



Optical Coherence Tomography Contribution Assessment in the Revascularization of Long Femoropopliteal Occlusive Lesions (TASC C and D): A Randomized Trial

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OCT (optical coherence tomography) contribution assessment in the revascularisation of long femoro-popliteal occlusive lesions (TASC C and D): a randomised trial.

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Abstract

Background: Endovascular treatment has become the first-line revascularisation technique for femoropopliteal lesions. This technique lacks of reliable and accurate morphological control of the arterial segment treated. Intraoperative 2-D angiogram consumes iodinated contrast media and increases X-ray exposure; this subsequently provides none 3D information on the quality of the revascularisation completed, what could explain some of the early and late failures of the technique.

Aim

Our objective is to evaluate if intra-operative optical coherence tomography (OCT) control in addition to standard angiogram could improve the primary patency rate at 12 months in comparison to standard angiogram alone in patients with occlusive femoropopliteal lesions.

Method: the ToCaf trial is a multicentric, prospective, randomised, controlled, single-blind study including patients with long *de novo* occlusive femoropopliteal lesions. The randomisation will be achieved in 2 balanced groups of patients after crossing successfully the lesion: group 1 with intra-operative OCT control in addition to standard angiogram and group 2 with standard angiogram alone. The randomisation will be stratified by centre. The protocol has been submitted and approved by a French ethic's committee under ref CPP2019-12-098. The study has been registered under the reference NCT04434586 on the clinicaltrials.gov's website.

Results: The primary outcome of the study is the primary patency at 12 months. The number of patients that need to be treated is 166 (83 in each group) considering 5% of not workable data. Symptoms' improvement, target lesion revascularisation, target vessel revascularisation, quality of life questionnaires, cost-utility and cost-effectiveness will be analysed as secondary endpoint variables at 12 months.

Conclusion: The aim of the present study is to evaluate the potential benefit for patients on the result of endovascular revascularisation of long occlusive femoro-popliteal lesion at 12-month when using intraoperative OCT control .

Introduction

Peripheral arterial disease is a frequent condition, with a prevalence estimated as high as 20% in people over 65 years old [1]. The diagnosis is confirmed with the calculation of an ankle-brachial index (ABI) <0.9 associated with symptoms' severity graded accordingly to the Rutherford-Becker's classification.

Endovascular treatment for femoropopliteal lesions includes vessel preparation with balloon angioplasty (dilatation), followed or not by the implantation of one or several self-expansible stent (bare, covered or drug-eluting); as an alternative to stent implantation, recent publications exhibited also interesting results with the use of drug-eluting balloons [2-4].

One of the current limitations of the endovascular technique is the lack of reliable and accurate intra-operative morphological control to assess the quality of the revascularisation, especially in long lesions. After stent implantation or single balloon angioplasty, a 2-dimensional (2-D) digital subtraction angiography (DSA) run is usually performed, requiring iodinated contrast media and X-ray exposure. This latter, as expected, does not deliver 3-dimensional information on arterial lumen re-opening and/or on adequate stent application and/or conformation. This basic method of assessment may explain some of the early and late failures of the procedure [5-7].

The current treatment benchmark for long femoropopliteal occlusive lesion superior to 25-cm is the saphenous femoropopliteal bypass with a 12-month patency around 75% [8-10]; nevertheless autologous saphenous veins are not always available and patient frailty may discourage long open repair [11].

Optical coherence tomography (OCT), is an endovascular imaging technique enclosed on an 4Fr catheter developed over the last decade for vascular intraluminal analysis with higher resolution compared to IVUS (intravascular ultrasound $1\mu\text{m}$ in OCT vs. $100\mu\text{m}$ in IVUS.) [12-15]. OCT has been initially developed to explore coronary lesions and is now routinely used in coronary disease [16]. The principle is pretty similar to IVUS, although OCT uses light waves close to Infra-red (1250-1350 nm) rather than ultrasound.

A rotational acquisition within the vessel is automatically generated by the withdrawal of an optical sensor located at the end of the OCT catheter. Then, a dedicated software reconstructs the native images acquired and delivered fine details of the arterial wall

88 through longitudinal and axial views. OCT In its original description, the use of OCT requires
89 repeated injections of iodinated contrast medium boluses for flushing the vessel lumen to
90 limit the interposition of blood elements that would prevent proper arterial wall analysis
91 [17]. To make OCT acquisitions acceptable in the lower limb arteries, we have recently
92 proposed a standardised protocol where iodine was substituted by saline alone [18],
93 reducing the risk of postoperative renal failure in that population at risk. Moreover, other
94 studies have already confirmed the relevancy and safety of OCT use during recanalisation
95 procedures of lower limb arteries [19]. The medico-economic issue balances the cost of this
96 expensive technique (nearly 1090 €/probe VAT excluded) and the contribution of the OCT on
97 the optimisation of the angioplasty procedure that could lead to a better life quality in
98 reducing iterative reintervention along follow-up.

99 We thus propose here a study where the primary objective will be to evaluate the 12-month
100 patency rate of the systematic use of OCT for long endovascular revascularisation of
101 femoropopliteal artery. A medico-economic evaluation of OCT will be also conducted.

102

Material and Method

We designed a multicentric, prospective, randomised, controlled, single-blinded study that will include patients eligible for endovascular revascularisation with long *de novo* femoropopliteal occlusive lesions (TASC C and D). The study protocol has been registered under the reference NCT04434586 on the clinicaltrials.gov's website. Three centres with large experience (>500 superficial femoral and/or popliteal artery cases/year) in peripheral endovascular revascularisation will participate to the study:

- the Department of vascular surgery at CHU Lille,
- the Vascular centre at Groupe hospitalier Paris-Saint Joseph
- the Department of interventional radiology at la Clinique de l'Orangerie, Strasbourg.

Data will be collected after completion of the patient's informed consent. No difference in the usual care except the intraoperative OCT acquisition is to be considered.

Details on the inclusion and exclusion criteria are provided in Table 1.

Research protocol (Figure 1)

The protocol has been submitted to and approved by the CNIL (ref number: DEC19-543) and the CPP Sud-Ouest Outre-Mer (ref number: CPP2019-12-098) for the ethics part and to guarantee the protection of patients' data.

Patient's selection

Symptomatic patients will be screened with US-duplex scan and/or CTA and/or MRA and/or angiography. An independent core lab will retrospectively analyse the preoperative images to confirm the eligibility of the patient to the study.

Randomisation Procedure

The randomisation will take place in the operating room, after crossing the occluded arterial segment and confirming the presence of at least a permeable tibial axis.

Patients will be randomly assigned in 2 groups (single-blind):

- "control group", where the procedure is achieved with usual repeated 2D-angiogram acquisitions

- “OCT group”, where the procedure is achieved with combination of repeated 2D angiogram and OCT acquisitions (according to the protocol [16]).

The randomisation will be centralised, stratified towards the coordinator centre (CHU LILLE) and completed using a randomisation table provided by the study sponsor. The randomisation table will be generated by SAS software in a balanced parallel design (1:1) using variable size blocks, and integrated directly into the eCRF via the Clinsight software to ensure a centralised real-time randomisation procedure. A document describing the randomisation procedure will be kept confidentially with the DRCI (Direction de la Recherche Clinique) at CHU Lille.

Procedural steps

The procedure will take place in a cath lab or an operating room. Procedures will be performed under local anaesthesia associated or not with sedation or general anaesthesia. After ultrasound-guidance puncture of the common femoral artery, heparin will be injected according to the operator’s preferences.

A first 2D-arteriogram will be performed to confirm and identify the lesion, the distal level of re-entry, and the quality of the “run-off” vessels. Techniques used for crossing the lesion remains at the operators’ discretion.

Once the lesion is crossed, patient will be randomised to the study via the electronic platform. No information will be given to the patient as regards of the arm assigned.

The artery will be dilated >90 seconds at nominal pressure by a balloon of a diameter equivalent to the estimated diameter of the arterial segment treated.

In both groups, an angiogram will be performed on the entire treated arterial segment to evaluate the quality of the vessel preparation and the modality of the subsequent treatment is let at the discretion of the physician.

In the “OCT group”, automatically-generated OCT acquisitions will be at that time performed using an Illuminen Optis catheter (pullback 75mm, AbbottVascular). The parameters of saline injection will be set according to the protocol previously published and recently adjusted (60cc at 15cc/sec). The use of DEB (drug eluting balloon) and/or additional stenting will be achieved at the operators’ discretion, according to the elements showed on 2D-angiogram and/or OCT acquisitions. Final angiogram in both groups plus additional OCT acquisition for

the “OCT group” will be performed, described and reported. Any additional elements and/or concomitant procedures achieved during the index procedure will be reported. The femoral access will be closed either via manual compression and/or using dedicated closure percutaneous device.

Post-operative care

Patients will be placed under dual antiplatelet agents’ therapy for at least 3 months post-operatively.

US-duplex before discharge is recommended. The treated arterial segment must be controlled at least by US-duplex within the first post-operative month, and then at 6 and 12 months.

Patients will be prospectively followed on an outpatient basis. Major adverse clinical events (MACE) including secondary procedures, minor or major complications, death and medical therapy will be intentionally sought and reported. Follow-up will include clinical examination, ABI measurement and Doppler ultrasound at 1, 6 and 12 months. Dedicated questionnaires (EQ5D and WIQ) to assess the quality of life will be filled by the patients before the index procedure and along follow-up. The time for inclusion should be of 18 months with a last follow-up visit at 12 months. The overall duration of the study should last no more than 30 months.

Outcomes

Primary Objective

To evaluate the 12-month impact of the systematic use of OCT in endovascular revascularisation of long femoropopliteal arterial occlusion.

Secondary Objectives

To analysis the cost-effectiveness and cost-utility of the systematic use of OCT in endovascular revascularisation of long femoropopliteal arterial occlusion.

Primary outcome

The primary endpoint is the loss of primary patency at 12 months (peak systolic velocity $\geq 2.4\text{m/s}$ and/or restenosis $\geq 70\%$).

Secondary outcomes

The secondary endpoints include:

- Reduction in secondary interventions rate and improvement in baseline efficacy, assessed by target lesion revascularisation (TLR) and target vessel revascularisation (TVR) at 1, 6 and 12 months.
- Clinical improvement assessed by a Rutherford scale grade, ABI evolution, quality-of-life questionnaires (EQ5D and WIQ) and limb salvage rate at 1, 6 and 12 months.
- Incremental cost-effectiveness ratio (ICER) with primary patency rate as effectiveness criterion and incremental cost-utility ratio (ICUR)

Sample size assessment

The primary endpoint of the study is the loss of primary patency at 12 months. Previous published data on the results of femoro-popliteal recanalisation by angioplasty and stenting for very long ($>20\text{cm}$) Superficial femoral artery (SFA) lesions showed primary patency rates between 50 and 60% [20-23]. We thus selected the primary patency rate of what can be the control group (52.5%) in the STELLA PTX study [24, 25] and considered it as our reference mark.

The benchmark results when considering primary patency in treating such lesions remain the rates obtained with saphenous infra-popliteal bypass; at 12 months, this rate is above 75% with adequate autologous vein and appropriate distal “run-off” [8-10].

To prove that difference (52.5% versus 75%) with an 80% power and an alpha-risk at 5%, 78 subjects in each group are required (exact bilateral test, PASS 12). Considering a rate of data not workable at 5%, 166 subjects in total need to be recruited (83 for each group).

Statistical analyses

Statistical analyses will be independently performed by the Biostatistics Department of Lille University Hospital. Data will be analysed using SAS software (SAS Institute Inc, Cary, NC, USA) and all statistical tests will be two-sided and performed with type I error of 0.05.

Baseline characteristics will be described for each treatment group. Categorical variables will

be expressed as frequencies and percentages and quantitative variables will be expressed as mean and standard deviation or median and interquartile range for non-Gaussian distribution. Normality of distributions will be assessed graphically and by using the Shapiro-Wilk test. No formal statistical comparisons of baseline characteristics will be done; clinical importance of any imbalance will be noted. All analyses will be performed using all randomized participants based on their original group of randomisation, according to the intention-to-treat principle. A per-protocol analysis will be considered only for primary endpoint as a secondary analysis. Per-protocol population will include all randomised patients excluding those with major protocol violations (drug discontinuation, absence of postoperative completion of US duplex scan after 6 months). A detailed statistical analysis plan will be written before the database freezing. The final report will be written according to the CONSORT statement recommendations [26].

Primary outcome

The primary patency rate at 12 months will be reported in each group and compared using a mixed logistic regression model including the centre as random effect. The odds ratio (experimental procedure versus control procedure) will be derived from this model as the treatment effect size. We will also calculate absolute and relative risk differences as effect sizes from the marginal probabilities of patency rate, estimated by the mixed logistic regression model, using the method described by Austin [27].

In case of missing data (whatever the reason), a sensitivity analysis will be performed after handling missing values in primary endpoint by multiple imputation procedure under the missing at random assumption. Imputation procedure will be performed using main baseline characteristics and treatment group. Missing values will be imputed by using regression switching approach (chained equation with $m=10$ imputations) with predictive mean matching method for quantitative variables and logistic regression (binary, ordinal or polynomial) for categorical variables [28]. Treatment effect estimates obtained in multiple imputed data sets will be combined using the Rubin's rules [29].

Secondary outcomes

The secondary binary outcomes (rate of target lesion revascularization and rate of target vessel revascularisation), will be described at each follow-up visit (1, 6 and 12 months) and

compared between both groups be using the logistic regression model that will be used for the primary outcome.

The secondary ordinal outcome (Rutherford scale grade) will be described at each visit and compared between the 2 groups using a mixed ordinal logistic regression model adjusted for the baseline value and including the centre as random effect. The common odds ratio (assuming proportional odds) and the 95% confidence interval will be calculated as the treatment effect size.

The secondary quantitative outcome, namely the change in IPS, WIQ et EQ5D scores at 1, 6 and 12 months will be analysed using the constrained longitudinal data analysis (cLDA) model proposed by Liang and Zeger [30]. This model will be used given the potential advantages it has over the conventional longitudinal analysis of covariance (ANCOVA) model [31-32]. In the cLDA, both the baseline and post-baseline values of the analysed score are modeled as dependent variables using a linear mixed model (with an unstructured covariance pattern), and, in the linear model, the true baseline means are constrained to be the same for the 2 treatment groups. Hence, the cLDA provides an adjustment for the baseline values in estimating the treatment effects, using all available baseline and post-baseline values. The between-group mean differences in change of score from baseline to each visit date will be estimated by the time-by-group interaction as treatment effect size. The centre will be included in the model as random effect. If normality of model residuals are not satisfied, nonparametric analysis will be used; absolute changes between baseline and each visit will be calculated and compared between the 2 treatments groups using non-parametric analysis of covariance adjusted for baseline values [33-34].

Individual per-procedure complication and related serious adverse events will be described in each arm.

All secondary objectives will be considered as exploratory and no correction for multiple comparisons will be applied.

The incremental cost-effectiveness ratio and the incremental cost-utility ratio of the OCT acquisition will be computed by dividing the average costs differential to the differential primary patency rates at 12 months or differential number of quality-adjusted life years (QALYs) between the two treatment groups. QALYs will be calculated as the area under the curve (AUC) from the four available measures of EQ-5D scores (at baseline, 1 month, 6

months and 12 months) using linear interpolation. The French EQ-5D utility scores will be used [32]. Costs will be estimated in the health payers' perspective over a 12-month period. Following costs will be considered: procedure for primary revascularisation, related hospital admissions (initial and re-admissions), follow-up (visits and imaging acts in hospitals). Micro-costing will be conducted to estimate costs of vascular procedures. Hospital admissions will be valued by reference to the National costs study (ENC). The length of stay and ICU admission will be used as main cost-drivers for adjusting hospital costs. Tariffs or price paid by the hospitals will be used for valuing medical devices. Considering time horizon, costs and health outcomes will not be discounted. The confidence interval of the cost-effectiveness or cost-utility ratios will be estimated by non-parametric bootstrap. Deterministic and probabilistic sensitivity analyses will be conducted to test robustness of results. The acceptability curve will be drawn.

Study Oversight

Prof J. Sobocinski initiated the present study sponsoring by CHU Lille, which keeps possession of the whole responsibility for the conduct of the study and the publication of the results. A recommending scientific committee has already been selected to oversee the study along its duration. Its members are familiar with clinical trial methodology and not involved in the study. This committee will review the trial data and be consulted in the case of any specific analytical or safety issues.

Data Collection

Data will be recorded in an electronic case report forms (eCRF), developed using Clinsight (ENNOV). This software is certified for data management in clinical trials (with FDA compliance) recommendations. The eCRF will be used to data entry in each investigator site and every centre will be responsible of the patient's anonymisation. All data will be hosted on a secure server of the CHU LILLE. The eCRF will be created, tested and validated before the start of data entry. The data necessary for monitoring the primary and secondary endpoints will be identified and managed at regular intervals throughout the study. Data will be monitored by the data management team of the data-management department of CHU Lille by using the predefined data management rules and queries will be automatically edited. Finally, an overall automated monitoring will be done by the data manager at the

end of the data entry. In case of discrepancies, queries will be edited to resolve the problems encountered. After validation, the database will be frozen and exported to the statistical software package for analysis.

Data Protection

The personal data collected during the study will be reported on a source document and will then be entered by computer to form a computer database. These data are confidential in accordance with the law of January 6, 1978.

The data will be analysed in accordance with the reference methodology MR001 described by the Commission Informatique et Libertés (CNIL) in the Unit of Methodology, Biostatistics and Data Management directed by Prof. Alain Duhamel at CHU Lille.

Access to the data will be restricted to those directly involved in the study. The data may only be modified by an investigating physician participating to the study or a collaborator designated by the physician and participating to the study.

The data of this study will be archived for a minimum period of 15 years from the end of the research or its early termination without prejudice to the laws and regulations in force.

Patient's study disruption

The ITT analysis will be performed according to the treatment group to which the patients were assigned at randomisation, whatever the procedure they received and the duration of the follow-up. The patients who do not received the whole expected care during the index intervention after randomisation for any reasons will be follow-up during a year for recording the primary and secondary endpoints.

Study patients will have the right to withdraw from the study at any time and for any reason. Patient data gathered before the withdrawal of consent will be included in the analysis, and where permitted, available data may be included should consent be withdrawn. Once randomised, patients who withdraw will not be replaced.

The report indicating the premature exit of the study will have to list the reasons for this withdrawal:

- Lack of effectiveness

- Other medical problem personal
- Reasons withdrawal of participation consent
- Lost follow-up

Discussion – Conclusion

Here is proposed an original and unique randomised prospective study that would explore and document the potential benefit of the use of Optical Coherence Tomography (OCT) in the assessment of endovascular treatment of peripheral arterial occlusive lesions.

OCT is a quite recent imaging technology that is known to save radiation exposure at first and at the same time would be able to provide additional valuable data to better understand the initial (or during follow-up) quality of the arterial revascularisation.

By proposing the substitution of iodine contrast, usually use in OCT acquisition in coronary disease, to saline, OCT looks now more friendly to become a useful tool in peripheral complex endovascular revascularisations.

That study has also the objective to evaluate the attitude of the physicians with high experience in long lesion revascularisation as regards of the insight provided with the OCT acquisitions and will assess in 2 comparable groups the impact of OCT on the intraoperative strategy of revascularisation.

Through the primary objective, that study would be able to answer if OCT acquisitions would alter physicians' intraoperative strategies and as a consequence if physicians would be more aggressive implanting more or on the contrary less stents. Finally, it would be of interest to evaluate if those different attitudes would result in different patency rates at 12 months from a clinical perspectives but also considering the economic aspects.

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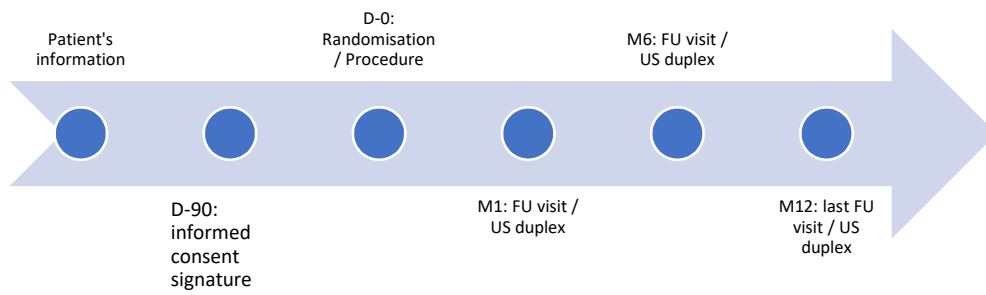


Figure 1 – Timeline schedule of the study

Criteria of inclusion	Criteria of exclusion
<ul style="list-style-type: none"> • Age \geq 18 years-old • TASC C and D lesions • Symptomatic patients (Rutherford 2-5) • <i>de novo</i> Femoro-popliteal occlusive lesions (from F1 to P1 included) • At least 1 patent tibial artery directly injecting the plantar arch • Femoral and/or pedal accesses 	<ul style="list-style-type: none"> • Age <18 years-old • Personal protection regime (guardianship, trusteeship) • Acute ischemia (<14 days) • Traumatic lesions • No argument allowing to consider a wound healing of the foot • History of stents and/or bypass on the ipsilateral femoro-popliteal axis • Untreated stenosis \geq30% on the ipsilat iliac axis and common femoral artery • Extensive lesions beyond P1 (middle or low popliteal artery) • Humeral access

Table 1 – Criteria for participating to the study

	Screening	Randomisation	Reference visit	FU#1 – 30d +/-10d	FU#2 – 6 mo +/-1mo	FU#3 – 12 mo +/-2mo	Standard cares	Research
<i>Patient's information</i>	+						+	+
<i>Past medical history</i>	+		+	+	+	+	+	
<i>Adverse events</i>				+	+	+	+	
<i>Consent form signature</i>	+							+
<i>US duplex</i>	+		+	+	+	+	+	
<i>CTA or MRA</i>	+/-						+	
<i>EQ5D and WIQ</i>	+		+	+	+	+		+
<i>Creatinine serum level</i>	+		+				+	
<i>Pre-albumine, CRP, HbA1c</i>			+				+	

Table 2 – Protocol timetable of the study

EQ5D: EuroQuol 5 Dimensions; WIQ: Walking Impairment Questionnaire; FU: follow-up