Coronary heart disease on coronary computed tomography angiography: in search of the vulnerable patient

Rosendael, S.E. van

Coronary Heart Disease on Coronary Computed Tomography Angiography

In search of the vulnerable patient

Sophie E. van Rosendael

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TABLE OF CONTENTS

CHAPTER 1

General introduction and outline of the thesis

The most common cause of death globally is cardiovascular disease.[1] Coronary heart disease or coronary artery disease is the most common cardiac pathology and is currently the third leading cause of death in the world associated with 17.8 million deaths per year.[2] Atherosclerosis, the main risk factor for cardiovascular disease, commences with activation of the endothelium before a cascade of events, namely lipid accumulation, fibrous elements and calcification, triggers activation of inflammatory pathways and narrowing of the vessel.[3] These processes result in an atheromatous plaque, which may cause cardiovascular complications. Based on the degree of diameter stenosis, poor supply of oxygen-rich blood to the heart muscle (ischemia), can lead to symptoms such as angina and dyspnea. The diagnostic evaluation of patients with stable chest pain suggestive of coronary artery disease can be assessed with a variety of tests. Non-invasive imaging tests for detection of ischemia like myocardial perfusion imaging, exercise electrocardiography or radionuclide scintigraphy are often used to determine functionally significant stenosis, based on the severity and extent of inducible ischemia of the myocardium. However, most acute coronary syndromes are caused by low grade coronary stenoses.[4] Atherosclerotic assessment with coronary computed tomography angiography (CCTA) is more frequently used as an alternative non-invasive modality to assess stable symptomatic patients. It has high specificity and sensitivity for the detection of anatomically significant coronary artery disease and provides good risk stratification for future cardiovascular events.[5,6]

Plaque quantification

CCTA is an anatomic diagnostic imaging modality using an intravenous contrast agent, that provides information regarding the coronary artery lumen and wall. The totality of plaque, the 'atherosclerotic plaque burden', the plaque location and plaque morphology can be estimated. CCTA is able to detect non-obstructive coronary artery disease (diameter stenosis <50%), which usually does not correlate with cardiac symptoms or positive stress tests, but identifies patients at an early stage. A majority of patients with a major adverse cardiovascular event have no cardiac symptoms or manifestations of coronary artery disease.[7] The development of events in these patients is often caused by the rupture of highly inflamed or unstable atherosclerotic plaques.[8]

Besides information regarding the atherosclerotic extent, CCTA allows quantification of the coronary arteries to derive compositional plaque analysis, high-risk plaque features, and luminal measures, associated with - independent from plaque burden- clinical outcomes.[9-11] High-risk plaque features on CCTA are the napkin ring sign, lesions with a large necrotic core, spotty calcification and positive remodeling.[12] Plaques with at least two of these features are denoted as high-risk and are associated with acute coronary syndrome.[12,13]

Understanding the nature and rate of plaque progression and identification of which patients are at increased risk of major adverse cardiovascular events is a topic of ongoing research. Given the association with adverse events, atherosclerotic progression - independent from baseline plaque volume - has been proposed as a surrogate marker for MACE.[14] An average absolute plaque progression of 1.0% percent atheroma volume was associated with events.[15,16] Lifestyle, pharmacological therapies and revascularization modify atherogenesis and may stabilize or even regress the disease. Statin

therapy is associated with slower total plaque progression, with specifically a larger progression of calcified plaque and a slower progression of noncalcified plaque.[17] The main predictor of events in patients treated with high-dose statins and low on-treatment LDL cholesterol levels was baseline percent atheroma volume.[14] Which factors are associated with the progression of atherosclerosis despite statin therapy, 'statin non-response', is discussed in Chapter 3.

Pericoronary adipose tissue

Prevention of major adverse cardiac events is challenging as many of the plaque ruptures in coronary arteries arise from lesions with less than 50% stenosis.[18] Consequently, the identification of vulnerable lesions at an early stage becomes more relevant. Pericoronary adipose tissue (PCAT), a biomarker associated with vascular inflammation, might improve risk stratification.[19,20] Vascular inflammation is a key factor in coronary atherosclerotic plaque formation, progression and rupture and affects the differentiation, proliferation and lipolysis of the adipocytes in the fatty tissue around the coronary arteries.[19, 21-24] This leads to smaller adipocytes with lower intracellular lipid content which is correlated with higher Hounsfield units, or attenuation values, on CCTA. The feasibility of PCAT attenuation obtained with CCTA and vascular inflammation detection has been shown.[19,25,26] Significant different PCAT attenuation values have been identified between coronaries with and without atherosclerosis, in culprit and non-culprit lesions and between flow-limiting and non-flow-limiting stenosis.[25-28] In Chapter 2 we discuss PCAT attenuation values evaluated in coronaries without atherosclerosis to establish reference values.

Epicardial coronary artery lumen volume to left ventricular mass

Cardiac CT enables the calculation of the ratio of the total epicardial coronary artery lumen volume to left ventricular myocardial mass (the V/M ratio) as well. The V/M ratio is considered a parameter capable of revealing a potential physiological imbalance between myocardial demand and coronary blood supply. Reduced V/M ratios are associated with reduced myocardial blood flow, more extensive coronary artery disease, and lesion-specific fractional flow reserve <0.80.[29-31] An abnormal low V/M ratio might also be expected in patients with high blood pressure as hypertension has been associated with reduced myocardial perfusion reserve.[32-41] Sustained elevated afterload in hypertensive patients causes left ventricular hypertrophy which is associated with an increase in myocardial oxygen demand and a reduction in maximal coronary vasodilator reserve.[42-47] The decrease in maximal vasodilator reserve causes a reduction of peak myocardial flow per unit mass of myocardium and could lead to ischemia during increased myocardial metabolic demands. Factors contributing to the reduction in maximal flow can be primary alterations of coronary vascular tone, an increase in diastolic myocardial wall tension (which could lead to an increase of coronary vascular resistance), or the development of ventricular hypertrophy without concomitant neovascularization.[48] In addition, perivascular and interstitial deposition of fibrillar collagen is found in hypertrophied left ventricles, and the amount of myocardial collagen is increased, leading to impaired ventricular pumping capacity.[49,50] Whether the reduced coronary flow reserve in hypertensive patients is caused by a reduced V/M ratio will be discussed in Chapter 5.

Outline of the thesis

Of all the imaging techniques used in the field of cardiology, this thesis focuses on the role that CCTA may have in the diagnosis, evaluation and risk stratification of coronary artery disease.

Chapter 2 describes values of PCAT, a 'sensor' of vascular inflammation, in patients without coronary artery disease. In Chapter 3 plaque progression on serial CCTA is measured and factors associated with plaque volume progression despite the use of statins are presented. In Chapter 4 we describe the sex- and age-specific differences and interactions in the onset of atherosclerosis and risk for major adverse cardiovascular events using the Leiden CCTA risk score, a comprehensive score that incorporates plaque extent, composition, severity and location into a single value. Chapter 5 investigates the coronary volume to left ventricular mass ratio obtained by CCTA in patients with hypertension. It is a parameter that investigates the relation between coronary vasculature and myocardial mass and capable of revealing physiological imbalance when present.

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CHAPTER 2

Vessel and sex differences in pericoronary adipose tissue attenuation obtained with coronary CT in individuals without coronary atherosclerosis

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Abstract

Introduction

Pericoronary adipose tissue (PCAT) attenuation, derived from coronary computed tomography angiography (CCTA), is associated with coronary artery inflammation. Values for PCAT attenuation in men and women without atherosclerosis on CCTA are lacking. The aim of the current study was to assess the mean PCAT attenuation in individuals without coronary artery atherosclerosis on CCTA.

Methods

Data on PCAT attenuation in men and women without coronary artery atherosclerosis on CCTA were included in this retrospective analysis. The PCAT attenuation was analyzed from the proximal part of the right coronary artery (RCA), the left anterior descending artery (LAD), and the left circumflex artery (LCx). For patient level analyses the mean PCAT attenuation was defined as the mean of the three coronary arteries.

Results

In 109 individuals (mean age 45 ± 13 years; 44% men), 320 coronary arteries were analyzed. The mean PCAT attenuation of the overall population was -64.4 ± 8.0 HU. The mean PCAT attenuation was significantly lower in the LAD compared with the LCx and RCA (-67.8 ± 7.8 HU vs. -62.6 ± 6.8 HU vs. -63.6±7.9 HU, respectively, p<0.001). In addition, the mean PCAT attenuation was significantly higher in men vs. women in all three coronary arteries (LAD: -65.7 ± 7.6 HU vs. -69.4 ± 7.6 HU, p=0.014; LCx: -60.6 ± 7.4 HU vs. -64.3 ± 5.9 HU, p=0.008; RCA: -61.7 ± 7.9 HU vs. -65.0 ± 7.7 HU, p=0.029, respectively).

Conclusion

The current study provides mean PCAT attenuation values, derived from individuals without CAD. Moreover, the mean PCAT attenuation is lower in women vs. men. Furthermore, the mean PCAT attenuation is significantly lower in the LAD vs. LCx and RCA.

Keywords: coronary artery disease; coronary computed tomography angiography; pericoronary adipose tissue attenuation; perivascular inflammation.

Abbreviations:

CAD = coronary artery disease
CCTA = coronary computed tomography angiography
LAD = left anterior descending artery
LCx = left circumflex artery
LM = left main artery
PCAT = pericoronary adipose tissue
RCA = right coronary artery

Introduction

Vascular inflammation contributes to coronary atherosclerotic plaque formation and atherosclerotic plaque rupture.[1,2,3] Over the past years, the link between pericoronary adipose tissue (PCAT) associated inflammation and atherosclerosis has been demonstrated in several studies.[4-6] PCAT attenuation reflects vascular inflammation, which is associated with unstable plaque features and is considered a sensitive inflammatory biomarker which may improve cardiovascular risk stratification.[4,7] Vascular inflammation can influence adipocyte lipid content through paracrine signalling by affecting biological processes such as adipocyte differentiation, proliferation and lipolysis in adjacent perivascular fat.[4,8] Moreover, Antonopoulos et al[4] demonstrated an inverse association of PCAT attenuation on coronary computed tomography angiography (CCTA) with histological adipocyte size and degree of adipocyte differentiation. Moreover, the authors demonstrated that PCAT with higher attenuation values on CCTA was correlated with smaller adipocytes with lower lipid content.[4] Many previous studies assessed PCAT attenuation in patients with atherosclerotic coronary arteries, whereas PCAT attenuation values in individuals without coronary atherosclerosis are lacking. Accordingly, the purpose of the current study is to evaluate the PCAT attenuation in the right coronary artery (RCA), the left anterior descending artery (LAD) and the left circumflex artery (LCx) in individuals without coronary atherosclerosis, to establish reference values.

Methods

Study design and participants

Consecutive individuals without coronary atherosclerosis on CCTA at the Leiden University Medical Centre (Leiden, The Netherlands) between 2012 and 2015 were identified and included in this retrospective, observational analysis. Individuals with suboptimal CCTA image quality or coronary anomalies, as well as individuals who had a CCTA scan at a tube voltage of 135 kV, were excluded (Figure 1). Baseline clinical demographic characteristics including medication use and cardiovascular risk factors were reported. The current study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the local ethics committee, who waived the need for written informed consent.

CCTA image acquisition

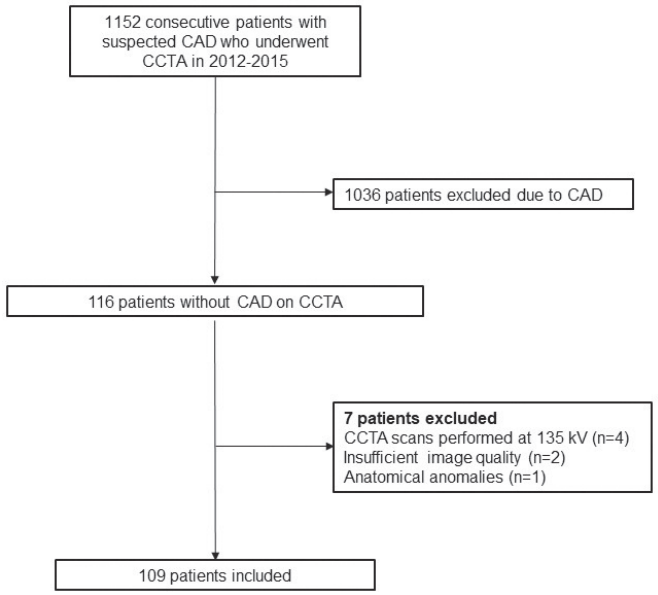
All CCTA scans were performed with a 320-slice multi-detector computed tomography scanner (Aquilion ONE, Toshiba Medical Systems, Otawara, Japan) with a gantry rotation time of 350ms. Tube voltage and tube current varied from 100-120 kV and 150-640 mA, depending on the individual's size. If the heart rate before the CCTA scan was >65 beats per minute, 25-150 mg of oral metoprolol was administered 1 hour before the CCTA scan, unless contraindicated. If the heart rate remained >65 beats per minute during the CCTA scan, up to 10 mg of intravenous metoprolol was administered additionally. Sublingual nitroglycerin (400-800 mg) was administered to all individuals before the scan.

CCTA analysis

Anatomical CCTA evaluation was performed using the 17-segment modified American Heart Association model.[9] Quantitative CCTA analysis was performed using dedicated software (QAngio CT Research Edition version 3.2.0.13; Medis Medical Imaging Systems, Leiden, The Netherlands). In brief, a 3-dimensional coronary tree was derived from the CCTA images. All coronary arteries with a diameter of ≥1.5mm were evaluated for the presence of atherosclerosis. For each coronary artery, multiplanar reconstructions were created. Lumen and vessel wall contours were automatically detected, with manual correction of the lumen vessel contours if needed.[10] The presence of coronary atherosclerosis was defined as a tissue structure >1 mm^2 within or adjacent to the coronary artery lumen that could be distinguished from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself.[11]

Figure 1. Study flowchart.

CAD = coronary artery disease; kV = kilovoltage; CCTA = coronary computed tomography angiography



Pericoronary adipose tissue attenuation analysis

The mean pericoronary adipose tissue (PCAT) attenuation was evaluated in all three major epicardial coronary arteries using dedicated software (QAngio CT Research Edition version 3.2.0.13, Medis Medical Imaging Systems, Leiden, The Netherlands). The PCAT was defined as the area with an attenuation between -30 and -190 Hounsfield Units (HU) within a radial distance from the outer vessel wall equivalent to the diameter of the vessel.[4,7] The proximal 40 mm segments of the LAD and LCx were analyzed (Figure 2). The proximal 10 to 50 mm segment of the RCA was evaluated, in order to avoid effects of the aortic wall (Figure 2).[4] To adjust for differences in attenuation between scans performed at different tube voltages, the mean PCAT attenuation of CCTA

scans performed at 100 kV was divided by a conversion factor of 1.11485.[4,12] At a per-patient level, the mean PCAT attenuation was defined as the average of the three major coronary arteries. A minimal artery length of 40 mm was necessary for PCAT attenuation measurements.

Statistical analysis

SPSS version 25 (IBM SPSS Statistics, IBM Corporation, Armonk, New York, USA) was used for statistical analyses. Continuous variables with a normal distribution are presented as mean ± standard deviation and were compared using the Student t-test or the one-way ANOVA test, as appropriate. The Bonferroni correction was applied in case of a significant difference in the overall three group comparison. Distribution of continuous variables was evaluated using histograms. Categorical variables are presented as absolute numbers and percentages and were compared using the χ^2 test. The correlation of the mean PCAT attenuation between the various epicardial coronary arteries was evaluated using the Pearson correlation test. Linear regression analyses were performed to investigate the association between mean PCAT attenuation and sex, adjusted for smoking status. A two-sided p-value <0.05 was considered significant.

Figure 2. Pericoronary Adipose Tissue (PCAT) analysis of the proximal segments of the left anterior descending artery (LAD), the left circumflex artery (LCx) and the right coronary artery (RCA). Including corresponding pericoronary adipose tissue colour maps and cross-sectional views of the start and end point of the analyzed segments.

HU=Hounsfield unit.

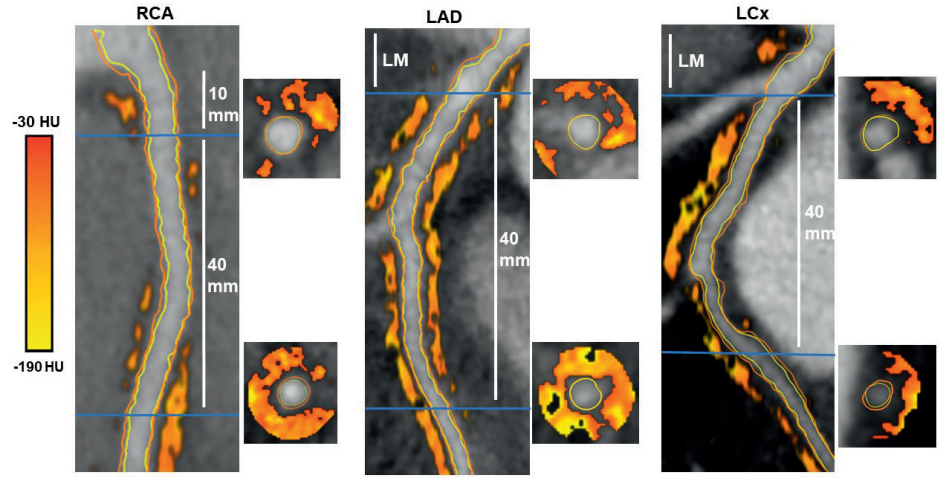


Table 1: Baseline characteristics of the population and according to sex

	Overall population (n=109)	Men (n=48)	Women (n=61)	p-value
Age, years	45 ± 13	44 ± 13	46 ± 13	0.426
BMI, kg/m²	24.6 ± 3.8	24.6 ± 3.6	24.7 ± 3.9	0.850
Symptoms, n (%)				
Typical angina	5 (4.6)	2 (4.2)	3 (4.9)	0.852
Atypical angina	39 (35.8)	14 (29.2)	25 (41.0)	0.201
Non-anginal	21 (19.2)	9 (18.8)	12 (19.7)	0.904
No pain	44 (40.4)	23 (47.9)	21 (34.4)	0.154
Dyspnea	7 (6.4)	2 (4.2)	5 (8.2)	0.394
Cardiac risk factors, n (%)				
Hypertension	28 (25.7)	8 (16.7)	20 (32.8)	0.056
Dyslipidemia	13 (11.9)	6 (12.5)	7 (11.5)	0.870
Diabetes mellitus	12 (11)	5 (10.4)	7 (11.5)	0.861
Family history of CAD	46 (42.4)	23 (47.9)	23 (37.7)	0.284
Current smoking	20 (18.3)	13 (27.1)	7 (11.5)	0.037
Obesity	12 (11.1)	3 (6.4)	9 (14.8)	0.150
Cardiovascular medication, n (%)				
Aspirin	15 (13.8)	9 (9.5)	24 (18.9)	0.801
Beta-blockers	6 (5.4)	10 (20.8)	18 (29.5)	0.333
Calcium channel blockers	28 (25.7)	1 (2.1)	4 (6.6)	0.277
ACE-inhibitors or angiotensin II receptor blockers	5 (4.6)	4 (8.3)	10 (16.4)	0.227
Diuretics	6 (5.4)	0 (0)	6 (9.8)	0.027
Statins	16 (14.7)	5 (10.4)	11 (18)	0.284
Tube voltage, n (%)				
100 kV	80 (74.1)	35 (74.4)	45 (73.8)	0.935
120 kV	28 (25.9)	12 (25.5)	16 (26.2)	0.935

Data are presented as mean ± SD and n (%). BMI = Body mass index; CAD = coronary artery disease; kV = kilovoltage.

Results

Baseline characteristics

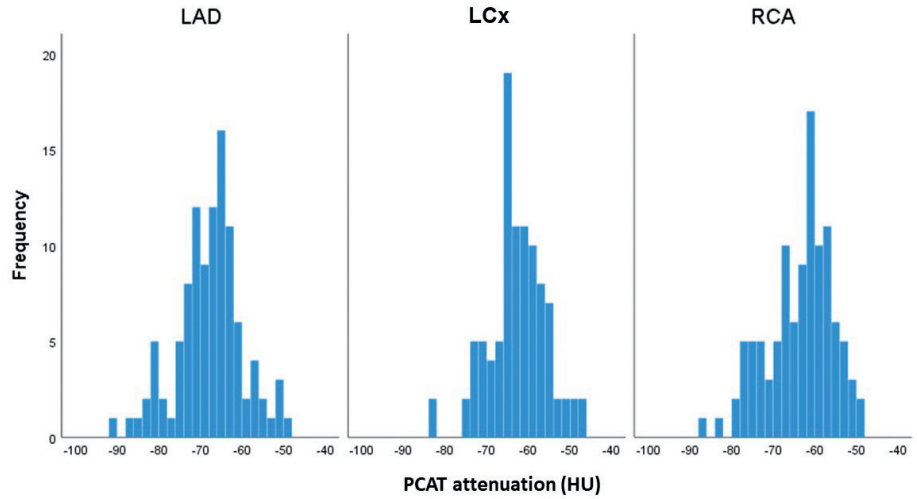
In total, 109 individuals (mean age 45±13 years; 44% male) including 320 coronary arteries without atherosclerosis on CCTA were included. A flowchart of the population is displayed in Figure 1. Seven coronary arteries (LCx: n=5, RCA: n=2) were too small for PCAT attenuation analysis and were excluded. Baseline demographic and clinical characteristics of the overall population and

according to sex are shown in Table 1. Of the overall population, hypertension was present in 28 (25.7%) and dyslipidemia in 13 individuals (11.9%). Men were more often smokers as compared to women (27.1% vs. 11.5%, p=0.037).

Pericoronary adipose tissue attenuation

The mean PCAT attenuation of the overall population was -64.4 ± 8.0 HU. The distribution of the mean PCAT attenuation around the epicardial coronary arteries is shown in Figure 3. The mean PCAT attenuation was significantly lower in the LAD vs. the LCx and vs. the RCA (-67.8 ± 7.8 HU vs. -62.6 ± 6.8 HU vs. -63.6 ± 7.9 HU, respectively, p<0.001, Figure 4). In addition, no significant correlations existed between the three individual coronary arteries with regard to the mean PCAT attenuation (Appendix Figure 1).

Figure 3. Distribution of the mean pericoronary adipose tissue (PCAT) attenuation of the left anterior descending artery (LAD), the left circumflex artery (LCx) and the right coronary artery (RCA).



Sex differences in pericoronary adipose tissue

At a per-person level, the mean PCAT attenuation was significantly higher in men as compared to women (-62.7 ± 7.9 HU vs. -66.3 ± 7.5 HU, p <0.001). Moreover, this sex-related difference in mean PCAT attenuation was noted in each of the three epicardial coronary arteries (LAD: -65.7 ± 7.6 HU vs. -69.4 ± 7.6 HU, p=0.014; LCx: -60.6 ± 7.4 HU vs. -64.3 ± 5.9 HU, p=0.008; RCA: -61.7 ± 7.9 HU vs. -65.0 ± 7.7 HU, p=0.029, respectively, Figure 5). Sex remained independently associated with the mean PCAT attenuation after adjustment for smoking status (β coefficient: 3.3 (95% Confidence Interval: 1.56; 5.07, p<0.001).

Figure 4. The comparison of the mean pericoronary adipose tissue (PCAT) attenuation among the left anterior descending artery (LAD), the left circumflex artery (LCx) and the right coronary artery (RCA).

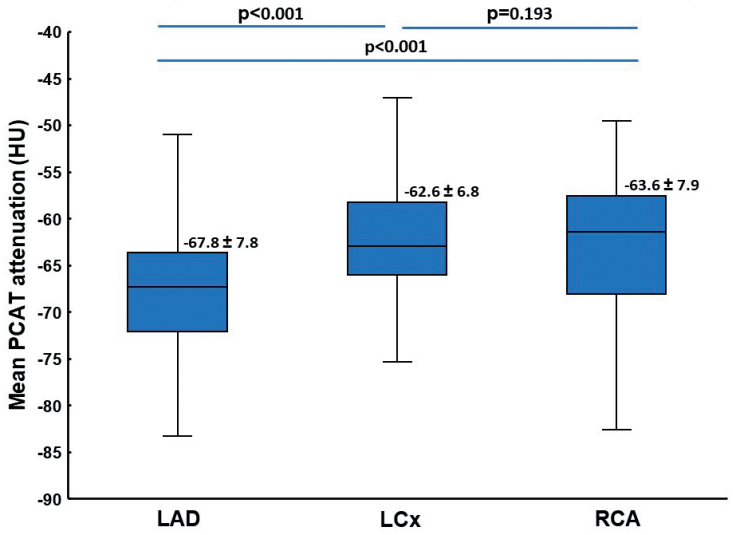
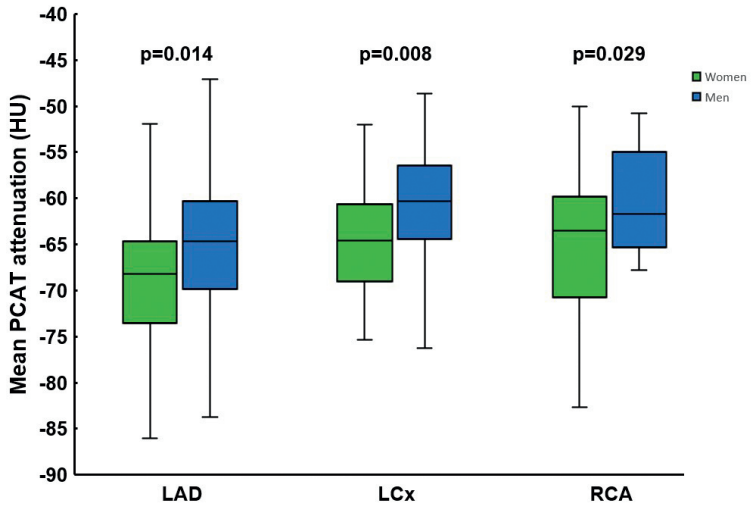


Figure 5. The mean pericoronary adipose tissue (PCAT) attenuation among the left anterior descending artery (LAD), the left circumflex artery (LCx) and the right coronary artery (RCA) according to sex.



Discussion

The current study assessed the mean PCAT attention in individuals without coronary atherosclerosis. The results demonstrate that the mean PCAT attenuation is significantly different between the LAD and RCA, and between the LAD and LCx. In addition, mean PCAT attenuation values were significantly higher in men compared to women in all three coronary arteries.

Previous studies have shown that many coronary artery plaque ruptures arise from non-obstructive atherosclerotic lesions.[13] Consequently, early identification of potentially vulnerable atherosclerotic lesions becomes increasingly relevant. Detection and quantification of vascular inflammation may further improve early risk stratification of patients, possibly even before the development of significant coronary artery plaques. Previous studies have shown the feasibility of non-invasive assessment of PCAT attenuation with CCTA for the detection of vascular inflammation.[4-6] Specifically, significant differences in PCAT attenuation have been shown between diseased and non-diseased coronary arteries.[14] Moreover, increased PCAT attenuation has been demonstrated between culprit and non-culprit lesions in patients who subsequently developed an acute myocardial infarction.[15] In addition, PCAT attenuation was also increased in patients with flow-limiting coronary artery lesions as compared to patients with non-flow limiting lesions.[5,6]

Information regarding PCAT attenuation values in coronaries without atherosclerosis is lacking. A prior study evaluating mean PCAT attenuation values in patients without CAD, showed slightly lower values in the non-atherosclerotic coronary arteries, compared to coronary arteries with CAD.[14]

Differences in PCAT attenuation among the different coronary arteries

In the current study, significant differences in mean PCAT attenuation between the coronary arteries were observed. Mean PCAT attenuation around the proximal LAD was lower compared to the RCA and LCx. This could potentially be explained by differences in anatomy between the three coronary arteries. Furthermore, studies showed that among the three coronary arteries, the LAD is predominantly and earlier subject to atherosclerosis.[16-18,19] In addition, higher plaque and calcium deposit burden were observed in the LAD compared to the RCA and LCx.[20-22] The lower PCAT attenuation values in the LAD from our study, may suggest that PCAT attenuation could be linked to vessel vulnerability for CAD.

Ma et al.[14] analyzed all three coronary arteries and found lower PCAT attenuation values in the LAD as well. In addition, Gaibazzi et al.[23] showed significant differences between the LAD/RCA and the LCx in vessels with no or <50% coronary artery stenosis at CCTA. The CRISP-CT study that incorporated PCAT attenuation in calculating the fat attenuation index (FAI) using a proprietary algorithm (CaRiHEART, Carito Diagnostics, Oxford, United Kingdom), showed no difference in perivascular FAI values between the three coronary arteries in patients with suspected CAD, but observed a difference in prognostic value between the three coronaries.[7]

Previous studies mainly focused on the RCA to represent overall pericoronary attenuation, without evaluating potential differences between the RCA, LAD and LCx.[6,15,24-26] The proximal RCA is characterized by the absence of confounding non-fatty structures such as side branches, coronary veins, or myocardium, and also by the highest volume of surrounding adipose tissue.[4,27] However, the current findings suggest that the mean PCAT attenuation measurement of the RCA is not interchangeable with the other coronary arteries.

Sex differences in PCAT attenuation

In the current study a significant difference in PCAT attenuation was noted between men and women. This observation is in agreement with results published recently by Ma et al[14] and Tzolos et al[28], showing significantly increased PCAT attenuation values in men versus women. Men are known to have an increased risk of developing CAD than women, and at a younger age.[29,30] Increased PCAT attenuation in men might reflect an increased burden of coronary artery inflammation, that contributes to the progression of coronary atherosclerosis. Additionally, sex-specific hormones may further contribute to the increased PCAT attenuation in men.[31]

Notably, the PCAT values obtained in present study are higher than those reported in previous studies. PCAT is relatively novel and many factors may influence this parameter. Considering technical factors, van Diemen et al.[32] showed significant differences in mean PCAT attenuation based on the CT scanner type used. Mean PCAT attenuation values using 64- and 256-slice CT scanners were -72.2 HU and -80.2 HU, respectively. Another key factor affecting the absolute PCAT attenuation is the kV setting and should be taken into account when evaluating PCAT attenuation. A higher tube voltage is associated with higher PCAT values[14]. Using different tube voltages necessitates adjustment for differences in PCAT attenuation as previously validated[12], but this is only done by a limited amount of studies[7,33]. Furthermore, PCAT attenuation is quantified in different centres by different software packages.

We think that absolute values of PCAT attenuation on CCTA need to be tested and validated across different CT scanners, tube voltages and software packages in different centres before standardized thresholds for PCAT attenuation can be defined and clinical application is possible.

Study limitations

This is a single-centre, retrospective observational study with a limited patient cohort. The observational design of the study has inherent limitations including selection bias and unmeasured confounding. Furthermore, this study could not characterize the patients regarding their ethnicity and explore ethnic differences in PCAT attenuation.

Conclusions

PCAT attenuation values were derived from CCTA images of coronary arteries without atherosclerosis. Mean PCAT attenuation differed significantly between the three coronary arteries and mean PCAT attenuation was significantly higher in men compared to women.

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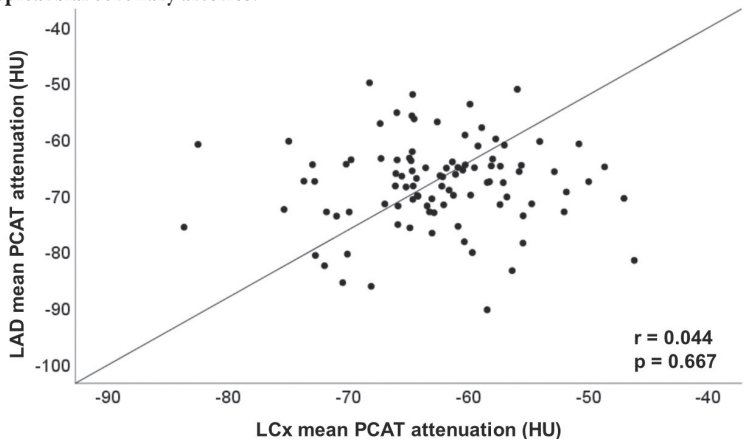
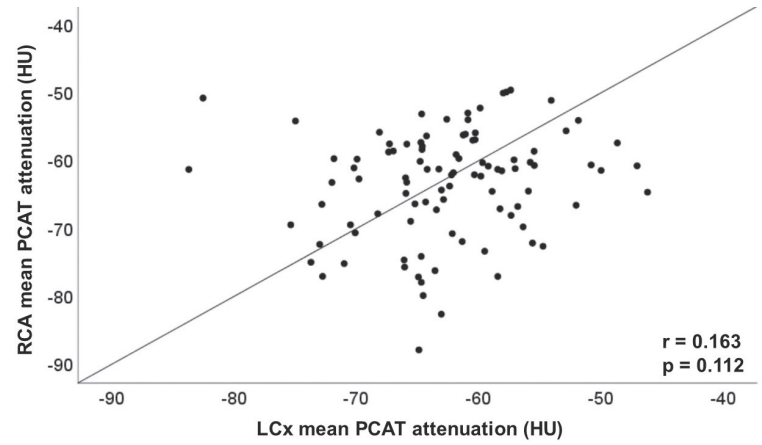
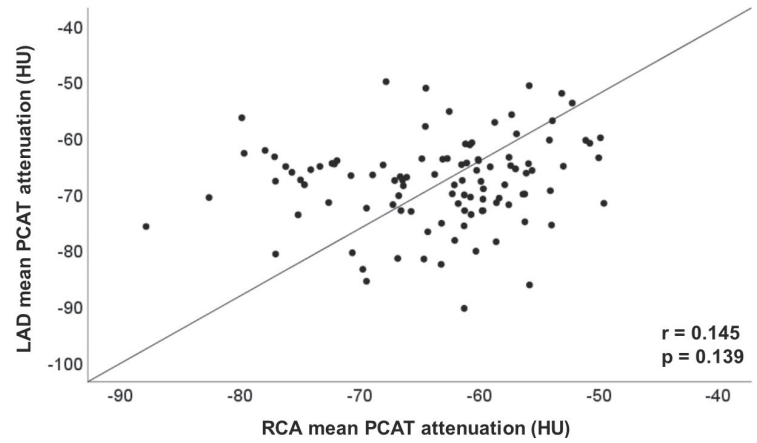
Appendix

Figure 1. Correlation of the mean pericoronary adipose tissue (PCAT) attenuation among the three epicardial coronary arteries.







CHAPTER 3

Clinical and Coronary Plaque Predictors of Atherosclerotic Non-response to Statin Therapy

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Abstract

Background: Statins reduce the incidence of major cardiovascular events, but residual risk remains. The study examined the determinants of atherosclerotic statin non-response.

Objectives: This study aimed to investigate factors associated with statin non-response defined atherosclerosis progression in patients treated with statins.

Methods: The multi-center PARADIGM registry included patients who underwent serial coronary computed tomography angiography (CCTA) ≥ 2 years apart, with whole-heart coronary tree quantification of vessel, lumen and plaque, and matching of baseline and follow-up coronary segments and lesions. Patients with statin use at baseline and follow-up CCTA were included. Atherosclerotic statin non-response was defined as an absolute increase in percent atheroma volume (PAV) of 1.0% or more per year. Further a secondary endpoint was defined by the additional requirement of progression of low-attenuation plaque or fibro-fatty plaque.

Results: We included 649 patients (62.0±9.0 years, 63.5% male) on statin therapy and 205 (31.5%) experienced atherosclerotic statin non-response. Age, diabetes, hypertension, and all atherosclerotic plaque features measured at baseline scan (high risk plaque [HRP] features, calcified and noncalcified PAV, and lumen volume) were significantly different between patients with and without atherosclerotic statin non response, while only diabetes, the number of high risk plaque features, non-calcified and calcified PAV were independently associated with atherosclerotic statin non-response (OR:1.41 (0.95-2.11), OR:1.15 (1.09-1.21), OR:1.06 (1.02-1.10), OR:1.07 (1.03-1.12), respectively). For the secondary endpoint (N=125, 19.2%), only non-calcified PAV and number of HRP features were the independent determinants (OR:1.08 (1.03-1.13) and OR:1.21 (1.06-1.21), respectively).

Conclusion: In patients treated with statins, baseline plaque characterization by plaque burden and high-risk plaque is associated with atherosclerotic statin non-response. Patients with the highest plaque burden including HRP were at highest risk for plaque progression, despite statin therapy. These patients may need additional therapies for further risk reduction.

Key-words: plaque progression, atherosclerosis; statin non-response; coronary computed tomography angiography.

Condensed abstract

The study examined determinants of atherosclerotic statin non-response in patients using statins. 649 patients (62.0 ± 9.0 years, 63.5% male) from the multi-center PARADIGM registry with statin use at baseline and follow-up CCTA were included. 205 patients (31.5%) experienced atherosclerotic statin non-response. In patients treated with statins, baseline plaque characterization by plaque burden and high-risk plaque is associated with atherosclerotic statin non-response defined as important progression of coronary atherosclerosis. Patients with the highest plaque burden including HRP were at highest risk for plaque progression, despite statin therapy. These patients may be candidates for additional risk reducing therapies.

Abbreviations

CAD: coronary artery disease; CCTA: coronary computed tomography angiography; MACE: major cardiovascular events; PAV: percent atheroma volume; HRP: high risk plaque; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Introduction

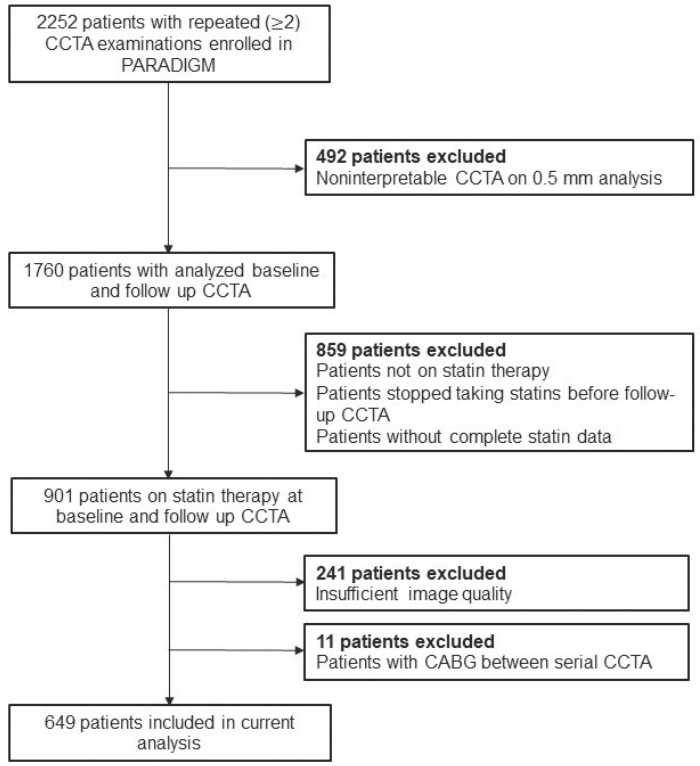
Statins have consistently been shown to reduce the incidence of future cardiovascular events, and higher intensity statins provoke more risk reduction than low dose statins.[1] Favorable effects of statins include reduction in low-density lipoprotein (LDL) cholesterol, C-reactive protein (CRP), increase of high-density lipoprotein (HDL), and limitation of atherosclerosis progression.[2] However, residual cardiovascular risk remains despite statin therapy, especially in patients with a large burden of atherosclerosis, several risk factors or persisting elevated CRP or LDL cholesterol.[3,4]

Atherosclerotic extent has been identified as a potent driver of major cardiovascular events (MACE), even in patients treated with statins.[5,6] Atherosclerosis represents a lifetime exposure to risk factors and is the direct substrate for the acute coronary syndrome. In 1039 patients treated with high intensity statins and undergoing baseline intravascular ultrasound imaging, baseline percent atheroma volume was the main predictor for MACE, despite the achievement of very low on-treatment LDL cholesterol levels.[5] In addition, progression of atherosclerosis has been associated with MACE, and has been proposed as a surrogate marker for MACE in medication trials.[2]

Besides atherosclerotic extent, CCTA allows quantification of the entire coronary tree to derive compositional plaque analysis, luminal measures and high-risk markers which have been associated with several clinical outcomes, independent from plaque burden.[7-9] The PARADIGM registry aimed to understand the nature and rate of plaque progression and identify the factors determining it. The primary analysis demonstrated a slower total plaque progression associated with the use of statins during the study period. Subdividing according to compositional plaque type, progression of calcified plaque was larger with statins, while non-calcified plaque progression was slower.[10] Further subdividing into plaque composition showed an association of statins with a more rapid transformation of low-density noncalcified plaque toward high density calcium.[11] Also plaque progression associated with increases in calcium scores have been evaluated. This analysis shows that an increase in calcium score translates to an increase in calcified plaque, while calcium score progression in patients using statins equals increased progression of both calcified and noncalcified plaque.[12] Further, the prognostic value of plaque progression has been demonstrated, independently from baseline plaque volume.[13,14] Specifically, the average absolute plaque progression of patients with events was 1.0% of percent atheroma volume. The current analysis differentiates by identifying patients that are likely to progress in plaque volume despite the use of statins. Given the association of plaque progression with events, these patients will represent a high-risk cohort.

We hypothesized that a comprehensive evaluation of atherosclerosis identifies patients whose atherosclerosis will progress despite the use of statin therapy. The aim of the current study examined which factors - in patients treated with statins and undergoing serial CCTA - are associated with atherosclerotic statin non-response defined atherosclerosis progression.

Figure 1. Flowchart of study population.
CCTA, coronary computed tomography angiography; CABG: coronary artery bypass graft



Methods

Patients

The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed Tomo-Graphic Angiography Imaging) registry study is a dynamic, multinational (13 sites, 7 countries) registry with prospective follow-up data for patients who underwent serial CCTA ≥2 years apart for clinical indications.[10,15] The institutional review board of all participating sites approved the study protocol. For the current analysis, patients who were on statin therapy at baseline and follow-up CCTA were selected (N=901). Patients whose CCTA image quality was insufficient for slice based quantitative plaque analysis (N=241) and those who underwent CABG between serial CCTA (N=11) were excluded, leaving 649 patients in the current cohort (Figure 1). Patients were evaluated by their physician or nurse at time of baseline and follow-up CCTA and data regarding demographics, medication use, cardiovascular risk factors, and laboratory tests were collected. Standardized definitions for cardiovascular risk factors were used.

Table 1. Laboratory and CCTA findings at baseline and follow-up

	Baseline (N=649)	Follow-up (N=649)	P-value
Laboratory results			
Total cholesterol, mg/dl	180.6 ± 44.6	160.8 ± 37.3	<0.001
LDL cholesterol, mg/dl	108.0 ± 40.5	88.7 ± 30.3	<0.001
HDL cholesterol, mg/dl	49.6 ± 13.0	49.1 ± 13.0	<0.001
Triglycerides, mg/dl	144 ± 78	125 ± 67	<0.001
HbA1c, %*	6.79 ± 1.39	6.70 ±1.15	0.835
CRP, mg/dl**	0.79 (0.28-2.14)	0.59 (0.18-1.20)	0.127
CCTA findings			
PAV, %	4.7 (1.3-10.8)	7.5 (2.7-15.2)	<0.001
Calcified, %	1.1 (0.1-3.7)	2.6 (0.58-7.2)	<0.001
Non-calcified, %	2.8 (0.71-6.3)	3.3 (1.0-7.4)	<0.001
Number of HRP, n	0.49 ± 0.82	0.55 ± 0.84	0.037
Number of HRP features, n	4.5 ± 3.8	5.0 ± 3.9	<0.001
Lumen volume, mm^3	1750 ± 962	1708 ± 952	<0.001

*N=204
**N=253
CRP, C-reactive protein; HbA1c, Hemoglobin A1c; HDL, high-density lipoprotein; HRP, high-risk plaque; LDL, low-density lipoprotein; PAV, percent atheroma volume
Values are mean ± SD or median (interquartile range).

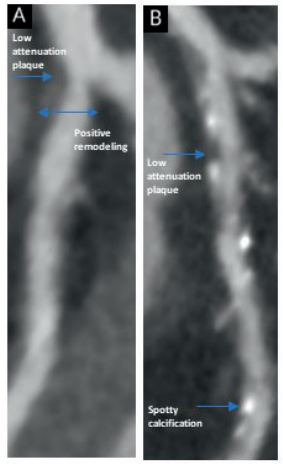
CCTA analysis

CCTA acquisition was performed in accordance with the Society of Cardiovascular Computed Tomography guidelines.[16] Baseline and follow-up DICOM files from each site were transferred to the core laboratory for blinded quantitative plaque analysis. Coronary atherosclerosis was evaluated on multiplanar and cross-sectional images and evaluations were performed by level-III readers, with systematic quality checks for intra- and inter-observer concordance, as previously described.[10] Paired CCTA scans were analyzed by two independent readers blinded to clinical data. Semi-automated software (QAngioCT Research Edition v2.1.9.1, Medis Medical Imaging Systems, Leiden, The Netherlands) was used, with manual corrections where needed.

Segments from the entire coronary tree ≥2mm in diameter were evaluated for coronary lumen, vessel wall and plaque. Atherosclerosis was defined as tissue ≥1 mm^2 within the lumen that could be discriminated from the surrounding pericardial tissue, epicardial fat, or lumen, identified in >2 planes.[17] Baseline and follow-up coronary segments were matched based on fiduciary landmarks (e.g. distance from ostium, branch vessels) to obtain a similar number of segments in both CT scans. Segmental data was summed to obtain per-patient level quantities. Similar to segments, coronary lesions were evaluated pairwise with the option to develop a new plaque at follow-up

CCTA. Segments and lesions being revascularized between serial CCTA were censored in for both scans. CCTA Plaque was subdivided into calcified and non-calcified based on the Hounsfield Unit threshold of 350 HU. Whole-heart atherosclerotic burden was defined as percent atheroma volume (PAV), calculated as plaque volume / vessel volume * 100%. Low attenuation and fibro-fatty plaque together were defined by -30 to 130 HU. Coronary lesions were defined as high-risk plaque (HRP) in the presence of ≥2 of the following features; low-attenuation plaque, positive remodeling (remodeling index >1.1 compared with a proximal non-diseased coronary site), or spotty calcification.[18] Several coronary plaque features were calculated based on prior literature and representatives of coronary stenosis, extent, and composition.[7,10,19]

Figure 2. Example of plaque on baseline (A) and follow up (B) of the proximal left anterior descending artery in a patient with statin non-response.
Example of plaque progression in a patient with coronary artery disease.
(A) Curved multi-planar view of high-risk plaque features in the proximal left anterior descending artery
(B) Curved multi-planar view of the same left anterior descending artery with plaque progression



Outcomes

The primary outcome was the association of baseline clinical, laboratory, and CCTA findings with atherosclerotic statin non-response, defined as the absolute increase of 1.0 percentage points in PAV/year. Increase in PAV/year of 1.0% was selected based on its prognostic significance with MACE in prior CT and intravascular ultrasound literature.[20,21]

Statin use has been associated with low-attenuation and fibro-fatty plaque regression, and increased high-density calcium progression.[14] Therefore, a sub analysis was performed with an added requirement of increased low-attenuation and fibro-fatty plaque at follow-up CT. Hence the secondary endpoint definition was defined as >1.0% increase in PAV/year in combination with progression of low-attenuation or fibro-fatty plaque (consisting of plaque with Hounsfield units -30 to 130).

Statistical analysis

Continuous variables were presented as means ± standard deviation if normally distributed and median (25-75th interquartile range) if non-normally distributed. Categorical data was presented as counts (%). Paired comparisons between baseline and follow-up data was performed with the Paired T test or Wilcoxon signed-rank test. Unpaired data was compared with the independent T-test or Mann Whitney U test, or Chi-square test as appropriate. Logistic regression was utilised to examine associations with atherosclerotic statin non-response and its independent determinants. Univariate analysis was performed including: baseline demographics, cardiovascular risk factors, baseline lipid profile and baseline CCTA findings such as PAV, number of high risk plaques (HRP), number of HRP features and lumen volume. Stepwise multivariate logistic regression was performed including the same variables as the univariate analysis. Notably, we chose to include calcified and non-calcified PAV in this multivariate analysis, rather than total PAV alone, because they provide independent value. Both univariate and multivariate analyses were reported in terms of odds ratios (ORs) with corresponding 95% confidence intervals (CI). In order to measure correlation between baseline variables and increase in %PAV/year, scatter plots were made. All p-values are 2-sided and significance was defined by <0.05.

Table 2. Baseline characteristics and CCTA findings at baseline and follow-up stratified according to statin response

	Atherosclerotic statin non-response + N=205	Atherosclerotic statin non-response - N=444	P-value
Baseline demographics			
Age, years	63.8 ± 8.6	61.2 ± 9.1	0.001
Male sex, n	133 (64.9)	279 (62.8)	0.616
Body mass index, kg/m^2	25.6 ± 3.4	25.5 ± 3.2	0.626
Cardiovascular risk profile			
Diabetes, n	71 (34.6)	108 (24.4)	0.007
Hypertension, n	137 (66.8)	256 (57.9)	0.031
Current smoking, n	42 (20.5)	74 (16.7)	0.248
Family history for CAD, n	58 (28.3)	105 (23.6)	0.205
Prior revascularization, n	43 (21.0)	81 (18.2)	0.410
Interval revascularization, n	42 (20.5)	54 (12.2)	0.005
Medication			
Aspirin	146 (71.2)	270 (60.8)	0.010
Beta-blockers	83 (40.7)	192 (43.4)	0.511
ACE-inhibitor and/or angiotensin II receptor blockers	105 (51.2)	156 (35.1)	0.001

Table 2. Continued

	Atherosclerotic statin non-response + N=205	Atherosclerotic statin non-response - N=444	P-value
Baseline laboratory results			
Total cholesterol, mg/dl	176.1 ± 43.4	182.8 ± 44.9	0.087
LDL cholesterol, mg/dl	106.4 ± 38.0	108.8 ± 41.8	0.508
HDL cholesterol, mg/dl	47.5 ± 11.9	50.7 ± 13.4	0.004
Triglycerides, mg/dl	140 ± 72	146 ± 81	0.403
HbA1c, %*	7.0 ± 1.3	6.6 ± 1.4	0.048
CRP, mg/dl**	0.80 (0.32-2.20)	0.75 (0.15-1.98)	0.145
Follow up laboratory results			
Total cholesterol, mg/dl	153 ± 37	164 ± 37	0.002
LDL cholesterol, mg/dl	83 ± 29	91 ± 31	0.003
HDL cholesterol, mg/dl	47 ± 12	50 ± 13	0.025
Triglycerides, mg/dl	120 ± 57	128 ± 71	0.204
HbA1c, %*	6.9 ± 1.1	6.6 ± 1.1	0.155
CRP, mg/dl**	0.57 (0.3-1.0)	0.6 (0.07-1.3)	0.788
Baseline CCTA findings			
PAV, %	9.9 (5.2-16.7)	2.8 (0.61-7.4)	<0.001
Calcified, %	3.4 (1.1-7.6)	0.50 (0.00-2.3)	<0.001
Non-calcified, %	5.8 (2.9-9.7)	1.7 (0.31-4.8)	<0.001
Number of HRP, n	0.75 ± 1.0	0.36 ± 0.67	<0.001
Number of HRP features, n	6.4 ± 4.0	3.6 ± 3.3	<0.001
Lumen volume, mm^3	1574 ± 813	1831 ± 1013	<0.001
CT-interval, yr	3.3 (2.5-4.3)	3.4 (2.7-4.9)	0.012
Follow up CCTA findings			
PAV, %	17.6 (10.8-26.5)	4.2 (1.4-9.1)	<0.001
Calcified, %	6.9 (3.0-14.0)	1.7 (0.2-4.4)	<0.001
Non-calcified, %	8.7 (5.1-13.3)	2.0 (0.5-4.2)	<0.001
Number of HRP, n	0.89 ± 1.0	0.39 ± 0.69	<0.001
Number of HRP features, n	7.3 ± 3.9	3.9 ± 3.4	<0.001
Lumen volume, mm^3	1464 ± 771	1821 ± 1006	<0.001

Abbreviations as in Table 1
Values are mean ± SD or median (interquartile range)

Results

Patients

The study included 649 patients on statin therapy (62.0 ± 9.0 years, 63.5% male). During an interval of 3.6 ± 1.3 years, total and LDL cholesterol decreased, from 180 ± 45 mg/dl to 160 ± 37 mg/dl, P<0.001, and from 108 ± 41 mg/dl to 89 ± 30 mg/dl, P<0.001, Table 1. Per-patient whole heart PAV increased at follow-up (from 4.7% to 7.5%, P<0.001), similarly, all atherosclerotic features (number of HRPs and HRP features, calcified and noncalcified PAV) increased while the lumen volume decreased (Table 1).

Determinants of atherosclerotic statin non-response

In total, 205 (31.5%) patients were defined as atherosclerotic non-responders (Figure 2). Of the clinical variables, age, the presence of diabetes and hypertension were different in patients experiencing atherosclerotic non-response versus the remaining patients (Table 2). All baseline CCTA plaque variables were higher (except lumen volume) in the non-responders. Follow up laboratory results showed significantly lower values of total cholesterol, LDL and HDL cholesterol in the atherosclerotic non-response group compared to the group with atherosclerotic response (Table 2).

The univariate associations of different variables and atherosclerotic statin non-response are presented in Table 3. Age, diabetes, hypertension, interval revascularization, HDL cholesterol and HbA1c were all associated with statin non-response. In addition, all CCTA findings individually showed significant association with statin non-response as well. Stepwise multivariate logistic regression including all univariate variables, identified diabetes, baseline non-calcified and calcified PAV, and HRP features, as independent determinants of atherosclerotic statin non-response (Table 3). In patients with LDL lower than 70 mg/dl (N=157) at follow up, HRP features and noncalcified PAV were the only significant variables (Table 4).

Results for the secondary endpoint - atherosclerotic non-response defined as >1.0% in PAV/year and an increase in low-attenuation or fibro-fatty plaque - are shown in Appendix table 1. Age, BMI, and all atherosclerotic plaque features were higher in patients with atherosclerotic statin non-response. In the multivariable model, only the number of HRP features and the noncalcified PAV were independent associates (Appendix Table 2).

The scatter plot of baseline PAV and increase in %PAV per year showed a positive correlation of $R^2 = 0.142$ (Figure 3). The correlation between baseline LDL cholesterol and increase in %PAV per year was non-significant ($R^2 < 0.001$).

Table 3. Univariable and multivariable predictors of atherosclerotic statin nonresponse

	Univariate (OR and 95% CI)	P-value	Multivariate (OR and 95% CI)	P-value
Baseline demographics				
Age, years	1.03 (1.01-1.05)	0.001		
Male sex, n	0.92 (0.65-1.29)	0.616		
Body mass index, kg/m^2	1.01 (0.96-1.07)	0.626		
Cardiovascular risk profile				
Diabetes, n	1.64 (1.15-2.36)	0.007	1.41 (0.95-2.11)	0.009
Hypertension, n	1.46 (1.04-2.07)	0.031		
Current smoking, n	1.28 (0.84-1.95)	0.248		
Family history for CAD, n	1.27 (0.88-1.85)	0.205		
Prior revascularization, n	1.33 (0.92-1.92)	0.410		
Interval revascularization, n	1.86 (1.20-2.90)	0.005		
Baseline laboratory results				
Total cholesterol, mg/dl	1.00 (0.99-1.00)	0.087		
LDL cholesterol, mg/dl	1.00 (1.00-1.00)	0.508		
HDL cholesterol, mg/dl	0.98 (0.96-0.99)	0.004		
Triglycerides, mg/dl	1.00 (1.00-1.00)	0.403		
HbA1c, %*	1.23 (1.00-1.50)	0.048		
CRP, mg/dl**	1.02 (1.00-1.05)	0.145		
Baseline CCTA findings				
PAV, %	1.10 (1.07-1.12)	<0.001		
Calcified, %	1.15 (1.11-1.20)	<0.001	1.07 (1.03-1.12)	<0.001
Non-calcified, %	1.13 (1.09-1.17)	<0.001	1.06 (1.02-1.10)	<0.001
Number of HRP, n	1.72 (1.40-2.11)	<0.001		
Number of HRP features, n	1.23 (1.17-1.29)	<0.001	1.15 (1.09-1.21)	<0.001
Lumen volume, mm^3	1.00 (1.00-1.00)	<0.001		

Abbreviations as in Table 1

Table 4. Multivariable predictors of atherosclerotic statin nonresponse

	Odds-ratio (95% CI)	P-value
Restricted to patients with LDL < 70 at follow up		
Number of HRP features	1.15 (1.04-1.26)	0.005
Noncalcified PAV	1.11 (1.04-1.19)	0.002

Abbreviations as in Table 1

Discussion

The main finding is that baseline plaque burden and HRP features were the strongest determinants of atherosclerotic statin non-response defined as significant plaque progression.

Atherosclerotic plaque burden represents the lifetime exposure to cardiovascular risk factors, lifestyle and genetic predisposition and is the direct substrate for cardiovascular events. Either by CCTA or invasive coronary angiography, the extent of observed disease relates proportionally to future incidence of death, acute coronary syndrome, stroke, or revascularization procedures.[6,22] In addition to baseline atherosclerosis, the progression of plaque has emerged as a surrogate marker of risk for MACE.[23] Statins are the cornerstone of risk reduction therapies by reducing serum LDL-cholesterol, CRP, and the associated decrease of lipid rich plaque and increase in calcification burden that is observed in statin users.[2,5,10] A meta-analysis including 174,149 patients randomly assigned to statin therapy vs controls observed an approximately 20% reduction in major vascular events per 1 mmol/L reduction in LDL cholesterol.[1] Similarly, statins have been demonstrated to halt plaque progression; and the ability of statins to slow plaque progression likely contributes to their protective effects on clinical events.[2,24]

However, residual MACE risk exists despite the achievement of very low LDL-cholesterol levels. In the randomized FOURIER (Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk) trial, secondary prevention patients who received statins and the proprotein convertase subtilisin-kexin type 9 (PSCK-9) inhibitor evolocumab achieved LDL-cholesterol levels of 30 mg/dl, but still experienced events in 9.8% compared to 11.3% of patients treated with statins without evolocumab.[3]

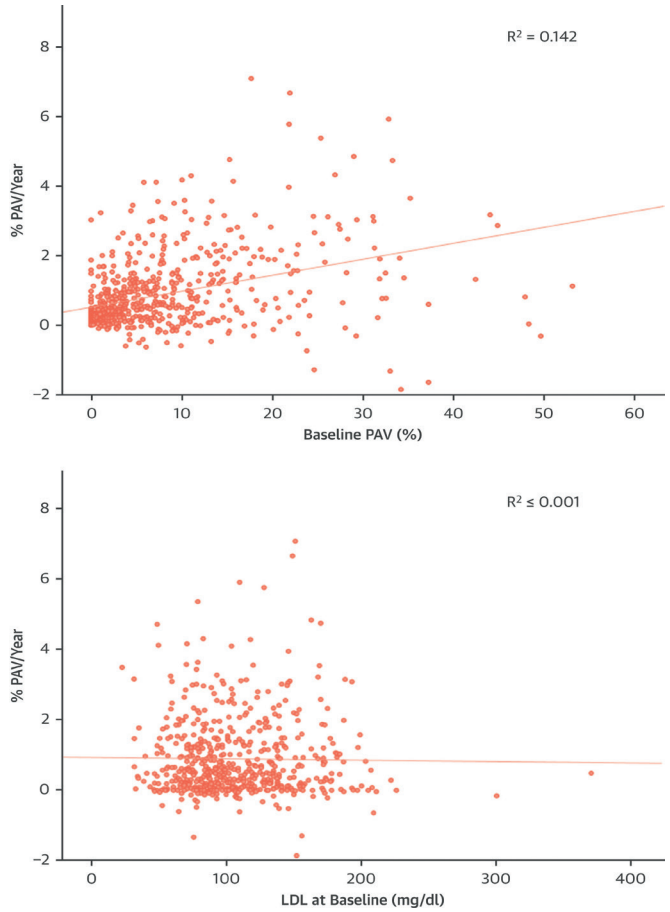
CCTA plaque characterization as determinant for atherosclerotic statin non-response

A strong indicator of future major vascular events is the baseline amount of atherosclerotic plaque itself. In a post-hoc analysis from the SATURN (Study of Coronary Atheroma by Intravascular Ultrasound: effect of Rosuvastatin vs. Atorvastatin), Puri et al. investigated predictors for MACE in a high-risk population of patients referred for invasive coronary angiography. During 2 years follow-up, LDL-cholesterol decreased to <70 mg/dl and 101 events (predominated by revascularization) were noted in the 1039 patients in the study.[5] A strong independent association was observed for baseline PAV and MACE, while on-treatment LDL-cholesterol did not predict risk. Patients within the lowest PAV quartile experienced events in 5.1% compared to 12% for those in the highest PAV quartile. A pooled analysis of >4000 patients undergoing IVUS in six clinical trials demonstrated similar robust prognostic value for baseline plaque burden.[20]

CCTA allows detailed analysis of the whole coronary tree including arterial remodeling, compositional measures, and high-risk plaque features. Their value for MACE has not explicitly been examined in statin taking patients. Similarly, associations between high-risk plaque markers and atherosclerosis progression have not been examined. More than 1.0% annual progression in PAV has been previously proposed as a clinically relevant threshold associated with MACE.[14,20] Re-

duction of LDL cholesterol with statin therapy has shown the potential of plaque regression on average, however, this does not hold for all patients. This study aimed to identify those that are at highest risk for further plaque progression despite the use of statins. We observed that baseline PAV (calcified and noncalcified), HRP features, and diabetes were independent determinants of atherosclerotic statin non-response. Since statins have been associated with reduced progression of low-attenuation and fibro-fatty plaque, and increased progression of high-density calcium[11], we repeated the analyses with a secondary endpoint that also required progression of plaque between -30 and 130 HU to progress at follow-up CT. The results were fairly similar, with non-calcified PAV and HRP features being the only independent determinants.

Figure 3. Scatter plots of baseline variables and %PAV/year.
PAV, percent atheroma volume; LDL, low-density lipoprotein



The results suggest that patients with the largest baseline plaque burden and measures of plaque vulnerability represent the highest risk. Statin therapy will reduce risk, but prior data showed considerable residual risk when LDL cholesterol approaches zero.[25] Potentially these patients will be derive additional benefit from other therapies such as icosapent ethyl[26], colchicine[27], anti-platelet or anti-coagulation therapy, but this will require further study.

Cholesterol levels were not associated with atherosclerotic non-response in the current study, which may relate to the fact that all patients received statin therapy and that those with large LDL reductions and reassuring clinical course may not have been referred for serial CCTA. Prognostic value of cholesterol has previously been established as predictor for clinical events in unselected populations.[28] Absence of effect of CRP is likely related to the low average levels, indicating limited systemic inflammation in the current population. Average CRP at baseline and follow-up was <1 mg/dl, much lower than trials that demonstrated its value as determinant for residual cardiovascular risk in patients on cholesterol lowering therapy.[29]

Limitations

The observational design of the study has all inherent limitations including selection bias and unmeasured confounding. The average on treatment LDL at follow up was 88.7 mg/dl. Prior literature has shown that lower levels result in more plaque regression, which may have influenced the study findings. [23] Collinearity between the several quantitative plaque features is a limitation. Furthermore, duration between CT-scans was slightly shorter in patients with statin non-response, possibly caused by recurrence of symptoms. Quantitative CCTA evaluation, as current, is time consuming and therefore not readily available for clinical practice. Fully automated software packages will need to be developed. In addition, the clinical value of our findings is unknown and needs further investigation.

Conclusions

In patients treated with statins, baseline plaque characterization by plaque burden and high-risk plaque is associated with atherosclerotic statin non-response defined as significant progression of coronary atherosclerosis. Patients with the highest plaque burden including HRP were at highest risk for plaque progression, despite statin therapy. These patients may be candidates for additional risk reducing therapies.

Perspectives

Competency in medical knowledge

Statins reduce major cardiovascular events, but residual cardiovascular risk remains. The current study demonstrated that baseline plaque burden and the number of high-risk plaque features were the strongest determinants of significant plaque progression, which has been previously shown to correlate with events.

Future perspectives

Besides statins, other therapies are available that reduce cardiovascular disease risk, and more are being developed. Future research should evaluate whether patients with high baseline plaque burden and high risk plaque may be candidates for these therapies.

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Appendix

Table 1. Baseline characteristics according to statin response

	Atherosclerotic statin non-response + n=125	Atherosclerotic statin non-response - n=524	p-value
Baseline demographics			
Age, years	64.0 ± 8.3	61.6 ± 0.1	0.007
Male sex, n	133 (64.9)	279 (62.8)	0.345
Body mass index, kg/m^2	26.0 ± 3.2	25.3 ± 3.3	0.049
Cardiovascular risk profile			
Diabetes, n	42 (33.6)	137 (26.2)	0.096
Hypertension, n	81 (64.8)	312 (59.8)	0.301
Current smoking, n	23 (18.4)	93 (17.8)	0.873
Family history for CAD, n	37 (29.6)	126 (24.0)	0.198
Prior revascularization, n	22 (17.6)	102 (19.5)	0.634
Interval revascularization, n	23 (18.4)	73 (13.9)	0.206
Baseline laboratory results			
Total cholesterol, mg/dl	175.4 ± 45.6	181.9 ± 44.1	0.154
LDL cholesterol, mg/dl	103.2 ± 37.9	109.2 ± 41.1	0.148
HDL cholesterol, mg/dl	46.7 ± 11.6	50.4 ± 13.2	0.005
HbA1c, %	7.0 ± 1.3	6.8 ± 1.4	0.275
CRP, mg/dl	1.0 (0.50-2.30)	0.71 (-0.22-2.1)	0.362
Baseline CCTA findings			
PAV, %	8.0 (4.6-14.7)	3.7 (1.0-9.9)	<0.001
Calcified, %	2.3 (0.90-6.6)	0.8 (0.01-3.3)	<0.001
Non-calcified, %	4.6 (2.5-7.7)	2.3 (0.5-6.1)	<0.001
Number of HRP, n	0.72 ± 1.0	0.43 ± 0.76	<0.001
Number of HRP features, n	5.8 ± 3.8	4.1 ± 3.7	<0.001
Lumen volume, mm^3	1616 ± 810	1782 ± 992	<0.001

CRP, C-reactive protein; HbA1c, Hemoglobin A1c; HDL, high-density lipoprotein; HRP, high-risk plaque; LDL, low-density lipoprotein; PAV, percent atheroma volume
Values are mean ± SD or median (interquartile range).

Table 2. Multivariable predictors of atherosclerotic statin nonresponse

	Odds-ratio (95% CI)	**p-value**
Baseline CCTA findings		
Number of HRP features	1.21 (1.06-1.21)	<0.001
Noncalcified PAV	1.08 (1.03-1.13)	0.003

Abbreviations as in Appendix Table 1

CHAPTER 4

Sex and age-specific interactions of coronary atherosclerotic plaque onset and prognosis from coronary CT

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Abstract

Aims

The totality of atherosclerotic plaque derived from coronary computed tomography angiography (CCTA) emerges as a comprehensive measure to assess the intensity of medical treatment that patients need. This study examines the differences in age onset and prognostic significance of atherosclerotic plaque burden between sexes.

Methods and results

From a large multi-center CCTA registry the Leiden CCTA score was calculated in 24,950 individuals. A total of 11,678 women (58.5±12.4 years) and 13,272 men (12.5±55.6 years) were followed for 3.7 years for MACE (death or myocardial infarction). The age where the median risk score was above zero was 12 years higher in women versus men (64-68yr vs 52-56yr respectively, p<0.001). The Leiden CCTA risk score was independently associated with MACE: score 6-20: HR 2.29 (1.69-3.10); score>20: HR 6.71 (4.36-10.32) in women, and score 6-20: HR 1.64 (1.29-2.08); score>20: HR 2.38 (1.73-3.29) in men. The risk was significantly higher for women within the highest score group (adjusted p-interaction=0.003). In pre-menopausal women, the risk score was equally predictive comparable with men. In post-menopausal women, the prognostic value was higher for women (score 6-20: HR 2.21 [1.57-3.11]; score>20: HR 6.11 [3.84-9.70] in women; score 6-20: HR 1.57 [1.19-2.09]; score>20: HR 2.25 [1.58-3.22] in men), with a significant interaction for the highest risk group (adjusted p-interaction=0.004).

Conclusion

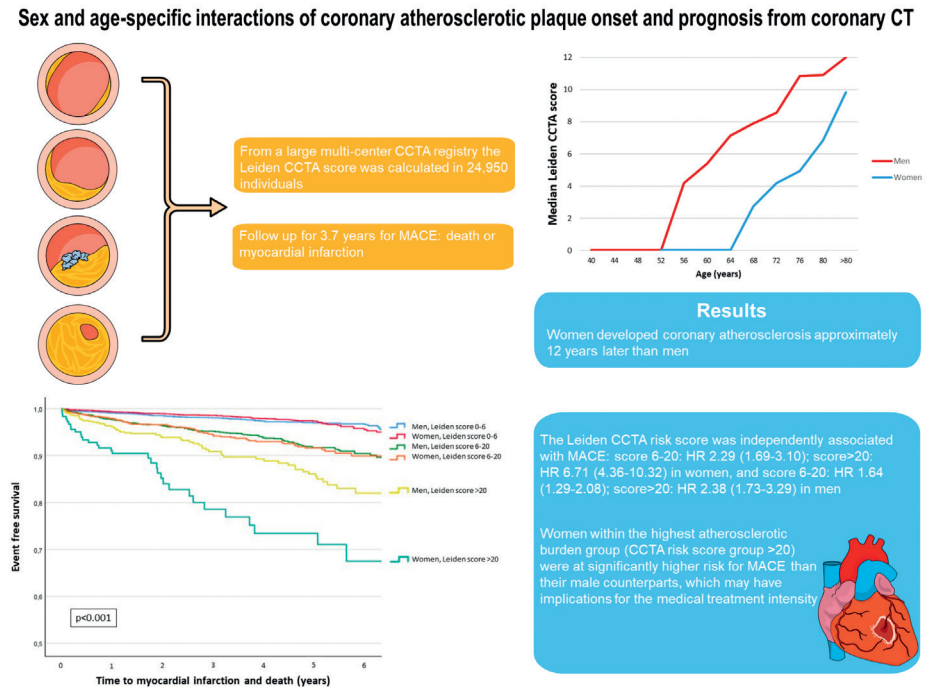
Women developed coronary atherosclerosis approximately 12 years later than men. Post-menopausal women within the highest atherosclerotic burden group were at significantly higher risk for MACE than their male counterparts, which may have implications for the medical treatment intensity.

Key-words: Coronary computed tomography angiography (CCTA); Coronary artery disease; Sex differences; Prognosis.

Abbreviations: CAD: coronary artery disease; CCTA: coronary computed tomography angiography; MACE: major cardiovascular events;

Graphical abstract

Abbreviations: CCTA, coronary computed tomography angiography; MACE, major adverse cardiovascular event;



Introduction

Atherosclerotic assessment with coronary computed tomography angiography (CCTA) provides excellent risk stratification for future major adverse cardiovascular events (MACE).[1,2] From the totality of plaque in the coronary tree, the 'atherosclerotic plaque burden' can be estimated, which is emerging as a comprehensive risk measure to determine the intensity of medical treatment that patients need (lifestyle changes, medications or coronary revascularization). Women develop coronary atherosclerosis later and they experience acute coronary syndromes (ACS) at an older age.[3-5] The National Registry of Myocardial Infarction from the United States reported an approximately 7-year age difference among 1,143,513 patients admitted with myocardial infarction.[4] The questions arise whether coronary plaque in women is just delayed by a certain time interval and whether the magnitudes of risk are similar and whether plaque should be treated equally between sexes. Studies have identified sex differences in the prognostic value of anatomical CAD, showing a higher risk in women for non-obstructive plaque extent, plaque in the left main, and calcified plaque size and extent by Agatson calcium scoring.[6-9] Ideally, the prognostic importance of coronary atherosclerosis is examined by using a score that incorporates stenosis severity, plaque location, extent, and composition.[10] This study investigated sex- and age-specific interactions in atherosclerotic onset and risk for MACE from a large cohort of stable patients undergoing clinically indicated CCTA.

Methods

Patients

The CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes: an InteRnational Multicenter) registry is a dynamic, multicenter, international, observational cohort that prospectively collects clinical, procedural and follow-up data from patients who underwent clinically indicated CCTA, as previously described.[11] The registry includes 27,125 consecutive individuals, enrolled from June 2009 until March 2016. In the current study we excluded patients with known CAD (defined as previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting), uninterpretable CCTA for CAD assessment and missing clinical information (sex, stenosis severity, or plaque composition information for all coronary segments). Finally, 24,950 patients were included in the present study. Institutional review board approval was obtained at each site, with either informed consent or waiver of informed consent.

CCTA image acquisition and interpretation

Each participating site obtained CCTA images using ≥64 detector row CT scanners from different vendors. Image acquisition, image post-processing and interpretation were in accordance with the society of Cardiovascular Computed Tomography guidelines.[12,13] CAD was defined as any lesion ≥1 mm^2 that existed within the coronary lumen or adjacent to the lumen that could be distinguished from surrounding epicardial fat or the artery lumen itself.[11] Coronary plaque was classified as calcified, partially calcified or non-calcified[1] and each plaque was graded for stenosis severity: 0%, 1-24%, 25-49%, 50-69%, 70-99% and 100%. Obstructive CAD was defined as ≥50% stenosis.

Leiden CCTA score

The Leiden CCTA score was calculated as previously described.[10] In brief, the score provides different weights for coronary plaque presence, extent, severity, composition, and location to integrate a patient's total atherosclerotic burden into a single score (Appendix Figure 1). Since plaque composition and severity information for every coronary segment is used for score calculation, imputation, necessary in less than 5% of the patients, was performed for missing segmental plaque information. Missing segmental stenosis or composition information was imputed using the value from the nearest coronary segment. For example, when plaque information of the distal LCx was missing and the proximal LCx was affected by non-obstructive, non-calcified plaque, the distal LCx was scored as a segment with non-obstructive, non-calcified plaque as well. Patients with missing coronary dominance were considered to have a right dominant coronary anatomy.

Endpoint

The primary outcome was the difference in CCTA score between women and men for similar age. Secondary outcomes were differences in rates of major adverse cardiovascular events (MACE) defined as all-cause death and myocardial infarction. Follow-up methodology has previously been described.[11] In summary, each site systematically performed patient follow-up by a dedicated nurse or physician. For the assessment of mortality in the United States, the Social Security index was reviewed. For the other countries, the occurrence of death was determined through telephone or

email contact with the patient's family or a review of medical records. The occurrence of MACE was confirmed through a combination of direct interviewing of patients using scripted interviews, with confirmation of the event by screening patients' medical files.

Statistical analysis

Continuous data was represented as mean ± standard deviation (SD) when normally distributed, and as median and interquartile range (IQR) when not normally distributed. Categorical variables were presented as counts with percentages. For two-group comparisons of continuous variables, the two sample T-test or Mann-Whitney U was used, as appropriate, and for categorical variables the Pearson Chi-square test was used. Univariable and multivariable hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox-regression analysis to assess the association between the CCTA risk score and the secondary endpoint. The multivariable models were created including age and cardiovascular risk factors (hypertension, hypercholesterolemia, diabetes mellitus, current smoking and family history of CAD) as covariates. The comprehensive CCTA scores for these analyses were stratified into 3 groups: 0 to 5, 6 to 20 and >20, as these values were proven to discriminate adverse events best.[10] For unadjusted analyses, the cumulative event-free survival rates between women and men were estimated with the Kaplan Meier method and compared using the log-rank statistic. When not specified as a multivariable or risk-adjusted model, the CCTA risk score was evaluated univariably in the cohort within sex and age subgroups. In order to emulate the menopausal threshold, the cohort was dichotomized into two groups according to age. Women ≥55 years were classified as post-menopausal, for pre-and post-menopausal analyses.[14]

A 2-sided P-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 25 (IBM, Armonk, New York) and R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

The study included 24,950 patients in total with available Leiden CCTA score (53% men, age 55.6 ± 12.5 years) and a median follow-up time of 3.7 years (interquartile range 1.8 – 5.2 years). Baseline demographic and clinical characteristics according to sex are shown in Table 1. Women presented more often with symptoms (non-anginal: 13.5% vs. 12.1%; atypical: 39.5% vs. 32.5%; typical: 18.8% vs. 13.5%; shortness of breath: 38.9% vs. 25.4%, p<0.001). In addition, women were more likely to have hypertension and a family history of CAD (53.6% vs. 48.2%, p<0.001 and 39.2% vs. 32.3%, p<0.001, respectively). Conversely, men were more often smokers as compared to women (23.2% vs. 15.9%, p<0.001).

Table 1. Clinical characteristics and CCTA findings

	Women N = 11678	Men N = 13272	p-value
Leiden CCTA score, median (IQR)	0.0 (0-5.9)	3.9 (0-10.8)	<0.001
Demographics, mean ± standard deviation			
Age, years	58.5 ± 12.4	55.6 ± 12.5	<0.001
BMI, kg/m^2	27.0 ± 5.9	27.3 ± 4.6	<0.001
Ethnicity			<0.001
Caucasian	3361 (52.4)	4276 (58.6)	
East Asian	2135 (33.3)	2296 (31.5)	
African	488 (7.6)	309 (4.2)	
Latin-American	318 (5.0)	281 (3.9)	
South-Asian, Middle Eastern or other	110 (1.7)	133 (1.8)	
Cardiac symptoms, n (%)			<0.001
No chest pain	3041 (28.2)	4984 (41.8)	
Non-anginal	1455 (13.5)	1441 (12.1)	
Atypical	4258 (39.5)	3878 (32.5)	
Typical	2027 (18.8)	1612 (13.5)	
Shortness of breath	3926 (38.9)	2795 (25.4)	
Cardiovascular risk factors, n (%)			
Diabetes Mellitus	1806 (15.6)	1970 (15.0)	0.192
Hypertension*	6207 (53.6)	6336 (48.2)	<0.001
Hypercholesterolemia†	6153 (53.0)	6920 (52.6)	0.481
Family history for CAD‡	4510 (39.2)	4212 (32.3)	<0.001
Current smoker	1834 (15.9)	3047 (23.2)	<0.001
Cardiovascular medications, n (%)			
Aspirin	2669 (36.2)	3684 (39.3)	<0.001
Beta blocker	2341 (31.9)	2556 (27.7)	<0.001
ACE-I / ARB	1078 (16.9)	1186 (15.7)	0.051
Statin	2026 (31.7)	2718 (33.2)	0.060

Values are median & IQR, mean ± standard deviation or %

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease.

Definitions: *Blood pressure ≥ 140/90 mmHg and/or treatment with antihypertensive medication; †Total cholesterol ≥ 230mg/dL or triglycerides ≥ 200mg/dL and/or treatment with lipid-lowering medication; ‡ Presence of coronary artery disease in first-degree family members at age <55 years in males and <65 years in females.

Atherosclerosis extent and severity characteristics according to sex

Per-patient level, more than half of women had no coronary artery disease (CAD) on CCTA as compared with men: 58.1% vs 41.9%, p<0.001 (Table 2 and Figure 1). In addition, women were less likely to have non-obstructive and obstructive CAD compared to men (26.2% vs. 32.3%, p<0.001 and 15.7% vs. 25.8%, p<0.001 respectively). A consistent pattern was seen on per-segment level; women had fewer coronary segments exhibiting atherosclerosis than men (1.5 ± 2.3 vs. 2.6 ± 3.1, P <0.001), caused by fewer non-calcified, partially calcified and calcified plaque (0.3 ± 0.9 vs 0.5 ± 1.1, p<0.001; 0.5 ± 1.3 vs 1.0 ± 1.9, p<0.001; 0.7 ± 1.5 vs 1.1 ± 2.0, p<0.001, respectively) and fewer coronary segments with obstructive and non-obstructive lesions (0.4 ± 1.0 vs 0.7 ± 1.5, p=0.030 and 1.0 ± 1.8 vs 1.7 ± 2.4, p<0.001, respectively) than men. The number of proximal segments with plaque (LM, pLAD, pRCA, pLCX) was lower in women (0.7 ± 1.1 vs 1.1 ± 1.3, p<0.001), and plaque in the left main artery occurred more frequently in men (16.9% vs 9.0%, p<0.001).

Age-dependent increase of Leiden CCTA risk score by sex

The Leiden CCTA risk scores increased with age for both women and men, with a delayed age onset in women (Figure 2, Appendix Table 2). The age where the median Leiden CCTA risk score was above zero was 12 years higher in women versus men (64-68 yr in women vs 52-56 yr in men, p<0.001). As appreciated by the figure, the difference in CCTA score was smaller with increasing age. We observed significantly higher median risk scores in men compared to women, for all age categories. As seen in Figure 3, this trend remained significant when age was categorized into deciles.

Sex and age interactions of the prognostic value of Leiden CCTA risk score

In univariable cox regression analysis, higher Leiden CCTA risk score groups were associated with MACE compared with the lowest CCTA group (score 6-20: HR 3.07 [2.32-4.06], score >20: HR 10.98 [7.41-16.27]) and men (score 6-20: HR 2.56 [2.04-3.20]; score >20: HR 4.59 [3.41-6.19]) (Table 3). When adjusted for age and risk factors, the scores remained independent predictors of events in both groups and sexes with higher magnitudes of risk for women (score 6-20: HR 2.29 [1.69-3.10]; score >20: HR 6.71 [4.36-10.32] in women, and score 6-20: HR 1.64 [1.29-2.08]; score >20: HR 2.38 [1.73-3.29] in men). There was a significant interaction between sex and CCTA risk scores when modeled as a continuous variable, with or without risk factor adjustment (p-interaction=0.001) (Appendix Table 2). When categorized according to the groups, the prognostic value of the CCTA score > 20 was higher for women vs. men (adjusted P-interaction = 0.003) (Appendix Table 3).

The Kaplan-Meier survival curves are shown in Figure 4. A dose-dependent relationship is observed between the degree of CCTA risk score and worse event-free survival. The event-free survival rate for a CCTA risk score of 0-6 was 88.4% for women and 92.3% for men. For a risk score of 6-20, the event-free survival rate was 84.5% for women and 86.6% for men, and in patients with a risk score >20, an event-free survival rate of 67.5% and 78.1% was observed (Log-rank overall p<0.001).

Overall, 13,957 (55.9%) patients were older than 55 years, of which 7,076 were women (classified as postmenopausal). In premenopausal women, the adjusted hazard ratios were comparable with

men (score 6-20: HR 2.34 [1.10-4.99]; score >20: HR 2.28 [0.30-17.56] in women; score 6-20: HR 2.32 [1.45-3.74]; score >20: HR 3.33 [1.38-8.08] in men) (Table 4). In postmenopausal women, the prognostic value was higher for women, especially in the highest Leiden CCTA risk score group (score 6-20: HR 2.21 [1.57-3.11]; score >20: HR 6.11 [3.84-9.70] in women; score 6-20: HR 1.57 [1.19-2.09]; score >20: HR 2.25 [1.58-3.22] in men). There was a significant interaction in post-menopausal patients between sex and CCTA risk score >20 (p-interaction<0.001), also with risk factor adjustment (adjusted p-interaction=0.004) (Appendix Table 4).

Prediction of major adverse cardiac events in individuals without CAD

In patients without CAD on CCTA leading to a risk score of 0, age was a significant predictor of MACE in both men and women (HR: 1.03, p<0.001 and HR: 1.04, p=0.015, respectively) (Appendix Table 5). In addition, hypertension was significant in predicting MACE in women and hypercholesterolemia in men.

Table 2. Subcomponents of the Leiden CCTA score

	Women N = 11678	Men N = 13272	p-value
Per-patient			
Normal	6782 (58.1)	5564 (41.9)	<0.001
Non-obstructive CAD	3061 (26.2)	4290 (32.2)	<0.001
Obstructive CAD	1835 (15.7)	3418 (25.8)	<0.001
1-vessel	1121 (9.6)	1801 (13.6)	<0.001
2-vessel	413 (3.5)	899 (6.8)	<0.001
3-vessel / left main artery	301 (2.6)	718 (5.4)	<0.001
Per-segment			
No. segments with CAD	1.5 ± 2.3	2.6 ± 3.1	<0.001
No. segments with obstructive CAD	0.4 ± 1.0	0.7 ± 1.5	<0.001
No. segments with non-obstructive CAD	1.0 ± 1.8	1.7 ± 2.4	<0.001
No. segments with proximal CAD	0.7 ± 1.1	1.1 ± 1.3	<0.001
Any left main CAD	9.0%	16.9%	<0.001
Obstructive left main CAD	1.1%	1.8%	0.030
Non-obstructive left main CAD	8.3%	15.1%	<0.001
No. segments with non-calcified plaque	0.3 ± 0.9	0.5 ± 1.1	<0.001
No. segments with partially calcified plaque	0.5 ± 1.3	1.0 ± 1.9	<0.001
No. segments with calcified plaque	0.7 ± 1.5	1.1 ± 2.0	<0.001

Values are median & IQR, mean ± standard deviation or %
Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography

Discussion

The current study showed an approximate 12-year delay in the onset of coronary atherosclerosis for women. In addition, the overall plaque burden, as quantified by the validated Leiden CCTA score, was significantly lower in women with more non-obstructive disease. Women within the highest atherosclerotic burden group were at significantly higher risk for MACE, which was driven by those who were post-menopausal (>55 years of age).

The diagnosis of stable angina manifests at a later age in women than in men. Hemingway et al. demonstrated that among 56,441 women and 34,885 men, women with 'new' angina were significantly older by approximately 4 years (71.6 ± 9.9 vs 67.9 ± 10.5 years).[15] Similarly, women with suspected CAD presented at an older age in more recent data from Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial, which investigated 10,003 symptomatic patients referred for non-invasive coronary testing (mean age of women 62.4 ± 7.9 vs 59.0 ± 8.4 years for men).[16] With coronary artery calcium testing, Wang et al demonstrated that the number of calcified plaques, associated with elevated rates of mortality, increased approximately ten years earlier among men than women.[17]

CCTA is a sensitive technique for the diagnosis and quantification of atherosclerotic plaque burden.[2] Years before patients develop high grade stenosis that may provoke myocardial ischemia and subsequent anginal symptoms, CCTA is able to detect asymptomatic coronary atherosclerosis.[18] The totality of this atherosclerotic burden has emerged as a strong prognosticator for future hard cardiovascular clinical endpoints. Prior reports have identified sex-specific differences in the phenotypical manifestation of atherosclerosis, with more non-obstructive, non-calcified, and diffuse disease for women and also sex-specific differences in the prognostic value of plaque.[19-22]

Figure 1. Stenosis severity according to sex
(A) Sex based difference in prevalence of no coronary artery disease
(B) Sex based difference in prevalence of coronary artery disease divided by obstructive and non-obstructive
Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography.

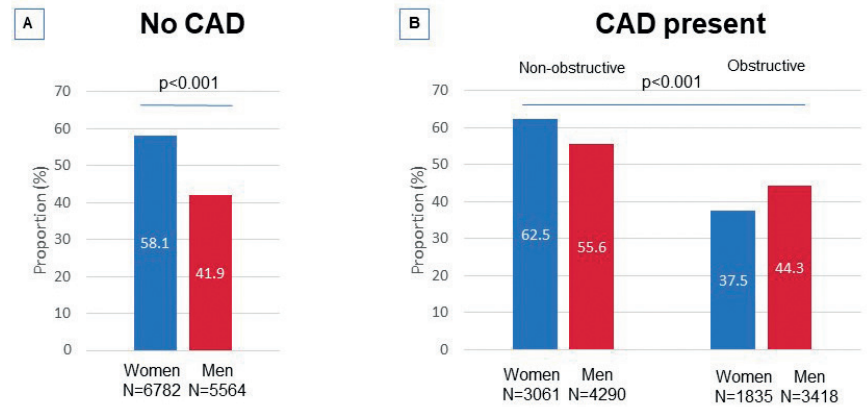
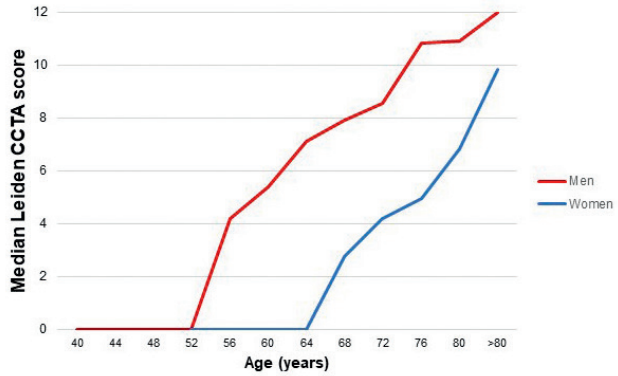


Figure 2. Median Leiden CCTA score per age category
Sex-based difference in median CCTA risk score per age category (4 years)
CCTA, coronary computed tomography angiography.



Higher event rates for women with non-obstructive atherosclerosis and left main stenosis are shown, and there is a higher discriminatory value of coronary atherosclerosis to predict MACE.[7,21] Shaw et al. demonstrated incremental prognostic value of non-obstructive CAD above clinical risk in women, but not in men, among 1127 patients undergoing CCTA for suspected CAD.[9] During >5 years of follow up, Xie et al observed among 5,166 patients a significantly higher predictive value of plaque in the left main coronary artery, detected with CCTA, for the prediction of MACE.[7]

The current study examined sex and age specific differences with the utilization of the Leiden CCTA risk score, a comprehensive whole-heart atherosclerotic risk score incorporating stenosis severity, composition, location and extent of atherosclerosis and integrates the larger non-obstructive, non-calcified burden in women and obstructive burden in men. A more simple score as SYNTAX that only accounts for obstructive disease, or the SIS score which only assesses the number of involved segments, might be less accurate. The outcomes in current study using the Leiden CCTA risk score, are demonstrably worse in women as compared to these scores. The incorporation of the stenosis location with especially high scores for plaque in the LM might be an explanation. A strong association has been observed between non-obstructive CAD in the LM on CCTA and adverse events among women.[7]

In line with expectations and previous research, women were older when coronary atherosclerosis was visible on CCTA, with an approximate delay of 12 years. Naoum et al provided age- and sex-specific nomograms of CAD burden showing age cutoffs at the presence of CAD (SIS score ≥1) of 49 years for men and 65 years for women.[23] This is a larger age difference than generally seen in patients presenting with ACS or when developing angina.[3-5,15,16] The average age when women develop symptomatic CAD is during menopause, which is a phase of accelerated atherosclerotic development, and thus the age difference between the sexes becomes smaller. Women and men within the lowest and middle group of atherosclerotic burden according to the Leiden CCTA score, were at similar risk for future MACE, and compared with the lowest CCTA score group, similar elevation in risk was seen for both sexes. As observed in many prior publications, independent prognostication was observed beyond clinical risk profile. Within the highest atherosclerotic plaque group, women had higher risk than their male counterparts, and this was caused by those older than 55 years old (considered post-menopausal).

Figure 3. CCTA risk score by age deciles and sex
Median Leiden CCTA risk score displayed per age decile and sex.
CCTA, coronary computed tomography angiography.

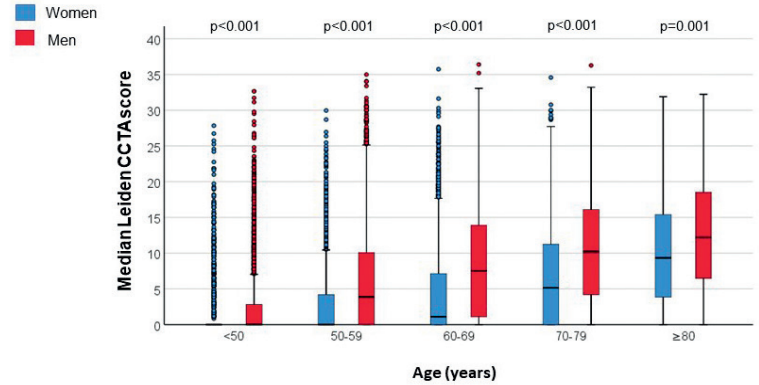
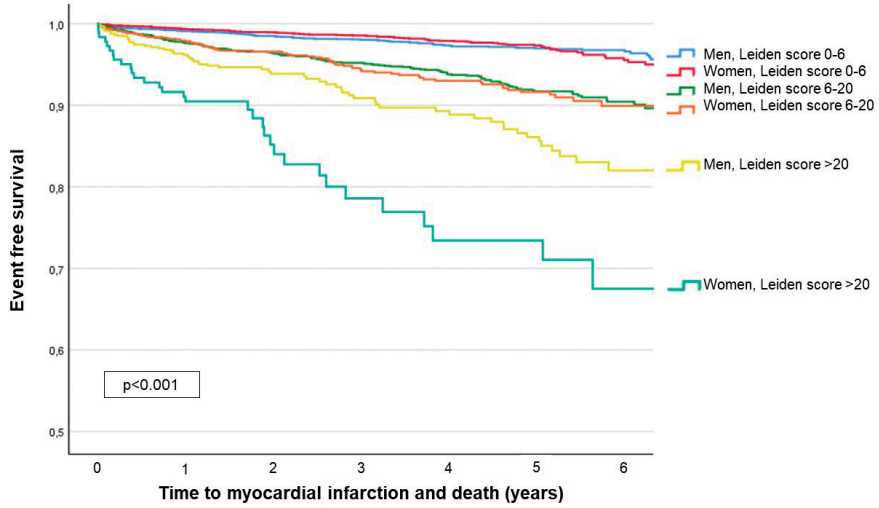


Table 3: Cox regression analysis stratified by sex*

	Women HR (95% CI)	p-value	Men HR (95% CI)	p-value
CCTA Leiden risk score				
CCTA risk score 0-6	Reference category		Reference category	
CCTA risk score 6-20	3.07 (2.32-4.06)	<0.001	2.56 (2.04-3.20)	<0.001
CCTA risk score >20	10.98 (7.41-16.27)	<0.001	4.59 (3.41-6.19)	<0.001
CCTA Leiden risk score adjusted for age and risk factors**				
CCTA risk score 0-6	Reference category		Reference category	
CCTA risk score 6-20	2.29 (1.69-3.10)	<0.001	1.64 (1.29-2.08)	<0.001
CCTA risk score >20	6.71 (4.36-10.32)	<0.001	2.38 (1.73-3.29)	<0.001

Definitions:
*N = 17750
** Including classical cardiovascular risk factors: hypertension, hypercholesterolemia, diabetes mellitus, current smoking status and family history of CAD.
Abbreviations: CI, confidence interval; HR, hazard ratio; CCTA, coronary computed tomography angiography.

Figure 4. Survival curves for women and men per CCTA score category*
Kaplan Meier figure for men and women according to the different CCTA risk score groups.
*N = 17750
CCTA, coronary computed tomography angiography.



These findings have implications for treatment of stable CAD. The total atherosclerotic plaque burden is emerging as a target to determine the intensity of medical treatment that patients should receive, given its strong relationship with events.[1] This hypothesis was tested in the SCOT-HEART (Scottish Computed Tomography of the Heart), which randomized 4146 patients with stable chest pain to standard care or standard care plus CCTA.[24] During 4.8 years of follow-up an approximately 40% reduction was observed in myocardial infarction and cardiac death, potentially attributable to more appropriate allocation of preventive medical treatments and/or coronary revascularization. Statins were also prescribed more often in a CT-based patient management strategy as compared to ICA in another randomized controlled trial and adherence was improved.[25] A recent metanalysis pooling both PROMISE and SCOT-heart emphasizes the importance of diagnosing non-obstructive CAD in symptomatic women with atherosclerotic cardiovascular disease (ASCVD) risk >=7.5%, due to a significantly higher MACE risk as compared to those with ASCVD <=7.5%.[26]

In the current study, the elevated risk for women compared to men was noted especially in those with the highest Leiden CCTA score and who were post-menopausal. These findings link the known acceleration of atherosclerosis development with a significant increase in relative risk for women, despite a comparable burden of atherosclerotic disease. There are several explanations. Estrogen in pre-menopausal women is atheroprotective by affecting the serum lipid concentrations beneficially and by causing vasodilatory effects on the blood vessels, and through inhibition of remodeling associated with vascular injury and endothelial cell damage.[27,28] A reduction in these mechanisms may promote plaque progression and additionally plaque destabilization and the acute coronary syndrome. Another explanation could be the larger impact on coronary flow for a comparable atherosclerotic burden between the sexes. Women have smaller luminal volume of the 17 segment coronary tree and a similar magnitude of plaque may provoke increased future cardiac damage.[29] In addition, less collateral flow, lower coronary flow reserve and more vascular stiffness in women might also be contributory.[30,31]

Finally, these findings may have implications for risk scores assessing a patient's total atherosclerotic burden. Age and sex should be considered as an additional parameter integrated into such scores.

Table 4: Cox regression analysis in men and women divided by age groups*

	Women HR (95% CI)	p-value	Men HR (95% CI)	p-value
Model 1**				
Premenopausal (≤55 years)				
CCTA risk score 6-20	1.98 (0.89-4.42)	0.096	2.91 (1.83-4.62)	<0.001
CCTA risk score >20	4.01 (0.55-29.29)	0.171	3.53 (1.27-9.79)	0.016
Postmenopausal (>55 years)				
CCTA risk score 6-20	3.15 (2.29-4.32)	<0.001	1.90 (1.45-2.47)	<0.001
CCTA risk score >20	11.45 (7.51-17.44)	<0.001	3.38 (2.43-4.70)	<0.001
Model 2†				
Premenopausal (≤55 years)				
CCTA risk score 6-20	2.34 (1.10-4.99)	0.028	2.32 (1.45-3.74)	0.001
CCTA risk score >20	2.28 (0.30-17.56)	0.428	3.33 (1.38-8.08)	0.008
Postmenopausal (>55 years)				
Women				
CCTA risk score 6-20	2.21 (1.57-3.11)	<0.001	1.57 (1.19-2.09)	0.002
CCTA risk score >20	6.11 (3.84-9.70)	<0.001	2.25 (1.58-3.22)	<0.001

Definitions:
*N = 17750
** Not including any clinical variables.
† Including age and classical cardiovascular risk factors (i.e. hypertension, hypercholesterolemia, diabetes mellitus, current smoking status and family history of CAD).
Abbreviations: CI, confidence interval; HR, hazard ratio; CCTA, coronary computed tomography angiography.

Limitations

The study is of observational nature with all its inherent limitations including selection bias and unmeasured confounding. We cannot rule out sex-specific differences in post-CCTA medication prescription or revascularization strategies, which may differ and have affected outcomes. Similarly, physicians or women may have preferred a conservative or less intensive medical treatment, but this data is not available. All-cause mortality was used as endpoint instead of cardiac specific mortality, which could have influenced the risk indices. In addition, follow-up information regarding MACE was only available in two thirds of patients. The CCTA score was based on visual assessment of

plaque and stenosis on segmental level. Potentially, a quantitative approach to assessment of plaque burden would have increased the accuracy of measurement.

Conclusion

The current study showed an approximately 12-years delay in the onset of coronary atherosclerosis for women. In addition, the overall plaque burden as quantified by the validated Leiden CCTA score, was significantly lower in women with more non-obstructive disease. Women within the highest atherosclerotic burden group were at significantly higher risk for MACE than men, which was driven by those who were post-menopausal (>55 years of age). The findings should raise awareness among clinicians regarding potential higher risks in this patient group, and may have therapeutic implications for initiation of the most intensive preventive medical therapies even in the absence of prior coronary events.

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Appendix

Figure 1. Computation of Leiden CCTA risk score
Reprinted, with permission from van Rosendael et al. (10)
Abbreviations: CCTA, coronary computed tomography angiography; D1, first diagonal branch; D2, second diagonal branch; IM/AL, intermediate or anterolateral branch; LAD, left anterior descending artery; LCA, left coronary arteries; LCx, left circumflex artery; LM, left main artery; L-PDA, left posterior descending artery; L-PL, left posterolateral branch; OM, obtuse marginal branch; RCA, right coronary artery; R-PDA, right posterior descending artery; R-PL, right posterolateral branch.

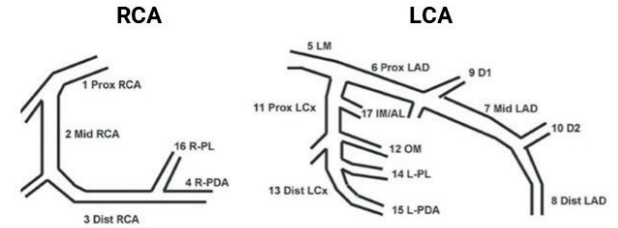

Table 1: Median Leiden CCTA score per age category

	40-44 yr	44-48 yr	48-52 yr	52-56 yr	56-60 yr	60-64 yr	64-68 yr	68-72 yr	72-76 yr	76-80 yr	>80 yr
Women	0 (0-0)	0 (0-0)	0 (0-2.2)	0 (0-4.22)	0 (0-4.95)	0 (0-5.88)	2.75 (0-8.39)	4.20 (0-9.49)	4.95 (0-10.91)	6.85 (1.2-13.94)	9.85 (3.85-15.91)
Men	0 (0-3.85)	0 (0-5.39)	0 (0-7.45)	4.20 (0-10.40)	5.39 (0-11.70)	7.13 (0-13.10)	7.91 (2.75-14.75)	8.55 (2.30-15.47)	10.85 (4.8-16.36)	10.92 (4.55-17.87)	12.0 (6.25-18.25)
p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.013

CCTA, coronary computed tomography angiography

Table 2: Cox-regression analysis with interaction terms of sex and Leiden CCTA risk score*

	Multivariable HR (95% CI)	p-value
Model 1**		
Leiden CCTA risk score	1.14 (1.11-1.18)	<0.001
Sex	0.83 (0.65-1.05)	0.124
Leiden CCTA risk score * Sex	0.97 (0.95-0.99)	0.001
Model 2†		
Leiden CCTA risk score	1.13 (1.10-1.17)	<0.001
Sex	1.19 (0.94-1.52)	0.151
Leiden CCTA risk score * Sex	0.97 (0.95-0.99)	0.001

Definitions:
*N = 17750
** Not including any clinical variables.
† Including age and classical cardiovascular risk factors (i.e. hypertension, hypercholesterolemia, diabetes mellitus, current smoking status and family history of CAD).
Abbreviations: CI, confidence interval; HR, hazard ratio; CCTA, coronary computed tomography angiography.

Table 3: Cox regression analysis with interaction terms of sex and Leiden CCTA risk score categories*

	Multivariable HR (95% CI)	p-value
Model 1**		
CCTA risk score 6-20	2.81 (2.35-3.36)	<0.001
CCTA risk score >20	5.06 (3.74-6.86)	<0.001
Sex	1.03 (0.86-1.23)	0.752
CCTA risk score 6-20 * Sex	1.09 (0.91-1.31)	0.331
CCTA risk score >20 * Sex	2.14 (1.35-3.39)	0.001
Model 2†		
CCTA risk score 6-20	1.89 (1.56-2.29)	<0.001
CCTA risk score >20	2.84 (2.06-3.92)	<0.001
Sex	1.23 (1.02-1.48)	0.027
CCTA risk score 6-20 * Sex	1.09 (0.91-1.31)	0.333
CCTA risk score >20 * Sex	2.02 (1.27-3.21)	0.003

Definitions:
*N = 17750
** Not including any clinical variables.
† Including age and classical cardiovascular risk factors (i.e. hypertension, hypercholesterolemia, diabetes mellitus, current smoking status and family history of CAD).
Abbreviations: CI, confidence interval; HR, hazard ratio; CCTA, coronary computed tomography angiography.

Table 4: Cox regression with interaction term of sex and Leiden CCTA risk score categories divided by age groups*

	Multivariable HR (95% CI)	p-value
Model 1**		
Premenopausal (≤55 years)		
CCTA risk score 6-20	2.41 (1.51-3.82)	<0.001
CCTA risk score >20	2.92 (0.99-8.64)	0.053
Sex	0.94 (0.59-1.50)	0.800
CCTA risk score 6-20 * Sex	0.82 (0.52-1.31)	0.409
CCTA risk score >20 * Sex	1.40 (0.15-13.12)	0.770
Postmenopausal (>55 years)		
CCTA risk score 6-20	2.44 (1.99-3.00)	<0.001
CCTA risk score >20	4.39 (3.16-6.08)	<0.001
Sex	1.23 (1.00-1.51)	0.053
CCTA risk score 6-20 * Sex	1.28 (1.04-1.57)	0.019
CCTA risk score >20 * Sex	2.53 (1.57-4.10)	<0.001
Model 2†		
Premenopausal (≤55 years)		
CCTA risk score 6-20	2.43 (1.49-3.97)	<0.001
CCTA risk score >20	2.80 (0.92-8.49)	0.070
Sex	0.91 (0.57-1.46)	0.702
CCTA risk score 6-20 * Sex	0.81 (0.51-1.29)	0.372
CCTA risk score >20 * Sex	1.01 (0.11-9.61)	0.993
Postmenopausal (>55 years)		
CCTA risk score 6-20	1.81 (1.46-2.24)	<0.001
CCTA risk score >20	2.75 (1.96-3.86)	<0.001
Sex	1.41 (1.14-1.74)	0.001
CCTA risk score 6-20 * Sex	1.18 (0.96-1.45)	0.116
CCTA risk score >20 * Sex	2.04 (1.26-3.30)	0.004

Definitions:
*N = 17750
** Not including any clinical variables.
† Including age and classical cardiovascular risk factors (i.e. hypertension, hypercholesterolemia, diabetes mellitus, current smoking status and family history of CAD).

Table 5: Cox regression analysis in patients without CAD on CCTA*

	Women HR (95% CI)	p-value	Men HR (95% CI)	p-value
Age	1.03 (1.01-1.05)	0.015	1.04 (1.02-1.06)	<0.001
Hypertension	1.65 (1.02-2.66)	0.042	1.43 (0.89-2.30)	0.141
Diabetes Mellitus	0.94 (0.48-1.85)	0.853	1.14 (0.59-2.20)	0.705
Current smoking	0.99 (0.47-2.09)	0.986	1.05 (0.58-1.89)	0.876
Hypercholesterolemia	0.63 (0.39-1.00)	0.051	0.61 (0.37-0.99)	0.046
Family history of CAD	1.14 (0.69-1.88)	0.621	1.07 (0.61-1.85)	0.820

*N = 17750

CHAPTER 5

Coronary Volume to Left Ventricular Mass Ratio in Patients With Hypertension

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Abstract

The coronary vascular volume to left ventricular mass (V/M) ratio assessed by coronary computed tomography angiography (CCTA) is a promising new parameter to investigate the relation of coronary vasculature to the myocardium supplied. It is hypothesized that hypertension decreases the ratio between coronary volume and myocardial mass via myocardial hypertrophy, which could explain the detected abnormal myocardial perfusion reserve reported in hypertensive patients. Individuals enrolled in the multi-center ADVANCE registry undergoing clinically indicated CCTA for analysis of suspected coronary artery disease (CAD) with known hypertension status, were included in current analysis. The V/M ratio was calculated from CCTA by segmenting the coronary artery lumen volume and left ventricular myocardial mass. In total, 2378 subjects were included in this study of which 1346 (56%) had hypertension. LV myocardial mass and coronary volume were higher in subjects with hypertension compared to normotensive individuals (122.7±32.8g vs. 120.0±30.5g, p=0.039, and 3105.0±992.0mm^3 vs. 2965.6±943.7mm^3, p<0.001, respectively). Subsequently, the V/M ratio was higher in patients with hypertension compared to those without (26.0±7.6mm^3/g vs. 25.3±7.3mm^3/g, p=0.024). After correcting for potential confounding factors, the coronary volume and ventricular mass remained higher in hypertensive patients (least square (LS)) mean difference estimate: 196.3 (95% CI: 119.9, 272.7)mm^3, p<0.001, and 5.60 (95% CI: 3.42, 7.78) g, p<0.001, respectively) but the V/M ratio was not significantly different (LS mean difference estimate: 0.48 (95% CI: -0.12, 1.08) mm^3/g, p=0.116). In conclusion, our findings do not support the hypothesis that the abnormal perfusion reserve would be caused by reduced V/M ratio in hypertensive patients.

Keywords: coronary artery lumen volume; left ventricular mass; volume to mass ratio; hypertension; coronary artery disease.

Introduction

Hypertension causes changes in the coronary circulation characterized by a reduction of the coronary vascular reserve.[1-10] Left ventricular (LV) hypertrophy, usually a complication of hypertension due to sustained elevated afterload, is associated with a reduction in maximal coronary vasodilator reserve[11-13] and an increase in myocardial oxygen demand.[14-16] The ratio of the total epicardial coronary artery lumen volume to left ventricular myocardial mass (V/M ratio) is considered a parameter capable of revealing a potential physiological imbalance between coronary blood supply and myocardial demand.[17] Low V/M ratios were associated with more advanced coronary artery disease (CAD), reduced myocardial blood flow and lesion-specific fractional flow reserve <0.80.[18,19] Based on previous studies observing reduced coronary flow reserve in patients with hypertension, we hypothesized that hypertensive patients may have a lower V/M ratio compared to normotensive patients.

Methods

ADVANCE (Assessing Diagnostic Value of Noninvasive FFRCT in Coronary Care) is a multinational (38 sites in Europe, North America and Japan) registry with prospective follow-up data of patients being investigated for clinically suspected CAD designed to understand the effect of CCTA-derived Fractional Flow Reserve on clinical practice. The study design has been described earlier in detail.[20] Summarized, subjects were enrolled from July 15, 2015 to October 20, 2017. Patients >18 years of age with documented stenosis of at least 30% on coronary computed tomography angiography (CCTA) were included. Patients with an insufficient CCTA image quality, an inability to comply with follow-up requirements and a life expectancy <1 year were excluded.

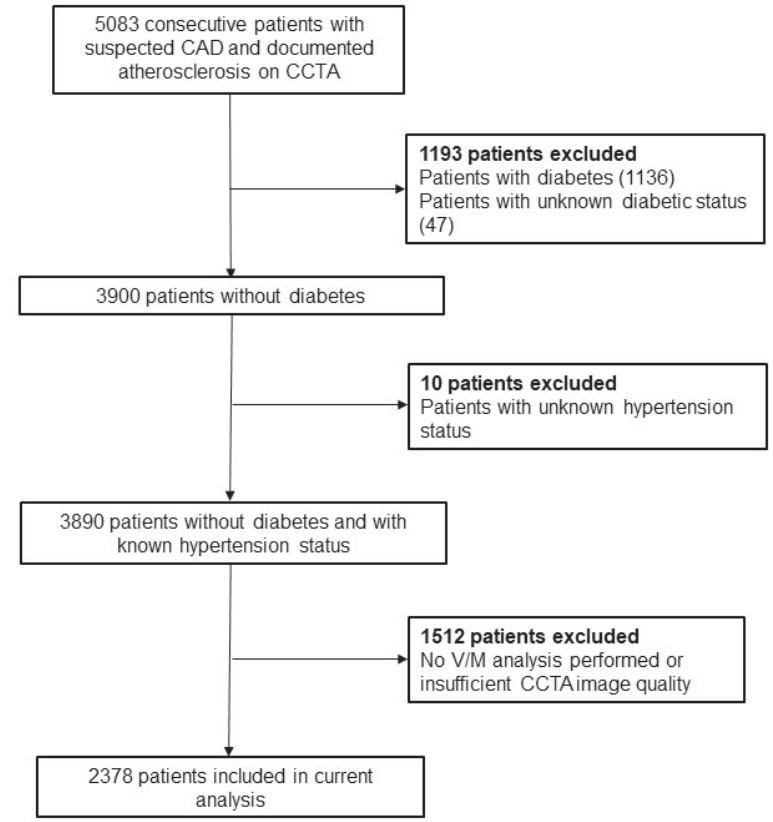
For the current analysis, patients with known hypertension status and available coronary artery lumen volume and LV myocardial mass analysis were included (Figure 1). Diabetic patients were excluded to reduce the confounding effects of diabetes on V/M.[21] The study was conducted in accordance with the Declaration of Helsinki. All individuals provided written consent following local Institutional Review Board review and approval.

Table 1. Baseline characteristics of the overall population and according to hypertension status.

	Total (N=2378)	Hypertension (N=1346)	No Hypertension (N=1032)	p-value
Age, (y)				
N	2272	1288	984	<0.001
Mean ± SD	66.1 ± 10.4	67.8 ± 9.6	63.9 ± 11.0	
Min, Max	15.0, 93.0	34.0, 93.0	15.0, 92.0	
Male sex	1564 (65.8%)	849 (63.1%)	(69.3%)	0.002
BMI, (kg/m²)				
N	2347	1332	1015	<0.001
Mean ± SD	26.1 ± 4.7	26.4 ± 4.9	25.6 ± 4.4	
Min, Max	14.9, 63.7	15.8, 63.7	14.9, 55.5	
Diamond Forrester CAD Likelihood				
N	2251	1281	970	0.544
Mean ± SD	50.9 ± 20.0	51.2 ± 19.9	50.6 ± 20.1	
Min, Max	5.3, 92.5	8.0, 92.5	5.3, 92.5	
Hyperlipidaemia				
Yes	1368 (57.5%)	888 (66.0%)	480 (46.5%)	<0.001
No	995 (41.8%)	448 (33.3%)	547 (53.0%)	
Unknown	15 (0.6%)	10 (0.7%)	5 (0.5%)	
Tobacco Use				
Current Smoker	364 (15.3%)	191 (14.2%)	173 (16.8%)	0.072
Ex-Smoker	815 (34.3%)	484 (36.0%)	331 (32.1%)	
Never Smoked	1020 (42.9%)	571 (42.4%)	449 (43.5%)	
Unknown	179 (7.5%)	100 (7.4%)	79 (7.7%)	
Angina Status				
Typical	465 (19.6%)	264 (19.6%)	201 (19.5%)	0.028
Atypical	868 (36.5%)	467 (34.7%)	401 (38.9%)	
Dyspnea	274 (11.5%)	148 (11.0%)	126 (12.2%)	
Non-cardiac Pain	150 (6.3%)	85 (6.3%)	65 (6.3%)	
None	604 (25.4%)	375 (27.9%)	229 (22.2%)	
Unknown	17 (0.7%)	7 (0.5%)	10 (1.0%)	
CCS Angina Class				
Grade I	109/ 465 (23.4%)	55/ 264 (20.8%)	54/ 201 (26.9%)	0.210
Grade II	264/ 465 (56.8%)	152/ 264 (57.6%)	112/ 201 (55.7%)	
Grade III	42/ 465 (9.0%)	27/ 264 (10.2%)	15/ 201 (7.5%)	
Grade IV	6/ 465 (1.3%)	5/ 264 (1.9%)	1/ 201 (0.5%)	
Unknown	44/ 465 (9.5%)	25/ 264 (9.5%)	19/ 201 (9.5%)	

Data are presented as mean ± standard deviation or number (percentage),as appropriate. BMI = body mass index; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society.

Figure 1. Flowchart of study population.
CAD, coronary artery disease; CCTA, coronary computed tomography angiography; V/M, coronary volume and left ventricular mass



All CCTA scans were performed with ≥64-row multi-detector computed tomography (CT) scanners. If the pre-scan heart rate was above 60 beats per minute, patients received metoprolol before the CCTA scan, unless contraindicated. Sublingual nitrates was administered to all patients before scanning. Coronary arteries with a diameter of ≥ 2 mm were evaluated for stenosis severity in accordance with current guidelines according to the clinical site procedures.[22] HeartFlow Inc. (Redwood City, California, United States of America), a central core laboratory, computed the V/M analyses, which has been described previously.[20,23-26] In short, a patient-specific anatomic epicardial model of the coronary tree was derived from the CCTA images provided. The total coronary arterial lumen volume is calculated by the summation of all the segmented coronary arteries. The volume of the myocardium extracted from CCTA was multiplied by 1.05g/ml, an average value for myocardial tissue density, resulting in the left ventricle myocardial mass.[27] Subsequently, the ratio between the total coronary artery lumen volume and the LV myocardial mass was calculated. Because of software development during the study time period, the analysis of the V/M ratio could not be performed in all patients.

The diagnoses of hypertension were based on the medical history in the electronic case report forms and defined as systolic blood pressure values of ≥140 mmHg and/or diastolic blood pressure values of ≥90 mmHg requiring treatment. Among patients with anatomically obstructive and without obstructive CAD the coronary artery lumen volume and LV myocardial mass were separately analyzed. Obstructive CAD was defined as ≥50% diameter stenosis.

Statistical analyses were performed with SAS version 9.4 (SAS institute, Cary, North Carolina, USA). Continuous variables with a normal distribution are presented as mean ± standard deviation and were compared using the Student t-test or One-way ANOVA, as appropriate. Non-normally distributed continuous variables are presented as median with (25-75th interquartile range (IQR)) and were compared using the Mann-Whitney U test. Categorical variables are presented as absolute numbers and percentages and were compared using the χ^2 test. In order to correct for potential confounding effects on the coronary artery lumen volume, LV myocardial mass and V/M ratio, analysis of covariance models were used. Age, BMI, hyperlipidemia, sex, number of vessels with obstructive CAD and the degree of maximum stenosis were used as covariates in this analysis. The differences in total coronary artery lumen volume, LV myocardial mass and V/M ratio between hypertensive and normotensive patients are presented as Least Square (LS) mean difference estimate with corresponding 95% confidence intervals (CI). A two-sided p-value <0.05 was considered statistical significant.

Results

5083 individuals were enrolled in the ADVANCE registry. Of these, 2378 non-diabetic patients with known hypertension status and measured V/M ratio were included in current analysis. Hypertension was present in 1346 patients (60%). Baseline patient demographic and clinical characteristics of the enrolled patients are shown in Table 1. Patients with hypertension were older (67.8 ± 9.6 vs. 63.9 ± 11.0 years, p<0.001) and had a higher body mass index (BMI) (26.4 ± 4.9 vs. 25.6 ± 4.4 kg/m^2, p<0.001). Additionally, hypertensive patients had more frequently a history of hyperlipidemia (p<0.001) and were more likely to be female (p=0.002).

Hypertensive patients had more frequently obstructive CAD by anatomical CCTA evaluation (p=0.017) (Table 2). In the quantitative analysis, the volume of epicardial coronary arteries was higher in patients with hypertension (3105.0 ± 992.0 mm^3 vs. 2965.6 ± 943.7 mm^3, p=0.001). The LV myocardial mass was higher in hypertensive patients as well (122.7 ± 32.8 g vs. 120.0 ± 30.5 g, p=0.039). This resulted in a higher V/M ratio in patients with hypertension compared to patients without hypertension (26.0 ± 7.6 mm^3/g vs. 25.3 ± 7.3 mm^3/g, p=0.024). When correcting for the differences in baseline and CCTA characteristics, the coronary volume and myocardial mass remained significantly higher in hypertensive patients (LS mean difference estimate: 196.3 (95% CI: 119.9, 272.7) mm^3, p<0.001; LS mean difference estimate: 5.60 (95% CI: 3.42, 7.78) g, p<0.001, respectively) (Table 4 and Figure 2). Whereas the V/M ratio showed no significant difference between hypertensive and normotensive patients (LS mean difference estimate: 0.48 (95% CI: -0.12, 1.08) mm^3/g, p=0.116).

Table 2. Coronary computed tomography angiography parameters of patients according to hypertension status.

	Total (N=2378)	Hypertension (N=1346)	No Hypertension (N=1032)	p-value
CCTA anatomical finding				
Without obstructive stenosis < 50%	711 (29.9%)	376 (27.9%)	335 (32.5%)	0.017
Obstructive stenosis ≥ 50%	1663 (69.9%)	968 (71.9%)	695 (67.3%)	
Unknown	4 (0.2%)	2 (0.1%)	2 (0.2%)	
Non-severe stenosis ≤ 70%	1676 (70.5%)	943 (70.1%)	733 (71.0%)	0.596
Severe stenosis > 70%	698 (29.4%)	401 (29.8%)	297 (28.8%)	
Unknown	4 (0.2%)	2 (0.1%)	2 (0.2%)	
Degree stenosis				
Normal (0%)	15 (0.6%)	6 (0.4%)	9 (0.9%)	0.040
Minimal (0-30%)	136 (5.7%)	62 (4.6%)	74 (7.2%)	
Mild (30-50%)	560 (23.5%)	308 (22.9%)	252 (24.4%)	
Moderate (50-70%)	965 (40.6%)	567 (42.1%)	398 (38.6%)	
Severe (70-90%)	493 (20.7%)	288 (21.4%)	205 (19.9%)	
Sub-total/occluded (≥ 90%/ occluded)	205 (8.6%)	113 (8.4%)	92 (8.9%)	
Unknown	4 (0.2%)	2 (0.1%)	2 (0.2%)	
Number of vessels with anatomically obstructive CAD (> 50% DS)				
0	711 (29.9%)	376 (27.9%)	335 (32.5%)	0.004
1	1062 (44.7%)	592 (44.0%)	470 (45.5%)	
2	420 (17.7%)	259 (19.2%)	161 (15.6%)	
3	181 (7.6%)	117 (8.7%)	64 (6.2%)	
4	0	0	0	
Unknown	4 (0.2%)	2 (0.1%)	2 (0.2%)	
Rate of obstructive CAD per vessel				
LAD stenosis < 50%	1069 (45.0%)	584 (43.4%)	485 (47.0%)	0.080
LAD stenosis ≥ 50%	1309 (55.0%)	762 (56.6%)	547 (53.0%)	
LCX stenosis < 50%	1860 (78.2%)	1030 (76.5%)	830 (80.4%)	0.022
LCX stenosis ≥ 50%	518 (21.8%)	316 (23.5%)	202 (19.6%)	
RCA stenosis < 50%	1760 (74.0%)	963 (71.5%)	797 (77.2%)	0.002
RCA stenosis ≥ 50%	618 (26.0%)	383 (28.5%)	235 (22.8%)	
Coronary volume - myocardial mass				
Epicardial coronary artery volume (mm^3)				
N	2378	1346	1032	0.001
Mean ± SD	3044.5 ± 973.6	3105.0 ± 992.0	2965.6 ± 943.7	
Min, Max	704.6, 7891.2	732.1, 7891.2	704.6, 7198.4	

Table 2. Continued

	Total (N=2378)	Hypertension (N=1346)	No Hypertension (N=1032)	p-value
Left ventricle myocardial mass (g)				
N	2378	1346	1032	0.039
Mean ± SD	121.6 ± 31.8	122.7 ± 32.8	120.0 ± 30.5	
Min, Max	54.9, 324.1	54.9, 324.1	56.9, 308.9	
Coronary volume /mass (mm^3/g)				
N	2378	1346	1032	0.024
Mean ± SD	25.7 ± 7.5	26.0 ± 7.6	25.3 ± 7.3	
Min, Max	6.8, 62.5	6.8, 61.9	7.2, 62.5	

Data are presented as mean ± standard deviation or number (percentage), as appropriate. CAD = coronary artery disease; CCTA = coronary computed tomography angiography; DS = diameter stenosis; LAD = left anterior descending artery; LCX = left circumflex artery; RCA = right coronary artery;

As CAD has known effects on coronary volume, the groups with and without obstructive CAD were analyzed separately (Table 3). Obstructive CAD was present in 1663 subjects (69.9%), of whom 968 (58.2%) had hypertension. In individuals with obstructive CAD, patients with hypertension were more often male (p=0.009), were older (p<0.001), had a higher BMI (p=0.004) and had more frequently a history of hyperlipidemia (p<0.001) (Table 3). Coronary volume did not differ significantly between hypertensive and normotensive patients with obstructive CAD (3026.4 ± 971.5 mm^3 vs. 2937.5 ± 918.5 mm^3; p=0.058). Moreover, the LV mass was not significantly different between the two groups (123.6 ± 33.4 g vs. 121.8 ± 29.4 g; p=0.243). Accordingly, the V/M ratio was comparable between the two groups (25.2 ± 7.3 mm^3/g vs. 24.7 ± 7.2 mm^3/g, p=0.209). When we correct for potential confounding variables, the epicardial coronary artery volume and myocardial mass were significantly higher in hypertensive patients compared to normotensive patients (LS mean difference estimate: 135.21 (95% CI: 45.3, 225.1) mm^3, p=0.003 and LS mean difference estimate: 4.92 (95% CI: 2.30, 7.55) g, p<0.001 respectively) (Table 5 and Figure 2). However, the V/M ratio was not significantly different between the two groups (LS mean difference estimate: 0.15 (95% CI: -0.54, 0.84) mm^3/g, p=0.671).

Hypertension was present in 376 out of 711 (53%) patients without obstructive CAD. Hypertensive patients were more frequent female (p=0.024), older (p<0.001), had a higher BMI (p=0.006) and had more frequently a history of hyperlipidemia (<0.001) (Table 3). Coronary volume was higher in hypertensive patients compared to normotensive in patients without obstructive CAD (3305.8 ± 1019.1 mm^3 vs. 3023.8 ± 995.4 mm, p<0.001), while LV mass did not differ significantly between the groups (120.5 ± 31.1 g vs. 116.2 ± 32.4 g, p=0.074). Consequently, the V/M ratio was significantly higher (28.1 ± 7.9 mm^3/g vs. 26.5 ± 7.2 mm^3/g, p=0.007) in hypertensive patients compared to normotensive patients. Coronary artery volume remained significantly higher in patients with hypertension after correction for potential confounding variables (LS mean difference estimate: 352.20 (95% CI: 208.37, 496.04) mm^3, p<0.001) (Table 6 and Figure 2). The myocardial mass after correction for confounding variables was significantly higher in patients with hypertension as well (LS mean difference estimate: 7.24 (95% CI: 3.33, 11.14) g, p<0.001). The V/M ratio remained significant higher in the hypertensive patients (LS mean difference estimate: 1.33 (95% CI: 0.15, 2.51) mm^3/g, p=0.028) (Table 5).

Figure 2. Bar chart showing the Least Squares means, after correcting for potential confounding factors, of the coronary volume, left ventricular mass and V/M ratio for patients with and without hypertension.
A*: Total cohort
B*: Subjects with obstructive coronary artery disease
C: Subjects without obstructive CAD
* = The variable 'Number of vessels with obstructive coronary artery disease' is removed in current analysis due to collinearity with 'Maximum Stenosis %'. Inference did not change, but values changed slightly.
CAD, coronary artery disease; V/M, coronary volume and left ventricular mass

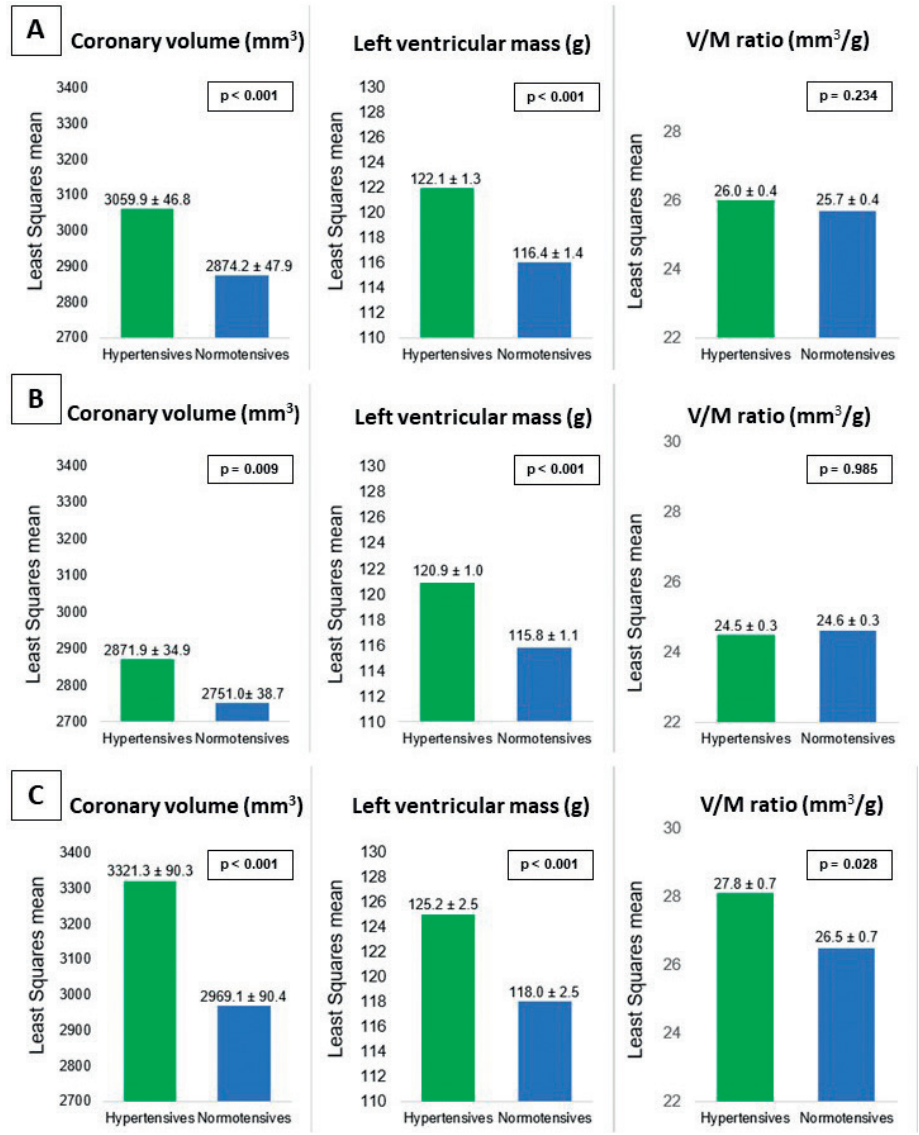


Table 3. Baseline characteristics and coronary computed tomography and coronary computed tomography angiography parameters of patients with anatomically obstructive and without obstructive CAD according to hypertension status

	Obstructive CAD (≥ 50% DS)				Without obstructive CAD (<50% DS)			
	Total (N=1663)	Hypertension (N=968)	No Hypertension (N=695)	p-value	Total (N=711)	Hypertension (N=376)	No Hypertension (N=335)	p-value
Baseline patient characteristics								
Age, (y)								
N	1597	930	667	<0.001	672	357	315	<0.001
Mean ± SD	66.6 ± 10.3	68.0 ± 9.6	64.6 ± 10.7		65.0 ± 10.7	67.2 ± 9.5	62.4 ± 11.4	
Min, Max	26.0, 93.0	40.0, 93.0	26.0, 92.0		15.0, 90.0	34.0, 89.0	15.0, 90.0	
Male sex	1150 (69.2%)	645 (66.6%)	505 (72.7%)	0.009	412 (57.9%)	203 (54.0%)	209 (62.4%)	0.024
BMI, (kg/m²)								
N	1648	960	688	0.004	695	370	325	0.006
Mean ± SD	25.9 ± 4.5	26.2 ± 4.6	25.5 ± 4.2		26.4 ± 5.2	26.9 ± 5.4	25.9 ± 4.8	
Min, Max	14.9, 53.1	15.8, 53.1	14.9, 42.6		15.9,63.7	18.0, 63.7	15.9, 55.5	
Diamond Forrester CAD Likelihood								
N	1585	926	659	0.656	663	354	309	0.206
Mean ± SD	53.2 ± 20.0	53.0 ± 20.0	53.4 ± 19.9		45.6 ± 19.0	46.5 ± 18.9	44.6 ± 19.2	
Min, Max	8.0, 92.5	8.0, 92.5	8.0, 92.5		5.3, 92.5	8.0, 92.5	5.3, 88.9	
Hyperlipidaemia								
Yes	959 (57.7%)	636 (65.7%)	323 (46.5%)	<0.001	406 (57.1%)	251 (66.8%)	155 (46.3%)	<0.001
No	697 (41.9%)	327 (33.8%)	370 (53.2%)		297 (41.8%)	120 (31.9%)	177 (52.8%)	
Unknown	7 (0.4%)	5 (0.5%)	2 (0.3%)		8 (1.1%)	5 (1.3%)	3 (0.9%)	

Table 3. Continued

	Obstructive CAD (≥ 50% DS)				Without obstructive CAD (<50% DS)			
	Total (N=1663)	Hypertension (N=968)	No Hypertension (N=695)	p-value	Total (N=711)	Hypertension (N=376)	No Hypertension (N=335)	p-value
Rate of obstructive CAD per vessel								
LAD stenosis < 50%	354 (21.3%)	206 (21.3%)	148 (21.3%)	0.995	NA	NA	NA	NA
LAD stenosis ≥ 50%	1309 (78.7%)	762 (78.7%)	547 (78.7%)		NA	NA	NA	
LCX stenosis < 50%	1145 (68.9%)	652 (67.4%)	493 (70.9%)	0.120	NA	NA	NA	NA
LCX stenosis ≥ 50%	518 (31.1%)	316 (32.6%)	202 (29.1%)		NA	NA	NA	
RCA stenosis < 50%	1045 (62.8%)	585 (60.4%)	460 (66.2%)	0.017	NA	NA	NA	NA
RCA stenosis ≥ 50%	618 (37.2%)	383 (39.6%)	235 (33.8%)		NA	NA	NA	
Coronary volume - myocardial mass								
Epicardial coronary artery volume (mm³)								
N	1663	968	695	0.058	711	376	335	<0.001
Mean ± SD	2989.2 ± 950.5	3026.4 ± 971.5	2937.5 ± 918.5		3172.9 ± 1017.1	3305.8 ± 1019.1	3023.8 ± 995.4	
Min, Max	704.6, 7415.5	732.1, 7415.5	704.6, 7055.6		889.6, 7891.2	1181.3, 7891.2	889.6, 7198.4	
Left ventricle myocardial mass (g)								
N	1663	968	695	0.243	711	376	335	0.074
Mean ± SD	122.9 ± 31.8	123.6 ± 33.4	121.8 ± 29.4		118.5 ± 31.7	120.5 ± 31.1	116.2 ± 32.4	
Min, Max	54.9, 324.1	54.9, 324.1	56.9, 247.1		58.3, 308.9	63.3, 264.6	58.3, 308.9	
Coronary volume / mass (mm³/g)								
N	1663	968	695	0.209	711	376	335	0.007
Mean ± SD	25.0 ± 7.3	25.2 ± 7.3	24.7 ± 7.2		27.3 ± 7.6	28.1 ± 7.9	26.5 ± 7.2	
Min, Max	6.8, 62.5	6.8, 59.2	7.2, 62.5		9.8, 61.9	10.7, 61.9	9.8, 51.0	

Discussion

The current study assessed the impact of hypertension on the V/M ratio. The hypothesis was that the known reduced myocardial perfusion reserve in hypertensive patients may be partially explained by an abnormally low V/M ratio, likely due to myocardial hypertrophy not accompanied by increase in vascular volume. The main results demonstrate that the V/M ratio was not decreased in hypertensive patients suggesting that the increased myocardial mass was compensated by increased vascular volume leading to preserved V/M ratio.

The V/M ratio has been shown to be reduced in patients with CAD.[18] This is expected as CAD typically affects the coronary lumen and the vasodilatory capacity. We recently found that V/M-ratio is reduced also in patients with diabetes, even when CAD was taken into account as a confounding factor.[21] In the current paper, we excluded patients with diabetes and also analyzed the patients with and without obstructive CAD separately. An interesting finding was that in patients without obstructive CAD, the V/M ratio was higher in hypertensive patients despite increased myocardial mass. In patients with obstructive CAD, V/M ratio was not significantly different between patients with and without hypertension, likely due to the confounding effect of CAD on the V/M ratio.

The concept of the V/M ratio was first described by Gould et al.[28] and the methodology of assessing the V/M ratio is based on allometric scaling laws. Allometric scaling laws provide a model to predict the functional and structural properties of the cardiovascular system of mammals.[29.] Choy et al.[30] investigated scaling laws of myocardial flow and mass in a porcine heart, and reported a very tight linear relationship between coronary artery lumen volume and myocardial mass. Previous studies investigating the V/M ratio, have shown that individuals with a low V/M ratio had reduced myocardial blood flow on positron emission tomography compared to patients with a high V/M ratio.[18] Furthermore, Taylor et al.[19] concluded that the V/M ratio was independently associated with a FFR below the ischemic threshold (≤0.80).

We hypothesized that the abnormal myocardial perfusion in patients with hypertension was caused by a reduced V/M ratio. LV hypertrophy is frequently associated with hypertension, increases the myocardial mass and is considered a mechanism contributing to abnormal myocardial perfusion. However, the present study shows a corresponding increase in coronary artery volume, leading to a preserved V/M ratio in patients with hypertension.

The increased coronary lumen volume in patients with hypertension we observed in the current study is in line with previous research, showing lumen enlargement of proximal elastic arteries.[31,32] Carotid and coronary arteries represent large vessels, often referred to as "elastic arteries" or "conducting arteries" and are both central, predominantly elastic and transport large volumes of blood away from the left ventricle to perfuse vital organs.[33] In addition, atherosclerotic disease and its potential confounding effect needs to be taken into account when calculating the V/M ratio, since the presence of atherosclerosis and reduced coronary volume has been linked. When the cohort is divided into patients with and without obstructive CAD, patients with obstructive CAD remain to

have no significant different V/M ratio between hypertensive and normotensive patients. However, we observed in hypertensive patients without obstructive CAD even a higher V/M ratio compared to normotensive patients. The increase in coronary lumen volume is apparently larger than the increase of the ventricular mass. This effect is diminished in patients with obstructive CAD by the presence of more extensive atherosclerosis. Zhou et al.[34] observed that the diameter of the coronary artery is inversely associated with the severity of CAD. In addition, endothelial dysfunction because of atherosclerosis, with a subsequent reduction of vasodilator capacity contributes to a reduced coronary volume in these patients as well.[35]

Table 4. Coronary volume, cardiac mass and coronary volume/mass ratio corrected for potential confounding variables

Model Effect	LS Mean Difference (95% CI)	p-value
Total Segmented Volume		
Hypertension (Yes/No)	196.3 (119.9, 272.7)	<0.001
Age		0.735
BMI		<0.001
Hyperlipidemia (Yes/No)		0.002
Sex (Male/Female)		<0.001
Number of Vessels with Obstructive CAD (0,1,2,3)		<0.001
Maximum Stenosis % (0, >0 - <30, ≥30 - <50, ≥50 - ≤70, >70 - ≤90, >90)		<0.001
Myocardial Mass		
Hypertension (Yes/No)	5.60 (3.42, 7.78)	<0.001
Age		<0.001
BMI		<0.001
Hyperlipidemia (Yes/No)		<0.001
Sex (Male/Female)		<0.001
Number of Vessels with Obstructive CAD (0,1,2,3)		0.047
Maximum Stenosis % (0, >0 - <30, ≥30 - <50, ≥50 - ≤70, >70 - ≤90, >90)		<0.001
Volume/Mass Ratio		
Hypertension (Yes/No)	0.48 (-0.12, 1.08)	0.116
Age		<0.001
BMI		<0.001
Hyperlipidemia (Yes/No)		0.629
Sex (Male/Female)		0.007
Number of Vessels with Obstructive CAD (0,1,2,3)		<0.001
Maximum Stenosis % (0, >0 - <30, ≥30 - <50, ≥50 - ≤70, >70 - ≤90, >90)		<0.001

BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; LS = least squares.

The observational design of the study has inherent limitations including selection bias and unmeasured confounding. The registry may have been subject to referral bias inherent in local practices. In addition, information regarding the severity and duration of hypertension in the patients was lacking and in our population the increase of left ventricular mass was small, despite being statistically significant. Antihypertensive treatment has been associated with the reduction of LV hypertrophy and might have a favorable effect on the matching between myocardial mass and perfusion.[36] ACE-inhibitors were found to increase cardiac nitric oxide release and reduce oxygen consumption in coronary microvessels.[37,38] Lack of data regarding antihypertensive treatment, could be viewed as a limitation of the present study as well. Equally, this paper did not adjust for the presence or absence of other cardiac diseases that affect myocardial blood flow reserve, such as valvular disease and hypertrophic cardiomyopathy. Lastly, the lack of information regarding the total plaque burden can be considered a limitation.

Table 5. Coronary computed tomography angiography parameters corrected for potential confounding variables in patients with obstructive CAD

Model Effect	LS Mean Difference (95% CI)	p-value
Total Segmented Volume		
Hypertension (Yes/No)	135.21 (45.3, 225.1)	0.003
Age		0.790
BMI		<0.001
Hyperlipidemia (Yes/No)		0.002
Sex (Male/Female)		<0.001
Number of Vessels with Obstructive CAD (0, 1, 2, 3)		<0.001
Maximum Stenosis % (≥50 - ≤70, >70 - ≤90, >90)		<0.001
Myocardial Mass		
Hypertension (Yes/No)	4.92 (2.30, 7.55)	<0.001
Age		<0.001
BMI		<0.001
Hyperlipidemia (Yes/No)		<0.001
Sex (Male/Female)		<0.001
Number of Vessels with Obstructive CAD (0, 1, 2, 3)		0.031
Maximum Stenosis % (≥50 - ≤70, >70 - ≤90, >90)		0.002
Volume/Mass Ratio		
Hypertension (Yes/No)	0.15 (-0.54, 0.84)	0.671
Age		<0.001
BMI		<0.001
Hyperlipidemia (Yes/No)		0.371
Sex (Male/Female)		0.002
Number of Vessels with Obstructive CAD (0, 1, 2, 3)		<0.001
Maximum Stenosis % (≥50 - ≤70, >70 - ≤90, >90)		<0.001

BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; LS = least squares.

Table 6. Coronary computed tomography angiography parameters corrected for potential confounding variables in patients without obstructive CAD

Model Effect	LS Mean Difference (95% CI)	p-value
Total Segmented Volume		
Hypertension (Yes/No)	352.2 (208.37, 496.04)	<0.001
Age		0.950
BMI		0.001
Hyperlipidemia (Yes/No)		0.239
Sex (Male/Female)		<0.001
Maximum Stenosis % (0, >0 - <30, ≥30 - <50)		0.352
Myocardial Mass		
Hypertension (Yes/No)	7.24 (3.33, 11.14)	<0.001
Age		0.014
BMI		<0.001
Hyperlipidemia (Yes/No)		0.043
Sex (Male/Female)		<0.001
Maximum Stenosis % (0, >0 - <30, ≥30 - <50)		0.352
Volume/Mass Ratio		
Hypertension (Yes/No)	1.33 (0.15, 2.51)	0.028
Age		0.002
BMI		<0.001
Hyperlipidemia (Yes/No)		0.731
Sex (Male/Female)		0.627
Maximum Stenosis % (0, >0 - <30, ≥30 - <50)		0.413

Conclusion

In contrast to our hypothesis, the V/M ratio was not decreased in patients with hypertension compared to patients without hypertension and the abnormal coronary flow reserve in hypertensive patients is not likely caused by a reduced arterial volume to myocardial mass. Further studies are required using different cohorts in order to investigate the relationship of flow reserve and V/M ratio.

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CHAPTER 6

Summary, Conclusions and Future Perspectives

Summary

This thesis investigated how CCTA, a non-invasive imaging technique, may be used in clinical practice to better characterize coronary heart disease and to improve risk-stratification. CCTA is an imaging technique for the evaluation of coronary artery disease throughout the entirety of disease severity and enhances information regarding plaque extent, plaque composition, and PCAT surrounding the arteries.

In Chapter 2 of this thesis, CCTA was used to assess PCAT attenuation values in patients with no atherosclerosis on CCTA. A total of 109 individuals were included and the proximal parts of 320 coronary arteries were evaluated. PCAT was defined and calculated as the average attenuation of all voxels between -30 and -190 Hounsfield units (HU) and sampled within a radial distance from the outer vessel wall equal to the vessel diameter. There was a significant difference in mean PCAT attenuation between the left anterior descending artery (LAD), the left circumflex artery (LCx) and the right coronary artery (RCA), with lower values in the LAD compared to the LCx and RCA (LAD: -67.8 ± 7.8 HU vs. LCx: -62.6 ± 6.8 HU vs. RCA: -63.6±7.9 HU, p<0.001). Furthermore, sex differences were observed in all three coronary arteries with significantly higher PCAT attenuation values in men compared to women. These results underscore the importance of analyzing all three vessels and the need to adjust for sex when analyzing PCAT. In addition, our PCAT attenuation values were relatively higher compared to previous studies. PCAT attenuation has been shown to be significantly associated with technical as well as patient characteristics, and these factors need to be taken into account when analyzing PCAT.[1-3] With regard to technical factors, significant differences in mean PCAT attenuation are demonstrated based on the model of the CT scanner used. Further, pixel spacing and tube voltage and current were also significantly associated with differences in PCAT attenuation as well as the heart rate of the patient.

In Chapter 3, serial CCTA scans of 649 patients have been evaluated to assess factors associated with statin non-response, defined as an absolute increase of 1.0% or more percent atheroma volume per year, despite the use of statins. Statin non-response was present in 205 (31.5%) patients, and factors independently associated were diabetes, the number of high-risk plaque features, noncalcified and calcified percent atheroma volume (OR:1.41 (0.95-2.11), OR:1.15 (1.09-1.21), OR:1.06 (1.02-1.10), OR:1.07 (1.03-1.12), respectively). When an additional requirement was added and statin non-response was defined as >1.0% increase of percent atheroma volume per year and progression of fibro-fatty plaque or low-attenuation plaque (N=125, 19.2%) only the number of high-risk plaque features and non-calcified percent atheroma volume at baseline were independent associates (OR: 1.21 (1.06-1.21) and OR: 1.08 (1.03-1.13), respectively). These results suggest that patients with high-risk plaques and with the largest plaque burden at baseline represent the highest risk for statin non-response. Given the association of plaque progression with major adverse cardiovascular events, additional risk-reducing therapies might be necessary in these patients.

In Chapter 4 the Leiden CCTA risk score was assessed in 24,950 patients to translate the patient's totality of plaque in the coronaries into a single score and to investigate age- and sex-related differences. The score (range 0 to 42) incorporates plaque extent, severity, location and composition, with higher weights for more proximal disease, higher stenosis severity, and more noncalcified or mixed plaque composition. The score was stratified into 3 groups: 0-5, 6-20 and >20, as these values were previously shown to discriminate adverse events best.[4] The risk score increased with age for both sexes, however the age where the median risk score was above 0 was between 52 and 56 for men and between 64 and 68 for women (p<0.001). This sex difference became smaller with increasing age, but the score remained significantly higher for men in every age group. Cox-regression analysis adjusted for confounders age and cardiovascular risk factors showed an independent association between the CCTA risk score and major adverse cardiovascular events (Leiden CCTA risk score 6-20: HR 2.29 [1.69-3.10]; Leiden CCTA risk score >20: HR 6.71 [4.36-10.32] in women, and Leiden CCTA risk score 6-20: HR 1.64 [1.29-2.08]; Leiden CCTA risk score >20: HR 2.38 [1.73-3.29] in men) with for women higher magnitudes of risk. For pre-and post-menopausal analyses, the cohort was dichotomized into pre- and postmenopausal groups based on age. These analyses showed comparable adjusted hazard ratios between premenopausal women and men (<55 years). Post-menopausal analyses showed higher prognostic values for women, especially in the group with the highest Leiden CCTA risk score (Leiden CCTA risk score 6-20: HR 2.21 [1.57-3.11]; Leiden CCTA risk score >20: HR 6.11 [3.84-9.70] in women; Leiden CCTA risk score 6-20: HR 1.57 [1.19-2.09]; Leiden CCTA risk score >20: HR 2.25 [1.58-3.22] in men). The increased risk for women within the highest atherosclerotic burden group appears to be driven by post-menopausal women. More intensive preventive medical therapies may be suitable for this group, even in the absence of prior events. Chapter 5 describes the analysis of the coronary vascular volume to left ventricular mass (V/M) ratio obtained by CCTA in 2378 patients. All segmented coronary arteries were summed for the calculation of the total coronary arterial lumen volume. The myocardial volume was extracted from CCTA and multiplied by the specific density of the myocardium (1.05g/ml), resulting in the left ventricle mass. 1346 (56%) patients had hypertension and we hypothesized a lower V/M ratio in these individuals compared to normotensive patients, as hypertension has been associated with reduced coronary vascular reserve.[5-14] However, after adjustment both coronary volume and ventricular mass were higher in hypertensive patients (Least square mean difference estimate: 196.3 (95% CI: 119.9, 272.7)mm^3, p<0.001, and Least square mean difference estimate: 5.60 (95% CI: 3.42, 7.78) g, p<0.001, respectively) whereas the V/M ratio was not significantly different between both groups (Least square mean difference estimate: 0.48 (95% CI: -0.12, 1.08) mm^3/g, p=0.116). These findings suggest that in our cohort, the reduced coronary vascular reserve in hypertensive patients is not caused by an abnormal coronary flow reserve.

Conclusions and Future Perspectives

CCTA has developed into a reliable, noninvasive imaging technique with high accuracy for the detection and exclusion of coronary artery disease. A scan without atherosclerosis in the coronaries excludes plaque as the cause of the cardiac symptoms and predicts a long-term low risk for cardiovascular events. Advances in CT technologies allow detailed atherosclerotic assessment with plaque quantification and assessment of PCAT surrounding the arteries.[15]

PCAT attenuation has been postulated as a novel biomarker to detect coronary inflammation earlier and in this thesis we attempted to establish reference values. It is a relatively new parameter which is influenced by several factors, many studies use different methods of measurement and there is no clear consensus on the gold standard. More research is needed to better understand the association of PCAT with atherogenesis and events, and how it can best be implemented clinically.

Changes in plaque over time can be identified by serial CCTA scans and plaque progression is associated with worse outcomes. Statins reduce major cardiovascular events, but residual cardiovascular risk remains. As described in this thesis, the number of high-risk plaque features and baseline plaque burden were the strongest determinants of statin non-response. Whether these patients may be candidates for other cardiovascular risk-reducing pharmaceutical therapies necessitates further research.

The atherosclerotic burden has been comprehensively shown to be a strong prognosticator of events. We measured the atherosclerotic burden with the Leiden CCTA risk score and explored sex differences between the onset of atherosclerosis. This thesis identified differences in magnitudes of risk between sexes. There is an approximate 12-year delay in the onset of atherosclerosis for women, however women with extensive atherosclerosis, are at significantly higher risk for MACE than men, mainly driven by the post-menopausal cohort. Age and sex could be considered as extra parameters to be integrated into such scores. Further, more strict thresholds in scores for women and more intensive medical therapies may also be needed in these patients.

The V/M ratio was after correcting for potential confounders preserved in patients with hypertension compared to patients without hypertension. These findings do not support the hypothesis, that the abnormal perfusion reserve would be caused by a reduced V/M ratio, however we cannot exclude this as a possibility in different cohorts, and this needs further investigation.

Last, photon-counting CT, a new promising technique with improved spatial resolution is expected to substantially improve cardiovascular imaging. Artifacts such as blooming which results in overestimation of stenosis will be reduced. Improved visualization and evaluation of intraluminal stents and high-risk plaque features can be expected as well.[16]

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Appendices

Samenvatting

In dit proefschrift is onderzocht hoe coronair CT, een niet-invasieve beeldvormingstechniek, kan worden gebruikt in de klinische praktijk om aderverkalking van de kransslagvaten beter te karakteristeren en om risicostratificatie te verbeteren. Coronair CT kan vernauwingen van de kransslagvaten gedurende de hele ernst van de ziekte evalueren en geeft gedetailleerde informatie over de omvang en samenstelling van de plaque en over het vetweefsel rondom de arteriën.

In Hoofdstuk 2 van dit proefschrift werd middels coronair CT, pericoronair vet (PCAT) attenuatie geëvalueerd in patiënten die een CT hebben ondergaan maar waarop geen aderverkalking was gezien.

In totaal werden 109 individuen geïncludeerd en van 320 kransslagaders werden de proximale delen geëvalueerd. PCAT werd gedefinieerd en berekend als de gemiddelde attenuatie van alle voxels tussen -30 en -190 Hounsfield units (HU) en gemeten binnen een radiale afstand van de buitenste vaatwand gelijk aan de diameter van het vat. Er was een significant verschil in gemiddelde PCAT waarden tussen de drie grote kransslagarteriën, genaamd de linker anterieur dalende arterie (LAD), de linker circumflex arterie (LCx) en de rechter kransslagarterie (RCA), met lagere waarden in de LAD in vergelijking met de LCx en RCA (LAD: -67,8 ± 7,8 HU versus LCx: -62,6 ± 6,8 HU versus RCA: -63,6 ± 7,9 HU, p<0,001). Verder waren er sekseverschillen waargenomen in alle drie de kransslagaders met significant hogere PCAT waarden bij mannen vergeleken met vrouwen. Deze resultaten benadrukken het belang van het evalueren van alle drie de kransslagvaten en het rekening houden met het geslacht bij het analyseren van PCAT. Bovendien waren onze PCAT waarden relatief hoger in vergelijking met eerdere studies. Er is aangetoond dat PCAT significant geassocieerd is met zowel technische als patiëntkenmerken, en dat met deze factoren rekening moet worden gehouden wanneer PCAT wordt geanalyseerd. Met betrekking tot technische factoren zijn er significante verschillen in gemiddelde PCAT waarden aangetoond op basis van verschil in het model van de gebruikte CT-scanner. Verder zijn instellingen bij het maken van een CT-scan zoals de pixel afstand, buisstroom en voltage ook significant geassocieerd met verschillen in PCAT evenals de hartslag van de patiënt.

In Hoofdstuk 3 zijn seriële coronaire CT scans van 649 patiënten geëvalueerd om factoren te beoordelen die verband houden met statine non-respons, gedefinieerd als een absolute toename van 1,0% of meer percent atheroma volume per jaar, ondanks het gebruik van statines. Statine non-respons was aanwezig bij 205 (31,5%) patiënten en factoren die onafhankelijk geassocieerd waren, waren diabetes, het aantal hoog risico plaquekenmerken, niet-verkalkt en verkalkt percent atheroma volume bij baseline (OR: 1,41 (0,95-2,11), OR: 1,15 (1,09-1,21), OR: 1,06 (1,02-1,10), OR: 1,07 (respectievelijk 1,03-1,12). Bij het toevoegen van een extra vereiste waardoor statine non-respons werd gedefinieerd als >1,0% toename van het percent atheroma volume per jaar en progressie van fibro-fatty plaque (76 tot 130 HU) of plaque met een lage attenuatie (-30 tot 75 HU) (N=125, 19,2%) waren alleen het aantal hoog risico plaque kenmerken en niet-verkalkt percent atheroma volume bij baseline, onafhankelijke factoren (OR: 1,21 (1,06-1,21) en OR: 1,08 (1,03-1,13) respectievelijk). Deze resultaten suggereren dat patiënten met plaques met hoog risico kenmerken

en met de grootste plaquebelasting bij baseline het grootste risico op statine non-respons hebben. Gezien de associatie van plaqueprogressie met ernstige nadelige cardiovasculaire events, zou bij deze patiënten aanvullende risicoverlagende therapieën nodig kunnen zijn. In Hoofdstuk 4 werd de Leiden CCTA risico score uitgerekend bij 24950 patiënten om de totale hoeveelheid plaque in de kransslagaders van de patiënt te vertalen tot één score en om leeftijds- en geslacht gerelateerde verschillen te onderzoeken. De score (van 0 tot 42) omvat de omvang, ernst, locatie en samenstelling van plaque, met hogere scores voor meer proximale laesies, hogere stenose ernst en meer niet-verkalkte of gemengde plaque samenstelling. De score werd gestratificeerd in 3 groepen: 0-5, 6-20 en >20, aangezien deze waarden eerder het beste events bleken te discrimineren. De risicoscore nam toe met de leeftijd voor beide geslachten, maar de leeftijd waarop de mediane risicoscore hoger was dan 0, lag tussen 52 en 56 voor mannen en tussen 64 en 68 voor vrouwen (p<0,001). Dit sekseverschil werd kleiner met toenemende leeftijd, maar de score bleef significant hoger voor mannen in elke leeftijdsgroep. Cox-regressieanalyse gecorrigeerd voor de confounders leeftijd en cardiovasculaire risicofactoren lieten een onafhankelijk verband zien tussen de risicoscore en events (hartinfarct en overlijden) (Leiden CCTA risicoscore 6-20: HR 2,29 [1,69- 3,10]; Leiden CCTA risicoscore >20: HR 6,71 [4,36-10,32] bij vrouwen, en Leiden CCTA risicoscore 6-20: HR 164 [1,29-2,08]; Leiden CCTA risicoscore >20: HR 2,38 [1,73-3,29] bij mannen) met voor vrouwen een hoger risico. Voor pre- en postmenopauzale analyses werd het cohort gedichotomiseerd in pre- en postmenopauzale groepen op basis van leeftijd. Deze analyses lieten vergelijkbare gecorrigeerde hazard ratio's zien tussen premenopauzale vrouwen en mannen (<55 jaar). Postmenopauzale analyses lieten hogere prognostische waarden zien voor vrouwen, vooral in de groep met de hoogste Leiden CCTA risicoscore (Leiden CCTA risicoscore 6-20: HR 2,21 [1,57-3,11]; Leiden CCTA risicoscore >20: HR 6,11 [3,84-9,70] bij vrouwen; Leiden CCTA risicoscore 6-20: HR 1,57 [1,19-2,09]; Leiden CCTA risicoscore >20: HR 2,25 [1,58-3,22] bij mannen). Het verhoogde risico voor vrouwen binnen de groep met de hoogste atherosclerotische belasting lijkt te zijn gedreven door postmenopauzale vrouwen. Voor deze groep kunnen intensievere preventieve medische therapieën geschikt zijn, zelfs als er nog geen eerdere events zijn geweest. Hoofdstuk 5 beschrijft de analyse van de verhouding tussen het volume van de kransslagvaten en de linkerventrikelmassa (V/M ratio) verkregen door coronair CT in 2378 patiënten. Alle segmenten van de kransslagvaten werden opgeteld voor de berekening van het totale coronaire arteriële lumenvolume. Het myocardvolume werd geëxtraheerd uit de CT en vermenigvuldigd met de specifieke dichtheid van het myocardium (1,05 g/ml), resulterend in de massa van het linkerventrikel. 1346 (56%) patiënten hadden een hoge bloeddruk, ook wel hypertensie, en wij veronderstelden een lagere V/M-ratio bij deze individuen in vergelijking met normotensieve patiënten, aangezien hypertensie in verband is gebracht met een verminderd coronaire vasculaire reserve. Echter, gecorrigeerde analyses lieten zien dat zowel het coronairvolume, als de ventriculaire massa, hoger is bij patiënten met hypertensie (gemiddeld verschil: 196,3 (95% BI: 119,9; 272,7) mm^3 , p<0,001 en gemiddeld verschil: 5,60 (95% BI: 3,42; 7,78) g, p<0,001, respectievelijk) terwijl de V/M-ratio niet significant verschillend was tussen beide groepen (gemiddeld verschil: 0,48 (95% BI: - 0,12; 1,08) mm^3/g, p=0,116). Deze bevindingen suggereren dat in ons cohort de bekende verminderde coronaire vasculaire reserve bij hypertensieve patiënten niet wordt veroorzaakt door een verminderde V/M ratio.

Conclusies en toekomstperspectieven

Coronair CT heeft zich ontwikkeld tot een betrouwbare, niet-invasieve beeldvormingstechniek met hoge nauwkeurigheid voor de detectie en uitsluiting van coronaire atherosclerose. Een scan zonder atherosclerose in de kransslagaders sluit plaque uit als oorzaak van de cardiale symptomen en voorspelt een langdurig laag risico op cardiovasculaire events. Vooruitgang in CT-technologieën maakt gedetailleerde atherosclerotische beoordeling mogelijk met plaque kwantificering en beoordeling van het pericoronaire vet rondom de slagaders.

PCAT attenuatie is gepostuleerd als een nieuwe biomarker om coronaire ontsteking eerder te detecteren en in dit proefschrift hebben we getracht referentiewaarden vast te stellen. Het is een relatief nieuwe parameter beïnvloed door verschillende factoren, met veel verschillende meetmethoden zonder nog een duidelijke consensus over de gouden standaard. Meer onderzoek is nodig om de associatie beter te begrijpen van PCAT met atherogenese en events, en hoe dit het beste klinisch kan worden geïmplementeerd.

Veranderingen in plaque in de loop van de tijd kunnen worden geëvalueerd met seriële coronair CT-scans en progressie van atherosclerose is geassocieerd met slechtere resultaten. Statines verminderen belangrijke cardiovasculaire events, maar er blijft een risico. Zoals beschreven in dit proefschrift, zijn het aantal hoog risico plaquekenmerken en het plaquevolume bij baseline de sterkste determinanten van statine non-respons. Of deze patiënten kandidaten kunnen zijn voor andere cardiovasculaire risico verlagende farmaceutische therapieën, vereist verder onderzoek.

Het is uitgebreid aangetoond dat de atherosclerotische belasting een sterke voorspeller van events is. We maten de atherosclerotische belasting met de Leiden CCTA risicoscore en onderzochten sekseverschillen tussen het ontstaan van atherosclerose en verschillen in de prognostische waarde van aderverkalking. Dit proefschrift identificeerde verschillen in grootte van risico tussen geslachten. Vrouwen krijgen ongeveer 12 jaar later atherosclerose in de kransslagvaten, echter hebben vrouwen met uitgebreide atherosclerose een significant hoger risico op hartinfarct en/of overlijden dan mannen met uitgebreide atherosclerose. Dit is met name gedreven door de postmenopauzale vrouwen. Uit deze resultaten blijkt dat leeftijd en geslacht als extra parameters zouden kunnen worden geïmplementeerd in dergelijke scores. Verder kunnen strengere drempelwaardes in scores voor vrouwen en meer intensieve medische therapieën ook nodig zijn bij deze patiënten.

De V/M-ratio was na correctie voor mogelijke confounders niet significant verschillend tussen patiënten met en zonder hypertensie in ons cohort. Deze bevindingen ondersteunen niet de hypothese, dat de abnormale perfusiereserve in patiënten met hypertensie zou worden veroorzaakt door een verminderde V/M ratio, echter kunnen we dit niet uitsluiten als een mogelijkheid in andere cohorten, en moet dus nog verder worden onderzocht.

Ten slotte wordt verwacht dat Photon Counting CT, een nieuwe veelbelovende techniek met verbeterde ruimtelijke resolutie, cardiovasculaire beeldvorming aanzienlijk zal verbeteren. Artefacten zoals 'blooming' wat resulteert in overschatting van een stenose zal worden verminderd. Verbeterde visualisatie en evaluatie van intraluminale stents en risicovolle plaquekenmerken kunnen ook worden verwacht.

List of Publications

van Rosendael SE, van Rosendael AR, Kuneman JH, Patel MR, Nørgaard BL, Fairbairn TA, Nieman K, Akasaka T, Berman DS, Koweek LMH, Pontone G, Kawasaki T, Sand NPR, Jensen JM, Amano T, Poon M, Øvrehus KA, Sonck J, Rabbat MG, Rogers C, Matsuo H, Leipsic JA, Marsan NA, Jukema JW, Bax JJ, Saraste A, Knuuti J. Coronary Volume to Left Ventricular Mass Ratio in Patients With Hypertension. Am J Cardiol. 2023 May 15:S0002-9149(23)00241-2. doi: 10.1016/j.amjcard.2023.04.025. Epub ahead of print. PMID: 37198076.

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Curriculum Vitae

Sophie van Rosendael werd op 8 november 1996 in Rotterdam geboren. Vanaf jonge leeftijd speelde zij tennis wat leidde tot een nummer 2 positie van haar leeftijd in Nederland en het mogen representeren van Nederland voor meisjes onder de 16 jaar. Na het behalen van haar middelbare schooldiploma aan het Coornhert Gymnasium te Gouda begon zij in 2014 met de studie geneeskunde aan de Vrije Universiteit in Amsterdam. Nadien startte zij in 2021 met een promotieonderzoek onder leiding van professor Jeroen Bax en professor Wouter Jukema naar de rol van CCTA bij coronairlijden bij de afdeling cardiologie. Na haar promotieonderzoek zal zij gaan starten met een postdoc aan de Icahn School of Medicine bij het Mount Sinai Hospital in New York.