PROTOCOL

Selective **Co**ronary **Re**vascularization in **C**arotid **A**rtery **D**isease patients after carotid revascularization (**SCORECAD** trial)

Working draft protocol version number: *Latvia RCT/CAD/25062024*
Universal Trial Number: *ClinicalTrials.gov TBA*

In the following, Institute of Science, Pauls Stradins Clinical University Hospital and its affiliates will be stated as "Stradins University Hospital".

DOCUMENT HISTORY		
Document version	Date	Applicable in country(-ies) and/or site(s)
1.0	25 June 2024	All

Study Objective To determine whether the diagnosis of ischemia-producing coronary stenosis together with selective coronary revascularization in carotid artery stenosis (CAS) patients following carotid revascularization can reduce adverse cardiac events and improve survival compared to carotid patients receiving standard cardiac evaluation and treatment.

Study Design Multicenter, prospective randomized clinical trial of patients with symptomatic or asymptomatic CAS patients, and no known CAD who had undergone a carotid revascularization procedure (endarterectomy or stenting). 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 (cardiac death, myocardial infarction, urgent (unplanned) coronary revascularisation) during 2 years follow up with secondary endpoints of myocardial infarction, cardiac death, urgent coronary revascularisation, cardiovascular death and 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
Study Sponsor:	Pauls Stradins Clinical University Hospital with a grant from the TBA.

I. BACKGROUND

Coronary artery disease (CAD) is the primary cause of morbidity and mortality in patients with carotid artery disease. Patients with asymptomatic carotid stenosis have a four-fold higher risk of myocardial infarction (MI) than stroke[1] and the presence of carotid stenosis is an independent predictor of cardiac death.[2,3] Patients undergoing carotid endarterectomy (CEA) have a higher risk of myocardial infarction (MI) than stroke and those with post-op MI have a 5 year survival of only 56%.[4] Despite this high cardiac risk and the knowledge that 60% of carotid endarterectomy patients have coronary angiographic evidence of significant CAD (>70% stenosis),[5] systematic pre-operative cardiac testing is not recommended for vascular surgery patients since randomized trials have shown no long-term survival benefit from pre-operative coronary revascularization.[6] Guidelines specifically note that cardiac testing should not be performed in patients with no coronary symptoms[7] and thus most patients undergo major vascular surgery without pre-operative cardiac testing and mortality of patients with post-op MI remains high despite evidence-based medical therapy.[8]

Myocardial ischemia is common in patients with CAD, is often asymptomatic (silent), and is a marker for adverse cardiac events and reduced survival.[9] Pre-operative non-invasive testing of patients undergoing carotid or peripheral vascular surgery showed that 25-40% of patients had silent ischemia and that silent ischemia was a predictor of adverse outcomes.[10-12] While cardiac stress testing provides valuable information on myocardial perfusion, it does not provide actionable information regarding coronary artery lesions which may be producing ischemia and which may benefit from revascularization. The ischemic potential of a coronary stenosis can be determined at the time of coronary angiography by measurement of fractional flow reserve (FFR). Randomized trials of patients with stable CAD and lesion-specific coronary ischemia as demonstrated by FFR≤0.80 in at least one large coronary artery have shown that FFR-guided coronary revascularization results in a significant reduction in death/MI at 5 years compared to medical therapy.[13,14]

A newly introduced non-invasive diagnostic modality, 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.[15] FFR_{CT} analysis is based on anatomic information provided by coronary CTA with computational analysis of coronary blood flow to provide fractional flow values throughout the coronary tree. FFR_{CT} accurately reflects invasively measured FFR[16] and can help guide patient management decisions.[17,18] The clinical usefulness of FFR_{CT} is well documented[19] and FFR_{CT} analysis is now being used in the US, Europe, Canada and Japan to evaluate stable patients with symptoms of CAD. The usefulness of FFR_{CT} in evaluation of patients without cardiac symptoms is unknown.

In a prospective, single-center, observational study of patients with no known CAD undergoing CEA, a strategy of pre-operative cardiac evaluation using coronary CTA and FFRCT, along with ischemia-guided coronary revascularization following CEA, resulted in a more than 50% reduction in all-cause

death, cardiac death, myocardial infarction, and MACE, with improved 5-year survival compared to patients receiving standard cardiac evaluation and care (84% vs 64%, p<.001)[20-21].
The purpose of this study is to determine the prevalence of silent coronary ischemia in patients undergoing carotid revascularization (endarterectomy of stenting) using coronary CTA and FFR_{CT} and to evaluate the potential usefulness of FFR_{CT} in selecting patients for coronary revascularization to reduce cardiac events and improve survival.

II. OBJECTIVE

The primary objective of this study is to determine whether among symptomatic and asymptomatic CAS patients with no known CAD who had undergone carotid artery revascularization (endarterectomy of stenting) a strategy of best medical therapy (BMT) plus selective coronary revascularization based on FFRct 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 $FFR_{CT} \leq 0.80$ distal to stenosis in a major (≥2 mm) coronary artery with severe ischemia defined as $FFR_{CT} \leq 0.75$.

III. STUDY ENDPOINTS

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

IV. STUDY DESIGN

This study targets a population of patients with symptomatic or asymptomatic carotid artery stenosis (CAS) (symptomatic to asymptomatic 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 carotid artery revascularisation with planned post-operative best medical therapy. Within 14 days following carotid revascularisation, patients will be randomly assigned to BMT alone or BMT plus coronary CT angiography (which must be completed within 14 days of randomization) and FFRct 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-FFRct group, will be provided to treating physicians to help guide patient management with Vascular Heart Team consideration for coronary angiography and revascularization as appropriate for each patient. Coronary revascularisation (PCI or CABG), if indicated, is strongly reccomended 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 document[22]. Sample size power calculations assumed a hazard ratio of 0.5 with estimated sample size up to 300 patients (up to 150 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 or asymptomatic critical carotid stenosis (symptomatic patients with at least Rankin III.) which has been successfully revascularized by carotid endarterectomy or stenting 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 FFRct 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 hystory 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$\leq$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. Large neurologic deficit (Rankin scale >III)

16. 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, medication or radiation exposure. 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, weight, presenting symptoms and neurologic status.
    b. A summary of index carotid 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 (pulmonaly oncology, etc.) might be collected at selected sites.

3. Post-procedure follow up data from clinical visits and/or phone calls 3 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 symptomatic to asymptomatic CAS.

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 requrements. A Clinical Adjudication committee will evaluate all Study Endpoints.

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