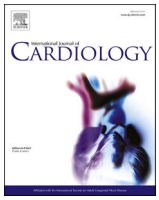
International Journal of Cardiology 444 (2026) 134023

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard



# Sex differences in plaque burden and outcomes in symptomatic patients with suspected coronary artery disease

David Molnar [a,b,*], Juhani Knuuti [a,c], Jeroen J. Bax [d], Antti Saraste [a,e], Teemu Maaniitty [a,c]

[a] Turku PET Centre, Turku University Hospital, University of Turku, Kiinamyllynkatu 4-8, 20520 Turku, Finland
[b] Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden
[c] Department of Clinical Physiology, Nuclear Medicine and PET, Turku University Hospital, Turku, Finland
[d] Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands
[e] Heart Center, Turku University Hospital, University of Turku, Turku, Finland

ARTICLE INFO

*Keywords:*
Sex differences
Plaque burden
Myocardial infarction
acute coronary syndrome
Long-term outcome
artificial intelligence-based quantitative computed tomography

ABSTRACT

*Background:* Sex-related differences in coronary artery disease (CAD) burden and outcomes are increasingly recognized but not fully understood, particularly when assessed using advanced imaging techniques.
*Objectives:* To investigate sex differences in coronary plaque characteristics and their association with long-term cardiovascular outcomes in symptomatic patients undergoing coronary computed tomography angiography (CTA).
*Methods:* A total of 2271 symptomatic patients without prior obstructive CAD underwent CTA, followed by artificial intelligence-based quantitative plaque analysis (AI-QCT) extracting plaque features including total plaque volume (TPV), non-calcified plaque (NCP), low-density plaque (LDP), and calcified plaque (CP). CAD severity was classified in accordance with CAD-RADS. Long-term outcomes, including myocardial infarction (MI), acute coronary syndrome (ACS) and death, were tracked over a median follow-up of 7.3 years. Analyses were stratified by sex and CAD-RADS category.
*Results:* Women ($n = 1316$) were older but had significantly lower plaque burden across all CAD-RADS categories compared to men ($n = 955$). Despite this, women had non-negligible number of MI ($n = 31$) and ACS ($n = 46$), with the highest rate in CAD-RADS 3 (1.1 % MI and 1.6 % ACS), whereas in men (totally 37 MI, 54 ACS), event rates were highest in CAD-RADS 4 (1.9 % MI and 2.5 % ACS). No cardiovascular events were recorded in CAD-RADS 0 for either sex. In multivariable Cox regression, stenosis severity was the strongest predictor of events in men, while TPV was more predictive in women. In gradient boosting machine (GBM) analysis, TPV and stenosis severity had the highest overall relative importance in explaining events.
*Conclusions:* This study demonstrates important sex-based differences in CAD phenotype and prognosis. Women had lower plaque burden, yet experienced adverse events with lower CAD-RADS, suggesting that current risk stratification may underestimate their risk. AI-QCT provides enhanced plaque characterization, which may in the future improve individualized assessment, especially in women.

## 1. Introduction

Computed tomography (CT) is the most widely used non-invasive method for in-vivo imaging of the coronary arteries. Thanks to rapid technical developments, coronary CT angiography (CTA) has increasingly come to replace invasive coronary angiography and has been proven to provide information beyond simple stenosis detection, specifically on plaque burden, plaque morphology and pathophysiological characteristics [1–3].

The extraction of morphological plaque features was for years firmly in the domain of manual reading, with limited use in large scale population research due to time-consuming segmentation work. Lately, with

*Abbreviations:* CTA, Computed tomography angiography; AI-QCT, Artificial intelligence-based quantitative computed tomography; CAD, Coronary artery disease; LDP, Low-density plaque; CAD-RADS, Coronary artery disease reporting and data system; MI, Myocardial infarction; ACS, Acute coronary syndrome; NCP, Non-calcified plaque; TPV, Total plaque volume; PAV, Percent atheroma volume; CP, Calcified plaque; GBM, Gradient boosting machine.

* Corresponding author at: Turku PET Centre, Turku University Hospital, University of Turku, Kiinamyllynkatu 4-8, 20520 Turku, Finland.
*E-mail address:* david.molnar@utu.fi (D. Molnar).

https://doi.org/10.1016/j.ijcard.2025.134023
Received 3 September 2025; Received in revised form 5 November 2025; Accepted 10 November 2025
Available online 11 November 2025

the harnessing of artificial intelligence, automatic or semi-automatic software solutions have become available for detailed plaque analysis, one being an FDA-approved, AI-based solution for quantitative CTA analysis (AI-QCT) [4,5].

While calcification has long been acknowledged as one of the hallmarks of atherosclerosis, it is evident from numerous studies that absence of calcification does not exclude coronary artery disease (CAD), and indeed, obstructive CAD is found in a number of patients with zero calcium score [6,7]. Recognizing this, several high-risk plaque characteristics have been described on CTA [8–11], e.g., low-density plaques (LDP), spotty calcification, and positive remodelling.

The impact of sex on plaque morphology has been described mainly based on intravascular ultrasound, and findings are suggestive of true pathophysiological differences, such as men having a higher propensity to suffer from plaque rupture, women from plaque erosion [12], while women also tend to develop complications with a lower overall plaque burden [13]. The effects of hormonal status and menopause on CAD and associated events is relatively obscure, with few studies addressing this potentially influential process. In a recent post-mortem study of patients (185 women and 515 men) suffering from mostly cardiac sudden death, the authors concluded, that there were few morphological differences in CAD between pre-menopausal women and men, but after menopause women seem to gradually develop CAD to reach parity with men in the oldest age group [14].

In the present study, AI-QCT analysis was performed in 2271 patients evaluated for stable chest pain. The aim was to explore sex differences with respect to plaque characteristics and long-term clinical outcome stratified by CAD burden, as defined by CAD-RADS 2.0 [15].

## 2. Methods

### 2.1. Informed consent and ethical permit

The study conforms to the Declaration of Helsinki and the study protocol has been approved by the Ethics Committee of the Hospital District of Southwest Finland without requirement for written informed consent due to the observational study design.

### 2.2. Study cohort

The study cohort was composed of symptomatic patients evaluated with coronary CTA for suspected CAD between 2007 and 2016 at the Turku University Hospital in Finland. Patients with previously known obstructive CAD or prior myocardial revascularization were not included. Out of totally 2411 consecutive patients, 137 (5.7 %) were excluded from the present study due to non-retrievable CTA image data. Three patients were lost to follow-up. The remaining 2271 patients, 955 men (42.1 %) and 1316 women (57.9 %), all had morphological plaque analysis performed with AI-QCT.

Demographic and clinical data was gathered from electronic medical records, while long-term follow-up data on all-cause mortality, myocardial infarction (MI) and unstable angina until 2020 was retrieved from hospital discharge registry data (Auria Clinical Informatics) and individually verified against electronic medical records. Acute coronary syndrome (ACS) was defined as MI or unstable angina requiring hospitalization in alignment with ESC guidelines [16].

### 2.3. Computed tomography imaging

Non-contrast CT scans for calcium scoring were first performed, followed by coronary CTA after the administration, as needed, of intravenous metoprolol (0–30 mg) to reach a target heart rate of 60 bpm, and isosorbide dinitrate aerosol (1.25 mg) or sublingual nitrate (0.8 mg) to dilate the coronary arteries. Low-osmolal iodine contrast was used. Two hybrid PET-CT scanners with 64-row detectors were used (GE Discovery VCT and GE D690, General Electric Medical Systems, Waukesha, USA). Preferably, prospective ECG-gating was used. The protocol has been previously described in greater detail [17].

### 2.4. AI-QCT analysis

In addition to standard clinical analysis, CTA images were re-analyzed in a blinded manner with an FDA-approved AI-QCT software (Cleerly LABS; Cleerly, Inc.; Denver, USA). Briefly, it employs a series of convolutional neural networks to extract quantitative data on CAD, which include the: degree of stenosis by diameter, total plaque volume (TPV), percent atheroma volume (PAV, or the TPV normalized to vessel volume), low-density plaque volume (LDP; $\leq$ 30 HU), non-calcified plaque volume (NCP; 31–350 HU), calcified plaque volume (CP; >350 HU). All patients were classified according to CAD-RADS 2.0[15] based on AI-QCT data. In short, patients with no detectable plaque or stenosis were defined as CAD-RADS 0, with either stenosis of <25 % or any detectable plaque as CAD-RADS 1, with stenosis of $\geq$25 % and < 50 % as CAD-RADS 2, stenosis of $\geq$50 and < 70 % as CAD-RADS 3, and with stenosis $\geq$70 % as CAD-RADS 4–5.

### 2.5. Statistical analysis

All statistical analysis was performed in R [18], version 4.2.2. Statistical significance was defined as two-tailed $p < 0.05$. Test for normality was performed using visual examination of histograms and the Shapiro-Wilk test. As continuous data was not normally distributed, the median with its interquartile range is reported. Categorical data is reported as percentages. The Mann-Whitney *U* test was used to explore differences in continuous variables between groups, while the Fisher exact test was used to explore differences between groups for categorical variables. Fisher's test was used for pairwise comparison of outcome variables between CAD-RADS groups for each sex. The Mantel-Haenszel test was performed for comparison of trends over CAD-RADS groups between sexes. To further confirm differences in trend over CAD-RADS groups, Poisson regression with introduction of a quadratic term was performed.

Linear regression analysis was performed for total plaque volume as an outcome of age, with Kendall's Tau calculated. Uni- and multivariable Cox regression analysis was performed for the presence of MI and ACS. All variables of potential interest were included in the univariable analysis, whereas stepwise multivariable analysis was restricted to the variables being statistically significant in the univariable analysis. Gradient Boosting Machine (GBM) analysis with 80 %/20 % split for training/evaluation and n-fold cross-validation for finding the optimal number of trees was performed with variables significant in univariable analysis to identify the relative contribution of variables to the explanation of MI and ACS. Effects from differences in follow-up times were explored with Kaplan-Meier curves and by normalizing events to patient years of follow-up. All analyses except for the GBM analyses were performed with the data split for sex.

## 3. Results

### 3.1. Patient characteristics

There were 1316 women (58 %) and 955 men (42 %) in the selected cohort. The median age of the women was generally higher in the cohort, and statistically significantly higher in all CAD-RADS groups except 0 and 3 **[**Table 1**]**. There were however no statistically significant differences in age between patients with MI or ACS and without events in either sex. The proportion of smokers was higher in men in all CAD-RADS groups except 0 and 4. Other baseline characteristics were not significantly different between the sexes, except for a slightly higher prevalence of dyslipidemia in women in CAD-RADS group 2.

**Table 1**
Clinical background data and AI-QCT findings in men ($n = 955$) and women ($n = 1316$) stratified by CADRADS 2.0. Men are presented in the four left columns, women in the four right columns. The order among columns by sex is from left to right: no events, myocardial infarction (MI), acute coronary syndrome (ACS: MI or unstable angina), and MI, ACS or death. All continuous numerical data is presented as the median with its interquartile range in parentheses. Categorical data is presented as percentage with counts in parentheses. Significance ($p < 0.05$) is denoted with "A", borderline significance with "a" for comparison between sexes, and "B" and "b" respectively for comparison between groups with and without events by sex. Abbreviations are explained in a footnote.

| | Men (n = 955) | | | | | | | | Women (n = 1316) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No events | | MI | | ACS | | MI, ACS or death | | No events | | MI | | ACS | | MI, ACS or death | |
| CAD-RADS 0 | $n = 14$ | | $n = 0$ | | n = 0 | | $n = 0$ | | $n = 82$ | | n = 0 | | n = 0 | | n = 1 | |
| Age [years] | 52.50 | (47.8–55.2) | | | | | | | 58.00 | (52–63) | | | | | | |
| BMI | 27.44 | (24.5–30.6) | | | | | | | 26.35 | (22.8–30.7) | | | | | | |
| Smokers [%] | 28.57 | (n = 4) | | | | | | | 7.23 | ($n = 6$) | | | | | | |
| Diabetes, any [%] | 28.57 | ($n = 4$) | | | | | | | 18.07 | ($n = 15$) | | | | | | |
| Prediabetes [%] | 14.29 | ($n = 2$) | | | | | | | 8.43 | ($n = 7$) | | | | | | |
| Hypertension [%] | 21.43 | (n = 3) | | | | | | | 28.92 | ($n = 24$) | | | | | | |
| Dyslipidemia [%] | 57.14 | (n = 8) | | | | | | | 55.42 | (n = 46) | | | | | | |
| Angina, typical [%] | 7.14 | (n = 1) | | | | | | | 19.28 | ($n = 16$) | | | | | | |
| CAD-RADS 1 | $n = 364$ | | n = 4 | | $n = 5$ | | $n = 19$ | | $n = 681$ | | n = 7 | | n = 9 | | $n = 45$ | |
| Age [years][A] | 57.00 | (49–62) | 53.50 | (48–63.2) | 58 | (49–69) | 61.00 | (55.5–73) | 62.00 | (56–68) | 64.00 | (61–72) | 64 | (61–72) | 68.00[B] | (63–72) |
| BMI | 27.19 | (24.8–30) | 24.77 | (23.5–25.2) | 24.86 | (24.7–25.5) | 26.10 | (24.7–30.1) | 27.50 | (24.4–31.3) | 29.40 | (23.7–29.7) | 29.4 | (23.4–29.9) | 27.40 | (23.7–32.1) |
| Smokers [%][A] | 17.03 | ($n = 62$) | 50.00 | (n = 2) | 40 | (n = 2) | 26.32 | (n = 5) | 9.54 | ($n = 65$) | 0.00 | (n = 0) | 0 | (n = 0) | 4.44 | ($n = 2$) |
| Diabetes, any [%] | 25.27 | ($n = 92$) | 0.00 | (n = 0) | 20 | (n = 1) | 31.58[b] | (n = 6) | 23.20 | ($n = 158$) | 14.29 | (n = 1) | 22.22 | (n = 2) | 28.89 | (n = 13) |
| Prediabetes [%] | 14.29 | ($n = 52$) | 0.00 | (n = 0) | 20 | (n = 1) | 5.26[b] | (n = 1) | 11.75 | ($n = 80$) | 14.29 | (n = 1) | 11.11 | (n = 1) | 15.56 | (n = 7) |
| Hypertension [%] | 45.88 | ($n = 167$) | 75.00 | (n = 3) | 80 | (n = 4) | 73.68[B] | (n = 14) | 49.49 | ($n = 337$) | 71.43 | (n = 5) | 77.78 | (n = 7) | 64.44[B] | ($n = 29$) |
| Dyslipidemia [%] | 57.42 | ($n = 209$) | 50.00 | (n = 2) | 60 | (n = 3) | 57.89 | ($n = 11$) | 59.18 | ($n = 403$) | 57.14 | (n = 4) | 44.44 | (n = 4) | 62.22 | ($n = 28$) |
| Angina, typical [%] | 14.01 | ($n = 51$) | 50.00 | (n = 2) | 60 | (n = 3) | 21.05 | (n = 4) | 21.15 | ($n = 144$) | 14.29 | (n = 1) | 22.22 | (n = 2) | 20.00 | (n = 9) |
| TPV [$mm^3$][A] | 57.65 | (26.9–108.5) | 81.50 | (61.3–147) | 85.4 | (77.6–86.2) | 85.40 | (51.6–110) | 32.70 | (15.1–60.8) | 69.60 | (35.9–102.8) | 50.4 | (38.7–92.4) | 67.30[B] | (36.3–93.7) |
| PAV [%][A] | 1.50 | (0.7–2.8) | 2.25 | (1.6–5.2) | 2.50 | (2.0–2.7) | 2.70 | (1.5–3.8) | 1.20 | (0.6–2.2) | 2.20 | (1.3–4.1) | 2.10 | (1.3–3.7) | 2.00[B] | (1.2–4.0) |
| Stenosis by diam. Max. [%][a] | 12.00 | (7.0–18.0) | 19.00 | (15.0–19.8) | 19.00 | (17.0–19.0) | 15.00 | (8.5–20.0) | 10.00 | (5.0–16.0) | 14.00 | (5.0–19.5) | 11.00 | (7.0–16.0) | 14.00 | (8.0–18.0) |
| Stenosis ≥50 %, any vessel [%] | 0.00 | (n = 0) | 0.00 | (n = 0) | 0 | (n = 0) | 0.00 | (n = 0) | 0.00 | (n = 0) | 0.00 | (n = 0) | 0 | (n = 0) | 0.00 | (n = 0) |
| CAD-RADS 2 | $n = 185$ | | n = 8 | | $n = 10$ | | $n = 37$ | | $n = 260$ | | n = 6 | | n = 8 | | $n = 31$ | |
| Age [years][A] | 63.00 | (57–70) | 58.50 | (55–65.2) | 58.5 | (55.2–62.8) | 63.00 | (59–71) | 66.00 | (60–71) | 67.50 | (64.8–71) | 69.00 | (66.2–72) | 70.00[B] | (67–75) |
| BMI | 27.18 | (25–30.3) | 27.10 | (26.4–28.2) | 27.3 | (26.9–30.4) | 27.10 | (25.4–32.7) | 28.30 | (24.8–32.7) | 28.80 | (23.2–29) | 28.80 | (22.8–29.9) | 25.33 | (23–28.2) |
| Smokers [%][A] | 17.84 | (n = 33) | 12.50 | (n = 1) | 10 | (n = 1) | 16.22 | (n = 6) | 7.69 | (n = 20) | 0.00 | (n = 0) | 0 | (n = 0) | 12.90 | (n = 4) |
| Diabetes, any [%] | 33.51 | (n = 62) | 12.50 | (n = 1) | 20 | (n = 2) | 27.03 | (n = 10) | 32.69 | ($n = 85$) | 16.67 | (n = 1) | 25 | (n = 2) | 19.35 | (n = 6) |
| Prediabetes [%] | 13.51 | ($n = 25$) | 12.50 | (n = 1) | 20 | (n = 2) | 13.51 | (n = 5) | 16.54 | ($n = 43$) | 0.00 | (n = 0) | 12.5 | (n = 1) | 6.45 | (n = 2) |
| Hypertension [%][a] | 59.46 | ($n = 110$) | 50.00 | (n = 4) | 60 | (n = 6) | 67.57[B] | (n = 25) | 70.38 | ($n = 183$) | 50.00 | (n = 3) | 50 | (n = 4) | 58.06 | (n = 18) |
| Dyslipidemia [%][A] | 66.49 | ($n = 123$) | 75.00 | (n = 6) | 60 | (n = 6) | 62.16 | ($n = 23$) | 73.46 | ($n = 191$) | 50.00 | (n = 3) | 62.5 | (n = 5) | 58.06[b] | (n = 18) |
| Angina, typical [%] | 20.54 | ($n = 38$) | 37.50 | (n = 3) | 30 | (n = 3) | 24.32 | (n = 9) | 30.00 | ($n = 78$) | 33.33 | (n = 2) | 37.5 | (n = 3) | 25.81 | (n = 8) |
| TPV [$mm^3$][A] | 247.60 | (156.3–366.0) | 296.20 | (226.5–403.9) | 290.8 | (170–360.8) | 328.90[B] | (245.4–676.8) | 136.80 | (81.8–258.4) | 210.05 | (141.4–310.9) | 167.75 | (139.1–282) | 264.80[B] | (149.5–380) |
| PAV [%][A] | 7.00 | (4.1–10.9) | 9.85 | (5.7–12.8) | 8.30 | (4.3–11.2) | 9.30 | (6.5–16.7) | 5.20 | (3.1–9.9) | 8.35 | (6.1–11.4) | 6.10 | (4.9–10.9) | 7.50[B] | (5.9–13.7) |
| Stenosis by diam. Max. [%] | 33.00 | (29.0–38.0) | 39.00 | (30.8–45.8) | 36.50 | (31.5–44.5) | 37.00 | (30.0–43.0) | 33.00 | (29.0–40.0) | 38.50 | (33.3–42.3) | 34.50 | (30.0–40.8) | 36.00 | (31.0–43.0) |
| Stenosis ≥50 %, any vessel [%] | 0.00 | (n = 0) | 0.00 | (n = 0) | 0 | (n = 0) | 0.00 | (n = 0) | 0.00 | (n = 0) | 0.00 | (n = 0) | 0 | (n = 0) | 0.00 | (n = 0) |
| CAD-RADS 3 | n = 123 | | n = 7 | | n = 15 | | $n = 35$ | | $n = 118$ | | n = 15 | | $n = 21$ | | $n = 32$ | |
| Age [years] | 66.00 | (60–70) | 63.00 | (60.5–71.5) | 65 | (60.5–71.5) | 65.00 | (60–70.5) | 69.00 | (63.2–73) | 72.00 | (61.5–77) | 70 | (62–75) | 70.00 | (66–78) |
| BMI | 27.35 | (24.9–30.5) | 28.80 | (27.8–34.6) | 27.75 | (26.3–30) | 27.75 | (25.7–29.3) | 29.60 | (25.8–33.1) | 26.85 | (23.6–29.3) | 27.42 | (24.4–29) | 27.42 | (24.2–29.2) |
| Smokers [%][A] | 14.63 | (n = 18) | 0.00 | (n = 0) | 6.67[b] | (n = 1) | 14.29[B] | (n = 5) | 12.71 | (n = 15) | 20.00 | (n = 3) | 19.05 | (n = 4) | 18.75 | (n = 6) |
| Diabetes, any [%] | 42.28 | (n = 52) | 28.57 | (n = 2) | 20 | (n = 3) | 40.00 | (n = 14) | 38.98 | (n = 46) | 33.33 | (n = 5) | 28.57 | (n = 6) | 31.25 | (n = 10) |
| Prediabetes [%] | 18.70 | (n = 23) | 14.29 | (n = 1) | 13.33 | (n = 2) | 11.43 | (n = 4) | 15.25 | (n = 18) | 13.33 | (n = 2) | 14.29 | (n = 3) | 12.50 | (n = 4) |
| Hypertension [%][a] | 67.48 | ($n = 83$) | 71.43 | (n = 5) | 80 | (n = 12) | 65.71 | (n = 23) | 75.42 | ($n = 89$) | 80.00 | (n = 12) | 80.95 | ($n = 17$) | 78.13 | (n = 25) |

(*continued on next page*)

**Table 1** (*continued*)

| | Men (n = 955) | | | | | | Women (n = 1316) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | No events | | MI | | ACS | MI, ACS or death | No events | | MI | | ACS | MI, ACS or death |
| Dyslipidemia [%] | 68.29 | (*n* = 84) | 85.71 | (n = 6) | 66.67 | (n = 10) | 62.86 | (*n* = 22) | 74.58 | (*n* = 88) | 86.67 | (n = 13) | 80.95 | (n = 17) | 71.88 | (n = 23) |
| Angina, typical [%] | 30.08 | (n = 37) | 28.57 | (n = 2) | 40 | (n = 6) | 40.00 | (n = 14) | 22.03 | (n = 26) | 40.00 | (n = 6) | 38.10 | (n = 8) | 34.38 | (n = 11) |
| TPV [$mm^3$]$^A$ | 507.40 | (310.2–782.5) | 440.70 | (322.1–788.9) | 436 | (282.2–730.2) | 496.50 | (272.2–990.6) | 284.05 | (203–507) | 788.90 | (273.6–1045.2) | 627.3 | (280.8–968.3) | 525.55$^B$ | (289.9–832.2) |
| PAV [%]$^a$ | 14.20 | (8.9–22.9) | 15.90 | (10.5–20.3) | 13.80 | (10.1–23.3) | 15.90 | (9.2–26.7) | 11.90 | (7.1–16.8) | 17.80 | (13.6–31.7) | 17.80 | (12.8–29.7) | 15.85$^B$ | (13.7–24.0) |
| Stenosis by diam. Max. [%] | 57.00 | (52.5–62.0) | 59.00 | (56.5–61.0) | 56.00 | (54.0–61.0) | 55.00 | (53.0–60.0) | 55.00 | (52.0–59.8) | 56.00 | (54.0–60.0) | 56.00 | (54.0–60.0) | 56.00 | (53.8–61.0) |
| Stenosis ≥50 %, any vessel [%] | 100.00 | (n = 123) | 100.00 | (n = 7) | 100 | (*n* = 15) | 100.00 | (n = 35) | 100.00 | (n = 118) | 100.00 | (n = 15) | 100 | (n = 21) | 100.00 | (n = 32) |
| CAD-RADS 4–5 | *n* = 136 | | n = 18 | | n = 24 | *n* = 42 | *n* = 53 | | n = 3 | | n = 8 | | n = 13 | | | |
| Age [years]$^A$ | 63.00 | (57–69) | 67.00 | (58.2–71) | 68.5 | (58.8–71.5) | 68.00$^b$ | (61.5–73) | 68.00 | (63–73) | 64.00 | (63–67.5) | 67.5 | (63.5–71.5) | 64.00 | (62–73) |
| BMI | 27.80 | (24.9–30.1) | 27.8 | (26.2–32.4) | 27.8 | (26.1–31.9) | 27.11 | (25.3–30.3) | 26.34 | (24.6–29.9) | 28.35 | (28.1–28.6) | 27.9 | (21.5–28.8) | 26.10 | (21.1–29.3) |
| Smokers [%] | 14.71 | (n = 20) | 22.22 | (n = 4) | 16.67 | (n = 4) | 14.29 | (n = 6) | 13.21 | (n = 7) | 33.33 | (n = 1) | 12.5 | (n = 1) | 23.08 | (n = 3) |
| Diabetes, any [%] | 36.03 | (*n* = 49) | 77.78$^B$ | (n = 14) | 66.67$^b$ | (n = 16) | 61.90$^B$ | (n = 26) | 30.19 | (n = 16) | 33.33 | (n = 1) | 25 | (n = 2) | 38.46 | (n = 5) |
| Prediabetes [%] | 18.38 | (n = 25) | 33.33$^B$ | (n = 6) | 25 | (n = 6) | 21.43$^B$ | (n = 9) | 16.98 | (n = 9) | 0.00 | (n = 0) | 12.5 | (n = 1) | 23.08 | (n = 3) |
| Hypertension [%] | 64.71 | (n = 88) | 83.33 | (n = 15) | 75 | (n = 18) | 76.19 | (n = 32) | 54.72 | (n = 29) | 100.00 | (n = 3) | 87.5 | (n = 7) | 69.23 | (n = 9) |
| Dyslipidemia [%] | 74.26 | (*n* = 101) | 83.33 | (n = 15) | 83.33 | (n = 20) | 69.05$^B$ | (n = 29) | 71.70 | (n = 38) | 100.00 | (*n* = 3) | 87.5 | (n = 7) | 69.23 | (n = 9) |
| Angina, typical [%] | 32.35 | (*n* = 44) | 44.44 | (n = 8) | 41.67 | (n = 10) | 35.71 | (n = 15) | 33.96 | (n = 18) | 33.33 | (n = 1) | 50 | (n = 4) | 30.77 | (n = 4) |
| TPV [$mm^3$]$^A$ | 542.65 | (297.6–1010.9) | 756.25 | (618.3–1024) | 711.5 | (612.2–1009.2) | 818.90$^B$ | (618.3–1121.9) | 307.40 | (204.1–534.7) | 340.00 | (225.3–797.6) | 230.25 | (113.1–879.4) | 335.50 | (113.9–805.3) |
| PAV [%] | 15.70 | (9.1–26.0) | 23.20 | (19.1–25.9) | 22.25 | (18.0–25.6) | 23.35$^B$ | (19.1–28.7) | 12.00 | (7.8–20.2) | 10.90 | (7.5–24.4) | 9.05 | (5.4–26.1) | 10.90 | (5.8–22.1) |
| Stenosis by diam. Max. [%] | 77.00 | (72.0–96.3) | 73.00 | (72.0–75.0) | 73.50 | (72.0–78.0) | 74.00 | (72.0–86.3) | 77.00 | (74.0–100.0) | 73.00 | (71.5–74.0) | 73.00 | (72.3–75.3) | 74.00 | (73.0–78.0) |
| Stenosis ≥50 %, any vessel [%] | 100.00 | (n = 136) | 100.00 | (n = 18) | 100 | (n = 24) | 100.00 | (n = 42) | 100.00 | (n = 53) | 100.00 | (n = 3) | 100 | (n = 8) | 100.00 | (n = 13) |

BMI = body mass index, TPV = total plaque volume, PAV = percent atheroma volume

### 3.2. Imaging results

Few patients were free from atherosclerosis based on AI-QCT analysis, with only 14 men (1.5 %) and 83 women (6.3 %) having findings conforming to CAD-RADS 0 **[**Table 2**]**. A total of 383 men (40.1 %) and 726 women (55.2 %) had findings consistent with CAD-RADS 1, while a total of 222 men (22.5 %) and 291 women (22.1 %) had findings consistent with CAD-RADS 2. CAD-RADS of 3 was established in 158 men (16.5 %) and 150 women (11.4 %), CAD-RADS of 4 or higher in 178 men (18.6 %) and 66 women (5.0 %). Obstructive CAD, i.e., CAD-RADS of 3 or higher was thus present in 336 men (35.1 %) and 216 women (16.4 %). Agreement between AI-QCT and visual, clinical reading in classification of obstructive CAD was 85.25 %, with 552 versus 695 cases.

Total plaque volume was significantly higher in men in all CAD-RADS >0 **[**Table 1**]**. Also, men showed significantly higher volumes of NCP and LDP across CAD-RADS >0. Notably, LDP, when normalized to vessel volume, was significantly higher in men in all CAD-RADS >0, whereas no substantial differences were found between sexes with regards to CP (plaque components omitted in Table 1).

Total plaque volume showed a moderate increase with age in both sexes on linear regression **[**Fig. 1a and b**]**, and a positive correlation with Kendall's tau being 0.29 in men and 0.28 in women, $p < 0.001$ for both. Of the plaque components, CP had the strongest correlation to age **[**Fig. 1c and d**]** with Kendall's tau of 0.33 in men and 0.31 in women, p < 0.001 for both. Plaque composition, when stratified by age groups, showed a relative increase in CP fraction with age in both sexes **[**Fig. 2a and b**]**. The fraction of LDP increased over CAD-RADS groups in both sexes, although accounting for the smallest relative volume **[**Fig. 3a and b**]**.

### 3.3. Long-term clinical outcome

Data on clinical outcomes was complete except for three patients lost to follow-up, with a median follow-up of 7.3 years. No cardiac events were recorded in patients belonging to CAD-RADS group 0, however one woman died from non-cardiac causes (cancer).

In patients with non-obstructive CAD (CAD-RADS 1 or 2), a total of 12 men (2.0 %) and 13 women (1.3 %) suffered MI, while ACS (MI or unstable angina) was diagnosed in 15 men (2.5 %) and 17 women (1.7 %). Among all patients with CAD, i.e., CAD-RADS ≥1, a total of 37 men (3.9 %) and 31 women (2.5 %) had MI, while ACS was experienced by 54 men (5.7 %) and 46 women (3.7 %).

Significantly higher cardiac event rates were found in men with increasing severity of atherosclerosis, showing the highest event rate in CAD-RADS group 4 **[**Fig. 4a**]**, with 1.38 cases of MI and 1.89 cases of ACS per 100 person years. In women, the highest event rate was found among patients in CAD-RADS group 3 **[**Fig. 4b**]**, with 1.46 cases of MI and 2.07 cases of ACS per 100 person years. Pairwise Fisher's test across CAD-RADS-groups showed strong significance for rates of both MI and ACS in CAD-RADS 4 in men ($p < 0.001$) and CAD-RADS 3 in women (p < 0.001) being different from CAD-RADS 1. The Mantel-Haenszel test confirmed significant differences in the trend over CAD-RADS groups in event rates also between sexes (p < 0.001). Poisson regression with a quadratic term introduced for women also confirmed that the trend over CAD-RADS groups in women was not monotonic (quadratic estimate:

**Table 2**
Distribution of CAD-RADS categories by sex.

| | CAD-RADS 0 | CAD-RADS 1 | CAD-RADS 2 | CAD-RADS 3 | CAD-RADS 4–5 |
|---|---|---|---|---|---|
| Men (n = 955) | 14 (1.5 %) | 383 (40.1 %) | 222 (23.2 %) | 158 (16.5 %) | 178 (18.6 %) |
| Women (*n* = 1316) | 83 (6.3 %) | 726 (55.2 %) | 291 (22.1 %) | 150 (11.4 %) | 66 (5.0 %) |

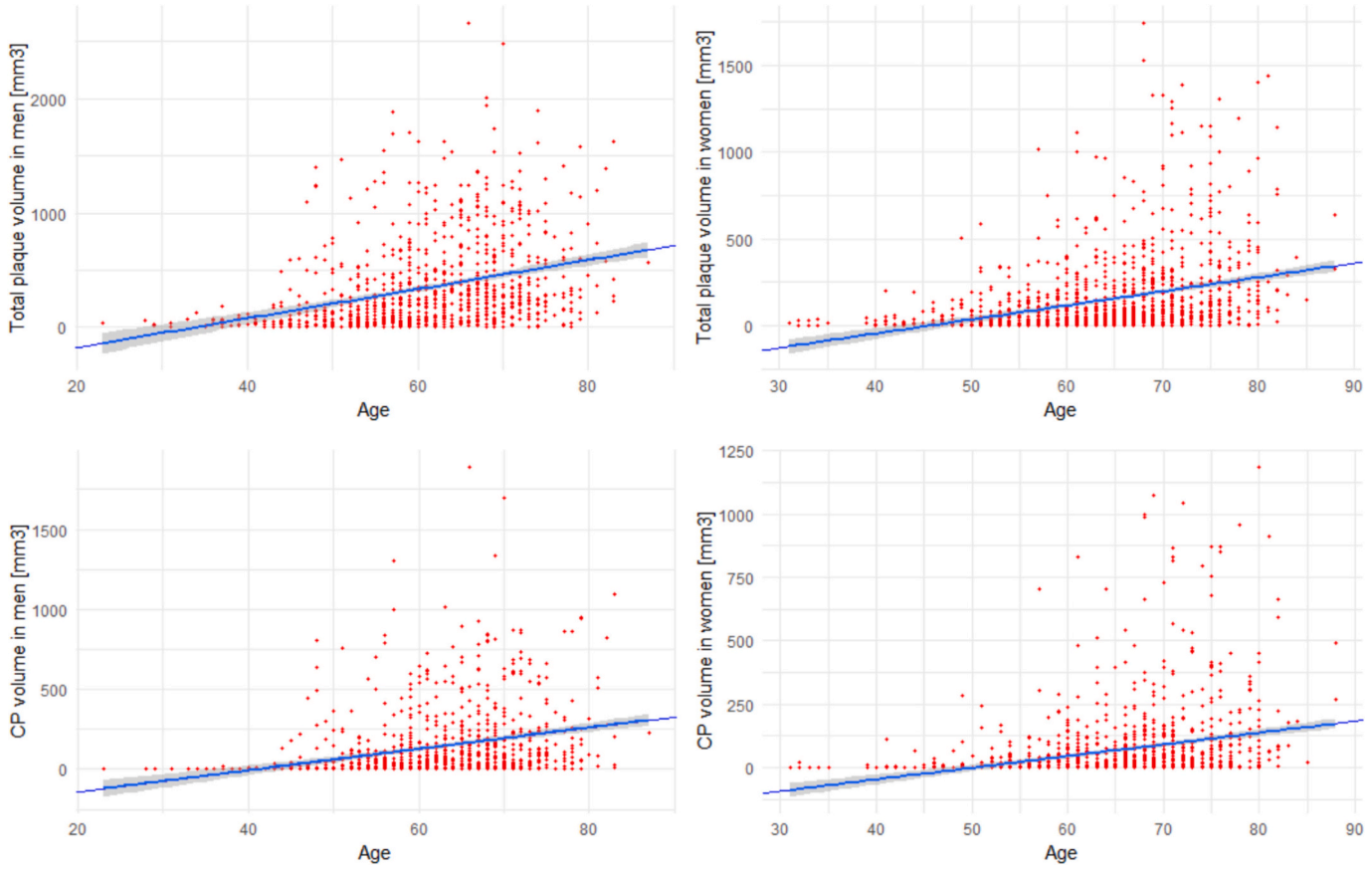



**Fig. 1.** a-b. Total plaque volume as a function of age in men (Kendall's tau 0.29, $p < 0.001$) and women (Kendall's tau 0.28, $p < 0.001$). c-d. Calcified plaque volume as a function of age in men (Kendall's tau 0.33, $p < 0.001$) and women (Kendall's tau 0.31, $p < 0.001$).

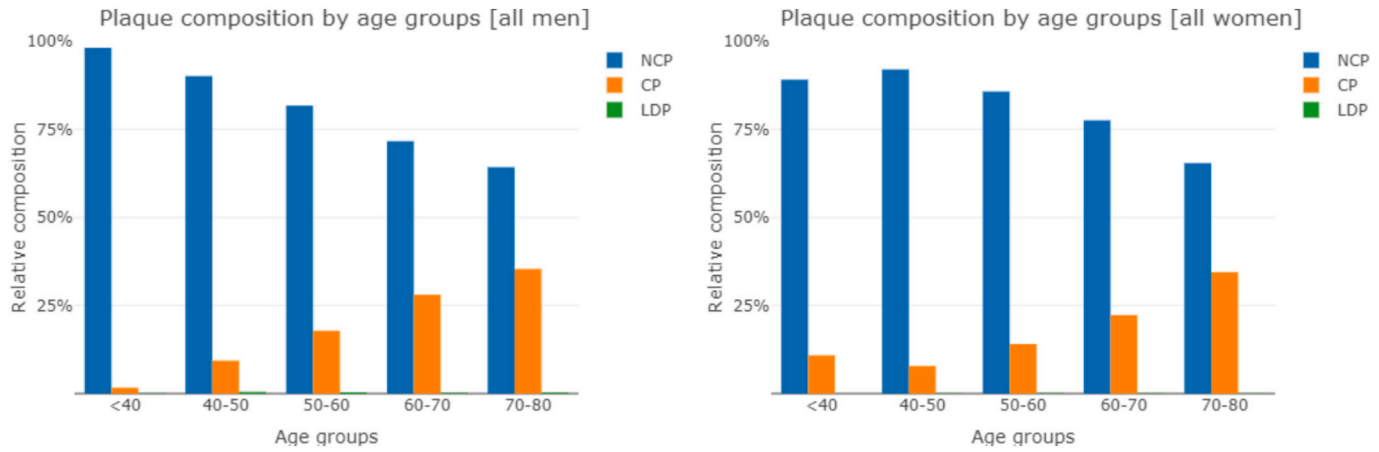



**Fig. 2.** a-b. Plaque composition by age groups in men and women classified as CAD-RADS 1–4+. Non-calcified (NCP), calcified (CP) and low-density plaques (LDP) are shown.

−0.41, $p = 0.03$).

Kaplan-Meier curves **[**Figs. 5a-d**]** showed a marked difference in event-free survival between CAD-RADS groups for MI, with CAD-RADS 4 having the steepest decline over time in men and CAD-RADS 3 in women. The tendency was similar, but less pronounced for ACS.

Of the 2271 patients included in the present study, a total of 213 underwent early revascularization, defined as either PCI or CABG within six months of the CTA. Patients with obstructive CAD or ambiguous CTA results performed downstream $H_2$ [15]O-PET (positron emission tomography) to measure myocardial perfusion, which then guided therapy towards early revascularization or medical treatment. For sensitivity purposes, statistical analyses were repeated after exclusion of all patients who underwent early revascularization, but no meaningful differences were observed in the results.

### 3.4. *Predictors of clinical outcome*

In univariable Cox regression for the binary outcome of MI, the following variables were significant in both sexes: stenosis by diameter, TPV, PAV, NCP volume, and CP volume. In women, but not men, LDP

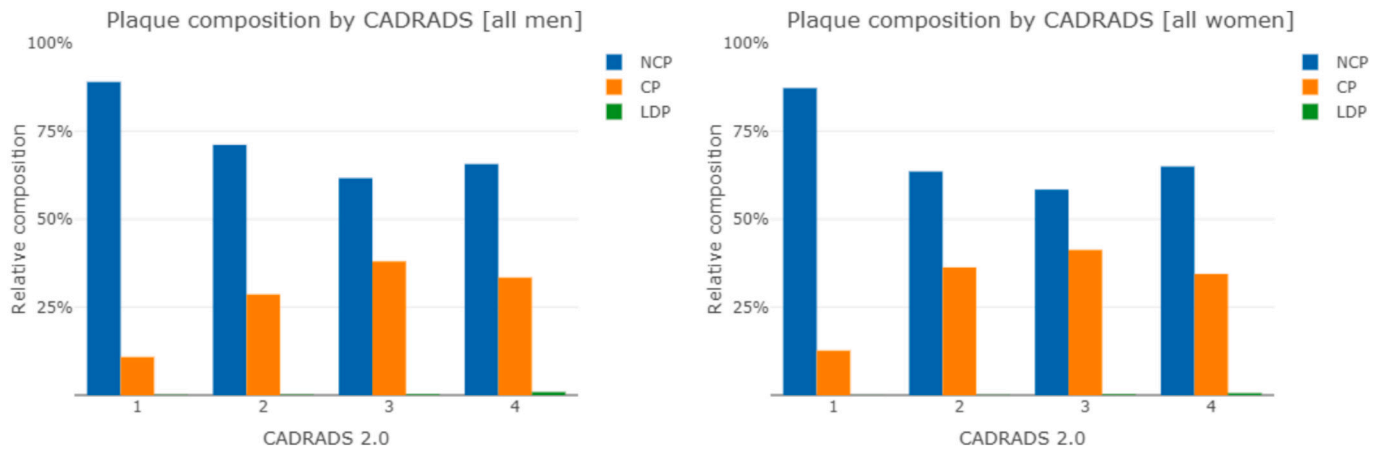



**Fig. 3.** a-b. Plaque composition by CAD-RADS groups in men and women classified as CAD-RADS 1–4+. Non-calcified (NCP), calcified (CP) and low-density plaques (LDP) are shown.

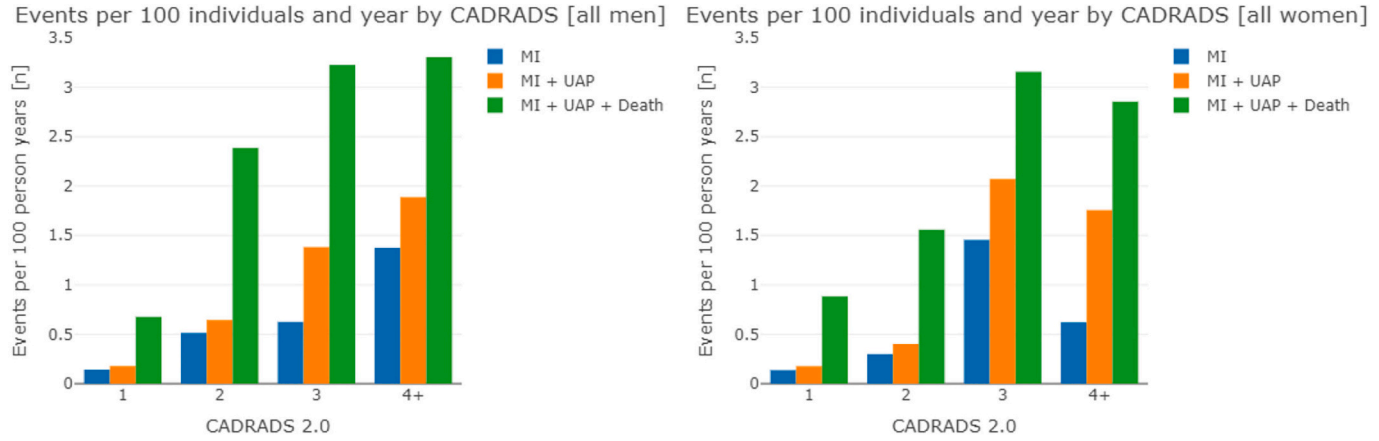



**Fig. 4.** a-b. Rate of events per 100 person years by CAD-RADS groups in men and women classified as CAD-RADS 1–4+. Myocardial infarction (MI), acute coronary syndrome (ACS) and death from any cause are shown.

volume and age were also significant [Table 3a].

In stepwise multivariable Cox regression, variables significant in univariable analysis were added in the order: stenosis, TPV, PAV, NCP volume, LDP volume, CP volume, age [Table 3c].

Only stenosis remained significant after adding the second variable in men (HR 1.021; $p = 0.002$; CI 1.0074–1.034) whereas only TPV remained significant in women (HR per quartile increase in TPV 1.34; $p < 0.001$; CI 1.16–1.54). This translates into a 2.1 % increase in MI risk per 1 % increase in stenosis by diameter in men, and a 34 % increase in MI risk for every quartile of increase in TPV in women. In men, stenosis still remained significant after adding PAV (HR 1.017; $p = 0.017$; 1.0030–1.031), whereas in women no significance was retained.

Analyses were repeated for ACS as outcome. In univariable analysis the following variables were significant in both sexes: stenosis by diameter, TPV, PAV, NCP volume, CP volume and age. In women, but not men, LDP volume was also significant [Table 3b]. In multivariable analysis [Table 3d] stenosis retained significance in both men (HR 1.023; CI 1.012–1.034; $p < 0.001$) and women after adding TPV, but TPV had a lower $p$-value in women (HR 1.26 per quartile increase in TPV; CI 1.12–1.42; $p < 0.001$). The following interactions were separately tested in Cox regression: [stenosis + TPV × sex] ($p = 0.055$), [stenosis × sex] ($p = 0.39$) and [TPV × sex] ($p = 0.019$). These results suggest that TPV rather than stenosis severity is the driver behind the sex differences seen in the regression analyses.

For sensitivity reasons, all regression analyses were repeated with logistic regression with similar results (not presented).

In GBM analysis [Fig. 6a and b] variables significant in univariable analysis were included, with the exception of CP, which showed the strongest co-linearity with age. TPV had the highest relative influence followed by stenosis for the explanation of MI (31.1 % and 19.1 % respectively), while stenosis and TPV had the highest relative influence for ACS (35.7 % and 27.4 % respectively). The AUC for the model's binary predictions of MI and ACS was 0.829 and 0.813 respectively, indicating good discrimination. For sensitivity purposes, analyses were repeated split by sex (not reported graphically), where stenosis severity remained in second and first place respectively for MI and UAP in men, while TPV had the highest relative influence in women for both MI and UAP.

## 4. Discussion

In this large observational study of patients with suspected obstructive coronary artery disease, we utilized AI-enabled quantitative computed tomography angiography to assess sex differences in plaque burden and their prognostic implications. Our findings emphasize important sex-specific differences in both the extent and composition of atherosclerotic plaques, as well as in clinical outcomes over a median follow-up of more than 7 years.

As expected, women had a significantly lower prevalence of obstructive CAD compared to men, despite being older (overall median age of 64 vs. 61). Notably, women had significantly lower TPV, NCP, and LDP across all CAD-RADS groups. Despite this, the cumulative rates of

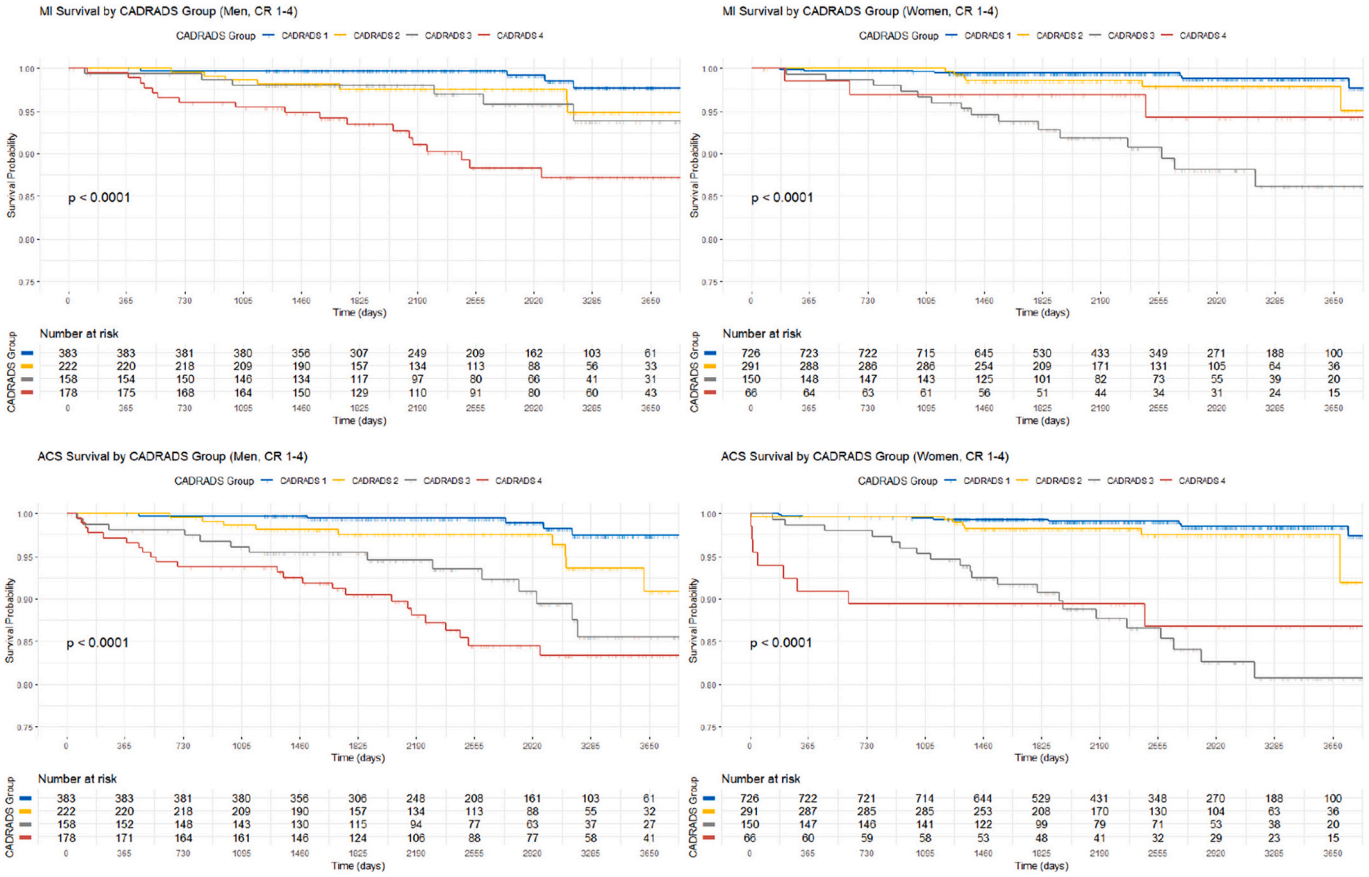



**Fig. 5.** a-b. Kaplan-Meier curves for event free survival of myocardial infarction (MI) in men and women by CAD-RADS groups. c-d. Kaplan-Meier curves for event free survival of acute coronary syndrome (ACS) in men and women by CAD-RADS groups.

**Table 3a**
Results of univariable Cox regression analyses in men and women with MI as outcome and clinical data and plaque characteristics as predictors. The hazard ratio with its 95 % confidence interval for total (TPV), non-calcified (NCP), low-density (LDP) and calcified (CP) plaque volumes is shown per quartile increase in the underlying variables.

| Outcome: MI | Men, univariable cox regression | | | | Women, univariable cox regression | | | |
|---|---|---|---|---|---|---|---|---|
| | HR | 95 % CI | *p*-value | Sig. | HR | 95 % CI | p-value | Sig. |
| Age | 1.03 | 1.00–1.07 | 0.0761 | NS | 1.09 | 1.04–1.14 | 3.00E-04 | Sig. |
| BMI | 1.04 | 0.97–1.12 | 0.251 | NS | 0.98 | 0.91–1.05 | 0.5097 | NS |
| Smoking | 1.22 | 0.83–1.79 | 0.318 | NS | 0.95 | 0.62–1.46 | 0.8198 | NS |
| Diabetes | 0.95 | 0.77–1.17 | 0.6501 | NS | 1.02 | 0.81–1.29 | 0.8545 | NS |
| Hypertension | 0.63 | 0.38–1.04 | 0.0722 | NS | 0.84 | 0.48–1.46 | 0.5365 | NS |
| Dyslipidemia | 0.62 | 0.35–1.10 | 0.1033 | NS | 0.98 | 0.53–1.79 | 0.9455 | NS |
| Stenosis by diameter | 1.02 | 1.01–1.04 | < 0.0001 | Sig. | 1.03 | 1.02–1.04 | < 0.0001 | Sig. |
| TPV (per quartile) | 1.57 | 1.26–1.96 | 1.00E-04 | Sig. | 1.46 | 1.31–1.62 | < 0.0001 | Sig. |
| PAV | 1.06 | 1.03–1.08 | < 0.0001 | Sig. | 1.09 | 1.06–1.11 | < 0.0001 | Sig. |
| NCP volume (per quartile) | 1.60 | 1.26–2.02 | 1.00E-04 | Sig. | 1.53 | 1.32–1.77 | < 0.0001 | Sig. |
| LDP volume (per quartile) | 1.01 | 1.00–1.02 | 0.208 | NS | 1.00 | 1.00–1.00 | 0.0204 | Sig. |
| CP volume (per quartile) | 1.26 | 1.10–1.45 | 8.00E-04 | Sig. | 1.20 | 1.14–1.27 | < 0.0001 | Sig. |

events (MI + ACS) were not negligible in women with non-obstructive CAD (2.2 % and 4.8 % in CAD-RADS groups 1 and 2) and the highest in women with 50–69 % stenosis (24 % in CAD-RADS group 3). This highlights the limitations of relying solely on luminal stenosis or anatomical severity as a predictor of risk, especially in women.

Upon long-term clinical follow-up (median 7.3 years), cardiac event rates in men increased over CAD-RADS groups, with the highest event rates found in CAD-RADS group 4–5 (≥ 70 % stenosis). In women, however, the highest cardiac event rates were found in CAD-RADS 3 (50–69 % stenosis). This indicates potential sex-specific thresholds for risk stratification. The trend was strongest for MI, with 1.46 cases of MI per 100 person years in CAD-RADS 3 in women as compared to 0.63 in men. When including unstable angina, the trend was somewhat attenuated, but remained statistically significant. Death from any (including non-cardiac) cause, as expected, was rather uniform in both sexes over CAD-RADS groups 2–4+, while being lower in CAD-RADS 1, plausibly explained by lower age in patients classified as CAD-RADS 1 compared to CAD-RADS groups 2–4+ (57 vs. 65 years in men and 62 vs. 68 years in women).

In men, stenosis severity emerged as the strongest independent predictor of both MI and ACS in Cox regression, whereas in women, TPV had the highest prognostic relevance. In GBM analysis, which is a machine-learning based approach, where a model providing the best discrimination is selected after dividing the data into a training and

**Table 3b**
Results of univariable Cox regression analyses in men and women with ACS as outcome and clinical data and plaque characteristics as predictors. The hazard ratio with its 95 % confidence interval for total (TPV), non-calcified (NCP), low-density (LDP) and calcified (CP) plaque volumes is shown per quartile increase in the underlying variables.

| Outcome: ACS | Men, univariable cox regression | | | | Women, univariable cox regression | | | |
|---|---|---|---|---|---|---|---|---|
| | HR | 95 % CI | p-value | Sig. | HR | 95 % CI | p-value | Sig. |
| Age | 1.04 | 1.01–1.07 | 0.0055 | Sig. | 1.08 | 1.04–1.12 | 1.00E-04 | Sig. |
| BMI | 1.02 | 0.96–1.09 | 0.4525 | NS | 0.96 | 0.90–1.03 | 0.2532 | NS |
| Smoking | 1.01 | 0.75–1.37 | 0.9246 | NS | 1.08 | 0.75–1.57 | 0.6735 | NS |
| Diabetes | 0.92 | 0.78–1.09 | 0.3226 | NS | 1.08 | 0.88–1.32 | 0.4758 | NS |
| Hypertension | 0.73 | 0.48–1.12 | 0.1491 | NS | 0.88 | 0.56–1.40 | 0.599 | NS |
| Dyslipidemia | 0.84 | 0.53–1.34 | 0.4658 | NS | 0.91 | 0.55–1.50 | 0.7172 | NS |
| Stenosis by diameter | 1.03 | 1.02–1.04 | < 0.0001 | Sig. | 1.03 | 1.02–1.04 | < 0.0001 | Sig. |
| TPV (per quartile increase) | 1.52 | 1.26–1.83 | < 0.0001 | Sig. | 1.44 | 1.32–1.57 | < 0.0001 | Sig. |
| PAV | 1.06 | 1.04–1.08 | < 0.0001 | Sig. | 1.09 | 1.06–1.11 | < 0.0001 | Sig. |
| NCP (per quartile increase) | 1.59 | 1.30–1.93 | < 0.0001 | Sig. | 1.51 | 1.33–1.71 | < 0.0001 | Sig. |
| LDP (per quartile increase) | 1.01 | 1.00–1.02 | 0.0829 | NS | 1.00 | 1.00–1.00 | 0.0016 | Sig. |
| CP (per quartile increase) | 1.23 | 1.09–1.39 | 9.00E-04 | Sig. | 1.20 | 1.14–1.25 | < 0.0001 | Sig. |

**Table 3c**
Results of sequential multivariable Cox regression analyses (step 1–3) in men and women with MI as outcome and clinical data and plaque characteristics as predictors. The significant variable or variable with the lowest p-value is shown for each step. For total (TPV) the HR is shown per quartile increase in the underlying variables.

| Outcome: MI | Men, stepwise multivariable cox regression | | | | Women, stepwise multivariable cox regression | | | |
|---|---|---|---|---|---|---|---|---|
| Model | Sign. | HR | 95 % CI | p-value | Sign. | HR | 95 % CI | p-value |
| Stenosis | Stenosis | 1.02 | 1.01–1.04 | < 0.0001 | Stenosis | 1.03 | 1.02–1.04 | < 0.0001 |
| Stenosis + TPV | Stenosis | 1.02 | 1.01–1.03 | 0.0021 | TPV | 1.34 | 1.16–1.54 | 1.00E-04 |
| Stenosis + TPV + PAV | Stenosis | 1.02 | 1.00–1.03 | 0.0172 | – | – | – | NS |

**Table 3d**
Results of sequential multivariable Cox regression analyses (step 1–3) in men and women with ACS as outcome and clinical data and plaque characteristics as predictors. The significant variable or variable with the lowest p-value is shown for each step. For total (TPV) the HR is shown per quartile increase in the underlying variables.

| Outcome: ACS | Men, stepwise multivariable cox regression | | | | Women, stepwise multivariable cox regression | | | |
|---|---|---|---|---|---|---|---|---|
| Model | Sign. | HR | 95 % CI | p-value | Sign. | HR | 95 % CI | p-value |
| Stenosis | Stenosis | 1.03 | 1.017–1.04 | < 0.0001 | Stenosis | 1.03 | 1.02–1.04 | < 0.0001 |
| Stenosis + TPV | Stenosis | 1.02 | 1.01–1.03 | < 0.0001 | TPV | 1.26 | 1.12–1.42 | 1.00E-04 |
| Stenosis + TPV + PAV | Stenosis | 1.02 | 1.01–1.03 | 0.0016 | Stenosis | 1.02 | 1.01–1.04 | 0.001 |

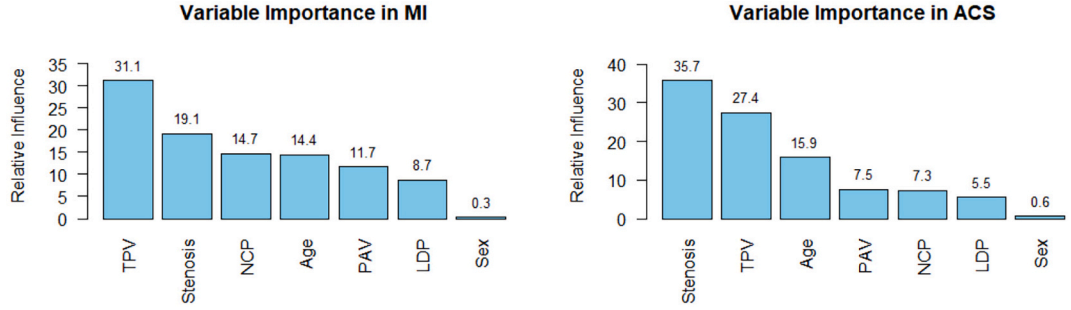



**Fig. 6.** a-b. Results of gradient boosting machine (GBM) analysis showing the relative importance of variables for the explanation of the binary outcome of myocardial infarction (MI) and acute coronary syndrome (ACS).

evaluation set, TPV and degree of stenosis had the highest overall relative influence on classification in the entire cohort. The lower relative importance of stenosis severity in women on analyses split by sex, which is accordant with our findings of higher event rates with lower CAD-RADS in women, may reflect differences in plaque biology and rupture potential, as well as in downstream myocardial response to ischemia.

Among the 1.5 % of men and 6.3 % of women who had no coronary atherosclerosis (CAD-RADS 0), no cardiac events, defined as MI or ACS, were registered. Although event rates per 100 person years were low in CAD-RADS 1 and 2 (corresponding to non-obstructive CAD), the number of events was not negligible, with MI occurring in 2.0 % of men and 1.3 % of women and ACS in 2.5 % of men and 1.7 % of women. This is to be compared with all patients with detectable CAD (CAD-RADS 1–4+), where 3.9 % of men and 2.5 % of women had MI, while 5.7 % of men and 3.7 % of women had ACS, i.e., numbers roughly twice as high. Altogether, a relatively large proportion of ACS occurred in patients with non-obstructive CAD (37 % in women and 27 % in men), which is consistent with previously reported findings [19].

Although AI-QCT offers granular and detailed morphological data,

we were not able to explain the discrepancy between sexes in the occurrence of MI and ACS based on plaque characteristics. In contrast to standard clinical CTA reading, invasive coronary angiography, and intravascular ultrasound, AI-QCT has the advantage of being non-invasive, as well as highly automatized, with arguably less reader-specific issues such as bias, or inter-reader variability [20]. Notably, AI-QCT has been reported to have a higher sensitivity than standard clinical reading for plaque detection in lower CAD-RADS groups [4]. Strong correlation between plaque volumes on AI-QCT and invasive intravascular ultrasound with near-infrared spectroscopy has been previously demonstrated [21], suggesting, that the method offers a potent tool for plaque analysis.

### 4.1. Clinical implications

The notion, that women are more likely to have adverse cardiac events with less advanced CAD, is not new [13] and has been suggested to reflect differences in the pathophysiology of MI between sexes, with an increased likelihood of plaque erosion in women as opposed to an increased likelihood of plaque rupture occurring in men [12]. The current results suggest that the underlying pathophysiological processes are too subtle to differentiate based on currently available plaque morphological features, such as those derived from AI-QCT. However, AI-QCT likely offers increased precision in the classification of morphological findings, especially among the lower categories of CAD-RADS, whereas routine clinical CTA reading usually is confined to the differentiation of obstructive from non-obstructive disease. CAD-RADS classification in patients with suspected CAD has been previously shown to have prognostic value in a study comprising nearly 10,000 patients with suspected CAD and a median follow-up of 4.3 years, although analyses were not stratified by sex [22]. Based on our findings, it is reasonable to expect, that reliable CAD-RADS classification would improve the accuracy in identifying high-risk individuals, especially among women. Conversely, identification of very-low-risk individuals, i.e., those with no demonstrable CAD (CAD-RADS 0), might be one of the advantages of AI-QCT.

The best predictors of MI on Cox regression were degree of stenosis in men and TPV in women, where specific interaction testing with respect to sex revealed that TPV is the driver of the difference. It is reasonable to assume, that there should be a relationship between the two entities, which is consistent with findings of a recent study by de Knegt et al. [23] They investigated 855 patients with CAD, roughly a third each being asymptomatic, having chest pain but no ACS and having ACS respectively, and found that non-obstructive plaques were the most important contributor to TPV, irrespective of which group the patient belonged to.

As expected, in both men and women, TPV increased with age, and the proportion of CP increased with age, however somewhat less overtly in women. Overall, plaque composition was heavily dominated by NCP. LDP, which could be considered a high-risk plaque type [24], was present in very low amounts in CAD-RADS 1–2, increasing in patients CAD-RADS 3 or higher, i.e., patients having obstructive CAD. This tendency was observed in both sexes, but neither differences in LDP nor CP explained the sex differences in event rate in overall regression and GBM-analyses. Statistical power might have been too low to demonstrate effects, when comparing between patients with and without events within the different CAD-RADS groups.

The women in our cohort were slightly older than the men (64 vs. 61 years), and were more numerous (1316 vs. 955). The higher age among women is likely a function of delayed onset of atherosclerosis in women to past menopause [14], while the relative oversampling of women might stem from increased longevity, a generally lower CAD burden in women with chest pain, and therefore a higher total exposure to CTA as the primary diagnostic procedure. A large prospective study by Mortensen et al. [7] including nearly 24,000 persons investigated for suspected CAD had a median age of 58 years, and 55 % were women (as compared to our 58 %). Also, they reported comparable overall prevalence of obstructive CAD (21.2 % in men and 21.3 % in women), with a slight skew towards women.

### 4.2. Strengths and limitations of the study

High quality imaging data paired with long-term follow-up data from a fairly large, real-world clinical cohort is the main strength of the present study. Another major strength is the use of an FDA-approved, AI-based model for standardization of detailed plaque analysis. Automatic measurements not only increase sensitivity for the detection of small lesions but are also likely to be more consistent over time and less sensitive to human errors and bias. AI-QCT has previously been extensively validated and compares well to expert visual reading. The sex-stratified analysis and application of advanced statistical modeling, including machine-learning models, further enhance the robustness and clinical relevance of our findings.

The main weakness of the present study is the comparatively small number of events, especially among patients with non-obstructive CAD, which limits sensitivity in a detailed analysis of plaque characteristics versus outcomes. The study cohort was derived from a single center and may not be generalizable to broader populations. Potentially, generalizability and comparability might also be limited by the fact that CT scanners of the 64-slice generation were used for image acquisition. However, diagnostic performance of AI-QCT in detecting obstructive CAD has previously been shown to be unaffected by commonly used scanning parameters and scanner types [25], matched by the excellent concordance between visual clinical reading and AI-QCT-based classification of obstructive and non-obstructive disease that we could ourselves verify. Furthermore, this population allowed for longer follow-up, a clear strength of our study. However unlikely it seems that our main conclusions would have been altered, had the images been acquired with contemporary scanners, small differences can be expected in results, and further exploration in future studies is warranted. While we adjusted for several clinical covariates, residual confounding cannot be excluded. Additionally, menopausal status was not available, limiting deeper insights into the hormonal effects on plaque morphology and outcomes in women. Although AI-QCT allows for detailed plaque quantification, it does not replace functional assessment or histopathological validation. Therefore, in future investigations, the addition of optical coherence tomography for identification of plaque erosion and rupture in culprit lesions could provide valuable insights, thereby possibly explaining sex differences.

## 5. Conclusions

This study demonstrates significant sex-related differences in coronary plaque characteristics and their relationship with long-term outcomes in patients with suspected obstructive CAD evaluated with CTA. Men had higher CAD burden than women by all metrics, while women showed fewer high-risk features but were not spared from events. Women had their highest risk of cardiac events at a lower level of CAD burden than men. Total plaque volume and the degree of maximal stenosis had the strongest association with events, with the latter having less impact in women. Notably, cardiovascular event rates were zero in patients free from CAD, and generally low in other non-obstructive CAD-RADS groups.

The relatively high event rates in women with moderate stenosis support more aggressive diagnostic and therapeutic strategies. The use of AI-QCT enables granular characterization of plaque beyond stenosis severity, which may be especially beneficial in women, where functional impairment may be disproportionate to anatomical disease.

## CRediT authorship contribution statement

**David Molnar:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation,

Formal analysis, Conceptualization. **Juhani Knuuti:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Jeroen J. Bax:** Writing – review & editing. **Antti Saraste:** Writing – review & editing, Conceptualization. **Teemu Maaniitty:** Writing – review & editing, Methodology, Data curation, Conceptualization.

## Funding

The study was funded by the Finnish Foundation for Cardiovascular Research, Finnish State Research Funding, and the Research Council of Finland. Cleerly, Inc. performed the image analysis without costs and provided an unrestricted research grant for the University of Turku. Dr. Molnar's work has been co-funded by the European Union's Horizon Europe Framework program for research and innovation 2021–2027 under the Marie Sklodowska-Curie grant agreement No. 101126611, the Swedish Medical Society, the Swedish Heart-Lung Foundation, the Swedish Heart Union and the Gothenburg Medical Society. Dr. Knuuti received consultancy fees from GE Healthcare and Synektik and speaker fees from Bayer, Lundbeck, Boehringer-Ingelheim, Pfizer and Siemens, outside of the submitted work. Dr. Bax received speaker fees from Abbott, outside of the submitted work. Dr. Saraste received consultancy fees from Astra Zeneca, Novo Nordisk and Pfizer, and speaker fees from Abbott, Astra Zeneca, BMS, Janssen and Pfizer outside of the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

## References

[1] M. Ferencik, T. Mayrhofer, S.B. Puchner, et al., Computed tomography-based high-risk coronary plaque score to predict acute coronary syndrome among patients with acute chest pain–results from the ROMICAT II trial, J. Cardiovasc. Comput. Tomogr. 9 (6) (2015) 538–545, https://doi.org/10.1016/j.jcct.2015.07.003.

[2] J.E. van Velzen, F.R. de Graaf, M.A. de Graaf, et al., Comprehensive assessment of spotty calcifications on computed tomography angiography: comparison to plaque characteristics on intravascular ultrasound with radiofrequency backscatter analysis, J. Nucl. Cardiol. 18 (5) (2011) 893–903, https://doi.org/10.1007/s12350-011-9428-2.

[3] M. Kolossvary, J. Karady, B. Szilveszter, et al., Radiomic features are superior to conventional quantitative computed tomographic metrics to identify coronary plaques with napkin-ring sign, Circ. Cardiovasc. Imaging 10 (12) (2017), https://doi.org/10.1161/CIRCIMAGING.117.006843.

[4] A.D. Choi, H. Marques, V. Kumar, et al., CT evaluation by artificial intelligence for atherosclerosis, stenosis and vascular morphology (CLARIFY): a multi-center, international study, J. Cardiovasc. Comput. Tomogr. 15 (6) (2021), https://doi.org/10.1016/j.jcct.2021.05.004.

[5] W.F. Griffin, A.D. Choi, J.S. Riess, et al., AI evaluation of stenosis on coronary CTA, comparison with quantitative coronary angiography and fractional flow reserve: a CREDENCE trial substudy, JACC Cardiovasc. Imaging 16 (2) (2023), https://doi.org/10.1016/j.jcmg.2021.10.020.

[6] C. Sama, A. Abdelhaleem, D. Velu, et al., Non-calcified plaque in asymptomatic patients with zero coronary artery calcium score: a systematic review and meta-analysis, J. Cardiovasc. Comput. Tomogr. 18 (1) (2024), https://doi.org/10.1016/j.jcct.2023.10.002.

[7] M.B. Mortensen, S. Gaur, A. Frimmer, et al., Association of age with the diagnostic value of coronary artery calcium score for ruling out coronary stenosis in symptomatic patients, JAMA Cardiol. 7 (1) (2022), https://doi.org/10.1001/jamacardio.2021.4406.

[8] A. Saraste, J. Knuuti, Prognosis of non-obstructive coronary plaques with high-risk CT morphology, Eur. Heart J. Cardiovasc. Imaging 15 (3) (2014) 255–256, https://doi.org/10.1093/ehjci/jet272.

[9] D.R. Obaid, P.A. Calvert, A. Brown, et al., Coronary CT angiography features of ruptured and high-risk atherosclerotic plaques: correlation with intra-vascular ultrasound, J. Cardiovasc. Comput. Tomogr. 11 (6) (2017), https://doi.org/10.1016/j.jcct.2017.09.001.

[10] S. Motoyama, M. Sarai, H. Harigaya, et al., Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome, J. Am. Coll. Cardiol. 54 (1) (2009) 49–57, https://doi.org/10.1016/j.jacc.2009.02.068.

[11] S. Motoyama, H. Ito, M. Sarai, et al., Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up, J. Am. Coll. Cardiol. 66 (4) (2015) 337–346, https://doi.org/10.1016/j.jacc.2015.05.069.

[12] A.J. Lansky, V.G. Ng, A. Maehara, et al., Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes, JACC Cardiovasc. Imaging 5 (3 SUPPL) (2012), https://doi.org/10.1016/j.jcmg.2012.02.003.

[13] J. Chandrasekhar, R. Mehran, Sex-based differences in acute coronary syndromes insights from invasive and noninvasive coronary technologies, JACC Cardiovasc. Imaging 9 (4) (2016), https://doi.org/10.1016/j.jcmg.2016.02.004.

[14] E. Hakamaa, S. Goebeler, M. Martiskainen, et al., Sex differences in coronary atherosclerosis during the pre- and postmenopausal period: the Tampere sudden death study, Atherosclerosis (2024) 390, https://doi.org/10.1016/j.atherosclerosis.2024.117459.

[15] R.C. Cury, J. Leipsic, S. Abbara, et al., CAD-RADS™ 2.0–2022 Coronary Artery Disease-Reporting and Data System: An Expert Consensus Document of the Society of Cardiovascular Computed Tomography (SCCT), the American College of Cardiology (ACC), the American College of Radiology (ACR), and the North America Society of Cardiovascular Imaging (NASCI), J Cardiovasc Comput Tomogr. 16 (6) (2022), https://doi.org/10.1016/j.jcct.2022.07.002.

[16] R.A. Byrne, X. Rossello, J.J. Coughlan, et al., 2023 ESC guidelines for the management of acute coronary syndromes, Eur. Heart J. 44 (38) (2023) 3720–3826, https://doi.org/10.1093/eurheartj/ehad191.

[17] S. Kajander, E. Joutsiniemi, M. Saraste, et al., Cardiac positron emission tomography/computed tomography imaging accurately detects anatomically and functionally significant coronary artery disease, Circulation 122 (6) (2010), https://doi.org/10.1161/CIRCULATIONAHA.109.915009.

[18] R_Core_Team, R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, Preprint posted online 2018, https://www.R-project.org/, 2025.

[19] U. Hoffmann, M. Ferencik, J.E. Udelson, et al., Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain, Circulation 135 (24) (2017) 2320–2332, https://doi.org/10.1161/CIRCULATIONAHA.116.024360.

[20] R. Bernardo, N.S. Nurmohamed, M.J. Bom, et al., Diagnostic accuracy in coronary CT angiography analysis: artificial intelligence versus human assessment, Open Heart. 12 (1) (2025) e003115, https://doi.org/10.1136/openhrt-2024-003115.

[21] H. Omori, H. Matsuo, S. Fujimoto, et al., Determination of lipid-rich plaques by artificial intelligence-enabled quantitative computed tomography using near-infrared spectroscopy as reference, Atherosclerosis (2023) 386, https://doi.org/10.1016/j.atherosclerosis.2023.117363.

[22] Z. Huang, S. Zhang, N. Jin, et al., Prognostic value of CAD-RADS classification by coronary CTA in patients with suspected CAD, BMC Cardiovasc. Disord. 21 (1) (2021), https://doi.org/10.1186/s12872-021-02286-x.

[23] M.C. de Knegt, J.J. Linde, P.E. Sigvardsen, et al., The importance of nonobstructive plaque characteristics in symptomatic and asymptomatic coronary artery disease, J. Cardiovasc. Comput. Tomogr. 18 (2) (2024), https://doi.org/10.1016/j.jcct.2024.01.014.

[24] M.C. Williams, J. Kwiecinski, M. Doris, et al., Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction, Circulation 141 (18) (2020), https://doi.org/10.1161/circulationaha.119.044720.

[25] R.A. Jonas, E. Barkovich, A.D. Choi, et al., The effect of scan and patient parameters on the diagnostic performance of AI for detecting coronary stenosis on coronary CT angiography, Clin. Imaging 84 (2022) 149–158, https://doi.org/10.1016/j.clinimag.2022.01.016.