

Sex differences in plaque characteristics by intravascular imaging in patients with coronary artery disease



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KEYWORDS

- atherosclerosis
- intravascular ultrasound
- near-infrared spectroscopy
- sex

Abstract

Aims: We aimed to study sex differences in coronary plaque burden and plaque composition in patients with coronary artery disease (CAD).

Methods and results: Virtual histology intravascular ultrasound (VH-IVUS) and near-infrared spectroscopy (NIRS) imaging of a non-culprit coronary artery was performed in 178 (23.5%) women and 581 (76.5%) men who underwent invasive management of stable angina pectoris (SAP) or acute coronary syndrome (ACS). Women were older and had a worse cardiovascular risk profile than men, but less extended angiographic coronary disease. Irrespective of the presenting diagnosis, women had lower VH-IVUS-derived plaque burden than men (38.1% vs. 40.5% in SAP, and 35.9% vs. 38.8% in ACS). Standardised (mean 211 vs. 263 mm³ in SAP, and 199 vs. 245 mm³ in ACS) total plaque volume was lower in women. Volumes of fibrous tissue, fibro-fatty tissue, necrotic core and dense calcium were also lower in women. NIRS-derived lipid core burden index (LCBI) was lower in women, in particular in SAP (mean LCBI in the worst 4 mm 220 vs. 240). The observed differences remained significant after adjustment for clinical characteristics.

Conclusions: Women had more favourable plaque characteristics than men, despite their worse risk profile. Long-term follow-up studies are required to evaluate the clinical consequences.

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Introduction

Relevant differences have been reported in the genesis, development and pathophysiology of coronary atherosclerosis between women and men, which have not been fully unravelled^{1,2}. In women, coronary artery disease (CAD) appears up to 10 years later in life than in men and prevalent angiographic obstructions are less severe at all ages^{3,4}. Importantly, however, the incidence of an acute coronary event is not primarily determined by the extent and severity of the luminal stenosis, but rather by the characteristics of the atherosclerotic plaque^{5,6}. Hence, sex differences in coronary plaque composition are of potential importance.

During the last decades, catheter-based coronary imaging modalities have been developed to detect high-risk “vulnerable” plaques before their disruption⁶. In this context, virtual histology intravascular ultrasound (VH-IVUS) is capable of identifying thin-cap fibroatheroma (TCFA) lesions, which are prone to rupture^{7,8}. Near-infrared spectroscopy (NIRS) has the potential to quantify the lipid core within coronary plaques, which may represent activity of atherosclerosis^{9,10}. This paper expands on these findings, and aims to reveal any sex differences in the measurements that appeared relevant.

Methods

STUDY PATIENTS AND MATERIAL

We combined the European Collaborative Project on Inflammation and Vascular Wall Remodelling in Atherosclerosis - Intravascular Ultrasound (AtheroRemo-IVUS) and the third Integrated Biomarker and Imaging (IBIS-3) studies, which had a similar design^{11,12}. Both studies were conducted in the Erasmus MC and enrolled patients undergoing coronary angiography (CAG) or percutaneous coronary intervention (PCI) for stable angina pectoris (SAP) or acute coronary syndromes (ACS).

INTRAVASCULAR IMAGING

Following the CAG or PCI of culprit lesions, a non-culprit segment with a lumen diameter $\geq 50\%$ and a length ≥ 40 mm was selected. IVUS data of the “study segment” were then acquired with the Volcano s5/s5i Imaging System (Volcano Corp. [now Philips Volcano], San Diego, CA, USA using the Eagle Eye® Gold IVUS catheter (20 MHz) (Volcano Corp.) at an automated pullback speed of 0.5 mm/s. IVUS images were analysed off-line in a blinded core laboratory (Cardialysis BV, Rotterdam, the Netherlands). VH-IVUS was performed using pcVH 2.1 and qVH (VIAS software; Volcano Corp.) software⁷. VH-IVUS data were available for 178 women and 581 men.

In 64 women and 211 men, NIRS imaging of the study segment was also performed by the Advanced TVC Imaging System™ (Infraredx, Inc., Burlington, MA, USA). NIRS imaging was limited to a “region of interest” (RoI), defined as the longest possible section of the study segment between two side branches. The lipid core burden index of the RoI ($LCBI_{RoI}$) was determined as well as the $LCBI_{10mm}$ and $LCBI_{4mm}$ in the 10 and 4 mm segments with highest values, respectively. NIRS images were analysed off-line at the Cardialysis core laboratory.

CLINICAL ENDPOINTS

We collected data on the incidence of all-cause mortality, ACS, and unplanned coronary revascularisation (i.e., major adverse cardiac events [MACE]) in the patients who participated in AtheroRemo-IVUS during one-year follow-up.

STATISTICAL ANALYSIS

We studied clinical characteristics and imaging findings in relation to sex. The presenting diagnosis was an important confounder of these relations. Therefore, we present results in SAP and ACS patients separately.

Normality of continuous variables was evaluated. Sex differences were then studied by the Student’s t-test (normal distribution) or the Mann-Whitney test (skewed distribution). Log transformations were applied if statistical analyses required normal distribution. Differences in categorical variables were studied by chi-square tests, or Fisher’s exact tests.

Linear regression was applied to reveal associations between sex (independent) and imaging measures (dependent). Results are presented as mean difference between women and men with 95% confidence intervals (CI). The association between sex and the presence of high-risk lesion characteristics was analysed by logistic regression. Results are presented as odds ratios (ORs) with 95% CI. We considered age, admission diagnosis, diabetes mellitus, systolic blood pressure, hypertension, dyslipidaemia, smoking, family history and body mass index (BMI) confounders of the relation between sex and imaging outcomes. We therefore applied multivariate regression with adjustment for these variables.

A two-sided p-value of <0.05 was considered significant for all analyses. We used SPSS, Version 20.0 for Windows (SPSS 20.0; IBM Corp., Armonk, NY, USA) for our calculations.

ETHICS

The medical ethics committee of the Erasmus MC approved our studies. Written informed consent was obtained from all patients.

Results

PATIENT BASELINE CHARACTERISTICS (Table 1)

Women had different characteristics from men. Differences with respect to age, cardiovascular risk factors (diabetes, hypertension, smoking) and haemodynamic status were most pronounced in patients presenting with ACS. Differences in cardiovascular history (previous MI, previous PCI) were most striking in SAP. In general, women were older and had a higher cardiovascular risk profile than men, but less extended angiographic CAD.

INTRAVASCULAR IMAGING (Table 2, Table 3, Figure 1, Figure 2)

Women had lower absolute and standardised total plaque volumes than men, with standardised mean differences ranging from 34.9 to 41.1 mm³. Absolute (data not shown) and standardised volumes of fibrous tissue, fibro-fatty tissue, necrotic core and dense calcium were also lower in women. When corrected for body surface area (BSA), plaque volumes remained lower in women; however,

Table 1. Patient baseline characteristics according to sex and by indication of the index procedure.

	Stable angina pectoris			Acute coronary syndromes		
	Women	Men	p-value	Women	Men	p-value
No. of patients	83	286		95	295	
Risk factors						
Age, years	65.5 (57.1, 72.3)	63.0 (56.3, 70.7)	0.14	64.6 (55.5, 71.8)	58.8 (51.0, 65.8)	<0.001
BMI, kg/m ² *	27.5 (24.7, 31.2)	27.2 (25.3, 30.1)	0.48	26.4 (23.6, 29.2)	26.5 (24.4, 29.3)	0.84
BSA, m ²	1.9 (1.7, 2.0)	2.1 (2.0, 2.2)	<0.001	1.8, (1.7, 1.9)	2.1 (1.9, 2.2)	<0.001
Diabetes mellitus	25.3	24.5	0.88	20.0	10.9	0.022
Hypertension	75.9	60.5	0.010	62.1	41.8	<0.001
Dyslipidaemia	67.5	69.2	0.76	41.1	48.3	0.22
Current smoker	18.1	19.6	0.039	31.5	38.8	0.033
Cardiovascular history						
Previous MI	25.3	39.9	0.015	30.5	24.8	0.26
Previous PCI	36.1	48.6	0.045	21.1	19.7	0.77
Previous CABG	1.2	3.5	0.28	2.1	2.0	0.97
Previous stroke	9.6	8.7	0.80	4.2	4.1	0.95
History of PAD	3.6	7.3	0.23	5.3	4.1	0.62
History of heart failure	3.6	4.2	0.81	1.1	1.7	0.66
Admission						
No. of diseased vessels [†]			0.30			0.036
0	13.3	8.0		9.5	3.4	
1	50.6	46.2		55.8	54.9	
2	28.9	35.3		29.5	29.8	
3	7.2	10.5		5.3	11.9	

Continuous variables are presented as median (25th-75th percentile) values. Categorical data are presented as percentages. *Data are available in 167 women and 533 men. [†] Defined as coronary artery disease with ≥50% vessel obstruction by visual estimation or quantitative coronary angiography. BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass grafting; CAD: coronary artery disease; MI: myocardial infarction; PAD: peripheral artery disease; PCI: percutaneous coronary intervention

differences became smaller and did not reach statistical significance. We found no sex differences in the presence of high-risk lesions, including TCFA lesions.

NIRS-derived LCBI values were slightly lower in women than in men, in particular in SAP. Women had lower maximum LCBI than men (160 versus 271 in SAP and 182 versus 571 in ACS), but LCBI distributions were not clearly left-shifted. Consequently, Mann-Whitney tests were non-significant.

ADJUSTMENT FOR CONFOUNDERS (Table 4)

The observed sex differences in plaque characteristics remained significant after adjustment for confounders. Irrespective of age, cardiovascular risk factors and cardiovascular history, women had more favourable VH-IVUS-derived plaque burden (PB) and plaque volumes, and NIRS-derived LCBI values.

ONE-YEAR CLINICAL OUTCOMES

In AtheroRemo-IVUS, 41 patients died or had a non-fatal ACS during one-year follow-up. We found no statistically significant differences between women and men (5.1% versus 5.9%, p-value 1.00 in SAP, and 9.6% versus 7.7%, p-value 0.57 in ACS). In SAP patients, the one-year incidence of MACE was significantly lower

in women (6.8% versus 19.6%, p-value 0.020), which was mainly due to non-planned coronary revascularisations.

Discussion

The women who were included in our study of patients with (documented) CAD had an adverse clinical cardiovascular risk profile compared with men. Still, the extent of significant CAD was considerably lower, whereas coronary plaque composition, based on state-of-the-art imaging, was somewhat more favourable.

Our finding that women presenting with SAP or ACS had less extensive CAD than men, despite having more comorbid risk factors, is largely in accordance with previous studies^{3,13}. In PROSPECT, women had fewer (vessels with) non-culprit lesions and lower plaque volumes, including lower necrotic core volumes³. Interestingly, in PROSPECT, sex differences in plaque burden and plaque composition were mainly found in patients below the age of 65. In fact, as the PROSPECT investigators demonstrated, age appeared to be an important confounder in studies of sex-related differences in coronary sclerosis. Since the extent and structure of atherosclerotic lesions may also differ between SAP and ACS patients, we decided to stratify according to that presenting feature. Our study lacked power to further stratify for age.

Table 2. VH-IVUS findings according to sex and by indication of the index procedure.

	Stable angina pectoris			Acute coronary syndromes		
	Women	Men	<i>p</i> -value	Women	Men	<i>p</i> -value
No. of patients	83	286		95	295	
Plaque burden, %	38.1 (10.5)	40.5 (11.0)	0.11	35.9 (12.3)	38.8 (11.4)	0.031
	38.6 (30.2, 44.4)	41.2 (33.0, 48.1)	0.069	36.3 (25.7, 44.9)	39.3 (30.8, 46.8)	0.042
Lesion remodelling	0.89 (0.18)	0.88 (0.24)	0.39	0.89 (0.33)	0.91 (0.25)	0.39
	0.90 (0.77, 1.02)	0.88 (0.76, 1.00)	0.46	0.87 (0.76, 1.01)	0.92 (0.76, 1.02)	0.32
Total plaque volume, mm ³	209 (128)	268 (153)	0.001	188.5 (10.7)	247.5 (8.1)	<0.001
	172 (120, 280)	249 (158, 344)	0.001	170.5 (109.2, 253.4)	223.2 (147.5, 315.7)	<0.001
Standardised plaque volume *						
Total plaque volume, mm ³	211 (90)	263 (139)	0.010	199 (104)	245 (128)	0.002
	200 (145, 261)	238 (152, 358)	0.010	201 (112, 260)	223 (150, 316)	0.004
Fibrous tissue volume, mm ³	53.0 (37.8)	76.7 (60.6)	0.039	48.5 (42.4)	72.3 (58.2)	0.002
	48.0 (27.6, 69.9)	62.7 (29.5, 111.1)	0.006	44.3 (11.9, 68.8)	58.3 (31.5, 98.3)	0.001
Fibro-fatty tissue volume, mm ³	8.6 (7.3)	16.4 (16.5)	0.003	7.8 (8.8)	13.7 (16.5)	<0.001
	6.6 (3.4, 12.4)	10.5 (4.6, 24.8)	<0.001	4.7 (1.2, 11.4)	7.9 (3.8, 17.5)	<0.001
Necrotic core volume, mm ³	22.4 (20.7)	31.8 (30.0)	0.084	21.7 (22.6)	29.3 (26.7)	0.001
	16.8 (6.9, 31.6)	21.6 (9.6, 49.2)	0.028	16.7 (3.4, 29.9)	22.3 (9.5, 42.0)	0.006
Dense calcium volume, mm ³	11.9 (12.7)	17.5 (20.2)	0.041	12.0 (16.6)	12.9 (14.8)	0.016
	8.0 (2.3, 19.4)	10.6 (4.1, 22.5)	0.036	5.3 (1.4, 17.4)	8.4 (2.8, 17.7)	0.074
Plaque volume corrected for BSA†						
Total plaque volume/BSA	4.6 (0.5)	4.7 (0.6)	0.45	4.5 (0.6)	4.6 (0.6)	0.19
	4.7 (4.3, 5.0)	4.7 (4.3, 5.2)	0.37	4.7 (4.1, 5.0)	4.7 (4.3, 5.0)	0.36
Fibrous tissue volume/BSA	2.9 (1.3)	3.1 (1.2)	0.15	2.5 (1.8)	3.1 (1.4)	0.012
	3.2 (2.6, 3.7)	3.4 (2.6, 4.0)	0.066	3.2 (1.8, 3.6)	3.4 (2.7, 3.9)	0.013
Fibro-fatty tissue volume/BSA	1.0 (1.4)	1.5 (1.3)	0.013	0.8 (1.5)	1.2 (1.4)	0.005
	1.2 (0.6, 2.0)	1.6 (0.8, 2.5)	0.004	1.1 (-0.3, 1.9)	1.4 (0.7, 2.1)	0.006
Necrotic core volume/BSA	1.9 (1.4)	2.1 (1.5)	0.29	1.6 (1.9)	2.1 (1.4)	0.009
	2.2 (1.3, 2.9)	2.4 (1.5, 3.2)	0.16	2.2 (0.7, 2.9)	2.4 (1.6, 3.0)	0.030
Dense calcium volume/BSA	1.1 (1.6)	1.4 (1.5)	0.14	0.7 (2.2)	1.2 (1.5)	0.059
	1.5 (0.3, 2.4)	1.7 (0.7, 2.4)	0.14	1.2 (-0.1, 2.3)	1.4 (0.5, 2.2)	0.22
Plaque composition						
Fibrous tissue, %	58.1 (10.7)	56.6 (11.9)	0.21	58.9 (14.2)	59.4 (10.6)	0.38
	57.7 (49.8, 66.2)	56.9 (49.8, 63.5)	0.35	60.2 (49.9, 68.1)	60.1 (52.7, 66.1)	0.93
Fibro-fatty tissue, %	9.4 (4.9)	11.3 (7.3)	0.022	9.0 (6.5)	10.2 (6.4)	0.058
	9.1 (5.6, 12.2)	9.7 (6.6, 14.5)	0.032	8.2 (4.5, 12.0)	9.0 (6.3, 12.4)	0.033
Necrotic core, %	20.9 (7.8)	20.6 (7.0)	0.58	21.3 (9.8)	21.2 (7.9)	0.42
	21.4 (17.0, 25.6)	21.0 (17.0, 25.0)	0.72	20.8 (15.0, 27.7)	21.1 (16.7, 26.0)	0.82
Dense calcium, %	11.6 (7.9)	11.5 (7.3)	0.70	10.7 (9.0)	9.1 (6.3)	0.93
	11.1 (4.9, 16.1)	10.3 (6.1, 16.1)	0.97	8.3 (4.4, 15.3)	7.9 (4.9, 12.6)	0.36
High-risk lesions						
≥1 TCFA lesion	42.2	36.7	0.37	37.9	47.1	0.12
≥1 lesion with PB ≥70%	14.5	18.5	0.39	14.7	15.3	0.90
≥1 lesion with MLA ≤4.0 mm ²	22.9	24.8	0.72	30.5	21.4	0.067
Continuous variables are presented as mean (standard deviation) and median (25 th -75 th percentile) values. The mean difference between women and men (and the corresponding <i>p</i> -value) is based on analyses of log-transformed values. Categorical data are presented as percentages. *Standardised volumes are obtained as follows: 42.13*(individual patient's segment volume/individual patient's segment length), with 42.13 mm being the median imaged segment length in all patients (women and men together). † Standardised volume data corrected for body surface area. BSA: body surface area; CI: confidence interval; MLA: mean luminal area; PB: plaque burden; TCFA: thin-cap fibroatheroma						

Table 3. Near-infrared spectroscopy findings according to sex and by indication of the index procedure.

No. of patients	Stable angina pectoris			Acute coronary syndromes		
	Women	Men	<i>p</i> -value	Women	Men	<i>p</i> -value
	31	127		33	84	
LCBI region of interest	41 (45)	52 (51)	0.030	50 (46)	73 (93)	0.10
	23 (6, 67)	36 (14, 74)	0.20	43 (13, 69)	48 (20, 102)	0.34
LCBI worst 10 mm	130 (142)	163 (153)	0.042	145 (117)	193 (170)	0.49
	78 (31, 181)	118 (40, 232)	0.25	115 (48, 218)	158 (71, 262)	0.20
LCBI worst 4 mm	220 (216)	240 (194)	0.075	220 (163)	283 (203)	0.65
	160 (54, 356)	197 (83, 337)	0.41	195 (93, 326)	296 (107, 396)	0.14

Variables are presented as mean (standard deviation) and median (25th-75th percentile) values. The mean difference between women and men (and the corresponding *p*-value) is based on analyses of log-transformed values. CI: confidence interval; LCBI: lipid core burden index

Still, it should be emphasised that our findings were maintained after adjustment for age (among other factors).

We found small differences in plaque composition between women and men, but the distribution of high-risk lesions, including TCFA lesions, was similar. Based on a Korean cohort of ACS patients, Hong and colleagues reported a higher prevalence of TCFA lesions in women, which might be explained by the fact that they studied culprit lesions only¹⁴. In PROSPECT (studying culprit and non-culprit lesions), no differences were found in the frequency of different plaque phenotypes. Also, plaque composition seems to be related to age, with most evident sex differences in younger patients³. Our study was mainly performed in the elderly, and included those presenting with SAP; subtle sex differences in plaque morphology might therefore have remained undiscovered.

Nevertheless, necrotic core, a key determinant of plaque vulnerability, was lower in women.

No studies have published sex-specific NIRS-derived data in ACS patients. Bharadwaj and colleagues studied 128 SAP patients and found no differences in LCBI_{4mm} between women and men¹⁵. Their LCBI values were higher than in our study, probably because of the poorer risk profile of their patients. In a previous report from our group, based on a lower number of patients, female sex was associated with low LCBI values, independent of age¹⁶. Data on the relationship between LCBI and other plaque characteristics are scarce. A study by Pu and colleagues demonstrated a weak positive relationship between (VH-derived) necrotic core and LCBI¹⁷. Although the LCBI values in our study are quite low, the observed sex differences might still be of interest, since NIRS may

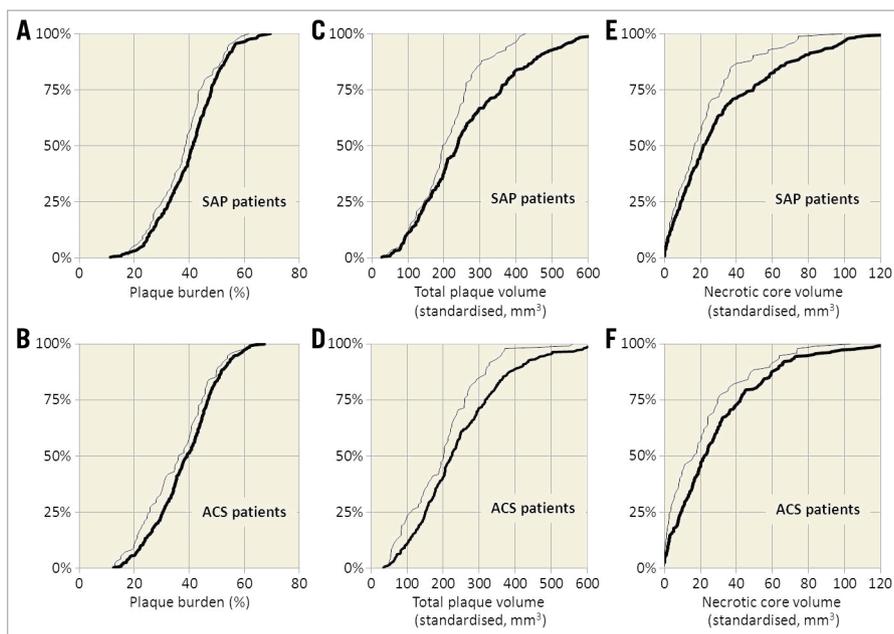


Figure 1. VH-IVUS-derived plaque burden in women versus men according to clinical presentation. Graphs show cumulative percentage curves for plaque burden (A, B), total standardised plaque volume (C, D), and necrotic core volume (E, F) between women (bold line) and men (thin line) with stable angina pectoris and acute coronary syndrome, respectively. ACS: acute coronary syndrome; SAP: stable angina pectoris; VH-IVUS: virtual histology intravascular ultrasound

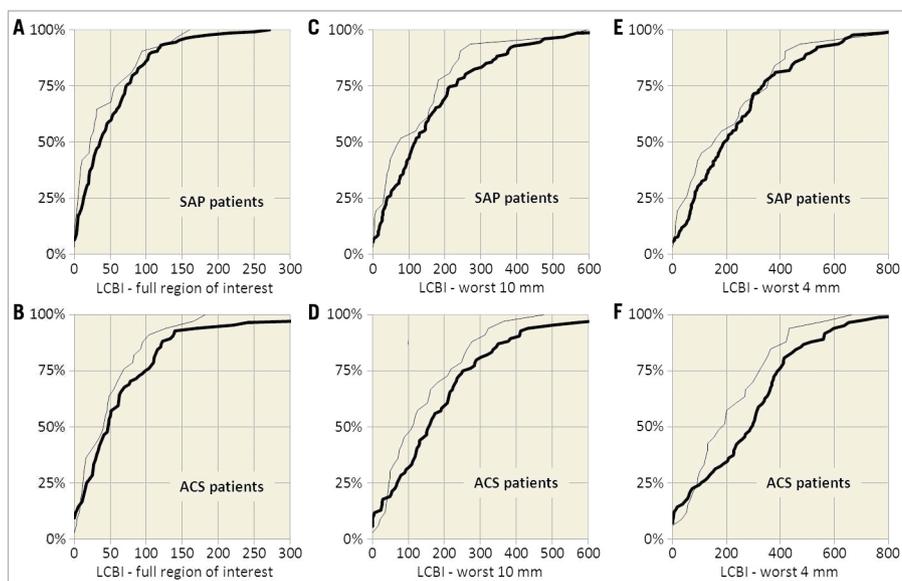


Figure 2. NIRS-derived LCBI in women versus men according to clinical presentation. Graphs show cumulative percentage curves for LCBI (A, B), worst 10 mm LCBI (C, D), and worst 4 mm LCBI (E, F) between women (bold line) and men (thin line) with stable angina pectoris and acute coronary syndrome, respectively. ACS: acute coronary syndrome; LCBI: lipid core burden index; SAP: stable angina pectoris

provide prognostic information that is not provided by traditional cardiovascular scoring systems¹⁸.

We found it puzzling to understand why women at a more advanced age and with more cardiovascular risk factors have lower plaque burden and lower LCBI than men. It might be hypothesised that the potential atherogenicity of specific risk factors or their clusters differ between sexes. For example, pre-menopausal women are largely protected against the development of CAD, most likely by their reproductive hormones¹⁹. Oestrogen might have anti-inflammatory effects, resulting in smaller lipid cores, less calcified plaques, and fewer TCFA²⁰. However, we enrolled post-menopausal women in whom oestrogen-mediated CAD retardation processes

are less likely. We had no information on hormone levels, or on hormone replacement therapy. Others have advocated that coronary microvascular dysfunction is an important pathological mechanism for ischaemia in women². A small imaging study found no correlation between LCBI and coronary microvascular dysfunction; however, it demonstrated a higher lipid deposition in patients with early stage CAD and epicardial dysfunction²¹. We had no data to support or disprove these early findings.

Plaque characterisation by IVUS-VH has consistently shown a good correlation with histology in human autopsy studies⁷, but not in porcine coronary arteries²². Furthermore, its ability to detect plaque erosion is limited given the current spatial resolution.

Table 4. Adjusted mean differences in plaque characteristics and serum biomarkers between women and men by the indication of index procedure.

	Stable angina pectoris	Acute coronary syndromes	p-value [‡]
IVUS characteristics*			
Plaque burden, %	4.0 (2.1, 5.9)	3.9 (2.1, 5.7)	<0.001
Total plaque volume, mm ³	59 (40, 75)	57 (39, 73)	<0.001
Standardised total plaque volume, mm ³	46 (28, 63)	45 (27, 61)	<0.001
Necrotic core volume, mm ³	8.5 (5.9, 10.5)	8.6 (6.0, 10.7)	<0.001
Standardised necrotic core volume	7.8 (5.0, 9.9)	7.9 (5.1, 10.2)	<0.001
NIRS characteristics*			
LCBI region of interest	14 (6, 19)	20 (8, 29)	0.003
LCBI worst 10 mm	36 (8, 56)	48 (10, 74)	0.018
LCBI worst 4 mm	49 (3, 83)	62 (3, 104)	0.041
Variables represent mean differences (value in a man minus value in a woman) and 95% confidence intervals for an “average” patient, by substituting the mean values for the variables that compose the corresponding multivariate model. *Based on a multivariate model that contains sex, age, diabetes, hypertension, smoking status and admission indication (ACS or not). [‡] p-value related to the variable patient sex in the corresponding multivariate model. IVUS: intravascular ultrasound; LCBI: lipid core burden index; NIRS: near-infrared spectroscopy			

However, despite concerns about its accuracy, we previously demonstrated that VH-IVUS is capable of discriminating patients according to cardiovascular risk²³. Furthermore, VH-IVUS helps to understand the pathophysiology of CAD and is valuable in comparing plaque characteristics between patient groups. The newer NIRS imaging technology provides more precise information about plaque composition on the basis of the specific chemical signature of the fibroatheroma. In that respect, NIRS overcomes some of the (VH-)IVUS limitations. On the other hand, NIRS also has limitations, as it does not provide information on the depth of data acquisition. NIRS has shown good specificity (90%) for lipid pool detection, but modest sensitivity (50%)⁹. Optical coherence tomography (OCT) has a higher axial and lateral resolution, but a lower penetration depth than IVUS, so that visualisation of the entire depth of a lesion is difficult, especially in the presence of lipid-rich tissue, where the optical signal is strongly attenuated. In the landmark OCTAVIA study, based on OCT imaging of the culprit vessel in STEMI patients, no sex differences were found in plaque erosion or plaque rupture, or in minimum cap thickness and plaque constituents²⁴. We can only speculate on OCT findings in AtheroRemo/IBIS-3 had we applied that modality in our patients. All in all, according to the state of the art, the combination of several intracoronary imaging modalities - such as the IVUS/NIRS combination which we applied in our study - currently provides the best assessment of coronary disease.

Study limitations

This was a single-centre study with a relatively small sample size and was too small to draw definite conclusions in relation to clinical outcome. Several studies have shown worse outcomes in symptomatic women with nonobstructive CAD (a condition which is more common among women), compared to normal subjects²⁵⁻²⁷. We were unable to confirm this observation in our study.

We investigated non-culprit lesions, which might have resulted in a sex-specific underestimation of the presence of plaque lesions, as PROSPECT showed fewer non-culprit lesions (despite similar culprit lesions) in women than in men.

The plaque vulnerability concept is under debate²⁸. Also, statin therapy and lifestyle changes seem to influence the composition of plaque in a favourable sense. Despite more stable plaques, people still suffer from the consequences of coronary atherosclerosis, including a growing number of women. Our study included mainly post-menopausal women, and our results may not be generalisable to younger women. Future studies should focus on visualising sex-related plaque changes, by combining various intravascular imaging techniques with cardiovascular outcome at an early stage of the atherosclerotic process.

Conclusions

In this cohort of patients with CAD, women had more favourable plaque characteristics than men, despite their worse cardiovascular risk profile. Thus, our study supports the notion of sex differences in the pathogenesis and development of CAD. Future studies are

required to investigate the clinical consequences of these findings during long-term follow-up.

Impact on daily practice

Sex-based differences in the genesis, development and prognosis of coronary artery disease have been reported by many studies. A better understanding of pathobiological mechanisms of atherosclerosis might not only improve individual risk stratification, but also explain differences in coronary artery disease (CAD) evolution between women and men. Coronary angiography has limitations regarding the objective appreciation of disease extent and morphology. This paper describes findings of intravascular ultrasound radiofrequency analyses and near-infrared spectroscopy imaging in women and men with CAD, including stable angina and acute coronary syndromes. Women had more favourable plaque characteristics than men, despite their higher age and worse clinical cardiovascular risk profile. Our findings support the hypothesis of sex-based differences in CAD pathogenesis and progression, and encourage further studies in this area.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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