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ORIGINAL PAPER

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

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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 (55.6 ± 12.5 years) were followed for 3.7 years for major adverse cardiovascular events (MACE) (death or myocardial infarction). The age where the median risk score was above zero was 12 years higher in women vs. men (64–68 years vs. 52–56 years, respectively, $P < 0.001$). The Leiden CCTA risk score was

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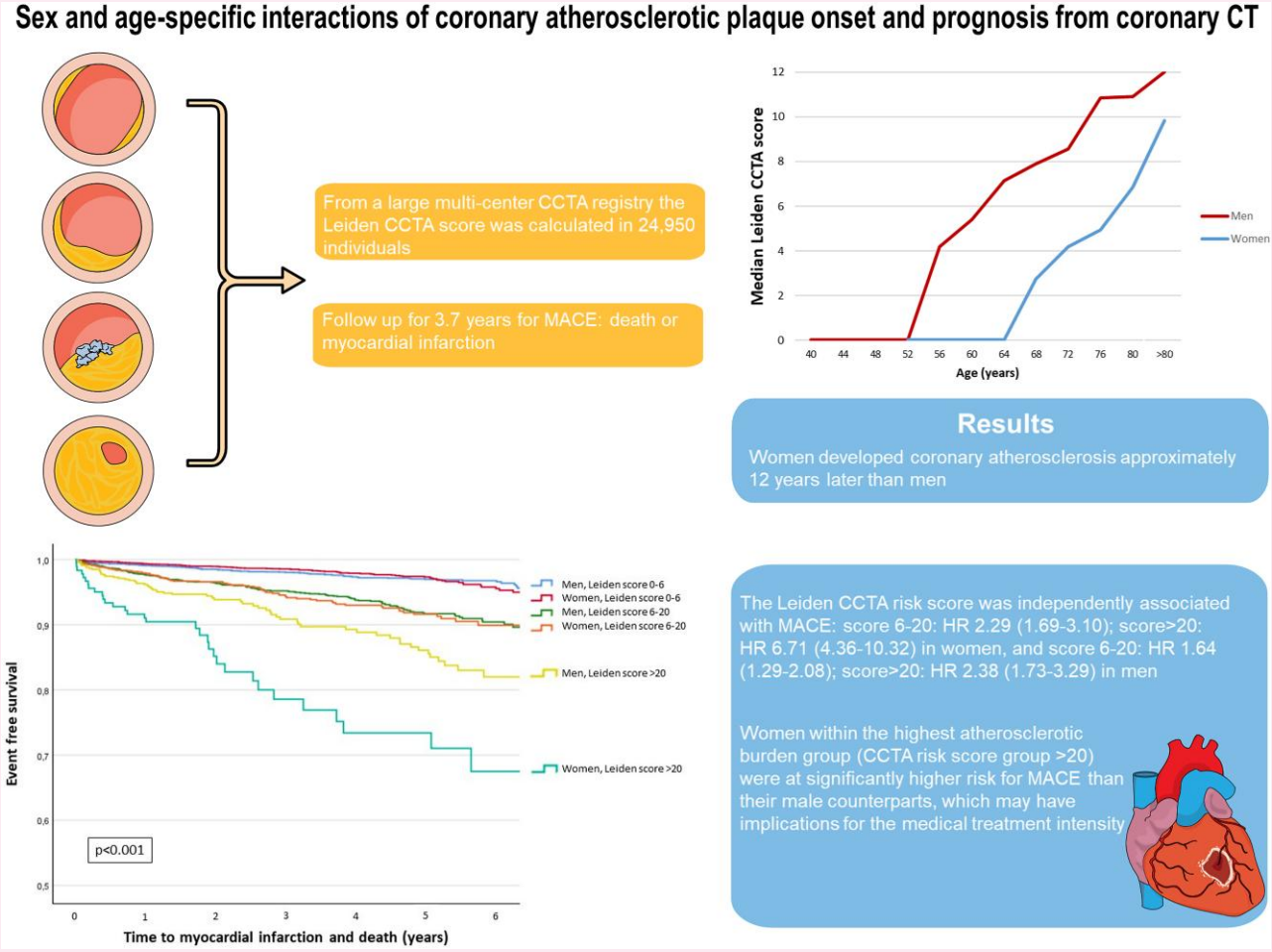
independently associated with MACE: score 6–20: HR 2.29 (1.69–3.10); score > 20: HR 6.71 (4.36–10.32) in women, and score 6–20: HR 1.64 (1.29–2.08); score > 20: HR 2.38 (1.73–3.29) in men. The risk was significantly higher for women within the highest score group (adjusted *P*-interaction = 0.003). In pre-menopausal women, the risk score was equally predictive and 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.

Graphical Abstract



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

Keywords coronary computed tomography angiography (CCTA) • coronary artery disease • sex differences • prognosis

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 coronary artery disease (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, multi-center, 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 this 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.

CTA 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 (see Supplementary data online, *Figure S1*). 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 left circumflex artery (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 scores 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 were 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 χ^2 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, hypercholesterolaemia, diabetes mellitus, current smoking, and family history of CAD) as covariates. The comprehensive CCTA scores for these analyses were stratified into three 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%, $P < 0.001$).

Atherosclerosis extent and severity characteristics according to sex

Per-patient level, more than half of women had no 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,

Table 1 Clinical characteristics and CCTA findings

	Women $N = 11\,678$	Men $N = 13\,272$	*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[a]	6207 (53.6)	6336 (48.2)	<0.001
Hypercholesterolemia[b]	6153 (53.0)	6920 (52.6)	0.481
Family history for CAD[c]	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 and IQR, mean ± standard deviation or %.
ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease.
[a]Blood pressure ≥ 140/90 mmHg and/or treatment with antihypertensive medication.
[b]Total cholesterol ≥ 230 mg/dL or triglycerides ≥ 200 mg/dL and/or treatment with lipid-lowering medication.
[c]Presence of CAD in first-degree family members at age <55 years in males and <65 years in females.

$P = 0.030$ and 1.0 ± 1.8 vs. 1.7 ± 2.4, $P < 0.001$, respectively) than men. The number of proximal segments with plaque (left main artery (LM), proximal left anterior descending artery (LAD), proximal right coronary artery (RCA), proximal LCx (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*, see Supplementary data online, *Table S2*). The age where the median Leiden CCTA risk score was above zero was 12 years higher in women vs. men (64–68 years in women vs. 52–56 years 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 9score 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 modelled as a continuous variable, with or without risk factor adjustment (*P*-interaction = 0.001) (see Supplementary data online, *Table S2*). 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) (see Supplementary data online, *Table S3*).

Table 2 Subcomponents of the Leiden CCTA score

	Women $N = 11\,678$	Men $N = 13\,272$	*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 and IQR, mean ± standard deviation or %.
CAD, coronary artery disease; CCTA, coronary computed tomography angiography.

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 7076 were women (classified as post-menopausal). In pre-menopausal women, the adjusted hazard ratios were compared 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 post-menopausal 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) (see Supplementary data online, *Table S4*).

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) (see Supplementary data online, *Table S5*). In addition, hypertension was significant in predicting MACE in women and hypercholesterolaemia in men.

Discussion

This 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 the 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 ischaemia 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]

Higher event rates for women with non-obstructive atherosclerosis and left main stenosis are shown, and there is a higher discriminatory

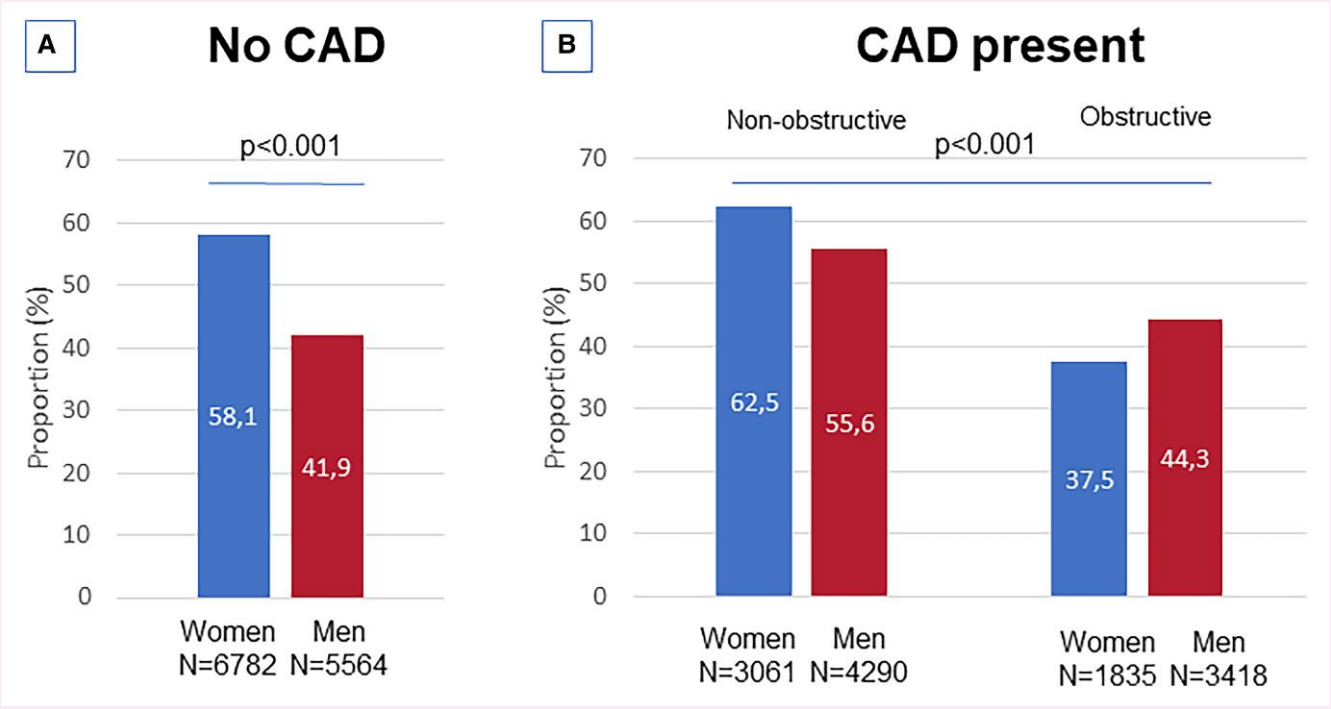


Figure 1 Stenosis severity according to sex. (*A*) Sex-based difference in prevalence of no CAD. (*B*) Sex-based difference in the prevalence of CAD divided by obstructive and non-obstructive. Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography.

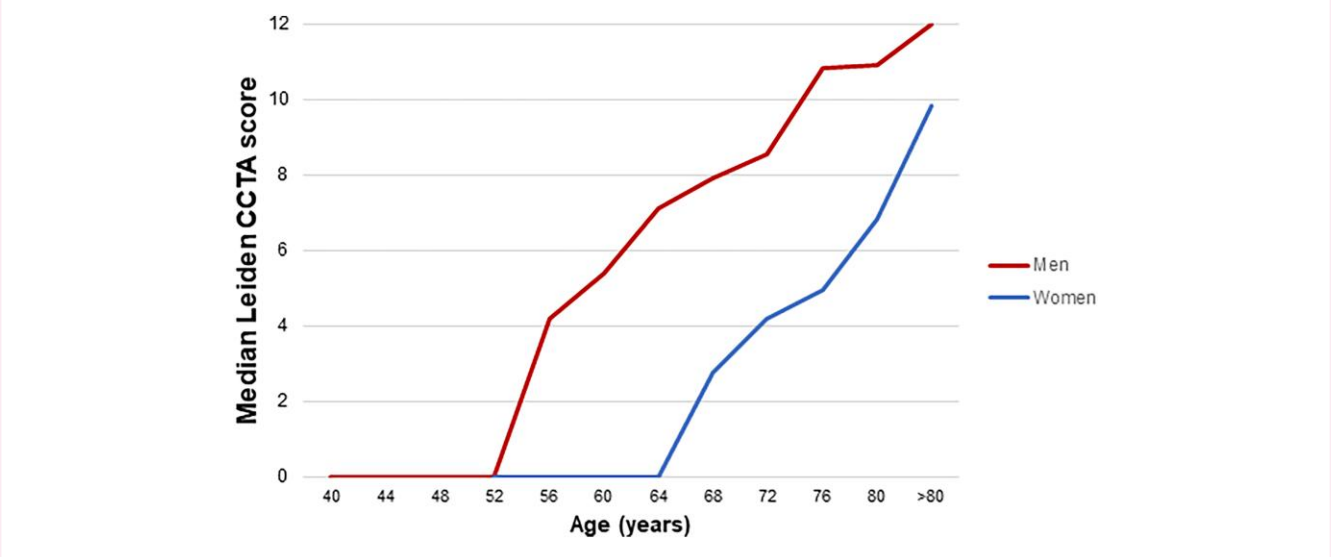


Figure 2 Median Leiden CCTA score per age category. Sex-based difference in median CCTA risk score per age category (4 years). CCTA, coronary computed tomography angiography.

value of coronary atherosclerosis to predict MACE.[7,21] Shaw et al. demonstrated the 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 5166 patients a significantly higher predictive value of plaque in the left main coronary artery, detected with CCTA, for the prediction of MACE.[7]

This 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 such as SYNTAX which only accounts for obstructive disease, or the segment involvement score (SIS) which

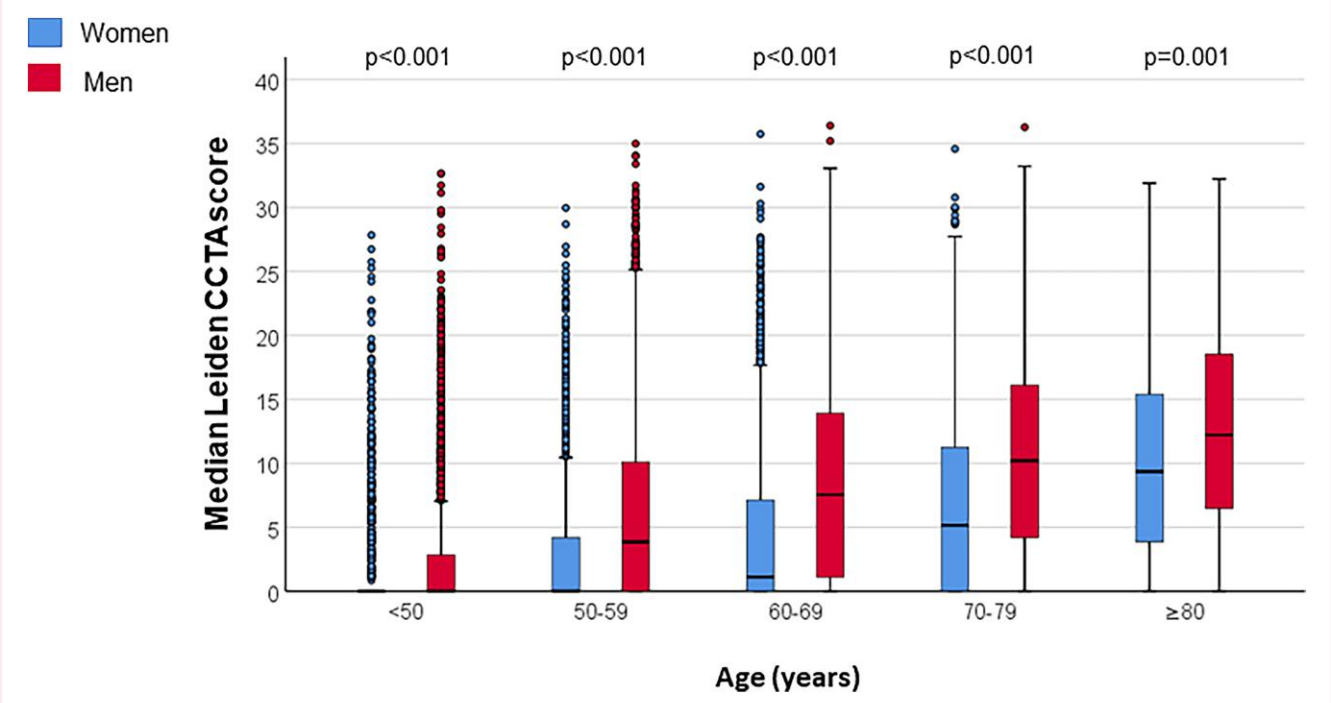


Figure 3 CCTA risk score by age deciles and sex. Median Leiden CCTA risk score displayed per age decile and sex. CCTA, coronary computed tomography angiography.

Table 3 Cox-regression analysis stratified by sex[a]

	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[b]				
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

[a]*N* = 17 750.
[b]Including classical cardiovascular risk factors: hypertension, hypercholesterolaemia, diabetes mellitus, current smoking status, and family history of CAD.
CI, confidence interval; HR, hazard ratio; CCTA, coronary computed tomography angiography.

only assesses the number of involved segments, might be less accurate. The outcomes in this 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 the clinical risk profile. Within the highest atherosclerotic plaque group, women had a

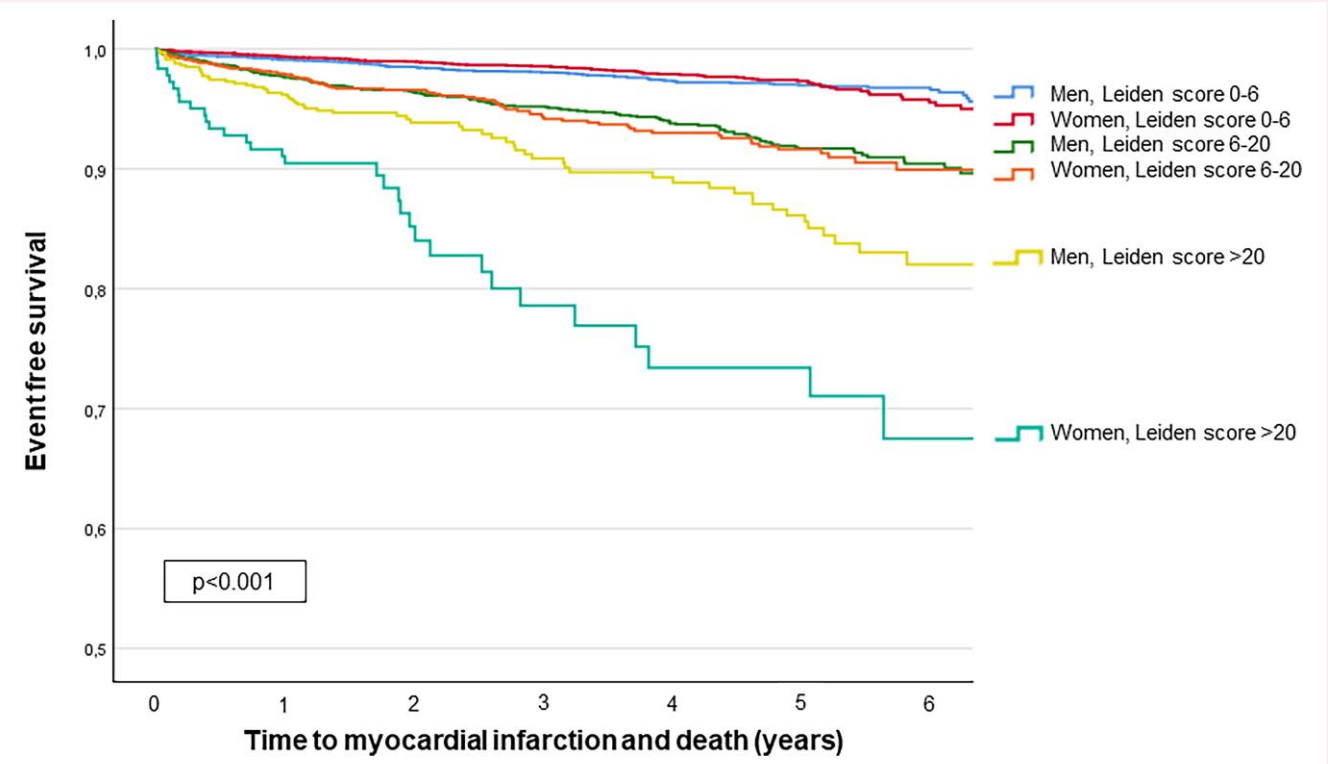


Figure 4 Survival curves for women and men per CCTA score category. *Kaplan–Meier figure for men and women according to the different CCTA risk score groups. *$N = 17\,750$. CCTA, coronary computed tomography angiography.

Table 4 Cox-regression analysis in men and women divided by age groups[a]

	Women HR (95% CI)	*P*-value	Men HR (95% CI)	*P*-value
Model 1[b]				
Pre-menopausal (≤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
Post-menopausal (>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[c]				
Pre-menopausal (≤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
Post-menopausal (>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

[a]$N = 17\,750$.
[b]Not including any clinical variables.
[c]Including age and classical cardiovascular risk factors (i.e. hypertension, hypercholesterolaemia, diabetes mellitus, current smoking status and family history of CAD).

higher risk than their male counterparts, and this was caused by those older than 55 years old (considered post-menopausal).

These findings have implications for the 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 invasive coronary angiography (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 this 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. Oestrogen 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 remodelling associated with vascular injury and endothelial cell damage.[27,28] A reduction in these mechanisms may promote plaque progression and additionally plaque destabilization and 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.

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

Conclusion

The current study showed an approximately 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 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.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

Conflict of interest: None declared.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ *et al.* Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol* 2007;**50**:1161–70.
2. Carrigan TP, Nair D, Schoenhagen P, Curtin RJ, Popovic ZB, Halliburton S *et al.* Prognostic utility of 64-slice computed tomography in patients with suspected but no documented coronary artery disease. *Eur Heart J* 2009;**30**:362–71.
3. Steingart RM, Packer M, Hamm P, Coglianese ME, Gersh B, Geltman EM *et al.* Sex differences in the management of coronary artery disease. Survival and ventricular enlargement investigators. *N Eng J Med* 1991;**325**:226–30.
4. Canto JG, Rogers WJ, Goldberg RJ, Peterson ED, Wenger NK, Vaccarino V *et al.* Association of age and sex with myocardial infarction symptom presentation and in-hospital mortality. *JAMA* 2012;**307**:813–22.
5. Hochman JS, Tamis JE, Thompson TD, Weaver WD, White HD, Van de Werf F *et al.* Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global use of strategies to open occluded coronary arteries in acute coronary syndromes IIb investigators. *N Eng J Med* 1999;**341**:226–32.
6. Shaw LJ, Min JK, Narula J, Lin F, Bairey-Merz CN, Callister TQ *et al.* Sex differences in mortality associated with computed tomographic angiographic measurements of obstructive and nonobstructive coronary artery disease: an exploratory analysis. *Circ Cardiovasc Imaging* 2010;**3**:473–81.
7. Xie JX, Eshtehardi P, Varghese T, Goyal A, Mehta PK, Kang W *et al.* Prognostic significance of nonobstructive left main coronary artery disease in women versus men: long-term outcomes from the CONFIRM (coronary CT angiography evaluation for clinical outcomes: an international multicenter) registry. *Circ Cardiovasc Imaging* 2017;**10**:e006246.
8. Lin FY, Shaw LJ, Dunning AM, Labounty TM, Choi JH, Weinsaft JW *et al.* Mortality risk in symptomatic patients with nonobstructive coronary artery disease: a prospective 2-center study of 2,583 patients undergoing 64-detector row coronary computed tomographic angiography. *J Am Coll Cardiol* 2011;**58**:510–9.
9. Shaw LJ, Shaw RE, Merz CN, Brindis RG, Klein LW, Nallamothu B *et al.* Impact of ethnicity and gender differences on angiographic coronary artery disease prevalence and in-hospital mortality in the American college of cardiology-national cardiovascular data registry. *Circulation* 2008;**117**:1787–801.
10. van Rosendael AR, Shaw LJ, Xie JX, Dimitriu-Leen AC, Smit JM, Scholte AJ et al. Superior risk stratification with coronary computed tomography angiography using a comprehensive atherosclerotic risk score. *JACC Cardiovasc Imaging* 2019;**12**:1987–97.
11. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah MH, Berman DS *et al.* Rationale and design of the CONFIRM (COronary CT angiography EvaluatioN for clinical outcomes: an InteRnational multicenter) registry. *J Cardiovasc Comput Tomogr* 2011;**5**:84–92.
12. Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK *et al.* SCCT Guidelines for the performance and acquisition of coronary computed tomographic angiography: A report of the society of cardiovascular computed tomography guidelines committee: endorsed by the north American society for cardiovascular imaging (NASCI). *J Cardiovasc Comput Tomogr* 2016;**10**:435–49.
13. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ *et al.* SCCT Guidelines for the interpretation and reporting of coronary CT angiography: a report of the society of cardiovascular computed tomography guidelines committee. *J Cardiovasc Comput Tomogr* 2014;**8**:342–58.
14. Phipps AI, Ichikawa L, Bowles EJ, Carney PA, Kerlikowske K, Miglioretti DL et al. Efining menopausal status in epidemiologic studies: A comparison of multiple approaches and their effects on breast cancer rates. *Maturitas* 2010;**67**:60–6.
15. Hemingway H, McCallum A, Shipley M, Manderbacka K, Martikainen P, Keskimäki I. Incidence and prognostic implications of stable angina pectoris among women and men. *JAMA* 2006;**295**:1404–11.
16. Hemal K, Pagidipati NJ, Coles A, Dolor RJ, Mark DB, Pellikka PA *et al.* Sex differences in demographics, risk factors, presentation, and noninvasive testing in stable outpatients with suspected coronary artery disease: insights from the PROMISE trial. *JACC Cardiovasc Imaging* 2016;**9**:337–46.
17. Wang F, Rozanski A, Dey D, Arnson Y, Gransar H, Friedman J *et al.* Age- and gender-adjusted percentiles for number of calcified plaques in coronary artery calcium scanning. *J Cardiovasc Comput Tomogr* 2019;**13**:319–24.
18. Schroeder B, Francis G, Leipsic J, Heilbron B, John Mancini GB, Taylor CM. Early atherosclerosis detection in asymptomatic patients: a comparison of carotid ultrasound,

coronary artery calcium score, and coronary computed tomography angiography. *Can J Cardiol* 2013;**29**:1687–94.
19. Williams MC, Kwiecinski J, Doris M, McElhinney P, D'Souza MS, Cadet S *et al.* Sex-Specific computed tomography coronary plaque characterization and risk of myocardial infarction. *JACC Cardiovasc Imaging* 2021;**14**:1804–14.
20. Shaw LJ, Bugiardini R, Merz CN. Women and ischemic heart disease: evolving knowledge. *J Am Coll Cardiol* 2009;**54**:1561–75.
21. Shaw LJ, Min JK, Nasir K, Xie JX, Berman DS, Miedema MD *et al.* Sex differences in calcified plaque and long-term cardiovascular mortality: observations from the CAC consortium. *Eur Heart J* 2018;**39**:3727–35.
22. Plank F, Beyer C, Friedrich G, Wildauer M, Feuchtner G. Sex differences in coronary artery plaque composition detected by coronary computed tomography: quantitative and qualitative analysis. *Neth Heart J* 2019;**27**:272–80.
23. Naoum C, Berman DS, Ahmadi A, Blanke P, Gransar H, Narula J *et al.* Predictive value of age- and sex-specific nomograms of global plaque burden on coronary computed tomography angiography for Major cardiac events. *Circ Cardiovasc Imaging* 2017;**10**:e004896.
24. SCOT-HEART Investigators; Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, Flather M et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018;**379**:924–33.
25. Feger S, Elzenbeck L, Rieckmann N, Marek A, Dreger H, Beling M *et al.* Effect of computed tomography versus invasive coronary angiography on statin adherence: A randomized controlled trial. *JACC Cardiovasc Imaging* 2021;**14**:1480–3.
26. Mansour M, Radaideh Q, Alaiwah MN, Alnimer Y, Devabhaktuni SR, Dhar G *et al.* Major adverse cardiac events in symptomatic women with non-obstructive CAD on coronary CTA: pooled analysis from PROMISE and SCOT-HEART. *Int J Cardiovasc Imaging* 2022;**38**:683–93.
27. Mendelsohn ME, Karas RH. Estrogen and the blood vessel wall. *Curr Opin Cardiol* 1994;**9**:619–26.
28. Farhat MY, Lavigne MC, Ramwell PW. The vascular protective effects of estrogen. *FASEB J* 1996;**10**:615–24.
29. Hiteshi AK, Li D, Gao Y, Chen A, Flores F, Mao SS *et al.* Gender differences in coronary artery diameter are not related to body habitus or left ventricular mass. *Clin Cardiol* 2014;**37**:605–9.
30. Pepine CJ, Kerensky RA, Lambert CR, Smith KM, von Mering GO, Sopko G *et al.* Some thoughts on the vasculopathy of women with ischemic heart disease. *J Am Coll Cardiol* 2006;**47**(3 Suppl):S30–5.
31. Jacobs AK. Coronary intervention in 2009: are women no different than men? *Circ Cardiovasc Interv* 2009;**2**:69–78.