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

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CHAPTER 4

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

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Abstract

Aims

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

Methods and results

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

Conclusion

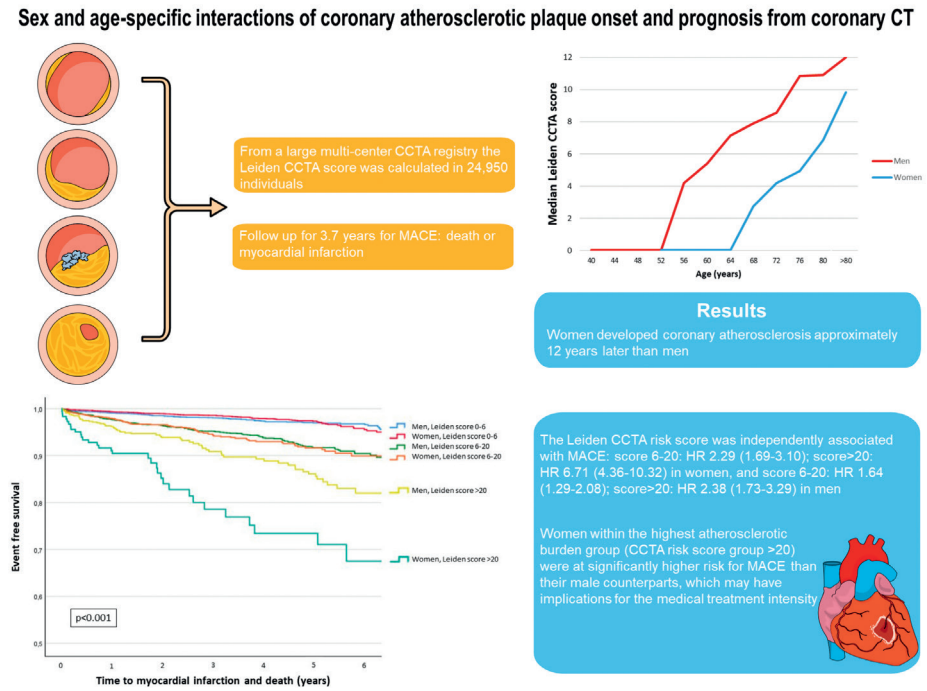
Women developed coronary atherosclerosis approximately 12 years later than men. Post-menopausal women within the highest atherosclerotic burden group were at significantly higher risk for MACE than their male counterparts, which may have implications for the medical treatment intensity.

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

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

Graphical abstract

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



Introduction

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

Methods

Patients

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

CCTA image acquisition and interpretation

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

Leiden CCTA score

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

Endpoint

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

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

Statistical analysis

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

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

Results

Patients

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

Table 1. Clinical characteristics and CCTA findings

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

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

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

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

Atherosclerosis extent and severity characteristics according to sex

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

Age-dependent increase of Leiden CCTA risk score by sex

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

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

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

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

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

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

Prediction of major adverse cardiac events in individuals without CAD

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

Table 2. Subcomponents of the Leiden CCTA score

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

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

Discussion

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

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

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

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

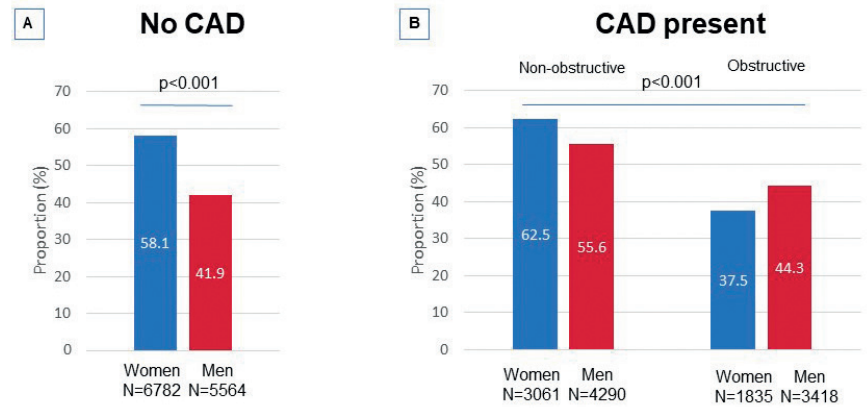
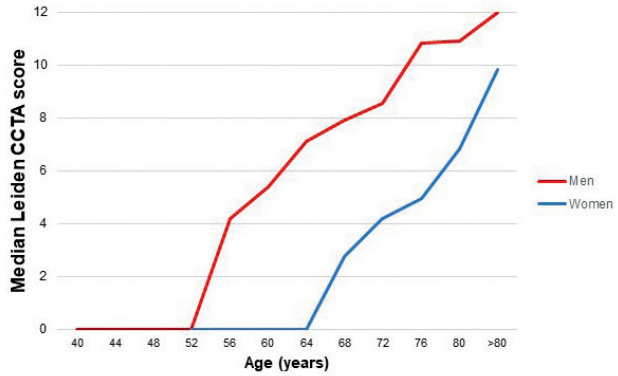


Figure 2. Median Leiden CCTA score per age category
Sex-based difference in median CCTA risk score per age category (4 years)
CCTA, coronary computed tomography angiography.



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

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

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

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

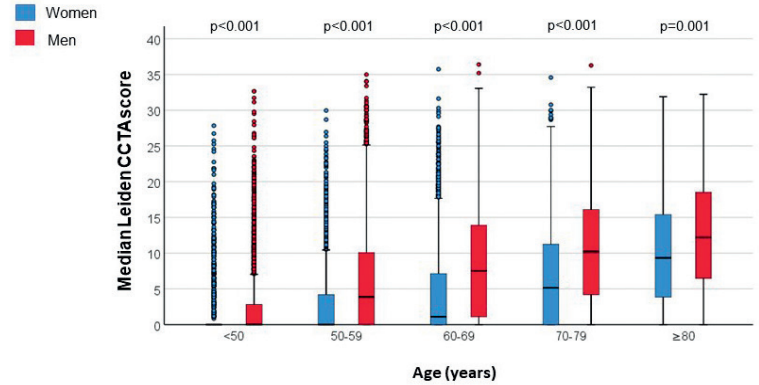
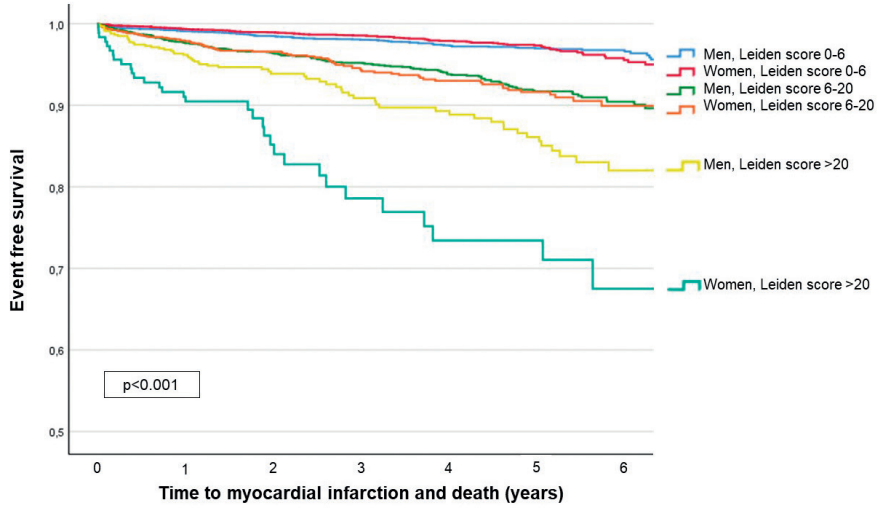


Table 3: Cox regression analysis stratified by sex*

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

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

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



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

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

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

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

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

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

Limitations

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

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

Conclusion

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

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Appendix

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

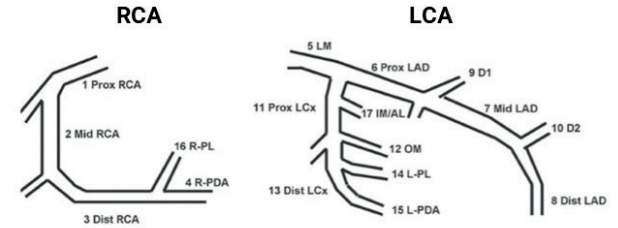

Table 1: Median Leiden CCTA score per age category

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

CCTA, coronary computed tomography angiography

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

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

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

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

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

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

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

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

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

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

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

*N = 17750