Structural and Prognostic Clinical Insights in Cardiovascular Imaging

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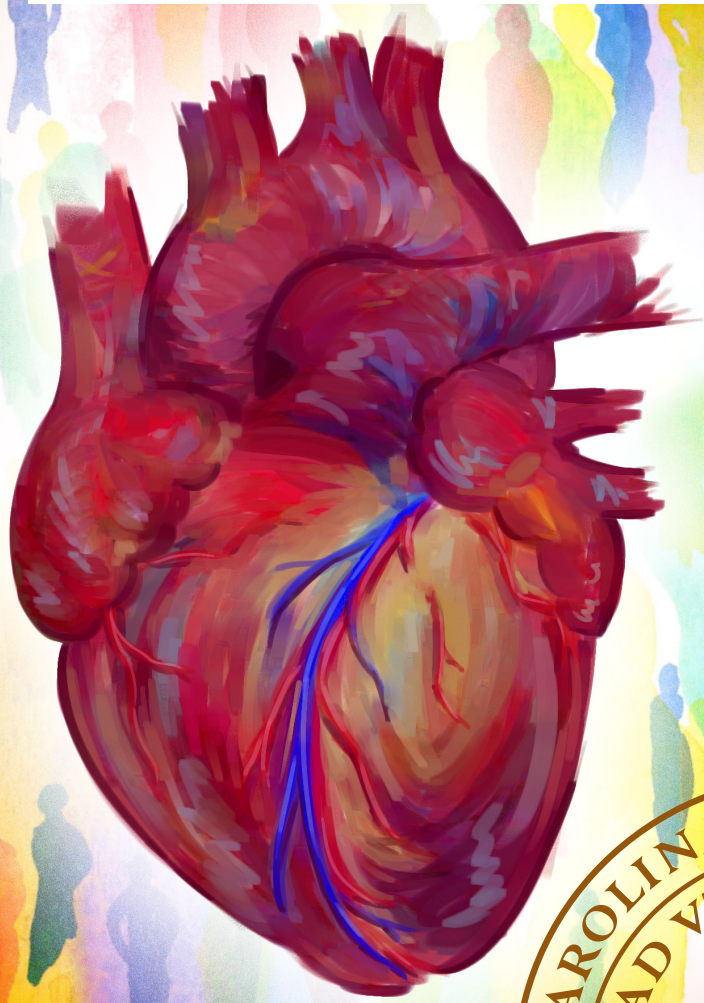

Structural and Prognostic Clinical Insights in Cardiovascular Imaging

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Hanna Markstad

LUND
UNIVERSITY

DOCTORAL DISSERTATION
Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 17th of October at 09.00 in Segerfalksalen, BMC, Sölvegatan 17, 223 62 Lund
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Abstract:

In Paper I, 4703 subjects from the Malmö Cost Cancer cohort, with a mean follow-up of 16.5 years, were evaluated for future risk of ischemic stroke in relation to levels of s-LOX1. An increased risk was found for higher level of sLOX-1 OR 1.75 (1.28-2.39), p<0.001, increasing in presence of carotid plaque OR 2.42 (1.71-3.44), p<0.001. Endothelial cells were exposed to oxLDL, resulting in release of sLOX-1. Plaque and plasma content of sLOX-1 was analyzed for 202 patients in the Carotid Imaging Project who underwent carotid endarterectomy. A significant association between plasma sLOX-1 and plaque content of sLOX-1 was found (r=0209, p=0.004). Plaques with higher level of sLOX-1 had more features of inflammation.

In Paper II, cardiac veins of 99 heart failure patients were mapped using cardiac computed tomography angiography (CCTA) and transferred to a 17-segment model of the left ventricle myocardium. No differences in number or distribution of cardiac veins for any patient or technical factors was found.

In Paper III, obesity was related to presence of coronary and carotid artery disease, in the absence or presence of metabolic syndrome (MetS) criteria for 23,674 participants in the Swedish CArdioPumonary bioImaging Study (SCPAIS). For obese without MetS, severity of coronary stenosis was increased OR 1.47 (1.34-1.62, p<0.0001) compared to normal weight without MetS. When evaluating individual criteria for MetS regarding increased atherosclerosis, high blood pressure was most important.

In Paper IV, presence and characteristics of coronary myocardial bridging (MB), detected by CCTA, for 434 chest-pain patients was compared to 196 non-chest pain subjects from SCAPIS. MB was common for both groups. Chest pain patients did not have more MB. For non-chest pain subjects, number of premature ventricular contractions was higher for subjects with MB in proximal LAD. Subjects with ventricular arrhythmia had more often MB in proximal LAD than subjects without ventricular arrhythmia.

The thesis advances the understanding of the development and progression of cardiovascular disease in prediction, inflammation in circulation and in plaques, mapping of anatomical and other features of vessels in pre-procedural settings and in relation to symptoms, to severity of atherosclerosis in the setting of obesity, using cardiovascular imaging.

Key words: Cardiovascular Imaging, Cardiac Computed Tomography Angiograpy, Cardiac CT, Risk-factors, Myocardial Bridging, s-LOX1

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To my loved ones
Tillsammans kommer man långt

Table of Contents

Preface

What was impossible yesterday is possible today, and future imaging needs to incorporate clinical advantages and realizations in reports, diagnostic algorithms and diagnostic tools This thesis combines expertise and knowledge from several fields, and the findings within this work are all in line with making progress together.

In this thesis, cardiovascular imaging is used to predict future cardiovascular disease, map anatomical structures to better guide treatment, stratify risk factors, and assess possible risks in image findings, with better patient care (or never becoming a patient at all) as the ultimate goal.

In Paper I, the biomarker soluble lectin-like oxidized lipoprotein receptor (sLOX-1) correlated to a higher risk of future stroke, even more so in the presence of carotid plaque detected by ultrasound. The level of sLOX-1 in plaques and plasma could also be linked to plaque inflammation.

In Paper II, cardiac veins were mapped using cardiac computed tomography angiography (CCTA), and findings were correlated with cardiac segments to guide pacemaker lead placement.

In Paper III, the severity of coronary atherosclerosis detected by CCTA was increased for obese and overweight individuals compared to normal weight in the absence of metabolic syndrome: high blood pressure, high blood sugar, high serum triglycerides, and low serum high-density lipoprotein (the waist criterion was excluded). This was not seen for carotid arteries. The different criteria of metabolic syndrome were investigated for their relation to atherosclerosis in coronary and carotid arteries, the latter detected by ultrasound. For coronary arteries, elevated blood pressure and high blood glucose remained significant after adjustments, and for carotid arteries, elevated blood pressure remained significant.

In Paper IV, the prevalence and characteristics of myocardial bridging detected by CCTA were compared between chest-pain patients and non-chest-pain subjects. Myocardial bridging was common in both cohorts. Among subjects without chest pain, ventricular arrhythmias, including PVCs, was associated with myocardial bridging.

The imaging specialty is constantly evolving, which is why clinicians and imaging specialists need to work closely together in order to make this progress lead to advantages for patients and the public – me and you.

Populärvetenskaplig sammanfattning

Medicinsk vetenskap strävar efter att förebygga, förstå, bota och lindra sjukdomar. I medicinsk bildvetenskap används bilder i samma syfte. Denna avhandling syftar till att förutspå framtida sjukdom, kartlägga anatomiska strukturer för att kunna guida behandling på bästa sätt, relatera riskfaktorer till bilddiagnostiska fynd och hitta möjliga riskfaktorer. Avhandlingen spänner över flera områden och syftar till att i förlängningen förbättra för patienter och förebygga sjukdom.

Det första arbetet i avhandlingen visade att individer med högre nivåer av en markör i blod, som medverkar i omsättningen av blodfetter, hade högre risk att få stroke i framtiden, och i än högre grad om de dessutom hade förändringar i halspulsådern som setts med ultraljud. Samma markör var också relaterad till inflammation i plack och blodet.

Det andra arbetet gjordes med patienter som hade grav hjärtsvikt och dessutom behövde en hjärtsviktspacemaker. Vi kartlade hjärtats vener med datortomografi av hjärtat och relaterade dem till de hjärtsegment som används av hjärtläkare för att kunna vägleda placeringen av pacemakerelektroder.

I det tredje arbetet undersöktes studiedeltagare med både datortomografi av hjärtat och ultraljud av halspulsådern. Det visade sig att det var vanligare med kranskärlsplack hos kraftigt överviktiga och överviktiga jämfört med hos normalviktiga när ingen av grupperna uppfyllde kriterierna för metabolt syndrom, dvs de hade normalt blodtryck, normalt blodsocker, normala blodfetter och normalt/högt HDL – kolesterol med hög densitet, det som ibland kallas ”goda kolesterolet”. Kriteriet ”stort midjemått” togs bort från analysen eftersom nästan alla hade det. De olika kriterierna för metabol hälsa undersöktes i relation till kranskärlsförändringar och förändringar i halspulsådern. För kranskärlen var högt blodtryck och högt blodsocker betydelsefulla för utveckling av åderförkalkning och för halspulsådern enbart högt blodtryck, efter att vi tagit hänsyn till andra faktorer som kunde påverka.

I det fjärde arbetet undersöktes hjärtats artärer med datortomografi av hjärtat och vi kartlade hur vanligt det var när artärerna istället för att vara belägna en bit från hjärtmuskeln, låg mot eller i hjärtmuskulaturen. Det visade sig att det var vanligt, både hos patienter som hade bröstsmärta och hos studiedeltagare utan bröstsmärta. Hos studieindividerna utan bröstsmärta kunde man se ett visst samband mellan hjärtrytmrubbningar och när kärlen låg mot eller i hjärtmuskulaturen.

Bilddiagnostik som specialitet utvecklas ständigt och det som var omöjligt igår är möjligt idag. Detta gör att bilddiagnostiker och andra specialister behöver arbeta nära varandra för att kunna dra nytta av framsteg och landvinningar inom andra områden, så att de leder till förbättringar för patienter och befolkningen i stort – du och jag.

Original papers in thesis

This thesis is based on the following papers and manuscript, referenced in the upcoming text by their roman numbers. Complete reprints of all papers and the manuscript are included at the end of the thesis. Papers I and III are reprinted by open access licenses, while Paper II is reprinted with permission of the publisher, Sage Publications.

I. **Hanna Markstad,*** Andreas Edsfeldt,* Ingrid Yao Mattison, Eva Bengtsson, Pratibha Singh, Michele Cavalera, Giuseppe Asciutto, Harry Björkbacka, Gunilla Nordin Fredrikson, Nuno Dias, Petr Volkov, Marju Orho-Melander, Jan Nilsson, MD, Gunnar Engström, Isabel Goncalves. *High Levels of Soluble Lectinlike Oxidized Low-Density Lipoprotein Receptor-1 Are Associated With Carotid Plaque Inflammation and Increased Risk of Ischemic Stroke* J Am Heart Assoc. 2019 Feb 19;8(4).
*Both authors contributed equally.

II. **Hanna Markstad**, Zoltan Bakos, Ellen Ostenfeld, Mats Geijer, Marcus Carlsson, Rasmus Borgquist. *Preoperative CT of cardiac veins for planning left ventricular lead placement in cardiac resynchronization therapy* Acta Radiol. 2019 Jul;60(7):859-865.

III. Lars Lind, **Hanna Markstad**, Håkan Ahlström, Oskar Angerås, John Brandberg, Mattias Brunström, Gunnar Engström, Jan E Engvall, Maria J Eriksson, Mats Eriksson, Anders Gottsäter, Emil Hagström, Benno Krachler, Erik Lampa, Maria Mannila, Peter M Nilsson, Fredrik H Nyström, Anders Persson, Björn Redfors, Anette Sandström, Raquel Themudo, Sebastian Völz, Johan Ärnlöv, Carl Johan Östgren, Göran Bergström. Obesity is associated with coronary artery stenosis independently of metabolic risk factors: The population-based SCAPIS study. Atherosclerosis. 2022 Dec;362:1-10.

IV. **Hanna Markstad**, Gracijela Bozovic, Ellen Ostenfeld, Adrian Pistea, Danielle van Westen, Lisa Ander Olsson, Linda S Johnson, Gunnar Engström, Isabel Goncalves, *Myocardial bridging, chest pain and ventricular arrhythmias: from SWEDEHEART register & Swedish CardioPulmonary BioImage Study,* Unpublished manuscript.

Articles not included in the thesis

1. Zoltan Bakos, Ellen Ostenfeld, **Hanna Markstad**, Anna Werther-Evaldsson, Anders Roijer, Håkan Arheden, Marcus Carlsson, Rasmus Borgquist. *A comparison between radial strain evaluation by speckle-tracking echocardiography and cardiac magnetic resonance imaging, for assessment of suitable segments for left ventricular lead placement in cardiac resynchronization therapy*. Europace. 2014 Dec;16(12):1779-86.
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11. Carl Johan Östgren, Julia Otten, Karin Festin, Oskar Angerås, Göran Bergström, Kerstin Cederlund, Gunnar Engström, Maria J Eriksson, Mats Eriksson, Tove Fall, Anders Gummesson, Emil Hagström, Urban Hellman, Stefan K James, Tomas Jernberg, Johan Kihlberg, David Kylhammar, **Hanna Markstad**, Peter Nilsson, Anders Persson, Margaretha Persson, Carlo Pirazzi, Rebecca Renklint, Annika Rosengren, Stefan Söderberg, Johan Sundström. *Prevalence of atherosclerosis in individuals with prediabetes and diabetes compared to normoglycaemic individuals-a Swedish population-based study.* Cardiovasc Diabetol. 2023 Sep 27;22(1):261.
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Author´s contributions to Paper I-IV

	Study-design	Ethics application	Data-collection	Data analysis	Statistics	Figures/ tables	Interpretation of results	Writing manuscript draft	Revision of manuscript	Response to reviewers
Paper I	2	0	0	2	3	3	2-3	3	3	3
Paper II	1	0	3	3	1	3	1-2	0	1	0
Paper III	1	0	3	3	1	0	1	0	2	0
Paper IV	3	3	3	3	3	3	3	3	3	-

Abbreviations

CCTA	Cardiac Computed Tomography Angiography
CI	Confidence Interval
CRT	Cardiac Resynchronization Therapy
CT	Computed Tomography
D	Diagonal Branch of Left Ascending Coronary Artery
HDL	High Density Lipoprotein
IM	Intermediate Coronary Artery
LAD	Left Ascending Coronary Artery
LDL	Low Density Lipoprotein
LOX-1	Lectin-like Oxidized Low Density Lipoprotein Receptor 1
sLOX-1	soluble Lectin-like Oxidized Low Density Lipoprotein Receptor 1
M	Marginal Branch of Circumflex Coronary Artery
MB	Myocardial Bridging
MDC	Malmö Diet and Cancer Study
MetS	Metabolic Syndrome
oxLDL	Oxidized Low Density Lipoprotein
PVC	Premature Ventricular Complexes
RCA	Right Coronary Artery
SCAPIS	Swedish CArdioPulmonary bioImage Study
VT	Ventricular Tachycardia

Introduction

Cardiovascular diseases

Cardiovascular diseases are declining in many countries in Europe but remain the primary cause of death worldwide (1, 2). Cardiovascular diseases can be prevented by reducing risk factors such as high blood pressure, smoking, blood lipids, overweight and obesity, inactivity, diabetes mellitus, and air pollution (3-6), whilst risk factors as sex, genetics, and age are constant or altered only by passage of time. Cardiovascular diseases are by far most commonly caused by complications of the underlying systemic disease atherosclerosis. (7, 8)

Stroke

Stroke is defined as a permanent loss of function, sensation, or other abilities by damage to brain cells, either by an ischemic or hemorrhagic event. Ischemic stroke is the most common (87%). (9) The onset is rapid and occurs when the blood supply to a part of the brain is blocked or when a blood vessel ruptures. (10) Permanent brain damage develops within minutes when the brain cells are deprived of oxygen and nutrients, and fast diagnosis and treatment are key to successful recovery. (11, 12) An ischemic stroke can be caused by a blood clot forming locally or transported from a different part of the body, i.e., the atrial appendage during atrial fibrillation, or a local narrowing of the vessels due to vasospasm or atherosclerotic plaques. Carotid arteries are assessed for stenosis after a transient ischemic attack or when risk factors for stroke are present. If the stenosis is considered significant in relation to symptoms, an operation where the plaque is removed, endarterectomy, is indicated. (13, 14)

Stroke is a leading cause of death and disability worldwide, being the second most common cause of death worldwide. (15) Globally, 1 in 4 adults over the age of 25 will have a stroke in their lifetime. (16) For the affected individual, the consequence of a stroke is often devastating and lifelong; 50% of stroke victims are chronically disabled. In Sweden, 25000 people are victims of stroke every year. In addition, as many as 12000 experience a transient ischemic attack, a serious warning sign for stroke, where

neurological loss is regained. (17) The annual cost for care after stroke in Sweden, including care out of hospital but not including next-of-kin care, amounts to 18,3 million Swedish Krona. (17)

After lifestyle modifications, preventive medication is considered. These includes antihypertensives, statins, antiplatelet, and anticoagulation medication, the adverse effects of the latter two being increased risk of bleeding. The ability to predict who is at risk of future stroke could prevent both death and disabilities, unnecessary preventive medication, and reduced costs for society.

Coronary heart disease

When the blood supply to the cardiac muscle is blocked, either by a blood clot, a ruptured coronary artery plaque, or in less common settings such as severe vessel spasm and coronary artery dissection, the cardiac muscle, myocardium, receives less oxygen and nutrients than its demand, resulting in chest pain. Permanent damage, infarction, of more than 50% of the myocardium occurs after just short of 5 hours (18). Coronary heart disease is still the most common cause of death globally and has been so for 30 years. (19) In the US, the disease peaked in the 1960s (a major reason to initiate the population-based Framingham Study mentioned below, intended to map risk factors of cardiovascular disease).(20) The most common symptom of a heart attack is severe chest pain, angina pectoris. Stable angina can be triggered by physical exercise and ceases upon rest. The pain is usually located behind the sternum and can radiate out, particularly in the left arm, occasionally radiating towards the neck or jaw. Symptoms can also include shortness of breath. Unstable angina can have a sudden onset, even at rest, and has a higher risk of progressing to myocardial infarction. Diagnosis of myocardial infarction includes ECG and blood sample testing for markers of myocardial damage (21, 22). If positive, a coronary invasive angiogram during which a thrombus or stenosis can be treated, is performed. (23, 24) When indicated in acute settings, the procedure should be initiated as soon as possible, preferably within two hours. If testing is doubtful, cardiac coronary tomography angiography (CCTA) or myocardial scintigraphy can be considered. Preventive care includes lifestyle changes, and preventive medication includes statins, anti-hypertensives, anti-platelet medications, and, if recurrent angina, also nitrates.(25)

Heart failure

Heart failure is common and increasing in prevalence with an aging population and with a higher proportion of survivors after a myocardial infarction. In short, heart failure occurs when the heart is unable to pump enough blood to meet the body's

requirements. (26) There are several reasons for this, one being a previous myocardial infarction. Others include heart valve dysfunction (stenosis or insufficiency), cardiomyopathy, and arrhythmias. Heart failure can be classified based on ejection fraction – how well the heart can empty its chambers – and symptoms.

Different types of heart failure include diastolic and systolic failure, acute and chronic, and right- and left-sided heart failure.

Heart failure classification relates the severity of heart failure to preserved ejection fraction, symptoms, and structural changes. A widely used classification is the NYHA Classes of heart failure (27), ranging from Class I to Class IV, where the patient's limitations in terms of symptoms stratify patients.

NYHA Class IV corresponds to: An inability to carry on any physical activity without discomfort. Symptoms of heart failure is present even at rest. If any physical activity is undertaken, discomfort increases.

A different widely used classification relates to the reduction of left ventricular ejection fraction, a setting first described by Luchi et al in 1982 (28). Later proposed international definitions stratifies this more thoroughly. (29) The classification separates heart failure with reduced ejection fraction, 40% or less (HFrEF), mildly reduced ejection fraction, between 41 and 49% reduction (HFmrEF) and heart failure with preserved ejection fraction (HFpEF), meaning ejection fraction 50% or greater.

When heart failure is diagnosed, and lifestyle changes such as smoking cessation and weight loss have been addressed, medical treatment is indicated, among them ACE-inhibitors and β-blockers. (30, 31)

Pacemaker treatment

Pacemakers are electronic devices designed to restore or maintain a regular and steady heart rhythm. The most common indications for pacemakers are rhythm-affecting conditions such as sinus node dysfunction and atrioventricular block. These pacemakers typically have two leads—one placed in the right atrium and one in the right ventricle.

When, in addition to rhythm dysfunction (typically LBBB block and prolonged QRS duration, >130ms), a patient has severe heart failure, a third lead is placed, aiming for pacing of the left ventricle in cardiac resynchronization therapy (CRT). This lead is traditionally introduced via the coronary sinus, onward in the great cardiac vein, and further placed into one of the cardiac veins draining the left ventricle, aiming for

electronic pacing of the left ventricle. (32) In case of no suitable vein, the lead placement procedure is costly and possibly harmful as the risk exceeds the benefits.

As will be discussed more below, anatomic variance is greater regarding cardiac veins than coronary arteries. CCTA can be used to depict the cardiac veins by prolonging the delay for the intravenous contrast to a venous phase. However, not all veins are suitable for CRT-lead placement. Veins with a course in the interventricular grooves, or closer than 1 cm to the septum, are unfit for pacing as it would lead to septal pacing. Also, veins in close contact with the diaphragm can cause diaphragmatic pacing, which is unpleasant and unwanted. Thirdly, veins with too acute off-take from the coronary sinus are technically hard to access and thus not favorable. Conduction system pacing has lately expanded to include left bundle block pacing and His bundle pacing, as alternative treatments to cardiac resynchronization therapy, where the lead is placed directly in the cardiac conduction system in the interventricular septum. (33)

Atherosclerosis

Atherosclerosis is a systemic disease, and the formation of an atherosclerotic plaque is a process over time. The precursors of a plaque, fatty streaks (aggregation of lipid-containing macrophages) and intima thickening (accumulation of smooth muscle cells and fibrosis), can be found early in life.(34, 35) Fatty streaks and intima thickening can regress, but also progress to an atherosclerotic plaque. (36) In order for a plaque to progress, two major factors are vital – the presence of lipids in the blood and inflammation. Lipids in the form of low-density lipoprotein, LDL, a particle that carries cholesterol through the blood, pass from the blood into the intima, where it accumulates and gets oxidized by enzymes and oxygen radicals to oxidized LDL (oxLDL). oxLDL is taken up by activated monocytes and macrophages, which turn into foam cells if internalizing enough oxLDL. Macrophages produce chemokines, signaling for smooth muscle cells to migrate, and inflammatory signaling substances contributing to the attraction of T-cells and dendritic cells that take part in forming the plaque. Free fatty materials are left in the intima when a foam cell goes through apoptosis. Collagen and smooth muscle cells make up the fibrous cap of the atheroma. Part of an atheroma can be calcified, but it remains unclear if this is a de-escalating part of this process or a pro-inflammatory response. (8) Microscopic or spotty calcification may provoke thrombosis, and larger calcifications may act as a more protective and stabilizing factor for the plaque against pressure changes. (37) Modulating the immune response by blocking the proinflammatory cytokine interleukin-β (38) or by early

medication with colchicine (39) can prevent acute cardiovascular events. Interestingly, modifying inflammation can also lower hypertension. (40)

The symptoms of atherosclerosis are either gradual, with increasing pain or loss of function as the plaque obstructs the blood flow and the supply to the downstream organ/tissue is less than its demand, or sudden, as a thrombus forms or a plaque ruptures, Figure 1, E and D/F, respectively.

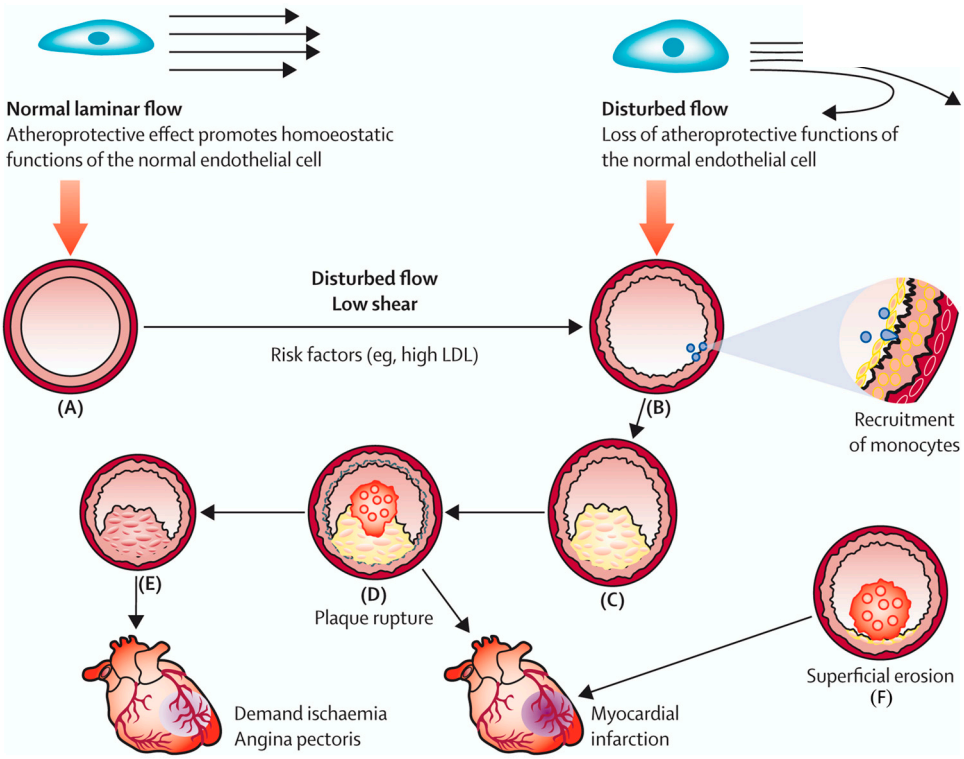

Figure 1. Gradual or acute symptoms caused by atherosclerosis
Reprinted from The Lancet. 383(9932), Heusch et al., Cardiovascular remodeling in coronary artery disease and heart failure, 1933-43, Copyright (2014), with permission from Elsevier. (41)

The distribution of atherosclerosis is more pronounced at sites where normal laminar blood flow is disturbed, such as bifurcations. (42, 43) Where a plaque has already started to form, blood flow is disturbed or even turbulent, and the vessel wall epithelium undergoes changes that escalate adhesion of platelets and blood cells. In addition, the altered architecture causes plaques to be more rupture-prone, where a large lipid core, a thin fibrotic cap, and spotty calcifications can sometimes be diagnosed by CCTA. In contrast, neovascularization and an increased number of inflammatory cells are visualized in histology.

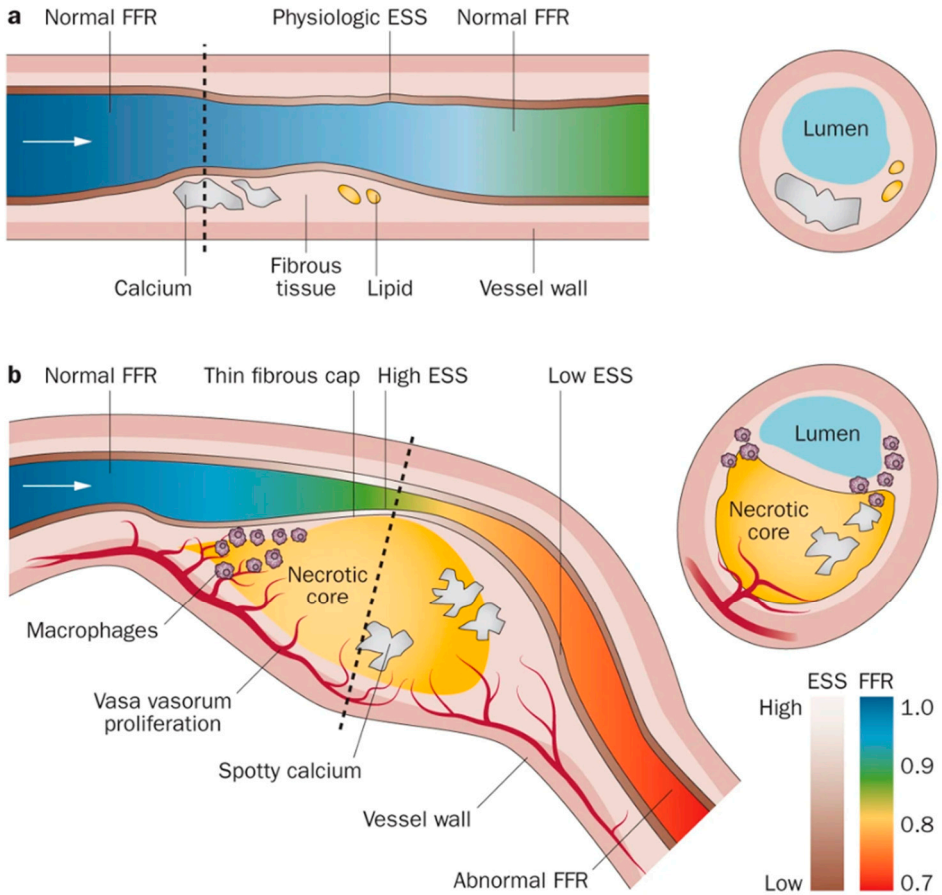

Figure 2. a) Stable fibrocalcific lesion with calcification and small lipid pools. The plaque leads to mild narrowing of the lumen; however, there is no ischaemia after the lesion (FFR >0.8; green). ESS near the plaque is in the normal physiological range, indicating undisturbed flow. **b)** Rupture-prone vulnerable plaque with a large lipid-rich necrotic core, thin fibrous cap, neovascularization, spotty calcium and presence of inflammatory cells. Despite the positively remodelled vessel wall at the site of the plaque, the lesion causes severe luminal narrowing and ischaemia (FFR <0.8; red). The downstream plaque region with low and oscillatory ESS promotes plaque growth, whereas the upstream low ESS at the shoulder regions is more inflamed (indicated by presence of macrophages), which might lead to plaque destabilization. High ESS at the most stenotic part can trigger plaque rupture. Abbreviations: ESS, endothelial shear stress; FFR, fractional flow reserve.
Reprinted from Nature Reviews Cardiology 11, 390–402 (2014), Maurovich-Horvat P et al., Comprehensive plaque assessment by coronary CT angiography, Copyright (2014), with permission from Springer Nature.**(44)**

Figure 2b) displays lower pressure in the vessel downstream of the plaque, termed fractional flow reserve, and higher endothelial shear stress at the most stenotic region.

Fractional flow reserve measures the severity of stenosis compared to unobstructed blood flow.

Low endothelial shear stress promotes plaque formation. (42) Still, when endothelial shear stress increases as the lumen narrows due to plaque progression, sites with high endothelial shear stress can destabilize the fibrous cap (45), create a greater necrotic core, and lead to calcium progression (46), making a plaque more prone to rupture. (47)

Biomarkers

Biomarkers – objective measures for physiological parameters, for diseases, and pharmacologic response to treatment (48) – were first recorded by the historic civilizations of Sumer and Babylonia in Mesopotamia, where findings dated as early as 4000 B.C., show physicians of the time documented findings in urine on clay tablets (49). Later, Hippocrates (c 460-c 370 B.C.) compiled the findings of the time in the book Corpus Hippocraticum, including treatment plans, ethical rules, and laws worked out in his school of thought, forming the foundation of medicine. (50)

Blood samples are common biomarkers of more recent medicine. The Dutch microbiologist Antoine van Leeuwenhoek first published microscopic observations of red blood cells in a 1674 letter to what later became the Royal Society of London.(51) The erythrocyte sedimentation rate, used to determine an individual's health status, was first described by the Polish pathologist Edmund Biernacki in 1896.(52) He subsequently linked increased segmentation rate to the presence of fibrinogen in ill subjects (53).
The term "biomarkers" includes measures and observations from a much broader span than merely those derived from body liquids, for instance, respiratory and heart rate. Registration of the pulse is first described in the Edwin Smith's papyrus from ancient Egypt c 1600 B.C., where the direct correlation between the pulse and the heart is mentioned, also describing heart failure, citation below. (54)

> *"When the heart is diseased, its work is imperfectly performed; the vessels proceeding from the heart become inactive so that you cannot feel them […] If the heart trembles, has little power and sinks, the disease is advancing."*

Biomarkers of today are used not only to diagnose disease but also to predict the probability of future disease and adverse events; predictive biomarkers. For instance, elevated blood pressure increases risk for future cardiovascular events such as stroke, heart attack, and heart failure (20, 55, 56), and is thus also a prognostic biomarker.

Other biomarkers for cardiovascular disease include elevated circulating blood sugar, elevated BMI, increased abdominal fat, age, male sex, and elevated blood lipids (57).

Examples of biomarkers for disease are N-terminal pro-brain natriuretic peptide (BNP) and BNP, both specific biomarkers for heart failure.(58)

The link between high blood lipids and heart attacks was first described in 1938 by Carl Müller, where some 10 related patients all presented with xanthoma, and 5 of whom *"died suddenly and unexpectedly, apparently with symptoms of paralysis of the heart"* (59). These were all cases of homozygote familial hypercholesterolemia, a hereditary condition present in about 1/1000000. The heterozygote variant is more common and comes in various severities depending on genetic expression. (60) Testing for elevated blood lipids is part of clinical workup for all cardiovascular disease. Blood lipids such as LDL (low density lipoprotein) cross the endothelial membrane into the intima of an artery and gets oxidized to oxLDL by enzymes and oxygen radicals.

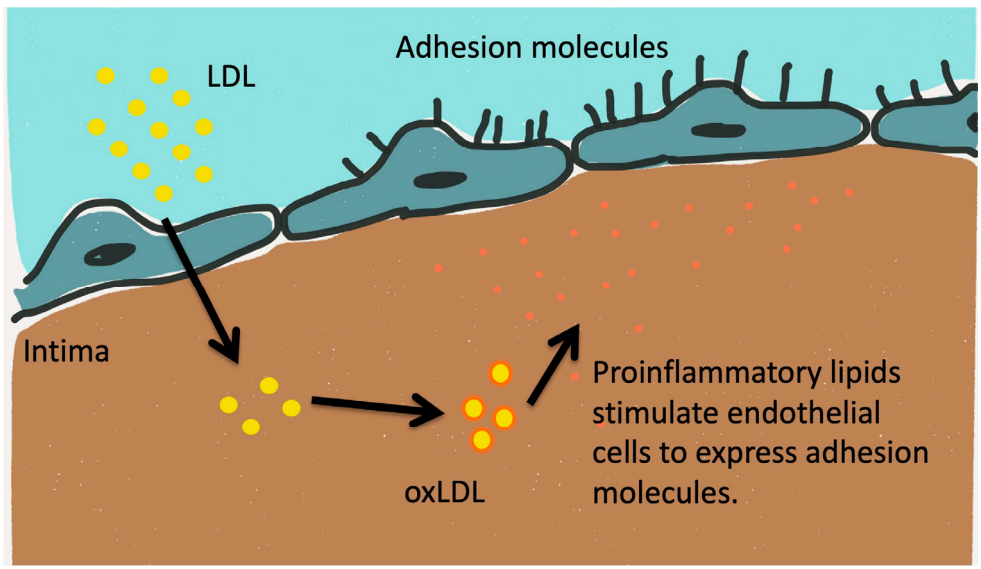

Figure 3. LDL cross endothelial membrane Adapted from Annu Rev Pathol. 2006;1 Hansson GK, Robertson AK, Söderberg-Nauclér C. Inflammation and atherosclerosis. 297-329. Copyright (2006) with permission from ANNUAL REVIEWS (61)

Oxidized LDL activates endothelial cells and macrophages to produce adhesion molecules and chemokines, as shown in Figure 3. The normal defense is to clear the intima from oxLDL by macrophages internalizing oxLDL. If oxLDL is abundant, the main scavenger receptor for LDL on endothelial cells, lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), is upregulated (34, 62). This happens in response to

higher levels of oxLDL, but also to hyperglycemia, proinflammatory cytokines, and shear stress (63). Macrophages that have internalized high amounts of oxLDL develop into foam cells. Up to this point, this is a reversible process, but once a foam cell has reached its maximum capacity, it undergoes apoptosis, leaving free fat in the intima. A soluble form of LOX-1 (sLOX-1) is present in the blood, and it is assumed that sLOX-1 increases with increased expression of LOX-1. sLOX-1 is elevated in settings of acute stroke. (64)

Cardiac anatomy

Ancient Egypt regarded the heart as the engine of the body and also the seat of intelligence (65). Egyptian hieroglyphs are the first pictograms of the heart, a highly important symbol and the only organ left in the body prior to embalming, Figure 4.

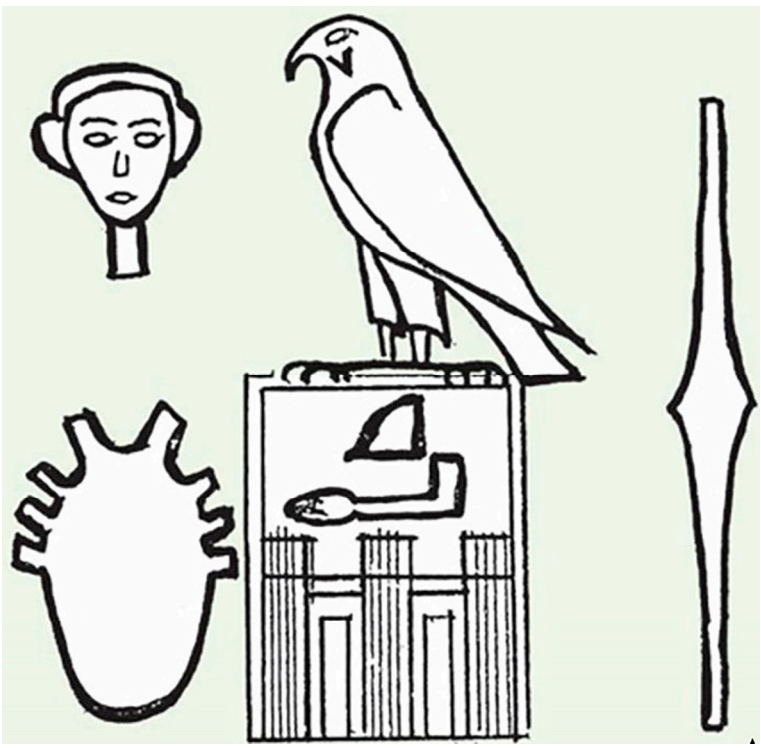

Figure 4. Ancient hieroglyphs representing the heart. Titulary of the Pharaoh Horus Qa (about 3000 BCE) where a precise anatomic illustration of the heart is represented as a vase with eight handles, the disposition of which recall the anatomic position of aorta, pulmonary artery, superior and inferior vena cava and four pulmonary veins. Reprinted under Creative Common licence BY 4.0, orginal publication Zampieri F, Thiene G, Zanatta A. Cardiocentrism in ancient medicines. Int J Cardiol Heart Vasc. 2023 Aug 25;48 (66)

In 13th-century Cario, Ibn al-Nafis wrote a commentary on the anatomy of Avicenna, where he for the first time described coronary circulation as other than obtaining its nourishment by sediment left by the blood in the right ventricle.(67) The heart is a dual system pumping organ, where the pulmonary circulation pumps blood from the right atrium, through the tricuspid valve, to the right ventricle, through the pulmonary valve, via the pulmonary trunk to the lungs through the pulmonary arteries. After oxygenation via gas exchange in the lung alveoli, the blood returns to the left heart through the pulmonary veins that empty into the left atrium, passes the mitral valve, and continues to the left ventricle – the central and most important part of the pumping mechanism – and onwards through the aortic valve and then further to the body. Surface anatomic relations are depicted in Figure 5 and Figure 6. The blood passively returns from the body through the superior or inferior vena cava, respectively. Just above/after the aortic valve, the arteries supplying the heart arise, the coronary arteries.

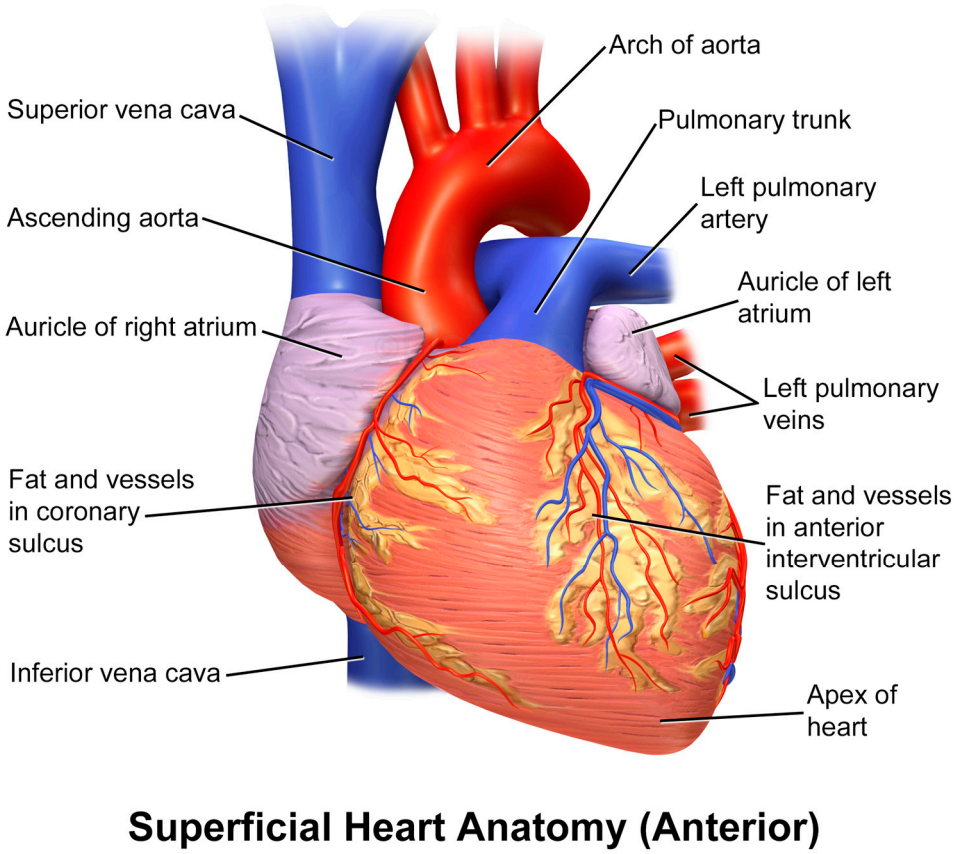

Figure 5. Reprinted under Creative Commons license, original publication: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicin 1 (2).

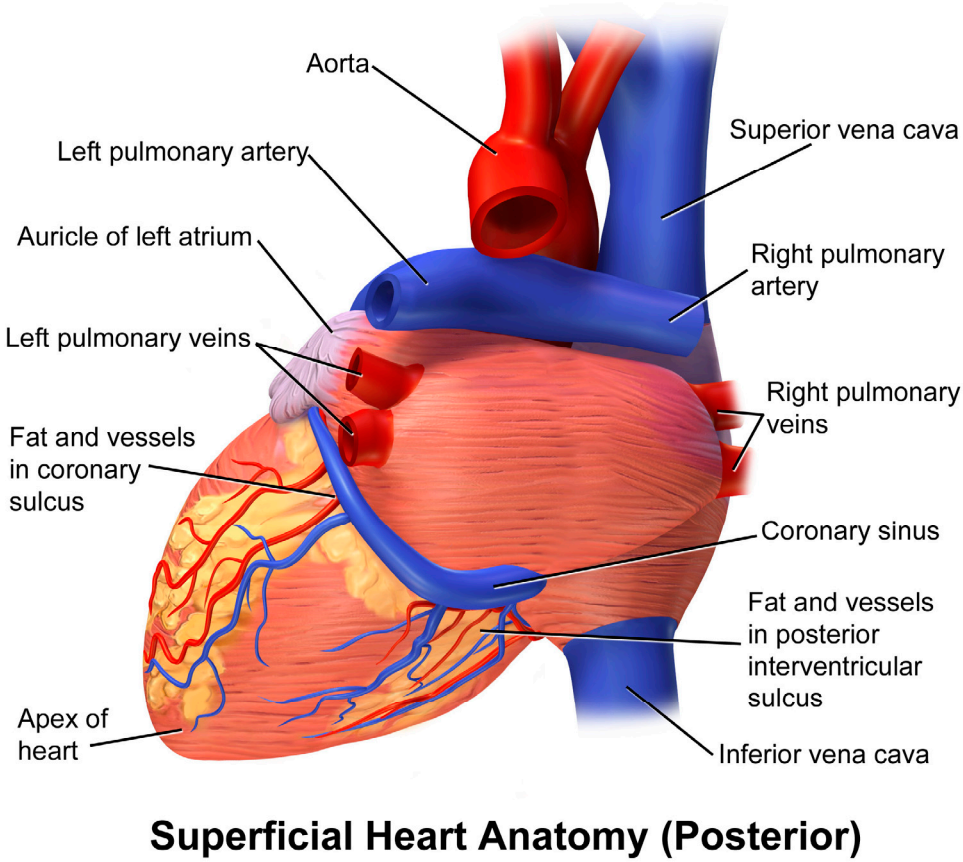

Figure 6. Reprinted under Creative Commons license, original publication: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicin 1 (2).

The most common anatomic variant, around 80% of individuals, exhibit one right coronary artery supplying the right heart and the septum as well as the posterolateral part of the left ventricle, and a separate left coronary artery supplying the left ventricle via the left ascending artery and the circumflex artery (right dominance). Other common variants include when the circumflex or left ascending artery supplies the septum and the posterolateral part of the left ventricle (left dominance) or where both the right and left artery supply the septum and/or the posterolateral part of the left ventricle (balanced dominance).

SCCT guidelines for reporting cardiac computed tomography angiography (CCTA) divide coronary arteries into coronary segments (68), allowing clear communication of where a lesion, stenosis, or dissection is located, Figure 7. The most important segments include, for the right chamber and septum, the proximal right coronary artery (RCA)

segment 1, the mid RCA segment 2, and the distal RCA segment 3. For the left ventricle, the left main stem, segment 5, the proximal left ascending coronary artery (LAD) segment 6, mid LAD segment 7, and distal LAD segment 8. The proximal circumflex artery is assigned 11 and distal circumflex artery 13.

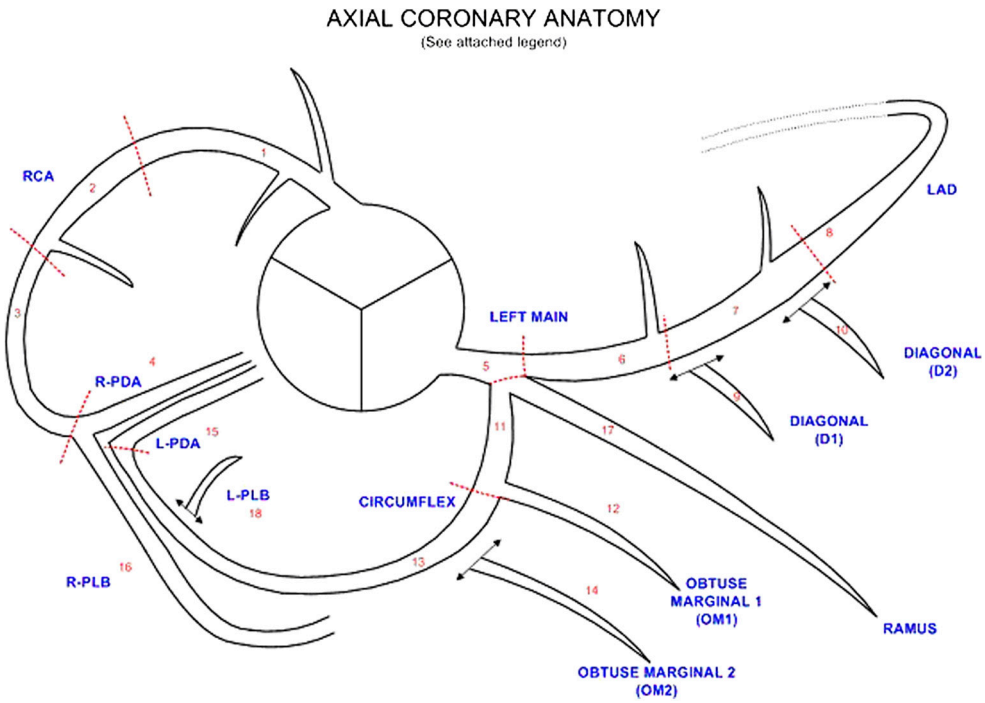

Figure 7. SCCT Coronary Segmentation Diagram. Axial coronary anatomy definitions derived, adopted, and adjusted from WG Austen, JE Edwards, RL Frye, GG Gensini, VL Gott, LS Griffith, DC McGoon, ML Murphy, BB Roe: A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association.
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Cardiac veins and coronary sinus display larger anatomic variance Figure 8 (69-71). The most common variant is when the coronary sinus empties into the right atrium. On the basis of the heart, the inferior interventricular vein runs in the interventricular sulcus, draining the septum. In contrast, the great cardiac vein runs parallel to the circumflex artery to the point where the left main coronary artery splits into LAD and the circumflex artery, at which point the vein leaves the course of the circumflex artery and instead follows LAD. In addition, veins are found along the left ventricle near diagonal and marginal arterial branches.

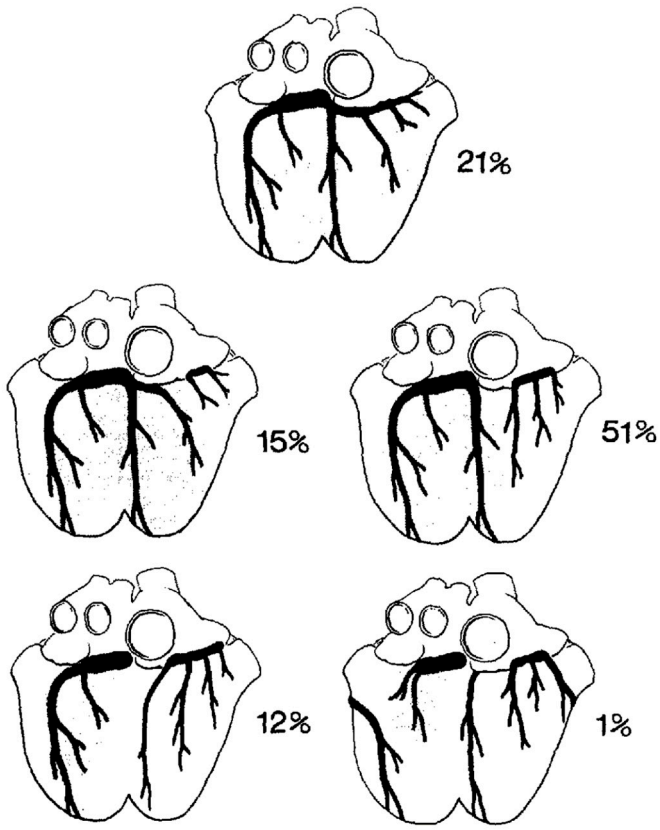

Figure 8. Inferior aspect of the heart. The distribution patterns of the tributaries of the coronary sinus and the venous myocardial drainage (shaded zones) vary to a considerable degree: in 21% of cases the coronary sinus collects all the ventricular veins, in 13% only a few cardiac veins flow to the sinus coronarius. The remaining veins open directly into the right auricle, most of them join the anterior cardiac venous system.
Reprinted from Surg Radiol Anat. 9(2):, M von Lüdinghausen, Clinical anatomy of cardiac veins, Vv. cardiacae, 159-68, Copyright (1987), with permission from Springer Nature. (69)

As the heart contracts to pump blood to the lungs and the body, it repeatedly fills and empties. Left ventricular volume is at its largest at the very beginning of diastole and at its smallest at the end of diastole or the beginning of systole.

The contractions affect the arteries and the heart's veins by having different filling pressures throughout the cardiac cycle. The cardiac veins are at their largest diameter in systole. (72) The arteries also change in diameter over the cardiac cycle. (72) As the heart contracts, both arteries and veins change location, which is essential during cardiac computed tomography angiography, discussed below.

Myocardial bridging is an anatomic variant where a coronary artery is located within the cardiac muscle instead of on the surface of the heart. This is believed to be congenital and is more commonly seen in patients with hypertrophic cardiomyopathy. (73) The prevalence and clinical relevance of myocardial bridging have been debated. (74)

Epidemiology

John Snow is considered the father of modern epidemiology. During the cholera epidemics in London during the first half of the 19th century, he and his team created a map of London where the cases were depicted. This led them to believe the disease was waterborne, as cases clustered around a water pump on Broad Street. The fundamentally novel approach lay in viewing the cases not as individual ones, but as pieces of the larger puzzle constituted of the environment they lived in. (75)

Modern epidemiology can be defined as the study of the occurrence and distribution of health-related diseases or events in populations, including their determinants and control. Different study designs include observational studies (e.g., cross-sectional, case-control, and prospective cohort studies) and experimental studies (such as randomized controlled trials). The different study designs limit the conclusions one can draw, as causative relations cannot be concluded from observational studies. However, observational studies provide valuable information regarding the prevalence of disease, which influences how prioritized a disease or health-related event should be in research and society. The Framingham study was one of the first larger population-based observational studies designed to seek out risk factors for cardiovascular disease. Initiated by the US Public Health Service and developed in 1948, this study is still ongoing in the third generation of participants, indeed, a longitudinal design. (76) In the same era, Doll and Hill gathered a cohort of patients admitted to London Hospitals, some of whom were patients with lung cancer. They were all interviewed regarding smoking habits, the conclusion being that smoking is strongly associated to lung cancer. (77) The Department of Clinical Sciences in Malmö, the academic institution behind this thesis, has historically undertaken several longitudinal cohort studies of the general population, such as "The men of 1914", "Malmö Diet and Cancer Cohort", and is presently one of the sites for the national SCAPIS (Swedish CArdioPulmonary bioImage) study. The Malmö Diet and Cancer study showed an association between intake of pork and processed meat, and colorectal cancer, and Paper I in this thesis includes data from the cohort. (78) Data from SCAPIS is included in this thesis in Paper III and IV. Paper II included in this thesis is a proof-of-concept study, part of the CRT-clinic study, a prospective randomized controlled study. (79) A stronger

indication that a risk factor has a causal effect can be achieved in Mendelian randomization studies. This is a type of observational study, where a risk factor is first tested to be associated with a disease, and a genetic variant is tested to be associated with a disease. Then the genetic variant associated with the risk factor is tested in relation to the disease. Lastly, the genetic estimates are used to calculate a causal estimate of the risk factor. (80)

Like all studies, epidemiological studies are affected by random error, where chance or fluctuations of measurements influence the data. This effect can be reduced by a larger number of measurements or study participants. Specifically, epidemiological studies are also affected by three types of systematic error: selection bias, information bias, and confounding. Selection bias occurs when selecting the participants in a study. The study participants must reflect the target population one wants to draw conclusions for as closely as possible. If one wants to know the prevalence of a disease in Sweden, we must recruit study participants from places representative of where Swedes live, in cities or the countryside. A study recruiting only from the countryside would not be representative of all Swedes. Different types of bias occur when study participants respond or do not respond to a study invitation. A person concerned over cardiovascular disease due to family history might be more prone to participate in the study, creating a self-selection bias. Information bias occurs when cases or non-cases are misclassified. One type of information bias happens when a study participant does not remember exposure in the past and is misclassified due to this recall bias. Confounding occurs when an extraneous variable is associated with both the outcome and the exposure. This distorts the relationship between an exposure and an outcome, which might lead to a false conclusion on causality.

Cardiovascular Imaging in thesis

The clinical workup of cardiovascular medicine relies partly on imaging. Non-invasive imaging modalities in cardiovascular imaging include computed tomography (CT) and ultrasound, whereas invasive imaging includes histology of a lesion or process, and coronary angiography by catheterization. The latter allows for treatment of lumen narrowing in coronary arteries via percutaneous coronary intervention, a procedure where balloons and/or stents are introduced via catheters to widen the narrowed site in the coronary artery.

Three of the papers in this thesis include findings from CT imaging: Paper II of cardiac veins and Papers III and IV of cardiac arteries. Paper I and III include findings from carotid artery ultrasound and histology.

Computed Tomography

The first clinical image by computed tomography (CT) was produced in 1971. Computed tomography is an imaging modality based on X-rays, which were first described in 1895 by Wilhelm Röntgen (81). X-rays are generated by aiming electrons from a cathode to hit an anode, which results in X-rays. Original X-ray images were two-dimensional and require a second exposure to accurately locate a structure within a body. All structures are superimposed in the images. In the second half of the 20th century, computational methods made it possible to create an image where the body was instead represented as slices, with structures depicted as they lay inside the body. In 1979, Allan M. Cormack and Godfrey N. Hounsfield shared the Nobel Prize in Physiology or Medicine for their findings leading up to the development of computed tomography. (82)

The most common anode material in computed tomography is Tungsten. The CT is constructed so the patients lie on a bed while the machine forms a ring-like structure around the patient – the gantry. The generator and the detector spin around the patient at a speed down to 250ms per revolution. Photons with high enough energy to pass through the human body are registered on the opposite side. Depending on the atoms constituting the tissues the photons travel through, the photons interact differently, and the tissues attenuate differently. Thus, discrimination between lungs, bones, heart, as well as normal arteries vs arteries with atherosclerotic plaques is possible.

High temporal resolution is key when imaging moving organs such as the heart. The temporal resolution is dependent on the rotation time, and much of the rotation is used for image creation. This is why temporal resolution is higher when only 180 degrees of data is used. Temporal resolution is a critical factor in acquiring high-quality cardiac computed tomography angiography (CCTA) images. Ideally, the entire heart is covered in one heartbeat. Another factor related to image quality is delivering enough radiation to create an image of low enough noise, which is in turn related to tube capacity. Spatial resolution is proportional to detail in the image, and in part to the sharpness, while reconstruction algorithms can improve perceived sharpness.

Detector specifications, such as detector width, detector constitution, detector element size, efficiency, and speed of response, all influence the image quality. Today's CT system can simultaneously sample several slices, depending on the number of detector rows and the number of radiation sources used. The maximum number of rows in a detector today is 320. The width of each detector row multiplied by the number of detector rows is the total detector width. A 0.625mm wide detector row in a 128-row CT has the total detector width of 8cm in a single source CT.

Coronary computed tomography angiography CCTA

In order to acquire images of the heart and coronary vessels, the image acquisition must be synchronized with the beating of the heart. The patient is monitored with an ECG registered simultaneously with the image data and reconstructed so that each set of images represents a cardiac phase. In the setting of CCTA, cardiac phase is often defined as % of the cardiac cycle after a QRS-complex and otherwise as the time from a QRS-complex in milliseconds. The latter is better used when the heart rhythm is irregular.

Briefly mentioned above, fractional flow reserve is a measure to assess the degree of stenosis in coronary arteries. Fractional flow reserve can be measured invasively during coronary catheterization to better guide treatment with stents. The cut-off value for treatment is ≤0.8 in FFR, as suggested after the FAME study (83). CT-FFR is a non-invasive way to get comparable values from CCTA exams using algorithms. Studies have shown that using CT-FFR to select patients for invasive coronary angiography, resulting in fewer angiograms performed, is safe. (84, 85)

Preparing the patient

As briefly touched on above, the patient's heart rate and variability determine in which part of the cardiac cycle the heart will be still for the longest time. To make this brief moment as long as possible, and to avoid the need to scan in both diastolic and systolic part of the cardiac cycle, patients are premedicated with intravenous or oral β-blockers to lower the pulse (86), aiming for a pulse below 60 beats per minute (or 65, depending on scanner type available), if not contraindicated. Oral β-blockers take up to 60 minutes to have full effect, why it is important to call the patients in sufficient time to measure blood pressure, insert a periferal cannula and inform the patient prior to the exam.

In addition, patients are premedicated with nitroglycerine, either sublingual or sublabial, to enable accurate stenosis grading. This has the same effect as when administered in the setting of anginal pain - the arteries are widened, and they can be assessed more adequately.

Contrast medium

Contrast medium enhancement is needed to examine luminal alterations of the vessels. Iodine contrast mediums are used and administered intravenously, tailored to patient size, scan protocol used, and timed so that the contrast is present at the site of interest, Figure 9. (87, 88) Contrast protocols differ widely between institutions worldwide, and there are no defined international recommendations and guidelines as of yet. (89)

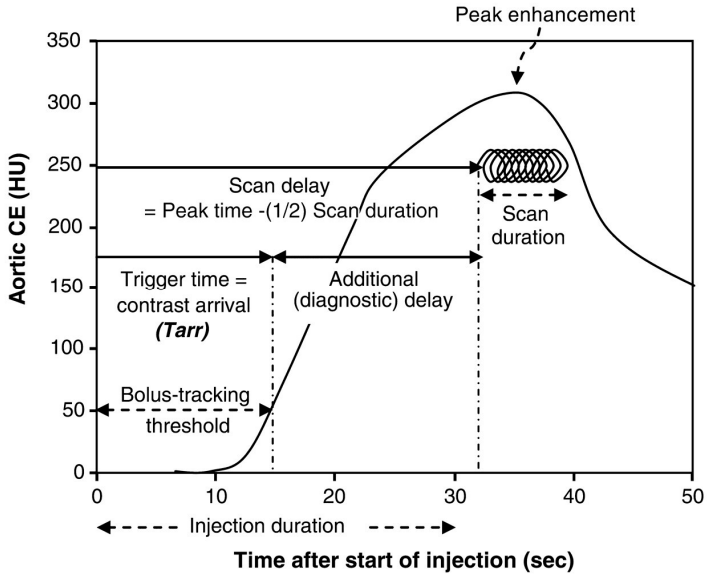

Figure 9. Graph of contrast medium injection, enhancement, and scan time variables illustrates the determination of scan delay from measured contrast material arrival time (Tarr) and additional diagnostic delay. Scan delay should be determined by considering contrast medium injection duration, contrast material arrival time, and scan duration. Contrast material arrival time can be measured with a test-bolus or bolus-tracking method. In the figure, when bolus-tracking is used, contrast material arrival time corresponds to the time for the aortic enhancement (CE) to reach a 50-HU threshold. The scan delay is determined as the sum of contrast material arrival time plus an additional (diagnostic) delay. The additional diagnostic delay should be formulated considering the injection duration and scan duration such that the peak enhancement is centered in the middle of CT scan (scan delay = peak time – (1/2) scan duration). Reprinted from Bae KT. Intravenous contrast medium administration and scan timing at CT: considerations and approaches. Radiology. Jul;256(1):32-61. Copyright (2010) with permission from Radiological Society of North America (RSNA) (87)

Contrast medium is tailored so that larger patients receive more contrast in order to enhance properly. Arterial imaging requires faster administration and earlier image acquisition to enhance arteries brightly compared to imaging of parenchymatous organs such as the liver. Usage of lower kV allows for lower dose of contrast. (88, 90, 91) By rule of thumb, when changing the dose and injection rate from a 100kV scan protocol to an 80kV scan protocol, both can safely be reduced by 50%.

The different elements attenuate differently, but all attenuate less as the energy level of the X-rays increases. The attenuation curve for Iodine is indicated by the red line in the figure below. In practice, this means that the lower keV the electrons have, the more they attenuate, and the brighter a structure stands out on an X-ray exam. Higher keV is achieved by raising the kV of the tube. In Figure 10 , the mean tube voltage of 80kV corresponds to roughly the mean energy of 56keV in the graph (the maximum energy for x-rays produced at 80kV is 80keV).

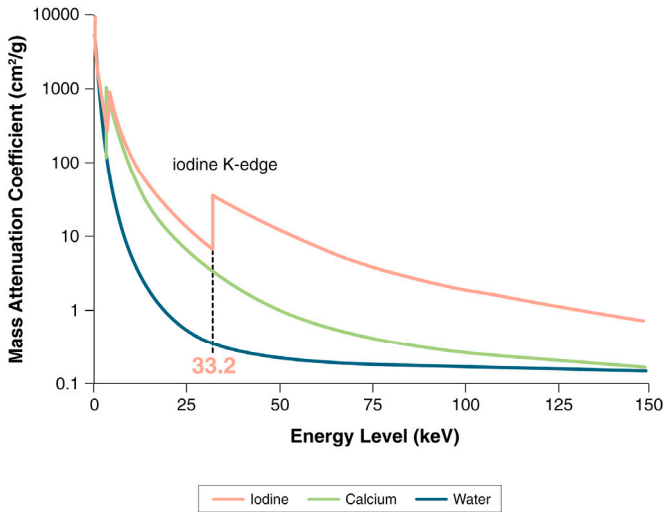

Figure 10. Mass Attenuation Coefficients for Iodine, Calcium, and Water at Different Photon Energies Note the attenuation peak of iodine (Z = 53) at 33 keV. This peak represents the K edge of iodine. Reprinted from JACC Cardiovasc Imaging, Jun;8(6), Danad I, Fayad ZA, Willemink MJ, Min JK. , New Applications of Cardiac Computed Tomography: Dual-Energy, Spectral, and Molecular CT Imaging, 710-23, Copyright (2015), with permission from Elsevier (92)

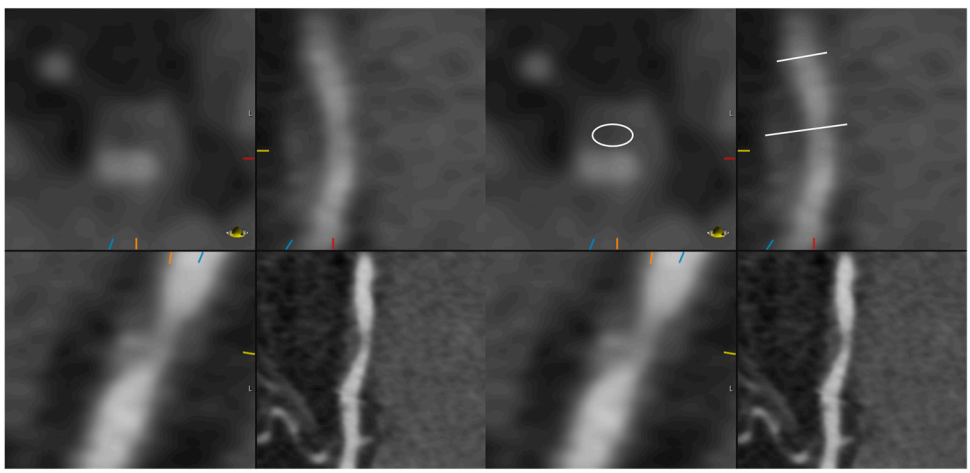

Figure 11. Example of a coronary artery plaque in RCA with low attenuation, napkin-ring sign and positive remodeling. Oval shape encircles a low attenuating area. The two white lines marks the artery diameter, the ratio between longer and shorter line being ≥1.1. With kind permission from the patient.

As mentioned above, the coronary arteries change location over the cardiac cycle. In general, the arteries are most still in mid-diastole for a pulse less than 70 beats per minute, while they are still for the longest time in end systole. (93) Each patient is different, with a gradual scale from diastole to systole being the most preferable phase

of scanning in the interval, depending on anatomic variation and differing between vessel territories. For pulse 61 (sometimes 66 or even 70, depending on CT scanner type and brand) and above, or when the heart rate is unstable, images in both systole and diastole are acquired when performing cardiac CT, and are needed to minimize motion artefacts in images. (94)

Coronary abnormalities such as atherosclerotic plaques are visible as vessel wall changes, sometimes with luminal narrowing. In contrast to invasive coronary angiography, where catheters are inserted into the arteries and contrast is given in the coronary arteries, and only luminal changes can be detected, CCTA allows for imaging of the wall and surrounding structures. Thus, positive remodeling, where the plaque makes the artery wider at the site of the plaque than adjacent non-affected artery, can be detected. CCTA has, over time, partly shifted focus from stenosis assessment to plaque detection. In addition, some plaques exhibit features associated with worse outcome; high-risk features.

Plaques with two or more high-risk features should be reported. High-risk features include positive remodeling, spotty calcifications, napkin-ring sign, and low attenuating (<30HU) plaques.(95) In Figure 11 shows an example of a coronary artery plaque with positive remodeling and napkin-ring sign, and in Figure 12, from a donated heart, CT features of coronary artery plaques with corresponding histology.

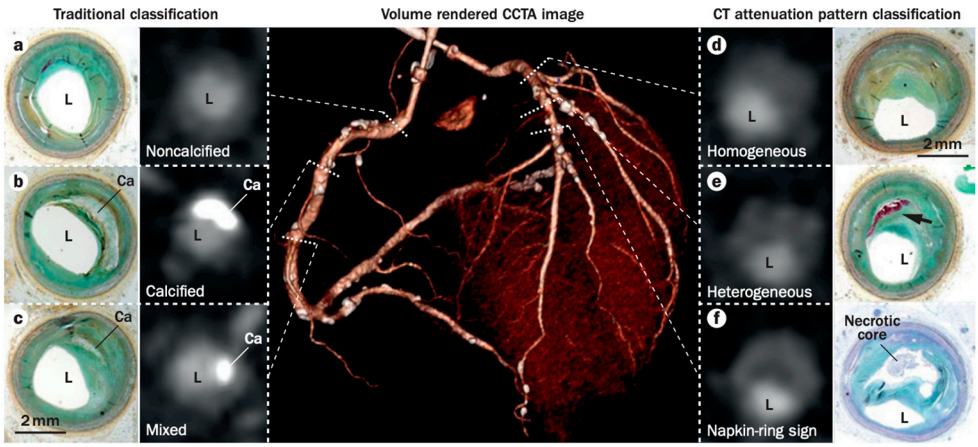

Figure 12. Traditional and attenuation pattern-based plaque classification schemes in CCTA. The centre panel shows a volume-rendered CCTA image of a cadaver heart. The traditional plaque classification scheme differentiates between a | noncalcified, b | calcified, and c | partially calcified (mixed) plaques. CT attenuation pattern-based classification (right panel) differentiates between d | homogeneous, e | heterogeneous, and f | napkin-ring plaques. The corresponding histology slides show a | pathological intimal thickening, b | fibrous plaque with sheet calcification, c | pathological intimal thickening with spotty calcification, d | a fibrous plaque, e | early fibroatheroma with intraplaque haemorrhage (arrow), and f | a late fibroatheroma with large necrotic core. Abbreviations: Ca, calcium; L, lumen.
Reprinted from Nature Reviews Cardiology 11, 390–402 (2014), Maurovich-Horvat P et al., Comprehensive plaque assessment by coronary CT angiography, Copyright (2014), with permission from Springer Nature.**(44)**

Ultrasound

An imaging modality where sound waves travel through the examined tissue, ultrasound is unsuitable for tissues containing air, or dense regions such as mineralized bone and heavily calcified plaques. A transducer is held to the skin, prepared with gel to fill the small airspaces between the transducer and the skin's surface. The transducer both emits the sound sent through the body and receives the reflected sound. The detected reflected sound is transformed into images of the examined body (96). In addition to creating an anatomical map, ultrasound can also be used for measuring the velocity of fluids, useful when assessing heart valves or quantifying the degree of stenosis in carotid artery plaques. Ultrasound was first used to examine the human body, more specifically the human brain, in 1942 by Karl Theodore Dussik in Austria. The first echocardiography – imaging of the heart by ultrasound – was done and also implemented clinically at Lund University Hospital, where Inge Edler and Helmuth Hertz had been developing the method since October 1953 (97).

The non-invasive and relatively inexpensive machines make ultrasound quite accessible globally. Today, ultrasound is used in diverse areas, from examining organs such as the liver and kidneys, gallbladder, and bile ducts to arterial and venous vessels. Ultrasound is also used to guide invasive procedures such as drainage tube placement and tissue sampling. In this thesis, ultrasound was used to examine carotid arteries in Paper I and Paper III. In Paper I, subjects in the Malmö Diet and Cancer Study were examined by ultrasound of the right carotid artery to assess atherosclerosis. In the CPIP cohort, patients were examined with carotid ultrasound to assess the degree of stenosis. In Paper III, subjects were examined by ultrasound of both carotid arteries to assess atherosclerosis. Figure 13 shows an example of an ultrasound image of a carotid artery with an atherosclerotic plaque and thickening of the vessel wall.

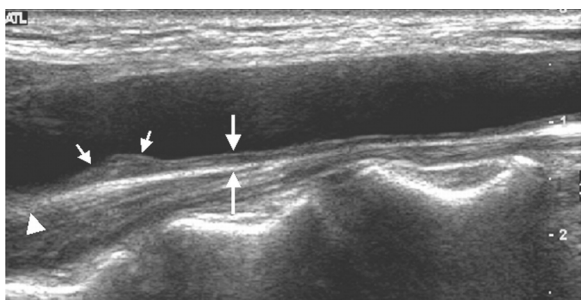

Figure 13. Longitudinal scan of carotid ultrasonogram. Measurement of CCA-IMT (large arrows) at the far wall of the common carotid artery is shown. The carotid plaque (small arrows) in the distal common carotid artery is seen. The arrowhead represents carotid bifurcation.
CCA-IMT: Common Carotid Intima-Media Thickness
Reprinted from AJNR Am J Neuroradiol 2007 May;28(5): Lee EJ et al. Relevance of common carotid intima-media thickness and carotid plaque as risk factors for ischemic stroke in patients with type 2 diabetes mellitus. 916-9.

Histology

As mentioned above, Antoni van Leeuwenhoek undertook experiments with erythrocytes. This was made possible by his invention of the one-lens microscope, by which he examined other samples from the human body. (99) To enable examination by histology, the tissue must be prepared. This can be divided into different stages, namely fixation, embedding, sectioning, and staining. As tissues slowly degrade if untreated, different fixation methods were developed. A commonly used method is fixation in formalin. After this, the tissue can be embedded in paraffin and then sliced into thin sections, whereafter they are stained with different staining methods in order to give different cell components contrasting colors. (100) For example, hematoxylin is a classic stain for coloring cell nuclei purple/blue, whereas eosin is a stain used to color connective tissue, cytoplasm, and other extracellular components red. In more modern times, antibodies have been manufactured to stain after adhering to different surface proteins, such as α-actin in smooth muscle cells, macrophages, or as in the first pane in Figure 14, acidic sphingomyelinase, a type of bioactive lipid. This technique is termed immunohistochemistry, and new antibodies are constantly being developed, examples in Figure 14. (101).

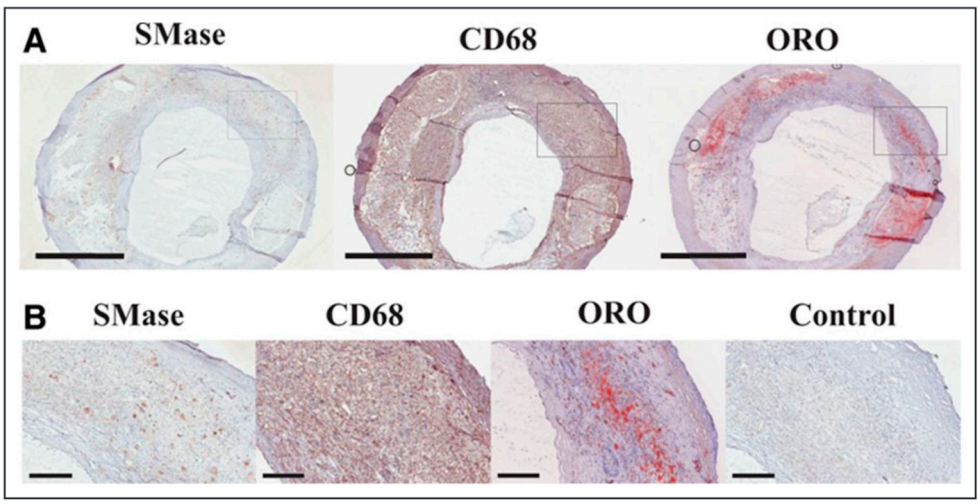

Figure 14. A) Histological staining for acidic sphingomyelinase (A-SMase), macrophage (CD68), and lipid (oil red O [ORO]) location and the presence in the human atherosclerotic plaque. **B)** Amplifications of the inset showing colocalization between SMase, CD68, and ORO, as well the negative control for A-SMase. Scale bars, 2 mm (A) and 300 μm (B).
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Aims

The overall aim for this thesis was, using imaging findings in the pursuit to predict, plan, advice and find relevance in the setting of cardiovascular disease.

Specific aims of the individual papers were:

I. To predict the risk of future ischemic stroke related to levels of circulating soluble lectin-like oxidized low-density lipoprotein receptor-1 (s-LOX1), with and without presence of carotid artery plaque, and 2) to study the release mechanisms of sLOX-1 and how sLOX-1 relates to plaque inflammation.

II. To map cardiac veins prior to cardiac synchronization therapy pacemaker implantation and transfer findings into a 17-segment model of left ventricle myocardium, in the setting of heart failure pacemaker lead placement, and 2) to investigate whether the cause of heart failure, sex, ECG appearance, or used scan protocol or machinery was associated with the number and distribution of coronary vein tributaries.

III. To relate 1) obesity and 2) overweight to severity of coronary and carotid artery disease in the absence or presence of metabolic risk factors, and 3) to evaluate the individual criteria for metabolically healthy obese and their association with atherosclerosis in carotid and coronary arteries.

IV. To compare presence and characteristics of coronary myocardial bridging in chest-pain patients versus non-chest pain subjects, and 2) to relate presence of ventricular arrhythmia to myocardial bridging in LAD for non-chest pain subjects.

Materials and Methods

Study population(s) and methods

Paper I

Malmö Diet and Cancer Cohort (MDC) cohort

All inhabitants in Malmö City were invited to participate in the study between 1991 and 1996. In total, 28,449 individuals accepted participation and completed the screening examinations. In addition, 6,103 subjects, randomly selected, were invited to participate in a more targeted cardiovascular sub-study of carotid artery disease. These subjects underwent carotid artery ultrasound, and 5,508 of them also donated fasting blood samples. All subjects gave informed consent, and the local ethical committee approved the study (LU 51-90). 805 subjects were excluded due to prior stroke (n=48) and missing baseline data, plasma LDL (n=26), or cholesterol (n=731).

Inclusion questionnaires obtained information on diabetic history, intake of antidiabetic, lipid-lowering, blood-pressure-lowering medication, and history of previous and current smoking. Subjects were measured without prior fasting, wearing light clothing and no shoes, in height (m), weight (kg), and their waist circumference was obtained. A blood sample was drawn; cholesterol and glucose levels were analyzed on a fresh sample. LDL levels were calculated according to the Friedewald formula. (103). A centrifuged EDTA-treated plasma sample was frozen to -80 degrees C for all participants.

Follow-up was obtained by consulting the national health and death registers. All participants were followed from baseline examination until first hospitalization for acute ischemic stroke, death, emigration, or end of follow-up, which was set to December 31, 2010, corresponding to a mean follow-up time of 16.5 +/-3.6 years.

Subjects also underwent an ultrasound of the right carotid artery, including 3 cm of the common carotid artery, the carotid bifurcation, and 1 cm of the internal and external carotid artery, respectively. A focal thickening of the intima-media layer of more than 1.2mm and a minimum area of 10mm was considered a plaque.

In total, 4,703 subjects were available to study s-LOX1 in relation to incidence of ischemic stroke.

Carotid Plaque Imaging Project (CPIP) cohort

Between November 2005 and October 2012, 202 patients who underwent carotid endarterectomy (two who underwent bilateral operation) at Skåne University Hospital, a tertiary referral center, were included in the study. For all patients, the indications for surgery (104) were met: they either were symptomatic (diagnosed with stroke, amaurosis fugax, and transient ischemic attack) and luminal stenosis over 70% or asymptomatic and luminal stenosis over 90%.

To measure sLOX-1, blood samples were collected the day before surgery, whereas lipoprotein and CRP levels were analyzed locally on fresh blood samples. The carotid plaques were collected at surgery and snap frozen in liquid nitrogen. A 1-mm-thick slice from the most stenotic region of each plaque was removed for histology. In 66 of the plaques, an additional 1-mm-thick slice was removed for genetic analysis. The remaining parts of the plaques were homogenized. (105)

In plaque homogenate supernatants, analyses were made for Interleukin-6, macrophage inflammatory protein-1β, soluble CD40 ligand, tumor necrosis factor-α and fractalkine.

Cryosections (8μm) of the most stenotic region of the plaque were stained for neutral lipids. The cryosections were assessed for percentage and/or co-localization of macrophages, vascular smooth muscle cell α-actin, intraplaque hemorrhage, collagen I–positive area, collagen III–positive areas, LOX-1, and nuclei. The percentage of the respective stained areas were quantified blindly.

For the LOX-1 gene, plaque tissue from 66 carotid plaques were used, where the gene expression of the regulating gene for oxLDL receptor 1 was assessed as previously described. (106)

Proximity Extension Assay (provided by O-link) is a method where specific antibodies carrying unique DNA tags bind to corresponding proteins in samples, the DNA is then replicated by PCR, and the level is measured. By this method, level of sLOX-1 was measured in EDTA plasma samples from both cohorts, MDC and CPIP. sLOX-1 was also measured in plaque homogenates from CPIP. Plasma samples from both cohorts were prior to analysis stored frozen in -80°C. sLOX-1 was expressed as arbitrary units on a $\log_2$ scale.

Healthy donors provided peripheral blood mononuclear cells (PBMCs) where these cells were isolated. These cells were subsequently seeded into a non–tissue-treated round-bottomed well plate in complete RPMI (Roswell Park Memorial Institute

medium), a cell medium where nutrients and other components support the growth and survival of cells) with 2% human serum.

Human umbilical vein endothelial cells (HUVECs) and human coronary artery smooth muscle cells were passaged and cultured in Medium 200 and Medium 231, respectively, including serum growth supplement to reach a confluency of about 90%. The cells were then seeded into a tissue-cultured, flat-bottomed, well plate. The cells were thereafter starved in respective medium for 24h, and then stimulated. PBMCs were stimulated with TNF-α (10–100 ng/ mL), interleukin-1β (10 ng/mL) and transforming growth factor-β (1–10 ng/mL). PBMCs, human coronary artery smooth muscle cells, and HUVECs were also stimulated with copper-oxLDL (25 μg/mL). (107) HUVECs were stimulated with native LDL (100 μg/mL), high-density lipoprotein (50 μg/mL), and very LDL (100 μg/mL). Medium was stored in -20°C and further analyzed for sLOX-1 using sLOX-1 human ELISA, in all cultures.

HUVECs were detached from the plate, and HUVECs and PBMCs were stained and run immediately on a Gallios flow cytometer to assess cell viability.

Paper II

Patient cohort

At our tertiary referral hospital, 99 consecutive patients who met international recommendations for CRT pacing were enrolled in the study. The local ethics committee approved the study, and all patients gave informed written consent. To be included, patients had to have a QRS duration >120ms in the ECG, a left ventricle ejection fraction less than 35% and symptoms of heart failure corresponding to NYHA class II-V after medical treatment had been optimized. Patients with severe renal failure (EGFR <30mL/min) and/or chronic atrial fibrillation were excluded.

In order to aid preoperative planning prior to CRT-lead placement, contrast enhanced cardiac CT scans were conducted, where the contrast was targeted to enhance the cardiac veins, with the purpose to identify possible landing sites for CRT-lead placement. All patients underwent a cardiac CT examination tailored to patients' weight, heart rate, and regularity, either by Philips 128-detector iCT (Philips Medical Systems, Best, The Netherlands), 256-detector row iCT (Philips Medical Systems), or 256-detector row Siemens Definition Flash (Siemens Medical Systems, Erlangen, Germany).

Cardiac CT examinations

Contrast was given by contrast injector. For the Philips systems, contrast was timed via bolus triggering with a region of interest set in either the ascending or the descending

thoracic aorta. The triggering threshold was set to 150 Hounsfield units. For the Siemens system, test bolus with region of interest in ascending aorta was used. Two different contrast agents were used, either Omnipaque 350 mgI/mL or Iomeron 400 mgI/mL. To obtain contrast enhancement in the cardiac veins, for the patient cohort with severe heart failure, an additional 15 second delay was added compared to arterial enhancement. This resulted in diagnostic images in regards of venous enhancement for all patients.

Cardiac vein analysis

To link existing cardiac veins to cardiac segments according to the standard 17-segment model of the left ventricular myocardium, (108) CT images were reconstructed into a short-axis view of the left cardiac chamber, illustrated in Figure 15. All reconstructed images were analyzed for presence of cardiac veins by an experienced thoracic radiologist (Hanna Markstad), together with an experienced electrophysiologist (Rasmus Borgquist). All vein branches were then analyzed for clinical relevance. This meant that veins with a diameter less than 1,5mm prior to emptying in the great cardiac vein, veins less than 1-2cm in total length, veins with a very acute angle versus the great cardiac vein (meaning impossible to place an electrode in) or veins with a septal course (in practice meaning veins less than 1 cm from the interventricular groove), on both on the anterior and inferior cardiac segments, were excluded, determined not eligible for pacemaker lead placement.

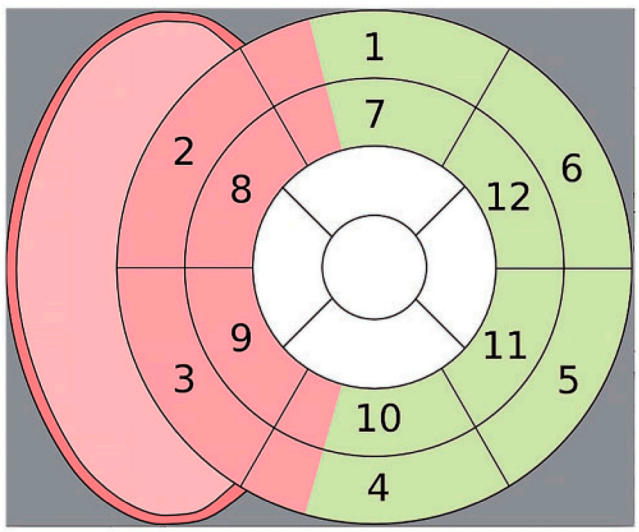


Figure 15. An adapted 17-segment model of the heart, where segments eligible for CRT electrode placement are colored light green, and all other parts of the LV segments and the right ventricular free wall are colored light red. The numbers represent the respective number of each segment, as used in the standard 17-segment model (19).

Data from a representative patient is shown in Figure 16.

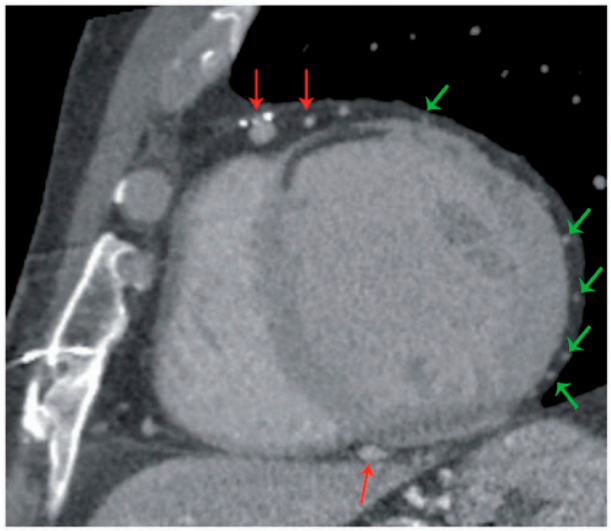


Figure 16. MDCT image showing mid segments at the level of the papillary muscles of the left ventricle. Red arrows indicate middle cardiac vein (lower red arrow), great anterior cardiac vein (upper left red arrow), and paraseptal branches (upper right red arrow) not of interest for CRT electrode placement; green arrows indicate veins that could be suitable for CRT electrode placement.

Veins eligible for lead placement was defined as all veins originating from coronary sinus after the middle cardiac vein (placed in the inferior interventricular sulcus) and the great anterior cardiac vein (placed in the anterior interventricular sulcus, plus side-branches from the middle- and great anterior cardiac veins in case their course was less than 2 cm from the septum. We defined a suitable left ventricular segment as a segment with at least one vein that fitted these criteria, and in cases where two veins traversed the same segment, the segment was counted as one.

Paper III

In the third paper included in this thesis, we wanted to be able to provide better advice for doctors and patients with obesity or overweight in relation to cardiovascular disease. The clinical workup in the setting of cardiovascular diseases includes measuring blood pressure, blood lipids, markers for diabetes, etc. Definitions for who is metabolically healthy are not entirely coherent. The most common way to define metabolic disturbances is to use the National Cholesterol Education Program (NCEP) consensus criteria for metabolic syndrome (MetS). (109) When metabolic biomarkers, excluding weight, are within the normal range, a patient is termed "Metabolically healthy". The existing knowledge on how obesity itself affects the risk for cardiovascular disease is

divergent, and no prior study had taken into consideration both carotid and coronary artery atherosclerosis in relation to obesity.

Study cohort

Paper III and Paper IV both incorporate data from the Swedish CardioPulmonary Imaging Study (SCAPIS). The SCAPIS project enrolled 30,154 participants from the six largest university sites in Sweden. Individuals were invited to participate during 2013-2018 and ranged in age between 50-65 years. 50% of all invited accepted the invitation, 51% of them were women. Detailed information on recruitment has been previously published (110). Paper III included individuals with both good-quality carotid ultrasound and coronary computed tomography angiograms, and data on risk factors included in the criteria for metabolic syndrome. Individuals with prior self-reported stroke, peripheral artery disease, angina pectoris, myocardial infarction, and coronary revascularization (n=1066) were excluded. This left 23,674 individuals for evaluation in Paper III. The Ethics Committee in Umeå approved the study for all sites, and written informed consent was given by all participants.

Carotid ultrasound

For all participants, both the left and right carotid arteries were examined for presence of atherosclerosis using a standardized protocol with a Siemens Acuson S2000 ultrasound scanner with a 9L4 linear transducer. The protocol included assessing for plaques in the common carotid artery, bulb, and internal carotid artery. Plaques were defined as focal structures protruding into the arterial lumen by at least 0.5 mm, or 50% of the surrounding Intima-Media Thickness (IMT), or an intima-lumen thickness >1.5 mm.

Coronary computed tomography angiography - CCTA

The cardiac imaging protocol used in SCAPIS has been described in detail previously. (110) In brief, after exclusions due to impaired renal function or contrast allergy, all participants were examined on dual-source CT scanners. All participants were given β-blocker (metoprolol) and sublingual glyceryl nitrate prior to the examination in order to lower and stabilize heart rhythm and to dilate the coronary arteries, respectively. For enhancement of coronary arteries and detection of non-calcified plaques, all participants were given Omnipaque 350mgI/mL at a dose of 325 mg/kg body weight. The first CT cardiac scan was a gated non-contrast scan used to calculate calcium score according to Agatston (111). Five different CT protocols were used, tailored to heart rate and variability, presence of calcification on the non-contrast scan, and body weight. Thus, participants were examined at 100 or 120 kV. Images were reconstructed and coronary segments were examined for presence of plaque and degree of stenosis, as

previously described (112), by categories: 1) no atherosclerosis, 2) 1–49% stenosis, 3) ≥50% stenosis. Luminal obstruction was defined by visually estimating diameter stenosis using the average of the longest and shortest diameters at the site of stenosis and comparing with adjacent healthy part of the vessel (if present). Plaques were characterized as calcified or non-calcified. In case of blooming artefacts (presence of calcium making accurate stenosis assessment impossible), segments were coded as 1–49% stenosis, and segments where pulsation artefacts or other technical reasons made the segment unassessable were coded as missing data. The highest degree of stenosis in the coronary vessel bed defined the classification of individuals. A segment involvement score (SIS) was calculated (113). The calcium score deducted from the non-contrast scan defined three groups: 1) 0 (60% of the sample), 2) 1–100 (28% of the sample), 3) >100 (12% of the sample).

Risk factors

All blood samples were collected after an overnight fast. Glucose, total cholesterol, HDL-cholesterol, and triglycerides were analyzed according to local routine at the respective site. HDL-cholesterol was defined as total cholesterol minus HDL-cholesterol. Blood pressure was measured twice in both arms after 5 min rest lying down on the back. The mean value of the two measurements from the arm with the highest mean level was used. Waist circumference in centimeters was measured at the level of the iliac crest. Weight in kg and height in meters were measured, and BMI was calculated (weight/height^2).

Lifestyle factors

Questionnaires were filled out to obtain information on disease history and lifestyle factors. Exercise was categorized by frequency in five categories: 0 = no exercise, 1 = only occasionally exercise, 2 = 1–2 times a week, 3 = 2–3 times a week, and 4 = more than 3 times a week. Education was stratified into a three-level scale: 1) less than 10 years, 2)10-12 years, and 3) more than 12 years in school.

BMI/MetS subgroups

Three BMI-based groups were defined: 1) normal weight, BMI <25 kg/m^2, 2) overweight, BMI 25–29.9 kg/m^2, and 3) obese, BMI ≥30 kg/m^2. Metabolic syndrome was defined by the National Cholesterol Education Program (NCEP) consensus criteria; elevated waist circumference (≥94 cm in men and ≥80 cm in women), elevated triglycerides (>1.7 mmol/L), reduced HDL-cholesterol (<1.0 mmol/L in men and <1.3 mmol/L in women), elevated blood pressure (systolic ≥130 mmHg and/or diastolic ≥85 mmHg), and elevated fasting glucose (>5.6 mmol/L). If three or more criteria were present, the subject was considered to suffer from metabolic

syndrome (MetS). We defined six subgroups based on BMI and presence or absence of metabolic syndrome: a) normal weight without MetS, b) normal weight with MetS, c) overweight without MetS, d) overweight with MetS, e) obese without MetS, and f) obese with MetS.

Paper VI

Study population

For the final paper included in this thesis, we compared two groups: one consisting of patients with chest pain, and one of subjects from the general population without chest pain.

Chest pain patients from the SWEDEHEART register

SWEDHEART is the National Registry for patients with suspected or confirmed diseases of the heart, cardiac surgery, cardiac procedures, acute and chronic cardiac diseases, and a selection of diagnostic methods, including coronary computed tomography angiography (CCTA). (114) For adult patients, the indication for the angiography, background information, and findings on CCTA are routinely filed in the registry.

We included 511 consecutive chest-pain patients examined by CCTA, according to international guidelines (115), at Skåne University Hospital during 2018-2020. Seventy-seven patients were excluded, 45 without a contrast scan, 21 due to artefacts, six who did not fulfil the chest pain criteria (ruling out coronary artery disease according to guidelines) (95), and three who were also invited to the SCAPIS study, and lastly, one without an electronic health record. Thus, 434 chest pain patients remained for analysis after exclusions. The study was approved by the Swedish Review Authority (diary number: 2017/1022), wavering informed consent.

Non-chest pain subjects from SCAPIS

As for paper III, the second cohort for paper IV originates from The Swedish CArdioPulmonary BioImage Study (SCAPIS). For paper IV we included 200 randomly selected subjects examined by CCTA and ECG at the Malmö site of SCAPIS during two of the years the study took place (2016-2017). Three individuals were excluded due to technical imaging artefacts and one to previous by-pass surgery, so that 196 subjects remained for analyses.

SCAPIS has been approved by the Swedish Ethical Review Authority (decision numbers 2010-228-31; 2017/1022; 2020-00362). Written informed consent was obtained from all participants.

Computed tomography (CT)

-Acquisition

Coronary computed tomography angiography (CCTA) was performed on either a Siemens Definition Computed Tomography scanner (2x128 slice, Erlangen, Germany) or a Philips iCT scanner (256 slice, Eindhoven, the Netherlands).

All CCTAs were performed according to algorithms taking heart rate and regularity and body constitution in consideration using dose modulation to adjust kV and mAs as needed. Chest pain patients were scanned in accordance with clinical routine (with and/or without contrast), while all SCAPIS subjects were examined according to the research protocol that included both non-contrast and contrast scan.

For the dose-length product, this was calculated as the entire examination, meaning scanograms, non-contrast scans contrast monitoring and contrast angiogram were included. Unless contraindicated, oral and/or intravenous β-blockers and sublingual nitroglycerine were administrated to all.

Contrast CT angiography was performed using intravenous contrast, either Omnipaque 350mgI/mL (GE Health Care, Chicago, Illinois) or Iomeron 400mgI/mL (Bracco Altana Pharma GmbH, Konstanz, Germany). Contrast volume and injection rate were tailored to the individual patient size and type of scan protocol.

-Image analysis

Calcium score according to Agatston (111) was measured for all participants where a non-contrast scan was performed, and absence or presence of coronary artery disease was assessed by an experienced reader according to clinical routine and exported from either the SWEDEHEART registry or the SCAPIS electronic report form respectively. Coronary angiograms were assessed for incidence and characteristics of myocardial bridging (MB) by an experienced cardiac CT reader (Hanna Markstad, 12 years of experience at the time of analysis). The software used for MB assessment was Syngo.via (Siemens Healthineers AG, Erlangen, Germany), and all examinations were evaluated in sub-mm slices and multiplanar reconstructions.

24-hour EGC registration

For the non-chest pain subjects, a 24-hour ECG registration was made, and ECG data were analyzed using DeepRhythmAI (116), and registrations were standardized to 24 hours. We defined ventricular arrhythmia during the registration as more than 1000 premature ventricular complexes (PVCs) (117) and/or presence of ventricular tachycardia (VT), PVCs in bigeminy, PVCs in trigeminy, any coupled PVCs, triplets of PVCs. VT was defined as at least three consecutive PVCs with a heart rate above 100 beats per minute (118).

The occurrence of ventricular arrhythmia was related to prevalence of MB in individual cardiac segments, as well as the combination of LAD segments. As coronary artery plaque could be a possible confounder for arrhythmia (119), all association were corrected for presence of coronary plaque.

Risk factor assessment

Risk factors at baseline were, for chest-pain patients, obtained from the SWEDEHEART registry.

For the non-chest pain subject from the SCAPIS study, this was obtained from the baseline examination and by questionnaires. This included smoking status, anti-hypertensive, and lipid-lowering medication. Previous known diabetes, according to the baseline questionnaires, or new diagnosis according to baseline blood sample analysis, was used to define diabetes diagnosis. Systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg, or treatment with anti-hypertensive medication was used to define hypertension. Body height and weight were measured by standardized methods, and body mass index (BMI) was calculated as kg/m^2 (120).

Myocardial bridging assessment

Previously used definition of myocardial bridging (MB) was used to characterize MB (121, 122) and findings of MB was divided into 1) partial encasement (coronary artery on the myocardial surface but not totally covered by the myocardium), and 2) total encasement less than 1 mm, or 3) total encasement 1 mm or more as depicted in Figure 17.

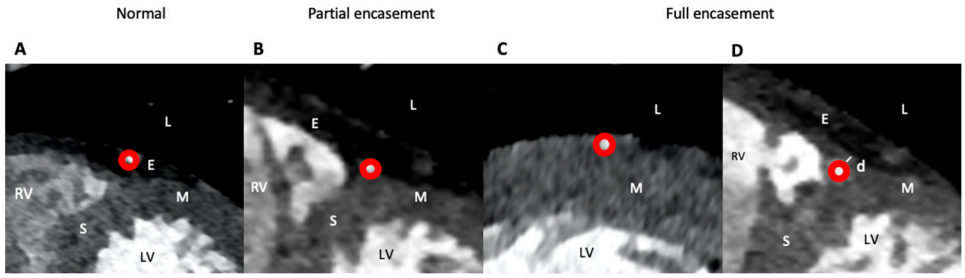


Figure 17. Classification of myocardial bridging (MB) on computed tomography.
Legend: The coronary arteries are usually epicardial. (A) Partial encasement occurs when the artery has direct contact with the myocardium. (B) In the case of full encasement, the artery is fully located within the myocardium, either with an unmeasurable distance (C) or with a measurable distance (D), being the distance depicted as d). The artery is marked with a red circle. RV Right Ventricle; S Interventricular septum; LV Left Ventricle; E Epicardial fat; L Lung; M Myocardium.

The occurrence and characteristics of MB was assessed in left main stem (segment 5), proximal LAD (segment 6), mid LAD (segment 7), distal LAD (segment 8), first to fifth diagonal branches (D1-5), intermediate branches (1-3) and first up to fifth marginal branches (M1-5). MB in right coronary artery and circumflex artery was not measured due to the difficulty in accurately distinguishing between the normal anatomy of the atrio-ventricular grooves and a real myocardial bridge.

MB length was measured from where the coronary artery first touched the myocardium to where the artery no longer was in contact with the myocardium, a new cardiac segment started, or the coronary artery ended visually. If a segment had more than one MB, only the first was included in the analysis. An MB that continued from a previous segment was registered as such but not measured further. MB shorter than or equal to 5 mm was not registered.

MB was considered to have a measurable depth when a MB had full encasement, Figure 17:D, and the depth exceeded 1 mm. The depth was measured perpendicular from outside the most superficial coronary lumen to where the myocardium ended, as previously suggested (123).

As the literature suggests MB being more common in LAD (124, 125), and the proximal LAD is such an important contributor to the blood supply of the left ventricle, the main pump of the heart, we conducted an extra analysis of the characteristics of the subjects with and without MB in segment 6, where we analyzed presence of plaque and sex differences.

In both cohorts and for each cohort separately, prevalence of MB was related to sex.

Intra-observer variability

Twenty randomly chosen individuals were assessed twice for prevalence of MB in proximal LAD, with 21-day interval between the different assessments, and the reader blinded to previous results.

Statistical analysis

All papers

For comparison, depending on the variable distribution, we used Student's *t*-test (for normally distributed variables) or (for non-normally distributed variables) the Mann-Whitney U test. When comparing more than two groups, we used the ANOVA test for normally distributed variables and the Kruskal–Wallis test for non-normally distributed variables. For dichotomous variables, the Chi^2 test or Fisher's exact test was used for comparison, as appropriate. Correlations between variables were assessed with the Spearman rank correlation test or the Pearson correlation test as appropriate.

Results are presented as means (standard deviation [SD]) or median (interquartile range [IQR]) (normal distribution confirmed visually from histograms) for continuous variables, or frequencies and percentages for categorical variables, as appropriate.

The significance level was set to a p-value <0.05.

All statistical analyses were performed using either IBM SPSS Statistics, different versions over the years and papers were used (versions 21-29) (www.ibm.com), GraphPad Prism 7 (GraphPad Software, 225 Franklin Street. Fl. 26, Boston, MA 02110, USA) or STATA16 (Stata Inc, College Station, TX, USA).

Paper I

To examine whether level of sLOX-1 was associated with risk for future stroke, the participants in MDC were divided into tertiles of sLOX-1, followed by analysis of incidence of stroke by sLOX-1 tertile. A Kaplan-Meier survival curve was created with the log-rank test to illustrate the incidence of ischemic stroke per tertile of sLOX-1. Cox proportional hazards regression was used to calculate hazard ratios in tertiles 2 and 3 of sLOX-1 compared with tertile 1 (used as reference) with corresponding CIs. To explore whether the presence of carotid plaque increased the risk for future stroke even more, this relation was investigated by dividing the participants into groups by tertile of sLOX-1 (tertile 1+2 compared to tertile 3) and presence/absence of carotid plaque.

Cox proportional regression was used to create two different models: 1) adjusted for age and sex, and 2) age, sex, current smoking, diabetes mellitus, waist measurement, systolic blood pressure, LDL, cholesterol, triglycerides, and CRP. Potential confounding factors were identified by a stepwise regression model with sLOX-1 as the dependent variable.

The measured plaque homogenate components were normalized to plaque wet weight. Results of the histological and immunohistochemical analysis are presented as percentage of plaque area. Spearman´s rank correlation or Mann-Whitney test was used, as the blood and plaque components analyzed were not normally distributed. To assess sLOX-1 release from the cells in the in vitro experiments, one-way ANOVA or Kruskal-Wallis with additional Dunn's test was performed.

Paper II

Statistical methods described in the section concerning statistical analysis for all papers above were used.

Paper III

As two outcomes were evaluated, coronary stenosis and carotid plaque, the variables were divided the variables accordingly. Coronary stenosis was defined on an ordinal scale with three levels of severity: 0 = no stenosis, 1 = 1–49% stenosis in any arterial segment or a calcified plaque with calcium blooming, and 2 = ≥50% stenosis. Carotid artery plaque was similarly defined on an ordinal scale with three levels:

0 = no plaque, 1 = plaque in one carotid artery, 2 = plaque in both carotid arteries. In order to obtain comparable estimates, we used a three-graded scale for both outcomes. Ordinal logistic regression analysis was carried out for both outcomes. Throughout the analyses, the waist criterion, elevated waist circumference (≥94 cm in men and ≥80 cm in women), was excluded from the other criteria for metabolic syndrome (MetS), as almost all obese and overweight subjects fulfilled this criterion. The exposure was the six BMI/MetS groups (nominal), with the normal weight subjects without MetS group as the reference group. Two degrees of adjustment were performed: 1) age, sex, and study site (nominal), and 2) non-HDL-cholesterol and the lifestyle factors of smoking, exercise habits, alcohol intake, and education level.

For the primary and secondary aims, the obese and overweight group without MetS were compared to the reference. As a sensitivity analysis for the primary and secondary aims, segment involvement score (SIS) and coronary artery calcium (CAC) were

evaluated. Since it measures the degree of coronary atherosclerosis rather than the degree of stenosis, SIS is more similar to our measure of carotid artery plaque (113). For the third aim, the obese and overweight groups were combined to improve the statistical power since both of these groups have been shown to have an increased risk of incident CVD (126).

For the first analysis of the third aim, obese/overweight subjects were divided into groups based on the number of fulfilled MetS criteria. The reference group was set as normal weight without MetS and the groups were evaluated relative to the reference group by ordinal logistic regression with two levels of adjustment for both coronary stenosis and carotid plaque presence. For the second set of analysis, obese/overweight individuals with one MetS criterion (still excluding the waist criterion) were grouped according to the type of criterion (blood pressure, glucose, HDL-cholesterol, and triglyceride levels) and compared to the reference group – normal weight without metabolic syndrome. Again, ordinal logistic regression was used with two levels of adjustment, both for coronary stenosis and carotid plaque.
For the third set of the third aim, the three groups according to BMI were compared using adjustment for age, sex, systolic blood pressure, non-HDL-cholesterol, HDL-cholesterol, triglycerides, fasting glucose, smoking, alcohol intake habits, education level, and exercise habits regarding risk of coronary artery stenosis.

Paper IV

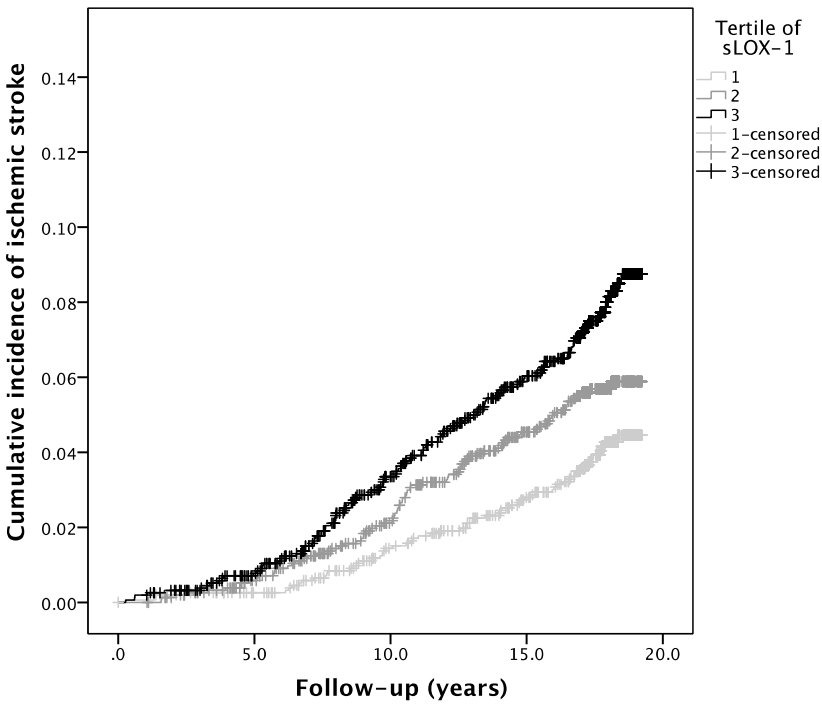
Logistic regression was used to analyze whether the presence of coronary plaque was confounding for ventricular arrhythmias. For intra-observer variability, Cohen´s weighted kappa statistic was used for categorical variables, with κ value 0.00–0.20 indicating slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.81–1.00 almost perfect agreement. (127)

Results

Paper I

sLOX-1 and Ischemic Stroke

Data for 4,703 subjects participating in the MDC study was analyzed. A significant association between the baseline plasma level of sLOX-1 and incidence of ischemic stroke during a mean follow-up of 16.5 years was found, Figure 18.



1	1567(4)	1539(18)	1481(20)	1401(19)
2	1568(9)	1527(23)	1439(35)	1309(16)
3	1568(12)	1514(38)	1376(37)	1238(26)

Figure 18. Kaplan-Meier survival curve per tertile of sLOX-1 in the MDC cohort.
The numbers below the figure denote the number of patients at risk per tertile of sLOX-1 and the number of events between brackets (). Log rank test for trend across tertiles: *p*-value <0.001.

After adjusting for age and sex, the hazard ratio for individuals in the highest tertile of s-LOX1 was 1.75 (95% CI, 1.28–2.39) compared to individuals in the lowest tertile. After further adjusting for current smoking, diabetes mellitus, waist circumference, systolic blood pressure, LDL, cholesterol, triglycerides, and CRP, the association remained significant (Table 1).

Table 1. Hazard ratio for future ischemic stroke per tertile of soluble LOX-1 (sLOX-1).

	sLOX-1			
	T1	**T2**	**T3**	***P*-value**	**Per 1 SD**
HR (95% CI) model 1	1	1.27 (0.91-1.77)	1.75 (1.28-2.39)	<0.001	1.30 (1.16-1.46)
HR (95% CI) model 2	1	1.11 (0.79-1.56)	1.41 (1.01-1.96)	0.004	1.20 (1.06-1.14)

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, current smoking, diabetes, waist, systolic blood pressure, LDL, cholesterol, triglycerides and C-reactive protein. T, tertile; SD, standard deviation; HR, hazard ratio; CI, confidence interval. The p-values are from the tests of trend across tertiles.

Subjects were then categorized based on both sLOX-1 tertile and absence or presence of carotid plaque. Subjects belonging to the highest tertile of sLOX-1 who also had a carotid plaque had a 2.4 times higher risk for future stroke compared to those belonging to the two lowest tertiles of sLOX-1 without a plaque (P<0.001). After adjusting for age, sex, current smoking, diabetes mellitus, waist circumference, systolic blood pressure, LDL, cholesterol, triglycerides, and CRP, this difference remained significant (Table 2).

Table 2. Hazards ratio of ischemic stroke according to presence or absence of carotid plaque and high sLOX1 (tertile 3) or low sLOX1 (tertile 1 or 2).

	No carotid plaque		**Carotid plaque**		
	Low sLOX-1 n=2078	**High sLOX-1 n=916**	**Low sLOX-1 n=956**	**High sLOX-1 n=580**	**P value**
Ischemic stroke during follow-up (%)	3.4	5.0	7.1	10.2	<0.001
HR (95% CI) Model 1	1	1.45 (1.00-2.10)	1.64 (1.17-2.29)	2.42 (1.71-3.44)	<0.001
HR (95% CI) Model 2	1	1.34 (0.92-1.96)	1.58 (1.12-2.24)	2.10 (1.45-3.04)	0.001

Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, current smoking, diabetes, waist, systolic blood pressure, LDL, cholesterol, triglycerides and C-reactive protein.

Clinical characteristics of the study cohort is presented in relation to tertile (T1-T3) of sLOX-1 (Table 3).

Table 3. Clinical characteristics of the MDC cohort according to tertile of soluble lectin-like oxidized low density lipoprotein receptor-1 (sLOX-1).

	sLOX-1			
	T1 n=1567	**T2 n=1568**	**T3 n=1568**	**P-value**
sLOX-1, mean ±SD	3.48 ±0.279	4.04 ±0.134	4.79 ±0.480	<0.001
Age (years), mean ±SD	56.6 ±5.97	57.9 ±5.95	58 ±5.88	<0.001
Males, n (%)	608 (38.8)	609 (38.8)	652 (41.6)	0.189
Current smoking, n (%)	186 (11.9)	324 (20.7)	499 (31.9)	<0.001
Diabetes, n (%)	90 (5.7)	107 (6.8)	159 (10.1)	<0.001
Use of anti-hypertensive medication, n (%)	223 (14.2)	240 (15.3)	288 (18.4)	0.005
Lipid-lowering treatment, n (%)	33 (2.1)	33 (2.1)	47 (3.0)	0.170
Waist (cm), median (IQR)	81 (73-92)	82 (73-92)	83 (74-94)	<0.001
C-reactive protein (mg/L), median (IQR)	1.00 (0.6-2.0)	1.30 (0.60-2.60)	1.80 (0.90-3.70)	<0.001
HbA1c %, median (IQR)	4.70 (4.40-5.00)	4.80 (4.50-5.10)	4.90 (4.60-5.20)	<0.001
Fasting lipoproteins (mmol/L)				
Cholesterol, mean ±SD	6.03 ±1.05	6.16 ±1.07	6.26 ±1.07	<0.001
Low-density lipoprotein, mean ±SD	4.04 ±0.948	4.17 ±0.973	4.29 ±0.992	<0.001
High-density lipoprotein, median (IQR)	1.40 (1.17-1.66)	1.35 (1.12-1.61)	1.29 (1.08-1.54)	<0.001
Triglycerides, median (IQR)	1.05 (0.79-1.46)	1.16 (0.870-1.60)	1.23 (0.93-1.69)	<0.001
Atherosclerosis				
Presence of carotid plaque (%)	28.7	34.3	38.8	<0.001
Stroke during follow-up, n (%)	61 (3.9)	83(5.3)	113(7.2)	<0.001

With higher age, the levels of sLOX-1 increased. Several cardiovascular risk factors, and additionally the presence of carotid plaques, demonstrated significant associations with increased levels of sLOX-1. Spearman correlations with sLOX-1 and C-reactive protein (CRP), lipids, and hemoglobin A1c are presented in Table 4.

Table 4. Spearman correlation between sLOX-1 and C-reactive protein as a marker of inflammation, HbA1c and circulating lipoproteins

sLOX-1	**r**	***p*-value**
C-reactive protein	0.236	<0.001
HbA1c	0.157	<0.001
Cholesterol	0.096	<0.001
Low-density lipoprotein	0.108	<0.001
High-density lipoprotein	-0.122	<0.001
Triglycerides	0.160	<0.001

The magnitude of these correlations was moderate or low (r≤0.236).

Age and gender, CRP, HbA1c, cholesterol, LDL, HDL, triglycerides, and presence of carotid plaque significantly correlated with sLOX-1 levels in a backward stepwise multiple variable linear regression model, beta coefficients for the model are found in Supplemental Material for Paper I.

In vitro stimulated release of sLOX-1

To investigate if oxLDL could induce cleavage of the LOX-1 receptor and thus shed the soluble part of the receptor, sLOX-1, cultured HUVECs, human coronary artery smooth muscle cells, and PBMCs were exposed to 25 µg/mL of oxLDL for 24 hours. This did result in an enhanced release of sLOX-1 from endothelial cells, Figure19:A. This was, however, not seen for smooth muscle cells or PBMCs. When stimulating HUVECs with native LDL, high-density lipoprotein, or very LDL, no effect on sLOX-1 release from endothelial cells was detected. No significant release of sLOX-1 was seen when stimulating with interleukin-1β and transforming growth factor-β. When stimulating PBMCs by exposure to TNF-α, Figure19:B, these cells released sLOX-1. These observations show that circulating sLOX-1 may originate from cells exposed to oxLDL and other proinflammatory stimuli.

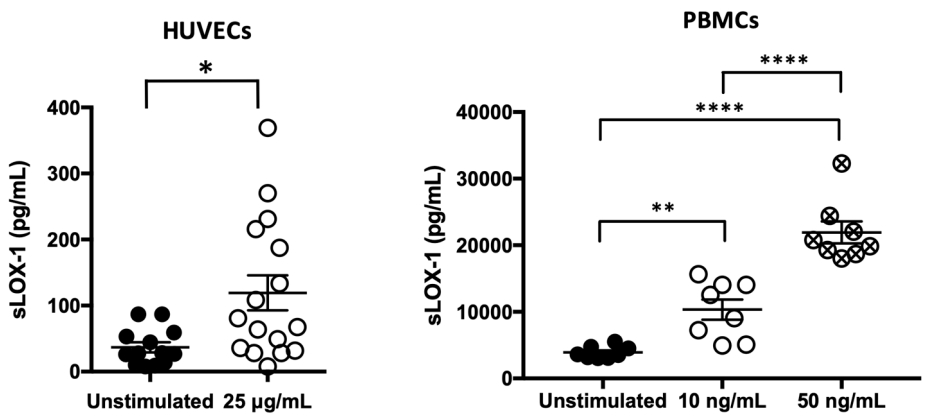


Figure 19. *In vitro* cultured A) human umbilical vein endothelial cells (HUVECs) stimulated with 25µg/mL of oxidized LDL induces a release of sLOX-1 into the medium (lines representing mean and SEM; results are pooled from three individual experiments) and B) peripheral blood mononuclear cells (PBMCs) stimulated with TNF-α induces the release of sLOX-1 in a dose dependent pattern (lines representing mean and SEM). Each data point represents a single well replicate. Level of significance is marked by *, *P*=0.01, **, *P*<0.01 ****, *P*<0.001.

sLOX-1 and Plaque Inflammation

Highly significant associations between plaque expression of proinflammatory cytokines/ chemokines and sLOX-1 were found, where sLOX-1 in plaque homogenates was the sum of sLOX-1 and cell-associated LOX-1, Table 4.

Table 4. Spearman's correlation between the plaque levels of sLOX-1, the plasma sLOX-1 levels, and the plaque composition regarding cytokines, chemokines, cell markers, lipids, intra-plaque hemorrhage, matrix metalloproteinases, and matrix proteins in all plaques (n=202). IL, interleukin; TNF, tumor necrosis factor; MIP, macrophage inflammatory protein; ox-LDL, oxidized low-density lipoproteins; MMP, matrix metalloproteinase.

	Plaque sLOX-1		**Plasma sLOX-1**	
	r	***P***	**r**	***P***
Cytokines/chemokines (pg/g)				
TNF-α	0.409	$5x10^{-9}$	0.214	$3x10^{-3}$
IL-6	0.298	$3x10^{-5}$	0.099	0.17
sCD40L	0.286	$7x10^{-5}$	0.096	0.19
MIP-1β	0.230	$1x10^{-3}$	0.083	0.25
Fractalkine	0.323	$6x10^{-6}$	0.204	$4x10^{-3}$
Cell markers (% area)				
α-actin (smooth muscle cells)	-0.096	0.17	0.013	0.83
CD68 (macrophages)	0.115	0.10	0.037	0.54
Glycophorin A (hemorrhage)	0.176	$1.3x10^{-2}$	0.009	0.89
Plaque lipids				
Oil Red O (% area)	0.226	$1x10^{-3}$	0.124	$3x10^{-2}$
Ox-LDL (μU/g)	0.369	$2x10^{-7}$	0.216	$3x10^{-3}$
Plaque levels of MMP (pg/g)				
MMP-2	0.322	$5x10^{-6}$	0.103	0.14
MMP-9	0.359	$3x10^{-7}$	0.151	$3x10^{-2}$

MMP-2 and MMP-9 displayed similar associations with plaque sLOX-1 levels and the percentage of area in histological sections of plaques stained for lipids (Table 4. In histological sections from the plaques, the staining for LOX-1 was higher close to areas that also stained for lipids and macrophages, Figure 20.

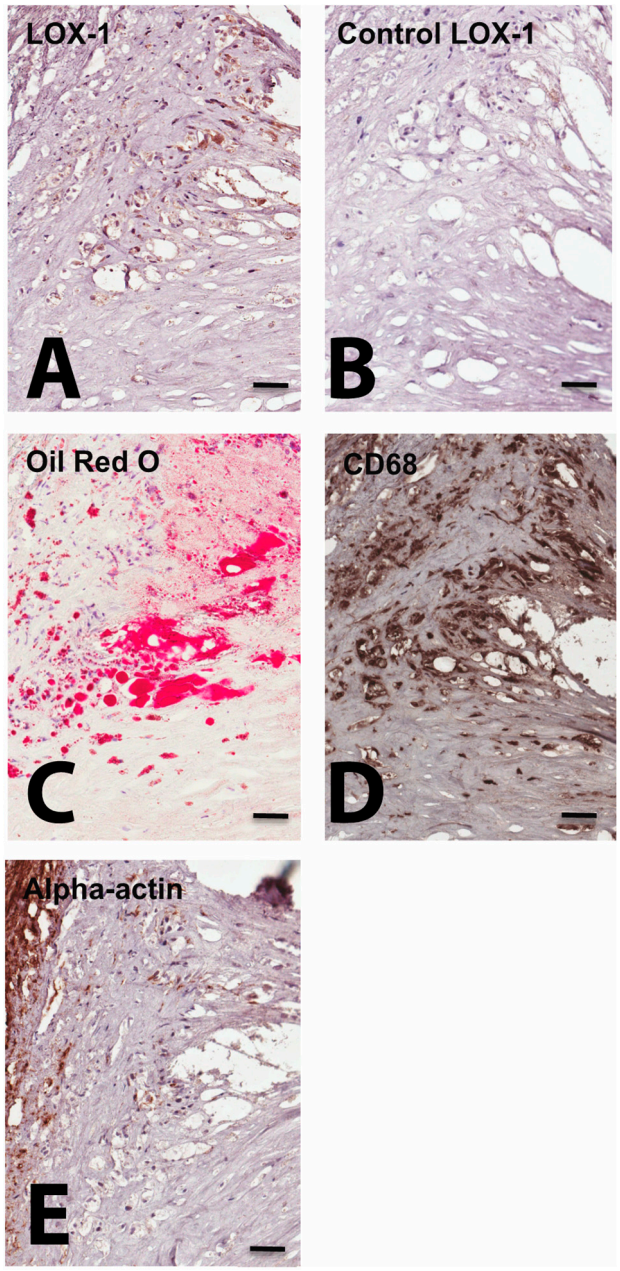


Figure 20. Immunohistochemistry showing the co-localization of LOX-1, CD68 and neutral lipids (Oil red O) in plaque tissue from CPIP. A) LOX-1, B) Isotype control, C) Oil red O (neutral lipids), D) CD68 (macrophages) E) α-actin (smooth muscle cells). Scale bars 50μm.

There were significant associations between plaque content of the LOX-1 ligand oxLDL and sLOX-1 in plaques (Table 4) and between levels of sLOX-1 in plaques and sLOX-1 in plasma (Figure 21).

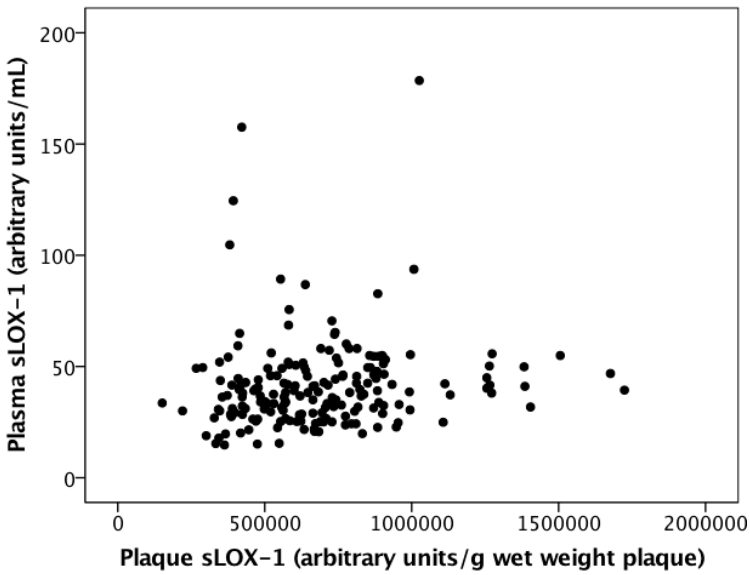


Figure 21. Scatter plot showing the positive correlation between plasma sLOX-1 (arbitrary units/mL) and plaque sLOX-1 (arbitrary units/gram wet weight plaque) content in the CPIP cohort (Spearman's correlation r=0.209, P=0.004).

There was a significant correlation between the percentage lipid-stained area in histological sections of plaques, and plasma sLOX-1 and plaque contents of oxLDL, TNF-a, fractalkine, MMP-9, Table 4.

Paper II

In total, 99 consecutive patients were included. All patients were eligible for cardiac resynchronization therapy (CRT). Patient baseline data are presented in Table 5.

Table 5. Clinical characteristics (n=99).

Age (years)	68±9
Women (n (%))	26 (26)
BMI (kg/m2)	28±5
Active smoking (n (%))	13 (13)
Diabetes (n (%))	13 (13)
Renal disease (n (%))	21 (22)
S-creatinine (mmol/L)	98±26
CABG (n (%))	17 (18)
NYHA class at baseline (n (%))	
II	26 (27)
III	58 (60)
IV	12 (13)
QRS width (ms)	170±19
LBBB (n (%))	73 (74)
Ischemic cardiomyopathy (n (%))	46 (47)
Paroxysmal atrial fibrillation (n (%))	10 (10)
LVEF (%)	23±6
Blood pressure (systolic) (mmHg)	126±17
Blood pressure (diastolic) (mmHg)	75±9
Hypertension (n (%))	54 (55)
PCI (n (%))	33 (34)
AMI (n (%))	35 (37)

BMI, body mass index; CABG, coronary artery bypass grafting; NYHA, New York Heart Association classification of heart failure; LBBB, left, bundle branch block; LVEF, left ventricular ejection fraction; PCI, percutaneous, coronary intervention; AMI, acute myocardial infarction.

The most common finding was that patients had two (n=33) or three (n=37) veins suitable for CRT lead placement. Only one suitable vein was found for 13 patients, whereas 16 patients had four or five suitable veins. One patient had non-diagnostic image quality, and no suitable vein could be found for this patient preoperatively. A mean of 2.6 ±0.9 suitable veins (range 1–5) covered a mean of 4.4 ±1.5 relevant mid or basal left ventricular segments (range 0–7). Patients had between 1 and 7 accessible segments; three accessible veins traversing five cardiac segments was most common (n=11). 90% of all patients (n=89) had three or more segments suitable for left ventricular lead placement (Figure 22).

The number of cardiac veins did not significantly differ between patients with dilated or ischemic cardiomyopathy. There were no significant differences in the number of veins or cardiac segments where at least one vein had its course in relation to patient sex or with/without a left bundle block morphology on ECG.

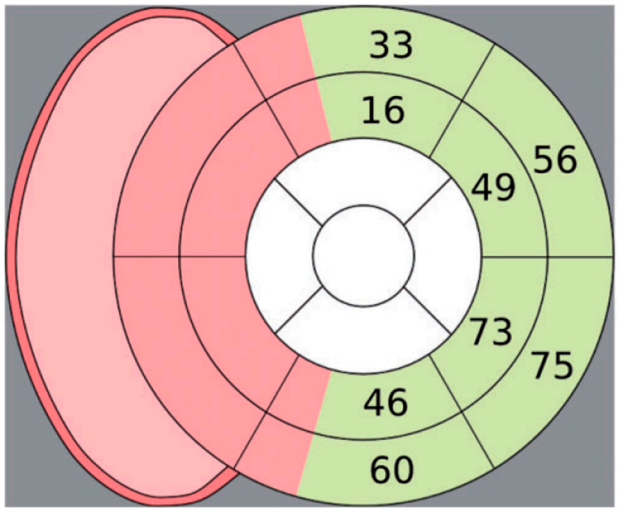


Figure 22. Illustration of suitable veins on a segmental level. Segments are divided as in Figure 15. The numbers represent the percentage of patients with suitable vein(s) in the respective segments.

No significant differences were found regarding contrast dose in terms of g iodine between men/women or type of cardiomyopathy. The total contrast dose over all groups was 386±62gI. The median radiation dose was 231mGy/cm (IQR 276mGy/cm). Men received a higher radiation dose than women, 258 [332] compared to 126 [187], p=0.002, but there was a significant interaction between gender and weight (r 0.33, p=0.001). There was no remaining difference after correcting for weight, p=0.97. There was a weak significant difference in radiation exposure when patients with dilated cardiomyopathy, 176 [260] mGy/cm were compared to patients with ischemic cardiomyopathy, 259 [296] mGy/cm, p=0.46. BMI and higher radiation dose correlated highly (r. 0.44, p< 0.001).

As expected, the different scanning protocols resulted in different radiation dose, median radiation dose was for retrospective scans 469 mGy/cm [IQR 355], for prospective scans 263 [IQR 98] mGy/cm, and for flash scans 91 [IQR 29] mGy/cm for retrospective, prospective, and flash protocols, respectively, p< 0.001 between groups (

Figure **23**).

When comparing patients scanned on different CT scanners, no difference was found in regards of number of detected veins (p=0.59), and no difference in the number of veins found between scanning protocol (p=0.56), no correlation in the number of veins and contrast volume (r 0.07, p=0.49) or between the two different brands of CT scanners (p= 0.74).

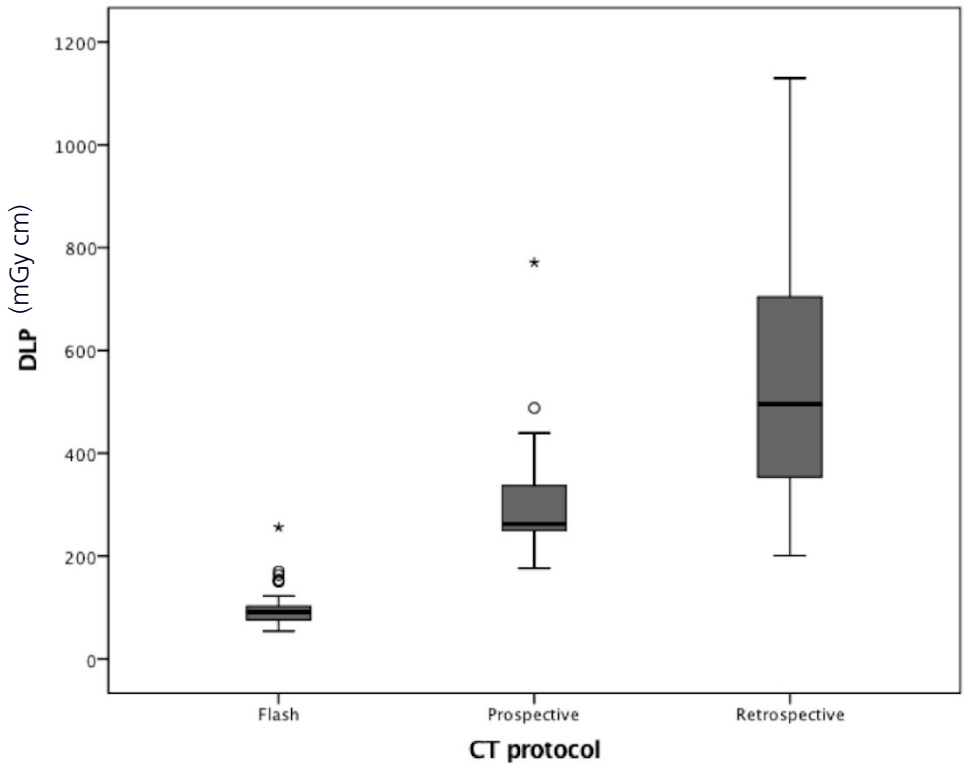


Figure 23. Radiation in DLP for different scanning protocols. Median radiation dose for Flash, Prospective and Retrospective scan protocol, (P < 0.001 between groups).
The boxes represent 25th percentile to 75th percentile, whiskers represent smallest and largest value within 1.5 times the interquartile range. Thicker lines define the median. DPL Dose Length Product, CT Computer Tomography, * representing significance between groups, ° indicating outliers.

Thus, cardiac veins could be mapped by Cardiac CT and transferred to a 17-segment model regardless of patient characteristics. No difference in number of or distribution of cardiac veins between different patient categories, CT machines, or CT protocols was found. Almost all patients had at least one vein suitable for CRT-lead placement.

Paper III

A total of 23,674 study participants had valid imaging examinations and risk factor information and were included in the analysis. Clinical characteristics for participants and the proportions of atherosclerosis in the two arterial beds, both stratified by the six different BMI and MetS criteria, are presented in Table 6 and Figure 24, respectively. Men had more coronary atherosclerosis, defined by degree of stenosis, in the coronary arteries than women ($p < 0.0001$). For men, at least 9.1% had at least one coronary

stenosis more than or equal to 50%, compared to 2.6% of women. For men, 48.9% had a coronary stenosis between 1-49%, compared to 29.3% in women. Similarly, men had more atherosclerosis in the carotid arteries ($p < 0.0001$). In this vascular bed, 29.8% men had atherosclerosis in both carotid arteries, compared to 19.7% of women.

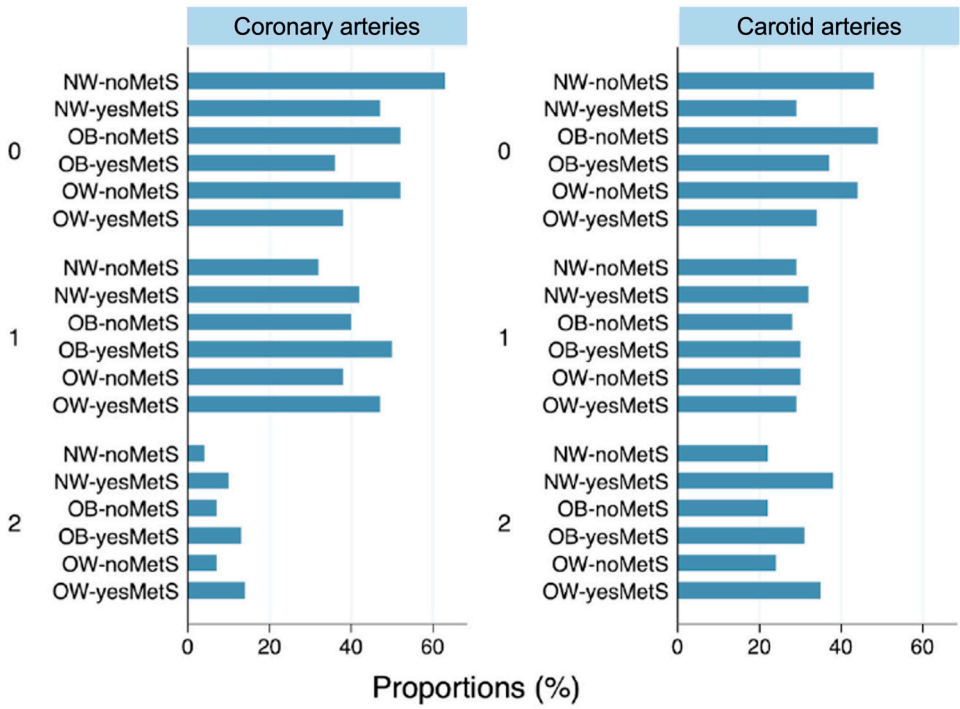


Figure 24. Proportions of atherosclerotic findings in the coronary and carotid arteries stratified by combinations of BMI and metabolic syndrome (MetS) criteria. NW - normal weight, OW - overweight, OB - obese. Both coronary artery stenosis and carotid plaque are on a three-level scale (0 - no stenosis, 1 - 1–49% stenosis, 2 - ≥50% stenosis for coronary artery stenosis and 0, 1, or 2 arteries with plaque for the carotid plaque). The number of subjects in each group is given in Table 7.

Obesity without MetS vs. normal weight without MetS

The severity of stenosis in the coronary arteries was increased for obese individuals without MetS compared to normal weight individuals without MetS, OR 1.47 (95%CI 1.34–1.62), $p < 0.0001$, presented in Table 8. This difference remained significant, OR 1.41 (95%CI 1.28–1.55), $p < 0.0001$, after adjustment for non-HDL-cholesterol and lifestyle factors, as well as for some self-reported non-CVD diseases (any cancer diagnosis 5.8%, rheumatoid diseases 3.5%, inflammatory bowel diseases 1.1% and chronic obstructive pulmonary disease 0.8% of the sample). Even after further adjustment for statin use, the difference remained significant, OR 1.36 (95%CI 1.24–

1.50), p < 0.0001. When testing menopausal status as a possible confounder for the women in the study cohort (15.7% percent of women were postmenopausal), the difference remained significant, OR 1.39, and the p-value remained < 0.0001.

The severity of carotid atherosclerosis did not increase significantly for the obese subjects without MetS in the age, sex, and site-adjusted model, OR 0.94 (95%CI 0.87–1.02), p = 0.11, Table 8. When adjusting for multiple factors, a significantly reduced risk for carotid atherosclerosis was found, Table 8, when comparing obese subjects without MetS to normal-weight subjects without MetS.

As hypertension is a strong risk factor for cardiovascular disease, study participants were divided by hypertension (n = 1,025) vs no hypertension (n = 1,905). Hypertension was defined as blood pressure ≥140/90 mmHg or antihypertensive medication. When the obese individuals without MetS were compared with normal-weight individuals without MetS following multiple adjustment, both groups showed increased risk of coronary artery stenosis, OR 1.22 (95%CI 1.08–1.38), p = 0.001, in the non-hypertensive group and OR 1.78 (95%CI 1.53–2.06), p < 0.0001, in the hypertensive group. Individuals with obesity, without both MetS and hypertension, were found to have an increased risk of coronary artery stenosis.

Inversely, when performing the analysis for the carotid arteries, obese individuals had a reduced risk of carotid atherosclerosis compared to normal weight individuals without MetS. In comparison, when instead looking at obese/overweight individuals without MetS but with hypertension, they had a reduced risk of carotid atherosclerosis following multiple adjustments, OR 0.72 (95%CI 0.65–0.80), p < 0.0001 in the non-hypertensive group and OR 1.22 (95%CI 1.08–1.38), p = 0.002, in the hypertensive group.

To find out whether mild coronary stenosis (1-49%) was increased for individuals with obesity without MetS compared to normal weight individuals without MetS, all subjects with coronary stenosis of more than or equal to 50% were excluded. For the remaining subjects, there was an increased risk of atherosclerosis in the coronary arteries in obese subjects without MetS, OR 1.41(95%CI 1.30–1.55), p < 0.0001, compared to normal weight subjects without MetS.

For the three subgroups of obese individuals 1) class I obesity – BMI 30-34.99 kg/m2 (n = 2369), 2) class II obesity – BMI 35-39.99 kg/m2 (n = 455), and 3) class III obesity – BMI >40 kg/m2 (n = 106), there was an increased risk of coronary artery stenosis compared to the normal-weight group without MetS, OR 1.46 (95%CI 1.31–1.61), 1.59 (95%CI 1.28–1.98) and 1.52 (95%CI 0.97–2.39) respectively in the analysis adjusted for age and sex.

Table 6. Characteristics of the sample divided by BMI groups and the presence of metabolic syndrome (MetS). Means and SD or proportions are shown.

	Normal weight without MetS	Normal weight with MetS	Overweight without MetS	Overweight with MetS	Obese without MetS	Obese with MetS	*p*-value for differences between groups
N	10,055	230	9640	2011	2930	2892	
Variable	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	57.2 (4.3)	58.7 (4.3)	57.3 (4.3)	58.5 (4.1)	56.9 (4.2)	57.8 (4.3)	<0.0001
Women (%)	63	62	44	45	56	45	<0.0001
Systolic BP (mmHg)	120 [16]	134 [15]	125 [15]	135 [15]	127 [16]	135 [16]	<0.0001
Diastolic BP (mmHg)	73.8 (10.1)	81.9 (8.9)	77.4 (9.8)	82.3 (9.4)	80.0 (10.1)	83.9 (9.8)	<0.0001
Non-HDL-cholesterol (mmol/l)	3.64 (.98)	4.3 (1.27)	3.94 (1.02)	4.31 (1.19)	3.93 (.97)	4.16 (1.15)	<0.0001
HDL-cholesterol (mmol/l)	1.89 (.5)	1.27 (.43)	1.63 (.43)	1.24 (.36)	1.57 (.38)	1.2 (.31)	<0.0001
Triglycerides (mmol/l)	0.93 (0.45)	1.97 (1.03)	1.14 (0.58)	2.02 (1.06)	1.19 (0.47)	2.02 (1.27)	<0.0001
BMI (kg/m^2)	22.7 (1.6)	23.8 (1.1)	27.0 (1.3)	27.8 (1.3)	32.9 (2.9)	34.0 (3.7)	<0.0001
Waist circumference (cm)	82.9 (7.7)	91.5 (6.2)	94.9 (7.2)	100.5 (6.8)	107.1 (9.4)	112.5 (9.9)	<0.0001
Fasting glucose (mmol/l)	5.3 (.7)	6.2 (1.7)	5.4 (.7)	6.2 (1.5)	5.5 (.7)	6.4 (1.8)	<0.0001
Diabetes diagnosis (%)	1.3	13	2.4	14	1.5	17	<0.0001
Antihypertensive treatment (%)	7.2	34	15	41	20	46	<0.0001
Statin treatment (%)	3.3	10.4	5.5	15	5.6	17	<0.0001
Antidiabetic treatment (%)	1.0	10.4	1.3	12.0	1.0	14.6	<0.0001
Alcohol (g/week)	6.7 (5.8)	6.8 (7.1)	7.7 (6.7)	7.5 (7.2)	6.7 (6.6)	6.9 (7.2)	<0.0001
Exercise habits levels (0 for sedentary and 4 for athlete)	0: 22% 1: 18% 2: 22% 3: 21% 4: 17%	0: 35% 1: 26% 2: 17% 3: 15% 4: 7%	0: 25% 1: 23% 2: 21% 3: 18% 4: 13%	0: 37% 1: 26% 2: 17% 3: 12% 4: 8%	0: 34% 1: 26% 2: 17% 3: 13% 4: 10%	0: 43% 1: 25% 2: 15% 3: 10% 4: 7%	<0.0001
Educational level	<10 years: 6% 10–12 years: 39% >12 years: 55%	<10 years: 8% 10–12 years: 53% >12 years: 39%	<10 years: 9% 10–12 years: 46% >12 years: 45%	<10 years: 12% 10–12 years: 50% >12 years: 38%	<10 years: 11% 10–12 years: 50% >12 years: 39%	<10 years: 15% 10–12 years: 54% >12 years: 31%	<0.0001
Smoking status	Never: 55% Previous: 33% Current: 12%	Never: 44% Previous: 33% Current: 23%	Never: 53% Previous: 36% Current: 11%	Never: 43% Previous: 38% Current: 19%	Never: 50% Previous: 40% Current: 10%	Never: 44% Previous: 41% Current: 15%	<0.0001
Number of metabolic syndrome components	.54 (.66)	3.17 (.43)	1.08 (.75)	3.33 (.56)	1.64 (.52)	3.52 (.67)	<0.0001
SIS	.77 (1.54)	1.48 (2.30)	1.06 (1.82)	1.68 (2.34)	1.07 (1.89)	1.67 (2.23)	<0.0001

SIS = segment involvement score. ANOVA or chi-square tests was used to evaluate if the groups were different.

Table 7. Number (No.) of individuals and proportions of atherosclerotic findings in the coronary (CCTA) and carotid arteries stratified by combinations of BMI and metabolic syndrome (MetS) criteria. NW = normal weight, OW = overweight, OB = obese. Both coronary artery stenosis and carotid plaque are on a three-level scale (0 = no stenosis, 1 = 1–49% stenosis, 2 = ≥50% stenosis for coronary artery stenosis and 0, 1, or 2 arteries with plaque for the carotid plaque).

	Coronary arteries				**Carotid arteries**		
Atherosclerosis group	**MetS/BMI-Group**	**No.**	**%**	**Atherosclerosis group**	**MetS/BMI-Group**	**No.**	**%**
0	NW-noMetS	5,472	63	0	NW-noMetS	4,902	49
	NW-MetS	90	48		NW-MetS	70	30
	OB-noMetS	1,296	53		OB-noMetS	1,446	50
	OB-MetS	878	38		OB-MetS	1,106	38
	OW-noMetS	4,638	55		OW-noMetS	4,368	45
	OW-MetS	682	40		OW-MetS	722	36
1	NW-noMetS	2,837	33	1	NW-noMetS	2,939	29
	NW-MetS	82	44		NW-MetS	75	33
	OB-noMetS	993	41		OB-noMetS	847	29
	OB-MetS	1,221	52		OB-MetS	894	31
	OW-noMetS	3,304	39		OW-noMetS	2,927	30
	OW-MetS	831	49		OW-MetS	596	30
2	NW-noMetS	311	4	2	NW-noMetS	2,188	22
	NW-MetS	16	8		NW-MetS	85	37
	OB-noMetS	136	6		OB-noMetS	626	21
	OB-MetS	235	10		OB-MetS	875	30
	OW-noMetS	465	6		OW-noMetS	2,318	24
	OW-MetS	188	11		OW-MetS	686	34

This was not found for carotid atherosclerosis; no increased risk was found for any of the three obesity subgroups without MetS compared to normal weight individuals without MetS in the analysis adjusted for age and sex.

The relation between severity of stenosis for individuals with overweight without MetS to normal weight individuals without MetS was similarly increased, OR 1.17 (95%CI 1.09–1.24), $p < 0.0001$. The difference remained highly significant after correcting for lifestyle factors and non-HDL-cholesterol but did not remain after adjustment for statin use, OR 1.06 (95%CI 0.99–1.13), p=0.067. The analysis for the carotid arteries showed no significant differences between the same two groups.

When individuals with MetS were compared to individuals without MetS, we found that both the severity of coronary stenosis and the extent of atherosclerosis in the carotid arteries were higher for individuals with MetS, irrespective of BMI, $p<0.0001$ for both outcomes, Table 8.

No significant interactions were found between MetS and BMI group in respect of atherosclerosis in coronary or carotid arteries.

After adjustment for age, sex, systolic blood pressure, non-HDL-cholesterol, HDL-cholesterol, triglycerides, fasting glucose, smoking, alcohol intake, education, exercise habits, and study site, obese subjects had an increased risk for coronary artery stenosis compared to normal weight individuals, OR 1.36 (95%CI 1.25–1.48), $p < 0.001$. This was not seen for overweight subjects, OR 1.06 (95%CI 0.99–1.13), $p = 0.08$.

No increased carotid atherosclerosis was found when comparing obese or overweight individuals without MetS (except the waist criterion) to normal weight individuals without MetS criteria. For overweight/obese individuals with one MetS criterion (in addition to the waist criterion), the amount of atherosclerosis in the carotid arteries was increased when compared to the reference group,

Table 9.

However, when comparing the same groups and looking at coronary arteries, significantly more severe stenosis was found for obese and overweight subjects without any MetS criteria when compared to normal weight subjects without MetS criteria, and the difference remained after adjustment for non-HDL-cholesterol and lifestyle factors,

Table 9.

The severity of both carotid artery and coronary artery atherosclerosis increased with the number of MetS criteria.

Table 8. Odds ratios (OR) for degree of coronary stenosis at coronary CT (upper part), carotid plaque (middle part), segment involvement score (SIS) and coronary artery calcium score (CAC) at coronary CT angiography for five groups of combinations of BMI and metabolic syndrome (MetS), with normal-weight subjects without MetS as the referent.

	Age, sex and site-adjusted		Multiple adjusted	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Coronary angiography stenosis				
Normal weight without MetS	Reference group			
Normal weight with MetS	1.78 (1.33, 2.38)	<0.0001	1.48 (1.09, 2)	0.012
Overweight without MetS	1.17 (1.09, 1.24)	<0.0001	1.10 (1.03, 1.17)	0.0056
Overweight with MetS	2.10 (1.89, 2.34)	<0.0001	1.80 (1.61, 2.02)	<0.0001
Obese without MetS	1.47 (1.34, 1.62)	<0.0001	1.41 (1.28, 1.55)	<0.0001
Obese with MetS	2.41 (2.19, 2.64)	<0.0001	2.16 (1.96, 2.38)	<0.0001
Carotid artery plaque				
Normal weight without MetS	Reference group			
Normal weight with MetS	1.97 (1.55, 2.51)	<0.0001	1.68 (1.30, 2.16)	<0.0001
Overweight without MetS	1.03 (0.97, 1.08)	0.34	0.96 (0.91, 1.02)	0.19
Overweight with MetS	1.47 (1.35, 1.62)	<0.0001	1.23 (1.12, 1.35)	<0.0001
Obese without MetS	0.94 (0.87, 1.02)	0.11	0.87 (0.80, 0.95)	0.0013
Obese with MetS	1.35 (1.25, 1.47)	<0.0001	1.16 (1.07, 1.26)	<0.0001
Sensitivity analysis				
SIS				
Normal weight without MetS	Reference group			
Normal weight with MetS	1.78 (1.37, 2.31)	<0.0001	1.49 (1.14, 1.96)	0.0041
Overweight without MetS	1.15 (1.09, 1.22)	<0.0001	1.10 (1.03, 1.17)	0.0036
Overweight with MetS	1.89 (1.71, 2.08)	<0.0001	1.64 (1.48, 1.81)	<0.0001
Obese without MetS	1.35 (1.24, 1.47)	<0.0001	1.32 (1.21, 1.44)	<0.0001
Obese with MetS	2.05 (1.88, 2.22)	<0.0001	1.89 (1.73, 2.06)	<0.0001
CAC				
Normal weight without MetS	Reference group			
Normal weight with MetS	2.03 (1.56, 2.64)	<0.0001	1.72 (1.31, 2.26)	<0.0001
Overweight without MetS	1.15 (1.08, 1.22)	<0.0001	1.09 (1.02, 1.16)	0.0006
Overweight with MetS	1.87 (1.79, 2.17)	<0.0001	1.75 (1.58, 1.94)	<0.0001
Obese without MetS	1.41 (1.29, 1.53)	<0.0001	1.33 (1.22, 1.46)	<0.0001
Obese with MetS	2.31 (2.12, 2.51)	<0.0001	2.10 (1.92, 2.29)	<0.0001

The analyses were adjusted for age, sex, study site, or for these variables plus non-HDL-cholesterol, smoking, education level, alcohol intake, and exercise habits (multi-adjusted). Ordinal logistic regression was performed with both CT angiography stenosis and carotid plaque on a three-level scale (no stenosis, 1–49% stenosis, and ≥50% stenosis for CT angiography stenosis and 0, 1, or 2 arteries with plaque for the carotid plaque). SIS and is given on a 13-level scale. CAC is given on a three-level scale (0, 1–100, >100 Agatston units).

Table 9. Odds ratios (OR) for coronary CT angiography stenosis (upper part) and carotid plaque (lower part) for four groups of overweight or obese subjects with either 0 metabolic syndrome (MetS) criteria, 1 MetS criterion, 2 MetS criteria, or >2 MetS criteria (not including the waist criterion) with normal-weight subjects without any MetS criteria as the referent.

	Age, sex, and site-adjusted		Multiple adjusted	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Coronary angiography stenosis				
Normal weight with 0 MetS criteria (n = 5921)	Reference group			
Obese/Overweight with 0 MetS criteria (n = 4734)	1.18 (1.07, 1.29)	0.00044	1.10 (1.01, 1.21)	0.037
Obese/Overweight with 1 MetS criterion (n = 6725)	1.70 (1.56, 1.84)	<0.0001	1.56 (1.43, 1.70)	<0.0001
Obese/Overweight with 2 MetS criteria (n = 3911)	2.20 (2.01, 2.42)	<0.0001	1.91 (1.73, 2.10)	<0.0001
Obese/Overweight with >2 MetS criteria (n = 2103)	3.42 (3.05, 3.84)	<0.0001	2.88 (2.55, 3.24)	<0.0001
Carotid artery plaque				
Normal weight with 0 MetS criteria (n = 5921)	Reference group			
Obese/Overweight with 0 MetS criteria (n = 4734)	0.96 (0.89, 1.04)	0.32	0.91 (0.84, 0.98)	0.011
Obese/Overweight with 1 MetS criterion (n = 6725)	1.37 (1.28, 1.47)	<0.0001	1.25 (1.17, 1.34)	<0.0001
Obese/Overweight with 2 MetS criteria (n = 3911)	1.55 (1.43, 1.68)	<0.0001	1.32 (1.21, 1.43)	<0.0001
Obese/Overweight with >2 MetS criteria (n = 2103)	2.06 (1.87, 2.27)	<0.0001	1.69 (1.53, 1.87)	<0.0001

The analyses were adjusted for age, sex, study site, or for these variables plus non-HDL cholesterol, smoking, education level, alcohol intake, and exercise habits. Ordinal logistic regression was performed with both CT angiography stenosis and carotid plaque on a three-level scale (no stenosis, 1–49% stenosis, and ≥50% stenosis for CT angiography stenosis and 0, 1, or 2 arteries with plaque for the carotid plaque).

All four MetS criteria individually increased the severity of coronary artery stenosis when comparing obese or overweight subjects with one MetS criterion (excluding the waist criterion) to normal-weight subjects without any MetS criteria When adjusted for non-HDL-cholesterol and lifestyle factors, glucose and blood pressure remained significant.

Blood pressure and triglyceride criterion increased the severity of coronary artery stenosis when comparing obese or overweight subjects with one MetS criterion (excluding the waist criterion) to normal-weight subjects without any MetS criteria When adjusted for non-HDL-cholesterol and lifestyle factors, only blood pressure remained significant. Table 10.

Table 10 Odds ratios (OR) for coronary CT angiography stenosis (upper part) and carotid plaque (lower part) for four groups of overweight or obese subjects with one metabolic syndrome (MetS) criteria – either the blood pressure, glucose, HDL, or triglyceride level, with normal-weight subjects without any MetS criteria as the referent.

	Age, sex, and site-adjusted		Multiple adjusted	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Coronary angiography stenosis				
Normal weight without MetS	Reference group			
Blood pressure criterion	1.84 (1.69, 2.02)	<0.0001	1.72 (1.56, 1.89)	<0.0001
Glucose criterion	1.41 (1.17, 1.70)	0.00030	1.39 (1.14, 1.69)	0.00096
HDL criterion	1.30 (1.06, 1.59)	0.011	1.15 (0.94, 1.42)	0.18
Triglyceride criterion	1.45 (1.22, 1.71)	0.000020	1.01 (0.84, 1.21)	0.95
Carotid artery plaque				
Normal weight without MetS	Reference group			
Blood pressure criterion	1.52 (1.41, 1.64)	<0.0001	1.42 (1.31, 1.54)	<0.0001
Glucose criterion	0.97 (0.82, 1.14)	0.67	0.97 (0.82, 1.14)	0.69
HDL criterion	1.11 (0.94, 1.31)	0.21	0.98 (0.83, 1.16)	0.82
Triglyceride criterion	1.18 (1.02, 1.36)	0.026	0.86 (0.74, 1.01)	0.060

The analyses were adjusted for age, sex, and study site or for these variables plus non-HDL-cholesterol, smoking, education level, alcohol intake, and exercise habits. Ordinal logistic regression was performed with both CT angiography stenosis and carotid plaque on a three-level scale a) no stenosis, b) 1–49% stenosis, and c) ≥50% stenosis for CT angiography stenosis and 0, 1, or 2 arteries with plaque for the carotid plaque).

Paper VI

Population characteristics

Characteristics of the two cohorts together and for each cohort separately are presented in Table 11. The non-chest pain subjects (SCAPIS) were older, had less hypertension, less dyslipidemia, and were less commonly current smokers compared to chest-pain patients (SWEDEHEART). No other differences were found regarding risk factors between the two cohorts. The patients referred for chest pain received a higher radiation dose than non-chest pain subjects, but there was no difference in grams of iodine used. Clinical characteristics from both cohorts for individuals with and without MB in LAD are presented in Table 12. Individuals without MB in LAD segment 6 received higher radiation dose, had more dyslipidemia, and displayed a tendency for lower BMI, but the latter was not significant.

Table 11. Clinical characteristics for *both cohorts:* Chest pain patients (SWEDEHEART) and non-chest pain subjects (SCAPIS).

	Chest pain patients n= 434	**Non-chest pain subjects** n=196	**p value**
Age (years)	54 [46-62]	58 [54-62]	<0.001
Female	217 (50)	109 (56)	0.19
BMI (kg/m^2)	27 ±4.7	27 ±4.7	0.79
Hypertension	151 (35)	41 (21)	<0.001
Current smoking	102 (24)	29 (15)	0.013
Diabetes	32 (7.4)	11 (5.6)	0.42
Dyslipidaemia	97 (22)	21 (11)	<0.001
Creatinine (µmol/L)	74 [64-84]	75 [66-88]	0.23
Contrast dose (gI)	28 [26-32]	29 [25-31]	0.46
DLP dose (mGycm)	167 [109-315]	112[89-197]	<0.001
Calcium score (AU)	0 [0-21]	0 [0-41]	0.15

Data expressed as n (%), mean +-SD or median [IQR].

Table 12. Clinical characteristics: both cohorts with and without myocardial bridging in proximal LAD.

	MB in proximal LAD n=219	**No MB in proximal LAD** n = 411	**p value**
Age (years)	56 [51-62]	55 [48-62]	0.418
Female	120 (55)	206 (50)	0.264
BMI (kg/m^2)	26 [23-29]	27 [24-30]	0.090
Hypertension	56 (26)	136 (33)	0.251
Current smoking	44 (20)	87 (21)	0.751
Diabetes	13 (5.9)	30 (7.3)	0.518
Dyslipidaemia	28 (13)	90 (22)	<0.01
Creatinine (µmol/L)	75 [64-86]	75 [65-85]	0.736
Contrast dose (gI)	29 [26-32]	28 [26-30]	0.180
DLP (mGycm)	124 [90-231]	164 [106-287]	<0.001
CaScore (AU)	0 [0-27]	0 [0-28]	0.533

Chest pain patients (SWEDEHEART) and non-chest pain subjects (SCAPIS). Data expressed as n (%) or median [IQR].

Prevalence of MB in the two cohorts

-Prevalence on an individual level

At least one subtype of MB in at least one coronary segment was found for 597 individuals (95%) out of the 630 included in the study. An MB of 1 mm or more was found in 214 (34%), 364 (58%) had MB less than 1 mm, and 469 (74%) had partial encasement in at least one segment. A summary of prevalence of MB per individual is presented in

Figure **25**.

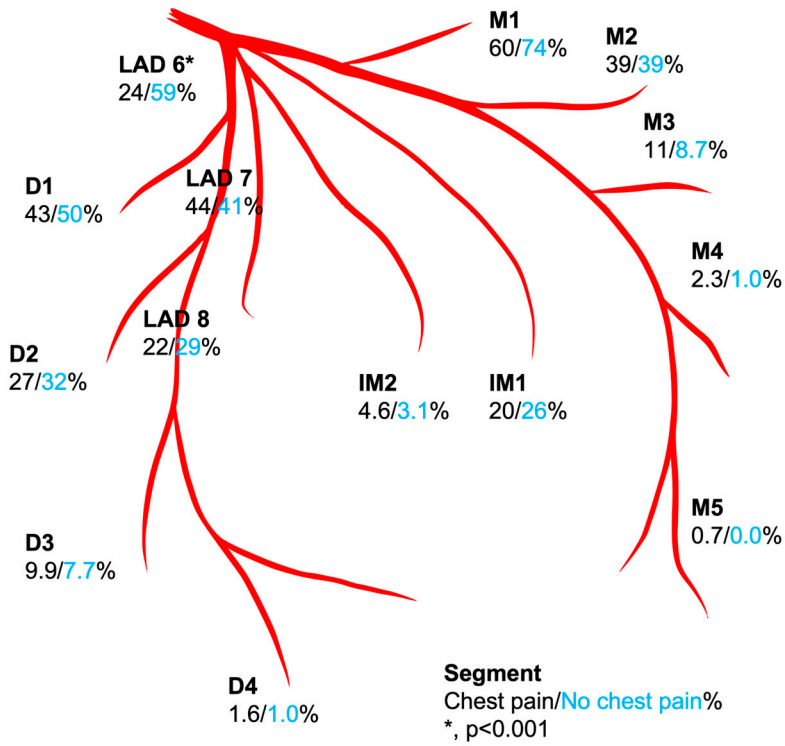


Figure 25 Prevalence of myocardial bridging per coronary segment for both cohorts
Representation of the left coronary tree showing the prevalence of myocardial bridging per assessed coronary segment in the two cohorts studied; chest pain patients (black numbers, SWEDEHEART) and non-chest pain subjects (blue numbers, SCAPIS).

The most common segments for MB in individuals from both cohorts were mid LAD, M1, and D1, where MB was present in >40%, followed by proximal and distal LAD,

D2, and IM, between 20-39%. The remaining segments had a ≤11% prevalence of MB. The prevalence of MB per individual is presented in Table 13.

Table 13. Myocardial bridging per individual in *both cohorts*

Segment studied	Both cohorts n = 630 (%)	Chest pain patients n= 434 (%)	Non-chest pain subjects n=196 (%)	p between groups
LAD 6	219 (35)	103 (24)	116 (59)	<0.001
LAD 7	272 (43)	191 (44)	81 (41)	0.529
LAD 8	154 (24)	97 (22)	57 (29)	0.069
LAD 6 or 7	392(62)	245 (57)	147 (75)	<0.001
LAD 6, 7 or 8	435(69)	277 (64)	158 (80)	<0.001
LAD 7 or 8	344(55)	237 (55)	107 (55)	0.997
D1	285 (45)	187 (43)	98 (50)	0.107
D2	180 (29)	117 (27)	63 (32)	0.182
D3	58 (9.2)	43 (9.9)	15 (7.7)	0.365
D4	9 (1.4)	7 (1.6)	2 (1.0)	0.562
D5	0	0	0	-
IM 1	137 (22)	86 (20)	51 (26)	0.081
IM 2	26 (4)	20 (4.6)	6 (3.1)	0.366
IM 3	3 (0.5)	2 (0.46)	1 (0.51)	0.934
M1	408 (65)	262 (60)	146 (75)	<0.001
M2	247 (39)	170 (39)	77 (39)	0.978
M3	64 (10)	47 (11)	17 (8.7)	0.407
M4	12 (1.6)	10 (2.3)	2 (1.0)	0.275
M5	3 (0.48)	3 (0.69)	0	0.243

Prevalence of myocardial bridging per individual for chest pain patients (SWEDEHEART) and non-chest pain subjects (SCAPIS) respectively. Data expressed as n (%).

Compared to non-chest pain subjects, chest-pain patients had lower prevalence of MB in segment 6/proximal LAD and in the first marginal branch, Table 13. Chest-pain patients had lower prevalence of MB when considering the combination of segments 6 and 7/proximal and mid LAD and segments 6, 7 and 8/proximal, mid and distal LAD. Men had a higher prevalence of MB in segments D1 (62% men, 40% women, p=0.003), D2 (47% men, 20% women, p<0.001), IM (33% men, 20% women, p=0.037), and M1 (83% men, 68% women, p=0.018).

Prevalence on a segmental level

In chest-pain patients, prevalence per cardiac segment was 1,345 (42%) and 732 (53%) in non-chest pain subjects (p<0.001), details in Table 14.

Table 14. Myocardial bridging in relation to analyzed segments for *both cohorts*

	Both cohorts		**Chest pain patients SWEDEHEART**		**Non-chest pain subjects SCAPIS**	
Segments analyzed	N	MB, n (%)	N	MB, n (%)	N	MB, n (%)
6	630	219 (35)	434	103 (24)	196	116 (59)
7	627	272 (43)	433	191 (44)	194	81 (42)
8	622	154 (24)	427	97 (23)	195	57 (29)
D1	610	285 (47)	420	187 (45)	190	98 (52)
D2	416	180 (43)	296	117 (40)	120	63 (53)
D3	168	58 (35)	123	43 (35)	45	15 (33)
D4	19	9 (47)	13	7 (54)	6	2 (33)
D5	1	0	0	0	1	0
IM1	288	137 (48)	195	86 (44)	93	51 (55)
IM2	34	26 (76)	26	20 (77)	8	6 (75)
IM3	4	3 (75)	2	2 (100)	2	1 (50)
M1	603	408 (68)	412	262 (64)	191	146 (76)
M2	430	247 (57)	303	170 (56)	127	77 (61)
M3	100	64 (64)	79	47 (59)	21	17 (81)
M4	25	12 (48)	23	10 (43)	2	2 (100)
M5	5	3 (60)	5	3 (60)	0	0 (-)
Total	4,582	2,077 (45)	3,191	1,345 (42)	1,391	732 (53)

Prevalence of myocardial bridging in relation to analyzed segments, in both cohorts, chest pain patients (SWEDEHEART) and non-chest pain subjects (SCAPIS) separately, (p<0.001 for total between cohorts). N= number of individuals with segment, n (%) = number and proportion of segments with myocardial bridging.

Type of MB and MB depth

There was a significant difference in that non-chest-pain subjects had more often MB compared to chest pain-patients, when comparing different types of MB, in proximal LAD/segment 6 when comparing the different types of MB, there was a significant difference between the cohorts for the proximal LAD, segment 6, (p<0.001), Figure 26, Table 15.

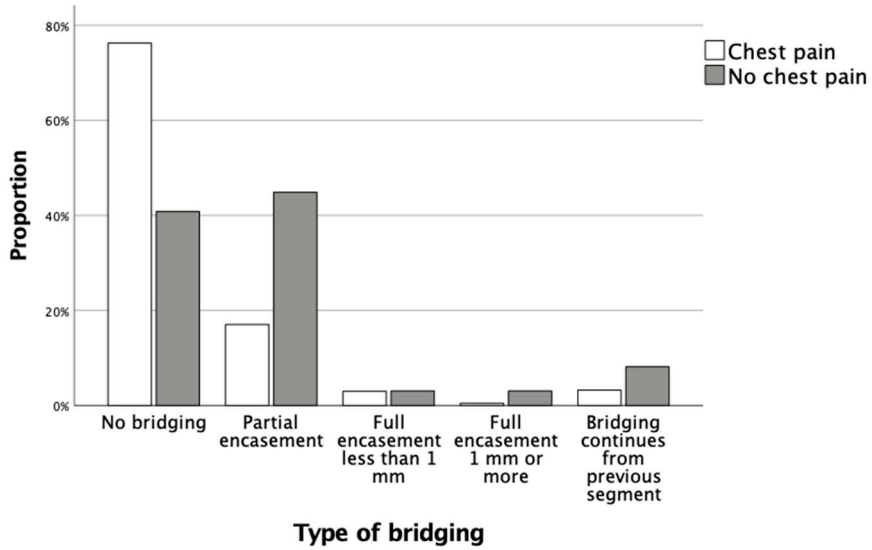


Figure 26 Myocardial bridging in proximal and mid LAD related to plaque. Proportion (%) of MB in segments 6 and 7 related to presence of plaque for *non-chest pain subjects (SCAPIS)*, p=0.018.

Chest pain patients had less partial encasement in proximal LAD (segment 6), IM, and M1 than non-chest pain subjects, Table 15.

For MB more than or equal to 1mm, MB was found to be deeper for non-chest pain subjects compared to chest pain patients. No other difference concerning depth of MB between the two groups were found, Table 15.

Table 15. Type and depth of the myocardial bridging for *both cohorts.*

Segment	Both cohorts N=630	Chest pain patients N=434 / Non-chest pain subjects N=196					P value Between cohorts and type of MB	P Between cohorts and dept of CB
	Full encasement Depth ≥1mm	Bridging continued from previous segment	No bridging	Partial encasement	Full encasement Depth <1mm	Full encasement Depth ≥1mm		
	N(%) Median [IQR]	N(%)	N(%)	N(%)	N(%)	N(%) Median [IQR]		
6	8(1.3) 2[2-3.75]	14(3.2) / 16(8.1)	331(76) / 80(41)	74(17) / 88(45)	13(3.0) / 6(3.1)	2(0.5) 3.5[2-.] / 6(3.1) 2[1.75-3.25]	1.1593E-16	0.429
7	17(2.7) 3[1-4]	12(2.8) / 7(3.6)	241(56) / 113(58)	132(30) / 43(22)	37(8.5) / 24(12)	10 (2.3) 2.5[0.75-4.25] / 7(3.6) 3[2-3]	0.157	0.961
8	4(0.6) 1[0.25-1.75]	23(5.3) / 13(6.6)	329(76) / 138(70)	59(14) / 34(17)	12(2.8) / 9(4.6)	3(0.7) 1[0-.] / 1(0.5) 1[1-1]	0.460	1
D1	43(6.8) 2[1-2]	- / -	134(31) / 70(36)	76(18) / 37(19)	87(20) / 43(22)	25(5.8) 2[1-2] / 18(9.2) 2[1-2]	0.740	0.925
D2	21(3.3) 2[1-2]	- / -	107(25) / 53(27)	54(12) / 28(14)	52(12) / 25(13)	11(2.5) 1[1-2] / 10(5.1) 2[1-2.25]	0.601	0.387
D3	4(0.63) 1[1-2.5]	- / -	50(12) / 25(13)	19(4.4) / 4(2.0)	21(4.8) / 10(5.1)	3(0.7) 1[1-.] / 1(0.5) 1[1-1]	0.521	1
D4	0	- / -	4(0.92) / 2(1.0)	2(0.46) / 0	5(1.2) / 2(1.0)	0 / 0	0.645	-
D5	0	- / -	0 / 1(0.51)	0 / 0	0 / 0	0 / 0	-	-
IM1	41(6.5) 2[1-2]	- / -	34(7.9) / 17(8.7)	17(3.9) / 16(8.2)	46(11) / 18(9.2)	23(5.3) 1[1-2] / 18(8.7) 2[2-2.25]	0.184	0.014
IM2	7(1.1) 1[1-2]	- / -	1(3.7) / 0	4(0.9) / 1(0.51)	10(2.3) / 4(2.0)	6(1.4) 1[1-2.5] / 1(0.5) 2[2-2]	0.830	0.571
IM3	1(0.16) 1[1-1]	- / -	0 / 1(0.51)	0 / 0	1(0.23) / 1(0.51)	1(0.23) 1[1-1] / -	0.368	-
M1	45(7.1) 1[1-2]	2(0.46) / 0	75(17) / 31(16)	112(26) / 64(33)	116(27) / 69(35)	32(7.4) 2[1-2] / 13(6.6) 2[1.5-2]	0.421	0.028
M2	19(3.0) 2[1-2]	- - - / -	81(19) / 41(21)	85(20) / 39(20)	69(16) / 36(18)	17(3.9) 2[1-2] / 2(1.0) 5[1-.]	0.219	0.655
M3	4(0.63) 1[1-2.5]	- - / -	15(19) / 4(2.0)	19(4.4) / 10(5.1)	24(5.5) / 7(3.6)	4(0.92) 1[1-2.5] / -	0.399	-
M4	0	- / -	5(0.12) / 0	7(1.6) / 1(0.51)	3(0.69) / 1(0.51)	0 / 0	0.510	-
M5	0	- / -	0 / 0	3(0.69) / 0	0 / 0	0 / 0	-	-

Chest pain patients (SWEDEHEART) and non-chest pain subjects (SCAPIS). Data expressed as n (%) or median [IQR]

MB length

The measured length of MB for chest pain-patients ranged from 5-147 mm in chest pain patients and 5-125 mm in non-chest pain subjects, displaying no statistically significant difference. Nor were there any other significant differences between the two groups in segments with measured length of MB.

MB and the presence of atherosclerotic plaque in proximal LAD

In proximal LAD/segment 6, atherosclerotic plaques was, for both cohorts combined found in 32%, for 29% in the chest-pain cohort, and for 38% in the non-chest pain cohort.

It was more common with atherosclerotic plaque in segment 6/proximal LAD, for subjects in the non-chest pain cohort with MB in segments 6 and 7, than for individuals without MB in segments 6 and 7 (85% vs 30%, p=0.018), Figure 27. No other significant associations regarding the presence of plaque and MB in proximal LAD was found, not among chest pain patients, nor among the non-chest pain subjects.

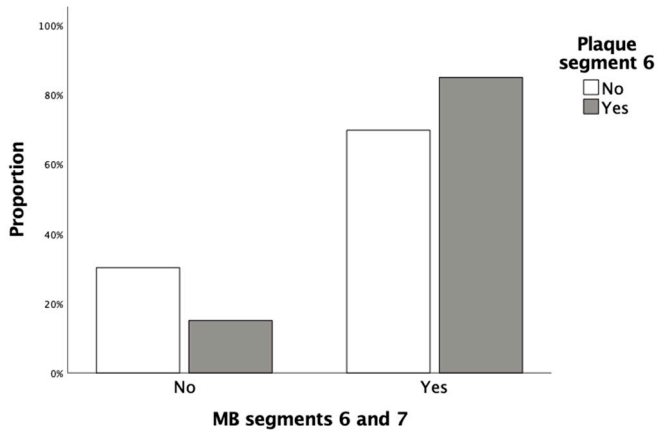


Figure 27 Myocardial bridging in proximal and mid LAD related to plaque. Proportion (%) of MB in segments 6 and 7 related to presence of plaque for non-chest pain subjects (SCAPIS), p=0.018.

MB in relation to ventricular arrhythmia

As mentioned above, the non-chest pain subjects underwent 24-hour ECG registration, where we assessed ventricular arrhythmia. Among the 196 subjects, 55 (28%) were found to have ventricular arrhythmia, and out of them, 85% were found to have MB in segments 6 and 7, and 15% had no MB in these segments (p=0.035), Figure 28B. After adjustment for presence of plaque as a possible confounder, a significant association remained, p=0.041.

Subjects with MB in segments 6 and 7/proximal and mid LAD had more PVCs than subjects without MB in these segments, p=0.040, Figure 28A. However, for PVCs in bigeminy, PVCs in trigemini, coupled PVCs, triplets of PVCs, and/or ventricular tachycardia, no other significant differences were found when relating to the presence of MB in other segments.

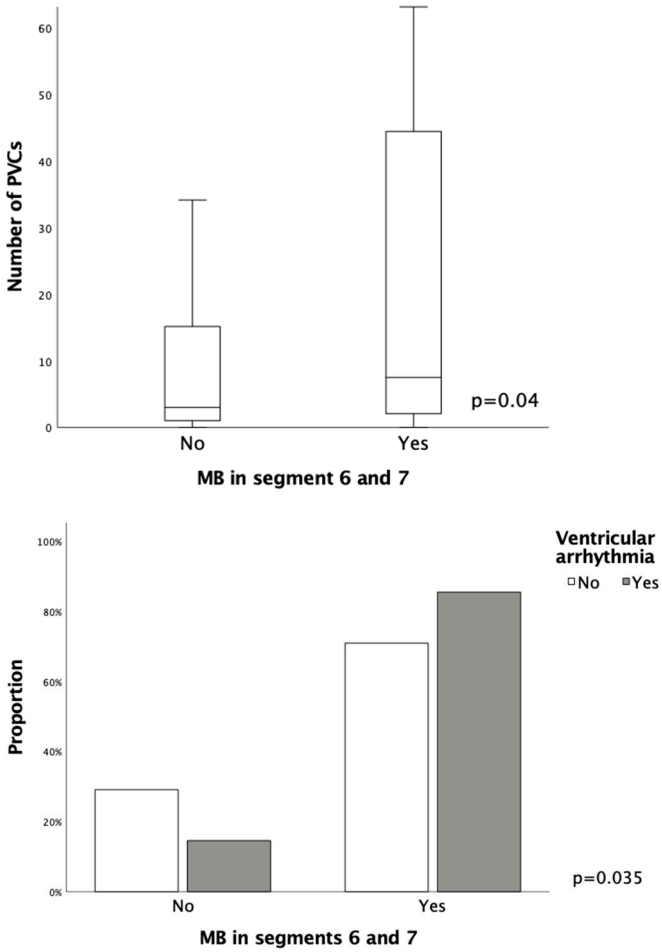


Figure 28. Arrhythmias related to myocardial bridging for non-chest pain subject (SCAPIS). Prevalence of ventricular arrhythmia for non-chest pain subjects (SCAPIS).
A) Boxplot showing the number of premature ventricular contractions (PVCs), during time for monitoring (standardized to 24h), related to the occurrence of myocardial bridging (MB), in segment 6 and 7, p=0.04. The boxes represent the 25th to 75th percentile, whiskers represent the smallest and largest value within 1,5 times the interquartile range. Thicker lines define the median.
B) Bar chart representing the percentage of non-chest pain subjects from the SCAPIS cohort with and without MB in segments 6 and 7 related to the occurrence of ventricular arrhythmia, p=0.035.

Intra-observer variability

For proximal LAD, moderate agreement (Cohen´s weighted kappa 0.57, Confidence Interval (CI) [0.14-1]), was demonstrated in the intra-observer variability analysis. For mid LAD, substantial agreement was demonstrated (Cohen´s weighted kappa 0.88 CI [0.64-1.1]) as well as for proximal and mid LAD combined, (Cohen´s weighted kappa 0.64 CI [0.056-1.3]) when assessing the prevalence of MB.

Discussion

In this thesis, cardiovascular imaging is used to uncover and analyze imaging findings. Data regarding biochemistry, histology, inflammation, risk factors, biomarkers, ECG registrations, and questionnaires were combined with imaging findings to explore different aspects of cardiovascular disease.

For cardiovascular disease in general, where atherosclerosis is an important underlying cause, methods to prevent the formation and progression of atherosclerotic plaques are needed. The cost to society of complications of atherosclerosis, including ischemic stroke and myocardial infarction, is enormous. The findings in Paper I demonstrate that the risk for future ischemic stroke was higher with higher level of sLOX-1, the cleavage product of the main scavenger receptor for oxLDL, LOX-1.

Paper I also provides clinical support for a role of LOX-1 in cardiovascular disease by demonstrating that exposure of endothelial cells to the LOX-1 ligand oxLDL increases the release of sLOX-1, subjects with high circulating levels of sLOX-1 have more severe carotid disease and an increased risk of ischemic stroke, and that carotid plaques with high levels of sLOX-1 are characterized by increased inflammation.

Also in the setting of acute stroke, sLOX-1 is also elevated. (128) In a case-control study, sLOX-1 was greater among individuals presenting with ischemic or hemorrhagic stroke in the past three days, in comparison to healthy controls. (128) Testing for sLOX-1 is not part of current clinical practice but has been suggested as a marker for cardiovascular disease. (129)

Besides addressing lifestyle changes, screening for risk factors, and preventive medication, finding new ways to alter plaque development is highly appealing. This makes targeting LOX-1 for inhibition when developing new drugs interesting. In a study with rats, LOX-1 inhibition led to less infarction and oedema, less hemorrhage, and more remaining neurological function (130). The authors also performed in vitro experiments where brain cells were deprived of glucose and oxygen. When these cells were also treated with LOX-1 inhibitors, they displayed less inflammation, better survival, and a more intact endothelial barrier. A recent study showed decreased

expression of LOX-1 when mice were treated with the drug liraglutide, a glucagon-like peptide-1 receptor agonist, used as a novel type of anti-diabetic medication, both on mRNA and protein expression levels. (80) The inhibition was, however, not selective, and more studies on the subject are needed.

Patients with systemic inflammatory conditions have more cardiovascular disease comorbidity. (131) Studies also link cancer and inflammation. Patients with cardiovascular disease have an increased risk for cancer, and patients with cancer have an increased risk for cardiovascular disease. (132) Targeting LOX-1 in cancer treatment has also been suggested. (133)

Paper II was a proof-of-concept study, where CCTA was used to depict cardiac veins, and the image findings were then transformed to a 17-segment plot of the left ventricular myocardium as an attempt to, in the future, better guide CRT-lead placement, in terms of which segments of the left ventricle were available. No differences were found concerning the number of veins or available segments in relation to patient sex, underlying type of cardiomyopathy, or ECG-morphology. No difference in the number of veins or available segments was found for different scanning protocols. This made future examinations possible in a high-pitch mode, resulting in lower radiation, allowing for exams with lower radiation dose in clinical practice. Cardiac veins can also be imaged by direct cardiac venography or occlusive cardiac venography. Occlusive cardiac venography is done by injecting contrast via catheters in the cardiac venous system and the contrast is kept in place by occlusive balloons. Both methods are invasive and involve a higher risk but are widely used. One study showed 9% complication rate for occlusive cardiac venography. (134) Complementary imaging methods to detect scarring and late mechanical activation has been advised by one study (135), and a meta-study showed that imaging-guided CRT-lead placement leads to lower risk of heart failure hospitalization. (136) Recent guidelines suggest alternative placement of pacemaker leads for conduction system pacing (33), reducing demand for imaging of cardiac veins.

The global obesity pandemic is a serious concern, tripling in prevalence since 1975 (137), and Paper III adds to the evidence that the condition is not benign and that further measures must be taken towards prevention and treatment. Obesity is a multi-factorial disease, where both hormones and genetics play crucial roles. In recent years, anti-diabetic medications consisting of gastrointestinal hormones with dramatic effects on weight loss have rocketed in popularity, and genetically tailored treatment has been suggested. (138)

Paper III is a cross-sectional cohort study where we found that, even in the absence of criteria of metabolic syndrome (MetS), excluding the waist criterion, coronary atherosclerosis detected by CCTA was more increased for obese subjects compared to normal weight subjects without MetS. Previous studies had only used the coronary calcium burden to evaluate the impact of obesity in metabolically healthy obese individuals on coronary atherosclerosis. (139) Obese subjects without metabolic syndrome had a higher risk of mild coronary atherosclerosis (1-49% stenosis) than normal subjects without metabolic syndrome, which might indicate that obesity plays a role in the early formation of coronary atherosclerosis. This could relate to the elevated state of inflammation in obese individuals.

The definition of metabolically healthy obese differs, and a novel definition is suggested (140), where high blood pressure, presence of diabetes mellitus, and waist /hip ratio are included. This is in line with our findings, where only blood pressure and glucose criteria (the waist criterion was excluded) remained after multiple adjustments when comparing obese individuals with one MetS criterion to normal-weight individuals without MetS criteria, who had increased coronary artery stenosis. For overweight individuals, only blood pressure remained. As hypertension is preceded by low-grade inflammation (141), and inflammation is a classic hallmark of obesity (142), the findings emphasize their critical roles in the development of cardiovascular disease. The results of Paper III are in line with previous findings that the risk of future cardiovascular disease increases with increasing number of criteria for MetS. (143)

In Paper III, the extent of carotid plaques was not increased for obese or overweight subjects without MetS compared to normal weight subjects without MetS. Using presence of carotid plaque as the outcome instead of intima-media thickness (IMT) might have influenced the results, however, previous studies using IMT have shown divergent results. (144, 145) Ultrasound of the carotid artery is more difficult to perform on obese subjects, and focal thickening of the intima in the carotid bulb is harder to visualize in obese subjects, especially plaques with low echogenicity. This might have underestimated carotid atherosclerosis.

The progression rate of atherosclerosis in relation to obesity is of interest, and future studies will explore this, comparing the SCAPIS cohort´s first and second exams. The progression of atherosclerosis could be considered when deciding when to initiate and how aggressively one should be concerning preventive medication.

In Paper IV, the presence of myocardial bridging was related to chest pain. Myocardial bridging was not more common among chest pain patients than among subjects from the general population. Myocardial bridging, according to the definition used in our

study, is very common. Other definitions exist (146-148), resulting in different prevalence, detected by CCTA between 3.5% and 100% (73), and consensus on the definition is needed. The high prevalence of myocardial bridging calls for careful consideration of when to report and how to advise individuals with myocardial bridging. The Italian Committee for Cardiology for Sport Fitness (COCIS) suggests testing for ischemia with single-photon emission computed tomography (SPECT) or invasive fractional flow reserve (FFR) for asymptomatic patients with a myocardial bridge longer than 10 mm and a depth over three mm, and if negative, no restrains on physical activity is suggested, (149) but there are no randomized trials supporting this. For symptomatic patients, pharmacological treatment is suggested (150), but when symptoms persist, invasive therapies such as percutaneous coronary intervention (PCI), de-roofing, and bypass grafting can be considered and have been used in small studies, but long-term results are uncertain, and randomized trials are lacking. (151)

For subjects from the general population, we found that the number of PVCs was higher among subjects with myocardial bridging in the proximal and mid LAD than for subjects without. We also found that, for subjects with ventricular arrhythmias, myocardial bridging in the proximal and mid LAD segments was more common. Smaller studies/case reports have previously reported arrhythmia in combination with myocardial bridging. (152-155) The reasoning behind a link between arrhythmia and myocardial bridging could be that since MB is most common in LAD, which provides blood supply to the conduction system, a decreased blood flow would result in arrhythmia. The findings indicate a relation between myocardial bridging and ventricular arrhythmias.

Atherosclerotic plaques have been suggested to be affected in terms of location in relation to myocardial bridging. The myocardial bridge is often spared from atherosclerosis, while the segment before the bridge is more affected. Intravascular pressure in the myocardial bridge differs from that in the artery without a myocardial bridge, with high shear stress in the bridged segment and low or altered shear stress at the site where the bridge starts. (151) In Paper IV, subjects without chest pain and MB in segment 6 and 7, plaque in segment 6 (the segment proximal to the MB) was more common than for individuals without MB in segments 6 and 7 (30% vs 85%, p=0.018), which is similar to findings of other studies. (156-158)

The relevance of myocardial bridging remains uncertain, but the finding that arrhythmia is related to myocardial bridging indicates the need for studies addressing this, possibly with functional testing, to clarify the clinical relevance better.

Cardiovascular imaging supports patient care by guiding when preventive measures are taken, advising decisions in various clinical settings, and when and where to target treatment or procedures. As the technical progress in the field is ever evolving, it is up to imaging specialists and clinicians to incorporate these advancements into clinical practice. This thesis investigations were conducted to explore who is at risk, factors involved in inflammation leading to the progression of atherosclerosis, and in turn later to cardiovascular disease, such as stroke and heart failure, with a focus on their relationship to imaging findings, contributing to better understanding and guidance in the field.

Strengths and Limitations

The strength of this thesis lies in the way various fields of expertise are combined with cardiovascular imaging to explore inflammation, symptoms, risk factors, or to ameliorate pre-procedural planning.

Paper I has some notable strengths. It was the first time high level of sLOX-1 was shown to be associated with future ischemic stroke in a large prospective cohort study. The MDC cohort has a mean follow-up time of 16.5 years, a considerable time. We studied sLOX-1 in both the human plaques and circulation, linking elevated levels of sLOX-1 to plaque inflammation.

Subjects with high levels of sLOX-1 had a higher risk of future ischemic stroke, and even more so when carotid artery plaque was present. This association remained after adjustment for risk factors. However, a causal relation cannot be drawn, as it is the observational part of the study. Also, all subjects with prior ischemic stroke were excluded, and the future risk for ischemic stroke in a population with prior stroke was not studied. The sLOX-1 levels were measured on baseline samples, and we cannot tell if an individual remained in the same tertile over time, nor if the sample was representative at the baseline or reflected a temporary state. However, the results support the idea that LOX-1 has a role in atherosclerotic development. Strong associations between sLOX-1 and risk factors for cardiovascular disease were found. When quantifying the level of sLOX-1 in plaque content, the assay measured all LOX-1, which means we could not distinguish primary sLOX-1 from primary cell-bound LOX-1 or even parts of LOX-1 created during plaque fragmentation. When endothelial cells were exposed to oxLDL, the release of sLOX-1 increased. Still, the study did not explore whether an increased level of sLOX-1 is a marker for increased LOX-1 signaling or if sLOX-1 has an inflammatory role in itself. However, studies have shown that blockage of LOX-1 has led to lower levels of sLOX-1 (159, 160), that statins have a modulating effect on LOX-1 synthesis (161, 162), and that sLOX-1 seems to reflect increased LOX-1 signaling (129), strengthening the support of LOX-1 having a central role in initiation and development of cardiovascular disease.

Paper II was a proof-of-concept study, and we do not know whether the procedures to implant CRT-pacemakers took a shorter time, given the knowledge of where cardiac veins were located. We cannot draw any conclusion regarding the outcome for patients, as the randomized part of the study (not included in the thesis) only regarded the viability and time of activation for cardiac segments, whereas the pacemaker implantation surgeon was presented with CT data for both controls and targeted subjects. (79) The randomized study included 70 patients and did not show a significant decrease in left ventricular volume at end systole 6 months after implantation, nor a significant difference in hospitalization due to heart failure or death during the first 2 years (2% of the intervention group vs. 10% of the control group; p = 0.07). However, a meta-study later found imaging-guided lead placement beneficial for outcome (163). Recent guidelines from the Heart Rhythm Society rate multimodality imaging, including cardiac MR, CT, and echo, for guiding lead placement as level two recommendations.

CCTA scans were not performed in the entire cardiac cycle, and we did not scan in the cardiac phase with the largest diameter of cardiac veins, as suggested by one study (72). However, another study found that the cardiac phase with the largest vein diameter differed between systolic and diastolic phases between individuals. (164) This might have influenced the number of veins considered too small in diameter for pacemaker lead implantation.

Although the radiation dose was given consideration in Paper II, some CT machines of today present options to make contrast enhancement easier to detect, with even lower radiation doses. Similar to CT technology, magnetic resonance (MR) has also improved, which might enable the detection of larger cardiac veins, avoiding radiation altogether. However, MR technology is not always compatible with pacemakers, and MR exam times are longer than CT, which should be considered.

Paper III incorporated a substantial number of subjects from six different cities in Sweden, where both CCTA and ultrasound examinations were performed and evaluated by a large number of readers/and/or performers. Centralizing or automating this might have improved reproducibility regarding the assessment of coronary and carotid atherosclerosis.

Scoring of CCTA exams was carried out per coronary segment (excluding distal segments), grading stenosis and noting which segments had atherosclerosis, resulting in a segment involvement score. This is an accepted way of grading the severity of atherosclerosis, but a different scoring method would be to score the number of plaques per segment. Large plaque burden is an independent predictor of adverse events when

detected by invasive imaging (165), and it is possible that a more detailed stratification of atherosclerotic burden would further improve the analysis.

Blood pressure was measured while the subjects were lying down in accordance with local Swedish routine, which is in contrast with the suggested international guidelines, where blood pressure is often measured with the subjects sitting. (166, 167) Measuring blood pressure with subjects lying down would result in somewhat higher blood pressure. (168)

Observational studies like the present one do not allow for causative conclusions, and it is possible that high BMI is caused by coronary atherosclerosis; however, this is unlikely. Coronary artery disease with ischemia might, however, cause increased pain during exercise, resulting in less exercise followed by weight gain.

In Paper IV, a large number of individuals were assessed by one reader concerning the presence and characteristics of myocardial bridging, with intraobserver-reader performance evaluated by Cohen´s kappa. Although results might be more reproducible with one reader, it would be ideal with more than one reader, or even an automated reader in the future. The large number of patients and subjects combined, and the scope of this thesis, did not allow for this, as it would have been too time-consuming.

The ECG registration was only done for non-chest pain subjects, and we do not know the frequency of arrhythmia or its relation to myocardial bridging for chest-pain patients.

Different scanning protocols performed on different CT scanners might have influenced the image quality and the possibility of accurately assessing myocardial bridging. The protocols were designed to accurately rule in/out coronary artery disease, and different scanning methods allowing for measuring the diameter of the coronary arteries over the cardiac cycle could possibly give more detail in the data and allow for other conclusions.

Data of the presence and characteristics of myocardial bridging could be analyzed with other cut-off values for myocardial bridging depth, for example could myocardial bridges deeper than 2 mm be analyzed in relation to chest pain vs no chest pain.

Future perspectives

Cardiovascular imaging continues to provide ever more detailed information, useful in both clinical and preventive settings.

Finding individuals who are at higher risk of having a stroke in the future and being able to motivate lifestyle changes more strongly or initiate preventive medication earlier would add healthy years and longer life expectancy. In addition, the cost of stroke care would be cut. This is already done by screening for hypertension at health checkups, but would be even more focused if we add carotid ultrasound and sLOX-1 testing. As sLOX-1 possibly relates to the level of inflammation, this could be considered, although other methods of measuring inflammation must be evaluated for accuracy and cost-effectiveness.

Mentioning the presence of carotid or coronary plaques in the clinical radiology report when present as "incidental findings" on exams carried out for other clinical work-up helps identify individuals at risk.

Statins modify LOX-1 signaling and are in clinical practice. Future medications to selectively block LOX-1 could further alter the progression of atherosclerosis, possibly by modifying inflammation.

In cardiovascular imaging, perivascular fat attenuation inflammation indicates an inflammatory process (169), and adding this information to plaque and stenosis assessment could give an indication of when to take more aggressive methods to counteract the progression of atherosclerosis.

Myocardial bridging is common, but future studies are needed to evaluate the full clinical relevance.

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About the author

Foto: Bo Lincoln

HANNA MARKSTAD was born in 1975 in Habo, Västergötland, Sweden. She studied medicine at Lund University, Sweden, and graduated in January 2003. She thereafter completed her internship in Jönköping, Sweden. After 9 months of maternal leave with her twins, she started her specialist training in Radiology in Hässleholm, Sweden, in December 2005. In December 2006, her training was transferred to Lund University Hospital. Her third child was born in 2008. She finished her specialist training in 2011 and subsequently started subspecializing in Thoracic Radiology. In 2012, she was asked to lead in Cardiac CT, where a skilled team of doctors, radiology nurses, and booking personnel has gradually grown around the method. Today, she is a senior consultant in Thoracic Radiology at the Department of Imaging and Physiology, Skåne University Hospital, Sweden.

In her research, she has combined Cardiovascular Imaging with adjacent areas of expertise to improve prognosis, pre-procedural planning, and guidance for clinicians in the setting of cardiovascular disease.

In her spare time, she enjoys sailing at sea with her husband, Bo Lincoln, reading fiction of various kinds and qualities, listening to the crisp sound of crystallized water (snow) from underneath the skies, wandering by foot or mountain bike in nature, lying down on the warm, pink granite rocks of Bohuslän after an ocean dip, and enjoying moments together with friends and family—all the things that make life worthwhile.

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