A Randomized Controlled Trial Comparing Crude Versus Heparin-Bonded PTFE Graft in Below the Knee Bypass Surgery for Critical Limb Ischemia (REPLACE Trial): Design and Protocol

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1 **A randomized controlled trial comparing crude versus heparin-bonded PRFE graft in**
2 **below the knee bypass surgery for critical limb ischemia (REPLACE trial). Design and**
3 **protocol.**

4
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17
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29

30 **Abstract**

31

32

33 Background

34 While autogenous venous graft is preferable in below the knee bypass surgery for patients in critical
35 limb ischemia, some 20% of patients will have no suitable vein for grafting, compelling a resort to
36 artificial graft materials. Retrospective sub-group analyses within published studies comparing
37 heparin-bonded PTFE with crude PTFE graft in below the knee bypass suggest that heparin-bonded
38 graft offers superior long-term patency rates, but this has not been prospectively verified in patients
39 with critical limb ischemia.

40

41 Research question

42 Is heparin-bonded PTFE graft superior to crude PTFE graft in below the knee bypass surgery for
43 critical limb ischemia?

44

45 Setting

46 Twenty vascular surgery departments in university hospitals in France.

47

48 Methods

49 Single blind randomised controlled trial with economic analysis. Patients assessed as having no
50 suitable autologous vein for bypass grafting in critical lower limb ischemia will be randomized to
51 receive either a heparin-bonded PTFE graft or a crude PTFE graft. A literature review suggested
52 expected 1-year patency rates of 53% for the crude ePTFE arm and 74% for the heparin-bonded
53 PTFE arm. Analyzing 1-year patency rate as a binary variable, for a significance level $\alpha=0.05$, and a
54 randomization ratio of 1:1, a total of 176 patients (88 in each arm) will be required to obtain

55 approximately 80% power to reject the null hypothesis. Assuming 10% dropout at 1 year and 20%
56 mortality, 228 patients will be randomized (114 patients in each arm).

57

58 Analysis

59 The primary outcome variable will be patency at one year assessed by duplex ultrasound color-flow
60 scan. Any intervention to open up or prevent a graft occlusion before one year will be classified as
61 loss of patency. Technical success, deaths, complications, major adverse cardiovascular and limb
62 events, length of hospitalization, and quality of life will also be recorded and analyzed as secondary
63 outcome variables. Cost-utility and cost-effectiveness analyses based on standard tariffs in the
64 French health insurance system will be performed.

Introduction

The prognosis for patients with newly diagnosed critical limb ischemia (CLI) is dismal: at one year 20% will have died, and another 30% will have an amputated limb (1). While optimization of medical therapy is important, revascularization procedures are generally indicated (2). Endovascular repair or a bypass procedure are similarly effective at avoiding amputation of the affected limb within two years of the procedure, though bypass surgery was associated with higher early morbidity and hospital costs (3).

Once an open surgical approach has been elected, a bypass procedure with autologous vein graft is clearly superior to PTFE graft (4), but a good quality vein of sufficient length and diameter for grafting is unavailable in about 20% of cases (5). The presence or absence of a good quality vein has been shown to be one of the main factors influencing the outcome of open, below-knee, popliteal artery revascularization (6-8). When an autologous vein graft is not available, a synthetic graft, or xenografted or allografted vein may all be considered, but loss of graft patency remains a significant problem (9). Binding heparin to the luminal surface of the PTFE graft material could reduce primary graft failure in femoro-popliteal bypass procedures, and appears to offer particular benefit in patients with CLI (10-13). However, most of these studies primarily recruited patients with claudication. A retrospective analysis of the subgroup of Lindholt patients with CLI showed that femoropopliteal bypass with heparin-bound PTFE graft offered significantly superior 1-year patency rates: 35 of 44 (80%) heparin-bound PTFE grafts were patent at 1 year, compared with 23 of 40 (58%) crude PTFE grafts (OR 0.348; 95% CI: 0.133; 0.912, $p=0.032$) (12). In addition, patients receiving heparin-bonded PTFE graft for CLI were more likely to have a patent graft at five years than those with crude PTFE grafts (13). In order to address these shortcomings in the existing evidence, the REPLACE trial will prospectively recruit patients with CLI for whom no autologous vein graft is available for randomization to grafting with either crude PTFE or heparin-bound PTFE.

Methods

The study hypothesis is that heparin-bound PTFE graft will be superior to crude PTFE graft in the treatment of CLI by below-knee bypass grafting in cases where no suitable venous conduit is available. Twenty vascular surgery departments in university hospitals in France will recruit patients to the study. The study protocol was approved by the national ethics committee CPP IDF III on 12 May 2017, and will be conducted in accordance with the Declaration of Helsinki, the EU Medical Device Directive (94/42/EEC) and the relevant French regulations (14). The study flow chart is given in figure 1.

Patients

Study recruitment opened on February 13, 2018 and is planned to continue for three years. It is planned to recruit 228 patients with CLI (Rutherford categories 4-6) for whom below-knee grafting is indicated but have no suitable autologous vein for grafting. See table 1 for a full list of inclusion and exclusion criteria.

Study devices

The crude PTFE grafts (Gore-Tex[®] Stretch Vascular Graft, WL Gore, Flagstaff, AZ, USA) and heparin-bonded PTFE grafts (Gore[®] Propaten[®] Vascular Graft, WL Gore, Flagstaff, AZ, USA) under comparison will be supplied by the manufacturer. The luminal surface of the Propaten[®] graft is bonded with fractionated active heparin of porcine origin. The CARMEDA[®] BioActive Surface serves to anchor heparin molecules to the luminal surface while still maintaining heparin's intrinsic bioactive properties., with the attendant risks of allergy and heparin-induced thrombocytopenia. Either type of graft is supplied with an additional exterior thin film incorporating removable rings.

117 The graft is cut to length, and the proximal anastomosis fashioned, before being passed through a
118 tissue tunnel, stretched to moderate tension with the aid of orientation markers incorporated in the
119 device, and the distal anastomosis performed. The use of any adjuvant technique such as a vein
120 collar is left at the discretion of the operating surgeon. All centers involved in the study routinely
121 perform below-knee prosthetic arterial grafting and no additional surgical training will be necessary
122 for their participation.

123 **Study objectives and end points**

124 The primary study end point is graft patency at one year. Primary patency will be defined as a
125 demonstrably patent graft on duplex ultrasound color-flow scan in which no intervention to re-open
126 up or prevent graft occlusion has been performed. Any intervention performed for disease distal to
127 the graft will not be considered a loss of primary patency. Dilations or minor revisions performed
128 for stenoses or other structural defects in the bypass graft before occlusion will also not be
129 considered to have resulted in loss of primary patency, if they are intended to prevent eventual graft
130 failure (15).

131 The study will also compare clinical, technical and economic outcomes in both treatment
132 groups. Secondary end-points analyzed will include technical success, defined as a patent bypass
133 with <30% stenosis of the proximal and the distal anastomoses on intraoperative arteriography; the
134 rate of general (death from any cause, major adverse cardiovascular events) or local (major adverse
135 limb event, hematoma, active bleeding, local infection, thrombosis, delayed wound healing, and
136 false aneurysm) perioperative complications requiring prolonged hospitalization and/or re-
137 intervention; lymphorrhea of more than three days' duration and post-operative paresthesia
138 requiring drugs. Secondary endpoints will also include primary sustained clinical improvement
139 defined as a wound healing and resolution of rest pain during follow-up, without any intervention to
140 open up or prevent a graft occlusion; and secondary sustained clinical improvement defined as
141 wound health, resolution of rest pain, and limb salvage, though a reintervention to open up or
142 prevent a graft occlusion may have been necessary. A major adverse limb event (MALE) is defined

143 as above-ankle amputation of the index limb or major reintervention such as a new bypass graft or
144 revision, or thrombectomy/thrombolysis. The ankle brachial index and quality of life (assessed with
145 the EQ-5D-3L questionnaire (16)) will be serially measured during follow-up. An economic
146 analysis will determine the cumulative costs associated with the primary bypass procedure and all
147 directly related follow-up, including follow-up exams and duplex imaging, adjunctive endovascular
148 and open surgical procedures at the target lesion, and the costs of amputation on the target limb
149 (including rehabilitation costs following amputation).

150 **Sample size calculation**

151 We reviewed the literature to find all publications reporting primary patency at 1 year for below-
152 knee bypasses using both Propaten[®] and crude PTFE in at least 50 limbs published between 2004
153 and 2015 (17). This suggested expected 1-year patency rates of 53% for the crude ePTFE arm and
154 74% for the Propaten[®] arm. Analyzing 1-year patency rate as a binary variable, for a significance
155 level $\alpha=0.05$, and a randomization ratio of 1:1, a total of 176 patients (88 in each arm) will be
156 required to obtain approximately 80% power to reject the null hypothesis. Assuming 10% dropout
157 at 1 year and 20% mortality (1) 228 patients will be randomized (114 patients in each arm).

158 **Statistical considerations**

159 Significance level will be set at 5%. Categorical variables will be compared between the two
160 study arms by Pearson's Chi-squared or Fisher's exact test to ensure adequate randomization. The
161 Mann-Whitney-U test or t-test will be performed to test for statistical differences in continuous
162 parameters between the two study arms.

163 Continuous data will be presented as means ($\pm$ standard deviation) or medians (interquartile
164 range, IQR) based on their distribution. Categorical variables will be presented as counts
165 (proportions).

166 Primary patency at 1 year will be analyzed as a binary variable. We will use logistic regression
167 analysis to compare primary patency at 1 year between the two groups, adjusting on stratification
168 criteria based on center, prior below the knee ipsilateral bypass and distal target arteries. Adjusted

odds ratios with 95% confidence intervals will be presented. The same method will be used for secondary patency.

Technical success and each complication or event will be analyzed as binary variables using Pearson's Chi-squared test or Fisher's exact test to compare the two groups. Primary and secondary sustained clinical improvement, death, MALE-free survival rate, and target vessel revascularization will be analyzed as time to event variables. Survival curves will be constructed using Kaplan-Meier estimates, and log rank test results will be displayed. For patients who died before the final follow-up examination or for patients lost to follow-up, the status of the last follow-up examination will be recorded. Mixed models will be used to analyze the evolution of ankle brachial index (ABI) from 1 to 24 months.

The primary endpoint analysis will be performed as a modified intention-to-treat analysis, excluding patients with major exclusion criteria. A sensitivity analysis will be performed alongside the per-protocol analysis which includes only patients who have completed the study without any protocol violations.

Handling of missing, unused or invalid data

For patients who died before the final follow-up examination or for patients lost to follow-up, the status of the last follow-up examination will be recorded. All analyses will be based on available data with missing data excluded. Any spurious data will be noted as appropriate in the final report. If patients in any treatment arm are excluded from the primary analysis because of missing data, sensitivity analysis will be performed using methods such as tipping point analysis.

The modified intention to treat population will include all randomized patients, including early failures, but excluding those who, after randomization, did not undergo the planned bypass. Patients will be analyzed in the treatment group to which they were randomized.

The per treatment evaluable (PTE) population consists of patients who have received their assigned treatment at the target lesion(s). The PTE population will exclude patients with major

194 protocol deviations. Analysis based on the PTE population will be performed as a sensitivity
195 (robustness) analysis.

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

200 A statistical analysis plan will be drafted before freezing the database and will detail any
201 changes in the statistical section of the protocol.

202 **Study procedures**

203 The diagnosis of CLI includes one of the following: more than two weeks of recurrent rest pain
204 that requires regular use of analgesics and is associated with ABI <0.40 in non-diabetics, ankle
205 pressure <50 mmHg, toe pressure <30 mmHg, TcPO₂ <30 mmHg, with or without tissue loss
206 (ulcers, gangrene) or infection (2) .

207 All patients presenting with CLI in a participating center will be screened for participation by a
208 research team member familiar with the study protocol.

209 Patient workup will occur in accordance with the standard hospital care for below the knee
210 bypass in each participating center. The baseline assessments described below must be performed
211 between 60 days and one day prior to study procedure, unless indicated otherwise.

212 **Patient history**

213 The patient's full medical history will be documented. The following risk factors and
214 comorbidities will be actively sought: age, height, weight, body mass index (BMI), gender,
215 hypertension, hyperlipidemia, diabetes mellitus, smoking, ischemic heart disease (history of
216 myocardial infarction, angina pectoris, previous percutaneous or surgical coronary
217 revascularization), history of peripheral vascular disease (previous percutaneous or surgical
218 revascularization), renal function, cerebrovascular disease (known carotid artery disease, history of
219 minor or major stroke or transient ischemic attack). Medication history should be documented

220 before, at the perioperative period and during the follow up. This history should include
221 anticoagulants (warfarin, unfractionated or low molecular weight heparins, etc.), antithrombotic
222 agents (acetylic salicylic acid, thienopyridines, glycoprotein IIb/IIIa inhibitors, direct thrombin
223 inhibitors, etc), statins or other lipid lowering agents and angiotensin converting enzyme
224 inhibitors. .

225 An ABI measurement will be obtained for the target limb. In cases where the ABI is above 1.3
226 or cannot be reliably measured, toe pressure measurement and determination of the toe brachial
227 index (TBI) will be used.

228 **Baseline morphologic data**

229 The anatomy of the entire ipsilateral arterial vasculature should be obtained from the
230 preoperative angiography, CT scan or MRI. The presence of multilevel disease by anatomic level or
231 arterial segment, inflow and outflow, specific location of the lesion, lesion length, stenosis or
232 occlusion will be documented in the eCRF.

233 **Treatment strategy and randomization procedures**

234 Aspirin or clopidogrel will be started at least 24 hours before the intervention or a loading dose
235 of 300 mg given orally at the outset of the procedure. If aspirin or clopidogrel are contraindicated,
236 ticlopidine will be an acceptable substitute.

237 At the beginning of the study a batch of Propaten[®] graft will be provided to each center by WL
238 Gore, replenished as necessary after each randomization. Operating procedures for Propaten[®] and
239 crude PFTE are similar. The proper graft size will be determined during the procedure but prior to
240 randomization. General anaesthesia is recommended unless loco-regional anaesthesia is required.

241 Randomization (using the web-based Ennov Clinical system) will be performed after the
242 operating surgeon has confirmed the presence of an acceptable recipient artery. Proximal and distal
243 anastomosis sites (common femoral artery, deep femoral artery, superficial femoral artery,
244 infrapopliteal artery, tibio-peroneal trunk, anterior tibial, posterior tibial or peroneal artery), type of
245 incision (internal, external, longitudinal, transversal), type of anastomosis (end to end, side to end,

246 end to side), location of the prosthetic tunnel (anatomic or extra-anatomic), and choice of graft
247 diameter will be left to the discretion of the surgeon, as will the use of any adjuvant technique (such
248 as a vein collar).

249 Each associated inflow or outflow lesion considered involved in the disease will be treated
250 during the same procedure by open or endovascular repair. Treatment of inflow and/or outflow
251 lesions with drug-eluting devices is not allowed. The use of adjuvant medication to prevent graft
252 thrombosis will be left to the discretion of the operating surgeon, but will be precisely documented.
253 Intra-operative data will be recorded on the eCRF.

254 At the end of the procedure, on-table angiography will be performed to assess graft function and
255 run off, using at least two different views angulated by at least 45°, with the patient in a prone
256 position.

257 **Anti-coagulation medication**

258 During the procedure, patients will receive appropriate anticoagulation and other therapy
259 according to standard hospital practice. Either unfractionated heparin or bivalirudin may be used for
260 procedural anticoagulation. The use of glycoprotein IIb/IIIa inhibitors will be left to the discretion
261 of the local surgical team, as will the choice of general anaesthetic agents, and the management of
262 any intra-operative events such as hypertension, arrhythmia or hemodynamic changes.

263 **Follow-up**

264 All patients will be followed for two years post-operatively. Clinic visits at four weeks, and six,
265 twelve, and twenty-four months will document quality of life, adverse events, current medication,
266 the ABI/TBI, and a duplex scan will be performed. In addition, telephone follow-up appointments
267 at three, nine, fifteen and eighteen months will gather information on adverse events and quality of
268 life using the EQ-5D-3L questionnaire.

269 **Randomization, blinding, and treatment allocation**

270 Eligible patients will be randomized intra-operatively using a web-based system after the
271 surgeon has confirmed the site for the distal anastomosis. The Gore ePTFE and Propaten® materials

272 are similar in appearance, but distinguishable by an experienced operator, who will also review the
273 patient during follow-up. The duplex scans will be assessed by a physician blind to the material
274 used. Gore[®] ePFTE and Propaten[®] are indistinguishable on ultrasound scanning.

275 **Study oversight**

276 The REPLACE study was initiated by Yann Gouëffic on behalf of the Association Universitaire
277 de Recherche en Chirurgie Vasculaire. The study sponsor is Nantes University Hospital, which
278 retains overall responsibility for the conduct of the trial and the publication of the results.

279 An advisory scientific committee will be selected to oversee the conduct of the study throughout
280 its duration. Its members will be well-versed in clinical trial methodology, and not otherwise
281 involved in the study. It will review the trial data, and be consulted in the event of specific
282 analytical or safety problems.

283 An advisory imaging committee not otherwise involved in the study will review the duplex
284 scans.

285 **Data collection**

286 All data necessary for statistical analysis will be gathered by means of a specifically-designed
287 electronic case report form (eCRF) for each patient (Ennov Clinical, Ennov Group Paris). A clearly
288 designated person will be responsible for its completion in each centre. Clinical data collection shall
289 be based on input templates similar to the eCRF. An independent clinical research associate (CRA)
290 from the Research Division Promotion Department will visit each center regularly to conduct
291 quality control on the data reported in the case report forms.

292 Reconciliation between the trial eCRF and other clinical record systems will be performed prior
293 to database locking and subsequent statistical analysis. An annual reconciliation will also be
294 performed each time the study's Annual Safety Report (ASR) is updated.

295 **Data protection**

296 Patients will only be identified in the eCRF by a code composed of their initials, an assigned
297 number, and the center number. This code will be the only information featuring in the eCRF that

298 enables a retrospective link with the patient's identity. Each patient's medical data shall only be
299 provided to the sponsor or any person duly authorized by the sponsor, and, where applicable, to
300 authorized health authorities, in strict confidence.

301 The sponsor and the supervisory authorities may request direct access to medical records for the
302 purposes of verification of the procedures and/or data in respect of the clinical trial, within the
303 limits authorized by the legislation and regulations.

304 The data compiled during the trial will be processed in compliance with all requirements of the
305 French data protection authority, the Commission nationale de l'informatique et des libertés (CNIL).
306 All trial data will be archived for at least 15 years after the end of the study.

307 **Economic evaluation**

308 The economic evaluation comparing Propaten[®] and crude ePTFE will be based on a cost-utility
309 analysis (CUA) and a cost-effectiveness analysis (CEA), following the French guidance for
310 economic evaluations (18).

311 The analysis will be conducted from the third-party payer perspective (French health care
312 insurance system) taking into account only direct hospital costs. The time horizon of the analysis
313 will be two years. Costs and measures will be discounted at a rate of 4%.

314 **Collection of resources consumed**

315 Resources consumed by each procedure will be recorded using the PMSI (the French medical
316 information system program) for a period of two years after initial surgery. The costs of the length
317 of hospitalization due to the intervention, any possible complications, follow-up, rehabilitation,
318 drug quantities, and imaging procedures will be obtained from the diagnosis-related group (DRG)-
319 based system used in France. Unit costs will be determined by conventional tariffs from the French
320 health care insurance system.

321 **Outcome measurement in the cost-utility analysis**

322 The outcomes for the CUA will be evaluated in terms of quality adjusted life years (QALYs)
323 computed from the EQ-5D-3L questionnaire data (16). The difference in QALYs between the two

324 procedures will be calculated by using an area under the curve analysis, with linear interpolation of
325 utility scores between baseline and 24-month assessments (19).

326 **Outcome measurement in the cost-effectiveness analysis**

327 The measure of outcome for CEA will be the number of life years gained (LYG) at 2 years.

328 Since costs typically follow a skewed distribution, costs and the incremental cost-effectiveness
329 ratio (ICER) of each intervention will be analyzed via a non-parametric bootstrap approach to
330 produce estimated confidence intervals at 95%.

331 The incremental cost-effectiveness ratio (ICER) describes the extra cost per additional unit of
332 patient outcome. ICERs will be calculated for both health outcomes (QALYs) and in-stent re-
333 stenosis, and compared to the costs of the Propaten[®] and crude ePTFE grafts expressed in monetary
334 units (€).

335

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400

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402

403

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406

407 Figure legend

408

409

410 **Figure 1 : study procedure**

411 AE: adverse events; QOL: quality of life

412

Figure 1: study flow chart

Table 1: study eligibility criteria

Inclusion	Exclusion
Age ≥ 18 y	No atheromatous disease
Patient presenting with CLI (Rutherford categories 4-6 (2)	Potentially child-bearing, pregnant or breastfeeding women
Below-knee bypass with artificial graft is indicated (with popliteal or tibial vessels as distal anastomosis sites)	History of coagulopathy or contra-indication to blood transfusion
Absence of suitable autologous vein	Prior or scheduled treatment for malignancy within one year of recruitment
Patient has granted fully informed written consent to study and study procedures, accepts follow-up	Severe concomitant disease with life expectancy < 1 y
	Known allergy to heparin
	Indication for ipsilateral major amputation
	Patient is currently participating in another investigational trial that potentially conflicts with REPLACE study endpoints (other than extended follow-up of now-established drugs, devices or procedures)
	Co-morbidity which could impact study participation, compliance or scientific integrity
	Patient is unable to give informed consent

Table 1: inclusion and exclusion criteria for recruitment to the REPLACE trial