Evaluation of coronary artery disease using coronary CT angiography in high-risk populations

Mona Svanteson

PhD Thesis

Institute of Clinical Medicine, Faculty of Medicine
University of Oslo

Oslo University Hospital

Department of Radiology
and Nuclear Medicine

Diakonhjemmet Hospital

Preventive Cardio-Rheuma clinic
Department of Rheumatology

© Mona Svanteson, 2020

Series of dissertations submitted to the
Faculty of Medicine, University of Oslo

ISBN 978-82-8377-617-1

All rights reserved. No part of this publication may be
reproduced or transmitted, in any form or by any means, without permission.

Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

Table of Contents

ACKNOWLEDGEMENTS **1**
ABBREVATIONS **3**
LIST OF PAPERS **4**
SUMMARY **5**
1.0 BACKGROUND **9**
1.1 Coronary artery disease 9
1.1.1 Treatment of coronary artery disease 10
1.2 Cardiovascular risk prediction and guidelines 11
1.3 Coronary computed tomography angiography 12
1.3.1 Imaging technique 13
1.3.2 Limitations and technological advances in CCTA 15
1.4 Coronary artery calcification score (CACs) 17
1.3.5 Plaque assessments 17
1.5 Epicardial adipose tissue (EAT) 19
1.6 Inflammatory joint diseases 19
1.7 Type 1 diabetes mellitus 20
2.0 AIMS OF THE STUDY **22**
3.0 MATERIAL AND METHODS **23**
3.1 Patient selection and study design 23
3.1.1 The RORA-AS-study (paper I and II) 23
3.1.2 The Dialong study (paper III) 25
3.2 Clinical data 26
3.3 Coronary CT angiography 27
3.3.1 Image analysis 29
3.3.1.1 Plaque assessment 30
3.3.1.2 Epicardial adipose tissue (EAT) evaluation 31
3.4 Statistical considerations 32
3.5 Ethics 34
4.0 SUMMARY OF RESULTS **36**
4.1 Paper I 36
4.2 Paper II 37
4.3 Paper III 38
5.0 DISCUSSION **39**
5.1 Methodological considerations 39
5.1.1 Study design 39
5.1.2 External validity 42
5.1.3 Image assessment 43

5.2 MAIN RESULTS 44
5.2.1 Selection of patients with ultrasound of the carotid arteries for CCTA (paper I) 45
5.2.2 The effect of statin-treatment and the role of CCTA (paper II) 46
5.2.3 Plaque characteristics and associations to clinical variables in type 1 diabetes (paper III) 47
5.2.4 Epicardial adipose tissue - a new image marker for CAD? (paper III) 49
5.2.5 CCTA in asymptomatic high-risk patient groups 50
6.0 CONCLUSIONS 53
7.0 CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES 54
REFERENCES 56

ACKNOWLEDGEMENTS

The work included in this thesis has involved contributions from many people in whom I am tremendously grateful. I first want to express my gratitude to all the participants in the RORA-AS and the Dialong-study, without them the project would not have been possible.

I have been fortunate to be surrounded by dedicated supervisors. First of all, I want to thank my main supervisor, Ylva Haig. I have deeply appreciated our discussions and your willingness to 24/7 share of your considerable knowledge during these years. You always managed to guide me on the right path with valuable advices and optimistic encouragement. Your enormous work capacity, wide knowledge and interest in radiology and research (and a lot more!) is a source to inspiration.

I am also deeply grateful to my co-supervisors Nils Einar Kløw, Anne Grete Semb and Tore Julsrud Berg. Nils Einar; thank you for giving me the opportunity to become a PhD-candidate. Your vast clinical and scientific experience and knowledge has been of great value to the project, and I have learned a lot from you during the years of collaboration. Anne Grete; your considerable contributions as the principal investigator in the RORA-AS study and your impressive experience from research in cardiology and rheumatology has been vital to this work. Thank you for including me in your group, and for always having your door open. Tore; thank you for letting me take part in the Dialong study, for enthusiastic sharing of your extensive expertise in diabetes, interesting discussions and optimistic support.

I am grateful to all of the co-authors: Silvia Rollefstad; your role in the RORA-AS study and your impressive analytic eye have brought invaluable contributions to this project.

Kristine Bech Holte; Thank you for your dedication in the Dialong-study. Your effort in building the Dialong database and your input to manuscript have been of great importance. Jonny Hisdal; thanks for your work in evaluating the carotid ultrasound images, and constructive feedback on manuscripts. Eirik Ikdahl; thanks for discussions of results and for reviewing manuscript. Cathrine Brunborg and Joe Sexton; thank you for invaluable statistical advices.

Thanks to my bosses at Ullevål: Lisbeth Skipenes Andersen; your support, understanding and flexibility during all these years have been deeply appreciated. Anne Catrine Martinsen; thank you for your encouragement, and for including me in future projects. Thanks to all my colleagues at Ullevål for their support, and also for making Ullevål a great place to work! I especially want to thank Lena Korsmo Karterud for help with the EAT-analyses, and also Kristin Aase, Mona Risdal, Knut Lundby, Håvard Bjørkedal and Jan Glittum; thank you for help with the scans, discussions of protocols and good times at the lab. Thanks also to Tone Enden for support and practical advices.

To all my friends; thanks for your continuous encouragement, and for distracting me with fun and quality time. To my fantastic mother; thank you for all practical help and your never-ending support. And finally, to Halvor and our children, Audun and Henrik; coming home to you degraded any “PhD-crisis.” You are the best.

Mona Svanteson

Oslo, 2019

Abbrevations

ACC	American College of Cardiology
ACS	Acute coronary syndrome
AHA	American Heart Association
AS	Ankylosing Spondylitis
BMI	Body mass index
CABG	Coronary artery bypass graft
CACs	Coronary artery calcification score
CAD	Coronary artery disease
CCTA	Coronary CT angiography
c-IMT	Carotid intima media thickness
CRP	C-reactive protein
CTDI	CT dose index
CVD	Cardiovascular disease
DLP	Dose-length product
EAT	Epicardial adipose tissue
ECG	Electrocardiogram
eGFR	estimated Glomerular Filtration rate
ESC	European Society of Cardiology
ESR	Erythrocyte sedimentation rate
EULAR	European League Against Rheumatism
FFR	Fractional flow reserve
HbA1c	Glycated haemoglobin A1c
HDL-c	High density lipoprotein-cholesterol
HU	Hounsfield units
ICA	Invasive coronary angiography
IJD	Inflammatory joint diseases
IVUS	Intravascular ultrasound
LDL-c	Low density lipoprotein-cholesterol
NSTEMI	Non ST-elevated myocardial infarction
OCT	Optical coherence tomography
PCI	Percutaneous coronary intervention
PsA	Psoriatic arthritis
RA	Rheumatoid arthritis

List of papers

This thesis is based on the following papers:

I.

Associations between coronary and carotid artery atherosclerosis in patients with inflammatory joint diseases. *Svanteson M, Rollefstad S, Kløw NE, Hisdal J, Ikdahl E, Semb AG, Haig Y.* RMD open. 2017;3(2):e000544.

II.

Effects of long-term statin-treatment on coronary atherosclerosis in patients with inflammatory joint diseases. *Svanteson M, Rollefstad S, Kløw NE, Hisdal J, Ikdahl E, Sexton J, Haig Y, Semb AG.* Submitted.

III.

Coronary plaque characteristics and epicardial fat tissue in long term survivors of type 1 diabetes identified by coronary computed tomography angiography. *Svanteson M, Holte KB, Haig Y, Kløw NE, Berg TJ.* Cardiovascular Diabetology. 2019;18(1):58. doi: 10.1186/s12933-019-0861-x.

SUMMARY

Background

Coronary CT angiography (CCTA) is an established method for ruling out coronary artery stenoses in symptomatic patients with low to intermediate risk for cardiovascular events, but the use in asymptomatic patients has been debated. Specific chronic, autoimmune diseases like inflammatory joint diseases (IJD) and type 1 diabetes increases the risk for coronary events. Cardiovascular disease (CVD) prevention is clinically challenging in these patients as the traditional risk-prediction models for CVD are inaccurate and chest pain may be absent or occur differently compared to the general population. Increased knowledge of the prevalence and characteristics of the coronary artery disease (CAD) may add improved understanding of the atherogenesis in IJD patients, as systemic inflammation may affect both the development of atherosclerosis as well as the response to statin treatment. Additionally, further evidence on atherosclerosis in type 1 diabetes are warranted, as most evidence is based on type 2 diabetes, even though the pathogenesis differs between the two diseases. Associations between CCTA findings and clinical variables may be valuable for future improvement of CVD prevention strategies for these patients.

Aims

The overall aim of this thesis was to evaluate the prevalence and characteristics of CCTA-verified CAD in two high-risk patient cohorts with autoimmune diseases (IJD and type 1 diabetes) and predominantly unspecific CAD symptoms, and further to assess associations between CCTA findings with clinical variables, including carotid atherosclerosis in the IJD

patients. Additionally, the long-term effect of statins on plaque morphology was evaluated in the patients with IJD, and the association between coronary atherosclerosis and epicardial adipose tissue (EAT) was evaluated in the patients with type 1 diabetes.

Material and methods

From the ROsuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and other IJD (RORA-AS)-study, we included patients with IJD and established carotid artery plaque(s) for a cross-sectional baseline evaluation of CAD (paper I), and a follow-up for response to statin treatment evaluation (paper II). From the cross-sectional Dialong study (Diabetes type 1 – long term survivors with a new syndrome of late complications), patients with >45 years duration of type 1 diabetes were included, and their friends/spouses were asked to join the control group of healthy individuals (paper III). All patients underwent CCTA. Coronary plaque volume (calcified, mixed, soft and total) and coronary artery calcification score (CACs) were calculated for all examinations, and epicardial adipose tissue (EAT) volumes were calculated for the patients with type 1 diabetes. Associations between coronary and ultrasound-verified carotid atherosclerosis were evaluated in the RORA-AS patients, and for both cohorts associations between CCTA measurements and clinical variables were assessed.

Results

At baseline, CAD was present in 55 out of 83 (66%) patients with IJD (paper I), and 32% (61 out of 188) of all detected plaques were defined as soft/mixed plaques. The best risk-prediction model for CCTA verified CAD (AUC 0.832, 95% CI: 0.730-0.935) consisted of age $\geq$55 years and the combined ultrasound measures of c-IMT (carotid intima media thickness) $\geq$0.7mm and carotid plaque height$\geq$1.5mm.

After 4.7 years of statin-treatment we observed an increase in CACs and calcified plaque volume, but a decrease in soft/mixed plaque volume (paper II). A reduced progression of CACs and total plaque volume was observed in patients who obtained the recommended low density lipoprotein-cholesterol (LDL-c) treatment target (<1.8mmol/L) at follow-up compared to patients with LDL-c >1.8mmol/L.

In the Dialong study, 85% of the type 1 diabetes patients had CAD compared to 47% of the controls (paper III). Mean weighted longitudinal LDL-c was linearly associated with total plaque volume and CACs. Low long term longitudinal HbA1c was associated with having plaque volume <25th percentile. No associations between the CCTA variables of atherosclerosis and EAT were observed.

Conclusions

This thesis shows a high prevalence of CCTA verified CAD in both high-risk cohorts of IJD and type 1 diabetes. Plaques were mainly characterized as calcified, but a higher prevalence of soft/mixed plaques in statin-naïve patients with IJD was observed. The decrease of soft/mixed plaque volume and increase in calcified plaque volume may imply that statin-treatment induced a conversion in plaque composition in IJD patients. LDL-c level was identified as an important factor for the atherosclerotic development in both cohorts, with long-term glycemic control as an additional factor in type 1 diabetes patients. The results from this thesis may contribute with data to improve CVD prevention strategies in patients with IJD and type 1 diabetes.

1.0 BACKGROUND

1.1 Coronary artery disease

Coronary artery disease (CAD) describes the presence of atherosclerosis in the coronary arteries. CAD is the leading cause of death internationally, although the mortality of CAD in Norway is lower than cancer (1, 2). The development of CAD is a complex interplay of various factors. Dyslipidemia, hypertension, diabetes, tobacco use, obesity, in addition to age, sex and heredity are traditional risk factors (3). Oxidative stress, inflammation and endothelial dysfunction have also been linked to the atherogenesis (4). Inflammatory markers, especially C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) have been associated with increased risk of CAD (5-7).

The plaque formation starts with extravasation of LDL-c into the intimal layer of the artery wall initiating the formation of fatty streaks (8). A recruitment of inflammatory cells is caused by macrophages with a secretion of pro-inflammatory cytokines, which results in further LDL-uptake into the intima layer, stimulation of cell proliferation, and the development of a fibrous cap covering the plaque core (4). The plaque morphology and characteristics is decisive for the vulnerability (9). A plaque is initially lipid-rich, termed soft and more prone to rupture and may cause myocardial infarction when localized in the coronary artery (10). Denser atherosclerotic plaques are associated with a more stable and less vulnerable plaque phenotype (11).

An atherosclerotic plaque may form a narrowing/obstruction of the coronary artery, resulting in reduced blood supply to the myocardium. Chest pain (angina pectoris) is the

most typical clinical symptom of myocardial ischemia. The manifestation may occur slowly as the artery gets obstructed over time, but CAD may also lead to acute coronary syndrome (ACS) due to plaque rupture, which may cause thrombus formation with subsequent occlusion of a coronary artery. Identification of vulnerable plaques at risk of rupture is of importance for preventing myocardial infarctions.

1.1.1 Treatment of coronary artery disease

Control of risk-factors and life-style management are preventive recommendations (12). Unfavorable factors such as unhealthy diet and inactivity increase the risk, and individualized patient education may be beneficial (13).

The medical therapy is separated into primary or secondary prevention. Primary prevention is recommended in patients at risk of CVD, while secondary prevention is initiated subsequent to a cardiac event. Low LDL-c has shown to reduce the risk of CVD (14). Lipid-lowering treatment with statins attacks the root cause of the atherogenesis, the retention of subendothelial apoB lipoprotein in the intima media (15). In addition to lowering lipids, statins have been shown to possess anti-inflammatory effects (16). Plaque-altering effects such as cell death in the lipid cores and plaque-stabilization due to micro-calcifications have also been described (17, 18). Statins are in general well tolerated, but side-effects such as myopathy and renal and hepatic dysfunctions have been reported (19). Several systematic reviews state that the large scale evidence from randomized controlled trials show that the benefits of statins outwash the low incidence of side-effects and risk of adverse effects (20, 21).

Revascularization of the myocardium with percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) are performed with the goal of improving the patients' prognosis or to treat symptoms (12). PCI is recommended when invasive coronary angiography (ICA) confirms >50% diameter narrowing stenosis in a vessel supplying >10% of the myocardium (22). Additional measurement of the fractional flow reserve (FFR) during the ICA is increasingly used for evaluation of the hemodynamic significance of the stenosis. An FFR value below 0.80 indicates significant stenosis and is an indication for PCI. The FAME-2 trial has suggested that FFR measurement may serve as guidance for the clinical value of PCI-treatment in borderline lesions (23).

1.2 Cardiovascular risk prediction and guidelines

The 10-year risk of having an acute coronary event is estimated by tools that incorporate the traditional risk-factors for cardiovascular disease; total cholesterol, systolic blood pressure, sex, age and tobacco-use. The European CVD risk calculator: Systematic Coronary Risk Evaluation is recommended by the European Society of Cardiology (ESC) and The NORRISK CVD risk calculator is based on the Norwegian population (24). Equal for these tools is that the patients are classified into low, intermediate, high or very high risk for a CVD event within 10 years, and further management of the patients are recommended in guidelines based on the risk scores. Patients at low CVD risk require no further investigations and patients at high CVD risk are recommended directly to the ICA due to the possibility of concurrent treatment when needed according to the existing guidelines.

CCTA is guideline-recommended in symptomatic patients with intermediate CVD risk and has not been recommended as a screening test in asymptomatic patients without

clinical suspicion of CAD (12). However, in the updated ESC guidelines from 2019, CCTA in patients with diabetes is stated to "may be considered in cardiovascular risk-assessment" (25). RA is mentioned as one of the diseases that "may deserve more intensive risk screening, counseling, and management," without further guiding of imaging strategies. The American College of Cardiology/American Heart Association (ACC/AHA) 2019 guidelines on CVD prevention states that risk scoring models are inaccurate in some patient cohorts, and CACs may be used to reclassify the risk estimate in such patients (26). The diabetes-specific guidelines does not recommend routine screening for CAD, but states that CACs for risk assessment may be appropriate in patients ≥40 years (27).

1.3 Coronary computed tomography angiography

CCTA is a non-invasive contrast-enhanced examination of the coronary arteries. The method is established and increasingly used world-wide for ruling out stenosis in patients at low- to intermediate risk for CVD. The diagnostic accuracy of CCTA has been thoroughly evaluated and the strengths are the high negative predictive value and high sensitivity (28-32). The lower positive predictive value and specificity of CCTA may be explained by the overestimation of stenosis in the presence of calcified plaques (33). The role of CCTA is therefore primarily to rule out stenosis with the goal of avoiding unnecessary ICAs. ICA is still the golden standard for lumen evaluation, and the possibility to concurrently treat the patient in the presence of a significant stenosis makes ICA the preferred examination in patients at high risk of a cardiac event. CCTA is however faster, cheaper, more available and most important non-invasive compared to ICA, which eliminates the risk of complications such as major bleedings from the access site, myocardial infarction, stroke, and in worst

case deaths, although the risk of major complications is low (2.5% with radial artery access) (34). CCTA is also superior to ICA for visualization of the anatomy, the arterial wall and also surrounding tissue.

Stenosis-evaluation in CCTA is limited to the degree of luminal narrowing. The hemodynamic significance of the stenosis may be evaluated by the use of fractional flow reserve (FFR) CT or myocardial perfusion imaging, but due to limitations in logistics, interpretation and resources, these techniques are not yet widely implemented in clinical use. The FFR CT is a computer-based method for estimating flow in the coronary arteries, and the results are comparable to the catheter-based FFR performed during ICA (35). FFR CT has the potential of improved selection of patients for the ICA without additional radiation exposure (36). Another imaging technique is myocardial perfusion which visualizes the potentially reduced perfusion in the myocardium and correlates it to the corresponding artery. The evidence shows improved specificity and positive predictive value of CCTA (37-39).

1.3.1 Imaging technique

The constant movements in the beating heart is challenging in CCTA. The use of electrocardiography (ECG)-gating is crucial to achieve images without disturbing motion artifacts. The image acquisition is performed in helical (spiral) or axial (sequential) scan-mode, depending on both heartrate and scanner-specific technology. Helical scans acquire data simultaneously with a constant movement of the table, and datasets from phases in the heart cycle within the acquisition-window are reconstructed retrospectively. In axial scan mode the patient table only moves between the data acquisition and the ECG signals correlates the datasets to the corresponding cardiac phases. The latest CT technology

enables imaging of the entire heart within one heartbeat. This is acquired either in helical mode using dual-source in combination with a high pitch, or in axial mode with a wide detector (16 cm) covering the whole heart (40-42).

1.3.1.1 Acquisition window

The R-R interval (0-100%) on the ECG represents a whole cardiac cycle (Fig.1).

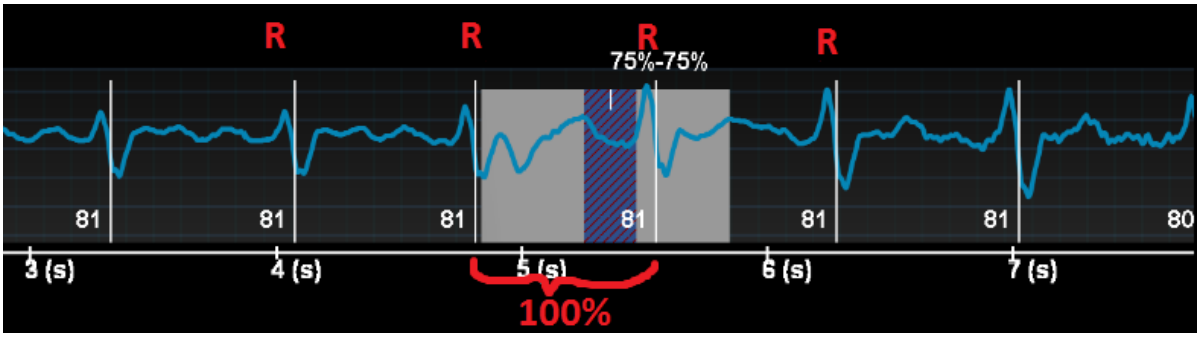


Fig.1 The R-R interval in the ECG covers one heartbeat and represents 100% of the cardiac cycle. The desired cardiac phases are referred to as the percentage between the R-tags.

The end-diastolic phase (75%) is advantageous and often used due to the least motion artifacts. At higher heart-rates, a better visualization may be achieved in earlier phases (i.e. 40%) of the R-R interval. The ECG-gating enables a prospective triggering of the data acquisition of preselected cardiac phases, or a retrospective reconstruction of datasets of desired phases. Prospective ECG-gating is preferable due to lower radiation dose. However; the dataset is restricted to a shorter acquisition-window; data is only available from the preselected phases of the cardiac cycle. A narrow acquisition window (e.g. solely 75% phase) should only be used when the heartrate is stable and below 65 beats per minute. Retrospective ECG-gating is normally used with a wider acquisition-window, which may be beneficial for patients with higher heartrates or arrhythmias. It is recommended in patients

who do not qualify for prospective ECG-gating due to e.g. higher heartrates or if functional assessment of ejection fraction of the left ventricle is warranted (43).

Medication with beta blockage is commonly used to lower the patients' heartrate and thereby prolonging the R-R-time. User-recommendations of the two gating techniques vary due to technical differences between vendors and generations of CT-scanners.

1.3.2 Limitations and technological advances in CCTA

CCTA is technically demanding and to gain successful examinations it is crucial to know the limitations of the available scanner in order to select the appropriate patients. The newest generation scanners offers technology that enables scanning of patients that previously were not suitable for CCTA due to any of the following characteristics; CACs>400 Agatston units, coronary artery stents, coronary artery bypass grafts, heart rate >80 beats/min, arrhythmia, obesity (BMI >30) (44).

Imaging of obese patients with a large chest circumference has been challenging. Due to the need for a fast rotation time, a powerful generator is required to achieve sufficient image quality. Recent generation CT-scanners have less limitation in the maximum mA, although reduced image quality due to increased noise in large-sized patients is still a limitation for many scanners and is often a trade-off with increased rotation-time. There is a large variety in technical specifications of the scanners being used for CCTA today, but temporal and spatial resolution, are important factors.

1.3.2.1 Temporal resolution

Temporal resolution is of great importance in CCTA, as the structures of interest are in constant movement. Motion artifacts often appear as double contours in the image which

may lead to impairment in image evaluability. Temporal resolution refers to the time interval in which images of a moving structure can be acquired. The evolvement of specialized cardiac reconstruction algorithms that only utilizes 180 degrees from the rotation data, in combination with faster rotation time has improved the temporal resolution significantly (45). This enables imaging of patients with arrhythmias and higher heartrates. Dual-source scanners have the advantage of using two tubes simultaneously for further improvement of temporal resolution (46).

1.3.2.2 Spatial resolution

The spatial resolution is an advantage with CCTA compared to other imaging modalities. Still, the pathology in the coronary arteries is small and a high spatial resolution is necessary. Blooming-artifacts may contribute to stenosis overestimation in presence of calcified plaques (47). Calcified plaques have a high density relative to the surrounding tissue in the coronary arteries which may cause a problem in the transition between calcified plaque and the lumen. Partial volume artifacts occur where there is a large difference in density in adjacent tissues. The Hounsfield units (HU) value produced is an average of the density values within the voxel. Isotropic, submillimeter voxels are mandatory for optimal spatial resolution, and this was already introduced with the 64-slice scanners. The introduction of iterative reconstruction has further decreased the noise and minimized blooming-artifacts from the calcium (48, 49). For 64-slice scanners or later generations, a cut-off in CACs may not be necessary for the decision of performing CCTA as the diagnostic accuracy has improved (50). Iterative reconstruction technique has also shown a better correlation with IVUS in plaque assessment compared to the traditional filtered-back projection (51). Some of the latest CT scanners have the ability to use high-resolution scan modes, which has shown a

better agreement to ICA for calcified plaques and improved diagnostic accuracy in evaluations of in-stent restenosis compared to standard spatial resolution (52, 53).

1.3.2.3 Radiation exposure

The radiation dose achieved from a CCTA has been significantly reduced after introduction of the latest generation CT scanners. Increased used of prospective ECG-gating and low tube voltages below 120kV in addition to iterative reconstruction technique have demonstrated dose reduction (54-56). The CT dose index ($CTDI_{vol}$) is an index of the average radiation dose per one tomographic image, but the dose-length-product (DLP) accounts for the total scan length ($CTDI_{vol}$ x scan length) (43). An organ-weighting conversion factor DLP x 0.014 for the chest is used to calculate the effective dose (43).

1.4 Coronary artery calcification score (CACs)

CACs is a test for quantifying the amount of calcifications in the coronary arteries. The method was introduced in 1990. The Agatston-score is the most frequently used and is easily calculated on the scanner´s software. It is based on an unenhanced 120kV-acquisition, and includes all contiguous voxels totaling ≥1 mm^2 in area with a CT attenuation of ≥130 HU (57). The CACs have grown to be a standardized, reliable and reproducible method, easily performed at a low radiation dose. It has a predictive value for adverse cardiac outcomes (58-60). In addition, CACs has shown to improve risk-stratification and it has a prognostic value superior to traditional risk-prediction models (60, 61).

1.3.5 Plaque assessments

Intravascular ultrasound (IVUS) and optical coherence tomography (OCT) are invasive, catheter-based methods for evaluation of the coronary lumen and the arterial wall, thus

identify vulnerable plaques (62, 63). OCT has a better spatial resolution compared to IVUS, but the lower penetration depth limits the plaque assessment of the deep layers of the vessel wall and in presence of larger plaques (63). However; several complications are described using IVUS; vasospasms, cerebral embolism, dissections and perforations of the arteries that may lead to myocardial infarctions, in addition to disadvantages like increased costs and procedure time (64). Also, the required catheter diameter for IVUS excludes the possibility of performing IVUS in small vessels. A non-invasive method is preferred, and CCTA has thereby emerged as a method for vulnerable plaque detection, with a high specificity, but a lower sensitivity compared to IVUS (65). Plaque morphology assessment with CCTA has been found comparable to IVUS (66).

CCTA has the possibility of distinguishing between different plaque phenotypes. Plaque characteristics have shown a predictive value for coronary events (67-69). Several characteristics for detection of the vulnerable plaque have been proposed due to independent associations to ACS; positive remodeling, low-attenuation plaque, spotty calcification, and the napkin-ring sign (70). Presence of two of these characteristics are recommended for the definition of a vulnerable plaque (71). Segment involvement score and segment stenosis score are also used as measurements of extent and severity of CAD. Increased CT-verified non-calcified plaque volume has been associated with increased risk for acute coronary events and also recurrent events after non ST-elevated myocardial infarctions (NSTEMI) (72-74).

1.5 Epicardial adipose tissue (EAT)

EAT has in recent years gained increased interest due to the reported associations with coronary atherosclerosis and high-risk plaques (75, 76), and has been suggested as a new image marker for CAD. The production of inflammatory cytokines in the adjacent anatomical surroundings of the coronary arteries have led to the hypothesis that EAT has a role in the pathogenesis of atherosclerosis (77). In asymptomatic individuals, EAT has been suggested to be linked to inflammation and an early development of coronary artery atherosclerosis (78).

1.6 Inflammatory joint diseases

Rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) are the most common of the IJD and the entities included in this thesis. IJD are autoimmune, chronic diseases that may cause swelling, stiffness and joint pain. Symptoms, radiographic characteristics and serological testing are important for the diagnosis of RA and AS, who have similar symptomatology. RA usually affects middle-aged females with symmetrical inflammation of smaller joints (hands and feet). AS is more prevalent in younger males, and involves the sacroiliac joints and the lumbosacral spine. PsA is linked to psoriasis, and the inflammation affects the peripheral joints, bursae, entheses and axial skeleton (79).

Although the pathogenesis somehow differs between the three entities, they all have an increased risk of cardiac events (80, 81). The risk for myocardial infarction in RA patients is similar to patients with diabetes mellitus or to 10 years older non-RA subjects (82). Disease activity has been linked to increased risk of CVD by multiple studies (83, 84), suggesting the

underlying systemic inflammation in these patients as an important risk factor. Additionally, treatment with anti-rheumatic medications has shown alterations in the lipid profiles and thus may influence the CVD risk (85).

CVD risk prevention is clinically challenging in IJD patients. Chest pain is difficult to distinguish, as it may be related to either the rheumatic disease itself or angina pectoris. More silent angina pectoris has been reported amongst RA patients compared to patients without RA, and the association between chest pain and coronary artery disease in these patients is low (86, 87). The traditional risk-prediction tools have shown low sensitivity in RA patients both in European and American RA patients (88, 89). NORRISK has added a multiplication factor of 1.4 to the estimated risk score for RA patients, as recommended by the ESC guidelines for CVD prevention (13). The European League against Rheumatism (EULAR) recommends a multiplication factor of 1.5 to the estimated CVD risk (90). The evidence shows that this is still underestimating the risk in this cohort (91, 92).

1.7 Type 1 diabetes mellitus

Diabetes mellitus is characterized by an absolute or a relative insulin deficiency, inadequate to prevent hyperglycemia. In type 1 diabetes, absolute or near absolute deficiency of insulin results in severe metabolic disturbance. The diagnosis of diabetes is made on the basis of a glycated hemoglobin (HbA1c) concentration >6.5 % (48 mmol/mol) but fasting or random glucose levels can also be used.

Patients with type 1 diabetes are at risk of getting several late complications; diabetic nephropathy, neuropathy, and retinopathy being the main microvascular complications (93).

Diabetes alone entails an intermediate risk for CVD (12). Cardiovascular autonomic neuropathy is prevalent in approximately 17%-22% in patients with diabetes and may impair the perception of angina (94). The absence of clinical symptoms of coronary ischemia, may cause diagnosis and treatment delays, and patients with diabetes suffer a higher rate of major adverse cardiac events and a worse outcome after PCI compared to the general population (95).

Type 1 diabetes differs from type 2 diabetes in the pathogenesis, the cause of insulin deficiency and also the presence of other comorbidities. The incidence of type 1 diabetes is in most cases at early age, which results in many years living with the diagnosis. Type 2 diabetes is related to lifestyle and more commonly debuts among adults. Atherosclerosis in diabetes has been more extensively studied in type 2 diabetes, but the randomized clinical trial/epidemiology trial Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) trial has been an important contribution to the evidence of hyperglycemia on microvascular complications in type 1 diabetes (96). Hyperglycemia has also been shown to be an important risk factor for cardiac events in epidemiology trials (96).The recently published Pittsburgh Epidemiology of Diabetes Complications (EDC) follow-up study showed that HbA1c is an important risk-factor of CVD and cardiac events, but the strongest predictor was vascular damage (represented by an increased urinary albumin excretion rate) (97), and thus they suggest that risk assessment should include a broader specter of factors.

2.0 AIMS OF THE STUDY

The overall objectives of this thesis were to evaluate prevalence and characteristics of CCTA-verified CAD including the extent and the severity in high risk patient cohorts with predominantly unspecific CAD symptoms (IJD and patients with type 1 diabetes). The aim was also to assess the associations between CCTA and clinical variables.

The specific aims for the thesis:

Paper I

To evaluate the prevalence and characteristics of CAD using CCTA in patients with IJD, and relate the CCTA findings to the earlier ultrasonography identified carotid atherosclerosis.

Paper II

To evaluate the effect of long-term statin treatment on the progression and characteristics of CAD, using CCTA in patients with IJD.

Paper III

To evaluate the prevalence and characteristics of CCTA-verified CAD in patients with long duration of type 1 diabetes compared to a control group, and to assess associations between CT recorded epicardial adipose tissue and longitudinal clinical variables.

3.0 MATERIAL AND METHODS

3.1 Patient selection and study design

3.1.1 The RORA-AS-study (paper I and II)

The RORA-AS study was an open, prospective intervention study, with a primary endpoint to evaluate change in carotid artery plaque(s) and stabilization after 18 months of Rosuvastatin treatment using ultrasound (98). Data deriving from the secondary outcome of coronary plaque evaluations are included in this thesis. Paper I describes cross-sectional evaluations at baseline prior to initiation of statin treatment and paper II includes longitudinal follow up data after nearly 5 years of statin treatment. Patients were included from the Preventive Cardio-Rheuma clinic at Diakonhjemmet Hospital in Oslo, which receives patient referrals from the department of rheumatology at Diakonhjemmet Hospital or from primary care physicians. Patients who undergo a CVD risk evaluation at the Preventive Cardio-Rheuma clinic have been diagnosed with IJD and are between 25 and 85 years. Additionally, at least one of the following criteria is fulfilled: known CVD risk factor(s), CVD symptoms, CVD heredity, or a wish from the patient to undergo CVD risk stratification. Demographic data, CVD risk-factors, co-morbidities, medication and laboratory data are registered on all referred patients. Ultrasound of the carotid arteries is included in the evaluation. Statin-naïve patients with RA, AS or PsA with asymptomatic ultrasound-verified carotid artery plaque(s) were included in the RORA-AS study. Exclusion criteria were contraindication to statin therapy, secondary hyperlipidemia, atrial fibrillation and estimated Glomerular Filtration rate (eGFR)<45mmol/ml. Both the baseline CCTA, performed in 2010-2011 and the follow-up in 2016, was conducted at Oslo University Hospital, Ullevål. All participants with a

baseline CCTA with sufficient image quality, no prior PCI with stent implantation, CABG or pacemaker implant and an eGFR >45mmol/ml, were asked to join the follow-up evaluation. Fig.2 shows the flowchart of the study, and inclusion of patients for paper I and II.

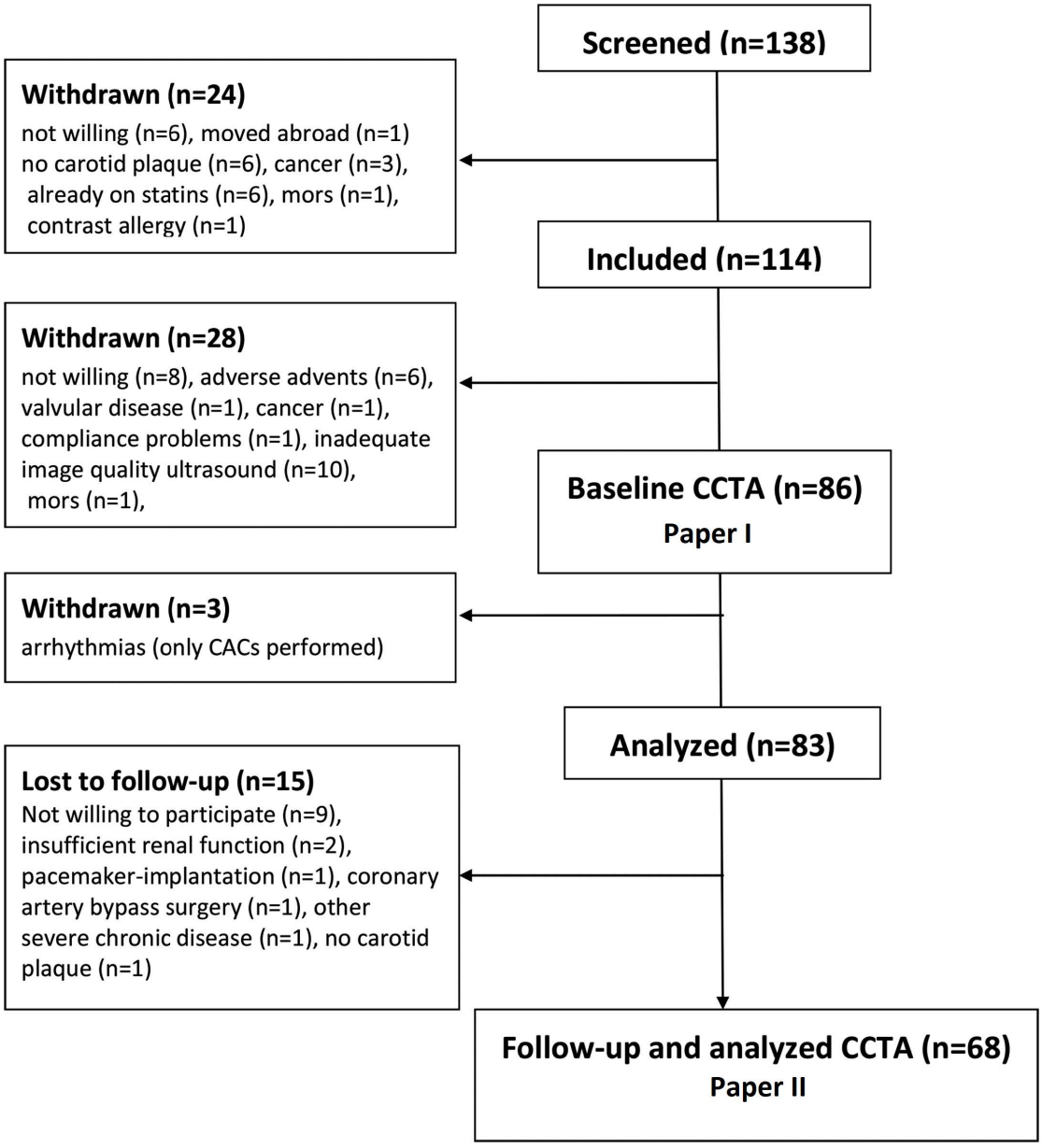


Fig.2 Flowchart of the RORA-AS study (paper I and II).

Interventional statin-treatment in the RORA-AS-study

The patients in the RORA-AS study were statin-naïve at baseline CCTA, and after a thorough examination and evaluation of a cardiologist, statin treatment was initiated with the goal of achieving LDL-c ≤ 1.8 mmol/L. The patients were closely followed with lipid-controls every three months up to ultrasound of the carotid arteries at 18 months. The patients were then referred to the primary care physician with a recommendation of continuing statin treatment with the LDL-c goal level ≤ 1.8 mmol/L. After nearly 5 years, the patients were reinvited to join the follow-up-study.

3.1.2 The Dialong study (paper III)

The Dialong study was a cross-sectional study conducted in 2015/2016. Patients were recruited from the Norwegian Diabetics' Center in Oslo, Norway, which perform diabetes-related follow-up on patients referred from general practitioners or hospitals in the South-Eastern Health Region in Norway. All patients attending the Norwegian Diabetics´ Center in 2015 with type 1 diabetes diagnosed in or before 1970 (n = 136) were invited to join the study, out of which 105 patients accepted. Most of the participants had attended the centre for > 30 years. Type 1 diabetes was defined based on the following characteristics; HbA1c> 6.5% (48 mmol/mol) and lack of insulin production by a fasting c-peptide concentration < 0.2 mmol/ml. The control-group (n=75) consisted of spouses and friends of the participants, excluded 1st degree relatives or an already known diagnosis of diabetes or HbA1c > 6.5% (48 mmol/mol).

Fig.3 shows the flowchart of the Dialong study. Patients with known coronary heart disease or insufficient renal function (eGFR <45) were excluded for CCTA. In the control group, one patient was excluded because of fast, irregular heart rate.

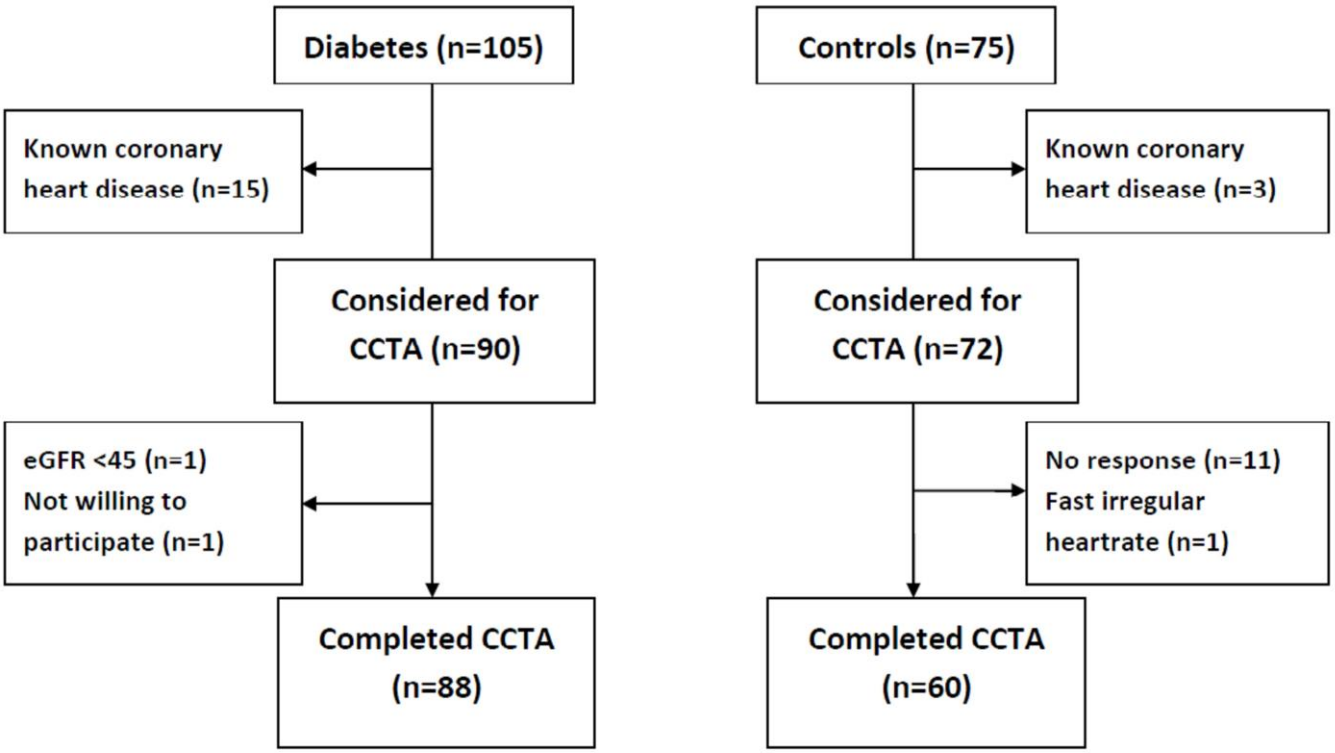


Fig.3 Flowchart of the Dialong study, showing both the diabetes group and the control group.

3.2 Clinical data

Clinical data were collected by study clinicians or nurses in both studies. In the RORA-AS-study, the recording of demographic data, risk factors, medication and laboratory data were performed at the Preventive Cardio-Rheuma Clinic at Diakonhjemmet hospital in a

standardized fashion (99). The data was thereafter collected from the patient chart and a questionnaire both at baseline and follow-up.

In the Dialong study, a retrospective chart review was performed by a study clinician at Oslo University Hospital, Ullevål. Longitudinal data (30 years) of systolic blood pressure, LDL-c and HbA1c were retrospectively available for the patients followed by the Norwegian Diabetics' Center. HbA1c values from 1980 to 2015 were calculated from both all available HbA1 (converted to HbA1c) and HbA1c measurements and an estimate of the mean HbA1c from diagnosis up until the first measurement (100). Longitudinal systolic blood-pressure and LDL-c were also calculated. Both current and calculated mean time-weighted variables were used to assess associations of these clinical variables with CACs and CCTA findings. A clinician examined the patient and a questionnaire was used to collect demographics, medical history and symptoms.

3.3 Coronary CT angiography

In the RORA-AS study, a Philips Brilliance 64-slice CT scanner (Philips Healthcare, Cleveland, Ohio, USA) was used both at baseline and follow-up. In the Dialong-study, the CCTAs were obtained by a newer generation scanner: a Siemens Somatom Definition FLASH-scanner. All patients had an ECG-triggered unenhanced scan performed for evaluation of CACs. The CCTA scan protocol was chosen in concordance with the achieved heartrate. The participants were if tolerated administered an oral beta blocker two hours before the scan. Additional beta blocker (5–20 mg Seloken, Astra Zeneca) was administered intravenously in the laboratory if necessary, with the goal of achieving a heart rate ≤65 beats/min. The CCTA scan parameters for all protocols are listed in Table 1.

Table 1. CCTA scan parameters

Study	RORA-AS (paper I and II)		Dialong (paper III)	
Scanner	Philips Brilliance 64		Siemens Dual Source Somatom Definition FLASH	
Scan-mode	Helical	Axial	Axial	High-pitch helical
kV	120	120	90-120	90-120
Rotation-time	0.4	0.4	0.28	0.28
mA	800	350-500	320-370	320-370
Pitch	0.2	n/a	n/a	3.4
Heartrate	66-100	≤65	<80	≤65 (stable)
Acquisition-window	0-100%	75%	HR ≤65: 70-80% HR:66-80: 30-80% HR: ≥80:	Single-phase, end-diastolic
ECG-gating	Retrospective	Prospective	Prospective	Prospective
Reconstruction	Filtered back projection	Filtered back projection	Iterative reconstruction	Iterative reconstruction
I.V.Contrast	90mL	130mL	80mL	60mL

For the CCTA performed with the Philips-scanner, 90–130 mL Omnipaque 350 mg/mL (GE Healthcare, Princeton, New Jersey) was administered. This was reduced to 60-80 mL for the Siemens-scanner due to reduced scan time. Nitroglycerin 0.4 mg (Nitrolingual, Pohl-Boskamp, Hohenlockstedt, Germany) was administered sublingually 1–3 min prior to the contrast injection. The mean±SD DLP was 439±26 mGycm^3 in the RORA-AS study and 156±151mGycm^3 in the Dialong study. The effective dose was calculated using the chest conversion factor 0.014, resulting in mean±SD effective dose of 6.1±3.7mSv and 2.2±2.1 mSv, respectively.

3.3.1 Image analysis

All images were evaluated and reported by a radiologist as in normal clinical routine. Additional image analysis was performed on a Philips Workstation (Intellispace v5, Philips Healthcare) with dedicated software (Comprehensive Cardiac, Plaque Analysis). Images were assessed using a modified 17-segment American Heart Association (AHA) model (101) (Fig.4).

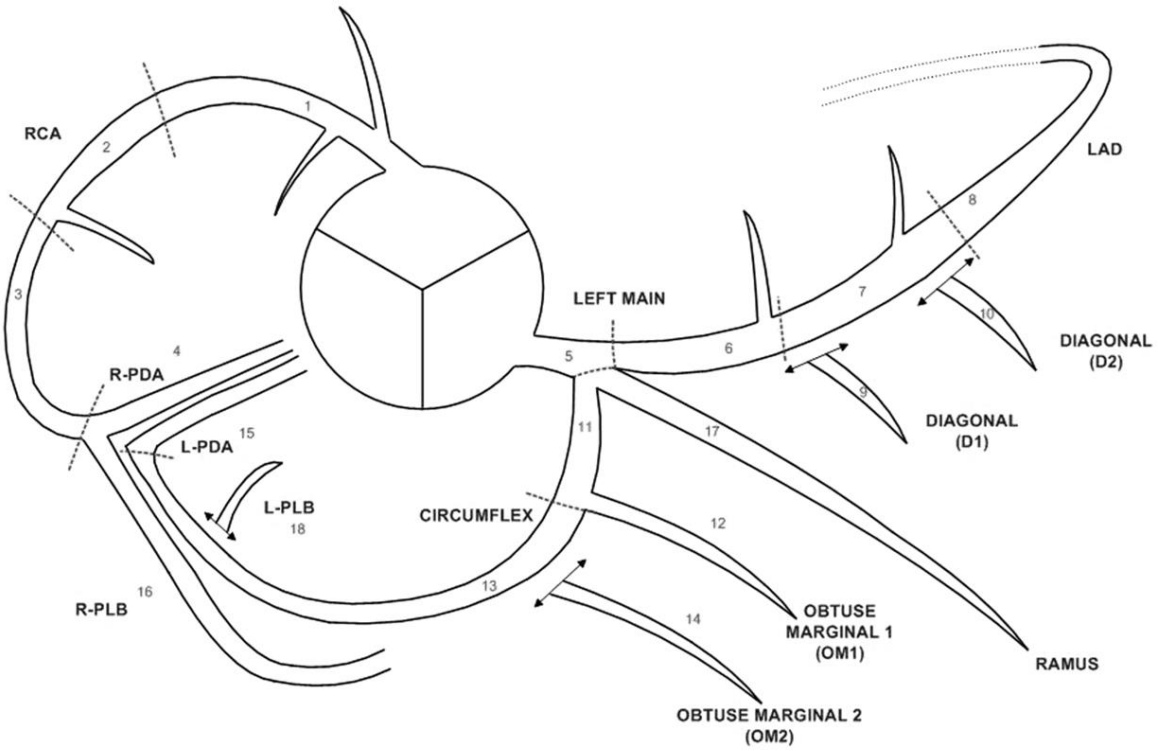


Fig.4 Society of Cardiovascular Computed Tomography (SCCT) coronary segmentation diagram.(102)

Reprinted from Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. Journal of cardiovascular computed tomography. 2014;8(5):342-58 with permission from Elsevier with license number:4576420391142.

All segments with subjectively sufficient image quality and a diameter >1.5 mm were included in the analyses. CACs was calculated using the Agatston method (57). CAD was defined as presence of any plaque. The degree of stenosis was measured as the degree (%) of luminal narrowing.

The segment involvement score and the segment stenosis score were used for evaluation of extent and severity of CAD (103). Segment involvement score was calculated as the sum of segments with plaque involvement (1-17). Segment stenosis score was scored based on the luminal narrowing in each segment (grading 1-4); Grade 1: 1% - 29% stenosis; Grade 2: 30% - 49% stenosis; Grade 3: 50% - 69% stenosis and Grade 4: 70% - 100% stenosis, with a total possible score of 0-68 (104).

3.3.1.1 Plaque assessment

The plaque assessment was performed using a semi-automatic software (Comprehensive Cardiac, Plaque Analysis, Philips Healthcare) (Fig.5). The software identifies the plaque, but manual verification is required for further plaque analysis. The definition of different plaque types varies from study to study. We used a HU-based approach, which is the most commonly used due to availability, and with a good correlation to IVUS (66).

The plaque volume (mm^3) was calculated for each plaque differentiated on plaque morphology. Plaques were categorized as calcified when $\geq$90% of voxels had a density of >130 HU, and mixed plaque when less than 50% of the volume had a density of >130 HU. Soft plaques had less than 10% voxels with a density of >130HU (105). The total plaque volume, total calcified volume and total mixed/soft plaque volume were calculated in all coronary segments for each patient. The soft and mixed plaque volume was calculated together for statistical purposes due to small amounts of soft plaques.

All the Image analyses were done by one investigator for all examinations. For 30% randomly selected examinations in the RORA-AS-study, two independent readers performed the analyses.

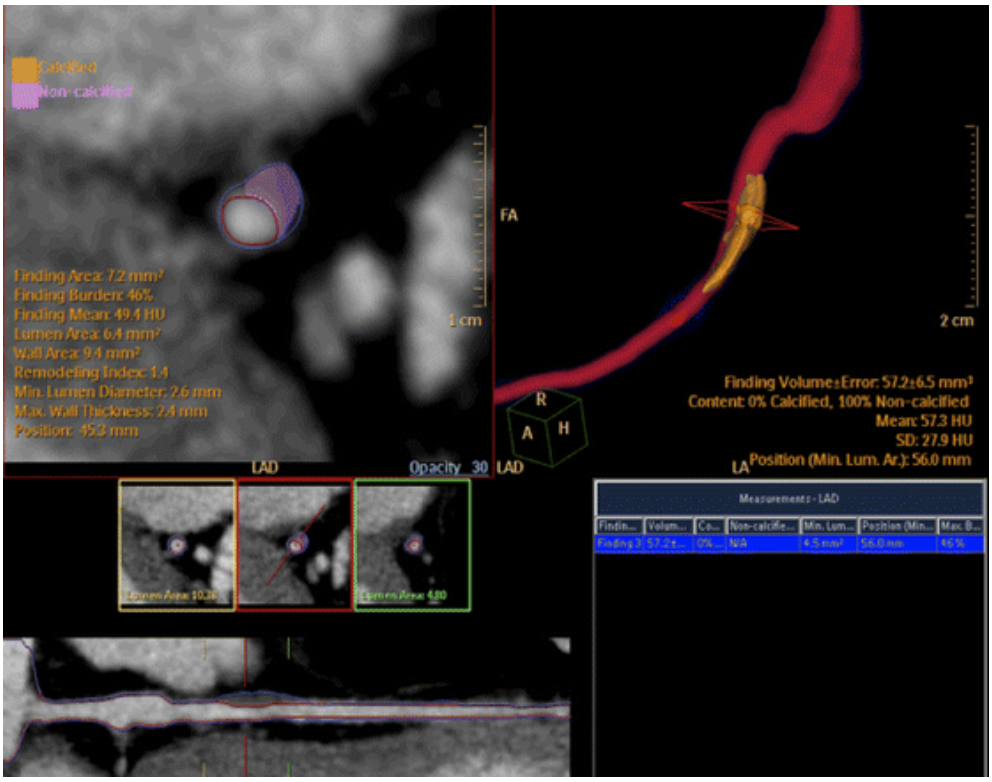


Fig. 5 The plaque analysis software. The software automatically detects the plaque, but the borders can be adjusted by the reader.

Reprinted from Oliver Klass, Susanne Kleinhans, Matthew J. Walker et al Coronary plaque imaging with 256-slice multidetector computed tomography: interobserver variability of volumetric lesion parameters with semiautomatic plaque analysis software with permission from Springer Nature Customer Service Centre GmbH with license number: 4640150725101.

3.3.1.2 Epicardial adipose tissue (EAT) evaluation

For paper III, EAT was evaluated on the unenhanced CT images using the software SliceOmatic 5.0 (TomoVision, Magog, Canada). All tissue with a density between -190 and -30 HU within the pericardial sac was defined as EAT and included in the total EAT volume (mm^3) (Fig.6). All 2.5mm axial slices from the upper border of the right coronary artery to the apex of the heart were assessed. One investigator performed the analyses on all patients and a second independent reader performed the analyses blinded to clinical information and study group on 30% randomly selected examinations.

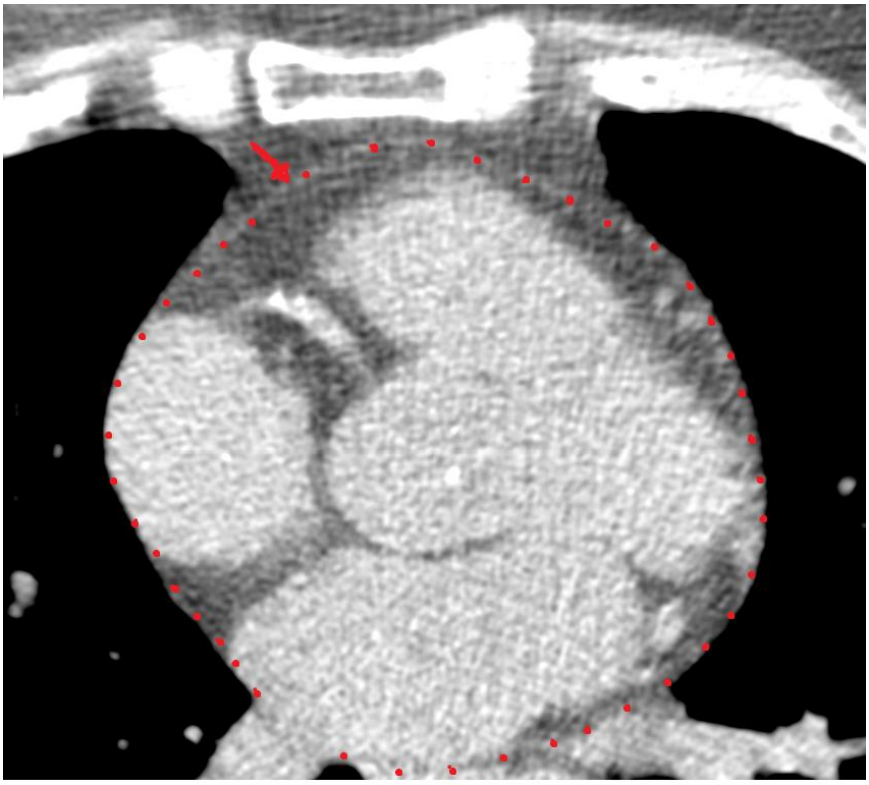


Fig.6 All tissue with a density between -190 and -30 HU within the pericardial sac (arrow) was defined as EAT and included in the total EAT volume (mm3).

3.4 Statistical considerations

All statistical analyses were performed using the Statistical Package for Social Sciences, version 22, 23 and 25 (IBM, SPSS Inc, Chicago, Illinois, USA). Findings with p-values below 0.05 were considered statistically significant for all tests. Nominal variables were presented as numbers (%), continuous variables as mean±SD for normally distributed variables and median with IQR (interquartile range) for non-normally distributed variables. Independent samples t-test, Analysis of Variance (ANOVA) and chi-square (X^2)-tests were used as appropriate to test whether differences in characteristics between the groups were statistically significant. In paper II, paired samples t-test was used to compare baseline and

follow-up continuous normally distributed variables. The Wilcoxon's signed rank test was used for non-normally distributed variables.

In all papers, we assessed associations between CCTA findings and clinical variables. Logistic regression analyses were used to assess associations for dichotomous outcomes, and linear regression analyses for continuous outcomes. To adjust for confounders, we applied multivariable regression analyses. Variables with a stronger correlation than 2.0 were included in the models. Correlation was tested using Pearson´s correlation coefficient for normally distributed variables, and Spearman´s correlation coefficient for variables not normally distributed. A stepwise, backwards method was performed in all analyses until only significant associated variables were left in the model. Log (In) transformed variables were used in the analysis if the residuals were non-normally distributed. To solve the problem of zero values we added one to each measure before transformation (log (X+1)). Models were checked by plotting residuals versus predicted values.

In paper I we sought to test different combinations of ultrasonography measurements to determine the optimal risk-prediction model. We included tests of sensitivity and specificity for each presented model, and the validity of the models were tested with area under the curve (AUC).

In paper III, stratified analyses of the type 1 diabetes patients and their controls were performed because of the longitudinal variables only available for the diabetes group. We were aware of the loss of power as a result of decreased study-size for this test. With n of 21, the logistic regression should only include two variables, but we included 4 (two in addition to sex and age). This means that the test may have been underpowered. However; we

included 95%CI to show the actual precision of the test, and because of narrow CI the test was found appropriate.

To test the intra and interrater reliability of the plaque volume and EAT measurements, the intraclass correlation coefficient (ICC) was used as a measure of agreement both between one reader´s repeated analyses and between two readers.

3.5 Ethics

Both studies included in this thesis were conducted after the recommendations of the Helsinki Declaration. All participants signed an informed consent and the Norwegian South East Health Authorities Regional Committee for Medical and Health Research Ethics approved the studies (RORA-AS: 2009/2219; Dialong-study: 2014/851). The RORA-AS study was registered at ClinicalTrials.gov with ID: NCT01389388 and The European Union Drug Regulating Authorities Clinical Trials (EudraCT) (nr.2008-005551-20).

All examinations were evaluated as part of clinical routine of the department of radiology, Oslo university hospital, Ullevål, in addition to study specific readings, to assure significant findings were correct communicated. The radiological reports from the routine CCTA evaluation were sent to the referring cardiologist who was responsible for further follow-up/treatment of the patients in both studies.

The radiation hazard was considered ethically accepted in the trade-off with benefits for the individual patient combined with increased knowledge of CAD in the study cohorts. Beta blockage optimization was done at baseline for the RORA-AS patients with the goal of performing the radiation dose-saving scan method (sequential scan mode). The participants

in the Dialong study were examined with a newer generation CT-scanner using low radiation dose. Prior to examinations of the controls, an estimation of the radiation dose used in the patient group was performed (median 1.6mSv), to ensure a low radiation dose for the control group.

4.0 SUMMARY OF RESULTS

4.1 Paper I

Associations between coronary and carotid artery atherosclerosis in patients with inflammatory joint diseases

In this paper we evaluated the prevalence and characteristics of coronary artery plaques in patients with IJD and established carotid artery atherosclerosis, and found that the majority (66%) of these patients had CAD. Calcified coronary plaques were most frequently present, although 1/3 of all detected plaques was defines as soft/mixed plaques. We also assessed associations of coronary artery plaques with carotid artery atherosclerosis measurements in order to evaluate the use of carotid ultrasonography measurements in CVD risk-prediction of IJD patients. The findings indicate that having carotid artery plaque alone is not sufficient for identifying patients with CAD, but a combination of carotid ultrasonography measurements and age may increase the detectability of CAD in these patients. The most accurate risk-prediction model for identifying CAD (AUC:0.832, 95%CI:0.730-0.935) was a combination of variables with cut-off values: age ≥55 years (OR:12.18, 95%CI:2.80-53.05), the intima media thickness (c-IMT) of the carotid artery - ≥0.7mm (OR:4.08, 95%CI:1.20-13.89) and carotid plaque height ≥1.5mm (OR:8.96, 95%CI:1.68-47.91), all $p<0.05$.

4.2 Paper II

Effects of long-term statin-treatment on coronary atherosclerosis in patients with inflammatory joint diseases

In this study we evaluated the progression of CAD after long-term statin-treatment in 68 patients with IJD, and the effect on plaque morphology using CCTA. We also assessed possible predictors of plaque progression, including patient characteristics, lipids and inflammatory markers. We found a progression of CAD in statin-treated patients with IJD. However, an increase in calcified plaque volume and a decrease in soft/mixed plaque volume may imply a conversion in plaque-composition (Fig 7). We also revealed that patients who obtained the LDL-c treatment target (< 1.8 mmol/L) experienced a more moderate progression of atherosclerotic plaque volume compared to those with LDL-c-levels above the LDL-c treatment target, indicating that reducing LDL-c to guideline-recommended target (< 1.8 mmol/L), may slower the progression of coronary atherosclerosis.

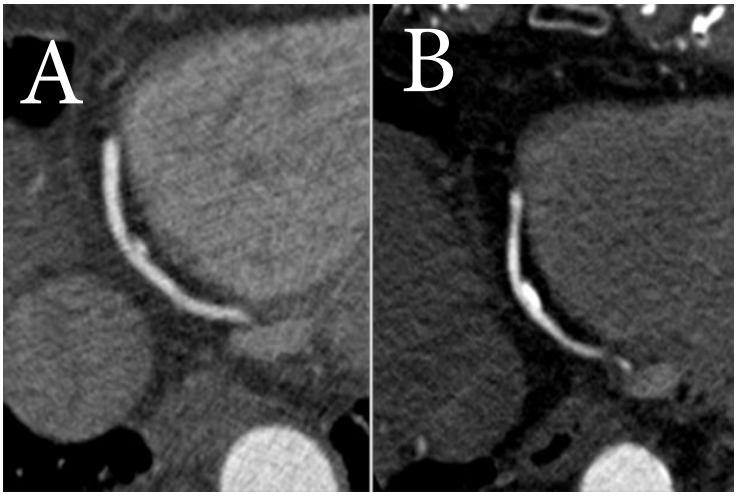


Fig.7 Example of a plaque characterized as mixed (panel A) at baseline and calcified (panel B) at follow-up.

4.3 Paper III

Coronary plaque characteristics and epicardial fat tissue in long term survivors of type 1 diabetes identified by coronary computed tomography angiography

In this study of patients who have survived more than 45 years with type 1 diabetes without a previous diagnosis of coronary heart disease, we found a greater extent and severity of CAD compared to healthy controls. Plaque volumes, segment involvement score, segment stenosis score and CACs were significantly higher in the type 1 diabetes group compared to the control group without diabetes, but morphological assessments showed mostly calcified plaques (82%). Elevated LDL-c over time was associated with increased plaque volume and CACs. Low LDL-c level and HbA1c over time, in addition to present HDL-c level, was associated with having a more favorable plaque volume (below the 25th percentile $\leq$3,6mm^3). The EAT volume did not differ between type 1 diabetes and controls. We found no associations between CAD and EAT volumes (Fig.8).

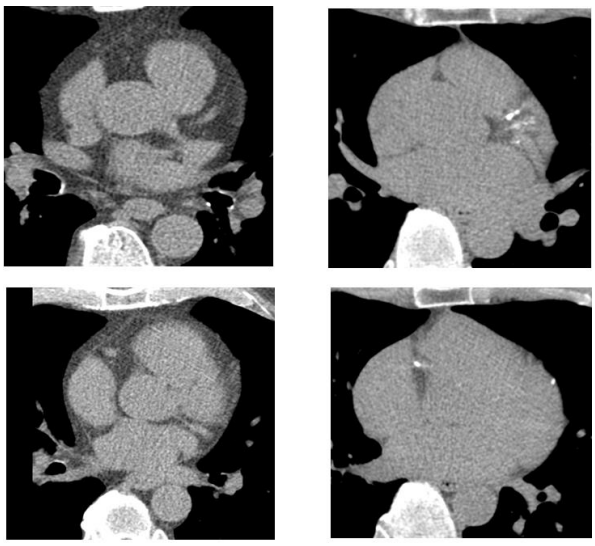


Fig 8 Examples of combinations of CACs and EAT volumes
Left: 58 year old male, CACs: 0, EAT: 143mm^3, waist circumference: 112cm.
Right: 61 year old male; CACs: 806, EAT: 12mm^3, waist circumference: 80cm.

5.0 DISCUSSION

5.1 Methodological considerations

5.1.1 Study design

To explore the aim of this thesis, data from the RORA-AS and the Dialong study were included. The following sections describe their design and methodological factors that may have affected the validity of the studies.

The RORA-AS study (paper I and II)

The RORA-AS-study was a prospective, longitudinal intervention-study, but paper I included only cross-sectional baseline data. The cross-sectional design is suitable for exploring prevalence at a specific time-point, but it excludes the possibility of assessing variables being predictors for CAD and coronary events, thus we only presented associations between CCTA findings with carotid ultrasound measurements and clinical variables.

All patients included were statin-naîve and had verified carotid artery plaques at baseline. Patients with carotid artery plaques are at higher risk of cardiovascular events (88), thus the prevalence of CAD in our study may be related to inclusion bias. However; Karpouzas et. al have evaluated the prevalence of CAD in RA-patients without pre-examined carotid arteries with comparable results to ours (106).

In paper II, longitudinal data were presented. The control of the intervention at the Preventive Cardio-Rheuma clinic in the RORA-AS study ceased after the ultrasound at 18-months, as the patients were followed-up by their primary care physician, but the patients were discharched with a recommendation of continued statin-treatment with similar LDL-c

treatment target goal. The design of our follow-up study may therefore be characterized as observational. Originally, we also planned the follow-up CCTA to after 18 months of intensive statin treatment, but decided to prolong the follow-up timepoint to 5 years due to numerous studies with short follow-up unable to show significant effects (107-109). After 18 months and till the follow-up after 5 years, the lipids and clinical factors may have been under less strict surveillance than within the first 18 months, which is a limitation to our study. However; the results may be representative to a real clinical setting, which is a methodological strength with such an observational design. The findings of less progression of plaques in the patients with obtained treatment target (< 1.8 mmol/L) at follow-up, may be interesting when discharging the patients from specialized clinical centers, such as the Preventive Cardio-Cheuma clinic at Diakonhjemmet hospital and more related to the clinical setting of the every-day world where the patients are followed-up by their primary care physician.

The lack of a control-arm consisting of patients receiving placebo is a clear limitation to the study. Atherosclerosis increases by time, and a comparison of groups receiving statin-treatment with placebo would have been enlightening. However; it was considered unethical not to follow the guidelines for preventive treatment in patients with established atherosclerosis, in this case plaques in the carotid arteries. Considering the negative association between LDL-c and CAD, placebo-treated patients may have higher LDL-c levels and a more advanced CAD progression, but less presence of calcified plaques compared to statin-users as has been shown in other cohort studies (110). Hypothetically, comparing a statin-treated group to a control-group may therefore have resulted in a larger difference in

both LDL-c level and plaque progression, and would most likely contribute to strengthen our results.

We were not able to detect associations between CAD and inflammation-markers, CRP, ESR or the RA-specific Disease Activity Score for 28 joints (DAS28) in our study. We cannot exclude a selection bias as our cohort was well treated with anti-inflammatory/anti-rheumatic drugs at baseline

The Dialong study (paper III)

The Dialong study was a cross-sectional case-control study with an overall aim to study long term complications of type 1 diabetes. The design allowed us to measure the prevalence of CAD at a certain time-point (2015) in a type 1 diabetes exposed group compared to a similar group without type 1 diabetes. The inclusion of the control-group provided additional data on the impact of long-term type 1 diabetes on the prevalence of CAD.

The number of survivors of type 1 diabetes is growing as these patients live longer today, but there is little evidence on the impact of living with type 1 diabetes for many years. The inclusion of patients with a >45 year long duration of type 1 diabetes was chosen to gain more evidence on the status of CAD in this population. The very long duration of type 1 diabetes may have led to a selective inclusion of the “healthiest” type 1 diabetes-population. Patients with prior diagnosed heart disease were excluded and patients with more severe disease may have died earlier and therefore not reached 45 years duration of type 1 diabetes. The number of these patients is unknown, and our study may thus suffer from a selection bias. Our findings of prevalence and characteristics of CAD are representative to the survivors of type 1 diabetes, and therefore do not likely reflect the total CAD burden in

type 1 diabetes patients in general. The finding of mainly calcified plaques in patients with a very long duration of type 1 diabetes (paper III) was as expected, since the patients represent the survivors. We may hypothesize that more soft/mixed plaque would have been present in a cohort with a shorter duration of type 1 diabetes, since our study excluded those with an earlier cardiac event.

The control group in the Dialong-study consisted of spouses and friends of the participants. Living together with a person with diabetes may influence dietary habits and lifestyle, and we cannot exclude that this has affected the findings in the control group. However; our control group is likely similar to the patients´ socioeconomic and environmental factors, eliminating potential confounders (111). The CACs in the control-group were comparable to a Danish study on healthy individuals (112), suggesting that the prevalence of CAD is somewhat similar to other normal populations.

5.1.2 External validity

The patients in this thesis are selected from two specialized centers in Norway: the Preventive Cardio-Rheuma clinic at Diakonhjemmet hospital and the Norwegian Diabetes center in Oslo. This may have led to inclusion of the “sickest” population with these diagnoses. However, the referral criteria to the Preventive Cardio-Rheuma clinic are rigid and also include patients who ask for a CVD risk evaluation. The Norwegian Diabetics’ Center performs diabetes-related follow-up on patients referred from general practitioners within the south-eastern health region. The patients participating in our studies may be representative to Caucasian patients in high-income countries with established health care services, although the generalizability to patients with IJD or type 1 diabetes in general is limited by the strict selection criteria.

The study size is relatively small for both studies. However, the number of patients in total suffering from IJD and type 1 diabetes is limited. The prevalence of RA is approximately 0.5% in Norway (113), and out of all patients with diabetes worldwide, only 5-10% are diagnosed with type 1 diabetes (114). Inclusion of patients in a large scale in these cohorts would have required multiple center participation.

We did not include all clinical variables that may have a role in the atherosclerotic process, and our selected variables therefore cannot fully elucidate the impact on the development and progression of atherosclerosis in these patient cohorts.

5.1.3 Image assessment

In all papers, we chose a HU-based approach to define the plaque phenotypes. The cut-offs used have also shown the best correlation to histology and sudden cardiac deaths (115). A major limitation with HU-based volume-measurements is poor reproducibility between different vendors (116). The volume measurements must be performed with the same software to be comparable (117). We used the same scanner for the baseline and follow-up in the RORA-AS-study, and all image analyses were performed with the same software.

We chose to measure CAC and different phenotypes of plaque volume, but excluded characteristics such as the napkin-ring sign, positive remodeling, and spotty calcification (74). These additional characteristics may have contributed to additional knowledge in the evaluation of the effect of statins on the coronary plaques in the RORA-AS-study, but the choice was based on the limited time-period of available software. In the Dialong study, the prevalence of mixed/soft plaques was also too low to gain any statistical strength with these additional measurements.

Blooming artifacts that cause overestimation of calcified plaques is a known limitation to CCTA (47). This has been diminished after the introduction of newer scanners using iterative reconstruction technique. Den Dekker et. al (50) suggested that a cut-off in CACs is no longer necessary for the decision of performing CCTA on 64-slice scanners or later generations. The CT stenosis measurements presented in this thesis (mainly segment stenosis score) are still more likely to be overestimated than underestimated.

Our double-reading was limited to a 30% randomly selected sample of patients. The plaque-assessment is time-consuming and we had access to the software only for a short, limited time period. The software we used has previously shown good interobserver variability for soft and mixed plaque, but poorer interobserver variability for calcified plaque (105). However, our results from the inter-and intraobserver analysis showed great agreement. The discrepancy between our results and the previous reported results may have been influenced by more soft/mixed plaques in our double-readings. Prior to the evaluations we also had a consensus on how to use the software and how to adjust manual settings. The calcified plaque volume measurements in our study showed good correlation to the robust CAC score.

5.2 Main results

The studies included in this thesis showed a large variation in the prevalence and characteristics of coronary atherosclerosis in the two cohorts with autoimmune diseases at high risk for CVD, although angina was only reported by 20% of the patients. The purpose of this thesis was not to compare the two cohorts, and with the strict selection criteria a comparison would not have been appropriate.

5.2.1 Selection of patients with ultrasound of the carotid arteries for CCTA (paper I)

In the general population, angina pectoris in combination with pretest probability score serve as indication for CCTA. However, in patients with IJD, chest pains are often unspecific or absent, and other selection criterias are warranted. Carotid ultrasound is incorporated in the CVD-risk evaluation at the Preventive Cardio-Rheuma clinic at Diakonhjemmet hospital, as in line with multiple guidelines (13, 118, 119). We explored the associations between ultrasound measurements and CT-verified CAD, and found that a combination of carotid ultrasonography measurements (age, c-IMT and carotid plaque height) may serve as selection-criteria for further investigation, although presence of carotid artery plaque alone is not sufficient for the identification of these patients. The optimal selection criteria for CCTA would only include patients in the need for further cardiac evaluation and exclude patients with no need for further assessment, in order to avoid unnecessary examinations. The model we presented is associated with CAD, as we were unable to detect associations between carotid ultrasonography measurements and significant coronary artery stenosis, that may very likely be due to a lack of power as only 11 patients had a significant coronary artery stenosis in the RORA -AS study. All patients with CAD may most likely not benefit from CCTA and the use of our selection-model may lead to a high number of unnecessary examinations. The associations between CAD and c-IMT, age and carotid plaque height may still be clinical interesting. The positive associations suggest that these factors should not be neglected in risk-stratification of these patients. The association with the age cut-off at 55 years may indicate increased risk at earlier stage compared to the general population, and risk-assessment at an earlier age may be beneficial for the patient.

Our conclusion in paper I supports the use of carotid ultrasound in CVD risk-assessment of patients with IJD. A clear limitation to our study is that we do not know the prevalence of coronary artery disease among IJD patients without carotid plaque, which would have been an important contribution to this investigation. However; ultrasound also has the benefit of serving as guidance in decision-making regarding preventive treatment, as carotid plaque(s) detected by ultrasound is an indication for lipid-lowering treatment according to the ESC guidelines (13, 119). Additionally, detection of carotid plaque(s) by ultrasound reclassifies 30-60% of the patients into higher risk-prediction groups, and therefore influences both the initiation and the intensity of the lipid-lowering treatment (120). Our findings may be a contribution for further investigations of selection criteria for CCTA.

5.2.2 The effect of statin-treatment and the role of CCTA (paper II)

Awareness of CVD risk in IJD patients and thereby also indications for statin-use has increased after RA was added into the risk-stratification tools in 2009. The use of statins is controversial, although the drug is increasingly used for prevention world-wide. The results presented in paper II show that the effect of statins on coronary plaques in patients with IJD is comparable to that reported in the general publication (107-110, 121, 122). Interestingly, the soft/mixed plaque volume was significantly reduced, suggesting that the plaques composition altered into more calcified after statin-treatment. Increased CACs can be seen as a marker of healing of plaques or as a disease-progression marker, considering the plaque-stabilizing effect (17). We did not evaluate the effect of patient outcome, but since non-calcified plaques are more prone to rupture, our findings support a more favorable plaque composition after the initiation of statins. We thereby concluded to support statin-

treatment in patients with IJD. However; a larger randomized trial would be preferred, as we did not include a placebo controlled group. As previously discussed, the progression of atherosclerosis without statins is therefore still unknown. Increased survival and reduced major adverse cardiac events have been reported as a result of lipid-lowering treatment in the general population (123), and similar evidence has recently been reported for patients with RA (124). The meta-analysis performed by de Rezende et al. claims that the evidence of the beneficial effect of statins shown by multiple studies suffers from publication bias (125). However; no publication bias was found in a recent systematic review (126). The disconcordance shows the controversy in the debate of statin-use.

The role of CCTA in evaluation of response to treatment and disease progression is an ongoing debate (127). The evidence of changed therapeutic decisions based on CAC results is growing (128), but the advantageous, non-invasive plaque morphology evaluation CCTA offer, may give CCTA a potential role in personalized medicine in the future. This warrants for further clinical research and optimization of plaque assessment softwares as these evaluations today are time-consuming.

5.2.3 Plaque characteristics and associations to clinical variables in type 1 diabetes (paper III)

Calcified plaques represent more stable and less vulnerable atherosclerotic disease (129, 130), and the high prevalence of calcified plaques in survivors of type 1 diabetes was expected due to the strict selection criteria of a very long duration of T1DM. The plaque morphology has also been shown to differ between patients with type 1 and type 2 diabetes, with a higher prevalence of calcified plaques in type 1 and more soft/mixed plaques in type 2 diabetes (131). We observed a large variation in CACs, but previous reports have shown

similar numbers of cardiac events in patients with high CACs (>400) and very high CACs (>1000), although patients with very high CACs are more likely to develop angina-like pain (129). Plaque erosions may also cause stenosis of hemodynamic significance and may be of greater importance in patients with high CACs. In patients with neuropathy the symptoms may occur differently or be absent, and the detection is difficult. The impact of subclinical CAD is unknown, but it may influence everyday activity without the classical symptoms. E.g fatigue is highly prevalent in type 1 diabetes with CVD as one associated variable (132, 133). An assessment of quality of life after CCTA and revascularization in asymptomatic high-risk cohorts would be interesting. Quillard et.al suggests that "superficial erosion" needs further attention as one third of all ACS are caused by plaque erosions and not rupture (134).

Interestingly, there was a large variation in plaque volume and CACs. Fifteen percent of the patients had normal coronary arteries without any plaque. Low, longterm LDL-c and HbA1c was associated with no or low plaque volume. These findings in patients with more than 45 years duration of diabetes type 1 strengthens the evidence of these as important factors for development and progression of atherosclerosis. Low LDL-c over time was linearly associated with plaque volume and CACs, which also supports the LDL-c as a treatment target in CVD prevention in type 1 diabetes. We observed an association of high HDL-c and less plaque volume in line with the previously described protective effect of HDL-c (135). We did however not highlight these findings, as HDL-c is a target that responds less to treatment. In the assessment of associations between plaque characteristics and clinical variables, we have not included all clinical variables that may play a role in the atherosclerotic process, e.g the inflammatory parameters. Thus, the selected variables do not fully elucidate the atherosclerotic process in type 1 diabetes.

5.2.4 Epicardial adipose tissue - a new image marker for CAD? (paper III)

EAT has been suggested as an image marker for CAD due to multiple studies reporting significant associations between EAT and coronary atherosclerosis (76, 136, 137). EAT as an active adipose tissue surrounding the coronary arteries may have a role in the development of coronary atherosclerosis. We did not find any associations between EAT and coronary atherosclerosis in our study on long-term survivors of type 1 diabetes. This relationship has been evaluated previously in a cohort with a shorter duration of type 1 diabetes (138). Although the authors conclude with a significant relationship between EAT and atherosclerosis, they do acknowledge that the statistical significance vanishes after adjustment of BMI, which is in agreement with our findings. The lack of associations to CAD in our study, suggests that EAT may not serve as an image marker for CAD in type 1 diabetes patients. Why this population differs from others, remains unclear. However; CAD is prevalent in type 1 diabetes despite healthy life-styles and absence of the traditional risk-factors. EAT has been associated with the metabolic syndrome in type 2 diabetes (139). Metabolic syndrome is not highly present in our cohort, which is representative to type 1 diabetes patients, but we did reveal positive associations between EAT and lipids like HDL-c and triglycerides, which are included in the criteria for the metabolic syndrome. Furthermore, the process of atherosclerosis is an interplay of many factors, and it is possible that EAT is of importance in interactions with specific factors, and less important in the absence of these. Further research is warranted to explore relationships to different variables to establish the role of EAT. Individuals without metabolic syndrome or a high presence of the traditional risk factors should also be included to assure that the results are not biased by homogeneous cohorts.

5.2.5 CCTA in asymptomatic high-risk patient groups

In the literature CACs and CCTA is referred to as both risk-modifying- and screening-tools for the use in asymptomatic patients (140-143). A clarification of the role of CACs and CCTA may be useful for a common understanding of the need for evidence in the implementation of a new imaging strategy. Evidence of its prognostic value may be adequate for a risk-modifying-tool. However; overuse of radiologic services may lead to overtreatment, complications, increased costs, and may also cause unnecessary patient concerns. Thus, evidence of the clinical efficacy, including evidence of improved patient outcome, is still limited. The 5-year-follow up study from the randomized, controlled SCOT-HEART-trial revealed a significant reduction in cardiovascular-related deaths between the CCTA group compared to the standard care group explained by a consequent change in treatment (144). However; evidence of improved patient outcomes in asymptomatic individuals is still lacking. The randomised controlled FACTOR-64 trial investigated the patient outcome in asymptomatic individuals with diabetes, and concluded with no benefit of screening with CCTA (145). Importantly, the study was underpowered with fewer events than anticipated and further exploration of the question is warranted.

CCTA may have other consequences that may contribute to improved patient outcome, e.g. lifestyle modifications or change in medical treatment. The SCOT-HEART-trial investigated the pharmaceutical consequences of CCTA compared to standard care alone in symptomatic patients, and found that one out of four patients had their preventive treatment changed (146). Such evaluations have not been performed in asymptomatic patients, but with the role as a risk-modifying tool, it is likely to impact preventive treatment. Visualization of CAC has shown increased adherence to preventive treatment (147, 148), and

cancellation of preventive medications as a result from negative CCTA has shown improved self-reported quality of life in symptomatic patients (149).

CCTA has previously not been recommended in asymptomatic patients, although there is little doubt that clinicians have been struggling with how to best manage CVD prevention in patients with IJD or type 1 diabetes. The recent guidelines from 2019 may extend the role of CACs and CCTA in risk assessment for some patient cohorts, as the increased prevalence of CAD, the inaccurate risk-prediction tools, and a more challenging symptomatology are addressed. The ESC guideline includes CCTA as a possible imaging strategy in asymptomatic patients with diabetes, while the ACC/AHA guideline only includes CACs. The level of evidence is acknowledged to be low, and the question on whether CACs alone is sufficient, or if CCTA should be included in risk assessment for asymptomatic patients is unanswered. Zero CACs is a strong predictor for a low 10-year CVD risk (150), but the prognostic value of CACs is not fully elucidated in statin-users as statins have shown to increase CACs (151). CCTA has also shown superior prognostic value compared to CACs alone in asymptomatic individuals (152-155). CACs has been suggested as a gatekeeper to CCTA (156), but additional pretest-likelihood scores and symptoms are of importance when using CACs is used to select patients to CCTA (157). A clarification of which patients who could benefit from screening and at what intervals and from what age CCTA should be introduced is needed, and finally, complementary recommendations of whom, when and how to treat are warranted, and this yields for further research.

One of the technical drawbacks of CCTA in patients at high risk has been overestimation of stenosis in the presence of large calcified plaques which may lead to

unnecessary invasive procedures. New advanced CT technology with iterative reconstruction and improved temporal and spatial resolution provides higher image quality (158), but the challenge of blooming artifacts caused by calcified plaques is still a non-negligible limitation in CCTA (159). Novel high-resolution scan-techniques have shown potential for further improvements (52), and additional functional assessment with FFR-CT or/and CT myocardial perfusion may further improve the diagnostic accuracy (39, 160, 161).The diagnostic performance of these novel techniques in patients with severe calcifications needs further exploration.

6.0 CONCLUSIONS

This thesis shows a high prevalence, but also a large variation of CAD in patients with IJD and long-term type 1 diabetes, many in whom CCTA was not clinically indicated. Following are the answers to the specific research questions (presented in 2.0 Aims):

1. CAD was detected in 66% of the statin-naîve patients with IJD and carotid artery plaque, and 32% (61 out of 188) of all detected plaques was defined as soft/mixed plaques. Presence of carotid artery plaque was alone not sufficient to identify patients in the need for further cardiac evaluation, but a combination of c-IMT, carotid plaque height and age gave a significant association with CAD in a multivariable regression analysis.

2. After 5 years of statin treatment CCTA showed a progression of CAD in the IJD patients, with alterations in plaque composition, from soft/mixed plaque into calcified plaque. Slower disease progression was observed in patients who had obtained recommended LDL-c treatment target at follow up.

3. In survivors of type 1 diabetes the prevalence of CAD was higher compared to controls, but the CT-verified plaques were mainly calcified. Longitudinal LDL-c and HbA1c were associated to CAD. There was no correlation between CAD and EAT.

7.0 CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

The optimal CVD prevention path, including examinations, risk-stratification and treatment of high-risk populations with predominantly unspecific CAD symptoms is yet to be defined. The detailed description of the coronary atherosclerotic characteristics presented in this thesis may be valuable in discussions and further improvements of management recommendations for the patient cohorts included in this thesis (patients with IJD and long-term survivors of type 1 diabetes).

Paper I contributes with evidence of associations between carotid and coronary atherosclerosis in IJD patients, and explores the use of carotid ultrasound implemented in CVD risk evaluation, to select patients for CCTA. Our study was small, and the use of carotid artery ultrasound for CCTA patient selection needs further exploration.

Paper II brought new insights on how statins affect the coronary atherosclerosis in patients with chronic inflammation. These patients are big spenders of health services and users of several long-term pharmaceuticals that influence both the lipid profiles and inflammation parameters. Knowledge of the effect of statins is of value in the treatment decisions for these patients.

The status of CAD in patients with more than 45 years of diabetes type 1 presented in paper III adds evidence to a growing and less studied cohort. The associations between CAD and clinical variables (LDL-c and HbA1c) are supportive to other reports and may strengthen the importance of controlling these factors in CVD management. Additionally,

the lack of association between EAT and CAD implies that more research is needed before implementing EAT as an image marker for CAD for all patient groups.

The CT technology advances continuously and rapidly. In the future, spectral CT may improve the quantification and differentiation between plaque characteristics (162). Plaque-evaluations are time-consuming, but artificial intelligence and deep learning may provide automatically generated information valuable in CVD risk-stratification. Additionally, the novel techniques FFR CT and myocardial perfusion may help to reduce the number of false positive coronary artery stenoses and contribute to a proper selection of patients for ICA. With improved technology, CCTA may play a larger role in the risk-assessment of high-risk patients with predominantly unspecific CAD symptoms and high CACs. However, larger randomized, controlled trials with sufficient CVD event-rates are warranted to evaluate the impact of CCTA on patient outcome and clinical decision-making in the presented patient cohorts.

References

1. Murray CJ, Lopez AD. Measuring the global burden of disease. N Engl J Med. 2013;369(5):448-57.

2. Kvåle R FG, Bakken IJ, Nguyen Trung T, Akerkar R, Dyngeland J. et.al Hjerte- og karregisteret • Rapport for 2012–2016 [Internet]. Oslo: Folkehelseinstituttet. 2018 [Cited 20.08.2019] Avaliable from https://www.fhi.no/publ/2018/hjerte--og-karregisteret-rapport-for-20122016/.

3. Munnur RK, Nerlekar N, Wong DT. Imaging of coronary atherosclerosis in various susceptible groups. Cardiovasc Diagn Ther. 2016;6(4):382-95.

4. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. J Am Coll Cardiol. 2009;54(23):2129-38.

5. Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, et al. C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet. 2010;375(9709):132-40.

6. Erikssen G, Liestol K, Bjornholt JV, Stormorken H, Thaulow E, Erikssen J. Erythrocyte sedimentation rate: a possible marker of atherosclerosis and a strong predictor of coronary heart disease mortality. Eur Heart J. 2000;21(19):1614-20.

7. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002;105(9):1135-43.

8. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. Nat Rev Dis Primers. 2019;5(1):56.

9. Thomsen C, Abdulla J. Characteristics of high-risk coronary plaques identified by computed tomographic angiography and associated prognosis: a systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging. 2016;17(2):120-9.

10. Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2013;61(12):1231-9.

11. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. Jama. 2014;311(3):271-8.

12. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J. 2013;34(38):2949-3003.

13. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the

special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur J Prev Cardiol. 2016;23(11):Np1-np96.

14. Boekholdt SM, Hovingh GK, Mora S, Arsenault BJ, Amarenco P, Pedersen TR, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol. 2014;64(5):485-94.

15. Tabas I, Williams KJ, Boren J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. Circulation. 2007;116(16):1832-44.

16. Diamantis E, Kyriakos G, Quiles-Sanchez LV, Farmaki P, Troupis T. The Anti-Inflammatory Effects of Statins on Coronary Artery Disease: An Updated Review of the Literature. Curr Cardiol Rev. 2017;13(3):209-16.

17. Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. J Am Coll Cardiol. 2015;65(13):1273-82.

18. Zheng G, Li Y, Huang H, Wang J, Hirayama A, Lin J. The Effect of Statin Therapy on Coronary Plaque Composition Using Virtual Histology Intravascular Ultrasound: A Meta-Analysis. PLoS One. 2015;10(7):e0133433.

19. Yebyo HG, Aschmann HE, Kaufmann M, Puhan MA. Comparative effectiveness and safety of statins as a class and of specific statins for primary prevention of cardiovascular disease: A systematic review, meta-analysis, and network meta-analysis of randomized trials with 94,283 participants. Am Heart J. 2019;210:18-28.

20. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388(10059):2532-61.

21. Mach F, Ray KK, Wiklund O, Corsini A, Catapano AL, Bruckert E, et al. Adverse effects of statin therapy: perception vs. the evidence - focus on glucose homeostasis, cognitive, renal and hepatic function, haemorrhagic stroke and cataract. Eur Heart J. 2018;39(27):2526-39.

22. Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35(37):2541-619.

23. Fearon WF, Nishi T, De Bruyne B, Boothroyd DB, Barbato E, Tonino P, et al. Clinical Outcomes and Cost-Effectiveness of Fractional Flow Reserve-Guided Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease: Three-Year Follow-Up of the FAME 2 Trial (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation). Circulation. 2018;137(5):480-7.

24. Selmer R, Lindman AS, Tverdal A, Pedersen JI, Njolstad I, Veierod MB. [Model for estimation of cardiovascular risk in Norway]. Tidsskr Nor Laegeforen. 2008;128(3):286-90.

25. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2019; doi:10.1093/eurheartj/ehz425.

26. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):e596-e646.

27. 10. Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes-2019. Diabetes Care. 2019;42(Suppl 1):S103-s23.

28. Mowatt G, Cook JA, Hillis GS, Walker S, Fraser C, Jia X, et al. 64-Slice computed tomography angiography in the diagnosis and assessment of coronary artery disease: systematic review and meta-analysis. Heart. 2008;94(11):1386-93.

29. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography by 64-row CT. N Engl J Med. 2008;359(22):2324-36.

30. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. J Am Coll Cardiol. 2008;52(21):1724-32.

31. Achenbach S, Ropers D, Pohle FK, Raaz D, von Erffa J, Yilmaz A, et al. Detection of coronary artery stenoses using multi-detector CT with 16 x 0.75 collimation and 375 ms rotation. Eur Heart J. 2005;26(19):1978-86.

32. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ, et al. Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter Registry) of 23,854 patients without known coronary artery disease. J Am Coll Cardiol. 2011;58(8):849-60.

33. Abdulla J, Pedersen KS, Budoff M, Kofoed KF. Influence of coronary calcification on the diagnostic accuracy of 64-slice computed tomography coronary angiography: a systematic review and meta-analysis. Int J Cardiovasc Imaging. 2012;28(4):943-53.

34. Jolly SS, Amlani S, Hamon M, Yusuf S, Mehta SR. Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: a systematic review and meta-analysis of randomized trials. Am Heart J. 2009;157(1):132-40.

35. Tang CX, Wang YN, Zhou F, Schoepf UJ, Assen MV, Stroud RE, et al. Diagnostic performance of fractional flow reserve derived from coronary CT angiography for detection of lesion-specific ischemia: A multi-center study and meta-analysis. Eur J Radiol. 2019;116:90-7.

36. Lu MT, Ferencik M, Roberts RS, Lee KL, Ivanov A, Adami E, et al. Noninvasive FFR Derived From Coronary CT Angiography: Management and Outcomes in the PROMISE Trial. JACC Cardiovasc Imaging. 2017; doi:10(11):1350-8.

37. Min JK, Leipsic J, Pencina MJ, Berman DS, Koo BK, van Mieghem C, et al. Diagnostic accuracy of fractional flow reserve from anatomic CT angiography. Jama. 2012;308(12):1237-45.

38. Koo BK, Erglis A, Doh JH, Daniels DV, Jegere S, Kim HS, et al. Diagnosis of ischemia-causing coronary stenoses by noninvasive fractional flow reserve computed from coronary computed tomographic angiograms. Results from the prospective multicenter DISCOVER-FLOW (Diagnosis of Ischemia-Causing Stenoses Obtained Via Noninvasive Fractional Flow Reserve) study. J Am Coll Cardiol. 2011;58(19):1989-97.

39. Pontone G, Baggiano A, Andreini D, Guaricci AI, Guglielmo M, Muscogiuri G, et al. Dynamic Stress Computed Tomography Perfusion With a Whole-Heart Coverage Scanner in Addition to Coronary Computed Tomography Angiography and Fractional Flow Reserve Computed Tomography Derived. JACC Cardiovasc Imaging. 2019; doi:10.1016/j.jcmg.2019.02.015.

40. Koplay M, Erdogan H, Avci A, Sivri M, Demir K, Guler I, et al. Radiation dose and diagnostic accuracy of high-pitch dual-source coronary angiography in the evaluation of coronary artery stenoses. Diagn Interv Imaging. 2016;97(4):461-9.

41. Nerlekar N, Ko BS, Nasis A, Cameron JD, Leung M, Brown AJ, et al. Impact of heart rate on diagnostic accuracy of second generation 320-detector computed tomography coronary angiography. Cardiovasc Diagn Ther. 2017;7(3):296-304.

42. Chen Y, Wei D, Li D, Liu Z, Hu Z, Li M, et al. The Value of 16-cm Wide-Detector Computed Tomography in Coronary Computed Tomography Angiography for Patients With High Heart Rate Variability. J Comput Assist Tomogr. 2018;42(6):906-11.

43. Halliburton SS, Abbara S, Chen MY, Gentry R, Mahesh M, Raff GL, et al. SCCT guidelines on radiation dose and dose-optimization strategies in cardiovascular CT. J Cardiovasc Comput Tomogr. 2011;5(4):198-224.

44. Westwood M, Al M, Burgers L, Redekop K, Lhachimi S, Armstrong N, et al. A systematic review and economic evaluation of new-generation computed tomography scanners for imaging in coronary artery disease and congenital heart disease: Somatom Definition Flash, Aquilion ONE, Brilliance iCT and Discovery CT750 HD. Health Technol Assess. 2013;17(9):1-243.

45. Apfaltrer P, Schoendube H, Schoepf UJ, Allmendinger T, Tricarico F, Schindler A, et al. Enhanced temporal resolution at cardiac CT with a novel CT image reconstruction algorithm: initial patient experience. Eur J Radiol. 2013;82(2):270-4.

46. Hara T, Urikura A, Ichikawa K, Hoshino T, Nishimaru E, Niwa S. Temporal resolution measurement of 128-slice dual source and 320-row area detector computed tomography scanners in helical acquisition mode using the impulse method. Phys Med. 2016;32(4):625-30.

47. Qi L, Tang LJ, Xu Y, Zhu XM, Zhang YD, Shi HB, et al. The Diagnostic Performance of Coronary CT Angiography for the Assessment of Coronary Stenosis in Calcified Plaque. PLoS One. 2016;11(5):e0154852.

48. Precht H, Thygesen J, Gerke O, Egstrup K, Waaler D, Lambrechtsen J. Influence of adaptive statistical iterative reconstruction algorithm on image quality in coronary computed tomography angiography. Acta Radiol Open. 2016;5(12):2058460116684884.

49. Renker M, Geyer LL, Krazinski AW, Silverman JR, Ebersberger U, Schoepf UJ. Iterative image reconstruction: a realistic dose-saving method in cardiac CT imaging? Expert Rev Cardiovasc Ther. 2013;11(4):403-9.

50. den Dekker MA, de Smet K, de Bock GH, Tio RA, Oudkerk M, Vliegenthart R. Diagnostic performance of coronary CT angiography for stenosis detection according to calcium score: systematic review and meta-analysis. Eur Radiol. 2012;22(12):2688-98.

51. Puchner SB, Ferencik M, Maehara A, Stolzmann P, Ma S, Do S, et al. Iterative Image Reconstruction Improves the Accuracy of Automated Plaque Burden Assessment in Coronary CT Angiography: A Comparison With Intravascular Ultrasound. AJR Am J Roentgenol. 2017;208(4):777-84.

52. Pontone G, Bertella E, Mushtaq S, Loguercio M, Cortinovis S, Baggiano A, et al. Coronary artery disease: diagnostic accuracy of CT coronary angiography--a comparison of high and standard spatial resolution scanning. Radiology. 2014;271(3):688-94.

53. Andreini D, Pontone G, Mushtaq S, Conte E, Guglielmo M, Mancini ME, et al. Diagnostic accuracy of coronary CT angiography performed in 100 consecutive patients with coronary stents using a whole-organ high-definition CT scanner. Int J Cardiol. 2019;274:382-7.

54. Hausleiter J, Martinoff S, Hadamitzky M, Martuscelli E, Pschierer I, Feuchtner GM, et al. Image quality and radiation exposure with a low tube voltage protocol for coronary CT angiography results of the PROTECTION II Trial. JACC Cardiovasc Imaging. 2010;3(11):1113-23.

55. Nelson RC, Feuerlein S, Boll DT. New iterative reconstruction techniques for cardiovascular computed tomography: how do they work, and what are the advantages and disadvantages? J Cardiovasc Comput Tomogr. 2011;5(5):286-92.

56. Richards CE, Obaid DR. Low-Dose Radiation Advances in Coronary Computed Tomography Angiography in the Diagnosis of Coronary Artery Disease. Curr Cardiol Rev. 2019;15(4):304-15.

57. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte JM, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. Journal of the American College of Cardiology. 1990;15(4):827-32.

58. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. Jama. 2012;308(8):788-95.

59. Nicoll R, Wiklund U, Zhao Y, Diederichsen A, Mickley H, Ovrehus K, et al. The coronary calcium score is a more accurate predictor of significant coronary stenosis than conventional risk factors in symptomatic patients: Euro-CCAD study. Int J Cardiol. 2016;207:13-9.

60. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008;358(13):1336-45.

61. Sarwar A, Shaw LJ, Shapiro MD, Blankstein R, Hoffmann U, Cury RC, et al. Diagnostic and prognostic value of absence of coronary artery calcification. JACC Cardiovasc Imaging. 2009;2(6):675-88.

62. Nair A, Kuban BD, Tuzcu EM, Schoenhagen P, Nissen SE, Vince DG. Coronary plaque classification with intravascular ultrasound radiofrequency data analysis. Circulation. 2002;106(17):2200-6.

63. Ali ZA, Karimi Galougahi K, Maehara A, Shlofmitz RA, Ben-Yehuda O, Mintz GS, et al. Intracoronary Optical Coherence Tomography 2018: Current Status and Future Directions. JACC Cardiovasc Interv. 2017;10(24):2473-87.

64. Hausmann D, Erbel R, Alibelli-Chemarin MJ, Boksch W, Caracciolo E, Cohn JM, et al. The safety of intracoronary ultrasound. A multicenter survey of 2207 examinations. Circulation. 1995;91(3):623-30.

65. Obaid DR, Calvert PA, Brown A, Gopalan D, West NEJ, Rudd JHF, et al. Coronary CT angiography features of ruptured and high-risk atherosclerotic plaques: Correlation with intra-vascular ultrasound. J Cardiovasc Comput Tomogr. 2017;11(6):455-61.

66. Kesarwani M, Nakanishi R, Choi TY, Shavelle DM, Budoff MJ. Evaluation of Plaque Morphology by 64-Slice Coronary Computed Tomographic Angiography Compared to Intravascular Ultrasound in Nonocclusive Segments of Coronary Arteries. Acad Radiol. 2017;24(8):968-74.

67. Yamamoto H, Kihara Y, Kitagawa T, Ohashi N, Kunita E, Iwanaga Y, et al. Coronary plaque characteristics in computed tomography and 2-year outcomes: The PREDICT study. J Cardiovasc Comput Tomogr. 2018;12(5):436-43.

68. Ferencik M, Mayrhofer T, Bittner DO, Emami H, Puchner SB, Lu MT, et al. Use of High-Risk Coronary Atherosclerotic Plaque Detection for Risk Stratification of Patients With Stable Chest Pain: A Secondary Analysis of the PROMISE Randomized Clinical Trial. JAMA Cardiol. 2018;3(2):144-52.

69. Dohi T, Mintz GS, McPherson JA, de Bruyne B, Farhat NZ, Lansky AJ, et al. Non-fibroatheroma lesion phenotype and long-term clinical outcomes: a substudy analysis from the PROSPECT study. JACC Cardiovasc Imaging. 2013;6(8):908-16.

70. Puchner SB, Liu T, Mayrhofer T, Truong QA, Lee H, Fleg JL, et al. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. J Am Coll Cardiol. 2014;64(7):684-92.

71. Cury RC, Abbara S, Achenbach S, Agatston A, Berman DS, Budoff MJ, et al. CAD-RADS(TM) Coronary Artery Disease - Reporting and Data System. An expert consensus document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Radiology (ACR) and the North American Society for Cardiovascular Imaging (NASCI). Endorsed by the American College of Cardiology. J Cardiovasc Comput Tomogr. 2016;10(4):269-81.

72. Versteylen MO, Kietselaer BL, Dagnelie PC, Joosen IA, Dedic A, Raaijmakers RH, et al. Additive value of semiautomated quantification of coronary artery disease using cardiac computed tomographic angiography to predict future acute coronary syndrome. J Am Coll Cardiol. 2013;61(22):2296-305.

73. Kristensen TS, Kofoed KF, Kuhl JT, Nielsen WB, Nielsen MB, Kelbaek H. Prognostic implications of nonobstructive coronary plaques in patients with non-ST-segment elevation myocardial infarction: a multidetector computed tomography study. J Am Coll Cardiol. 2011;58(5):502-9.

74. Maurovich-Horvat P, Ferencik M, Voros S, Merkely B, Hoffmann U. Comprehensive plaque assessment by coronary CT angiography. Nat Rev Cardiol. 2014;11(7):390-402.

75. Marwan M, Achenbach S. Quantification of epicardial fat by computed tomography: why, when and how? J Cardiovasc Comput Tomogr. 2013;7(1):3-10.

76. Nerlekar N, Brown AJ, Muthalaly RG, Talman A, Hettige T, Cameron JD, et al. Association of Epicardial Adipose Tissue and High-Risk Plaque Characteristics: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2017;6(8): doi:10.1161/jaha.117.006379.

77. Dey D, Nakazato R, Li D, Berman DS. Epicardial and thoracic fat - Noninvasive measurement and clinical implications. Cardiovasc Diagn Ther. 2012;2(2):85-93.

78. Goeller M, Achenbach S, Marwan M, Doris MK, Cadet S, Commandeur F, et al. Epicardial adipose tissue density and volume are related to subclinical atherosclerosis, inflammation and major adverse cardiac events in asymptomatic subjects. J Cardiovasc Comput Tomogr. 2018;12(1):67-73.

79. Sakkas LI, Bogdanos DP. Are psoriasis and psoriatic arthritis the same disease? The IL-23/IL-17 axis data. Autoimmun Rev. 2017;16(1):10-5.

80. Tobin AM, Veale DJ, Fitzgerald O, Rogers S, Collins P, O'Shea D, et al. Cardiovascular disease and risk factors in patients with psoriasis and psoriatic arthritis. J Rheumatol. 2010;37(7):1386-94.

81. Han C, Robinson DW, Jr., Hackett MV, Paramore LC, Fraeman KH, Bala MV. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol. 2006;33(11):2167-72.

82. Lindhardsen J, Ahlehoff O, Gislason GH, Madsen OR, Olesen JB, Torp-Pedersen C, et al. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis. 2011;70(6):929-34.

83. Mantel A, Holmqvist M, Nyberg F, Tornling G, Frisell T, Alfredsson L, et al. Risk factors for the rapid increase in risk of acute coronary events in patients with new-onset rheumatoid arthritis: a nested case-control study. Arthritis Rheumatol. 2015;67(11):2845-54.

84. Solomon DH, Reed GW, Kremer JM, Curtis JR, Farkouh ME, Harrold LR, et al. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. Arthritis Rheumatol. 2015;67(6):1449-55.

85. Naerr GW, Rein P, Saely CH, Drexel H. Effects of synthetic and biological disease modifying antirheumatic drugs on lipid and lipoprotein parameters in patients with rheumatoid arthritis. Vascul Pharmacol. 2016;81:22-30.

86. Maradit-Kremers H, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum. 2005;52(2):402-11.

87. Rollefstad S, Ikdahl E, Hisdal J, Kvien TK, Pedersen TR, Semb AG. Association of Chest Pain and Risk of Cardiovascular Disease with Coronary Atherosclerosis in Patients with Inflammatory Joint Diseases. Front Med (Lausanne). 2015;2:80.

88. Crowson CS, Matteson EL, Roger VL, Therneau TM, Gabriel SE. Usefulness of risk scores to estimate the risk of cardiovascular disease in patients with rheumatoid arthritis. Am J Cardiol. 2012;110(3):420-4.

89. Arts EE, Popa C, Den Broeder AA, Semb AG, Toms T, Kitas GD, et al. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. Ann Rheum Dis. 2015;74(4):668-74.

90. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 2010;69(2):325-31.

91. Crowson CS, Gabriel SE, Semb AG, van Riel P, Karpouzas G, Dessein PH, et al. Rheumatoid arthritis-specific cardiovascular risk scores are not superior to general risk scores: a validation analysis of patients from seven countries. Rheumatology (Oxford). 2017;56(7):1102-10.

92. Crowson CS, Rollefstad S, Kitas GD, van Riel PL, Gabriel SE, Semb AG. Challenges of developing a cardiovascular risk calculator for patients with rheumatoid arthritis. PLoS One. 2017;12(3):e0174656.

93. Papatheodorou K, Papanas N, Banach M, Papazoglou D, Edmonds M. Complications of Diabetes 2016. J Diabetes Res. 2016;2016:6989453.

94. Ziegler D, Gries FA, Spuler M, Lessmann F. The epidemiology of diabetic neuropathy. Diabetic Cardiovascular Autonomic Neuropathy Multicenter Study Group. J Diabetes Complications. 1992;6(1):49-57.

95. Nicholls SJ, Tuzcu EM, Kalidindi S, Wolski K, Moon KW, Sipahi I, et al. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials. J Am Coll Cardiol. 2008;52(4):255-62.

96. DCCT/EDIC. Risk Factors for Cardiovascular Disease in Type 1 Diabetes. Diabetes. 2016;65(5):1370-9.

97. Miller RG, Costacou T, Orchard TJ. Risk Factor Modeling for Cardiovascular Disease in Type 1 Diabetes in the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study: A Comparison With the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study (DCCT/EDIC). Diabetes. 2019;68(2):409-19.

98. Rollefstad S, Ikdahl E, Hisdal J, Olsen IC, Holme I, Hammer HB, et al. Rosuvastatin-Induced Carotid Plaque Regression in Patients With Inflammatory Joint Diseases: The Rosuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and Other Inflammatory Joint Diseases Study. Arthritis Rheumatol. 2015;67(7):1718-28.

99. Rollefstad S, Kvien TK, Holme I, Eirheim AS, Pedersen TR, Semb AG. Treatment to lipid targets in patients with inflammatory joint diseases in a preventive cardio-rheuma clinic. Ann Rheum Dis. 2013;72(12):1968-74.

100. Holte KB, Svanteson M, Hanssen KF, Haig Y, Solheim S, Berg TJ. Undiagnosed coronary artery disease in long-term type 1 diabetes. The Dialong study. J Diabetes Complications. 2019;33(5):383-9.

101. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation. 1975;51(4 Suppl):5-40.

102. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, et al. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr. 2014;8(5):342-58.

103. Ayoub C, Kritharides L, Yam Y, Chen L, Hossain A, Achenbach S, et al. Prognostic value of age adjusted segment involvement score as measured by coronary computed tomography: a potential marker of vascular age. Heart Vessels. 2018;33(11):1288-300.

104. Raff GL, Chinnaiyan KM, Cury RC, Garcia MT, Hecht HS, Hollander JE, et al. SCCT guidelines on the use of coronary computed tomographic angiography for patients presenting with acute chest pain to the emergency department: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr. 2014;8(4):254-71.

105. Klass O, Kleinhans S, Walker MJ, Olszewski M, Feuerlein S, Juchems M, et al. Coronary plaque imaging with 256-slice multidetector computed tomography: interobserver variability of volumetric lesion parameters with semiautomatic plaque analysis software. Int J Cardiovasc Imaging. 2010;26(6):711-20.

106. Karpouzas GA, Malpeso J, Choi TY, Li D, Munoz S, Budoff MJ. Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. Ann Rheum Dis. 2014;73(10):1797-804.

107. Terry JG, Carr JJ, Kouba EO, Davis DH, Menon L, Bender K, et al. Effect of simvastatin (80 mg) on coronary and abdominal aortic arterial calcium (from the coronary artery calcification treatment with zocor [CATZ] study). Am J Cardiol. 2007;99(12):1714-7.

108. Schmermund A, Achenbach S, Budde T, Buziashvili Y, Forster A, Friedrich G, et al. Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation. 2006;113(3):427-37.

109. Raggi P, Davidson M, Callister TQ, Welty FK, Bachmann GA, Hecht H, et al. Aggressive versus moderate lipid-lowering therapy in hypercholesterolemic postmenopausal women: Beyond Endorsed Lipid Lowering with EBT Scanning (BELLES). Circulation. 2005;112(4):563-71.

110. Henein M, Granasen G, Wiklund U, Schmermund A, Guerci A, Erbel R, et al. High dose and long-term statin therapy accelerate coronary artery calcification. Int J Cardiol. 2015;184:581-6.

111. Grimes DA, Schulz KF. Compared to what? Finding controls for case-control studies. Lancet. 2005;365(9468):1429-33.

112. Hjortkjaer HO, Jensen T, Hilsted J, Corinth H, Mogensen UM, Kober L, et al. Possible early detection of coronary artery calcium progression in type 1 diabetes: A case-control study of normoalbuminuric type 1 diabetes patients and matched controls. Diabetes Res Clin Pract. 2018;141:18-25.

113. Kvien TK, Glennas A, Knudsrod OG, Smedstad LM, Mowinckel P, Forre O. The prevalence and severity of rheumatoid arthritis in Oslo. Results from a county register and a population survey. Scand J Rheumatol. 1997;26(6):412-8.

114. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2009;32 Suppl 1:S62-7.

115. Han D, Torii S, Yahagi K, Lin FY, Lee JH, Rizvi A, et al. Quantitative measurement of lipid rich plaque by coronary computed tomography angiography: A correlation of histology in sudden cardiac death. Atherosclerosis. 2018;275:426-33.

116. Symons R, Morris JZ, Wu CO, Pourmorteza A, Ahlman MA, Lima JA, et al. Coronary CT Angiography: Variability of CT Scanners and Readers in Measurement of Plaque Volume. Radiology. 2016;281(3):737-48.

117. Oberoi S, Meinel FG, Schoepf UJ, Nance JW, De Cecco CN, Gebregziabher M, et al. Reproducibility of noncalcified coronary artery plaque burden quantification from coronary CT angiography across different image analysis platforms. AJR Am J Roentgenol. 2014;202(1):W43-9.

118. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017;76(1):17-28.

119. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019;10.1093/eurheartj/ehz455.

120. Semb AG, Ikdahl E, Hisdal J, Olsen IC, Rollefstad S. Exploring cardiovascular disease risk evaluation in patients with inflammatory joint diseases. Int J Cardiol. 2016;223:331-6.

121. Shin S, Park HB, Chang HJ, Arsanjani R, Min JK, Kim YJ, et al. Impact of Intensive LDL Cholesterol Lowering on Coronary Artery Atherosclerosis Progression: A Serial CT Angiography Study. JACC Cardiovasc Imaging. 2017;10(4):437-46.

122. Zeb I, Li D, Nasir K, Malpeso J, Batool A, Flores F, et al. Effect of statin treatment on coronary plaque progression – A serial coronary CT angiography study. Atherosclerosis. 2013;231(2):198-204.

123. Chou R, Dana T, Blazina I, Daeges M, Jeanne TL. Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. Jama. 2016;316(19):2008-24.

124. Kitas GD, Nightingale P, Armitage J, Sattar N, Belch JJF, Symmons DPM. A Multicenter, Randomized, Placebo-Controlled Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Patients With Rheumatoid Arthritis. Arthritis Rheumatol. 2019;71(9):1437-49.

125. de Rezende LFM, Rey-Lopez JP, de Sa TH, Chartres N, Fabbri A, Powell L, et al. Reporting bias in the literature on the associations of health-related behaviors and statins with cardiovascular disease and all-cause mortality. PLoS Biol. 2018;16(6):e2005761.

126. Li M, Wang X, Li X, Chen H, Hu Y, Zhang X, et al. Statins for the Primary Prevention of Coronary Heart Disease. Biomed Res Int. 2019;2019:4870350. doi: 10.1155/2019/4870350

127. Kwan AC, Aronis KN, Sandfort V, Blumenthal RS, Bluemke DA. Bridging the gap for lipid lowering therapy: plaque regression, coronary computed tomographic angiography, and imaging-guided personalized medicine. Expert Rev Cardiovasc Ther. 2017;15(7):547-58.

128. Hecht H, Blaha MJ, Berman DS, Nasir K, Budoff M, Leipsic J, et al. Clinical indications for coronary artery calcium scoring in asymptomatic patients: Expert consensus statement from the

Society of Cardiovascular Computed Tomography. Journal of Cardiovascular Computed Tomography. 2017;11(2):157-68.

129. Coylewright M, Rice K, Budoff MJ, Blumenthal RS, Greenland P, Kronmal R, et al. Differentiation of severe coronary artery calcification in the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2011;219(2):616-22.

130. Shemesh J, Tenenbaum A, Fisman EZ, Koren-Morag N, Grossman E. Coronary calcium in patients with and without diabetes: first manifestation of acute or chronic coronary events is characterized by different calcification patterns. Cardiovasc Diabetol. 2013;12:161.

131. Djaberi R, Schuijf JD, Boersma E, Kroft LJ, Pereira AM, Romijn JA, et al. Differences in atherosclerotic plaque burden and morphology between type 1 and 2 diabetes as assessed by multislice computed tomography. Diabetes Care. 2009;32(8):1507-12.

132. Goedendorp MM, Tack CJ, Steggink E, Bloot L, Bazelmans E, Knoop H. Chronic fatigue in type 1 diabetes: highly prevalent but not explained by hyperglycemia or glucose variability. Diabetes Care. 2014;37(1):73-80.

133. Segerstedt J, Lundqvist R, Eliasson M. Patients with type 1 diabetes in Sweden experience more fatigue than the general population. J Clin Transl Endocrinol. 2015;2(3):105-9.

134. Quillard T, Franck G, Mawson T, Folco E, Libby P. Mechanisms of erosion of atherosclerotic plaques. Curr Opin Lipidol. 2017;28(5):434-41.

135. Kontush A. HDL-mediated mechanisms of protection in cardiovascular disease. Cardiovasc Res. 2014;103(3):341-9.

136. Versteylen MO, Takx RA, Joosen IA, Nelemans PJ, Das M, Crijns HJ, et al. Epicardial adipose tissue volume as a predictor for coronary artery disease in diabetic, impaired fasting glucose, and non-diabetic patients presenting with chest pain. Eur Heart J Cardiovasc Imaging. 2012;13(6):517-23.

137. Lu MT, Park J, Ghemigian K, Mayrhofer T, Puchner SB, Liu T, et al. Epicardial and paracardial adipose tissue volume and attenuation - Association with high-risk coronary plaque on computed tomographic angiography in the ROMICAT II trial. Atherosclerosis. 2016;251:47-54.

138. Darabian S, Backlund JY, Cleary PA, Sheidaee N, Bebu I, Lachin JM, et al. Significance of Epicardial and Intrathoracic Adipose Tissue Volume among Type 1 Diabetes Patients in the DCCT/EDIC: A Pilot Study. PLoS One. 2016;11(7):e0159958.

139. Wang CP, Hsu HL, Hung WC, Yu TH, Chen YH, Chiu CA, et al. Increased epicardial adipose tissue (EAT) volume in type 2 diabetes mellitus and association with metabolic syndrome and severity of coronary atherosclerosis. Clin Endocrinol (Oxf). 2009;70(6):876-82.

140. Guo J, Erqou SA, Miller RG, Edmundowicz D, Orchard TJ, Costacou T. The role of coronary artery calcification testing in incident coronary artery disease risk prediction in type 1 diabetes. Diabetologia. 2019;62(2):259-68.

141. Andreini D. Screening CT Angiography in Asymptomatic Diabetes Mellitus? JACC Cardiovasc Imaging. 2016;9(11):1301-3.

142. Lee CH, Lee SW, Park SW. Diabetes and Subclinical Coronary Atherosclerosis. Diabetes Metab J. 2018;42(5):355-63.

143. Emami H, Takx RAP, Mayrhofer T, Janjua S, Park J, Pursnani A, et al. Nonobstructive Coronary Artery Disease by Coronary CT Angiography Improves Risk Stratification and Allocation of Statin Therapy. JACC Cardiovasc Imaging. 2017;10(9):1031-8.

144. Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, Flather M, et al. Coronary CT Angiography and 5-Year Risk of Myocardial Infarction. N Engl J Med. 2018;379(10):924-33.

145. Muhlestein JB, Lappe DL, Lima JA, Rosen BD, May HT, Knight S, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. Jama. 2014;312(21):2234-43.

146. Williams MC, Hunter A, Shah ASV, Assi V, Lewis S, Smith J, et al. Use of Coronary Computed Tomographic Angiography to Guide Management of Patients With Coronary Disease. J Am Coll Cardiol. 2016;67(15):1759-68.

147. Rozanski A, Gransar H, Shaw LJ, Kim J, Miranda-Peats L, Wong ND, et al. Impact of coronary artery calcium scanning on coronary risk factors and downstream testing the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) prospective randomized trial. J Am Coll Cardiol. 2011;57(15):1622-32.

148. Kalia NK, Miller LG, Nasir K, Blumenthal RS, Agrawal N, Budoff MJ. Visualizing coronary calcium is associated with improvements in adherence to statin therapy. Atherosclerosis. 2006;185(2):394-9.

149. Williams MC, Hunter A, Shah A, Assi V, Lewis S, Mangion K, et al. Symptoms and quality of life in patients with suspected angina undergoing CT coronary angiography: a randomised controlled trial. Heart. 2017;103(13):995-1001.

150. Joshi PH, Blaha MJ, Budoff MJ, Miedema MD, McClelland RL, Lima JAC, et al. The 10-Year Prognostic Value of Zero and Minimal CAC. JACC Cardiovasc Imaging. 2017;10(8):957-8.

151. Shaw LJ, Narula J, Chandrashekhar Y. The never-ending story on coronary calcium: is it predictive, punitive, or protective? J Am Coll Cardiol. 2015;65(13):1283-5.

152. Han D, Hartaigh BO, Gransar H, Lee JH, Rizvi A, Baskaran L, et al. Incremental prognostic value of coronary computed tomography angiography over coronary calcium scoring for major adverse cardiac events in elderly asymptomatic individuals. Eur Heart J Cardiovasc Imaging. 2018;19(6):675-83.

153. Takamura K, Fujimoto S, Kondo T, Hiki M, Kawaguchi Y, Kato E, et al. Incremental Prognostic Value of Coronary Computed Tomography Angiography: High-Risk Plaque Characteristics in Asymptomatic Patients. J Atheroscler Thromb. 2017;24(11):1174-85.

154. Min JK, Labounty TM, Gomez MJ, Achenbach S, Al-Mallah M, Budoff MJ, et al. Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals. Atherosclerosis. 2014;232(2):298-304.

155. Cho I, Chang HJ, B OH, Shin S, Sung JM, Lin FY, et al. Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the COronary CT Angiography EvaluatioN For Clinical Outcomes InteRnational Multicenter (CONFIRM) study. Eur Heart J. 2015;36(8):501-8.

156. Nabi F, Chang SM, Pratt CM, Paranilam J, Peterson LE, Frias ME, et al. Coronary artery calcium scoring in the emergency department: identifying which patients with chest pain can be safely discharged home. Ann Emerg Med. 2010;56(3):220-9.

157. van Werkhoven JM, de Boer SM, Schuijf JD, Cademartiri F, Maffei E, Jukema JW, et al. Impact of clinical presentation and pretest likelihood on the relation between calcium score and computed tomographic coronary angiography. Am J Cardiol. 2010;106(12):1675-9.

158. Arcadi T, Maffei E, Mantini C, Guaricci A, La Grutta L, Martini C, et al. Coronary CT angiography using iterative reconstruction vs. filtered back projection: evaluation of image quality. Acta Biomed. 2015;86(1):77-85.

159. Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK, et al. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: A report of the society of Cardiovascular Computed Tomography Guidelines Committee: Endorsed by the North American Society for Cardiovascular Imaging (NASCI). J Cardiovasc Comput Tomogr. 2016;10(6):435-49.

160. Norgaard BL, Leipsic J, Gaur S, Seneviratne S, Ko BS, Ito H, et al. Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in suspected coronary artery disease: the NXT trial (Analysis of Coronary Blood Flow Using CT Angiography: Next Steps). J Am Coll Cardiol. 2014;63(12):1145-55.

161. Yang DH, Kim YH, Roh JH, Kang JW, Ahn JM, Kweon J, et al. Diagnostic performance of on-site CT-derived fractional flow reserve versus CT perfusion. Eur Heart J Cardiovasc Imaging. 2017;18(4):432-40.

162. Mandal SR, Bharati A, Haghighi RR, Arava S, Ray R, Jagia P, et al. Non-invasive characterization of coronary artery atherosclerotic plaque using dual energy CT: Explanation in ex-vivo samples. Phys Med. 2018;45:52-8.

I

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL ARTICLE

Associations between coronary and carotid artery atherosclerosis in patients with inflammatory joint diseases

Mona Svanteson,[1,2] Silvia Rollefstad,[3] Nils Einar Kløw,[1,2] Jonny Hisdal,[4] Eirik Ikdahl,[3] Anne Grete Semb,[3] Ylva Haig[1]

To cite: Svanteson M, Rollefstad S, Kløw NE, *et al*. Associations between coronary and carotid artery atherosclerosis in patients with inflammatory joint diseases. *RMD Open* 2017;**3**:e000544. doi:10.1136/rmdopen-2017-000544

► Prepublication history and additional material for this paper are available online. To view please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2017-000544).

AGS and YH contributed equally.

Received 21 July 2017
Accepted 11 August 2017

[1]Department of Radiology, Oslo University Hospital, Oslo, Norway
[2]Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[3]Department of Rheumatology, Preventive Cardio-Rheuma Clinic, Diakonhjemmet Hospital, Oslo, Norway
[4]Department of Vascular Investigations, Oslo University Hospital, Oslo, Norway

Correspondence to
Mona Svanteson;
mona.svanteson@medisin.uio.no

ABSTRACT

Objective Low association between cardiac symptoms and coronary artery disease (CAD) in patients with inflammatory joint diseases (IJD) demands for objective markers to improve cardiovascular risk stratification. Our main aim was to evaluate the prevalence and characteristics of CAD in patients with IJD with carotid artery plaques. Furthermore, we aimed to assess associations of carotid ultrasonographic findings and coronary plaques.

Methods Eighty-six patients (61% female) with IJD (55 with rheumatoid arthritis, 21 with ankylosing spondylitis and 10 with psoriatic arthritis) and carotid artery plaque were referred to coronary CT angiography (CCTA). CAD was evaluated using the modified 17-segment American Heart Association model. Calcium score, plaque composition, segment involvement score and segment stenosis score were assessed and correlated to the carotid artery plaques and cardiovascular disease risk factors in logistic and linear regression analyses. Risk prediction models were tested with various cut-off values for associating variables.

Results Fifty-five patients (66%) had CAD assessed by CCTA and 36 (43%) of these had coronary plaques defined as either mixed or soft. Eleven patients (13%) had obstructive CAD. The best risk prediction model (area under the curve: 0.832, 95% CI 0.730 to 0.935) included the combination of variables with cut-off values: age ≥55 years (OR: 12.18, 95% CI 2.80 to 53.05), the carotid-intima media thickness ≥0.7 mm (OR: 4.08, 95% CI 1.20 to 13.89) and carotid plaque height ≥1.5 mm (OR: 8.96, 95% CI 1.68 to 47.91), p<0.05.

Conclusion Presence of carotid plaque is alone not sufficient to identify patients at risk for CAD, and a combination of ultrasonographic measurements may be useful in risk stratification of patients with IJD.

Trial registration number NCT01389388, Results.

Key messages

What is already known about this subject?

- Patients with inflammatory joint diseases are at higher risk of developing acute coronary syndrome, and the risk increases in the presence of carotid artery plaques.
- Low association between cardiac symptoms and coronary artery disease demands for objective markers for identification of patients in the need for further cardiac evaluation.

What does this study add?

- We assessed the associations between carotid and coronary plaques in patients with inflammatory joint diseases. The findings suggest that having carotid artery plaque is not alone sufficient for identifying patients with coronary artery disease, and a combination of carotid plaque measurements may be useful in identifying these patients.

How might this impact on clinical practice?

- The study supports the use of carotid ultrasound in cardiovascular risk stratification of patients with inflammatory joint diseases.

INTRODUCTION

Patients with inflammatory joint diseases (IJD) have a twofold higher risk of cardiovascular disease compared with the general population.[1–3] Patients with IJD more often experience silent and fatal coronary events than the general population.[4] The association between chest pain and coronary artery disease (CAD) is low in patients with IJD,[5] and it has been reported that the traditional risk stratification tools inadequately predict the risk in patients with rheumatoid arthritis (RA).[6] Accordingly, objective markers to improve cardiovascular disease risk prediction in patients with IJD are warranted. According to the European guidelines for prevention of cardiovascular disease in the general population, the presence of carotid plaques increases the risk for cardiovascular events,[7] and several studies support the use of ultrasound of the carotid arteries as a valuable tool for cardiovascular risk stratification in patients with RA.[8 9]

Although conventional angiography still is the gold standard for assessment of CAD, non-invasive coronary CT angiography (CCTA) has become an established method for excluding coronary artery stenosis in

patients with chest pain estimated at low or intermediate risk of cardiovascular disease.[10] CCTA also provides valuable information on the presence, localisation and morphology of atherosclerotic plaque(s).[11 12]

Patients with RA and carotid atherosclerosis have a 2.5–4 times higher risk of acute coronary syndrome compared with patients with RA without carotid plaques.[13] However, the association of carotid atherosclerosis and CAD, including plaque morphology, in patients with IJD, has to our knowledge not yet been evaluated. Such knowledge will be important for the evaluation of the use of carotid ultrasonography in cardiovascular disease risk stratification in patients with IJD.

The aim of the present study was therefore to evaluate the prevalence and characteristics of coronary plaques in patients with IJD and established carotid artery atherosclerosis. We also aimed to assess associations of coronary plaques with carotid atherosclerosis measurements in order to evaluate the use of ultrasonographic measurements in cardiovascular risk stratification of patients with IJD.

METHODS

Patients and study design

The study had a cross-sectional design using baseline data from the RORA-AS study (ROsuvastatin in patients with Rheumatoid Arthritis, Ankylosing Spondylitis and other inflammatory joint diseases).[14] Patients aged 35–80 years with IJD participating in the RORA-AS study, who were statin naïve and with B-mode ultrasound verified carotid artery plaque(s) were included and referred to CCTA between 2010 and 2012. Contraindication to statin treatment, secondary hyperlipidaemia, atrial fibrillation or arrhythmias were exclusion criteria for participation in the RORA-AS study, as previously more thoroughly described.[14]

All patients were evaluated by a cardiologist before referral to CCTA. Traditional risk factors were recorded, including laboratory testing of lipids and inflammatory markers: C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

The study was conducted in accordance with the Helsinki Declaration and approved by the Norwegian South East Regional Health Ethics Committee, registered at http://ClinicalTrials.gov-identifier: NCT01389388 and EudraCT database no. 2008-005551-20. All patients signed an informed consent.

Coronary artery atherosclerosis evaluation

CCTA image acquisition

CCTA imaging was performed with a Philips Brilliance 64-slice CT scanner (Philips Healthcare, Cleveland, Ohio, USA). A beta blocker (5–20 mg Seloken, Astra Zeneca) was administered prior to the CCTA scan to lower the heart rate to ≤65 beats/min (bpm). A non-contrast scan was initially conducted for evaluation of coronary artery calcification (CAC) (ECG gated, 120 kV, 55 mA, 0.4 ms rotation, 40×0.625 mm collimation). The contrast-enhanced scan (90–130 mL Omnipaque 350 mg/mL (GE Healthcare, Princeton, New Jersey)) was then performed with prospective ECG gating (conducted with 120 kV, 350–500 mA, 0.4 ms rotation, 64×0.625 mm collimation) when a heart rate ≤65 bpm was achieved. Retrospective ECG gating (conducted with 120 kV, 800 mA, 0.2 Pitch, 0.4 ms rotation, 64×0.625 mm collimation) was used for heart rates ≥65 bpm. Nitroglycerin 0.4 mg (Nitrolingual, Pohl-Boskamp, Hohenlockstedt, Germany) was administered sublingually 1–3 min prior to the contrast injection.

CCTA image analysis

Image analysis was performed on a Philips Workstation (Intellispace v5, Philips Healthcare) with dedicated software (Comprehensive Cardiac, Plaque Analysis) with previously reported high degree of interobserver variability.[15] All images were evaluated by two independent readers, and disagreements were solved by consensus. All segments with subjectively sufficient image quality and a diameter >1.5 mm were included in the analyses. Images were assessed using a modified 17-segment American Heart Association (AHA) model.[16] CAC was calculated with the Agatston method.[17] The plaque morphology was defined by the amount of calcifications, with a density >130 Hounsfield units in the plaque: calcified plaques in the presence of ≥ 50% calcifications, mixed plaques with less than <50% calcifications and soft plaques with no calcifications. CAD was defined as presence of any plaque.

The extent and severity of CAD was assessed by the segment involvement score and the segment stenosis score. Segment involvement score was calculated as the number of segments with plaque involvement (1–17). Segment stenosis score was calculated for assessment of the severity of the stenosis. Each segment was scored (grading 1–4) based on luminal narrowing: grade 1: 1%–29% stenosis; grade 2: 30%–49% stenosis; grade 3: 50%–69% stenosis; grade 4: 70%–100% stenosis, with a total score of 0–68.[18]

Carotid artery plaque evaluation

Ultrasound

A two-dimensional greyscale (B-mode) ultrasonography of the carotid arteries was performed with a Vivid-7 ultrasound scanner (General Electric Vingmed Ultrasound, Norway) using a 12 MHz linear matrix array transducer. The ultrasonography examinations were performed by one experienced sonographer in accordance with recommendations.[19] The carotid-intima media thickness (c-IMT) and plaque measurements were as previously described read off-line by two independent readers blinded to patient clinical information.[20] c-IMT was measured in both the left and right common carotid arteries, and a mean c-IMT was calculated. Our laboratory has previously reported an intraclass correlation coefficient of 0.985 (95% CI 0.975 to 0.991) on c-IMT measurements.[20] Plaques were identified in the longitudinal view

as protrusions >1.5 mm into the lumen when both the far and near walls had sharp edges, or when the protrusion was ≥2 times the nearby corresponding c-IMT, according to recommendations.[21]

Statistical analyses

Nominal variables were expressed as numbers (%), continuous variables as mean±SD for normally distributed variables and median with IQR for non-normally distributed variables. Independent samples t-test, X^2 tests and analysis of variance were used to compare variables between groups. The analysis of covariance was used to compare groups adjusted for sex, age and hypertension, with log-transformed variables for non-normally distributed variables.

Logistic regression analyses were used to identify variables associated with CAD. All variables with a stronger association than 0.2 in a univariate analysis were included in a multiple logistic regression model. A backward elimination method was performed until only significant predictors remained in the model. The two-sided significance level was set to <0.05. Goodness of fit of the model was tested using calibration plots. The same backward method was used to include variables in the multiple linear regression analyses with CAC, segment involvement score and segment stenosis score as dependent variables.

Variables associated with CAD (age, c-IMT and carotid plaque height) were further analysed using multiple logistic regression with various cut-off values. Risk prediction models with various combinations of the three variables were created. Sensitivity and specificity were calculated for the multivariate models to test the diagnostic accuracy of each model and the validity was tested with area under the curve (AUC). All statistical analyses were performed using IBM SPSS V.22.

RESULTS

Patient characteristics

A total of 86 patients were referred to CCTA. Three patients only underwent a non-contrast scan due to arrhythmias, and were only included in the CAC analyses. The other 83 patients were included in the final analyses; 53 (64%) with RA, 21 (25%) with ankylosing spondylitis (AS) and 9 (11%) with psoriatic arthritis (PsA). Table 1 shows the patient characteristics.

Cardiovascular disease risk factors, lipids, medications and inflammatory markers were comparable among patients with RA, AS and PsA. As expected, there were more women in the RA group compared with the AS and PsA groups; 73%, 33% and 50%, respectively.

CAD prevalence and characteristics

Fifty-five (66%) patients had CAD, and the presence of CAD among the three IJD groups was 39 (74%) in the RA group, 13 (62%) in the AS group and 3 (33%) in the PsA group (p=0.13) (table 2). Twenty-nine (53%) of the patients with CAD had multivessel disease and 11 (20%) had obstructive CAD defined as ≥50% stenosis in at least one coronary segment. Conventional angiography confirmed obstructive CAD in 10 of the patients. Three of these patients were treated with percutaneous coronary intervention and the other seven did not receive any intervention after clinical consensus discussions.

Eleven of the 18 (61%) patients with chest pain had CAD, and of these, 4 (22%) had obstructive CAD. All patients with obstructive CAD had CAC ≥100. Five (46%) of these had CAC 100–399 and 6 (54%) had CAC ≥400. Thirty-three (40%) patients had CAC 0, and five (15%) of these had non-calcified plaques.

In total, plaque findings were detected in 188/874 (22%) of all segments included in the analysis, with 127 (68%) defined as calcified plaques, 51 (27%) as mixed and 10 (5%) as non-calcified.

Associations between coronary atherosclerosis and carotid plaques and cardiovascular risk factors

Patients with CAD were older (p<0.01) and more often hypertensive (p=0.01) compared with patients without CAD (online supplementary table 1). No significant differences in cardiovascular risk factors, lipids, CRP and ESR were observed between patients with and without CAD.

The number of patients with bilateral plaques was higher in the CAD group than in the group without CAD, 25 (83%) vs 5 (17%), respectively, p=0.02. The mean number of plaques in the carotid arteries in the CAD group was 2.1±1.2 vs 1.4±0.8 (p<0.01) in those without CAD. There was a difference in mean c-IMT (0.77±0.16 mm vs 0.64±0.11 mm, p<0.01) and carotid plaque height (2.03±0.53 mm vs 1.75±0.43 mm, p=0.02) between those with or without CAD (figure 1). No significant differences were observed between the three IJD entities.

Table 3 presents the associations between CAD and cardiovascular risk factors including the carotid atherosclerosis characteristics. Age (OR: 1.21, 95%CI:1.08-1.35), mean c-IMT (OR:1.06, 95%CI:1.00-1.12)and mean carotid plaque height (OR: 5.35, 95CI:1.29-22.18) were significantly associated with CAD in a multivariate analysis.

Table 4 shows risk prediction models for diagnostic accuracy of CAD. Models A–F are univariate analyses with cut-off values for the associated variables age, c-IMT and carotid plaque height. Models G and F are multivariate models with various combinations of the cut-off values.

The strongest associated univariate models had the following cut-off values: age ≥55 years (OR 17.33, 95% CI 4.36 to 68.87) (model A), c-IMT ≥0.7mm (OR 4.74, 95% CI 1.76 to 12.76) (model D) and carotid plaque height ≥1.5 mm (OR 6.93, 95% CI 1.67 to 28.79) (model E), all p<0.01. When combining these in a multivariate model (model G), the AUC was 0.832 (95% CI 0.730 to 0.935), the sensitivity 94.5% and the specificity 60.7%.

There was no correlation between carotid atherosclerosis markers (±bilateral carotid plaques, number of

Table 1 Patient characteristics*

	IJD (n=86)	RA (n=55)	AS (n=21)	PsA (n=10)	p Value†
Age, years	60.8±8.5	62.2±8.6	58.8±8.3	57.2±7.6	0.11
Women, n (%)	52 (60.5)	40 (72.7)	7 (33.3)	5 (50.0)	0.01
Disease duration (years), median (IQR)	16 (8.0–25.0)	16 (7.0–22.3)	21 (9.5–28.0)	11.5 (1.5–29.5)	0.19
BMI, kg/m^2	25.3±3.2	25.0±2.6	25.4±2.6	26.4±3.7	0.44
Waist circumference, cm	91.4±11.1	90.4±8.6	91.6±8.6	96.8±11.3	0.24
Systolic BP, mm Hg	144±19	144±20	145±13	145±25	0.94
Diastolic BP, mm Hg	84±9	83±9	85±9	87±11	0.53
Hypertension, n (%)	51 (59.3)	32 (58.2)	14 (66.7)	4 (40.0)	0.76
Diabetes mellitus, n (%)	6 (7.0)	4 (7.3)	2 (9.5)	0 (0.0)	0.60
Smoking, n (%)	16 (18.6)	11 (20.0)	3 (14.3)	2 (20.0)	0.80
Family history of cardiovascular disease, n (%)	12 (14.5)	8 (14.5)	1 (4.8)	3 (30.0)	0.57
Previous cardiovascular disease, n (%)	9 (10.5)	6 (10.9)	3 (14.3)	0 (0.0)	0.47
Angina pectoris, n (%)	18 (20.9)	12 (28.6)	6 (28.6)	0 (0.0)	0.33
Hyperlipidaemia, n (%)	55 (64.0)	33 (60.0)	15 (71.4)	7 (70.0)	0.37
Lipids					
Total cholesterol, mmol/L	6.4±1.1	6.4±1.2	6.3±0.9	6.5±1.1	0.88
HDL cholesterol, mmol/L	1.7±0.5	1.8±0.5	1.5±0.5	1.6±0.5	0.07
LDL cholesterol, mmol/L	4.1±1.0	4.0±1.1	4.1±0.9	4.2±1.0	0.80
Triglycerides (mmol/L), median (IQR)	1.2 (0.9–1.8)	1.1 (0.9–1.6)	1.6 (1.1–2.1)	1.1 (0.7–2.9)	0.23
Medications					
Synthetic DMARDs, n (%)	48 (63.2)	34 (68.0)	6 (31.6)	9 (90.0)	0.95
Biologic DMARDs, n (%)	26 (34.2)	16 (32.0)	6 (31.6)	5 (50.0)	0.38
Inflammatory markers					
ESR (mm/hour)	14.4±9.3	15.3±9.6	12.1±9.8	13.9±6.0	0.42
CRP (mg/L), median (IQR)	2.0 (1.0–4.0)	3.0 (1.0–4.0)	1.0 (1.0–5.0)	2.5 (1.8–6.5)	0.39

Hypertension, ≥140 mm Hg systolic, hyperlipidaemia: total cholesterol ≥6.0 mmol/L.
*Values expressed as mean±SD, unless indicated otherwise.
†Data compared by analysis of variance.
AS, ankylosing spondylitis; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; ESR, erythrocyte sedimentation rate; HDL, high-density lipoprotein; IJD, inflammatory joint disease; LDL, low-density lipoprotein; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

carotid plaques, mean c-IMT and carotid plaque height) and variables representing extent (CAC, segment involvement score) or severity (segment stenosis score).

DISCUSSION

In this study, the majority of the patients with IJD and established carotid artery plaques had CAD. Calcified coronary plaques were most frequently present, but approximately 40% of the patients had mixed and/or soft plaques. We assessed the associations between carotid and coronary plaques. The findings suggest that presence of carotid artery plaque is not alone sufficient for identifying patients with CAD, but a combination of carotid plaque measurements may increase the detectability of these patients.

To our knowledge, only one study has reported on CAD in patients with IJD assessed by CCTA. Karpouzas *et al* detected a similar prevalence of CAD (71%) in a population consisting of patients with RA without pre-examined carotid arteries or chest pain.[22] Considering that all patients had carotid plaque(s), CAD was expected to be more frequent in our study; however, the prevalence of CAD in patients with IJD without carotid plaques is not fully elucidated. Although patients with RA with carotid plaques are at higher risk for acute coronary syndrome, there is still a lack of knowledge of early detection of atherosclerosis and its development towards a myocardial

Table 2 CCTA findings in inflammatory joint diseases

CCTA findings		All (n=83)	RA (n=53)	AS (n=21)	PsA (n=9)	p Value*
CAD, n (%)		55 (66.3)	39 (73.6)	12 (61.9)	3 (33.3)	0.13
Obstructive CAD, n (%)		11 (13.3)	6 (54.5)	5 (45.5)	0 (0.0)	0.46
CAC, mean±SD (n=86)		204.7±370.6	199.4±344.0	281.1±485.0	57.1±93.5	0.43
Segment involvement score, mean±SD		2.2±2.7	2.2±2.5	3.1±3.3	0.9±1.5	0.14
Segment stenosis score, mean±SD		2.4±3.3	2.3±3.2	3.6±4.0	0.5±1.3	0.08
Plaque composition	Calcified, n (%)	45 (54.2)	31 (58.5)	11 (55.0)	3 (30.0)	0.56
	Mixed, n (%)	26 (31.3)	15 (28.3)	9 (45.0)	2 (20.0)	0.68
	Soft, n (%)	10 (12.0)	6 (11.3)	4 (20.0)	0 (0.0)	0.34

*Data compared using analysis of covariance (adjusted for sex, age and systolic blood pressure).
AS, ankylosing spondylitis; CAC, coronary artery calcification; CAD, coronary artery disease; CCTA, coronary CT angiography; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

infarction. Interestingly, one-third of the patients in our study did not have CAD, despite having carotid artery plaque. This demonstrates that presence of carotid plaque alone is not sufficient to identify patients at risk for CAD.

The present study suggests both c-IMT and carotid plaque height as significantly associated variables with CAD. However, there is a disagreement in the literature regarding the value of c-IMT with concerns regarding lack of standardisation of definitions and measurements, in addition to high variability and low reproducibility.[23] Measurements of c-IMT were removed from the AHA guidelines in the assessment of cardiovascular risk in 2013.[24] However, c-IMT in combination with carotid plaque measurements is recommended as a risk modifier in some cases.[23] The value of c-IMT in patients with subclinical atherosclerosis regarding cardiovascular disease risk assessment is still unclear.[25]

In the risk prediction models in the present study, age was the variable that showed the strongest association with CAD. Age also had the largest effect on sensitivity. Model G (cut-off values of ≥0.7 mm for c-IMT and ≥1.5 mm for carotid plaque height) resulted in the highest sensitivity (95%). Sensitivity represents the most crucial value for CAD not to be overlooked; however, a good diagnostic tool also needs a high specificity. The specificity of the aforementioned model was only 61%, which suggests a fairly high rate of false positives. The low specificity in our model can be explained by lack of power, including only 28 patients without CAD in the analysis. Model C was tested with a cut-off for c-IMT of ≥0.9 mm, which according to European guidelines is considered abnormal.[23] Interestingly, this model turned out insignificant. We cannot exclude that this is due to a few number of patients having c-IMT ≥0.9 mm in our study. However, there is a small difference between the models and due to the limitations on c-IMT, clinical applicability may be difficult. Still, the results in our study may support the use of ultrasound (c-IMT and plaque height) in cardiovascular disease risk stratification of patients with IJD, and thus further studies on larger cohorts are warranted.[5] Risk prediction models are used in clinical decision-making, and can also be helpful in order to provide patients with information and help to make informed choices regarding their health and treatment. Such models may well improve the diagnostic accuracy for prediction of CAD; nevertheless,

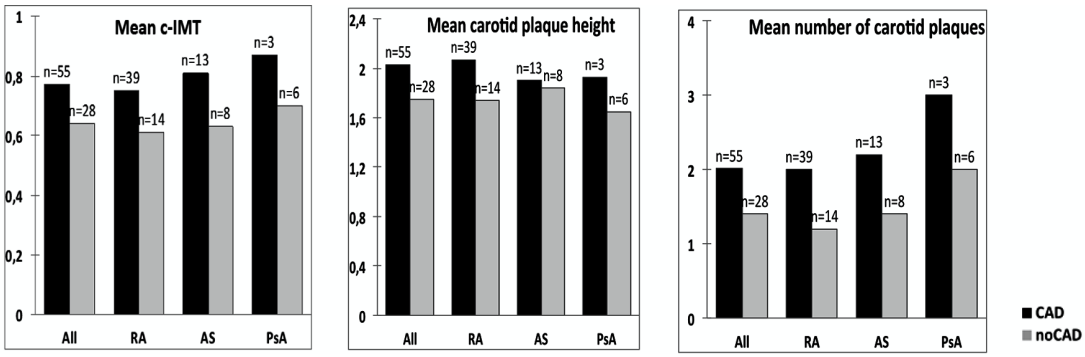


Figure 1 Difference in carotid atherosclerosis measurements (c-IMT, plaque height, number of carotid plaques) between patients with and without CAD. X^2 analysis including all patients (n=83): mean c-IMT; p<0.01, mean carotid plaque height; p=0.02 and mean number of carotid plaques; p=0.01. AS, ankylosing spondylitis; c-IMT, carotid-intima media thickness; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Table 3 Correlation of coronary artery disease and risk factors

	Univariate		Multivariate	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Sex	−0.03 (0.41 to 2.61)	0.95	0.58 (0.14 to 2.42)	0.46
Age	0.21 (1.12 to 1.37)	<0.01	1.21 (1.08 to 1.35)	<0.01
Hypertension	1.25 (1.31 to 9.26)	0.02		
DMARDs	−0.05 (0.35 to 2.56)	0.92		
Biological DMARDs	−0.89 (0.15 to 1.11)	0.08		
Bilateral plaques	1.34 (1.27 to 11.55)	0.02		
Number of carotid plaques	0.66 (1.12 to 3.37)	0.02		
Mean c-IMT	1.07 (1.03 to 1.12)	<0.01	1.06 (1.00 to 1.12)	<0.05
Carotid plaque height	1.37 (1.14 to 13.44)	0.03	5.35 (1.29 to 22.18)	0.02

Logistic regression analyses. Hypertension (≥140 mm Hg systolic).
c-IMT, carotid-intima media thickness; DMARDs, disease-modifying antirheumatic drugs.

they are statistical models that require proof of predictive values for cardiovascular events before they are applied in clinical practice.

Identifying patients in need for further cardiac evaluation would probably be of higher clinical value than solely identifying the presence of CAD. Non-obstructive CAD is an indication for prophylactic drug therapy, and the presence of carotid artery plaque alone is an indication for statin treatment. We found no correlation between variables representing extent (CAC and segment involvement score) and severity (segment stenosis score) of CAD and the carotid atherosclerosis variables (c-IMT, plaque height and bilateral plaques). These results suggest that these variables may not be useful for identification of extent and severity of CAD. On the other hand, we cannot exclude the possibility that these lacking correlations may represent statistical type II errors considering that we only had 11 patients with obstructive CAD and an all-over low segment stenosis score.

CAC and CCTA have been reported to have a prognostic value for predicting future coronary events in various cohorts[26–28]; however, the clinical value in asymptomatic individuals needs to be clarified. Corrales *et al* found a correlation between CACs and c-IMT in 95 patients with RA, but their conclusion was, however, that carotid ultrasonography was more sensitive than CACs for the detection of subclinical atherosclerosis.[29] No trial has reported on improved outcome due to screening for CAD in asymptomatic individuals, and previous studies do not recommend CCTA screening

Table 4 Risk prediction models for coronary artery disease using cut-off values

		OR (95% CI)	p Value	Sensitivity	Specificity	AUC (95% CI)
A	Age ≥55 years	17.33 (4.36 to 68.87)	<0.01*	94.5%	50.0%	0.723 (0.595 to 0.850)
B	Age ≥60 years	7.31 (2.60 to 20.58)	<0.01*	70.9%	75.0%	0.730 (0.613 to 0.846)
C	Mean c-IMT ≥0.9 mm	5.28 (0.63 to 44.01)	0.12*	100.0%	0.0%	0.564 (0.437 to 0.691)
D	Mean c-IMT ≥0.7 mm	4.74 (1.76 to 12.76)	<0.01*	65.5%	71.4%	0.684 (0.563 to 0.806)
E	Carotid plaque height ≥1.5 mm	6.93 (1.67 to 28.79)	<0.01*	94.5%	28.6%	0.616 (0.481 to 0.751)
F	Carotid plaque height ≥2.0 mm	2.27 (0.79 to 6.50)	0.13*	100.0%	0.0%	0.584 (0.456 to 0.711)
G	Age ≥55 years	12.18 (2.80 to 53.05)	<0.01†	94.5%	60.7%	0.832 (0.730 to 0.935)
	+Mean c-IMT ≥0.7 mm	4.08 (1.20 to 13.89)	0.02†			
	+Carotid plaque height ≥1.5 mm	8.96 (1.68 to 47.91)	0.01†			
H	Age ≥55 years	20.29 (3.82 to 107.90)	<0.01†	92.7%	64.3%	0.866 (0.781 to 0.950)
	+Mean c-IMT ≥0.8 mm	14.98 (2.11 to 106.23)	<0.01†			
	+Carotid plaque height ≥1.5 mm	4.50 (0.95 to 21.41)	0.06†			

*Univariate logistic regression analysis with CAD as the dependent variable.
†Multivariate logistic regression analysis.
AUC, area under the curve; c-IMT, carotid-intima media thickness.

of high-risk patient groups without cardiac symptoms. An aspect is that CCTA has shown to have relatively high false-positive findings due to an overestimation of the degree of stenosis in the presence of large calcified plaques.[30] We cannot exclude the possibility that the high amount of CAC in this study may have led to an overestimation of the stenoses measurements. Another consequence of performing CCTA in patients with high CAC may be an increase in complimentary, unnecessary invasive angiographic procedures, which involves exposure to radiation, use of contrast, costs and possible complications.

Finally, the main limitation to this study is the absence of a control group, thereby CAD in patients without any carotid artery plaque remains an unknown factor. This may have influenced our results and we cannot exclude that the correlation between CAD and the carotid atherosclerosis markers could have been different. We mainly included patients with RA, and the low number of patients in the other groups precludes any further conclusions regarding similarities or differences between the three IJD groups.

Another limitation is the cross-sectional design, which excludes the possibility to evaluate the impact of both carotid and coronary plaques on cardiovascular events in patients with IJD. Studies with longitudinal design are needed to evaluate the clinical value of CCTA and detection of early atherosclerosis in patients with IJD.

In conclusion, our results contribute to the documentation on coronary atherosclerosis in patients with IJD. Our findings suggest that carotid plaque alone is not sufficient to identify patients at risk for CAD. The correlation of c-IMT and carotid plaque height with CAD generates a hypothesis that these parameters may be potential useful markers in cardiovascular disease risk stratification in patients with IJD, and a combination of the variables increases the detectability of patients with CAD. This further supports the use of ultrasound of the carotid arteries in cardiovascular disease risk evaluation in this patient group.[9] Further studies are needed to evaluate the clinical value of carotid ultrasonography measurements and also CCTA in risk prediction of future coronary artery events in patients with IJD.

Acknowledgements We are grateful to Anne Stormyr Eirheim for performing ultrasound of the carotid arteries, and to Cecilie Okkenhaug for the laboratory procedures.

Contributors AGS, SR and EI were responsible for the study design. All authors were responsible for the data acquisition. MS, SR, EI, AGS and YH analysed the data. MS wrote the first draft. All authors critically revised the manuscript and approved the final version. AGS and YH share last authorship.

Funding This study has received funding from the South-Eastern Regional Health Authority of Norway.

Competing interests None declared.

Patient consent Obtained.

Ethics approval South-Eastern Regional Ethics Committee, Norway.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement MS, SR and AGS have access to all the data.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1. Han C, Robinson DW, Hackett MV, *et al*. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *J Rheumatol* 2006;33:2167–72.
2. Tobin AM, Veale DJ, Fitzgerald O, *et al*. Cardiovascular disease and risk factors in patients with psoriasis and psoriatic arthritis. *J Rheumatol* 2010;37:1386–94.
3. Lindhardsen J, Ahlehoff O, Gislason GH, *et al*. The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. *Ann Rheum Dis* 2011;70:929–34.
4. Maradit-Kremers H, Nicola PJ, Crowson CS, *et al*. Cardiovascular death in rheumatoid arthritis: a population-based study. *Arthritis Rheum* 2005;52:722–32.
5. Rollefstad S, Ikdahl E, Hisdal J, *et al*. Association of Chest Pain and Risk of Cardiovascular Disease with Coronary Atherosclerosis in Patients with Inflammatory Joint Diseases. *Front Med* 2015;2:80.
6. Crowson CS, Gabriel SE. Towards improving cardiovascular risk management in patients with rheumatoid arthritis: the need for accurate risk assessment. *Ann Rheum Dis* 2011;70:719–21.
7. Perk J, De Backer G, Gohlke H, *et al*. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Atherosclerosis* 2012;223:1–68.
8. Corrales A, González-Juanatey C, Peiró ME, *et al*. Carotid ultrasound is useful for the cardiovascular risk stratification of patients with rheumatoid arthritis: results of a population-based study. *Ann Rheum Dis* 2014;73:722–7.
9. Semb AG, Ikdahl E, Hisdal J, *et al*. Exploring cardiovascular disease risk evaluation in patients with inflammatory joint diseases. *Int J Cardiol* 2016;223:331–6.
10. Budoff MJ, Dowe D, Jollis JG, *et al*. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;52:1724–32.
11. Arbustini E, Dal Bello B, Morbini P, *et al*. Plaque erosion is a major substrate for coronary thrombosis in acute myocardial infarction. *Heart* 1999;82:269–72.
12. van Velzen JE, Schuijf JD, de Graaf FR, *et al*. Diagnostic performance of non-invasive multidetector computed tomography coronary angiography to detect coronary artery disease using different endpoints: detection of significant stenosis vs. detection of atherosclerosis. *Eur Heart J* 2011;32:637–45.
13. Evans MR, Escalante A, Battafarano DF, *et al*. Carotid atherosclerosis predicts incident acute coronary syndromes in rheumatoid arthritis. *Arthritis Rheum* 2011;63:1211–20.
14. Rollefstad S, Ikdahl E, Hisdal J, *et al*. Rosuvastatin-Induced Carotid Plaque Regression in Patients With Inflammatory Joint Diseases: The Rosuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and Other Inflammatory Joint Diseases Study. *Arthritis Rheumatol* 2015;67:1718–28.
15. Klass O, Kleinhans S, Walker MJ, *et al*. Coronary plaque imaging with 256-slice multidetector computed tomography: interobserver variability of volumetric lesion parameters with semiautomatic plaque analysis software. *Int J Cardiovasc Imaging* 2010;26:711–20.
16. Austen WG, Edwards JE, Frye RL, *et al*. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation* 1975;51(4 Suppl):5–40.

17. Agatston AS, Janowitz WR, Hildner FJ, *et al*. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827–32.
18. Raff GL, Chinnaiyan KM, Cury RC, *et al*. SCCT guidelines on the use of coronary computed tomographic angiography for patients presenting with acute chest pain to the emergency department: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr* 2014;8:254–71.
19. Roman MJ, Naqvi TZ, Gardin JM, *et al*. Clinical application of noninvasive vascular ultrasound in cardiovascular risk stratification: a report from the American Society of Echocardiography and the Society of Vascular Medicine and Biology. *J Am Soc Echocardiogr* 2006;19:943–54.
20. Semb AG, Rollefstad S, Provan SA, *et al*. Carotid plaque characteristics and disease activity in rheumatoid arthritis. *J Rheumatol* 2013;40:359–68.
21. Touboul PJ, Hennerici MG, Meairs S, *et al*. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. *Cerebrovasc Dis* 2012;34:290–6.
22. Karpouzas GA, Malpeso J, Choi TY, *et al*. Prevalence, extent and composition of coronary plaque in patients with rheumatoid arthritis without symptoms or prior diagnosis of coronary artery disease. *Ann Rheum Dis* 2014;73:1797–804.
23. Piepoli MF, Hoes AW, Agewall S, *et al*. European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis* 2016;2016:207–74.
24. Goff DC, Lloyd-Jones DM, Bennett G, *et al*. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 20142014;63(25 Pt B):2935–59;63(25 Pt B):2935–59.
25. van den Oord SC, Sijbrands EJ, ten Kate GL, *et al*. Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis. *Atherosclerosis* 2013;228:1–11.
26. Blanke P, Naoum C, Ahmadi A, *et al*. Long-Term Prognostic Utility of Coronary CT Angiography in Stable Patients With Diabetes Mellitus. *JACC Cardiovasc Imaging* 2016;9:1280–8.
27. Andreini D, Pontone G, Mushtaq S, *et al*. A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. *JACC Cardiovasc Imaging* 2012;5:690–701.
28. Hulten E, Villines TC, Cheezum MK, *et al*. Usefulness of coronary computed tomography angiography to predict mortality and myocardial infarction among Caucasian, African and East Asian ethnicities (from the CONFIRM [Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter] Registry). *Am J Cardiol* 2013;111:479–85.
29. Corrales A, Parra JA, González-Juanatey C, *et al*. Cardiovascular risk stratification in rheumatic diseases: carotid ultrasound is more sensitive than Coronary Artery Calcification Score to detect subclinical atherosclerosis in patients with rheumatoid arthritis. *Ann Rheum Dis* 2013;72:1764–70.
30. Qi L, Tang LJ, Xu Y, *et al*. The Diagnostic Performance of Coronary CT Angiography for the Assessment of Coronary Stenosis in Calcified Plaque. *PLoS One* 2016;11:e0154852.

II

Effects of long-term statin-treatment on coronary atherosclerosis in patients with inflammatory joint diseases

Mona Svanteson[1,2¶*], Silvia Rollefstad[3¶], Nils-Einar Kløw[1,2], Jonny Hisdal[4], Eirik Ikdahl[3], Joseph Sexton[5], Ylva Haig[1&], Anne Grete Semb[3&]

[1]Department of Radiology and Nuclear medicine, Oslo University Hospital, Oslo, Norway
[2]Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway
[3]Preventive Cardio-Rheuma clinic, Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
[4]Department of Vascular investigations, Oslo University Hospital, Aker, Oslo, Norway
[5]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

Key words: inflammatory joint diseases, atherosclerosis, plaques, statins, computed tomography

*Corresponding Author
E-mail: monasvanteson@gmail.com (MS)

¶ Shared first authors.
& Joint Senior Authors

Abstract

Background: The effect of statins over time on coronary atherosclerosis in patients with inflammatory joint diseases (IJD) is unknown. Our aim was to evaluate the change in coronary plaque morphology and volume in long-term statin-treated patients with IJD.

Methods: Sixty-eight patients with IJD and carotid artery plaque(s) underwent coronary computed tomography angiography before and after a mean of 4.7 (range 4.0-6.0) years of statin treatment. The treatment target for low density lipoprotein cholesterol (LDL-c) was ≤1.8 mmol/L. Changes in plaque volume (calcified, mixed/soft and total) and coronary artery calcification (CAC) from baseline to follow-up were assessed using the 17-segment American Heart Association-model.

Results: Median (IQR) increase in CAC after statin treatment was 38 (5-236) Agatston units ($p<0.001$). Calcified and total plaque volume increased with 5.6 (0.0-49.1) and 2.9 (0.0-23.5) mm^3, respectively ($p<0.001$ for both). The median (IQR) change in soft/mixed plaque volume was -10 (-7.1-0.0), p=<0.001. , Patients who had obtained the LDL-c treatment target at follow-up, experienced reduced progression of both CAC and total plaque volume compared to patients with LDL-c >1.8mmol/L (21 [2-143] vs. 69 [16-423], p=0.006 and 0.65 [-1.0-13.9] vs. 13.0 [0.0-60.8] mm^3, p=0.019, respectively).

Conclusions: A progression of total atherosclerotic plaque volume in statin-treated patients with IJD was observed. However, soft/mixed plaque volume was reduced, suggesting an alteration in plaque composition. Patients with recommended LDL-c levels at follow-up had reduced atherosclerotic progression compared to patients with LDL-c levels above the treatment target, suggesting a beneficial effect of treatment to guideline-recommended lipid targets in IJD patients.

Introduction

Patients with inflammatory joint diseases (IJD) have an increased risk of acute coronary syndrome [1]. Lipid-lowering treatment with statins is considered as highly effective prophylaxis for coronary artery disease in the general population due to improvements of both lipid-profiles and clinical outcome [2, 3]. Evidence regarding statin treatment in IJD patients is scarce, but promising results from post hoc analyses in 2 randomized controlled statin trials (TNT and IDEAL) revealed comparable lipid lowering effect and risk reduction for future cardiovascular disease (CVD) in patients with and without IJD [4]. Despite this, inadequate preventive treatment with statins has been reported in patients with IJD [5, 6]. In addition to lowering lipids, statins have been shown to possess anti-inflammatory effects [7]. Other positive plaque-related effects such as cell death in the lipid cores and plaque-stabilization due to micro-calcifications have also been described [8, 9]. Whether these statin effects will occur in patients with IJD is uncertain, due to the underlying systemic inflammation, the lipid increasing effect of anti-rheumatic medications and the polypharmacy these patients have [10]. Inflammation is part of the atherogenesis [11], and elevated inflammation as measured by CRP has been shown be a predictor of increased atherogenesis with clinical outcomes [12]. Assessments of plaque morphology are important and of great interest since non-calcified atherosclerotic plaques are more likely to result in acute coronary syndrome than the more stable calcified plaques [13].

Coronary computed tomography angiography (CCTA) has become an established non-invasive method for detection of coronary artery stenosis [14]. It is also a promising and increasingly used tool for characterization of coronary plaques with good correlation to intravascular ultrasound [15]. Statin-treatment has been shown by CCTA to induce regression of coronary plaques in patients without IJD [16], in addition to a slower

progression of coronary plaque volume in patients with low LDL-c level [17]. Increased coronary artery calcifications (CAC) have also been reported after statin treatment in the general population [18]. Taking into consideration that patients with IJD have high systemic inflammation and that disease activity has been shown to have an impact on carotid artery plaque composition [19] further warrants evaluation of the statin effect on atherosclerotic plaques in patients with IJD.

The aims of the present study were to evaluate the progression of coronary atherosclerosis/plaques after long-term statin-treatment in patients with IJD, and the effect on plaque morphology evaluated by CCTA. Furthermore, we assessed possible predictors of plaque progression, including patient characteristics, lipids and inflammatory markers.

Materials and methods

Patients and study design

The RORA-AS study (ROsuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and other inflammatory joint diseases) was an open, prospective intervention study, and a complete description of inclusion and exclusion-criteria has previously been reported [20]. In short, IJD patients with ultrasound-verified carotid plaque(s) were treated with rosuvastatin with an LDL-c target of ≤1.8 mmol/L, in accordance with the most recent European guidelines [21]. All patients signed an informed consent and the study was approved by the Norwegian South East Regional Committee for Medical and Health Research Ethics and registered with ClinicalTrials.gov Id: NCT01389388. The European Union Drug Regulating Authorities Clinical Trials (EudraCT) number is 2008-005551-20.

CCTA was performed for study purposes in 68 statin-naïve patients with IJD and carotid artery plaques between 2010 and 2012 with a follow-up CCTA in 2016. The follow-up time was prolonged compared to study protocol, due to lack of time available on the scanner. Patients with reduced kidney function (estimated glomerular filtration rate of <45 ml/minute), arrhythmias, previous coronary artery bypass surgery, stents or pacemaker-implantation were excluded. All patients filled in a questionnaire at baseline and follow-up for assessment of characteristics, symptoms of coronary disease and medications. Changes in lipid-profiles and inflammatory parameters were evaluated by laboratory tests drawn and analyzed at Diakonhjemmet Hospital using a COBAS 6000 and COBAS 8000, Roche Diagnostics Norway AS.

Medications

After baseline CCTA, all patients received rosuvastatin, with dose titration to achieve an LDL-c goal of ≤1.8mmol/L. The lipids were frequently monitored for the first 18 months. Due to national regulations the lipid lowering medication was switched to atorvastatin after the first 18 months unless there was a specific reason to continue rosuvastatin treatment, such as side effects or inadequate lipid lowering effect with other statins. After 18 months the patient was followed by the primary care physician who had received a discharge report including specification of diagnosis, present medication use, LDL-c goal and follow-up recommendations.

Imaging technique

All baseline and follow-up CCTA examinations were performed on a Philips Brilliance 64-slice CT scanner (Philips Healthcare, Cleveland, Ohio, USA) with protocols as previously described [22]. Initially, a non-contrast scan was conducted for evaluation of CAC. If tolerated, intravenous beta blockage (5-20 mg Seloken®, Astra Zeneca) was used to reduce the heart

rhythm and Nitroglycerin 0.4mg (Nitrolingual®, Pohl-Boskamp, Hohenlockstedt, Germany) was administered for the vasodilating effect sublingually 1-3 minutes prior to the contrast-enhanced scan. Prospective ECG-gating was used when achieving a heart rate ≤ 65 beats/min (bpm), while retrospective ECG-gating was required for higher heartrates. The contrast media Omnipaque™ 350 mg/ml (GE Healthcare, Princeton, New Jersey) was used in both the baseline and follow-up examinations.

Image analysis

The image analyses were performed on a Philips Workstation (Intellispace v5, Philips Healthcare) with dedicated software (Plaque Analysis, Comprehensive Cardiac, Philips Healthcare) [23]. The inter-observer variability was calculated on a per-segment level after two independent readers blinded to patient characteristics measured the plaque volume in left ascending artery in 30% of the patients, with an interclass correlation coefficient 0.92. The same segments were evaluated twice by one reader with an intra-observer variability of 0.93. The analyses were assessed using the 17-segment model of the American Heart Association [24]. All segments with sufficient image quality and a diameter >1.5 mm were included in the analyses.

CAC was calculated by the Agatston method [25]. The morphology of the plaques was defined according to plaque density, measured with Hounsfield Units (HU). Plaques were defined as calcified if ≥90% of the total volume had a density ≥130 HU, and soft when ≥10% had a density of ≥130HU. Mixed plaques were all in between [23]. Coronary artery disease (CAD) was defined as “presence of any plaque.” Segment involvement score (SIS) and segment stenosis score was used to assess extent and severity of the CAD with previously described definitions [22].

Statistical analysis

Descriptive data are presented with number (%) for dichotomized variables, mean±standard deviation (SD) for normally distributed characteristics or median with interquartile range (IQR) if not normally distributed. Analysis of variance and X^2 were used to compare variables between groups. The paired samples t-test was applied in assessment of changes in variables from baseline to follow-up. The Wilcoxons signed rank test was used for non-normally distributed variables.

Independent samples t-test was used to test the difference in atherosclerotic change between patients with obtained and non-obtained LDL-c goal at follow-up. Non-normally distributed variables were log-transformed before these analyses were conducted.

Linear regression models were constructed to assess predictors of change in plaque volumes and CAC. Correlated variables (patient characteristics, risk factors and lipids) with a stronger correlation than 0.2 (Pearsons correlation coefficient) or of especially clinical relevance were included in the model, and a stepwise backwards approach was chosen.

For further evaluation of atherosclerotic progression, we arbitrary divided the change in total plaque volume into percentiles (25%, 50% and 75%). Differences were evaluated with analysis of variance. Multiple logistic regression was used to identify predictors for $<25^{th}$ percentile and $>75^{th}$ percentile. All analyses were performed using IBM SPSS version 21.

Results

Of the 83 patients initially included at baseline, 15 patients were lost to follow up; 2 due to insufficient renal function, 1 due to pacemaker-implantation, 1 had a coronary artery bypass surgery, 1 due to severe chronic disease, 1 because of screening failure (no presence of carotid artery plaque at baseline) and 9 did not want to participate (Fig 1). Evaluations from

the remaining 68 patients are included in the analyses. Mean follow-up time was 4.7 (range 4.0-6.0) years.

Table 1 presents the patient characteristics at baseline. Two-thirds of the patients had RA (66%), and the majority of these patients were females (64%). Mean age was 60.5±8.6 years. Only a few patients had diabetes mellitus (6%) or previous CVD (10%), but other risk factors of CVD were prevalent; hypertension (47%), hyperlipidemia (64%) and smoking (22%).

CAD was detected in 42 (62%) patients at baseline, compared to 51 (75%) at follow-up. In total, atherosclerotic plaques were present in 133 of 913 (14.6%) segments at baseline compared to 203 of 874 (23.2%) at follow-up. Forty-six (34.6%) of the plaques were defined as mixed or soft at baseline compared to 16 (7.9%) at follow-up.

The atherosclerotic progression is shown in Table 2. Median (IQR) increase in CAC increase was 38(5-236) Agatston units ($p<0.001$). Calcified and total plaque volume increased with 5.6 (0.0-49.1) and 2.9(0.0-23.5) mm3, respectively ($p<0.001$ for both). The median (IQR) change in soft/mixed plaque volume was -10 (-7.1-0.0), p=<0.001. Regarding lipids, all levels were reduced except for high density lipoprotein cholesterol (HDL-c), as expected. The inflammatory markers were comparable at baseline and follow-up. Both segment involvement score and segment stenosis score increased ($p<0.001$ for both).

Fig 2 shows the mean change in plaque volume in the 3 IJD groups. The ankylosing spondylitis (AS) group had a larger reduction in soft/mixed plaque volume, and more extensive increase in calcified and total plaque volume than RA and psoriatic arthritis (PsA) patients.

At follow-up, 34 (50%) of the patients had an LDL-c level below study target (≤1.8mmol/L). Table 3 shows the difference in the CCTA-measurements between patients

with an LDL-c level above or below 1.8mmol/l at follow-up. The change in CAC, calcified plaque volume and total plaque volume was reduced in the group with an LDL-c ≤1.8 mmol/L. The reduction in soft/mixed plaque volume was numerically larger in the group with LDL-c-level above treatment target, although this difference was not statistically significant (p=0.71).

An LDL-c level >1.8mmol/l was associated with change in CAC (model A) and change in total plaque volume (model B), after adjusting for age and sex, but was not significantly associated with change in soft/mixed plaque volume (model C) (Table 4).

S1 Fig shows a near linear relationship between change in total mixed/soft plaque volume per patient and baseline mixed/soft plaque volume (R=0.898).

Fig 3 presents the difference in HDL-c, LDL-c, triglycerides and age between the percentiles of change in total plaque volume, with no significant difference between the groups. However, in the multiple logistic regression analysis, the HDL-c level at follow up was associated with <25th percentile (<2.9 mm^3) increase in total plaque volume, OR (95%CI): 3.36 (1.16-9.74), p=0.029, after adjusting for age and sex. In addition, LDL-c (OR: (95%CI): 1.3 (1.2-11.0), p=0.022) was associated with the >75th percentile (>23.5mm^3) of change in total plaque volume after adjusting for sex and age. All patients with ≥400 CAC increase had an LDL-c-level at follow-up above the treatment target.

The correlation between biologic DMARD-use and change in CAC, total plaque volume, soft/mixed plaque volume and calcified volume were: r=-0.14 (p=0.28), r=0.12 (p=0.36), r=0.03 (p=0.81) and r=-0.02 (p=0.88), respectively.

Discussion

In this study, we have shown that a progression of coronary atherosclerosis in statin-treated patients with IJD occurs after nearly 5 years of statin treatment. However, an increase in calcified plaque volume and a decrease in soft/mixed plaque volume suggested a conversion in plaque-composition. We also revealed that LDL-c-levels were associated with atherosclerotic progression in the sense that the patients who obtained LDL-c treatment target experienced a more moderate progression of atherosclerotic plaque volume compared to those with LDL-c-levels above the LDL-c treatment target of 1.8 mmol/L. To our knowledge, this is the first study to assess the effects of statin-treatment on coronary plaques in patients with IJD.

The CAC increased significantly from baseline to follow-up. CAC has a well-documented prognostic value for future cardiac events, and a linear relationship between CAC and CVD risk has been established [26-28]. CAC has been shown to be a greater determinant of atherosclerotic progression than traditional risk-factors, sex or age in asymptomatic individuals [29]. However, the relationship of CAC progression and events has not been fully elucidated in statin users [30]. Puri *et al.* described that an increase in CAC induced by statins had a positive plaque-stabilizing effect due to induction of micro-calcifications [8]. Shaw et al. suggested that CAC may loose its predictive value after initiation of plaque-altering therapies such as statins [30]. From the MESA-study [31] it was reported an inverse association between plaque density and risk of CVD events, suggesting that denser plaques may be protective for CVD events. Whether the increased CAC in our study was a marker for healing of plaques (induced by statins) or for progression of disease, is difficult to interpret. However, the volume measurements add valuable information to this evaluation, as the total plaque volume also increased significantly in our study. If the

increased CAC was solely due to statin-treatment, the volume may not increase significantly and thus, one may argue that the CAC increase in our study is, most likely, an effect caused by both plaque-stabilizing and disease progression.

Another important finding is the reduction in mixed/soft plaques from baseline to follow-up. The presence of soft plaques has been reported to be an independent predictor for acute coronary syndromes [32], and a reduction of soft/mixed plaque is likely to be beneficial for the patient. Previous studies have reported on a difference in plaque morphology between statin users and non-statin users [33]. Further, statins have shown a greater impact on the morphology of non-calcified/partially calcified plaques than on solely calcified plaques [34].

Interestingly, we observed a significantly lower progression of both CAC and plaque volume among the patients who maintained LDL-c-levels of ≤1.8 mmol/l at follow-up. The latter finding is in line with results from a 10-year follow-up study by Goh *et al.*, showing a slower progression of CAC in patients on aggressive statin treatment regimens [35]. Two other studies have found reduced progression of plaque volume additionally to CAC in patients who achieved lower LDL-c-levels [17, 36]. Zeb *et. al* found a slower progression in non-calcified atheroma after 1 year follow-up in statin-users compared to non-statin-users [37]. A recently published study, described a significant association between individual lipoprotein variability and coronary atheroma progression and also to adverse CVD events [38]. We did not manage to detect a significant difference in regression/progression in soft/mixed plaque volume in those with an LDL-c level above vs. below the LDL-c treatment target. However, there was a near linear relationship between the regression of the volume of mixed/soft plaque and mixed/soft plaque at baseline (S1 Fig). Thus, the group with the largest burden of soft/mixed plaques at baseline experienced most regression/alteration (i.e.

those with LDL-c >1.8mmol/l). This finding might be influenced by the "regression towards the mean-"phenomenon. However; the number of soft/mixed plaques was also significantly reduced. Fig 2 shows more plaque alterations/regression of soft/mixed plaque in the AS-group compared to the RA and PsA groups. The AS-group consisted of more males in comparison with the RA and PsA groups, which may explain the higher presence of more soft/mixed plaque at baseline.

In our study, LDL-c and HDL-c-levels in addition to age turned out as important predictors of atherosclerotic progression. The significant association between LDL-c level and progression of both CAC and total plaque volume was maintained after adjusting for sex and age in multivariate analyses. Along the same lines, the LDL-c level was predictive of the patient ending up with a total plaque volume above the 75^{th} percentile, suggesting that the LDL-c level also plays an important role in plaque progression in patients with IJD. Moreover, a higher HDL-c-level was a predictor for having a small increase in total plaque volume (<25^{th} percentile). This finding is consistent with previous reports on the protective effect of HDL-c on atherosclerosis [39].

Atherosclerosis is a multifactorial and complex disease in which inflammation has been shown to play an important role. The pleiotropic effect of statins has shown to also reduce the inflammation markers [7], which may be beneficial in patients with systemic inflammation. In our study, both ESR and CRP were not significantly reduced from baseline to follow-up, and neither was related to plaque progression/regression during the follow up period of 4.7 years. Furthermore, we did not find an association between markers of inflammatory disease activity at baseline and progression of CAD. The latter is probably due to the fact that the patient cohort was well treated with anti-inflammatory drugs when entering the study (mostly in remission or with low disease activity). The lack of association

between CAD and inflammatory markers in our study may therefor suffer from a type II error, as we may not have sufficient variations in these variables to detect statistically significant associations. We cannot exclude a type II error also in the negative associations to biologic DMARDS in present study. Only 13 patients were on biologic DMARDS which may have resulted in lack of power.

A clear limitation to our study is the absence of a placebo controlled arm of non-statin users, which would have been helpful in identification of plaque progression/regression caused by statins, especially the reported statin-effect on CAC progression. Furthermore, the loss of 15 patients to follow-up may have influenced our results, as the progression of atherosclerosis in these patients is unknown.

A recently published systematic review implies that CCTA has a potential role in assessment on the response of statin therapy on plaque volume and composition [40]. Such serial plaque assessments demand usage of the same software [41, 42]. In our study, plaque assessments were performed with a software previously shown to have a high degree of inter-observer variability on calcified and mixed lesions [23]. However; overestimation of calcified plaques due to blooming artifacts is a known limitation in CCTA [43]. Therefore we also evaluated CAC-score and number of plaques, with comparable results as with the volume-measurements. CAC is an established method with a high degree of reproducibility [44]. Importantly, the observer variability in our study was shown to be smaller than the actual change in plaque burden when comparing serial CT examinations [45].

After the 18 months follow-up in the study, the patients' cardiovascular preventive care was transferred to the primary care physician, who was responsible for further management of the statin-treatment. A lack of control of the medicine intake and lipid-levels in the period between 1.5 and 4.7 years may have influenced our results as we have not

measured sequential LDL-c levels at regular intervals during this period. However; we believe it is of clinical importance to evaluate the development of plaque progression and lipid profiles in a real-life, clinical setting. Interestingly, 50% of the patients maintained the LDL-c treatment target of ≤ 1.8 mmol/L during the follow up time, which is higher than reported from the general population [46].

In conclusion, we revealed a progression of atherosclerotic plaque volume in statin-treated patients with IJD. However, after long-term statin treatment the number of soft, unstable plaques was reduced, and the calcified plaques were more abundant. An explanation for this may be that statin treatment induced an alteration in plaque composition from mixed/soft plaques into calcified plaques in patients with IJD. Patients with recommended LDL-c levels below 1.8 mmol/L after nearly 5 years of statin-treatment, experienced a reduced atherosclerotic progression compared to patients with LDL-c levels above this treatment target. Our results support the importance of treatment to guideline recommended lipid targets in IJD patients. Longitudinal studies for assessment of the effect of statins and plaque morphology on CVD events in IJD patients are warranted.

References

[1] Han C, Robinson DW, Jr., Hackett MV, Paramore LC, Fraeman KH, Bala MV. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The Journal of rheumatology. 2006;33:2167-72.
[2] Hirayama A, Saito S, Ueda Y, Takayama T, Honye J, Komatsu S, et al. Qualitative and quantitative changes in coronary plaque associated with atorvastatin therapy. Circulation journal : official journal of the Japanese Circulation Society. 2009;73:718-25.
[3] MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet (London, England). 2002;360:7-22.
[4] Semb AG, Kvien TK, DeMicco DA, Fayyad R, Wun CC, LaRosa JC, et al. Effect of intensive lipid-lowering therapy on cardiovascular outcome in patients with and those without inflammatory joint disease. Arthritis and rheumatism. 2012;64:2836-46.
[5] Toms TE, Panoulas VF, Douglas KM, Griffiths H, Sattar N, Smith JP, et al. Statin use in rheumatoid arthritis in relation to actual cardiovascular risk: evidence for substantial undertreatment of lipid-associated cardiovascular risk? Annals of the rheumatic diseases. 2010;69:683-8.
[6] Ikdahl E, Wibetoe G, Rollefstad S, Salberg A, Bergsmark K, Kvien TK, et al. Guideline recommended treatment to targets of cardiovascular risk is inadequate in patients with inflammatory joint diseases. International journal of cardiology. 2019;274:311-8.
[7] Diamantis E, Kyriakos G, Quiles-Sanchez LV, Farmaki P, Troupis T. The Anti-Inflammatory Effects of Statins on Coronary Artery Disease: An Updated Review of the Literature. Current cardiology reviews. 2017;13:209-16.
[8] Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. Journal of the American College of Cardiology. 2015;65:1273-82.
[9] Zheng G, Li Y, Huang H, Wang J, Hirayama A, Lin J. The Effect of Statin Therapy on Coronary Plaque Composition Using Virtual Histology Intravascular Ultrasound: A Meta-Analysis. PloS one. 2015;10:e0133433.
[10] Choy E, Ganeshalingam K, Semb AG, Szekanecz Z, Nurmohamed M. Cardiovascular risk in rheumatoid arthritis: recent advances in the understanding of the pivotal role of inflammation, risk predictors and the impact of treatment. Rheumatology (Oxford, England). 2014;53:2143-54.
[11] Ross R. Atherosclerosis--an inflammatory disease. The New England journal of medicine. 1999;340:115-26.
[12] Ridker PM. Clinical application of C-reactive protein for cardiovascular disease detection and prevention. Circulation. 2003;107:363-9.
[13] Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. Journal of the American College of Cardiology. 2009;54:49-57.
[14] van Velzen JE, Schuijf JD, de Graaf FR, Boersma E, Pundziute G, Spano F, et al. Diagnostic performance of non-invasive multidetector computed tomography coronary angiography to detect coronary artery disease using different endpoints: detection of significant stenosis vs. detection of atherosclerosis. European heart journal. 2011;32:637-45.

[15] de Graaf MA, Broersen A, Kitslaar PH, Roos CJ, Dijkstra J, Lelieveldt BP, et al. Automatic quantification and characterization of coronary atherosclerosis with computed tomography coronary angiography: cross-correlation with intravascular ultrasound virtual histology. The international journal of cardiovascular imaging. 2013;29:1177-90.
[16] Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. Jama. 2007;297:499-508.
[17] Shin S, Park HB, Chang HJ, Arsanjani R, Min JK, Kim YJ, et al. Impact of Intensive LDL Cholesterol Lowering on Coronary Artery Atherosclerosis Progression: A Serial CT Angiography Study. JACC Cardiovascular imaging. 2017;10:437-46.
[18] Henein M, Granasen G, Wiklund U, Schmermund A, Guerci A, Erbel R, et al. High dose and long-term statin therapy accelerate coronary artery calcification. International journal of cardiology. 2015;184:581-6.
[19] Semb AG, Rollefstad S, Provan SA, Kvien TK, Stranden E, Olsen IC, et al. Carotid plaque characteristics and disease activity in rheumatoid arthritis. The Journal of rheumatology. 2013;40:359-68.
[20] Rollefstad S, Ikdahl E, Hisdal J, Olsen IC, Holme I, Hammer HB, et al. Rosuvastatin-Induced Carotid Plaque Regression in Patients With Inflammatory Joint Diseases: The Rosuvastatin in Rheumatoid Arthritis, Ankylosing Spondylitis and Other Inflammatory Joint Diseases Study. Arthritis & rheumatology (Hoboken, NJ). 2015;67:1718-28.
[21] Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European journal of preventive cardiology. 2016;23:Np1-np96.
[22] Svanteson M, Rollefstad S, Klow NE, Hisdal J, Ikdahl E, Semb AG, et al. Associations between coronary and carotid artery atherosclerosis in patients with inflammatory joint diseases. RMD open. 2017;3:e000544.
[23] Klass O, Kleinhans S, Walker MJ, Olszewski M, Feuerlein S, Juchems M, et al. Coronary plaque imaging with 256-slice multidetector computed tomography: interobserver variability of volumetric lesion parameters with semiautomatic plaque analysis software. The international journal of cardiovascular imaging. 2010;26:711-20.
[24] Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation. 1975;51:5-40.
[25] Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte JM, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. Journal of the American College of Cardiology. 1990;15:827-32.
[26] Shaw LJ, Giambrone AE, Blaha MJ, Knapper JT, Berman DS, Bellam N, et al. Long-Term Prognosis After Coronary Artery Calcification Testing in Asymptomatic Patients: A Cohort Study. Annals of internal medicine. 2015;163:14-21.
[27] Rodriguez-Granillo GA, Carrascosa P, Bruining N. Progression of coronary artery calcification at the crossroads: sign of progression or stabilization of coronary atherosclerosis? Cardiovascular diagnosis and therapy. 2016;6:250-8.

[28] Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). Journal of the American College of Cardiology. 2013;61:1231-9.
[29] Yoon HC, Emerick AM, Hill JA, Gjertson DW, Goldin JG. Calcium begets calcium: progression of coronary artery calcification in asymptomatic subjects. Radiology. 2002;224:236-41.
[30] Shaw LJ, Narula J, Chandrashekhar Y. The never-ending story on coronary calcium: is it predictive, punitive, or protective? Journal of the American College of Cardiology. 2015;65:1283-5.
[31] Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. Jama. 2014;311:271-8.
[32] Schmermund A, Achenbach S, Budde T, Buziashvili Y, Forster A, Friedrich G, et al. Effect of intensive versus standard lipid-lowering treatment with atorvastatin on the progression of calcified coronary atherosclerosis over 12 months: a multicenter, randomized, double-blind trial. Circulation. 2006;113:427-37.
[33] Nakazato R, Gransar H, Berman DS, Cheng VY, Lin FY, Achenbach S, et al. Statins use and coronary artery plaque composition: results from the International Multicenter CONFIRM Registry. Atherosclerosis. 2012;225:148-53.
[34] Singh P, Emami H, Subramanian S, Maurovich-Horvat P, Marincheva-Savcheva G, Medina HM, et al. Coronary Plaque Morphology and the Anti-Inflammatory Impact of Atorvastatin: A Multicenter 18F-Fluorodeoxyglucose Positron Emission Tomographic/Computed Tomographic Study. Circulation Cardiovascular imaging. 2016;9.
[35] Goh VK, Lau CP, Mohlenkamp S, Rumberger JA, Achenbach S, Budoff MJ. Outcome of coronary plaque burden: a 10-year follow-up of aggressive medical management. Cardiovascular ultrasound. 2010;8:5.
[36] Achenbach S, Ropers D, Pohle K, Leber A, Thilo C, Knez A, et al. Influence of lipid-lowering therapy on the progression of coronary artery calcification: a prospective evaluation. Circulation. 2002;106:1077-82.
[37] Zeb I, Li D, Nasir K, Malpeso J, Batool A, Flores F, et al. Effect of statin treatment on coronary plaque progression – A serial coronary CT angiography study. Atherosclerosis. 2013;231:198-204.
[38] Clark D, 3rd, Nicholls SJ, St John J, Elshazly MB, Kapadia SR, Tuzcu EM, et al. Visit-to-visit cholesterol variability correlates with coronary atheroma progression and clinical outcomes. European heart journal. 2018.
[39] Kontush A. HDL-mediated mechanisms of protection in cardiovascular disease. Cardiovascular research. 2014;103:341-9.
[40] Andelius L, Mortensen MB, Norgaard BL, Abdulla J. Impact of statin therapy on coronary plaque burden and composition assessed by coronary computed tomographic angiography: a systematic review and meta-analysis. European heart journal cardiovascular Imaging. 2018;19:850-8.
[41] Oberoi S, Meinel FG, Schoepf UJ, Nance JW, De Cecco CN, Gebregziabher M, et al. Reproducibility of noncalcified coronary artery plaque burden quantification from coronary CT angiography across different image analysis platforms. AJR American journal of roentgenology. 2014;202:W43-9.

[42] Symons R, Morris JZ, Wu CO, Pourmorteza A, Ahlman MA, Lima JA, et al. Coronary CT Angiography: Variability of CT Scanners and Readers in Measurement of Plaque Volume. Radiology. 2016;281:737-48.
[43] Dettmer M, Glaser-Gallion N, Stolzmann P, Glaser-Gallion F, Fornaro J, Feuchtner G, et al. Quantification of coronary artery stenosis with high-resolution CT in comparison with histopathology in an ex vivo study. European journal of radiology. 2013;82:264-9.
[44] Sabour S, Rutten A, van der Schouw YT, Atsma F, Grobbee DE, Mali WP, et al. Inter-scan reproducibility of coronary calcium measurement using Multi Detector-Row Computed Tomography (MDCT). European journal of epidemiology. 2007;22:235-43.
[45] Papadopoulou SL, Garcia-Garcia HM, Rossi A, Girasis C, Dharampal AS, Kitslaar PH, et al. Reproducibility of computed tomography angiography data analysis using semiautomated plaque quantification software: implications for the design of longitudinal studies. The international journal of cardiovascular imaging. 2013;29:1095-104.
[46] Kotseva K, De Bacquer D, De Backer G, Ryden L, Jennings C, Gyberg V, et al. Lifestyle and risk factor management in people at high risk of cardiovascular disease. A report from the European Society of Cardiology European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) IV cross-sectional survey in 14 European regions. European journal of preventive cardiology. 2016;23:2007-18.

Table 1: Patient characteristics at baseline

	IJD n=68 (100)	RA n=45 (66.1)	AS n=15 (22.1)	PsA n=8 (11.8)
Age (years), mean±SD	60.5±8.6	61.2±8.8	60.3±8.2	57.4±8.6
Women, n(%)	44 (63.8)	34 (73.9)	7 (46.7)	3 (37.5)
Disease duration (years), median (IQR)	17.1±11.9	15.8±1.7	22.7±2.7	13.6±5.0
BMI (kg/m^2), mean±SD	25.1±3.0	25.1±3.1	24.5±2.2	25.8±3.6
Waist circumference (cm), mean±SD	91±11	91±11	90±9.0	94±11
Systolic BP (mmHg) mean±SD	142±20	141±21	144±13	146±28
Diastolic BP(mmHg), mean±SD	83±9	83±9	83±7	86±12
HT,n(%)	32 (47.1)	21 (46.7)	8 (27.6)	3 (37.5)
Diabetes mellitus, n(%)	4 (5.8)	3 (6.5)	1 (6.7)	0 (0.0)
Smoking, n(%)	15 (21.7)	11 (23.9)	2 (13.3)	2 (25.0)
Family history of CVD, n(%)	11 (15.9)	7 (15.6)	1 (6.7)	3 (37.5)
Previous CVD, n(%)	7 (10.3)	5 (11.1)	2 (13.3)	0 (0.0)
Angina, n(%)	12 (17.4)	10 (21.7)	2 (13.3)	0 (0.0)
Hyperlipidemia, n(%)	44 (63.8)	27 (58.7)	4 (73.3)	6 (75.0)
Medications				
Synthetic DMARDs, n(%)	40 (62.5)	28 (65.1)	4 (30.8)	8 (100.0)
Biologic DMARDs, n(%)	22 (34.4)	13 (32.5)	5 (38.5)	4 (50.0)
NSAIDs, n(%)	19 (32.8)	13 (32.5)	4 (30.8)	2 (10.5)
Anti-hypertensives, n(%)	10 (14.7)	6 (15.4)	3 (33.3)	1 (16.7)
Inflammatory markers				
ESR (mm/hour), mean±SD	11.8±9.3	13.0±10.5	8.4±4.8	9.3±3.6
CRP (mg/L), mean±SD	3.6±4.7	4.0±5.1	2.6±3.6	2.8±2.9

IJD: inflammatory joint disease, RA: rheumatoid arthritis, AS: ankylosing spondylitis, PsA: psoriatric arthritis, BMI: body mass index, BP: blood pressure, HT: hypertension, CVD: cardiovascular disease, DMARDS: disease modifying anti-rheumatic drug, NSAIDs: Non-steroidal Anti-Inflammatory Drugs, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

Hyperlipidemia: total cholesterol $\geqslant$6.0mmol/l.

Hypertension: systolic BP >140 mmHg and diastolic BP >90 mmHg.

Table 2: CCTA findings, lipids and inflammatory markers at baseline and follow-up (per-patient-level)

	Baseline (n=68)	Follow-up (n=68)	p-value
CCTA findings			
CAC, Agatston units, median(IQR)	15(0-221)	73(6-514)	<0.001[a]
Total plaque volume, mm^3, median(IQR)	5.1(0.0-36.7)	8.0(0.5-77.2)	<0.001[a]
Calcified plaque volume, mm^3, median(IQR)	0.2(0.0-15.5)	9.5(6.0-77.2)	<0.001[a]
Mixed/soft plaque volume, mm^3, median(IQR)	0(0-8)	0(0-0)	0.001[a]
Segment Involvement Score	2.0±2.5	3.1±2.9	<0.001[b]
Segment Stenosis Score	2.9±4.0	5.7±6.3	<0.001 [b]
Lipids			
Total cholesterol, mmol/L	6.44±1.09	4.34±0.85	<0.001[b]
HDL cholesterol, mmol/L	1.75±0.55	1.81±0.61	0.059[b]
LDL cholesterol, mmol/L	4.02±1.02	1.97±0.70	<0.001[b]
Triglycerides, mmol/L	1.52±0.98	1.27±0.80	0.019[b]
Inflammation-markers			
ESR, mm/hour	13.71±9.17	11.88±11.93	0.24[b]
CRP, mg/L	3.71±3.86	3.70±5.76	0.99[b]

Values are presented as the mean ± SD unless otherwise stated.
[a]Wilkoxon signed rank test
[b]Paired samples t-test
* coefficient of variation: 4.3%
CCTA: coronary computed tomography angiography, CAC: coronary artery calcification, SD: standard deviation, HDL: high density lipoprotein, LDL: low density lipoprotein, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

Table 3. Lipid status and CAD-progression in patients with and not with LDL-c ≤ 1.8mmol/l

	LDL ≤1.8mmol/l n=34	**LDL >1.8mmol/l n=34**	**p-value**
LDL-c level Baseline, mmol/L , mean±SD	3.7±0.9	4.4±1.0	<0.001
LDL-c level Follow-up, mmol/L, mean±SD	1.5±0.2	2.4±0.7	<0.001
Change LDL-c level, mmol/L, mean±SD	-2.2±0.9	-1.9±1.3	0.38
Change CAC, median (IQR)	21 (2-143)	69 (16-423)	$<0.001_a$
Change Soft/Mixed plaque, mm^3, median (IQR)	0 (-3.5-0.0)	0 (-15.7-0.0)	0.71_a
Change calcified plaque, mm^3, median (IQR)	1.7 (0.0-17.3)	13.4 (1.5-107.6)	$<0.019_a$
Change Total Plaque, mm^3, median (IQR)	0.65 (-1.0-13.9)	13.0 (0.0-60.8)	$<0.001_a$

$_a$independent samples t-test using log-transformed variables.

CAD: coronary artery disease, LDL-c: low density lipoprotein cholesterol, SD: standard deviation, CAC: coronary artery calcifications, IQR: interquartile range

Table 4. Associations between progression of CAC (A), total plaque volume (B), soft/mixed plaque volume (C) with patient characteristics, risk factors and symptoms.

		Univariate		Multivariate	
		β (95%CI)	**p-value**	**β (95%CI)**	**p-value**
A_a	Age	5.62 (-2.51-13-75)	0.17	8.61 (0.95-10.27)	0.028
	Male	57.21 (-86.39- -200.80)	0.43	70.47 (-60.70-201.63)	0.29
	LDL-c >1.8mmol/l	199.63 (69.09-330.16)	<0.001	233.29 (103.50-363.07)	<0.001
	Non-sDMARDs user baseline	122.13 (-26.22-270.47)	0.11		
	Non-bDMARDs user baseline	70.39 (-82.99-223.77)	0.36		
	CRP follow-up	-2.85 (-15.03-9.34)	0.64		
	ESR follow-up	0.67 (-5.48-6.83)	0.83		
B_b	Age	0.57 (-0.97-2.12)	0.46	0.95 (-0.53-2.44)	0.21
	Male	21.87(-5.03-48.76)	0.11	23.02 (-2.78-48.82)	0.079
	LDLc >1.8mmol/L	30.42 (5.06-55.79)	0.019	34.13 (8.81-59.45)	<0.001
C_c	Age	-0.37 (-1.15-0.41)	0.35	-0.50 (-1.48-0.25)	0.19
	Male	-18.06 (-31.26- -4.85)	<0.001	-18.46 (-31.64- -5.46)	<0.001
	LDL-c >1.8mmol/L	-9.15 (-22.39-4.09)	0.17	-11.27 (-24.04-0.25)	0.079

Linear regression A_a: change in CAC as dependent variable, B_b: change in total plaque volume, C_c: change in soft/mixed plaque volume

CAC: coronary artery calcification, CI: confidence interval, LDL: low-density lipoprotein, sDMARDs: synthetic disease modifying anti-rheumatic drugs, bMARDS: biologic disease modifying anti-rheumatic drugs, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

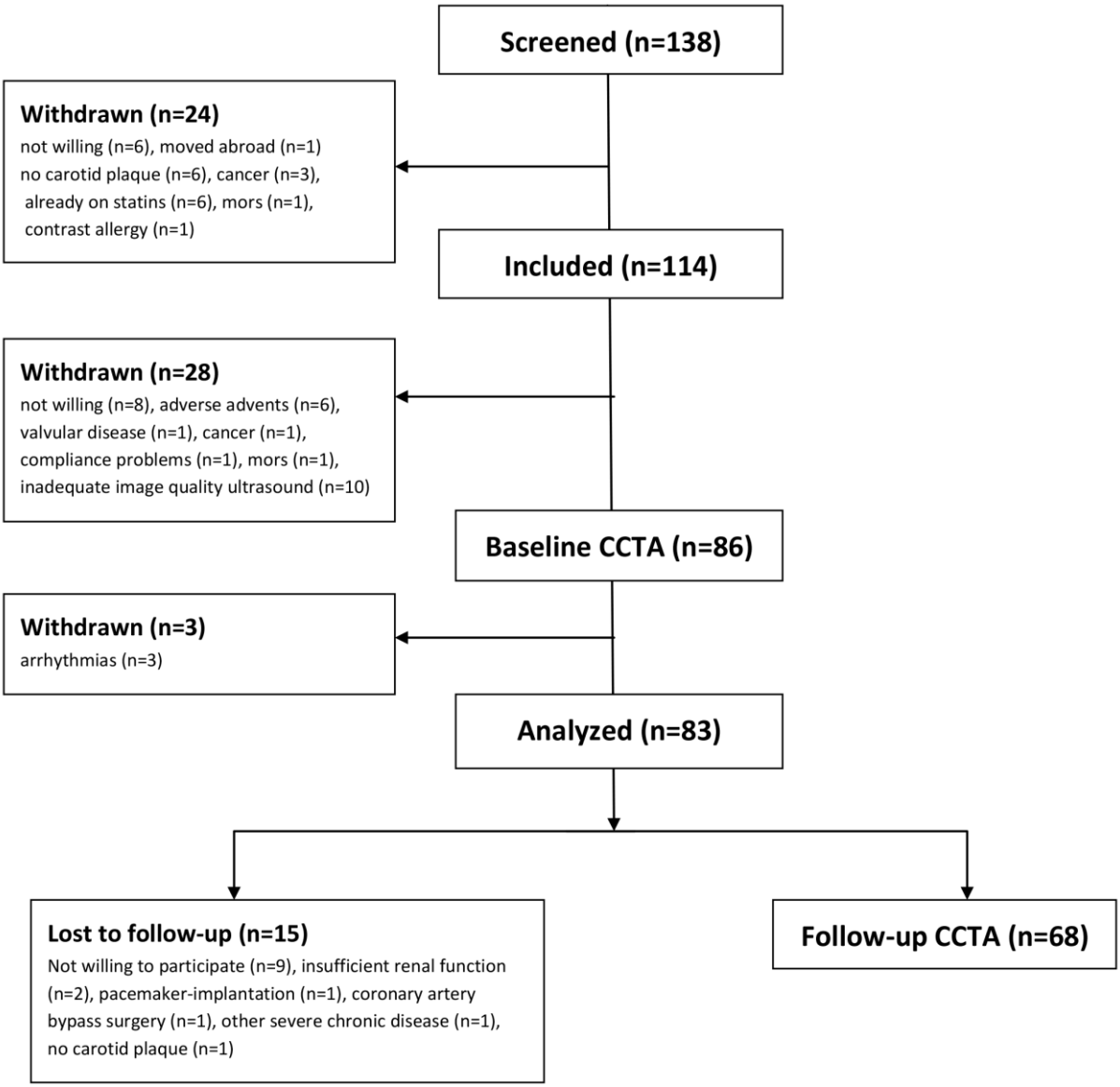


Fig 1. Study Flow Chart. Out of 83 patients analyzed at baseline CCTA, 68 patients were included at follow-up CCTA.

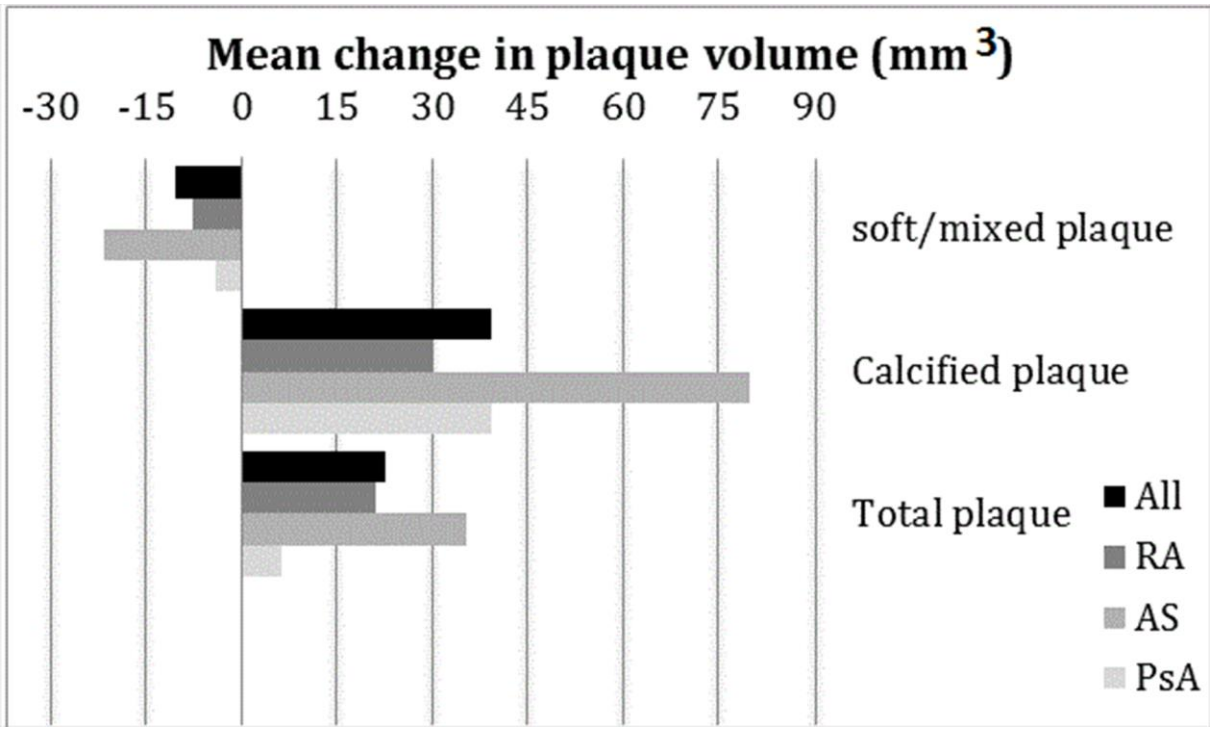


Fig 2. **Mean change in plaque volume in the 3 IJD groups.** Data shown as mean change in soft/mixed, calcified and total plaque volume (mm^3). The soft/mixed plaque was over-all reduced, and calcified and total plaque volume increased in all groups. The plaque alterations are highest in the AS-group.

RA:rheumatoid arthritis, AS:ankylosing spondylitis, PsA:psoriatic arthritis

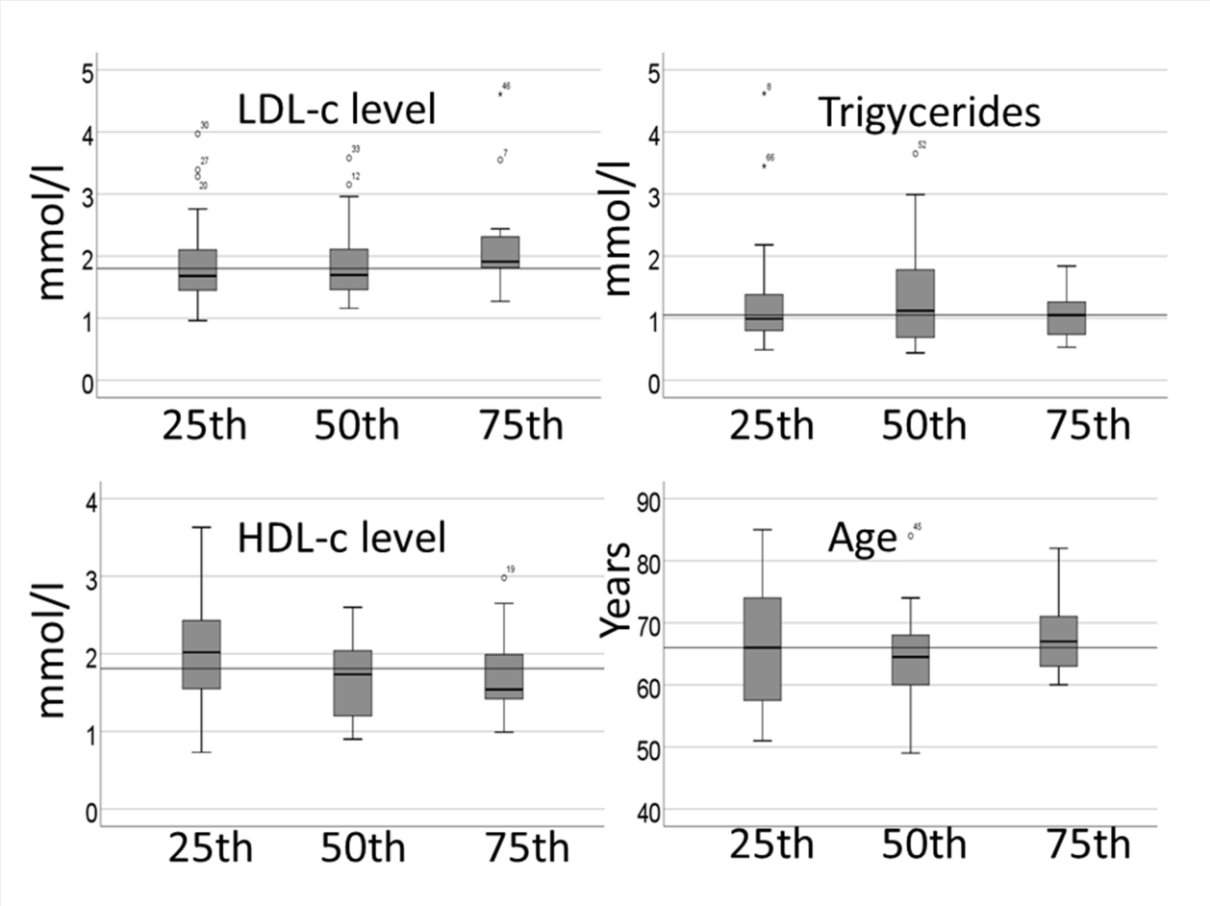
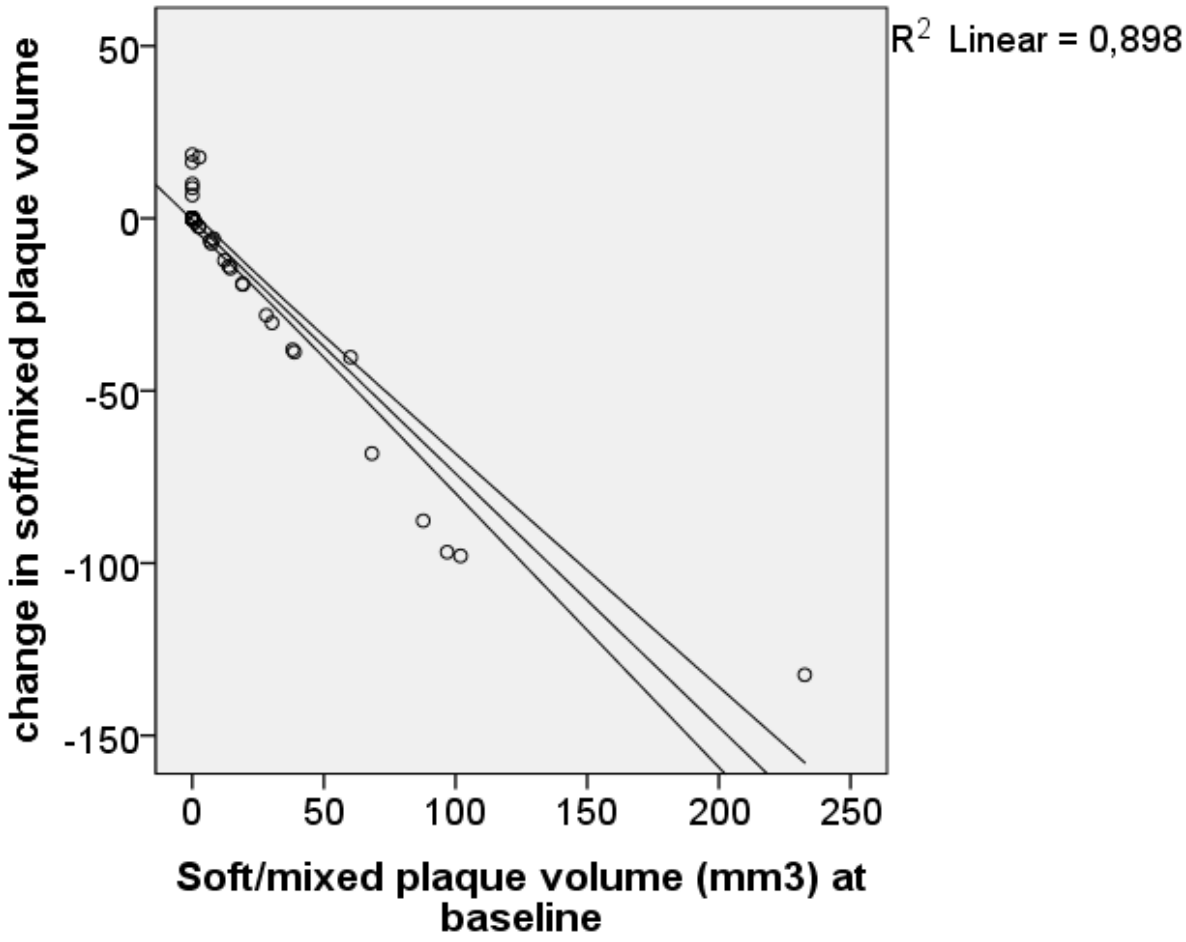


Fig 3. Difference in lipids and age between percentiles of increase in total plaque volume (mm^3). The reference line is set to median in all variables.

LDL-c; low density lipoprotein-cholesterol, HDL-c; high density lipoprotein-cholesterol.

Supporting information



S1 Fig. Change in soft/mixed plaque volume in relation to baseline soft/mixed plaque volume. A linear relationship between baseline soft/mixed plaque volume and change in soft/mixed plaque volume was detected (R=0.898, p<0.001).

III

Svanteson *et al. Cardiovasc Diabetol (2019) 18:58*
https://doi.org/10.1186/s12933-019-0861-x

Cardiovascular Diabetology

ORIGINAL INVESTIGATION **Open Access**

Coronary plaque characteristics and epicardial fat tissue in long term survivors of type 1 diabetes identified by coronary computed tomography angiography

Mona Svanteson[1,2*], Kristine Bech Holte[2,3], Ylva Haig[1], Nils Einar Kløw[1,2] and Tore Julsrud Berg[2,3,4]

Abstract

Objectives: The aim was to assess coronary atherosclerosis, plaque morphology and associations to cardiovascular risk factors and epicardial adipose tissue (EAT) in patients with long duration of type 1 diabetes mellitus (T1DM).

Materials and methods: Eighty-eight patients with ≥ 45 year T1DM duration and 60 controls underwent coronary CT angiography (CCTA) for evaluation of coronary artery plaque volume (total, calcified or mixed/soft), coronary artery calcification score (CAC) and EAT.

Results: Plaques were detected in 75 (85%) T1DM patients and 28 (47%) controls, $p < 0.01$. Median (interquartile range) plaque volume (mm^3) in T1DM vs. controls was: 21.0 (1.0–66.0) vs. 0.2 (0.0–7.1), $p < 0.01$ for calcified, 0.0 (0.0–8.7) vs. 0.0 (0.0–0.0), $p < 0.01$ for soft/mixed and 29.5 (3.9–95.8) vs. 0.4 (0.0–7.4), $p < 0.01$ for total plaque volume. Median CAC was 128 (13–671) vs. 1 (0.0–39.0), $p < 0.01$ in T1DM vs. controls. Median EAT volume did not differ between the groups; 52.3 (36.1–65.5) cm^3 vs. 55 (38.3–79.6), $p = 0.20$. No association between CAC or plaque volumes and EAT were observed. Low time-weighted LDL-cholesterol and HbA1c for 30 years were associated with having plaque volume < 25th percentile, OR (95% CI) 0.18 (0.05–0.70), $p = 0.01$ and 0.45 (0.20–1.00), $p < 0.05$, respectively. Time-weighted LDL-c was linearly associated with CAC (beta 0.82 (95% CI 0.03–1.62), $p = 0.04$) and total plaque volume (beta 0.77 (95% CI 0.19–1.36), $p = 0.01$).

Conclusion: Long-term survivors of T1DM have a higher prevalence of coronary atherosclerosis compared to controls. Low LDL-cholesterol and HbA1c over time have a protective effect on coronary atherosclerosis. EAT volume was not associated with coronary atherosclerosis in T1DM patients.

Keywords: Diabetes type 1, Atherosclerosis, Epicardial adipose tissue, Computed tomography

Introduction

Patients with type 1 diabetes mellitus (T1DM) have an increased risk of cardiac events, and coronary atherosclerosis increases the risk substantially [1]. Assessment of plaque morphology is important since non-calcified plaques are more likely to result in acute coronary syndrome than the more stable calcified plaques [2]. Plaque morphology has been shown to predict coronary events in type 2 diabetes mellitus (T2DM) [3]. Due to different pathogenesis between T1DM and T2DM, similar studies should also be conducted in patients with T1DM. Furthermore, epicardial adipose tissue (EAT) has gained increased interest due to reported associations with coronary atherosclerosis [4], and suggested linked to inflammation and early development of atherosclerosis [5].

Coronary computed tomography angiography (CCTA) has evolved as a non-invasive imaging technique for evaluation of stenoses in the coronary arteries, but it is also widely used in quantitative plaque assessments [6].

*Correspondence: monasvanteson@gmail.com
[1] Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway
Full list of author information is available at the end of the article

© The Author(s) 2019. This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

Evaluation of EAT volumes can also be performed on the same images [7]. Unenhanced coronary artery calcification (CAC) score has a prognostic value for cardiac events in asymptomatic individuals [8], but additional contrast-enhanced CCTA has shown to improve the risk-stratification in asymptomatic patients with both T1DM and T2DM [9].

We have previously reported on a higher prevalence of undiagnosed coronary heart disease among patients with a very long duration of T1DM compared to sex- and age-matched controls [10]. However, there is limited evidence on the morphology, extent and severity of the coronary plaques in T1DM patients versus persons without diabetes [11]. In the present study we have included a population of patients with a long duration of T1DM (>45 years) in order to identify factors associated with coronary atherosclerosis in a group of long-term survivors. This information may widen the understanding of the possible impact of long-term glycemic control on the morphology of coronary atherosclerosis, and the improved understanding of survival may be important in the management of these patients. Furthermore, a lack of association between CAC and EAT has earlier been reported in T1DM patients [12]. Due to diverse evidence regarding EAT [13], there is a need for complementary evaluation of possible associations with the atherosclerotic characteristics.

The aims of the present study were therefore to (i) assess the morphological characteristics of coronary atherosclerosis by CCTA, (ii) to evaluate the associations between CCTA variables with risk factors for coronary atherosclerosis and (iii) to evaluate differences in epicardial adipose tissue (EAT) volumes and associations with coronary atherosclerosis in patients with long-term T1DM compared to controls.

Materials and methods

Patients and study design

The cross-sectional Dialong study of long-term survivors of T1DM was conducted in 2015/2016. As previously described, a chart review of the diabetes participants from the previous 2–4 decades was performed, resulting in long-term longitudinal weighted variables of glycated hemoglobin (wHbA1c), low density lipoprotein cholesterol (wLDL-c) and systolic blood pressure (wSBP) [10]. These measurements were available from 1980, and were calculated as previously described [10, 14]. All the patients with T1DM diagnosed ≤1970 attending a state-funded specialised T1DM clinic; the Norwegian Diabetics' Centre (NDC) in Oslo, Norway were invited. Hundred-and-three patients joined the coronary artery disease substudy. Participants without earlier diagnosed coronary heart disease and eGFR >45 were referred to CCTA, resulting in 88 participants with T1DM for ≥45 years completing the CCTA. The sex and age matched control group undergoing CCTA (n=60) consisted of healthy, invited spouses/friends of the participants with T1DM. The regional ethics committee approved the study (project no. 2014/851) and all participants signed an informed consent.

Image acquisition

All examinations were performed on a 128-slice Dual Source Somatom Definition FLASH CT-scanner (Siemens Healthcare, Erlangen, Germany). An unenhanced scan was conducted for the evaluation of coronary artery calcification (CAC). If tolerated, beta blockage (5–20 mg metoprolol, Seloken®, Astra Zeneca) was used to reduce the heart rhythm and Nitroglycerin 0.4 mg (Nitrolingual®, Pohl-Boskamp, Hohenlockstedt, Germany) was administered sublingually. The scan protocol for the CCTA was chosen in concordance with the achieved heart rate as previously described [10]. The contrast media Omnipaque™ 350 mg/mL (GE Healthcare, Princeton, New Jersey) was used for all examinations.

Image analyses

Image analyses were performed on a Philips Workstation (Intellispace v5, Philips Healthcare, Cleveland, Ohio, USA) with dedicated software (Comprehensive Cardiac, Plaque Analysis, Philips Healthcare, Cleveland, Ohio, USA). Images were assessed using a modified 17-segment American Heart Association model [15]. All segments with a diameter >1.5 mm and subjectively sufficient image quality were included in the analyses. CAD was defined as presence of any plaque. CAC was calculated with the Agatston method [16]. The plaque volume (mm^3) was calculated for each plaque differentiated on plaque morphology. Plaques were categorized as calcified when ≥90% and soft when ≤10% of the volume had a density of >130 Hounsfield units (HU). All other plaques were defined as mixed plaques [17]. The total plaque volume, total calcified volume and total mixed/soft plaque volume were calculated for each patient. The soft and mixed plaque volume was calculated together for statistical purposes due to small amounts of soft plaques.

The extent and severity of CAD was assessed by the segment involvement score (SIS) and the segment stenosis score (SSS). SIS was calculated for assessment of extent as the number of segments with plaque involvement (range 1–17). SSS was calculated for assessment of the severity of the stenosis. Each segment was scored (grading 1–4) according to the Society of Cardiovascular Computed Tomography's recommended stenosis grading, based on luminal narrowing; Grade 1: 1–29% stenosis; Grade 2: 30–49% stenosis; Grade 3: 50–69% stenosis

and Grade 4: 70–100% stenosis, with a total possible SSS of 0–68 [18].

EAT was evaluated from the unenhanced CT images using SliceOmatic5.0 (TomoVision, Magog, Canada). All tissue with a density between − 190 and − 30 Hounsfield units' values within the pericardial sac was defined as EAT. All 2.5 mm axial slices were assessed, with the upper limit starting at the right coronary artery and bottom limit at the apex of the heart. Two independent readers analyzed a 30% random selection of the T1DM examinations, and similar for evaluation of intrarater variability.

Statistical analyses

Descriptive data are presented with numbers (%) for dichotomized variables and mean ± SD for normally distributed characteristics or median, interquartile range (IQR) if not normally distributed. Independent samples t-test or X^2 was used to compare variables among groups. Non-normally distributed variables were log-transformed before conducting the analyses.

Correlation between CCTA measurements and clinical variables was assessed by Spearman's rho. Linear regression was used to adjust for confounders. Variables with not normally distributed residuals were natural log (ln)-transformed. To solve problem of zero values we added one to each measure before transformation (log (X + 1)). Variables with a correlation of ≥ 0.2 or of special clinical relevance were included in the model, and a backwards approach was chosen. Tested variables included: age, sex, family history of coronary heart disease, smoking, hyperlipidemia, use of statins, retinopathy, persistent albuminuria, angina, waist circumference, systolic BP, diastolic BP, pulse pressure, wHba1c, wLDL-c, HDL-c, triglycerides, SR, CRP, troponins and proBNP. Models were checked by plots of residuals vs. predicted values. The 25th percentile of the total plaque volume was evaluated in a logistic regression analysis for the assessment of associations to a low plaque burden. All regression analyses were performed separately of the T1DM group and the controls due to lack of longitudinal variables in the control group. Inter-and intrarater variability were determined by the intraclass correlation coefficient (ICC). All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.

Results

Table 1 shows the clinical characteristics which partly have been published [10]. Briefly, age and sex were comparable between the groups. The T1DM-patients had higher heart rates, systolic blood pressure, pro-BNP, HDL-c, lower LDL-c and a higher use of statins compared with controls. Other traditional risk factors such as hyperlipidemia and smoking were equally distributed between the groups.

All the CCTA-measurements were significantly higher in the T1DM-group compared to the controls, except mean EAT volume which did not differ between the groups (p = 0.20) (Table 2).

We detected 23% (324 out of 1408) segments with plaques in the T1DM group; 265 (82%) calcified, 46 (14%) mixed and 13 (4%) soft plaques. In the control group we detected 9.2% (88 out of 960) segments with plaques; 79 (90%) calcified, 7 (8%) mixed and 2 (2%) soft. The distribution of the plaque types are shown in Fig. 1.

In a linear multivariable regression analysis with total plaque volume as dependent variable (Table 3), wLDL-c was the only associated variable after adjusting for sex and age with beta (95% CI) 0.77 (0.19–1.36), p = 0.01.

In a multivariable logistic regression analysis with the 25th percentile (n = 21) as dependent variable, the OR (95% CI) were; wLDL-c: 0.18 (0.05–0.70), p = 0.01, wHbA1c: 0.45 (0.20–1.00), p < 0.05, and HDL-c: 0.15 (0.04–0.65), p = 0.01 in an age and sex-adjusted model.

In a sex and age adjusted linear, multivariable regression analysis with log-transformed CAC as dependent variable associated variables were: wLDL-c (beta (95% CI) 0.87 (0.10–1.64), p = 0.03 and pro-BNP (beta (95% CI) 0.005 (0.001–0.010), p < 0.02). In the control group, the only significantly associated variables were female sex and age with beta: − 2.358 (− 3.305 to − 1.412), p < 0.01 and 0.113 (0.044–0.182), p < 0.01, respectively.

The CAC and calcified plaque volume correlated with r = 0.90, p < 0.01.

EAT volume

The inter- and intraobserver variability of EAT volume was evaluated with an ICC of 0.87 and 0.91, respectively.

No correlations between EAT and CCTA measurements were detected; CAC; r = − 0.04, p = 0.74, calcified plaque volume; r = 0.03, p = 0.77, mixed/soft plaque volume; r = 0.07, p = 0.54, total plaque volume; r = 0.07, p = 0.54 and SIS; r = 0.06, p = 0.59 and SSS; r = 0.08, p = 0.48.

Table 4 shows univariable and multivariable associations between EAT and risk factors for CAD. The only significant association found in the control group was between EAT and waist circumference.

Discussion

In this study of patients who have survived more than 45 years with T1DM without a previous diagnosis of coronary heart disease, we found a greater extent and severity of coronary atherosclerosis compared to controls. Plaque volumes, segment involvement score, segment

Table 1 Patient characteristics

	T1DM-patients (n = 88)	Controls (n = 60)	p-value*
Age (years)	61.3 ± 7.1	62.3 ± 6.8	0.38
Female, n%	47 (53.4)	34 (56.7)	0.70
Body mass index (kg/m^3)	25.8 ± 3.9	25.5 ± 4.2	0.69
Waist circumference (cm)	90.3 ± 13.2	89.1 ± 12.2	0.55
Previous CVD, n%	6 (6.8)	2 (3.3)	0.36
Angina, typical	2 (2.3)	0 (0.0)	0.49
Angina, atypical	21 (24.1)	14 (23.3)	
No angina	64 (73.6)	46 (76.7)	
Systolic blood pressure (mmHg)	146 ± 19.8	137 ± 19.3	< 0.01
wSystolic blood pressure (mmHg)	130 ± 10.6		
Diastolic blood pressure (mmHg)	75.3 ± 8.4	81.7 ± 9.7	< 0.01
Pulse pressure	71.6 ± 16.1	55.0 ± 14.1	< 0.01
Heart rate (bpm)	68 ± 10.3	62 ± 9.3	< 0.01
Hypertension[a], n%	23 (26.4)	11 (18.3)	0.25
Hyperlipidemia[b], n%	27 (31.0)	12 (20.0)	0.17
Family history of CVD, n%	10 (11.5)	13 (21.7)	0.05
Daily smokers, n%	5 (5.7)	6 (10)	0.62
Ex-smokers, n%	34 (38.6)	22 (36.7)	
pro-BNP (ng/L)	104.9 ± 110.1	67.4 ± 51.3	< 0.01
eGFR	85 ± 19.2	82 ± 12.8	0.18
Statin use, n%	40 (45.5)	6 (10.0)	< 0.01
HDL-c (mmol/L)	2.1 ± 0.5	1.8 ± 0.5	< 0.01
Statin years	2.8 ± 4.3		
LDL-c (mmol/L)	2.8 ± 0.8	3.9 ± 1.0	< 0.01
wLDL-c (mmol/L)	2.9 ± 0.6		
Triglycerides (mmol/L), median (IQR)	0.77 (0.39–2.85)	0.93 (0.52–2.96)	< 0.01
HbA1c (mmol/mol)	7.4 ± 0.81	5.4 ± 0.28	< 0.01
wHbA1c (mmol/mol)	7.9 ± 0.83		

Data are presented as mean ± SD unless otherwise stated

T1DM type 1 diabetes mellitus, *CVD* cardiovascular disease, *NT-proBNP* N terminal-pro B-type natriuretic peptide, *eGFR* estimated glomerular filtration rate, *HDL-c* high density lipoprotein-cholesterol, *LDL-c* low density lipoprotein cholesterol, *wLDL-c* weighted low density lipoprotein cholesterol, *HbA1c* glycated hemoglobin, *wHbA1c* weighted glycated hemoglobin

* Independent samples t-test

[a] Hypertension: previous documented hypertension in the chart or from relevant discharge letters, based on readings with sBP > 140 and/or dBP > 90

[b] Hyperlipidemia: documented hyperlipidemia or a previous total cholesterol reading of > 6.2 or LDL > 4.9 mmol/L

stenosis score and CAC were significantly greater in the T1DM group, but morphological assessments showed mostly calcified plaques (82%). Elevated LDL-c over time was associated with increased plaque volume and CAC. Low LDL-c level and HbA1 over time, in addition to present HDL-c level, was associated with having a more favorable plaque volume (below the 25th percentile ≤ 3.6 mm^3). The EAT volume did not differ between T1DM and controls. We found no associations between coronary atherosclerosis and EAT volume.

Our study shows a large variation in magnitude of atherosclerotic extent. Interestingly, after more than 45 years of diabetes, 15% have no plaques. As previously reported, 11 (13%) patients were revascularized with PCI or CABG compared to 2 (5%) in the control group [10]. The CAC score also varied substantially between the individuals. We excluded patients with prior cardiac events or known coronary heart disease in order to explore the coronary artery status among asymptomatic long-term T1DM survivors. Therefore, the results are only representative to asymptomatic T1DM patients, without established coronary heart disease. The total burden and characteristic of coronary atherosclerosis in T1DM patient is probably different than in our selected patients, but our study was not designed to investigate it.

Table 2 Coronary plaques, calcification and epicardial adipose tissue in T1DM patients and controls

	Type 1 diabetes (n = 88)	Controls (n = 60)	p-value*
Any plaque, n (%)	75 (85)	28 (47)	< 0.01
CAC, Agatston units	124 (13–671)	1 (0–3)	< 0.01
Calcified plaque volume (mm^3)	21.0 (1.0–66.0)	0.2 (0.0–7.1)	< 0.01
Mixed/soft plaque volume (mm^3)	0.0 (0.0–8.7)	0.0 (0.0–0.0)	< 0.01
Total plaque volume (mm^3)	29.5 (3.9–95.8)	0.4 (0.0–7.4)	< 0.01
Segment involvement score	3 (1–6)	1 (0–2)	0.01[a]
Segment stenosis score	4 (1–8)	1 (0–3)	< 0.01[a]
Epicardial adipose tissue (cm^3)	52.3 (36.1–65.5)	55 (38.3–79.6)	0.20[a]
Mean EAT attenuation (HU)	− 73.0 (− 76.0 to − 68.8)	− 76 (− 79.4 to − 70.9)	0.01[a]

Presented as median (IQR) unless otherwise stated

CAC coronary artery calcification, *SD* standard deviation, *SIS* segment involvement score, *SSS* segment stenosis score, *EAT* epicardial adipose tissue, *HU* Hounsfield units

* Mann–Whitney-U test

[a] Independent samples t-test

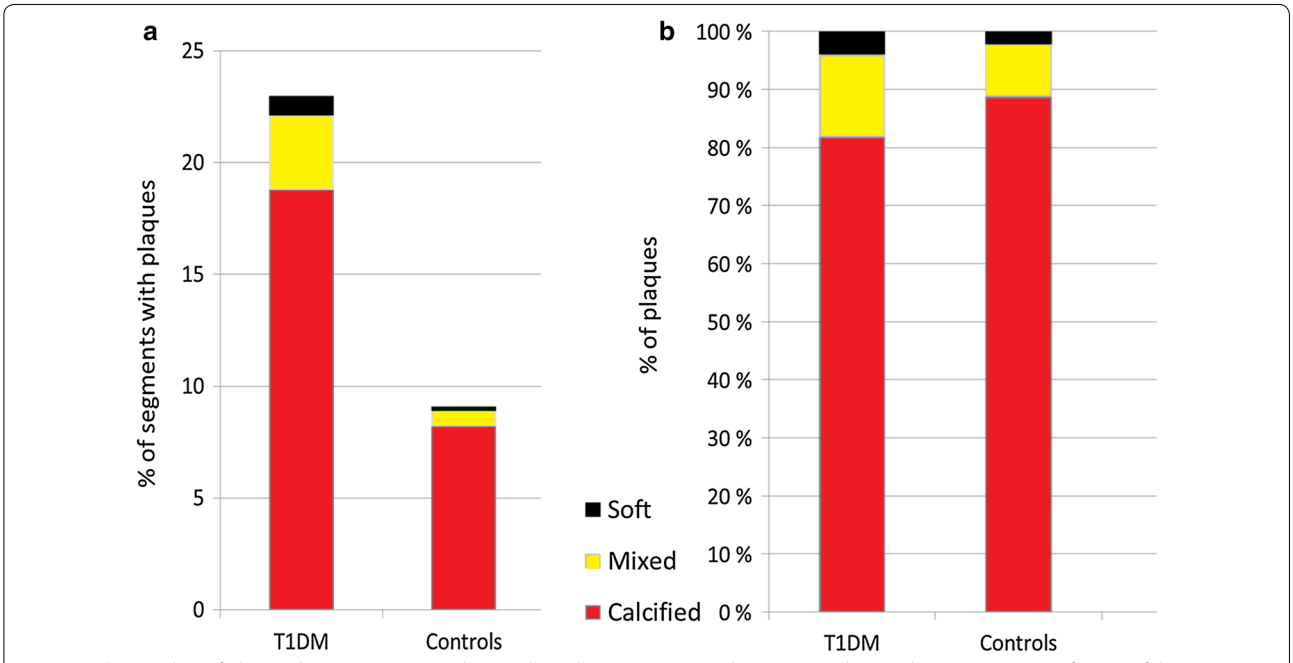


Fig. 1 **a** The number of plaques between T1DM and controls. In the T1DM-group, plaques were detected in 23% (324 out of 1408) of the segments, compared to 9.2% (88 out of 960) in the control group ($p < 0.01$). **b** The distribution of plaque types between T1DM and controls: calcified; 82% vs. 90%, mixed; 14% vs. 8% and soft; 4% vs. 2%, respectively

In our study, 82% of the plaques were calcified. Soft/mixed plaques have been shown in the MESA-study to be associated with worse outcomes than the more sta-ble calcified plaques [19]. Shemesh et al. investigated the degree of CAC in relation to cardiac events in asymptomatic subjects with and without diabetes [20]. They found that acute events did not occur in subjects with extensive CAC (> 600), but were more likely to occur in subjects with mild or moderate CAC [20]. These results were comparable to findings in the MESA-study; subjects with high CAC (> 400) and very high CAC (> 1000) had equal risk for experiencing cardiac events [21]. Our findings may thereby confirm that calcified plaques represent more stable and long standing atherosclerosis. As shown in a study by Djaberi et al. there are morphologically large differences in plaques between T1DM and T2DM [11]. They found 27% non-calcified plaques in their T1DM-group compared to 65% in the T2DM group. Our

Table 3 Associations between total plaque volume and risk factors for CAD in the diabetes group

	Univariable		Multivariable	
	β (95% CI)	p-value	β (95% CI)	p-value
Age	0.06 (0.00–0.19)	0.05	0.09 (0.00–0.14)	< 0.01
Female sex	− 1.63 (− 2.34 to − 0.91)	< 0.01	− 1.13 (− 1.83 to − 0.43)	< 0.01
wLDL-c	1.00 (0.35–1.64)	< 0.01	0.77 (0.19–1.36)	0.01
wHbA1c	0.44 (− 0.04 to 0.92)	0.07		
wSBP	0.06 (0.02–0.09)	< 0.01		
Waist circumference	0.03 (0.00–0.06)	0.04		

Table 4 Associations between epicardial adipose tissue and risk factors for CAD in the diabetes group

	Univariable		Age and sex-adjusted[a]		Multivariable	
	β (95% CI)	p-value	β (95% CI)	p-value	β (95% CI)	p-value
Age	0.20 (− 0.63 to 1.02)	0.635	0.21 (− 0.62 to 1.03)	0.614	0.9 (0.3–1.5)	0.004
Female sex	− 6.15 (− 17.63 to 5.33)	0.290	− 6.23 (− 17.77 to 5.30)	0.286	19.4 (9.4–29.4)	0.000
HDL-c	− 16.06 (− 26.29 to − 5.83)	0.002	− 17.10 (− 28.31 to − 5.89)	0.003	− 9.3 (− 18.1 to − 0.5)	0.038
TG	19.15 (4.97–33.32)	0.009	12.80 (− 0.11 to 25.72)	0.052	− 14.6 (− 27.2 to − 2.0)	0.024
Waist circumference	1.27 (0.93–1.61)	< 0.001	1.54 (0.97–2.11)	< 0.001	1.8 (1.3–2.3)	0.000
wHbA1c	9.14 (2.52–15.77)	0.007	9.12 (2.34–15.89)	0.009		
wLDL-c	7.68 (− 1.66 to 17.01)	0.106				
wSBP	0.083 (− 0.46 to 0.63)	0.763				
Systolic BP	0.18 (− 0.11 to 0.48)	0.214				
Diastolic BP	0.24 (− 0.44 to 0.95)	0.469				
Pulse pressure	0.21 (− 0.15 to 0.57)	0.249				

HDL-c high density lipoprotein cholesterol, *TG* triglycerides, *wHbA1c* weighted glycated hemoglobin, *wLDL-c* weighted low density lipoprotein cholesterol, BP; blood pressure, *wSBP* weighted systolic blood pressure

[a] Minimally multivariable model (only adjusted for age and sex)

participants have a more favorable plaque composition as only 18% of the plaques were defined as mixed/soft plaques. The CAC score in our study was also lower. The patients in the study of Djaberi et al. had shorter diabetes duration (mean of 23 years) compared to ≥ 45 years in our study. The inclusion of long-term survivors of T1DM in our study might explain the discrepancy. Other traditional risk factors were less frequent in our study, which might also contribute to their survival.

The DCCT/EDIC-study described mean HbA1c through 27 years as the strongest risk factor for cardiac events in addition to age in patients with T1DM [22]. In our study, chronic hyperglycemia based on high HbA1c measurements over more than 30 years was associated only with having a low amount of plaque volume (< 25th percentile), while wLDL-c was additionally linearly associated with CAC and total plaque volume. This discrepancy might be due to a higher median HbA1c and a lower median LDL-c level in the DCCT/EDIC-study compared to ours. Patients in the DCCT/ECIT-study were patients with a prior cardiac event, patients that were excluded in our study. The lower HbA1c in our participants may also be a contributing factor for their survival. However, the associations to having the lowest amount of plaque volume suggest that keeping both the LDL-c and HbA1c low over time may have a preventive effect on the development of coronary atherosclerosis. Also, similar plaque characteristics has been described for patients with and without diabetes with elevated HbA1c [23], adding evidence to a role for HbA1c in plaque development. Raised HbA1c is associated with a higher coronary atherosclerotic burden in patients without diabetes [24]. Therefore, we still believe that HbA1c, most likely, plays an important role in plaque development in T1DM-patients. Tinsley et al. also describes a 10 year survival dependent on glycemic control in T1DM patients with > 50 years duration, which further gives evidence to the importance of HbA1c in T1DM patients [25]. A comparison to T1DM patients with a previous cardiac event would be clarifying.

Reducing the LDL-c is the most effective prevention for atherosclerosis in the general population [26]. Statin-use

has shown to affect plaque development, observed as cell-death within the lipid cores in addition to the induction of micro-calcifications [27, 28]. These effects are described as plaque-stabilizing, and an inverse linear relationship of plaque density and coronary events are described [29]. Initiation of lipid-lowering treatment is guideline-recommended after 40 years of age in patients with T2DM, but in T1DM statins is recommended only in the presence of microalbuminuria or renal disease [1]. Patients with both type 1 and 2 DM have been shown to be undertreated with statins [30]. In our study, 46% of the T1DM-group reported statin-use, but with a short duration of statin-treatment (2.8 ± 4.3 years). Several publications have shown that high-intensity treatment (LDL-c level target < 1.8 mmol/mL) is required to achieve plaque regression in patients with DM [31, 32]. A higher CAC score has been reported after initiation of statin-treatment due to the conversion in plaque composition [33]. From this one would expect statin-use to have increased the CAC-score in our T1DM group. However, the duration of statin-use is short and the statin-effect cannot be fully evaluated in this cross-sectional study. The low LDL-c-levels and variations in our cohort may be a result of statin-use and accordingly, the findings of non-significant associations to CAC and plaque volume may be explained by a type II error.

Associations between EAT and coronary atherosclerosis are reported by multiple studies [34], suggesting that EAT have a role in the development of coronary atherosclerosis. We did not observe a difference in EAT volume between T1DM-patients and controls, despite a significant difference in coronary atherosclerosis. To our knowledge, EAT has not previously been associated with coronary atherosclerosis in T1DM patients, although associations of coronary atherosclerosis and EAT in patients with T2DM has been revealed [35, 36]. The inconsistent findings between T1DM and T2DM may imply that EAT potentially plays a different role between the types of DM. In T2DM metabolic syndrome, not commonly present in T1DM, has been associated with increased EAT volumes [37]. We did however reveal a strong association between EAT and waist circumference, which implies that visceral fat and fat within the pericardial sac are related. This is consistent with Darabian et al. [12], who found associations of EAT with greater BMI and waist to hip ratio. EAT has been suggested as a new image marker for atherosclerosis, and a lack of association in some patient groups may be important in this discussion. We cannot exclude that the negative associations in our study are a result of a type II error, due to the low amount of mixed/soft plaques.

The influence of glycemic control on EAT volume is unexplored. We did not find associations between EAT and HbA1c. Darabian et al. reported on a significant association between EAT and HbA1c in an age- and sex adjusted statistical model [12]. However, in their study the participants were younger, had a shorter duration of T1DM and a higher BMI compared to our participants. Also, the statistical significance was no longer present after BMI-adjustment. This is similar to our finding, when including waist circumference in the statistical model, the association between EAT and HbA1c was no longer significant.

The use of CCTA in high-risk, asymptomatic patients is debated. Although the radiation hazard and the technical challenge in presence of large calcified plaques are diminished after introduction of newer generation scanners, there is a lack of evidence whether CCTA improves outcomes in asymptomatic patients with diabetes. Muhlestein et al. found no reduction in acute events in their randomized trial [38]. This was also found in the DIAD-study, were patients with T2DM were randomized to myocardial perfusion imaging or not [39]. The identification of patients in the need for further cardiac evaluation is difficult in the absence of symptoms, and other potential selection criteria are warranted. The large variation of presence and extent of coronary atherosclerosis in patients with a long duration of T1DM found in our study supports further evaluation of selection based on other predictors in order to select the right patients for CCTA.

Our study is limited by a small sample size and a cross-sectional design. The control group is also small, and consists of spouses and friends of the patients. Living with a person with diabetes may influence diet and lifestyle, and we cannot exclude that this has affected our results. However, our results are in line with the DanRisk-study of only healthy individuals [40]. The reproducibility of plaque volume is a limitation in CCTA. In our study, most of the plaques detected were calcified, and plaque assessments were performed with a software previously shown to have a high degree of inter-observer variability on calcified and mixed lesions [17]. CAC, however; is an established method with a high degree of reproducibility [41], and our plaque volume score correlated well with CAC.

Conclusion

In conclusion, patients with a long duration of T1DM have a more extensive and severe atherosclerotic condition, consisting mainly of calcified plaques compared to controls. Maintaining low LDL-c and HbA1c level over time may have a preventive effect on atherosclerotic plaque development, while long-time LDL-c seems to be important for the plaque acceleration in these patients. We found no associations between EAT and coronary atherosclerosis. Larger

studies with longitudinal designs are warranted to evaluate the effect of extent and differences of plaque morphology on cardiovascular events in patients with T1DM.

Abbreviations
BP: blood pressure; CAC: coronary artery calcifications; CAD: coronary artery disease; CCTA: coronary computed tomography angiography; CVD: cardiovascular disease; EAT: epicardial adipose tissue; eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; HDL-c: high density lipoprotein-cholesterol; HU: Hounsfield units; LDL-c: low density lipoprotein cholesterol; NT-proBNP: N terminal-pro B-type natriuretic peptide; SD: standard deviation; SIS: segment involvement score; SSS: segment stenosis score; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; TG: triglycerides; wLDL-c: weighted low density lipoprotein cholesterol; wHbA1c: weighted glycated hemoglobin; wSBP: weighted systolic blood pressure.

Authors' contributions
TJB and KBH designed the study and enrolled patients. All authors were responsible for the data acquisition; MS, YH and NEK were responsible for all the CCTA measurements and KBH and TJB for all the clinical variables. MS, KBH, YH, and TJB analyzed the data. MS wrote the first draft. All authors read and approved the final manuscript.

Author details
[1] Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway. [2] Institute of Clinical Medicine, Faculty of Medicine, University of Oslo, Oslo, Norway. [3] Department of Endocrinology, Morbid Obesity and Preventive Medicine, Oslo University Hospital, Oslo, Norway. [4] The Norwegian Diabetics' Center, Oslo, Norway.

Acknowledgements
The authors thank Lena Korsmo Karterud (Department of Radiology and Nuclear Medicine, Oslo University Hospital, Oslo, Norway) for performing EAT-analyses in regards of interobserver variability, Catrine Brunborg (University of Oslo, Center for biostatistics and epidemiology) for statistical assistance, and Anne Karin Molvær (Norwegian Diabetics' Center) for clinical data collection. We are also grateful to all the study participants.

Competing interests
The authors declare that they have no competing interests.

Availability of data and materials
The data are available from the corresponding author on request.

Consent for publication
All participants provided written informed consent before enrollment in this study.

Ethics approval and consent to participate
The Norwegian South-East regional ethics committee approved the study (Project No. 2014/851), and all participants signed an informed consent.

Funding
Not applicable.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 5 March 2019 Accepted: 18 April 2019
Published online: 04 May 2019

References

1. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS guidelines for the management of dyslipidaemias. Eur Heart J. 2016;37:2999–3058.
2. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, et al. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. J Am Coll Cardiol. 2009;54:49–57.
3. Halon DA, Lavi I, Barnett-Griness O, Rubinshtein R, Zafrir B, Azencot M, et al. Plaque morphology as predictor of late plaque events in patients with asymptomatic type 2 diabetes: a long-term observational study. JACC Cardiovasc Imaging. 2018. https://doi.org/10.1016/j.jcmg.2018.02.025.
4. Marwan M, Achenbach S. Quantification of epicardial fat by computed tomography: why, when and how? J Cardiovasc Comput Tomogr. 2013;7:3–10.
5. Goeller M, Achenbach S, Marwan M, Doris MK, Cadet S, Commandeur F, et al. Epicardial adipose tissue density and volume are related to subclinical atherosclerosis, inflammation and major adverse cardiac events in asymptomatic subjects. J Cardiovasc Comput Tomogr. 2018;12:67–73.
6. Kolossvary M, Szilveszter B, Merkely B, Maurovich-Horvat P. Plaque imaging with CT—a comprehensive review on coronary CT angiography based risk assessment. Cardiovasc Diagn Ther. 2017;7:489–506.
7. Dey D, Nakazato R, Li D, Berman DS. Epicardial and thoracic fat—non-invasive measurement and clinical implications. Cardiovasc Diagn Ther. 2012;2:85–93.
8. LaMonte MJ, FitzGerald SJ, Church TS, Barlow CE, Radford NB, Levine BD, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. Am J Epidemiol. 2005;162:421–9.
9. Min JK, Labounty TM, Gomez MJ, Achenbach S, Al-Mallah M, Budoff MJ, et al. Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals. Atherosclerosis. 2014;232:298–304.
10. Holte KB, Svanteson M, Hanssen KF, Haig Y, Solheim S, Berg TJ. Undiagnosed coronary artery disease in long-term type 1 diabetes. The Dialong study. J Diabetes Complicat. 2019;33:383–9.
11. Djaberi R, Schuijf JD, Boersma E, Kroft LJ, Pereira AM, Romijn JA, et al. Differences in atherosclerotic plaque burden and morphology between type 1 and 2 diabetes as assessed by multislice computed tomography. Diabetes Care. 2009;32:1507–12.
12. Darabian S, Backlund JY, Cleary PA, Sheidaee N, Bebu I, Lachin JM, et al. Significance of epicardial and intrathoracic adipose tissue volume among type 1 diabetes patients in the DCCT/EDIC: a pilot study. PLoS ONE. 2016;11:e0159958.
13. Tanami Y, Jinzaki M, Kishi S, Matheson M, Vavere AL, Rochitte CE, et al. Lack of association between epicardial fat volume and extent of coronary artery calcification, severity of coronary artery disease, or presence of myocardial perfusion abnormalities in a diverse, symptomatic patient population: results from the CORE320 multicenter study. Circ Cardiovasc Imaging. 2015;8:e002676.
14. Holte KB, Juel NG, Brox JI, Hanssen KF, Fosmark DS, Sell DR, et al. Hand, shoulder and back stiffness in long-term type 1 diabetes; cross-sectional association with skin collagen advanced glycation end-products. The Dialong study. J Diabetes Complicat. 2017;31:1408–14.
15. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation. 1975;51:5–40.
16. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte JM, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15:827–32.
17. Klass O, Kleinhans S, Walker MJ, Olszewski M, Feuerlein S, Juchems M, et al. Coronary plaque imaging with 256-slice multidetector computed tomography: interobserver variability of volumetric lesion parameters with semiautomatic plaque analysis software. Int J Cardiovasc Imaging. 2010;26:711–20.
18. Raff GL, Chinnaiyan KM, Cury RC, Garcia MT, Hecht HS, Hollander JE, et al. SCCT guidelines on the use of coronary computed tomographic angiography for patients presenting with acute chest pain to the emergency department: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. J Cardiovasc Comput Tomogr. 2014;8:254–71.

19. Budoff MJ, Young R, Lopez VA, Kronmal RA, Nasir K, Blumenthal RS, et al. Progression of coronary calcium and incident coronary heart disease events: MESA (Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol. 2013;61:1231–9.
20. Shemesh J, Tenenbaum A, Fisman EZ, Koren-Morag N, Grossman E. Coronary calcium in patients with and without diabetes: first manifestation of acute or chronic coronary events is characterized by different calcification patterns. Cardiovasc Diabetol. 2013;12:161.
21. Coylewright M, Rice K, Budoff MJ, Blumenthal RS, Greenland P, Kronmal R, et al. Differentiation of severe coronary artery calcification in the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2011;219:616–22.
22. DCCT/EDIC. Risk factors for cardiovascular disease in type 1 diabetes. Diabetes. 2016;65:1370–9.
23. Zhang S, Dai J, Jia H, Hu S, Du H, Li N, et al. Non-culprit plaque characteristics in acute coronary syndrome patients with raised hemoglobinA1c: an intravascular optical coherence tomography study. Cardiovasc Diabetol. 2018;17:90.
24. Scicali R, Giral P, Gallo A, Di Pino A, Rabuazzo AM, Purrello F, et al. HbA1c increase is associated with higher coronary and peripheral atherosclerotic burden in non diabetic patients. Atherosclerosis. 2016;255:102–8.
25. Tinsley LJ, Kupelian V, D'Eon SA, Pober D, Sun JK, King GL, et al. Association of glycemic control with reduced risk for large-vessel disease after more than 50 years of type 1 diabetes. J Clin Endocrinol Metab. 2017;102:3704–11.
26. Tabas I, Williams KJ, Boren J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. Circulation. 2007;116:1832–44.
27. Puri R, Nicholls SJ, Shao M, Kataoka Y, Uno K, Kapadia SR, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. J Am Coll Cardiol. 2015;65:1273–82.
28. Zheng G, Li Y, Huang H, Wang J, Hirayama A, Lin J. The effect of statin therapy on coronary plaque composition using virtual histology intravascular ultrasound: a meta-analysis. PLoS ONE. 2015;10:e0133433.
29. Criqui MH, Denenberg JO, Ix JH, McClelland RL, Wassel CL, Rifkin DE, et al. Calcium density of coronary artery plaque and risk of incident cardiovascular events. JAMA. 2014;311:271–8.
30. Breuker C, Clement F, Mura T, Macioce V, Castet-Nicolas A, Audurier Y, et al. Non-achievement of LDL-cholesterol targets in patients with diabetes at very-high cardiovascular risk receiving statin treatment: incidence and risk factors. Int J Cardiol. 2018;268:195–9.
31. Nicholls SJ, Tuzcu EM, Kalidindi S, Wolski K, Moon KW, Sipahi I, et al. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials. J Am Coll Cardiol. 2008;52:255–62.
32. Stegman B, Puri R, Cho L, Shao M, Ballantyne CM, Barter PJ, et al. High-intensity statin therapy alters the natural history of diabetic coronary atherosclerosis: insights from SATURN. Diabetes Care. 2014;37:3114–20.
33. Henein M, Granasen G, Wiklund U, Schmermund A, Guerci A, Erbel R, et al. High dose and long-term statin therapy accelerate coronary artery calcification. Int J Cardiol. 2015;184:581–6.
34. Nerlekar N, Brown AJ, Muthalaly RG, Talman A, Hettige T, Cameron JD, et al. Association of epicardial adipose tissue and high-risk plaque characteristics: a systematic review and meta-analysis. J Am Heart Assoc. 2017. https://doi.org/10.1161/JAHA.117.006379.
35. Mohar DS, Salcedo J, Hoang KC, Kumar S, Saremi F, Erande AS, et al. Epicardial adipose tissue volume as a marker of coronary artery disease severity in patients with diabetes independent of coronary artery calcium: findings from the CTRAD study. Diabetes Res Clin Pract. 2014;106:228–35.
36. Versteylen MO, Takx RA, Joosen IA, Nelemans PJ, Das M, Crijns HJ, et al. Epicardial adipose tissue volume as a predictor for coronary artery disease in diabetic, impaired fasting glucose, and non-diabetic patients presenting with chest pain. Eur Heart J Cardiovasc Imaging. 2012;13:517–23.
37. Wang CP, Hsu HL, Hung WC, Yu TH, Chen YH, Chiu CA, et al. Increased epicardial adipose tissue (EAT) volume in type 2 diabetes mellitus and association with metabolic syndrome and severity of coronary atherosclerosis. Clin Endocrinol. 2009;70:876–82.
38. Muhlestein JB, Lappe DL, Lima JA, Rosen BD, May HT, Knight S, et al. Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. JAMA. 2014;312:2234–43.
39. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care. 2004;27:1954–61.
40. Lambrechtsen J, Gerke O, Egstrup K, Sand NP, Norgaard BL, Petersen H, et al. The relation between coronary artery calcification in asymptomatic subjects and both traditional risk factors and living in the city centre: a DanRisk substudy. J Intern Med. 2012;271:444–50.
41. Sabour S, Rutten A, van der Schouw YT, Atsma F, Grobbee DE, Mali WP, et al. Inter-scan reproducibility of coronary calcium measurement using Multi Detector-Row Computed Tomography (MDCT). Eur J Epidemiol. 2007;22:235–43.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

BMC