

PROTOCOL

Selective Coronary Revascularization in Peripheral Artery Disease patients after lower-extremity revascularization (SCOREPAD trial)

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DOCUMENT HISTORY		
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Study Objective To determine whether the diagnosis of ischemia-producing coronary stenosis together with selective coronary revascularization in PAD patients following lower-extremity revascularization can reduce adverse cardiac events and improve survival compared to PAD patients receiving standard cardiac evaluation and treatment.

Study Design Multicenter, prospective randomized clinical trial of patients with stable PAD and no known CAD who had undergone open or endovascular lower-extremity revascularization for CLTI or severe claudication. Eligible patients will be randomly assigned to receive (a) current guideline-directed care with evidence-based best medical therapy (BMT) and risk factor control or (b) in addition to BMT and risk factor

control, non-invasive cardiac evaluation using coronary CTA and FFRct to identify ischemia-producing coronary lesions together with selective ischemia-targeted coronary revascularization. The primary outcome measure will be MACE (myocardial infarction, urgent coronary revascularisation, cardiac death) during 2 years follow up with secondary endpoints of myocardial infarction, cardiac death, urgent coronary revascularisation, all-cause death.

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Study Sites: Pauls Stradins Clinical University Hospital plus up to 10 additional sites

CRO: Institute of Science, Pauls Stradins Clinical University Hospital

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I. BACKGROUND

Patients with symptomatic peripheral artery disease (PAD) are at high risk for adverse cardiac events and have poor long-term survival due to coexistent coronary artery disease (CAD).¹ The risk of death is particularly high for patients with critical limb threatening ischemia (CLTI) with 20% one-year and 60% five-year mortality.^{2,3} This mortality rate is higher than for symptomatic CAD and most cancers.⁴ Moreover, this high mortality rate has remained unchanged over the past 40 years despite remarkable advances in medical treatment and interventional therapies.⁵ In the randomized BASIL (Bypass Versus Angioplasty in Severe Ischaemia of the Leg) trial, which was conducted 20 years ago, all-cause mortality in both groups was 56% at 5 years.⁶ In a recent review of 168,553 Medicare beneficiaries revascularized with current endovascular techniques the 5-year mortality rate was 55%.⁷ Most recently the US based BEST-CLI trial and the European based BASIL-2 trial both reported 50% 5-year mortality in both arms of the study regardless of whether LE revascularization was using open or endovascular techniques. While it well known that most PAD patients have significant CAD and that symptomatic PAD is a powerful independent predictor of cardiovascular death, guidelines do not recommend pre-operative cardiac testing, particularly in patients without cardiac symptoms, due to lack of evidence that coronary revascularization improves long-term outcome.⁸ Rather, efforts to improve the survival of PAD patients have been focused on optimizing medical treatment and aggressive risk factor control to limit the progression of systemic atherosclerosis.⁹ While medical therapy has reduced mortality in large CAD trials that include patients with PAD¹⁰, there is no evidence that best medical therapy has improved the survival PAD patients following lower-extremity revascularization.^{5,11-13}

The potential benefit of coronary revascularization to improve the survival of PAD patients was first brought to light by Hertzner, et al. in a landmark study of 1000 coronary angiograms in vascular surgery patients 4 decades ago.¹⁴ However, this strategy fell by the wayside due to lack of randomized trial evidence showing that coronary revascularization improved long-term survival of PAD patients.⁸ The most recent trial, the Coronary Artery Revascularization Prophylaxis (CARP) trial¹⁵ was conducted two decades ago using angiography-guided coronary revascularization rather than the current standard of fractional flow reserve (FFR)-guided revascularization which has been shown to reduce mortality.^{16,17} Furthermore, the requirement for pre-operative coronary revascularization in CARP resulted in a two-month delay of the vascular surgery procedure, which is not an option for most CLTI patients. The alternative strategy of coronary revascularization *after* peripheral revascularization in order to reduce adverse coronary events and improve long-term survival has not been evaluated in controlled clinical trials. This may be due to lack of a reliable non-invasive method for identifying PAD patients with occult hemodynamically significant coronary stenosis who may benefit from coronary revascularization.

A new non-invasive cardiac diagnostic test, coronary CT-derived fractional flow reserve (FFR_{CT}) provides a unified anatomic and functional assessment of coronary artery disease which can reliably identify ischemia-producing coronary lesions.¹⁸ FFR_{CT} accurately reflects invasively measured FFR and can help guide patient management and coronary revascularization decisions.^{19,20} In a single center study, of CLTI patients with no known CAD who were scheduled for lower-extremity revascularization, systematic pre-operative FFR_{CT} evaluation revealed a high prevalence (69%) of unsuspected (silent) ischemia-producing coronary stenosis (FFR_{CT} ≤ 0.80).²¹ While this did not result in postponement of the revascularization procedure, it identified high-risk patients and facilitated multidisciplinary vascular team care, including selective coronary revascularization of high-risk coronary lesions following recovery from lower-extremity revascularization.²² This resulted in improved one, two and 3-year survival of PAD patients compared to control patients receiving guideline-directed cardiac evaluation and care.^{22,23} The purpose of this study is to determine whether FFR_{CT}-guided coronary revascularization of PAD patients with asymptomatic (silent) coronary ischemia after recovery from lower-extremity revascularization can reduce adverse cardiac events and improve survival compared to PAD patients with no coronary symptoms receiving standard cardiac evaluation and care.

II. OBJECTIVE

The primary objective of this study is to determine whether among symptomatic PAD patients with no known CAD who had undergone lower-extremity revascularization, a strategy of best medical therapy (BMT) plus selective coronary revascularization based on FFR_{CT} assessment of lesion-specific coronary ischemia can reduce adverse cardiac events and improve survival compared to BMT alone. Lesion-specific coronary ischemia is defined as FFR_{CT} ≤ 0.80 distal to stenosis in a major (≥ 2 mm) coronary artery with severe ischemia defined as FFR_{CT} ≤ 0.75.

III. STUDY ENDPOINTS

The primary endpoint of the study is a composite of cardiac death, myocardial infarction (MI) or urgent coronary revascularisation (MACE) during 2 years follow up. Secondary endpoints include MI, cardiac death, urgent coronary revascularisation, cardiovascular (CV) death, all-cause death during follow up.

IV. STUDY DESIGN

This study targets a population of patients with symptomatic PAD (CLTI or severe claudication in 1:1 ratio) and no prior cardiac history, no myocardial infarction, no coronary angiography or coronary CTA, and no coronary revascularization (PCI or CABG) who have undergone successful lower extremity revascularization with planned post-operative best medical therapy. Within 14 days following lower-extremity revascularization, patients will be randomly assigned to BMT alone or BMT plus coronary CT angiography (which must be completed within 14 days of randomization) and FFR_{CT} analysis to determine the functional significance of coronary lesions identified on the CT scan. Results of the CT scan and

FFR_{CT} analysis in patients randomized to the CT-FFR_{CT} group, will be provided to treating physicians to help guide patient management with Heart Team consideration for coronary angiography and revascularization as appropriate for each patient. Coronary revascularisation (PCI or CABG), if indicated, is strongly recommended within 3 months from the randomisation. Clinical follow up (based on date of randomization) is planned 6 months, one and 2 years. Additional long-term follow up out to 5-years is planned for participating centers. An independent academic clinical events committee will adjudicate all endpoints in a blinded manner. The definition of outcome events will be in accordance with Academic Research Consortium-2 consensus document²⁶. Sample size power calculations assumed a hazard ratio of 0.5 with estimated sample size up to 600 patients (up to 300 in each group), 90% power, alpha .05. The patient sample size may be reduced if statistical significance been achieved.

V. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

1. Inform consent obtained before any study-related activities
2. Age above or equal to 50 years with symptomatic lower extremity PAD (severe claudication or chronic limb-threatening ischemia, Rutherford 3,4,5) which has been successfully revascularized by open surgical or endovascular procedure within the past 14 days
3. Willing and able to undergo coronary CTA scan within 14 days of randomization and agrees to submission of CTA data set for HeartFlow FFR_{CT} analysis with results made available to treating physician

Exclusion Criteria

1. Known CAD, history of MI, prior coronary revascularization (PCI or CABG)
2. Patient underwent coronary angiography or coronary CTA before the randomization
3. Known history of 2nd or 3rd degree heart block; sick sinus syndrome; long QT syndrome
4. History of severe asthma, severe or bronchodilator-dependent COPD
5. Severe congestive heart failure (NYHA III or IV)
6. Severe arrhythmia, prior pacemaker or internal defibrillator lead implantation
7. Impaired chronic renal function (EPI-GFR_≤30ml/min)
8. Subjects with known anaphylactic allergy to iodinated contrast
9. Pregnancy or unknown pregnancy status in subject of childbearing potential
10. Evidence of ongoing or active clinical instability, including acute chest pain (sudden onset), cardiogenic shock, unstable blood pressure with systolic blood pressure <90 mmHg, or acute pulmonary edema

11. Any active, serious, life-threatening disease with a life expectancy of less than 2 years
12. Any active infection
13. Inability to comply with study procedures
14. Contraindication for guideline-guided longterm antiplatelet/anticoagulation regime after PCI/CABG
15. Participation in any interventional clinical study within 30 days prior to screening

VI. Rules for subject withdrawal and terminating the study

In accordance with the Declaration of Helsinki, as amended, each subject is free to withdraw from the study at any time. Investigator(s) also have the right to withdraw subjects from the study in the event of illness, adverse events (AEs), serious adverse events (SAEs), other reasons concerning the health or well being of the subject, or in the case of lack of cooperation. The reason for withdrawal must be noted in the Case Report Forms (CRFs). If the reason for withdrawal is a clinical AE or SAE, follow up of the subject will continue until the outcome is evident. The specific event or test result(s) must be recorded in the CRFs.

There are no formal termination criteria for this study. The sponsor reserves the right to terminate the study at any time. Investigators have the responsibility to comply with International Conference on Harmonization E6-Good Clinical Practice (ICH E6 - GCP) guidance. The sponsor, the IRB, or the health authorities may terminate a center for the following (but not limited to) reasons:

- 1) Failure of the investigator to comply with pertinent E6-GCP guidelines and regulations
- 2) Serious protocol violations
- 3) Submission of knowingly false information from the research facility.

VII. Ethical Considerations

The potential benefits to all subjects participating in this study is that they may receive closer monitoring and follow up with better compliance to guideline-recommended BMT and risk factor control. Patients randomized to the coronary CTA-FFRct arm of the study will have additional benefit of specific cardiac diagnosis and treatment. Prior studies have demonstrated that PAD patients often have unrecognized coronary artery disease and that they have a high risk of cardiovascular complications including MI and cardiovascular death. Current guideline-directed pre-procedure cardiac evaluation of PAD patients without cardiac symptoms does not include cardiac imaging or stress testing. Half of enrolled subjects within the study will undergo coronary artery CT scanning which is highly sensitive for detecting CAD. Subsequent FFRct analysis will identify those with hemodynamically significant coronary stenosis. The incremental potential risks to subjects participating in the study are solely and directly related to the performance of the additional cardiac diagnostic testing in half of the patients.

VIII.A. Risks of Coronary CTA

Coronary CTAs expose subjects to small amounts of ionizing radiation. Since the introduction of 64-detector row CTA scanners in 2005, numerous radiation dose reduction methods have been developed which now permit CTA performance with low overall radiation dose. Minimization of radiation dose while preserving image quality is a goal of the study; optimization of radiation dose may be achieved by a by a combination of 7 additive dose reduction strategies: ECG dose modulation; Weight-based tube voltage; Prospective ECG triggering; Minimization of "padding"; Minimization of Z-axis coverage; Limiting of the field of view (FOV); Automatic exposure control. Coronary CTA performance necessitates the use of iodinated contrast. Minor reactions to x-ray contrast material can occur, including itches or hives with an incidence of approximately 1 in 200 subjects. More severe reactions that are very infrequent include hypotension, laryngospasm and bronchospasm. The incidence of these reactions is estimated at about 1 in 5,000 and is treated with intravenous epinephrine. Extravasation of x-ray contrast material outside the vein during injection may occur and result in a painful soft tissue swelling and bruising. Subjects will be monitored for extravasation during injection and the amount of contrast material injected into the tissues is usually quite small without significant clinical consequences.

VIII.B. Risks of FFR_{CT} analysis

In subjects with Coronary CTA, FFR_{CT} analysis will be performed using the clinically acquired Coronary CTA data set. The FFR_{CT} analysis in these subjects does not require additional imaging. There is no additional risk to the subject.

IX. STUDY PROTOCOL REQUIREMENTS

1. After providing informed consent, each subject will undergo the following assessments as indicated on CRF:
 - a. Collection of demographic information, including height and weight
 - b. A summary of index PAD revascularization procedure
 - c. A summary of the subject's relevant medical and surgical history (Diabetes mellitus, Dyslipidemia, Arterial hypertension, Smoking)
 - d. Recording of concurrent and concomitant medications
2. Coronary CTA (cCTA) Procedure
 - 1) Perform cCTA with strict adherence to SCCT guidelines including, but not limited to:
 - a. Heart rate control: administration of β -blockers, if needed, to achieve a heart rate of <60 bpm
 - b. CT image acquisition after administration of sublingual nitrate spray or after administration of sublingual nitrate tablet (3-5 minutes)

- c. using breath-holding and other techniques to minimize motion artifact
 - d. contrast protocols: bi-phasic injection protocol
 - e. kV/mA settings per ALARA principles. Patients who weigh more than 70kg should be scanned at 120kV.
- 2) The additional thorax CT findings (pulmonary oncology, etc.) might be collected at selected sites.
 3. Post-procedure follow up data from clinical visits and/or phone calls 6 months, one and 2 years (annually up to 5 years for patients entering prolonged study at participating sites).
 4. Open label randomization will be done after patient screening at approximate rate 1:1 CLTI to claudicants (Rutherford III,IV).

X. Case Report Forms

Electronic or paper case report forms will used.

XI. Institutional Review

Before starting this study, the protocol will be submitted to the regulatory bodies/local health authorities (in accordance with local regulations) and the study will not start before the EC/IRB gives written approval or a favorable opinion in accordance with ICH E6-GCP and all applicable regulatory bodies/local health authorities give approval or a favorable opinion as required.

XII. Informed consent

Written and oral information about the study in a language understandable by the subject will be given to all subjects by the investigator and/or designee. The subject's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the subject with the date of that signature indicated. The investigators will keep the original consent forms and copies will be given to the subjects. The informed consent will also be signed and dated by the person who conducted the informed consent discussion.

XIII Confidentiality regarding study subjects

The investigator(s) must assure that the privacy of the subjects, including their personal identity and all other personal medical information, will be maintained at all times. In documents or image material submitted to the sponsor, subjects will not be identified by their names, but by an identification code. Personal medical information may be scrutinized for the purpose of verifying data recorded in the CRF. This may be done by properly authorized persons, the quality assurance unit, or regulatory authorities. Personal medical information will always be treated as confidential.

XIV Financial Disclosure

The investigator(s) (or investigating institution) will provide the sponsor with accurate financial disclosure regarding real or potential financial conflicts of interest.

XV Insurance

As there is no any invasive investigation product been tested, the local site clinical liability insurance will be in power to cover malpractice.

XVI Adverse event and serious adverse event reporting

Only endpoints and adverse events (AE) listed in amendment should be repoted according to ICH-GCP requirements. A Clinical Adjudication committee will evaluate all Study Endpoints.

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