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

3

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21

22

23

24 **Abstract**

25

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

32

33 **Aim**

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

37

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

46

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

52

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

56 Introduction

57

58 Peripheral arterial disease is a frequent condition, with a prevalence estimated as high as
59 20% in people over 65 years old [1]. The diagnosis is confirmed with the calculation of an
60 ankle-brachial index (ABI) <0.9 associated with symptoms' severity graded accordingly to the
61 Rutherford-Becker's classification.

62

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

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

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

79 Optical coherence tomography (OCT), is an endovascular imaging technique enclosed on an
80 4Fr catheter developed over the last decade for vascular intraluminal analysis with higher
81 resolution compared to IVUS (intravascular ultrasound 1 μ m in OCT vs. 100 μ m in IVUS.) [12-
82 15]. OCT has been initially developed to explore coronary lesions and is now routinely used
83 in coronary disease [16]. The principle is pretty similar to IVUS, although OCT uses light
84 waves close to Infra-red (1250-1350 nm) rather than ultrasound.

85 A rotational acquisition within the vessel is automatically generated by the withdrawal of an
86 optical sensor located at the end of the OCT catheter. Then, a dedicated software
87 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

103 **Material and Method**

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

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

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

115

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

117

118 **Research protocol (Figure 1)**

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

122

123 Patient's selection

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

127

128 Randomisation Procedure

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

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

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

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

136

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

144

145 Procedural steps

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

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

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

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

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

160 In the "OCT group", automatically-generated OCT acquisitions will be at that time performed
161 using an Illuminen Optis catheter (pullback 75mm, AbbottVascular). The parameters of saline
162 injection will be set according to the protocol previously published and recently adjusted
163 (60cc at 15cc/sec). The use of DEB (drug eluting balloon) and/or additional stenting will be
164 achieved at the operators' discretion, according to the elements showed on 2D-angiogram
165 and/or OCT acquisitions. Final angiogram in both groups plus additional OCT acquisition for

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

170

171 Post-operative care

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

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

177

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

186

187

188 **Outcomes**

189 Primary Objective

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

192 Secondary Objectives

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

195

196 Primary outcome

197 The primary endpoint is the loss of primary patency at 12 months (peak systolic velocity
198 $\geq 2.4\text{m/s}$ and/or restenosis $\geq 70\%$).

199

200 Secondary outcomes

201 The secondary endpoints include:

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

209

210 **Sample size assessment**

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

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

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

223

224 **Statistical analyses**

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

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

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

241

242 **Primary outcome**

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

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

257

258 **Secondary outcomes**

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

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

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

268 The secondary quantitative outcome, namely the change in IPS, WIQ et EQ5D scores at 1, 6
269 and 12 months will be analysed using the constrained longitudinal data analysis (cLDA)
270 model proposed by Liang and Zeger [30]. This model will be used given the potential
271 advantages it has over the conventional longitudinal analysis of covariance (ANCOVA) model
272 [31-32]. In the cLDA, both the baseline and post-baseline values of the analysed score are
273 modeled as dependent variables using a linear mixed model (with an unstructured
274 covariance pattern), and, in the linear model, the true baseline means are constrained to be
275 the same for the 2 treatment groups. Hence, the cLDA provides an adjustment for the
276 baseline values in estimating the treatment effects, using all available baseline and post-
277 baseline values. The between-group mean differences in change of score from baseline to
278 each visit date will be estimated by the time-by-group interaction as treatment effect size.
279 The centre will be included in the model as random effect. If normality of model residuals
280 are not satisfied, nonparametric analysis will be used; absolute changes between baseline
281 and each visit will be calculated and compared between the 2 treatments groups using non-
282 parametric analysis of covariance adjusted for baseline values [33-34].

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

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

287

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

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

305

306 **Study Oversight**

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

313

314 Data Collection

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

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

328

329 Data Protection

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

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

336

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

340

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

343

344 Patient's study disruption

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

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

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

356 - Lack of effectiveness

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

360

361 ***Discussion – Conclusion***

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

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

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

371

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

376

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

382

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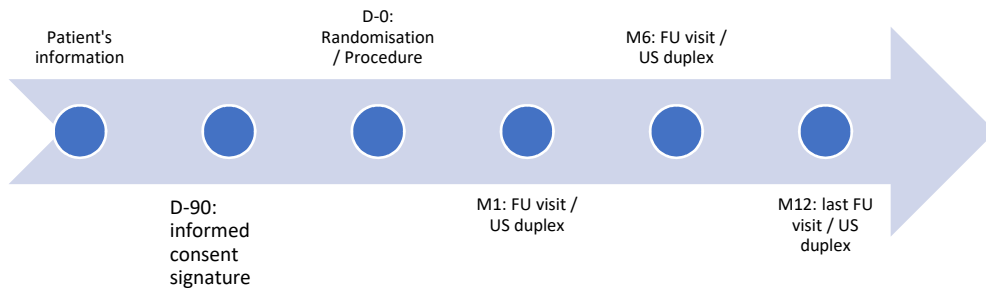


Figure 1 – Timeline schedule of the study

Criteria of inclusion	Criteria of exclusion
<ul style="list-style-type: none"> • Age ≥ 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 ≥30% 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