

Visualization of “Coronary Artery Disease” for modification of RISK factors. Prevention of Disease Progression in Patients with Non-Obstructive Coronary Atherosclerosis,

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NCT number: NCT06413641

Date of the document: 27 August 2024

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Abbreviations

AI-QCPA.	Artificial intelligence-enabled quantitative coronary plaque analysis
AMI	Acute Myocardial Infarction
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft Surgery
CAD	Coronary Artery Disease
CAD-RADS	Coronary Artery Disease–Reporting and Data System
COVID-19	Coronavirus 2019
CTA	Coronary CT Angiography
EQ-5D	European Quality of Life 5 Dimensions score
HbA1C	Glycated Hemoglobin A1C
eCRP	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
GCP	Good Clinical Practice
ICA	Invasive Coronary Angiography
LAP	Low Attenuation Lipid Core Plaques
LDL	Low-density Lipoprotein
MACE	Major Adverse Clinical Events
NOCAD	No Obstructive Coronary Artery Disease
PET	Position Emission Tomography
PCI	Percutaneous Coronary Intervention
PCSK9	Proprotein Convertase Subtilisin/kexin type 9 Serine Protease
PROMISE	PROspective Multicenter Imaging Study for Evaluation of Chest Pain
QoL	Quality of Life
SAQ-7	7-Item Seattle Angina Questionnaire
SPECT	Single-photon Emission Computed Tomography

1.0 Study organization:

This study is initiated by the Department of Cardiology, Cardiovascular Imaging unit, Aarhus University Hospital (AUH) and will be conducted in collaboration with four Danish sites with long-standing experience in coronary CTA imaging. Collaborators are colleagues and research nurses with long-term experience in management and rehabilitation of patients with CAD.

2.0 Investigators

2.1 Principal investigators

- Archana Kulasingam, MD, PhD student (Dept Cardiology, Aarhus University Hospital; Department of Clinical Medicine, Aarhus University, DK)
- Jesper Møller Jensen, MD, PhD (Dept Cardiology, Aarhus University Hospital, DK)
- Bjarne Linde Nørgaard, Professor, DMSci, PhD (Dept Cardiology, Aarhus University Hospital; Department of Clinical Medicine, Aarhus University, DK)
- Martin Busk, Ass Professor, MD, PhD (Dept Cardiology, Lillebælt Hospital, Vejle, DK)
- Simon Winther, Ass Professor, MD, DMSci, PhD (Dept Cardiology, Gødstrup Hospital, DK)
- Kristian Hay Kragholm, Ass Professor, PhD (Dept Cardiology, Aalborg University Hospital, Aalborg, DK)
- Niels Peter Sand, Professor, MD, PhD (Dept Cardiology, Southwest Jutland Hospital, Esbjerg, DK)

2.2 Collaborators

- The coordinating center is Dept. Cardiology, AUH.
- Local collaborators are Helle Kanstrup, MD, PhD, Martin Bødtker Mortensen, MD, PhD, and Sussie Laustsen, RN, Ph.D.
- Esbjerg: Study nurse, Joan Hummelgaard
- Gødstrup: Study nurse, Vibeke Lynggaard
- Lillebælt: Study nurse, Inger Munch Lassen
- Aalborg: TBA

- Statistical planning has been performed in collaboration with Professor Erik Parner, Dept. Public Health, Section Biostatistics, AU. Erik Parner will be the statistical consultant during conduct of the study.
- Study design and conduct, Professor Peter Vedsted, Section of General Practice, Department of Public Health, Aarhus University, and Department of Clinical Medicine, Diagnostic Center-Silkeborg, Aarhus University, Denmark.
- Professors Damini Dey (Cedars-Sinai MC, LA, US) and Charly Taylor (HeartFlow Inc, Mountain View, US) are consultants on the coronary plaque analyses.
- eCRF and datamanagement, Jakob Hjort, Department of Clinical Medicine, Aarhus University, DK
- Advisory board: Professor Michael Blaha, Johns Hopkins, Ciccarone Center, Baltimore, US; and Professor Jonathon Leipsic, St Pauls's Hospital, Vancouver, Canada.

2.3 Steering committee

Bjarne Linde Nørgaard (Aarhus), Archana Kulasingam (Aarhus), Sussie Laustsen (Aarhus), Martin Busk (Vejle), Kristian Hay Kragholm (Aalborg), Simon Winther (Gødstrup), Niels Peter Sand (Esbjerg).

3.0 Background

Despite dramatic therapeutic advances over the last 3 decades, **coronary artery disease (CAD)** is still the leading cause of morbidity and mortality. In patients with symptoms suggestive of stable CAD, guidelines recommend non-invasive testing before referral to invasive coronary angiography (ICA) (1,2). Coronary CT angiography (CTA) is increasingly used in clinical practice worldwide due to its well described high diagnostic and prognostic accuracy in large cohorts, and recent technological advances enabling CT acquisition with very low radiation exposure, coronary atherosclerotic characterization and quantification, and physiological evaluation (3-8). In Denmark we have seen a dramatic increase in the use of CTA over the last decade (currently plateauing at appr. 20.000 scans per year) (9). In contrast to conventional non-invasive ischemia testing strategies (e.g. stress echocardiography, Single-photon emission computed tomography [SPECT], or Position Emission Tomography [PET]), CTA enables detailed evaluation of the coronary arteries, and thus identifies a broader spectrum of atherosclerotic disease stages. CTA determined total atherosclerotic burden, and high risk plaque features (e.g., low attenuation lipid core plaques [LAP], and positive

remodeling [Figure 1]), independently predict subsequent major adverse clinical events (MACE) above and beyond clinical risk scores, especially in non-obstructive CAD disease (NOCAD) (5-7). It has been demonstrated in meta-analyses, large scale registry investigations and 2 prospective randomized trials that clinical outcomes in patients with suspected stable CAD is more favorable following first-line CTA than conventional functional testing (4,5,10,11). In fact, in the recent randomized PROMISE (Prospective Multicenter Imaging Study Evaluation of Chest pain), most cardiovascular deaths and myocardial infarctions (67%) occurred in patients with a normal non-invasive ischemia testing result most of which were found to have NOCAD (5). This difference in outcomes following the two testing strategies is associated with improved preventive treatment, perhaps most importantly due to CTA-visualized NOCAD and high risk plaques (6,7,11), that is, identification of patients who are at high risk for future cardiovascular disease events. Notably, recent data indicate that certain patients with NOCAD have a poorer prognosis than patients with obstructive CAD (12,13). In Denmark, typically patients with coronary stenosis (~15-20% of patients undergoing CTA: source: West Danish Heart Registry) are referred to invasive angiography for possibly revascularization. On the other hand, the "new" cohort of NOCAD patients created by the widespread use of CTA sits between primary and secondary prevention, and guidelines do not provide actionable information on how this patient category is best managed. NOCAD is a progressive disease that will only worsen without relevant medical intervention.

Lipid lowering by statins is the cornerstone for preventive care in patients with CAD (14). Risk reduction is proportional to low-density lipoprotein cholesterol (LDL) lowering, i.e. each 1 mmol/L reduction in LDL lowers MACE by 22% in patients without previous myocardial infarction (14). Accordingly, the most recent European Society of Cardiology Guidelines for the management of dyslipidemias recommend preventive statin treatment in all patients with CAD, with plasma low density lipoprotein (LDL)-cholesterol targets of less than 1.4 mmol/L (15). Statin therapy is associated with coronary plaque stabilization through favorable changes in plaque morphology and plaque volumes (16-19). By serial coronary CTA, a significant decrease in high risk coronary plaque volumes have been demonstrated over 6 to 12 months (16). These changes include a reduction in LAP, an increase in calcified plaque volume as well as in fibrous cap thickness over 6-18 months of follow-up (16-19). In one study, a significant decrease in LAP volume was observed following 6 months treatment with rosuvastatin (2.5 or 5 mg) (17), while in another study fluvastatin 20 mg for up to 12 months resulted in a 70% reduction in the LAP volume (mean total-cholesterol reduced from 5.3 at baseline to 4.9 mmol/L at the end of follow-up, LDL levels were not

reported), while there was no change in LAP volumes among patients who did not take statins (18). **Modification of risk factors** is pivotal for the management of patients with CAD (14). Despite solid evidence of a beneficial effect of statins on prognosis the initiation of and adherence to treatment is inadequate with guideline-directed cholesterol level targets unfulfilled in the majority of patients (8,11,20-24). In an observational Danish study of patients with stable ischemic heart disease, only 44% were using lipid-lowering therapy (men, 52%; women 35%) (23). In a 2018 real-world report from this institution of symptomatic stable patients with severe diffuse CAD determined by CTA, after 6 months only 65% received lipid lowering therapy (men 72%; women 57%) (8). In another multicenter registry study, we found that more than 1/3 of patients with NOCAD were not prescribed lipid-lowering treatment or had any cholesterol measurements performed one year after the CTA investigation (24). These Danish experiences are in accord with findings in international studies (14,20,21). Premature statin discontinuation in CAD is associated with a substantial increase in the risk of myocardial infarction, stroke, and death when compared to patients who remain adherent (25,26). Statin adherence may be influenced by multiple factors, e.g. related to poor health status, lower socioeconomical class, increasing age, heterogeneity in health care settings and negative media coverage (14,20,21,26,27). Moreover, many NOCAD patients with an indication of preventive medication see it as only appropriate for "the sick" (not seeing themselves as sick) and may therefore seek to avoid medication. Opposite to patients with obstructive CAD in whom revascularization was performed, no structured specialist preventive program is offered to NOCAD patients, and possibly amongst many (both physicians and patients) a false assumption of "only obstructive CAD matters" exists. Accordingly, statin adherence in revascularized patients is higher than in patients with NOCAD (8,11). There has been much focus on statin-associated side effects as a frequent cause of statin discontinuation (14). The incidence of myalgia in statin treated patients varies between studies from 5% to 30% in observational studies (14,28,29), however, typically the prevalence of side effects do not differ from those in the placebo-treated groups (14,28,29), and in two recent randomized studies, the concept of statin-induced myalgia was challenged as being primarily a placebo effect (30,31), that is, side-effects that result from the expectation of harm from statin therapy. Therefore, an under-appreciated but clinically important topic, is the great potential that exists for improving statin adherence by reducing the patient-specific placebo effect. In addition to improving outcomes in NOCAD patients, the improvement in statin adherence would also lower the overall costs of treatment as it will reduce the need for using novel and expensive lipid-lowering biological therapies such as PCSK9 inhibitors.

Initiatives to improve statin compliance and to achieve cholesterol level targets in patients with NOCAD are needed. Statin compliance improving initiatives can roughly be categorized as either patient- or physician focused. Patient-centered programs generally involve educational aspects together with an offer of personalized risk assessment illustrating the benefits of statin therapy. Direct health provider to patient education is a key factor for continued statin adherence (32), whereas electronic and phone-based communication programs and physician education in general have been ineffective (33-34). Visual displays to communicate cardiovascular risk may enhance perception of risk (35-38). CTA imaging allows access to personal information related to future cardiovascular risk that was previously unavailable. Supporting the idiom that "a picture is worth a thousand words" small studies indicate that visual displays of personal CTA images to patients with a new diagnosis of CAD may favorably modify subsequent cardiovascular risk behavior including adherence to statins (35-38). In a small study of patients with NOCAD, we demonstrated that visualization of coronary artery calcification and a brief nurse consultation on risk modification versus standard follow-up in general practice may have a favorable influence on the plasma total cholesterol levels adherence to statins and preventive lifestyle behavior (38). Otherwise, no randomized evidence is available on these aspects. During the COVID-19 crisis we have seen dramatic advancements in IT based platforms enabling efficient health provider to patient video communication including the information from e.g. blood samples and imaging (39,40).

Figure 1. Non-obstructive CAD (NOCAD) by coronary CTA



CTA image of the left anterior descending coronary artery in a 65 year old male with atypical chest pain. No significant stenosis was present. However, extensive diffuse CAD was detected. Several high risk plaque features were present such as low attenuated (surrogate of "lipid core") plaques with positive remodeling (outward plaque growth) (white arrows). A few "low risk" calcified plaque components were present (yellow arrow). Preventive medication such as aspirin, potent statin, ezetrol and a beta-blocker were prescribed from the out-patient clinic. Since the patient had no obstructive lesions and invasive catheterization thus was deferred, no in-hospital specialist rehabilitation follow-up was planned despite presence of extensive "high risk" NOCAD.

4.0 Study hypothesis

Video-based feedback of CTA images together with a structured counselling session on risk factors and the importance of preventive statin treatment by a specialized nurse to patients with a new

diagnosis of NOCAD compared to usual care or specialist counseling alone is associated with more effective LDL lowering, less reported side-effects to statin therapy, and favorably changes of the atherosclerotic phenotype.

5.0 Patients and Methods

5.1 Patients

Inclusion:

Patients must meet all the following criteria:

- Age ≥ 18 years
- New diagnosis of NOCAD by CTA
- No known CAD (previous coronary revascularization)
- CAD-RADS 1-3 (appendix)
- LDL cholesterol > 2.0 mmol/L
- Life expectancy > 3 years
- Signed informed consent

Exclusion:

Patients must meet none of the following criteria:

- Post CTA test indication for ICA (e.g. one or more significant stenosis, inconclusive test result)
- Obstructive coronary disease (one or more coronary stenosis $\geq 70\%$, left main $> 40\%$)
- Ongoing lipid lowering medical treatment*
- BMI > 40
- Renal insufficiency (eGFR < 40 ml/min)
- Allergy to iodinated contrast media
- Contraindications to statins
- Participation in a cardiac rehabilitation or lifestyle modification programme
- Pregnancy
- Does not wish to participate

*Patients already on lipid lowering medical therapy can be included if the treatment was initiated <3 months before the time of the CTA test

5.2 Methods

5.2.1 Coronary CTA

Will be performed according to routine practice using a multi-platform regimen using contemporary high-end technology with a minimum of 64 detector scanners according to best practice on coronary CTA acquisition guidelines (41). Oral and/or intravenous beta-blockers or oral ivabradine will be administered if necessary targeting a heart rate <60 beats/min., and all patients will receive sublingual nitrates (spray, 0.8 mg) 3 minutes prior to the scan. An initial non-enhanced scan for assessment of the Agatston score will be performed. Coronary CTA acquisition will be performed using prospective electrocardiographic triggering with 70 or 140 kV tube voltage depending on patient weight.

5.2.2 Biochemistry

Blood samples will be taken for measurements of total cholesterol, high density lipoprotein, LDL, lipoprotein(a), high-sensitive c-reactive protein, and HbA1C. Measurements are performed according to local routine standards. There will be drawn approx. 12 ml blood at baseline, after 12 months, and after 5 years. The blood samples will be destroyed after analysis. No biological material will be stored.

5.2.3 Coronary plaque analysis

CTA is accurate for quantification of stenosis, atherosclerotic plaques and positive remodeling (Figure 1). The HeartFlow artificial intelligence-enabled quantitative coronary plaque analysis (AI-QCPA) tool is well validated for plaque analysis (7,42-44). Presence of high risk plaque features including quantification of each component is semi-automatically performed (Figure 2). Plaque analyses will be performed by personnel blinded to all clinical data. Plaque quantification analyses will be performed according to standard practice using established analysis software in vessels ≥ 2 mm's in diameter (Figure 2) (AI-QCPA, HeartFlow, Mountain View, CAL, US).

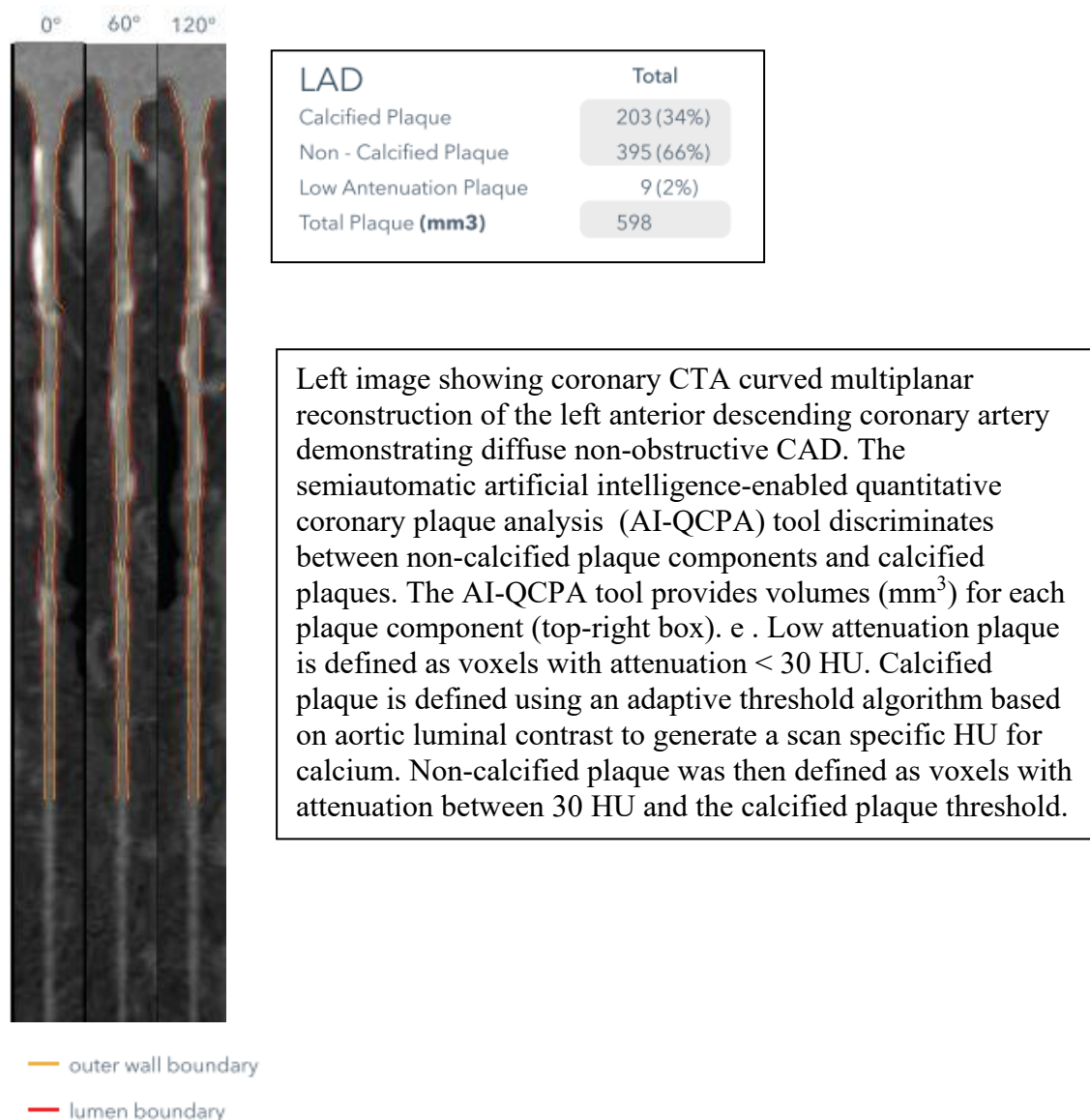
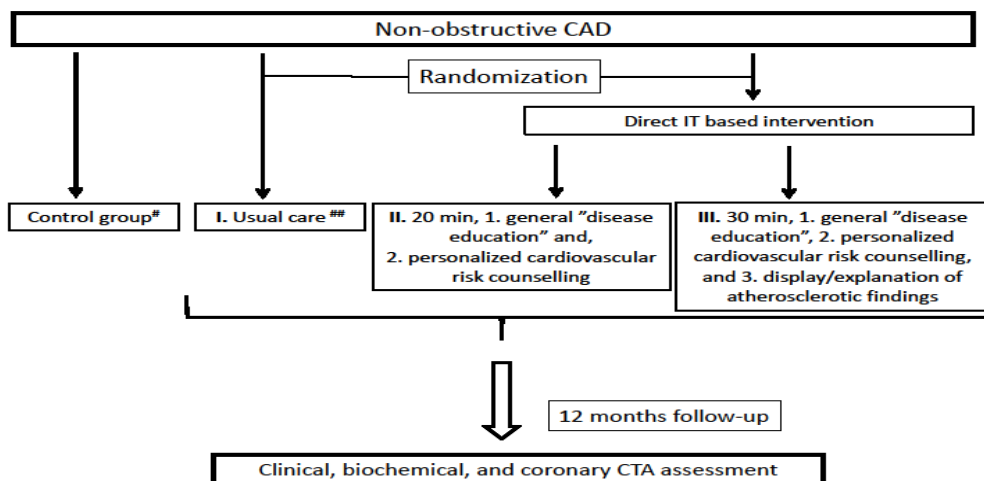


Figure 2. Coronary plaque semiautomated analysis

5.3 Trial design:

Prospective, multicenter, randomized, open-label trial. All patients will receive a short description of the CTA findings and therapeutic implications, and the general practitioner will receive specific recommendations on statin treatment and LDL targets. At baseline study patients will undergo a detailed interview with the study nurse to assess the medical history and will fill out questionnaires about quality of life and angina (appendix). Patients will be randomized 1:1:1 to post-CTA usual care follow up in general practice or one of two intervention strategies (“low” or “high” intensity intervention, Figure 3). Patients randomized to the intervention groups will be invited to an individualized video-based or ambulatory consultation by a special trained nurse within 2 weeks

from the index CTA test. We know from our coronary rehabilitation clinic (patients in whom PCI or CABG was performed) that only 50% of the patients are able to undergo a video-based consultation. Since NOCAD patients are expected to be younger than the latter group, we expect that 60-79% of study participants will be able to complete the video-based consultation. Patients in the intervention groups will be recommended the video-based consultation strategy and will if necessary be offered assistance in setting up the technical requirements needed for this solution. Alternatively, an ambulatory consultation will be offered. The European Society of Cardiology guidelines on cardiovascular prevention will be used to standardize the information about causes of atherosclerosis, and on cardiovascular prevention initiatives including smoking cessation, weight-loss initiatives, blood-pressure and -glucose control, statin treatment and LDL target levels (14). In the “high intensity” information group this information will be combined with visualization of the individual CTA images with focus on the atherosclerotic findings and the effect of statin treatment on the disease. After the “intervention” consultation all patients will be followed at the discretion of their general physician. Patient study flow is illustrated in Figure 4. Patients will report statin side effect scores after 3 and 12 months follow-up. After 12 months follow-up, re-CTA for plaque analysis will be performed in all 3 patient groups (Figure 3). After 5 years patients will be invited to a final blood sample for assessment of plasma cholesterol levels at their local hospital (similar to the baseline and 12 months follow-up blood samples), and questionnaires on angina and quality of life will be sent to study patients via E-boks (Figure 4). A control group comprising 400 patients with NOCAD (stratified based on age, gender, symptoms, and Agatston score) will be identified in the West Danish Heart Registry for comparisons with the study groups to assess the influence of study participation on changes in LDL (appendix). We anticipate that there will be no issue on recalling new and continuing symptoms during the primary 0 to 12 months study period in the present study cohort. On the other hand, multiple symptom assessments may potentially influence patients’ behavior including adherence to preventive medications. Therefore, the symptom (side effect) score (Appendix) will be assessed via a questionnaire that will be sent to participants via E-boks after 3 months and before the 12 months follow-up visit. Symptoms will be quantified through a visual analogue scale from 0 (no symptoms) to 10 (worst imaginable symptoms).



#N=400. Will be identified in the West Danish Heart registry (Appendix)

##Follow up in general practice

Figure 3. Study randomization process.

5.4 Treatment

In patients with CAD, as documented by CTA, we recommend guideline directed lifestyle modification (smoking cessation, weight-loss, exercise, blood-pressure and blood-glucose control), and high-intensity statin therapy (atorvastatin 80 mg) with an LDL minimal target of 1.8 mmol/L and $\leq 50\%$ relative to the non-treated LDL level with selective addition of ezetimibe in patients in whom LDL target was not obtained with the statin alone (expected 65% lowering of LDL levels) (14). In the event of NOCAD, the respective CTA physician will according to routine clinical practice typically issue a prescription on the drug. Control of study participants treatment targets will, according to routine clinical practice, be done by their general practitioner.

5.5 Endpoints and data sources

The primary endpoint is the change in LDL-cholesterol over 12 months (Δ LDL). Δ LDL is a strong "outcome" surrogate (each 1 mmol/L reduction is associated with a 22% reduction in major adverse cardiovascular events [15]). Main secondary endpoints are 1. statin side effect intensity at three months follow-up and 2. changes in high risk coronary plaque volumes (Figures 1 and 2) at 12 months follow-up. Clinical endpoints (Figure 4, Appendix) related to standard risk variables, biochemistry, and use of medication will be retrieved from patient medical files (electronic patient journal, see section 5.6). All endpoints are described in detail in the Appendix. Data on dietary and

exercise habits, educational level, working situation, quality of life, and symptoms (angina, and statin side effects), will be obtained from established questionnaires (Figure 4, Appendix-questionnaires). Questionnaires will be provided to study participants after study consent, at the 12 months follow-up visit, and after 5 years except for the questionnaire on statin side effects which will be presented to patients at the baseline visit and sent by mail after 3 months follow-up (Figure 4). The questionnaire forms can be completed in connection with the baseline or 12-months follow-up visits or brought home and sent to us in a stamped reply envelope form or by mail, while at 5 years questionnaires can be completed electronically as described above. Coronary CTA follow-up data will be retrieved from our standard clinical practice SyngoVia CT storage server (Siemens, Forchheim, Germany) and data will be analyzed as described above (section 5.2.3). Control group data will be retrieved from the West Danish Heart Registry (age, gender, symptoms, and Agatston scores), and the Danish Health Data Authority (LDL, HbA1C, and medication).

5.6 Data obtained from the patient journal

- a. Medical history: cardiovascular disease in the family, known hypertension or diabetes, smoking history (previous or current), alcohol consumption (units per day)
- b. Height and weight
- c. Blood pressure
- d. Use of cardiovascular medication (including dosage): calcium blockers, beta-blockers, nitrates, anticoagulants, antiplatelet agents, ACE inhibitors, cholesterol-lowering medications, digoxin, diuretics, insulin, metformin, sulfonylurea class, SGLT2 class, GLP-1 class.
- e. Biochemistry: Please see section 5.2.2.
- f. Clinical adverse events after 12 months of follow-up: All-cause death, acute myocardial infarction (AMI), stroke, total hospitalizations, coronary catheterization (ICA), additional downstream myocardial ischemia testing, percutaneous coronary intervention or coronary artery by-pass grafting

Project candidates are identified based on the clinical standard index-CTA analysis and a previous LDL measurement identified in the patient journal. After study inclusion, information on a-d will be obtained together with study blood sample measurements (section 5.2.2.). Study candidates will be informed that the information they gave before consent will be passed on to the researcher and will

be used in the project. Study participants will be informed that their consent gives the person in charge of the study, and representatives appointed by the this person, as well as any supervisory authority direct access to obtain information in the patient's medical record to assess information about the subject's health conditions necessary as part of the implementation of the research project as well as for control purposes, including self-control, quality control and monitoring which they are obliged to carry out.

5.7 Sample size

N=390. We assume that the high and low intensity intervention group when compared to the usual care group reduces LDL by 40% and 25%, respectively (24,38). The usual care group has a mean LDL of 3.1 mmol/L, and a standard deviation of 1.0 (24). A dropout rate of 10% in each group is expected. The high – low intensity intervention comparison requires a sample size of 130 in each group to detect a treatment effect of $0.90 \times (3.1 \times 0.75 \div 3.1 \times 0.60)$ with a statistical power of 0.92 based on the two sample t-test. The low intensity – usual care comparison will have a statistical power of 1,00 based on the two-sample t-test.

5.8 Data management plan

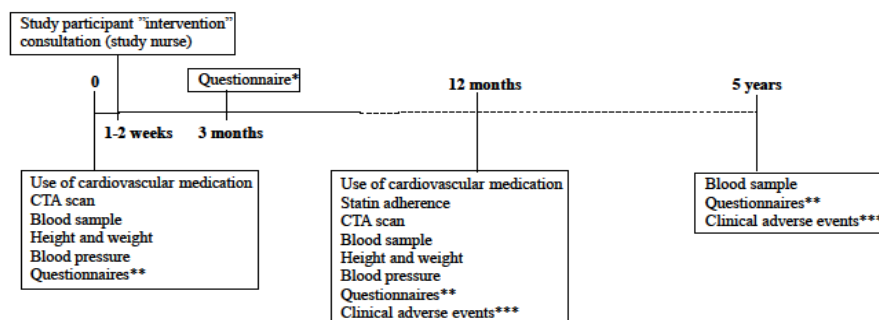
Clinical and biochemical data will be entered prospectively into a web-based case record form (TrialPartner) throughout the study conduct. After completion of the study period (baseline to 12 months), completion of plaque analyses will take place.

In the primary intention-to-treat analysis plan, Δ LDL will be compared between management groups by using a two-sample t-test with unequal variance. A hierarchical comparison design will maintain an overall significance level of 0.05. In the secondary analyses, Δ LAP, the proportion of patients with LDL <1.8 mmol/L will be analyzed in a binomial model and compared between treatment groups using the χ^2 -test. The change in weight, blood pressure, HbA1C, angina and side-effect/quality of life scores between treatment groups will be compared using a two-sample t-test with unequal variance. Exploratory Kaplan-Meier estimates of clinical adverse events (see section 5.5) from baseline until 12 months will be compared between groups by using the large-sample or permutation log-rank test as appropriate. The incidence of each clinical endpoint component over time will be estimated using the Aalen-Johansen method compared by using the large-sample or permutation Wald test as appropriate. The symptom score will be compared between high – low

intensity interventions and the low intensity – usual care using the two-sample t-test with unequal variance.

5.9 Database and Case Report Form

The eCRF will be generated prospectively based on the ordinary registration and stored at AUH for each patient included. The patient identities will be kept confidential. Study data will be entered directly in the registry and stored at AUH. The investigators are responsible for ensuring the accuracy, completeness, legibility and timeliness of the data recorded in the eCRFs.



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Figure 4. Patients study flow.

*Questionnaire on symptom side effects will be provided to study participants at baseline (0), and after 3 months.

Questionnaires on angina, QoL, educational level and working situation will be provided to the patients both at the baseline and 12 months follow-up visits. Questionnaires will be sent electronically to patients after 5 years. *All-cause death, acute myocardial infarction (AMI), stroke, hospitalization due to chest pain, coronary catheterization (ICA), additional downstream myocardial ischemia testing, percutaneous coronary intervention or coronary artery bypass grafting

6.0 Study patient recruitment

Potential project patients will be identified in the study by CT cardiologists based on the clinical inclusion criteria and results from the initial CT angiography. This information is retrieved from

patient files before written consent is given (see section 5.6). In order to accommodate variations in CTA practice between study sites, study recruitment may be performed in two ways: 1. In connection with the routine CTA appointment eligible patients (symptoms suggestive of angina, no known coronary artery disease, LDL >2.0 mM) will in writing be informed about the study, and they will be asked to consent in writing that the study nurse may contact them by telephone in the event of study candidacy, and if the patient is interested in study participation arrange a study information/ inclusion visit. After informed consent patients may be randomized in the same event. 2. If the clinical situation allows patients may be contacted and informed about the study on-site (immediately after the CTA has been performed) for possibly study inclusion and randomization. Patients referred to CTA without symptoms of CAD (e.g. patients undergoing CTA before pulmonary vein ablation) and a new diagnosis of NOCAD and otherwise fulfilling the inclusion- and exclusion criteria will be informed about the study immediately after the CTA investigation according to scenario 2. In the latter scenario, the study informant will either be the primary investigator or another CT-specialist involved with the study. Study candidates have the opportunity to bring a companion for the information session. All information of patients will take place in quiet and undisturbed rooms. After oral and written information to potential project patients, at least 24-hours reflection time on study participation is available for patients before obtaining the informed consent. All information of patients will take place in quiet and undisturbed rooms. For patients who are willing to participate in the study, informed written consent will be obtained.

7.0 Clinical relevance

Leveraging upon the widespread and growing use of CTA the present study may form the basis for a timely and limited resource consuming efficient management strategy in the large proportion in contemporary of patients with non-stenotic CAD. Demonstration of a simple management strategy for the first time to have favorable effects on patient-reported side-effect and CAD phenotype will have great impact on our perception of the natural course of CAD, and without doubt cause great attention with potential benefit for patients worldwide. The video consultation element is highly relevant in context of the current and future COVID-19 situation. The findings in this study may provide the fundament for launching of large scale multicenter studies aiming at individualizing the post-test management of patients with a new diagnosis of CAD.

8.0 Study eligibility

Of those patients with symptoms suggestive of CAD undergoing nonemergent CTA at Aarhus University Hospital (AUH, n ~1000 patients per year), approximately 350 patients have NOCAD. In patients referred to CTA on other indications (e.g. before pulmonary vein ablation), we estimate that 75 patients will be eligible for study participation. Overall, 30% already receive statin treatment, 85% have LDL >2.0 mmol/L, and 20% do not wish to participate in the study. Thus, we estimate that at AUH approximately 200 patients will be eligible for study inclusion per year. Based on similar considerations, we estimate that the annual number of study eligible patients at each of the other sites are 70-80. The study is grounded in existing national and international collaborations. The primary investigator has experience in conducting large scale multicenter trials.

9.0 Ethical considerations and safety

This study will be conducted in accordance with most recent updated version of the Declaration of Helsinki (2013), thus written informed consent will be obtained from each participant at study inclusion. The study will be approved by the Ethics Committee. General Data Protection Regulations (GDPR) and Data Protection Act are complied with. Regulations for Good Clinical Practice will be followed. Statin treatment has a societal Ia recommendation in patients with stable angina and CAD (1,2), and as primary intervention in patients with elevated serum-cholesterol and CAD (2,14). Statins have proven safe without any serious side-effects (15). The patient statin treatment algorithm as planned in the study is already an integrated part of patient management in Danish clinical practice.

Intravenous access related to the extra blood sample and installation of an intravenous line in relation to the 12-month CTA scan may be associated with slight physical discomfort. There are only few risks in having a blood sample taken or a short-term intravenous line installed and those are pain, and bleeding/hematoma.

The radiation exposure for the 12-month research scan will be the same as for the clinical index baseline CT-scan, i.e. approximately 2.5-4.0 mSv. The total estimated maximum of CT-derived 8 mSv is comparable to one ICA examination, and less than the radiation exposure inflicted by a single rest/stress SPECT examination and corresponding to a category IIb radiation classification (<https://nationaltcenterforetik.dk/Media/637858096811481954/Appendiks%202.pdf>).

Patients in the intervention groups will be offered either a video-based (or ambulatory consultation if the video-based strategy is not possible) on CAD and risk management. We recommend the

video-based strategy. However, an ambulatory visit can be performed as an alternative in the event that the video-based is not feasible for the patient. This strategy reflects current clinical practice in our coronary rehabilitation department. Patients will be informed that they may leave the study at any time point without any consequence for their subsequent treatment.

For this study the disadvantages for the patients will be the extra amount of time that they will have to use on the intervention consultation and the extra CTA and consultation after 12 months.

10.0 Timeline

Patient inclusions will start March 1.st, 2024, and enrollment completion is expected per April, 2025. Patient follow-up is expected completed per April 2026. Data analysis, and manuscript(s) preparation are planned to take place between April and December 2026.

11.0 Funding

Professor Bjarne Linde Nørgaard has taken the initiative for this study.

The study has been financially supported by the Novo Nordic Foundation (Grant# 0068200) with a grant of dk. 2.400.120- (Ph.d student, CTA skans, project nurse assistance, biochemistry, statistical support). The funding is administered by Aarhus University. No amount of the funding are paid directly to the researchers or other staff involved in the project. None of the researchers have any financial connection to the funder.

12.0 Publication

Positive, negative, and inconclusive results will be published in international peer-review journals. The protocol will be uploaded on clinical trials.gov homepage before ignition. For the article containing the main results and primary analysis will be: Archana Kulasingam (1.st author), Bjarne Linde Nørgaard (last author), Niels Peter Sand, Kristian Hay Kragholm, Simon Winther, Martin Busk, Jesper Møller Jensen, Erik Grove, Martin B. Mortensen, Helle Kanstrup. The remaining co-authors will be decided by the Steering Committee on the basis of involvement in the study (drafting of protocol, core laboratory function, ability to include patients). Substudies are encouraged, but no substudy will be allowed without consent from all members of the Steering Committee.

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