information and all the data are kept confidential and stored in secure data bases. The personal information of participants will be coded and password-protected.

The study outcomes will be disseminated by publication in a peer-reviewed journal. The relevant confidential information will be transferred into specific code to avoid potential leakage. Besides, trial design has also been registered at Clinical trians.gov(Number: NCT04801004).

Author Contributors: Authors have been included in this manuscript based on the ICMJE recommendations. XL, MZ, YD, and ZS planned and designed the study. MY and ZW reviewed the structure of this manuscript. XL, MY, ZW ZF, LG, QL, XF and HS contributed to patient enrollment and collection of patient data. ZS critically reviewed and approved this manuscript. All authors have read and approved the final manuscript.

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Competing interests : None

Patient informed consent : Obtained

Ethics approval : The study protocol has been approved by the Institutional review board and Human Research Ethics Committee of Zhongshan hospital, Fudan university(B2021-427).

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing: No additional data are available.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	8-9

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Design of the FP-RESTORE study: A protocol for prospective, observational study of real-world treatments with endovascular therapy in patients with femoropopliteal artery Tosaka III in-stent restenosis.

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Design of the FP-RESTORE study: A protocol for prospective, observational study of real-world treatments with endovascular therapy in patients with femoropopliteal artery Tosaka III in-stent restenosis.

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Abstract

Introduction: Femoropopliteal artery in-stent restenosis (FP-ISR) represents one of the main obstacles for stent implantation in PAD patients, especially Tosaka III FP-ISR, which is also referred to as in-stent occlusion. Diverse endovascular treatments of Tosaka III FP-ISR are available, and the results are unequivocal. However, real-world data are limited. This study aims to evaluate the efficacy, safety and health economics evaluation of various endovascular procedures in the treatment of Tosaka III FP-ISR.

Method and analysis

This study is a prospective, multicentre, real-world, observational clinical study. Patients diagnosed with Tosaka III FP-ISR and treated with endovascular procedures in 9 centres from 1 April 2021 to 31 December 2022 will be recruited. The relevant clinical information, ankle-brachial index and CT angiography will be collected. All the participants will undergo follow-up at 1, 6, 12, 18 and 24 months after the operation. The primary outcome is freedom from clinically driven target lesion revascularization (CD-TLR) at 24 months. Safety and health economics issues will also be reported.

Ethics and dissemination

The FP-RESTORE clinical trial has been registered at ClinicalTrials.gov (http://clinicaltrials.gov/). This study was also approved by the Institutional Review Board and Human Research Ethics Committee of Zhongshan Hospital, Fudan University (approval number: B2021-427). Moreover, written informed consent will

be obtained at the time of recruitment. The study outcomes will be disseminated by publication in a peer-reviewed journal to provide information for further clinical practice.

Trial registration number: NCT04801004.

Protocol version and date: V.1.1, 1 April 2021.

Strengths and limitations of this study

1. This study is a prospective, multicentre, real-world, observational clinical study.
2. This study focuses on the efficacy, safety and health economics evaluation of various endovascular operations in the treatment of Tosaka III FP-ISR.
3. This is an observational study, and no interference with endovascular treatments will occur.
4. The revascularization of Tosaka III FP-ISR usually have poor prognosis and may withdraw due to adverse events in early stage.

Introduction:

The femoropopliteal artery is one of most commonly treated peripheral artery diseases (PAD).[1] The treatment modalities mainly include conservative treatment, endovascular procedures and surgical operations, with endovascular treatment being more widely applied. However, femoropopliteal artery in-stent restenosis (FP-ISR) has become one of the main blocks for stent implantation in PAD patients with high

morbidity, especially Tosaka III in-stent restenosis, which is also referred to as in-stent obstruction.[2 3] Tosaka et al. reported that the freedom from recurrent ISR at 12 months was 22.7% for Tosaka III lesions compared with 72.5% and 65.6% for Tosaka I and II lesions, respectively.[4] Armstrong et al. reported that the freedom from recurrent restenosis at 24 months was 28% for Tosaka III lesions compared with 61% and 34% for TOSAKA I and II lesions, respectively.[5] This finding indicated that in-stent occlusion correlated with a worse prognosis than in-stent restenosis.

Giannopoulos et al. reported freedom from TLR of 88.9% in the laser debulking devices (LD) + drug coated balloons (DCB) group compared with 54.2% in the LD + balloon angioplasty (BA) group in a 12-month estimate for the treatment of Tosaka III FP-ISR.[6] Zhang et al. reported the results of DCB in the treatment of Tosaka III FP-ISR with primary patency and freedom from TLR estimates of 79.2% and 91.5%, respectively, at the 14-month follow-up.[7] Debulking devices (laser debulking or mechanical debulking devices) have also been widely used in the treatment of FP-ISR. Our previous meta-analysis demonstrated that patients with long and occlusive ISR lesions benefit more from debulking devices.[8] Previous studies have also reported roles for mechanical atherothrombectomy in the treatment of Tosaka III in-stent restenosis with freedom from TLR at 12 months ranging from 43.8% to 84.7%.[9-12] Given that the outcomes for endovascularly treated Tosaka III FP-ISR varied, there is a need for data from a real-world setting to evaluate the safety, efficacy and economic cost of different endovascular modalities in the treatment of Tosaka III FP-ISR. In a real-world setting, the trial could recruit patients with in-stent occlusion rather than

mild in-stent restenosis lesions.

Although there have been clinical reports about the preliminary and midterm stage results of different endovascular treatments in the treatment of Tosaka III FP-ISR patients, these results were still insufficient to reflect real-world clinical practice. Thus, we initiated a clinical trial named the FP-RESTORE study to examine the safety, effectiveness and economic cost of different endovascular therapies in the treatment of Tosaka III FP-ISR patients in a real-world setting across China.

METHODS

Study design

FP-RESTORE is a prospective, multicentre, real-world, observational clinical study that aims to evaluate the safety, efficacy and economic cost of different endovascular therapies in Tosaka III (totally occluded) in-stent restenosis. It is estimated that 300 subjects diagnosed with femoropopliteal artery Tosaka III in-stent restenosis and receiving endovascular treatments will be enrolled in nine centres from April 2021 to December 2022 nationwide in China. No restrictions on the endovascular techniques used will be employed to make it easier to compare the effects of different endovascular treatments in Tosaka III in-stent restenosis.

The main purpose is to observe the freedom from clinically driven target lesion revascularization (CD-TLR), primary patency, the improvement in quality-of-life score, and health economics evaluation.

The study was designed and initiated by the Department of Vascular Surgery, Zhongshan Hospital, Fudan University. No patient or public involvement is required.

Participants

To minimize bias in the selection of patients, investigators at participating sites are encouraged to enroll all eligible Tosaka III in-stent restenosis patients receiving endovascular treatments. The patients will be screened for enrolment from April 2021 to December 2022 in nine designated centres across China. A total of 300 patients who received stent implantation to treat PAD and developed Tosaka III FP-ISR will be recruited. Recruitment is non-competitive and will not affect clinical practice.

CRITERIA

Inclusion criteria

1. Tosaka III In-stent restenosis after stent implantation in PAD patients (Including acute and subacute thrombotic lesions).

2. Rutherford grade 2-5.

3. Stents should be located in the femoropopliteal artery.

4.The stenosis of iliac artery on the affected side is less than 30% or the residual stenosis after treatment is less than 30%.

5.Informed consent has been signed

Exclusion criteria

1. Tosaka I or II in-stent restenosis.

2. Stents are located in iliac artery or artery below the knee, or the preoperative CTA showed type 3 or 4 stent fracture.

3. Rutherford Grade 6.

4. Thromboangiitis obliterans (TAO)-based, arteritis-based or connective tissue

disorder-based FP-ISR.

5. Intraoperative conversion to hybrid or open surgery.

6. Patients refusing to sign informed consent forms.

7. Life expectancy of patients is less than 12 months.

8.The pregnant or nursing patients.

9. The patients with severe ischemia of lower extremity who would receive major amputation in plan.

10. Patients in whom antiplatelet or anticoagulant therapy is contraindicated.

11. Myocardial infarction or stroke within 3 months prior to enrolment.

12. Patient with known allergy to contrast agents or medications used to perform endovascular intervention.

13. Patients participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint.

14. Patients who refuse to cooperate with long-term follow-up or who have difficulty communicating.

Criteria for discontinuing

Subjects could discontinue participation in this trial at any time for any reason without any consequences. In addition, the investigators could decide whether the patient is excluded from the study depending on the following conditions.

1. The patients are lost to follow-up.

2. The patients voluntarily withdraw their informed consent.

3. In case of serious violation of the study protocol by investigators or subjects.

4. The subject must discontinue from the study for other reasons.

Once the subject discontinued participation in the trial, his or her relevant primary outcomes and secondary outcomes would be eliminated.

Endovascular procedure

All enrolled patients will be treated with endovascular therapies. In general, endovascular approaches are established from the contralateral common femoral artery or the ipsilateral common femoral artery or a brachial approach. Retrograde puncture access via the popliteal artery will be chosen once intervention with the antegrade approach is unsuccessful. General angiography will be performed to assess the lesion severity, length and location. Then, angiography of the target artery will be performed, and the guide wire will be passed through the in-stent occlusion lesion. Then, multiple types of endovascular treatments, including BA, DCB, drug eluting stent (DES) implantation, bare metal stent (BMS) implantation, intravascular lithotripsy, directional atherectomy, laser debulking, stent-graft implantation or a combination of the above, will be applied according to the characteristics of the lesion and physician preferences. Generally, BA and DCB will be used as the basis for endovascular treatment of FR-ISR. Thrombectomy devices will be applied in acute or subacute thrombosis lesions, and both laser debulking devices and atherectomy debulking devices are preferred in chronic long lesions. The devices used

intraoperatively will be based on the operator's preferences. Final angiography will be performed to assess the efficacy of endovascular treatment. Residual stenosis of less than 30% will be defined as technical success.

Recruitment

All suitable patients will receive a routine examination during admission. Patients will receive intraoperative angiography of lower extremity artery, and data on the lesion length, stenosis degree, extent of lesion, collateral circulation will be assessed. Moreover, eligible patients will be enrolled after signing the informed consent form.

Data collection

A standard case report form (CRF) has been established at the beginning of this study. This CRF will collect the patients' quality of life (QoL), systemic disease history, perioperative risk factor assessment, clinical symptom classification, lesion location and Trans-Atlantic Inter-Society Consensus II (TASC) classification, endovascular procedure details, treatment outcomes and complications as well as follow-up information. Two investigators will perform the data input independently, and data input verification will be conducted to reduce the chance of error. The original CRF will be archived by the sponsor, and a copy of the CRF will be kept at the centre and transferred into electronic records in a correlated data management system. This system covers preoperative assessment, intraoperative details and follow-up information.

Surveillance and follow-up

Follow-up will be coordinated by each participating centre independently. The follow-up information will be obtained via telephone interviews and outpatient clinical visits. The telephone interview follow-up information includes ambulation improvements, current medication, smoking status, wound healing (if necessary), rehospitalization and quality of life. Outpatient clinical visit follow-up information includes ABI, Rutherford classification, vascular ultrasound, the need for reintervention and the presence of new-onset lesions.

These relevant details will also be recorded in the CRF and transferred into electronic records in the lower extremity artery data management system. All centres participating in this study will have access to the data. The participant's personal information will be encrypted to prevent leakage. All the participants will undergo follow-up at 1, 6, 12, 18 and 24 months after the operation.

Outcome measures

The primary outcome of the study is freedom from clinically driven TLR at 24 months. CD-TLR is defined as any reintervention within the target lesion(s) because of recurrent symptoms. Freedom from CD-TLR is defined as the rate of the number of patients who did not receive reintervention versus the number of patients during the follow-up period.[13 14] The secondary outcomes include 1) primary patency, which was defined as the percentage of stent patency examined by DUS or CTA examination during follow-up; 2) technical success rate; 3) incidence of major adverse events; 4) freedom from CD-TLR at 1, 6, 12 and 18 months; 5) assessment using The Vascular

Quality of Life Questionnaire (VascuQol), which contains five domains to evaluate health-related quality of life (HRQL), including pain (4 items), symptoms (4 items), activities (8 items), social (2 items), and emotional (7 items); and 6) health economics evaluation, which is defined as all the costs related to the target vessel revascularization in the inpatient ward.

Adverse events

The adverse events will be categorized into minor and major adverse events, and the frequency of minor and major adverse events during the treatment period and follow-up period will both be recorded. The minor adverse events included arterial puncture complications, distal embolism without clinical manifestations, postoperative thrombosis without critical limb ischemia, and reversible contrast induced nephropathy. In addition, major adverse events include major amputation related to endovascular treatment, cardio- and cerebrovascular events, arterial puncture complications requiring intervention, progressive haemoglobin disease, acute renal failure and death. Once adverse events are identified, the corresponding centres will actively manage and report the adverse events. The adverse events and the process of treatment will be documented and reported to the corresponding ethics committee. Once death events occur, the corresponding centres and the participating investigator should immediately provide all necessary information to the ethics committee.

Sample size and statistical analysis

Taking into account a 10% lost to follow-up rate and a target enrolment of 300 patients, 270 patients will be included in the effectiveness analysis.

Statistical analysis will be performed using Stata SE 15.1 software (Stata Corp, College Station, TX, USA). Continuous data will be presented as the mean ± standard deviation, and categorical data will be presented as numbers (n) and percentages (%).

Normal distribution and homogeneous tests of variance will be performed in advance. For the data groups that have a normal distribution and homogeneous variances, comparisons between two groups will be made using unpaired Student's t tests and one-way ANOVA followed by Bonferroni tests for multiple group comparisons. For the data groups that do not have a normal distribution or homogeneous variances, nonparametric tests will be used. Univariate and multivariate analyses will be performed by logistic analysis. Generally, a two-sided *P* value < 0.05 will be considered statistically significant unless otherwise stated.

Discussion

The FP-RESTORE will be the first study to provide prospective data on the effectiveness, safety and health economics evaluation of different endovascular modalities in the treatment of Tosaka III FP-ISR in a real-world setting. The endovascular treatments employed in FP-ISR include BA alone, DCB, cutting balloon, BMS, covered stent, mechanical debulking devices, laser atherectomy or a combination of the above.[13-25] However, the methods and results widely vary, which makes it difficult to compare the outcomes and make valid conclusions. FP-

RESTORE is thus designed to evaluate and compare these endovascular procedures for Tosaka III FP-ISR. We hope our results will provide useful information and guidance about this issue and references for future controlled studies.

Clinically driven freedom from TLR is the primary outcome in our study. On the one hand, FP-RESTORE is designed to pay more attention to the clinical efficacy of various endovascular modalities; thus, clinically driven freedom from TLR could reflect the clinical effectiveness more intuitively. On the other hand, the inclusion criteria in real-world settings are not as strict as those of controlled studies; thus, a broader range of patients could be enrolled. Given that the patients are recruited throughout China, the imaging follow-up rate at different centres will vary widely, which may lead to missing information regarding primary patency. Thus, clinically driven freedom from TLR will serve as the primary outcome, whereas primary patency and other results will serve as secondary outcomes in this study.

Ethics and dissemination

The study protocol was approved by the Institutional Review Board and Human Research Ethics Committee of Zhongshan Hospital, Fudan University (B2021-427). All the patients will be informed of their voluntary participation and provide written informed consent. The trial protocol complies with the Declaration of Helsinki.

The study outcomes will be disseminated by publication in a peer-reviewed journal. The relevant confidential information will be transferred into a specific code to avoid potential leakage. In addition, the trial design has also been registered at ClinicalTrials.gov (Number: NCT04801004).

Author Contributions: The authors have been included in this manuscript based on the ICMJE recommendations. XL, MZ, YD, and ZS planned and designed the study. MY and ZW reviewed the structure of this manuscript. XL, MY, ZW ZF, LG, QL, XF and HS contributed to patient enrolment and collection of patient data. ZS critically reviewed and approved this manuscript. All authors have read and approved the final manuscript.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
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Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
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Objectives	#7	Specific objectives or hypotheses	6
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Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
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Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11
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Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
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Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
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Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
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Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
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Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

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Design of the FP-RESTORE study: A protocol for prospective, observational study of real-world treatments with endovascular therapy in patients with femoropopliteal artery Tosaka III in-stent restenosis.

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Design of the FP-RESTORE study: A protocol for prospective, observational study of real-world treatments with endovascular therapy in patients with femoropopliteal artery Tosaka III in-stent restenosis.

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Abstract

Introduction: Femoropopliteal artery in-stent restenosis (FP-ISR) represents one of the main obstacles for stent implantation in PAD patients, especially Tosaka III FP-ISR, which is also referred to as in-stent occlusion. Diverse endovascular treatments of Tosaka III FP-ISR are available, and the results are unequivocal. However, real-world data are limited. This study aims to evaluate the efficacy, safety and health economics evaluation of various endovascular procedures in the treatment of Tosaka III FP-ISR.

Method and analysis

This study is a prospective, multicentre, real-world, observational clinical study. Patients diagnosed with Tosaka III FP-ISR and treated with endovascular procedures in 9 centres from 1 April 2021 to 31 December 2022 will be recruited. The relevant clinical information, ankle-brachial index and CT angiography will be collected. All the participants will undergo follow-up at 1, 6, 12, 18 and 24 months after the operation. The primary outcome is freedom from clinically driven target lesion revascularization (CD-TLR) at 24 months. Safety and health economics issues will also be reported.

Ethics and dissemination

The FP-RESTORE clinical trial has been registered at ClinicalTrials.gov (http://clinicaltrials.gov/). This study was also approved by the Institutional Review Board and Human Research Ethics Committee of Zhongshan Hospital, Fudan

University (approval number: B2021-427). Moreover, written informed consent will be obtained at the time of recruitment. The study outcomes will be disseminated by publication in a peer-reviewed journal to provide information for further clinical practice.

Trial registration number: NCT04801004.

Protocol version and date: V.1.1, 1 April 2021.

Strengths and limitations of this study

1. This study is a prospective, multicentre, real-world, observational clinical study.
2. This study focuses on the efficacy, safety and health economics evaluation of various endovascular operations in the treatment of Tosaka III FP-ISR.
3. This is an observational study, and no interference with endovascular treatments will occur.
4. The revascularization of Tosaka III FP-ISR is associated with poor outcomes.

Introduction:

The femoropopliteal artery is one of most commonly treated peripheral artery diseases (PAD).[1] The treatment modalities mainly include conservative treatment, endovascular procedures and surgical operations, with endovascular treatment being more widely applied. However, femoropopliteal artery in-stent restenosis (FP-ISR) has become one of the main blocks for stent implantation in PAD patients with high

morbidity, especially Tosaka III in-stent restenosis, which is also referred to as in-stent obstruction.[2 3] Tosaka et al. reported that the freedom from recurrent ISR at 12 months was 22.7% for Tosaka III lesions compared with 72.5% and 65.6% for Tosaka I and II lesions, respectively.[4] Armstrong et al. reported that the freedom from recurrent restenosis at 24 months was 28% for Tosaka III lesions compared with 61% and 34% for TOSAKA I and II lesions, respectively.[5] This finding indicated that in-stent occlusion correlated with a worse prognosis than in-stent restenosis.

Giannopoulos et al. reported freedom from TLR of 88.9% in the laser debulking devices (LD) + drug coated balloons (DCB) group compared with 54.2% in the LD + balloon angioplasty (BA) group in a 12-month estimate for the treatment of Tosaka III FP-ISR.[6] Zhang et al. reported the results of DCB in the treatment of Tosaka III FP-ISR with primary patency and freedom from TLR estimates of 79.2% and 91.5%, respectively, at the 14-month follow-up.[7] Debulking devices (laser debulking or mechanical debulking devices) have also been widely used in the treatment of FP-ISR. Our previous meta-analysis demonstrated that patients with long and occlusive ISR lesions benefit more from debulking devices.[8] Previous studies have also reported roles for mechanical atherothrombectomy in the treatment of Tosaka III in-stent restenosis with freedom from TLR at 12 months ranging from 43.8% to 84.7%.[9-12] Given that the outcomes for endovascularly treated Tosaka III FP-ISR varied, there is a need for data from a real-world setting to evaluate the safety, efficacy and economic cost of different endovascular modalities in the treatment of Tosaka III FP-ISR. In a real-world setting, the trial could recruit patients with in-stent occlusion rather than

mild in-stent restenosis lesions.

Although there have been clinical reports about the preliminary and midterm stage results of different endovascular treatments in the treatment of Tosaka III FP-ISR patients, these results were still insufficient to reflect real-world clinical practice. Thus, we initiated a clinical trial named the FP-RESTORE study to examine the safety, effectiveness and economic cost of different endovascular therapies in the treatment of Tosaka III FP-ISR patients in a real-world setting across China.

METHODS

Study design

FP-RESTORE is a prospective, multicentre, real-world, observational clinical study that aims to evaluate the safety, efficacy and economic cost of different endovascular therapies in Tosaka III (totally occluded) in-stent restenosis. It is estimated that 300 subjects diagnosed with femoropopliteal artery Tosaka III in-stent restenosis and receiving endovascular treatments will be enrolled in nine centres from April 2021 to December 2022 nationwide in China. No restrictions on the endovascular techniques used will be employed to make it easier to compare the effects of different endovascular treatments in Tosaka III in-stent restenosis.

The main purpose is to observe the freedom from clinically driven target lesion revascularization (CD-TLR), primary patency, the improvement in quality-of-life score, and health economics evaluation.

The study was designed and initiated by the Department of Vascular Surgery, Zhongshan Hospital, Fudan University. No patient or public involvement is required.

Participants

To minimize bias in the selection of patients, investigators at participating sites are encouraged to enroll all eligible Tosaka III in-stent restenosis patients receiving endovascular treatments. The patients will be screened for enrolment from April 2021 to December 2022 in nine designated centres across China. A total of 300 patients who received stent implantation to treat PAD and developed Tosaka III FP-ISR will be recruited. Recruitment is non-competitive and will not affect clinical practice.

CRITERIA

Inclusion criteria

1. Tosaka III In-stent restenosis after stent implantation in PAD patients (Including acute and subacute thrombotic lesions).

2. Rutherford grade 2-5.

3. Stents should be located in the femoropopliteal artery.

4.The stenosis of iliac artery on the affected side is less than 30% or the residual stenosis after treatment is less than 30%.

5.Informed consent has been signed

Exclusion criteria

1. Tosaka I or II in-stent restenosis.

2. Stents are located in iliac artery or artery below the knee, or the preoperative CTA showed type 3 or 4 stent fracture.

3. Rutherford Grade 6.

4. Thromboangiitis obliterans (TAO)-based, arteritis-based or connective tissue

disorder-based FP-ISR.

5. Intraoperative conversion to hybrid or open surgery.

6. Patients refusing to sign informed consent forms.

7. Life expectancy of patients is less than 12 months.

8.The pregnant or nursing patients.

9. The patients with severe ischemia of lower extremity who would receive major amputation in plan.

10. Patients in whom antiplatelet or anticoagulant therapy is contraindicated.

11. Myocardial infarction or stroke within 3 months prior to enrolment.

12. Patient with known allergy to contrast agents or medications used to perform endovascular intervention.

13. Patients participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint.

14. Patients who refuse to cooperate with long-term follow-up or who have difficulty communicating.

Criteria for discontinuing

Subjects could discontinue participation in this trial at any time for any reason without any consequences. In addition, the investigators could decide whether the patient is excluded from the study depending on the following conditions.

1. The patients are lost to follow-up.

2. The patients voluntarily withdraw their informed consent.

3. In case of serious violation of the study protocol by investigators or subjects.

4. Patient is simultaneously participating in another investigational drug or device study.

5.Patient has any planned surgical or interventional procedure within 30 days after the study procedure.

Once the subject discontinued participation in the trial, his or her relevant primary outcomes and secondary outcomes would be eliminated.

Endovascular procedure

All enrolled patients will be treated with endovascular therapies. In general, endovascular approaches are established from the contralateral common femoral artery or the ipsilateral common femoral artery or a brachial approach. Retrograde puncture access via the popliteal artery will be chosen once intervention with the antegrade approach is unsuccessful. Angiography will be performed to assess the lesion severity, length and location. Then, angiography of the target artery will be performed, and the guide wire will be passed through the in-stent occlusion lesion. Then, multiple types of endovascular treatments, including BA, DCB, drug eluting stent (DES) implantation, bare metal stent (BMS) implantation, intravascular lithotripsy, directional atherectomy, laser debulking, stent-graft implantation or a combination of the above, will be applied according to the characteristics of the lesion and physician preferences. Generally, BA and DCB will be used as the basis for

endovascular treatment of FR-ISR. Thrombectomy devices will be applied in acute or subacute thrombosis lesions, and both laser debulking devices and atherectomy debulking devices are preferred in chronic long lesions. The devices used intraoperatively will be based on the operator's preferences. Final angiography will be performed to assess the efficacy of endovascular treatment. Residual stenosis of less than 30% will be defined as technical success.

Recruitment

All suitable patients will receive a routine examination during admission. Patients will receive intraoperative angiography of lower extremity artery, and data on the lesion length, stenosis degree, extent of lesion, collateral circulation will be assessed. Moreover, eligible patients will be enrolled after signing the informed consent form.

Data collection

A standard case report form (CRF) has been established at the beginning of this study. This CRF will collect the patients' quality of life (QoL), systemic disease history, perioperative risk factor assessment, clinical symptom classification, lesion location and Trans-Atlantic Inter-Society Consensus II (TASC) classification, endovascular procedure details, treatment outcomes and complications as well as follow-up information. Two investigators will perform the data input independently, and data input verification will be conducted to reduce the chance of error. The original CRF will be archived by the sponsor, and a copy of the CRF will be kept at the centre and transferred into electronic records in a correlated data management system. This

system covers preoperative assessment, intraoperative details and follow-up information.

Surveillance and follow-up

Follow-up will be coordinated by each participating centre independently. The follow-up information will be obtained via telephone interviews and outpatient clinical visits. The telephone interview follow-up information includes ambulation improvements, current medication, smoking status, wound healing (if necessary), rehospitalization and quality of life. Outpatient clinical visit follow-up information includes ABI, Rutherford classification, vascular ultrasound, the need for reintervention and the presence of new-onset lesions.

These relevant details will also be recorded in the CRF and transferred into electronic records in the lower extremity artery data management system. All centres participating in this study will have access to the data. The participant's personal information will be encrypted to prevent leakage. All the participants will undergo follow-up at 1, 6, 12, 18 and 24 months after the operation.

Outcome measures

The primary outcome of the study is freedom from clinically driven TLR at 24 months. CD-TLR is defined as any reintervention within the target lesion(s) because of recurrent symptoms. Freedom from CD-TLR is defined as the rate of the number of patients who did not receive reintervention versus the number of patients during the follow-up period.[13 14] The secondary outcomes include 1) primary patency, which was

defined as the percentage of stent patency examined by DUS or CTA examination during follow-up; 2) technical success rate; 3) incidence of major adverse events; 4) freedom from CD-TLR at 1, 6, 12 and 18 months; 5) assessment using The Vascular Quality of Life Questionnaire (VascuQol), which contains five domains to evaluate health-related quality of life (HRQL), including pain (4 items), symptoms (4 items), activities (8 items), social (2 items), and emotional (7 items); and 6) health economics evaluation, which is defined as all the costs related to the target vessel revascularization in the inpatient ward. Moreover, the health economics evaluation of technique failed participants will also be included.

Adverse events

The adverse events will be categorized into minor and major adverse events, and the frequency of minor and major adverse events during the treatment period and follow-up period will both be recorded. The minor adverse events included arterial puncture complications, distal embolism without clinical manifestations, postoperative thrombosis without critical limb ischemia, and reversible contrast induced nephropathy. In addition, major adverse events include major amputation related to endovascular treatment, cardio- and cerebrovascular events, arterial puncture complications requiring intervention, progressive haemoglobin disease, acute renal failure and death. Once adverse events are identified, the corresponding centres will actively manage and report the adverse events. The adverse events and the process of treatment will be documented and reported to the corresponding ethics committee. Once death events occur, the corresponding centres and the participating

investigator should immediately provide all necessary information to the ethics committee.

Sample size and statistical analysis

Taking into account a 10% lost to follow-up rate and a target enrolment of 300 patients, 270 patients will be included in the effectiveness analysis.

Statistical analysis will be performed using Stata SE 15.1 software (Stata Corp, College Station, TX, USA). Continuous data will be presented as the mean ± standard deviation, and categorical data will be presented as numbers (n) and percentages (%).

Normal distribution and homogeneous tests of variance will be performed in advance. For the data groups that have a normal distribution and homogeneous variances, comparisons between two groups will be made using unpaired Student's t tests and one-way ANOVA followed by Bonferroni tests for multiple group comparisons. For the data groups that do not have a normal distribution or homogeneous variances, nonparametric tests will be used. Univariate and multivariate analyses will be performed by logistic analysis. Generally, a two-sided P value < 0.05 will be considered statistically significant unless otherwise stated.

Patient and public involvement

Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

Discussion

The FP-RESTORE will be the first study to provide prospective data on the effectiveness, safety and health economics evaluation of different endovascular modalities in the treatment of Tosaka III FP-ISR in a real-world setting. The endovascular treatments employed in FP-ISR include BA alone, DCB, cutting balloon, BMS, covered stent, mechanical debulking devices, laser atherectomy or a combination of the above.[13-25] However, the methods and results widely vary, which makes it difficult to compare the outcomes and make valid conclusions. FP-RESTORE is thus designed to evaluate and compare these endovascular procedures for Tosaka III FP-ISR. We hope our results will provide useful information and guidance about this issue and references for future controlled studies.

Clinically driven freedom from TLR is the primary outcome in our study. On the one hand, FP-RESTORE is designed to pay more attention to the clinical efficacy of various endovascular modalities; thus, clinically driven freedom from TLR could reflect the clinical effectiveness more intuitively. On the other hand, the inclusion criteria in real-world settings are not as strict as those of controlled studies; thus, a broader range of patients could be enrolled. Given that the patients are recruited throughout China, the imaging follow-up rate at different centres will vary widely, which may lead to missing information regarding primary patency. Thus, clinically driven freedom from TLR will serve as the primary outcome, whereas primary patency and other results will serve as secondary outcomes in this study.

Dissemination

The trial protocol complies with the Declaration of Helsinki. The study outcomes will be disseminated by publication in a peer-reviewed journal. The relevant confidential information will be transferred into a specific code to avoid potential leakage. In addition, the trial design has also been registered at ClinicalTrials.gov (Number: NCT04801004).

Author Contributions: The authors have been included in this manuscript based on the ICMJE recommendations. XL, MZ, YD, and ZS planned and designed the study. MY and ZW reviewed the structure of this manuscript. XL, MY, ZW ZF, LG, QL, XF and HS contributed to patient enrolments and collection of patient data. ZS critically reviewed and approved this manuscript. All authors have read and approved the final manuscript.

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Provenance and peer review: Not commissioned; externally peer reviewed.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	8-9

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

Design of the FP-RESTORE study: A protocol for prospective, observational study of real-world treatments with endovascular therapy in patients with femoropopliteal artery Tosaka III in-stent restenosis.

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Design of the FP-RESTORE study: A protocol for prospective, observational study of real-world treatments with endovascular therapy in patients with femoropopliteal artery Tosaka III in-stent restenosis.

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Abstract

Introduction: Femoropopliteal artery in-stent restenosis (FP-ISR) represents one of the main obstacles for stent implantation in PAD patients, especially Tosaka III FP-ISR, which is also referred to as in-stent occlusion. Diverse endovascular treatments of Tosaka III FP-ISR are available, and the results are unequivocal. However, real-world data are limited. This study aims to evaluate the efficacy, safety and health economics evaluation of various endovascular procedures in the treatment of Tosaka III FP-ISR.

Method and analysis

This study is a prospective, multicentre, real-world, observational clinical study. Patients diagnosed with Tosaka III FP-ISR and treated with endovascular procedures in 9 centres from 1 April 2021 to 31 December 2022 will be recruited. The relevant clinical information, ankle-brachial index and CT angiography will be collected. All the participants will undergo follow-up at 1, 6, 12, 18 and 24 months after the operation. The primary outcome is freedom from clinically driven target lesion revascularization (CD-TLR) at 24 months. Safety and health economics issues will also be reported.

Ethics and dissemination

The FP-RESTORE clinical trial has been registered at ClinicalTrials.gov (http://clinicaltrials.gov/). This study was also approved by the Institutional Review Board and Human Research Ethics Committee of Zhongshan Hospital, Fudan

University (approval number: B2021-427). Moreover, written informed consent will be obtained at the time of recruitment. The study outcomes will be disseminated by publication in a peer-reviewed journal to provide information for further clinical practice.

Trial registration number: NCT04801004.

Protocol version and date: V.1.2, 1 August 2022.

Strengths and limitations of this study

1. This study is a prospective, multicentre, real-world, observational clinical study.
2. This study focuses on the efficacy, safety and health economics evaluation of various endovascular operations in the treatment of Tosaka III FP-ISR.
3. This is an observational study, and no interference with endovascular treatments will occur.
4. The revascularization of Tosaka III FP-ISR is associated with poor outcomes.

Introduction:

The femoropopliteal artery is one of most commonly treated peripheral artery diseases (PAD).[1] The treatment modalities mainly include conservative treatment, endovascular procedures and surgical operations, with endovascular treatment being more widely applied. However, femoropopliteal artery in-stent restenosis (FP-ISR) has become one of the main blocks for stent implantation in PAD patients with high

morbidity, especially Tosaka III in-stent restenosis, which is also referred to as in-stent obstruction.[2 3] Tosaka et al. reported that the freedom from recurrent ISR at 12 months was 22.7% for Tosaka III lesions compared with 72.5% and 65.6% for Tosaka I and II lesions, respectively.[4] Armstrong et al. reported that the freedom from recurrent restenosis at 24 months was 28% for Tosaka III lesions compared with 61% and 34% for TOSAKA I and II lesions, respectively.[5] This finding indicated that in-stent occlusion correlated with a worse prognosis than in-stent restenosis.

Giannopoulos et al. reported freedom from TLR of 88.9% in the laser debulking devices (LD) + drug coated balloons (DCB) group compared with 54.2% in the LD + balloon angioplasty (BA) group in a 12-month estimate for the treatment of Tosaka III FP-ISR.[6] Zhang et al. reported the results of DCB in the treatment of Tosaka III FP-ISR with primary patency and freedom from TLR estimates of 79.2% and 91.5%, respectively, at the 14-month follow-up.[7] Debulking devices (laser debulking or mechanical debulking devices) have also been widely used in the treatment of FP-ISR. Our previous meta-analysis demonstrated that patients with long and occlusive ISR lesions benefit more from debulking devices.[8] Previous studies have also reported roles for mechanical atherothrombectomy in the treatment of Tosaka III in-stent restenosis with freedom from TLR at 12 months ranging from 43.8% to 84.7%.[9-12] Given that the outcomes for endovascularly treated Tosaka III FP-ISR varied, there is a need for data from a real-world setting to evaluate the safety, efficacy and economic cost of different endovascular modalities in the treatment of Tosaka III FP-ISR. In a real-world setting, the trial could recruit patients with in-stent occlusion rather than

mild in-stent restenosis lesions.

Although there have been clinical reports about the preliminary and midterm stage results of different endovascular treatments in the treatment of Tosaka III FP-ISR patients, these results were still insufficient to reflect real-world clinical practice. Thus, we initiated a clinical trial named the FP-RESTORE study to examine the safety, effectiveness and economic cost of different endovascular therapies in the treatment of Tosaka III FP-ISR patients in a real-world setting across China.

METHODS

Study design

FP-RESTORE is a prospective, multicentre, real-world, observational clinical study that aims to evaluate the safety, efficacy and economic cost of different endovascular therapies in Tosaka III (totally occluded) in-stent restenosis. It is estimated that 300 subjects diagnosed with femoropopliteal artery Tosaka III in-stent restenosis and receiving endovascular treatments will be enrolled in nine centres from April 2021 to December 2022 nationwide in China. No restrictions on the endovascular techniques used will be employed to make it easier to compare the effects of different endovascular treatments in Tosaka III in-stent restenosis.

The main purpose is to observe the freedom from clinically driven target lesion revascularization (CD-TLR), primary patency, the improvement in quality-of-life score, and health economics evaluation.

The study was designed and initiated by the Department of Vascular Surgery, Zhongshan Hospital, Fudan University. No patient or public involvement is required.

Participants

To minimize bias in the selection of patients, investigators at participating sites are encouraged to recruit all eligible Tosaka III in-stent restenosis patients receiving endovascular treatments. The patients will be screened for enrolment from April 2021 to December 2022 in nine designated centres across China. A total of 300 patients who received stent implantation to treat PAD and developed Tosaka III FP-ISR will be recruited. Recruitment is non-competitive and will not affect clinical practice.

CRITERIA

Inclusion criteria

1. Tosaka III In-stent restenosis after stent implantation in PAD patients (Including acute and subacute thrombotic lesions).
2. Rutherford grade 2-5.
3. Stents should be located in the femoropopliteal artery.
4. The stenosis of iliac artery on the affected side is less than 30% or the residual stenosis after treatment is less than 30%.
5. Informed consent has been signed

Exclusion criteria

1. Tosaka I or II in-stent restenosis.
2. Stents are located in iliac artery or artery below the knee, or the preoperative CTA showed type 3 or 4 stent fracture.
3. Rutherford Grade 6.
4. Thromboangiitis obliterans (TAO)-based, arteritis-based or connective tissue

disorder-based FP-ISR.

5. Intraoperative conversion to hybrid or open surgery.

6. Patients refusing to sign informed consent forms.

7. Life expectancy of patients is less than 12 months.

8.The pregnant or nursing patients.

9. The patients with severe ischemia of lower extremity who would receive major amputation in plan.

10. Patients in whom antiplatelet or anticoagulant therapy is contraindicated.

11. Myocardial infarction or stroke within 3 months prior to enrolment.

12. Patient with known allergy to contrast agents or medications used to perform endovascular intervention.

13. Patients participating in another research study involving an investigational agent (pharmaceutical, biologic, or medical device) that has not reached the primary endpoint.

14. Patients who refuse to cooperate with long-term follow-up or who have difficulty communicating.

Criteria for discontinuing

Subjects could discontinue participation in this trial at any time for any reason without any consequences. In addition, the investigators could decide whether the patient is excluded from the study depending on the following conditions.

1. The patients are lost to follow-up.

2. The patients voluntarily withdraw their informed consent.

3. In case of serious violation of the study protocol by investigators or subjects.

4. Patient is simultaneously participating in another investigational drug or device study.

5.Patient has any planned surgical or interventional procedure within 30 days after the study procedure.

Once the subject discontinued participation in the trial, his or her relevant primary outcomes and secondary outcomes would be eliminated.

Endovascular procedure

All enrolled patients will be treated with endovascular therapies. In general, endovascular approaches are established from the contralateral common femoral artery or the ipsilateral common femoral artery or a brachial approach. Retrograde puncture access via the popliteal artery will be chosen once intervention with the antegrade approach is unsuccessful. Angiography will be performed to assess the lesion severity, length and location. Then, angiography of the target artery will be performed, and the guide wire will be passed through the in-stent occlusion lesion. Then, multiple types of endovascular treatments, including BA, DCB, drug eluting stent (DES) implantation, bare metal stent (BMS) implantation, intravascular lithotripsy, directional atherectomy, laser debulking, stent-graft implantation or a combination of the above, will be applied according to the characteristics of the lesion and physician preferences. Generally, BA and DCB will be used as the basis for

endovascular treatment of FR-ISR. Thrombectomy devices will be applied in acute or subacute thrombosis lesions, and both laser debulking devices and atherectomy debulking devices are preferred in chronic long lesions. The devices used intraoperatively will be based on the operator's preferences. Final angiography will be performed to assess the efficacy of endovascular treatment. Residual stenosis of less than 30% will be defined as technical success.

Recruitment

All suitable patients will receive a routine examination during admission. Patients will receive intraoperative angiography of lower extremity artery, and data on the lesion length, stenosis degree, extent of lesion, collateral circulation will be assessed. Moreover, eligible patients will be enrolled after signing the informed consent form.

Data collection

A standard case report form (CRF) has been established at the beginning of this study. This CRF will collect the patients' quality of life (QoL), systemic disease history, perioperative risk factor assessment, clinical symptom classification, lesion location and Trans-Atlantic Inter-Society Consensus II (TASC) classification, endovascular procedure details, treatment outcomes and complications as well as follow-up information. Two investigators will perform the data input independently, and data input verification will be conducted to reduce the chance of error. The original CRF will be archived by the sponsor, and a copy of the CRF will be kept at the centre and transferred into electronic records in a correlated data management system. This

system covers preoperative assessment, intraoperative details and follow-up information.

Surveillance and follow-up

Follow-up will be coordinated by each participating centre independently. The follow-up information will be obtained via telephone interviews and outpatient clinical visits. To improve the shortcoming of the detail of reintervention cannot be acquired in telephone follow-up, we would encourage the participants to provide the medical records of reintervention detail and conduct the outpatient visit immediately if he received reintervention during follow-up period. The telephone interview follow-up information includes ambulation improvements, current medication, smoking status, wound healing (if necessary), rehospitalization and quality of life. Outpatient clinical visit follow-up information includes ABI, Rutherford classification, vascular ultrasound, the need for reintervention and the presence of new-onset lesions.

These relevant details will also be recorded in the CRF and transferred into electronic records in the lower extremity artery data management system. All centres participating in this study will have access to the data. The participant's personal information will be encrypted to prevent leakage. All the participants will undergo follow-up at 1, 6, 12, 18 and 24 months after the operation.

Outcome measures

The primary outcome of the study is freedom from clinically driven TLR at 24 months. CD-TLR is defined as any reintervention within the target lesion(s) because

of recurrent symptoms. Freedom from CD-TLR is defined as the rate of the number of patients who did not receive reintervention versus the number of patients during the follow-up period.[13 14] The secondary outcomes include 1) primary patency, which was defined as the percentage of stent patency examined by DUS or CTA examination during follow-up; 2) technical success rate; 3) incidence of major adverse events; 4) freedom from CD-TLR at 1, 6, 12 and 18 months; 5) assessment using The Vascular Quality of Life Questionnaire (VascuQol), which contains five domains to evaluate health-related quality of life (HRQL), including pain (4 items), symptoms (4 items), activities (8 items), social (2 items), and emotional (7 items); and 6) health economics evaluation, which is defined as all the costs related to the target vessel revascularization in the inpatient ward. Moreover, the health economics evaluation of technique failed participants will also be included.

Adverse events

The adverse events will be categorized into minor and major adverse events, and the frequency of minor and major adverse events during the treatment period and follow-up period will both be recorded. The minor adverse events included arterial puncture complications, distal embolism without clinical manifestations, postoperative thrombosis without critical limb ischemia, and reversible contrast induced nephropathy. In addition, major adverse events include major amputation related to endovascular treatment, cardio- and cerebrovascular events, arterial puncture complications requiring intervention, progressive haemoglobin disease, acute renal failure and death. Once adverse events are identified, the corresponding

centres will actively manage and report the adverse events. The adverse events and the process of treatment will be documented and reported to the corresponding ethics committee. Once death events occur, the corresponding centres and the participating investigator should immediately provide all necessary information to the ethics committee.

Sample size and statistical analysis

Taking into account a 10% lost to follow-up rate and a target enrolment of 300 patients, 270 patients will be included in the effectiveness analysis.

Statistical analysis will be performed using Stata SE 15.1 software (Stata Corp, College Station, TX, USA). Continuous data will be presented as the mean ± standard deviation, and categorical data will be presented as numbers (n) and percentages (%).

Normal distribution and homogeneous tests of variance will be performed in advance. For the data groups that have a normal distribution and homogeneous variances, comparisons between two groups will be made using unpaired Student's t tests and one-way ANOVA followed by Bonferroni tests for multiple group comparisons. For the data groups that do not have a normal distribution or homogeneous variances, nonparametric tests will be used. Univariate and multivariate analyses will be performed by logistic analysis. Generally, a two-sided P value < 0.05 will be considered statistically significant unless otherwise stated.

Patient and public involvement

Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

Discussion

The FP-RESTORE will be the first study to provide prospective data on the effectiveness, safety and health economics evaluation of different endovascular modalities in the treatment of Tosaka III FP-ISR in a real-world setting. The endovascular treatments employed in FP-ISR include BA alone, DCB, cutting balloon, BMS, covered stent, mechanical debulking devices, laser atherectomy or a combination of the above.[13-25] However, the methods and results widely vary, which makes it difficult to compare the outcomes and make valid conclusions. FP-RESTORE is thus designed to evaluate and compare these endovascular procedures for Tosaka III FP-ISR. We hope our results will provide useful information and guidance about this issue and references for future controlled studies.

Clinically driven freedom from TLR is the primary outcome in our study. On the one hand, FP-RESTORE is designed to pay more attention to the clinical efficacy of various endovascular modalities; thus, clinically driven freedom from TLR could reflect the clinical effectiveness more intuitively. On the other hand, the inclusion criteria in real-world settings are not as strict as those of controlled studies; thus, a broader range of patients could be enrolled. Given that the patients are recruited throughout China, the imaging follow-up rate at different centres will vary widely, which may lead to missing information regarding primary patency. Thus, clinically

driven freedom from TLR will serve as the primary outcome, whereas primary patency and other results will serve as secondary outcomes in this study.

The patient's enrolment started at April 1, 2021 actually. The inclusion criteria " The length of occluded lesion is ≥ 5cm." and the exclusion criteria " or stent occlusion lesion less than 5cm in length" has been deleted in August 13, 2022 to keep consistent with Tosaka classifications. Since this study was a real-world setting observational study, we discussed with statistician in our group and concluded the modification of inclusion and exclusion was acceptable in post-hoc adaptation period.

Dissemination

The trial protocol complies with the Declaration of Helsinki. The study outcomes will be disseminated by publication in a peer-reviewed journal. The relevant confidential information will be transferred into a specific code to avoid potential leakage. In addition, the trial design has also been registered at ClinicalTrials.gov (Number: NCT04801004).

Author Contributions: The authors have been included in this manuscript based on the ICMJE recommendations. XL, MZ, YD, and ZS planned and designed the study. MY and ZW reviewed the structure of this manuscript. XL, MY, ZW ZF, LG, QL, XF and HS contributed to patient enrolments and collection of patient data. ZS critically reviewed and approved this manuscript. All authors have read and approved the final manuscript.

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Competing interests: None

Patient informed consent: Obtained

Ethics approval: The study protocol was approved by the Institutional Review Board and Human Research Ethics Committee of Zhongshan Hospital, Fudan University (B2021-427).

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing: No additional data are available.

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Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	#3	Date and version identifier	5
Funding	#4	Sources and types of financial, material, and other support	15
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	n/a
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	15
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	7
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will	8-9

		perform the interventions (eg, surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	9-10
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11-12
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	12
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	n/a
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	14

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	n/a
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	n/a
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	n/a
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	15
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	15
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11

Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	15
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	11
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n/a
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	15
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	15
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	15
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a