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Editor's Choice – RANDOMisation Screening for Drug coated or Drug Eluting Device Randomised Trials Among Patients Undergoing Endovascular FemorOPopliteal Procedures (RANDOM-STOP study)

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WHAT THIS PAPER ADDS

The RANDOM STOP study assessed the proportion of patients undergoing endovascular therapy for femoropopliteal arterial disease who would be eligible to take part in seven major RCTs for paclitaxel coated devices. The vast majority would not have been eligible for randomization in any of the seven RCTs. These findings raise questions regarding the validity of extrapolating RCT findings to routine vascular care.

Objective: The aim was to assess the proportion of patients undergoing endovascular therapy for femoropopliteal arterial disease (FP) who would be eligible to take part in seven major randomised controlled trials (RCTs) that investigated the efficacy of some of the currently available paclitaxel based (PTX) devices used in this clinical context. Various RCTs have shown a potential clinical benefit from the use of paclitaxel in FP endovascular therapy. Nonetheless, patients enrolled were highly selected and the generalisability of these findings in pragmatic cohorts is unclear.

Methods: Between 1 January and 31 December 2021, all consecutive patients who underwent endovascular procedures for symptomatic FP disease in 16 European centres were retrospectively screened and included in this analysis. The primary outcome measure was individual patient eligibility for inclusion into at least one of the seven RCTs. The reasons for exclusion (clinical and or radiological) as well as in hospital death and morbidity were also reported.

Results: A total of 1 567 consecutive patients (959 male, 61%), corresponding to 1 567 lower limbs, were included. Most patients (1 009 patients, 64.39%) were treated for chronic limb threatening ischaemia (CLTI). A total 1 280 patients (81.68%) were not eligible for inclusion in any of the evaluated RCTs. Of them, 741 (47.28%) were excluded for clinical and 1 125 (71.79%) for radiological reasons.

Conclusion: The analysed RCTs assessing the efficacy or effectiveness of PTX based endovascular therapies do not seem representative of the patient population with FP disease receiving endovascular therapy in routine clinical practice.

Keywords: Endovascular, Paclitaxel based device, Peripheral arterial disease, Randomised controlled trial, Vascular
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INTRODUCTION

Endovascular therapy, an alternative to open surgical revascularisation, is the primary treatment strategy for several patients with peripheral arterial disease (PAD), especially for those with significant comorbidity.[1–4] The minimally invasive nature of percutaneous endovascular revascularisation offers a short term benefit compared with surgery.[1] On the other hand, the increased risk of restenosis

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and target lesion revascularisation (TLR) might outweigh that short term benefit, especially in patients with life expectancy of more than two years and a good quality ipsilateral greater saphenous vein conduit.[5]

To inhibit neo-intimal hyperplasia after endovascular treatment and decrease the risk of restenosis, Paclitaxel (PTX) can be delivered locally into the arterial wall using drug coated balloons (DCBs) or drug eluting stents (DESs). Several randomised controlled trials (RCTs) investigating the efficacy of PTX based devices have shown improved patency and a reduced TLR requirement when using PTX based devices in the femoropopliteal segment (FP).[6–13] Nonetheless, these studies enrolled highly selected patients, in terms of both clinical and imaging criteria, and were not powered to detect differences in mortality and or amputation risk. Thus, their outcomes might not be fully applicable to the daily practice of most vascular practitioners. Additionally, these RCTs did not report the number of screened and excluded patients, which further complicates their applicability to everyday clinical practice, especially concerning patients who present with chronic limb threatening ischaemia (CLTI), who are often excluded from these studies.

The aim of this current study was to examine the applicability of seven major RCTs investigating Food Drug Administration (FDA) approved PTX based devices in patients undergoing FP vascular interventions for symptomatic PAD who presented in several vascular centres across Europe over one year (Supplementary Table S1).

MATERIALS AND METHODS

Study population and design

This was a multicentre retrospective observational study. All consecutive patients undergoing endovascular treatment of the FP segment for intermittent claudication (IC) or CLTI over a 12 month period (1 January to 31 December 2021) were assessed for eligibility to be randomised in any of the seven published RCTs included in this analysis (Table 1). Patients with the following characteristics were not considered for analysis as they would not meet the inclusion and or exclusion criteria of any of the seven RCTs: isolated procedure involving the common or deep femoral arteries, treatment of femoral or popliteal aneurysms, hybrid revascularisation (open surgery and angioplasty in one stage), patients undergoing primary major lower limb amputation without revascularisation, patients whose disease was managed conservatively, isolated aortic, iliac, or tibial vessel intervention, acute limb ischaemia, and vascular trauma. Data were collected locally, across 16 vascular centres in Europe, in a retrospective fashion, using electronic records and patient notes. Fully anonymised data were subsequently amalgamated centrally, using a purpose built database. Delivery of the study was coordinated by the Research Collaborative in Peripheral Arterial Disease (RCPAD), a pan-European scientific network of vascular specialists. One RCPAD collaborator led data collection at each study site and was responsible for data accuracy (Supplementary Table S2). Two independent investigators (including the site RCPAD collaborator/lead) reviewed each site data prior to final analysis. Queries with regards to missing or erroneous data were discussed by A.S. and E.K. with each site coordinator or lead. Missing data were queried in all cases with the originating sites.

Table 1. Evaluated randomised controlled trials (RCTs) of paclitaxel coated devices for the femoropopliteal arterial segment

RCT	Device	Protocol link with inclusion and exclusion criteria
IN.PACT SFA	IN.PACT Admiral drug coated balloon	clinicaltrials.gov/ct2/show/NCT01175850
LEVANT I and II	Lutonix drug coated balloon	clinicaltrials.gov/ct2/show/NCT00930813
ILLUMENATE	Stellarex drug coated balloon	clinicaltrials.gov/ct2/show/NCT01858363
RANGER SFA	Ranger drug coated balloon	clinicaltrials.gov/ct2/show/NCT03064126
EMINENT	Eluvia drug eluting stent	clinicaltrials.gov/ct2/show/NCT02921230
IMPERIAL	Eluvia drug eluting stent	clinicaltrials.gov/ct2/show/NCT02574481
Zilver PTX	Zilver drug eluting stent	clinicaltrials.gov/ct2/show/NCT00120406

PTX = paclitaxel; SFA = superficial femoral artery.

Ethics statement and regulatory approvals

The study complied with the Declaration of Helsinki. For United Kingdom sites, local regulatory approvals were waived due to the study's retrospective design, and the absence of any patient identifiable information being shared between collaborators/sites (as per the opinion of the East Midlands Leicester NHS Review Ethics Committee). The project was registered at each individual institution and local guidance and regulations were adhered to across the 16 sites, with local registration taking place at each site as per relevant local rules.

Aim and outcomes

The main aim was to assess the eligibility for inclusion of consecutive (unselected) patients undergoing percutaneous endovascular therapy of the FP segment for symptomatic PAD in seven major completed RCTs of paclitaxel coated devices (Table 1) (list of RCTs presented in Table 1). The primary outcome of interest was therefore exclusion of an individual patient from each of the evaluated RCTs for any reason as per each RCT's inclusion and exclusion criteria. The proportions of patients excluded from each RCT based on clinical criteria and or radiological criteria were the key secondary outcomes of interest.

Study procedures

Prior to commencement of data collection, the protocols of the evaluated RCTs were retrieved, as registered on the U.S.

Table 2. Demographic information of 1 567 consecutive patients undergoing endovascular therapy for symptomatic femoropopliteal segment arterial disease included in the analysis

Variable	Patients (n = 1 567)
Age − y	72.74 ± 10.94
Sex (male)	959 (61.19)
Laterality	
Right	838 (53.47)
Left	729 (46.52)
Hypertension	1 218 (77.72)
Diabetes mellitus	632 (40.33)
Chronic kidney disease	519 (33.12)
Smoker	396 (25.27)
Platelet abnormality	181 (11.55)
Immunosuppression	94 (5.99)
Septicaemia	46 (2.93)
Stroke or MI	
Within two weeks	24 (1.53)
Within six months	209 (13.33)
Pregnancy	0
Life expectancy < 2 y	113 (7.21)
On antiplatelet therapy	1 099 (70.13)
On statin therapy	991 (63.24)
DOAC intolerance	53 (3.38)
Contrast allergy	126 (8.04)
Already in an RCT	14 (0.89)

Data are presented as mean ± standard deviation or as n (%). MI = myocardial infarction; DOAC = direct acting oral anticoagulant; RCT = randomised controlled trial; CLTI = chronic limb threatening ischaemia.

National Library of Medicine Clinical Trials website (clinicaltrials.gov), and reviewed by two authors (A.S., E.K.; queries were discussed with a third author, K.S.) to extract the inclusion and exclusion criteria for each RCT. Names of the RCTs, devices assessed per study, and direct online links to the protocols are provided in Table 1; full inclusion and exclusion criteria per RCT are listed on Supplementary Table S1. This process was repeated with the inclusion and exclusion criteria as detailed in each study publication and cross referenced to those in the registered protocol. The extracted inclusion and exclusion criteria were then reviewed by two investigators independently, and any discrepancies were resolved by a referee (H.Z.).

A purpose built data collection form was created, consisting of demographic (Table 2), clinical (Table 3), radiological or anatomical (Table 4), and procedural data, corresponding to the extracted RCT inclusion and exclusion criteria. The data collection form was appraised in a meeting of the RCPAD steering committee prior to data collection commencing in the 16 participating centres. No patient identifiable or sensitive information was collected or shared.

Analysis

Individual patient data were collected at each centre and were amalgamated centrally. Data were inspected and missing values as well as outliers were discussed with the assigned coordinator for each centre.

Table 3. Clinical data of 1 567 patients undergoing endovascular therapy for symptomatic femoropopliteal segment arterial disease

Variable	Patients (n = 1 567)
Acute limb ischaemia	207 (13.23)
CLTI	1 009 (64.39)
Rutherford stage	
Stage 1	21 (1.34)
Stage 2	204 (13.01)
Stage 3	333 (21.25)
Stage 4	396 (25.27)
Stage 5	563 (35.92)
Stage 6	50 (3.19)
ABPI > 0.9	43 (2.74)
Previous treatment	403 (25.71)

Data are presented as n (%). CLTI = chronic limb threatening ischaemia; ABPI = ankle brachial pressure index.

To assess eligibility for each RCT, the following approach was employed: inclusion criteria were converted to their negative (e.g., if the inclusion criterion to a study was a vessel diameter of 4 − 6 mm, the criterion was altered to exclude anything outside that range) and collated to the list of pre-existing exclusion criteria for that study. This list was further subdivided into clinical and radiological or anatomical exclusion criteria.

Individual patients were then assessed per each RCT's exclusion criterion, and if those were met, they were also tallied in separate counters for clinical exclusion, radiological exclusion, or both, where appropriate. Only patients who did not meet any of the radiological or clinical exclusion criteria were considered eligible to take part in each individual RCT. This process was repeated for all seven of the RCTs, keeping a counter for which one, if any, individual participants were eligible for, or otherwise the reasons for, their exclusion. All analyses were performed using purpose built routines in MATLAB 2019a (The Mathworks, Natick, MA, United States). Analyses were performed by E.K. and independently validated by A.S., both of whom have formal statistical expertise.

RESULTS

Patients and eligibility

A total of 1 567 consecutive patients (959 male, 61%), corresponding to 1 567 lower limbs, were included (recruiting sites listed in Supplementary Table S2). The commonest comorbidities included hypertension (78%), diabetes (40%), and chronic kidney disease (33%). Overall, 1 009 (64%) presented with CLTI. Demographics and comorbidities are outlined in Table 2. Tables 3 and 4 provide anatomical and procedural information. No patients underwent a procedure for isolated iliac, common femoral, or tibial disease.

Eligibility for multiple randomised controlled trials

A total of 1 280 patients (82%) were not eligible for inclusion in any of the RCTs. A detailed presentation of the

Table 4. Radiological and procedural data of 1 567 patients undergoing endovascular therapy for symptomatic femoropopliteal segment arterial disease

Variable	Patients (n = 1 567)
Common femoral artery disease	43 (2.74)
Previous contralateral treatment	19 (1.21)
Intervention within the last 14 days	87 (5.55)
Concurrent iliac intervention	225 (14.35)
Concurrent tibial intervention	500 (31.90)
Previous stenting, no treatment	304 (19.40)
De novo lesion	1 104 (70.45)
In stent restenosis	457 (29.16)
Tosaka 1	265 (16.91)
Tosaka 2	90 (5.74)
Tosaka 3	102 (6.50)
Anastomotic stenosis	31 (1.97)
Thrombus	364 (23.22)
Acute thrombus	254 (16.20)
Proximal SFA disease	744 (47.47)
Mid SFA disease	996 (63.56)
Distal SFA disease	984 (62.79)
Proximal popliteal artery disease	729 (46.52)
Mid popliteal artery disease	486 (31.01)
Distal popliteal artery disease	330 (21.05)
CTO	759 (48.43)
CTO length − mm	113.40 ± 85.26
Flush with SFA origin	356 (22.71)
Lesion length, non-CTO − mm	152.42 ± 119.55
Vessel diameter − mm	5.15 ± 1.57
Number of run off vessels*	2 (1)
Run off vessel stenosis > 50%	58 (3.70)
PACSS score*	2 (1)
Severe calcification, IN.PACT	692 (44.16)
Severe calcification, Eminent	817 (52.13)
Subintimal crossing	437 (27.88)
Failure to cross	69 (4.40)
Vessel preparation	974 (62.15)
PTA	1 221 (77.91)
BMS	452 (28.84)
DCB	714 (45.56)
DES	217 (13.84)
Stent graft	127 (8.10)
Complications	311 (19.84)
Perforation	43 (2.74)
Embolisation	56 (3.57)
Dissection	185 (11.80)
In hospital	
Death	21 (1.34)
Re-intervention	115 (7.33)

Data are presented as n (%) or mean ± standard deviation. CTO = chronic total occlusion; SFA = superficial femoral artery; PACSS = peripheral artery calcium scoring system; PTA = percutaneous transluminal angioplasty; BMS = bare metal stent; DCB = drug coated balloon; DES = drug eluting stent

* Reported as median (interquartile range).

number of patients eligible to potentially take part in more than one RCT is presented in Table 5.

Eligibility for individual randomised controlled trials

IN.PACT SFA. A total of 1 533 patients (98%) were ineligible for this RCT, with 1 146 (73%) being excluded for clinical reasons, and 1 493 patients (95%) excluded for radiological or anatomical reasons. The commonest clinical reasons were Rutherford stage (634 patients, 40%), recent history of acute coronary syndrome or stroke (209 patients, 13%), and age (199 patients, 12%). The commonest radiological reasons for exclusion were run off disease (46%), lesion length (656 patients, 42%), and presence of popliteal artery disease (P2 and P3 segments, 599 patients, 38%). A total of 971 patients (62%) were excluded due to the use of adjuncts for vessel preparation. A detailed presentation of the number of patients excluded for each of the clinical and radiological or anatomical criteria can be found in Supplementary Table S3. Lastly, 1 106 patients (71%) were excluded for meeting both clinical and radiological or anatomical exclusion criteria.

Table 5. Number of patients eligible for one or more of the randomised control trials of randomised controlled trials (RCTs) of paclitaxel coated devices for the femoropopliteal arterial segment

RCTs eligible for	Patients
1	246 (15.70)
2	11 (0.70)
3	8 (0.51)
4	6 (0.38)
5	6 (0.38)
6	3 (0.19)
7	2 (0.13)
0	1 280 (81.68)

ILLUMENATE. A total of 1 532 patients (98%) were ineligible for this RCT, with 1 169 (75%) being excluded for clinical reasons, and 1 486 patients (95%) excluded for radiological or anatomical reasons. The commonest clinical reasons were a history of chronic kidney disease (519 patients, 33%), history of previous stenting (403 patients, 26%), Rutherford stage (634 patients, 40%), and recent history of acute coronary syndrome or stroke (209 patients, 13%). The commonest radiological reasons for exclusion were the use of additional treatment modalities (827 patients, 53%), the presence of severe calcification within the lesion (369 patients, 24%), and lesion length (599 patients, 38%). A total of 971 patients (62%) were excluded due to the use of adjuncts for vessel preparation (Supplementary Table S4). Lastly, 1 123 patients (72%) were excluded for meeting both clinical and radiological or anatomical exclusion criteria.

LEVANT. A total of 1 537 patients (98%) were ineligible for this RCT, with 1 190 (76%) being excluded for clinical reasons, and 1 477 patients (95%) excluded for radiological or anatomical reasons (Supplementary Table S5). The commonest clinical reasons were Rutherford stage (634 patients, 40%), a history of chronic kidney disease (519 patients, 33%), and a history of previous treatment (403 patients). The commonest radiological reasons for exclusion were lesion length (836 patients, 54%), presence of calcific disease (369 patients, 24%) and lesion thrombus (254 patients, 16%). Lastly, 971 patients (62%) were excluded due to the use of adjuncts for vessel preparation; 1 130 patients

(72%) were excluded for meeting both clinical and radiological or anatomical exclusion criteria.

RANGER SFA. A total of 1 538 patients (98%) were ineligible for this RCT, with 1 265 (81%) being excluded for clinical reasons, and 1 472 patients (94%) excluded for radiological or anatomical reasons (Supplementary Table S6). The commonest clinical reasons were Rutherford stage (634 patients, 40%), a history of chronic kidney disease (519 patients, 33%), and a history of previous treatment (403 patients 26%). The commonest radiological reasons for exclusion were the target vessel (P2 and P3 popliteal segments, 599 patients, 38%), lesion length (485 patients, 31%), and the presence of calcific disease (369 patients, 24%); 971 patients (62%) were excluded due to the use of adjuncts for vessel preparation and 1 199 (77%) were excluded for meeting both clinical and radiological or anatomical exclusion criteria.

EMINENT. A total of 1 545 patients (98.60%) were ineligible for this RCT, with 1 252 (80%) being excluded for clinical reasons, and 1 508 patients (97%) excluded for radiological or anatomical reasons (Supplementary Table S7). The commonest clinical reasons were Rutherford stage (634 patients, 40%), a history of chronic kidney disease (519 patients, 33%), and a history of previous treatment (403 patients 26%). The commonest radiological reasons for exclusion were the target vessel (P2 and P3 popliteal segments, 599 patients, 38%), lesion length (442 patients, 28%), and the presence of calcific disease (817 patients, 52%). Lastly, 971 patients (62%) were excluded due to the use of adjuncts for vessel preparation; 1 215 patients (78%) were excluded for meeting both clinical and radiological or anatomical exclusion criteria.

IMPERIAL. A total of 1 564 patients (99%) were ineligible for this RCT, with 1 265 (80%) being excluded for clinical reasons, and 1 564 patients (99%) excluded for radiological or anatomical reasons (Supplementary Table S8). The commonest clinical reasons were Rutherford stage (634 patients, 40%), a history of chronic kidney disease (519 patients, 33%), and a history of previous treatment (403 patients 26%). The commonest radiological reasons for exclusion were the presence of calcific disease (817 patients, 52%), lesion length (635 patients, 41%), and the distance of the lesion from the femoral head (356 patients, 23%). Lastly, 971 patients (62%) were excluded due to the use of adjuncts for vessel preparation; 1 262 patients (81%) were excluded for meeting both clinical and radiological or anatomical exclusion criteria.

Zilver PTX. A total of 1 304 patients (83%) were ineligible for this RCT, with 741 (47%) being excluded for clinical reasons, and 1 125 (72%) excluded for radiological or anatomical reasons (Supplementary Table S9). The commonest clinical reasons were a history of previous treatment (403 patients 26%), the pre-operative ankle brachial pressure index (155 patients, 10%), and contrast allergy (126 patients, 8%). The commonest radiological reasons for exclusion were lesion length (481 patients, 31%), the target vessel (P2 and P3 popliteal segment, 599 patients, 38%) and the presence of acute thrombus in the lesion (254 patients, 16%); 562 patients (36%) were excluded for meeting both clinical and radiological or anatomical exclusion criteria.

DISCUSSION

RCTs are considered the most rigorous studies in terms of assessing the efficacy or effectiveness of treatments.[14,15] Nonetheless, PAD RCTs occasionally enrol patients with favourable comorbid profiles, and potentially less complex lesions anatomically compared with real world observational PAD studies.[15–17] This might impact considerably on the interpretation of their results in clinical practice. The external validity of published PAD FP RCTs has not been assessed in multicentre international series. Further, no previous research has quantified the disconnect between real world practice and the evidence available in published PAD RCTs. In this study, only 18% of consecutive patients assessed would have been eligible for randomisation into at least one of the seven major FP RCTs investigating PTX based devices. Tissue loss (37%) and advanced renal disease (33%) were the main reasons for exclusion due to clinical criteria. Severe calcification, distal popliteal artery disease, and lesion length were the main radiological exclusion criteria. This suggests that the majority of patients treated in the daily practice of vascular interventionists have extensive advanced PAD and are more comorbid compared with the patients included in the currently available PTX based device literature. The presence of tissue loss and gangrene was a common exclusion criterion among all RCTs and only patients with rest pain could be enrolled. This leads to a significant underrepresentation of patients with CLTI (36% of the cohort presented with Rutherford class 5 and 6 and would have been excluded from all seven trials assessed). As a result, the ability of PTX to inhibit restenosis and reduce the need for TLR in patients with severe lower limb atherosclerosis remains unclear. The recently published Surgery or Endovascular Therapy for Chronic Limb threatening Ischaemia (BEST-CLI) trial, which specifically included patients with CLTI, did not shed further light into this issue, as several patients were not treated with PTX devices.[5] The ongoing Swedish Drug elution Trial in PAD (SWEDEPAD) RCT is assessing the efficacy of PTX based technologies to reduce the risk of major amputation and re-intervention in PAD.[18] This study will hopefully provide insights regarding the performance of PTX in CLTI. The ongoing BASIL-3 (ISRCTN14469736) trial in the United Kingdom will also hopefully add to the relevant evidence. However, given that there is no established class effectiveness of PTX based devices, the findings of these trials might be influenced from the proportional use of different endovascular modalities and the fact that most patients enrolled in these studies only undergo plain angioplasty.

Patients with severe renal impairment are often excluded from endovascular RCTs. Registry data show higher incidence of cardiovascular complications among those with

kidney disease.[19,20] The value of PTX use in this group therefore remains very unclear. Besides the exclusion of patients with advanced comorbidity, there is lack of RCT evidence regarding the effectiveness of PTX in complex FP disease. Severe FP calcification was a common exclusion criterion among the evaluated studies in the cohort, and different means of quantifying calcification have been used, which further complicates interpretation.[7–13] In this study cohort, the peripheral artery calcification scoring system (PACSS) was used to quantify the presence of severe calcification.[21] Overall, data regarding the performance of PTX in complex lesions are scarce.[22–24]

Interestingly, 62% of this cohort would have been excluded due to the use of adjuncts for vessel preparation prior to PTX use. Atherectomy, intravascular lithotripsy, and specialty balloons have been used as vessel preparation modalities in an effort to improve the acute and long term outcomes of PTX based devices or other modalities. Nonetheless, in all seven RCTs included in this study, only the use of plain balloon angioplasty was allowed as a vessel preparation strategy. More recently, small efficacy studies showed a benefit compared with plain angioplasty in terms of reduced bail out stenting rates and dissections.[25,26] There remains a clinical need for large scale, prospective trials, which will provide high quality evidence for adjunctive strategies prior to a definitive treatment with PTX based devices.

Finally, it should be noted that inclusion and randomisation of patients with PAD can be challenging even in studies with broad inclusion criteria. In the BASIL I trial, only 15% of treated individuals underwent randomisation.[27] More recently, the BEST-CLI trial failed to recruit 2100 patients, as planned, despite a five year recruitment period.[5]

All the above raise significant uncertainties regarding the data relating to the clinical and cost effectiveness of these new PAD technologies in routine practice.

The ultimate solution to providing high quality randomised evidence relating to treatment effectiveness could be in well designed large or international trials, potentially of adaptive nature (to include new treatments), funded by unbiased or unconflicted government or research institutions. This could potentially ensure that these studies will be reflective of and relevant to routine clinical practice in various healthcare systems.

Limitations

The retrospective nature of the cohort is a major drawback of this study; at the same time all consecutive patients treated in the participating sites were included. Additionally, only the seven largest trials of approved PTX based devices were included while other smaller RCTs or studies might have had broader inclusion criteria which were not identified in the literature searches. Also, one of the parameters that could not be evaluated was the lack of willingness of a patient to participate in an RCT. Further, reporting outcomes post-treatment was beyond the scope of this work and has not been assessed. Regardless of these limitations, this is an international multicentre study reporting on more than one thousand five hundred symptomatic patients, which adds to the existing literature in this area and clinical context.

Conclusions

The RANDOM-STOP study screened consecutive patients who underwent FP interventions in 16 European vascular centres. Most of these patients would not have been eligible for randomisation in any of the seven RCTs assessed. Main exclusion criteria included advanced comorbidities (advanced kidney disease and tissue loss) or extensive nature of the disease (severe calcification, long lesions, and distal popliteal disease).

Future studies should focus on the outcomes of PTX use in CLTI patients with complex lesions and further investigate the concept of vessel preparation using various modalities.

CONFLICT OF INTEREST

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2023.06.038.

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