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Major Adverse Cardiac Events in Symptomatic Women with Non-obstructive CAD on Coronary CTA: Pooled Analysis from PROMISE and SCOT-HEART

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Abstract

Purpose: The presence of non-obstructive coronary artery disease (CAD) on coronary computed tomography angiography (CTA) has been associated with the occurrence of major adverse cardiac events (MACE). However, factors associated with the development of MACE in women with non-obstructive CAD have not been fully elucidated. We sought to examine the influence of risk factors and coronary artery calcification on MACE in women with non-obstructive CAD on coronary CTA.

Methods and Results: Women from PROMISE and SCOT-HEART trials with none or non-obstructive CAD on coronary CTA comprised the study cohort. Baseline characteristics and clinical presentation were assessed. Survival analysis using Kaplan-Meier curves was done to

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compare outcomes stratified by the atherosclerotic cardiovascular disease (ASCVD) risk score and the Agatston score. The primary endpoint was a composite of all-cause mortality, myocardial infarction, and revascularization. 2,597 women had non-obstructive CAD or normal coronary CTA, with a median follow-up of 32 months. Compared to women without MACE, women with MACE had lower high-density lipoprotein cholesterol (HDL-C) levels and higher mean ASCVD risk scores. Further, women with non-obstructive CAD and ASCVD ≥7.5% had higher risk of MACE than those with ASCVD < 7.5% [3.2 % vs. 1.1%, adjusted HR (aHR) of 3.1 (95% CI 1.32, 7.23), P-value 0.009]. The Agatston calcium score, on the other hand, was not independently associated with MACE among this population of symptomatic women.

Conclusions: Symptomatic women with non-obstructive CAD on coronary CTA are at higher risk for MACE, with the ASCVD risk score being independently associated with the occurrence of adverse events.

Keywords

Coronary computed tomography angiography; coronary artery disease; myocardial infarction; coronary artery calcium score; atherosclerotic cardiovascular disease

INTRODUCTION

Coronary artery disease (CAD) accounts for substantial morbidity and mortality, despite persistent efforts aimed at enhancing diagnostic and therapeutic strategies.[1] In the context of a low-intermediate risk presentation, the current diagnostic approach relies on identifying symptomatic individuals with functionally obstructive CAD.[2] Yet, this paradigm has its intrinsic limitations, primarily due to the fact that the majority of acute coronary syndrome (ACS)-causing lesions are non-obstructive at baseline.[3,4] For instance, serial angiographic examinations have revealed that 68% of myocardial infarction (MI) events are caused by lesions that are non-obstructive (diameter stenosis <50%) at baseline.[5] With the advent of coronary computed tomography angiography (coronary CTA), noninvasive anatomical evaluation of the coronary vasculature for the detection and quantification of atherosclerotic plaque burden is becoming an integral part of clinical practice.[6, 7] Coronary CTA allows for the detection of CAD across a wide range of clinical presentations, and findings on coronary CTA correlate with future clinical outcomes.[8] Most notably, measures of plaque burden, even if non-obstructive, have been shown to be predictive of incident cardiac events.[9–11] The ability to characterize the anatomical and functional footprint of coronary atherosclerosis has further enhanced the ability to understand the natural history of stable CAD.

In relation to sex disparity, CAD pathogenesis and clinical manifestations differ between women and men. For instance, ACS in women often occur in the presence of non-obstructive CAD as a result of smaller vessel size, increased vascular stiffness, less robust collateral circulation, lower coronary flow reserve, and differences in vascular remodeling.[12, 13] Yet, even in the presence of obstructive CAD, the International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA) trial showed that women had more frequent angina, independent of CAD extent and ischemia severity; this indicates that the relationship between angina, atherosclerosis, and ischemia in women is complex.[14] Although women have a lower prevalence of coronary

artery calcification (CAC) compared to similar-aged men, the presence of detectable CAC in women has been associated with a 1.3-higher hazard for cardiovascular death compared with men.[15] The complex interaction between patient-level factors, as well as atherosclerotic plaque characteristics, accounts for persistent sex differences in cardiovascular outcomes. To date, no adequately sized study has examined the influence of risk factors, as well as coronary artery calcification, on the occurrence of major adverse cardiac events (MACE) in women with non-obstructive CAD. This study sought to define characteristics of women with non-obstructive CAD, and to determine factors associated with the occurrence of MACE, using a pooled analysis from the Scottish Computed Tomography of the HEART (SCOT-HEART) and the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) randomized clinical trials.[8,16]

METHODS

Study Population

In this prospective cohort study, patient-level analysis was performed after combining publicly available data from two randomized clinical trials: PROMISE and SCOT-HEART using R software, version 4.0.2 (RStudio, Boston, MA). This analysis was approved by the local IRB committee at the University of Arkansas for Medical Sciences (UAMS) as IRB-exempt, since the data received from the PROMISE and SCOT-HEART investigators was de-identified (ClinicalTrials.gov identifier for PROMISE: NCT01174550; SCOT-HEART: NCT01149590). The PROMISE trial randomized 10,003 symptomatic outpatients without known CAD to an initial strategy of anatomical evaluation or functional testing with a median follow-up of 2 years, while the SCOT-HEART trial randomly assigned 4,146 patients with stable chest pain to standard care vs. standard care with coronary CTA, with median follow-up of 1.7 years. Data from the initial SCOT-HEART analysis were used to compare baseline characteristics.[17] Female patients with no CAD and non-obstructive CAD on coronary CTA comprised the study cohort (n=2597). Subgroup analysis on women with non-obstructive CAD (n=1508) was done stratified by ASCVD risk score, coronary artery calcium score (CACS) and age. Female patients with uninterpretable coronary CTA scans, or those randomized to coronary CTA but who did not end up undergoing the scan were excluded. Two investigators independently merged data from both trials (MM & YL) to confirm accuracy, any discrepancy was addressed after mutual agreement between both investigators. Baseline characteristics from both trials were matched and merged using the tidyverse package in R[18].

Clinical Variables & Coronary Calcium Score

Baseline demographics, risk factors and clinical presentation, electrocardiographic (ECG) findings, CAD risk estimates and events with time indicators for each event were collected for the study cohort. Clinical data and risk factor were previously defined by the PROMISE and SCOT-HEART trials.[8,16] Non-obstructive CAD was defined as less than or equal to 49% diameter stenosis on coronary CTA. Further, sensitivity analysis with non-obstructive CAD defined as diameter stenosis less than 70% was performed. Patients with uninterpretable scans, those not undergoing the scan and those with obstructive CAD were excluded from the analysis (n=4,231). CACS was reported using the widely adopted Agatston method.[19]

The atherosclerotic cardiovascular disease (ASCVD) risk score was calculated using the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk.[20] Race was not a reported clinical variable by the SCOT-HEART investigators, and as such the assumption was that the predominant race was Caucasian in order to compute the ASCVD score for all participants. The primary endpoint was a composite of MACE including all-cause mortality, myocardial infarction, and revascularization. Both PROMISE and SCOT-HEART used a universal definition for myocardial infarction (MI) and revascularization.[21,22]

Statistical Analysis

Baseline characteristics are presented as proportions for categorical variables and mean with standard deviation or median with interquartile range for continuous variables, as appropriate. Chi-square test was used to compare categorical variables. Survival analysis using Kaplan Meier curves was done to compare outcomes in female patients with non-obstructive CAD vs female patients with no CAD on coronary CTA. Additionally, we conducted subgroup analysis on women with non-obstructive CAD after excluding women with normal coronary CTA. Survival analysis using Kaplan Meier curves was done to compare outcomes in female patients with non-obstructive CAD stratified by age, ASCVD risk score and CACS. Log-rank test was used to assess for statistical significance between survival curves. Variables that were significant in log rank test, were further evaluated in adjusted analysis. We conducted cox proportional hazard models to estimate hazard ratios (HR) with 95% confidence interval. Calculated HR for women with no CAD (i.e., normal angiography) vs non-obstructive CAD was adjusted for age, hypertension (HTN), diabetes, smoking status, statin use and obesity (defined as body mass index (BMI) > 30 kg/m^2). For the cox proportional hazard (CPH) model comparing women with non-obstructive CAD stratified by ASCVD, the calculated HR was adjusted for CACS, statin use and BMI (used as a continuous variable). Similarly, for the CPH model comparing women with non-obstructive CAD stratified by CACS, the calculated HR was adjusted for the ASCVD score. Schoenfeld test was used to confirm the proportionality assumption required for CPH modeling. All statistical analysis was performed using R version 4.0.2.

Patients with missing clinical variables or CACS were not included in the survival analysis (the proportion of missing variables was <7% for all variables (CACS missingness 7%, ASCVD missingness 0.4%), and missing variables were determined to be missing at random). Akaike information criterion (AIC) was used to help choose the best fitted CPH model and to avoid overfitting. A one-tailed p value less than 0.05 was considered significant. The Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines were used in the present analysis.

RESULTS

Study Population:

Our study population consisted of 2,597 female patients, (1,898 (73.1%) from PROMISE and 699 (26.9%) from SCOT-HEART) (Figure 1 supplement). 1089 (41.9%) women had normal coronary arteries, while 1,508 (58.1%) had non-obstructive CAD with diameter

stenosis 1–49%. Median follow-up was 32 months (interquartile range, 23–45 months), with a maximum follow-up period of 86 months.

Baseline Characteristics:

Mean age of the study cohort was 59.8 years. In terms of baseline characteristics, 15.3% were current smokers, while 55.3% had hypertension, and 16.4% had diabetes mellitus (Table 1). In terms of pretest probability, 79.1% (2055) had an intermediate pretest probability (modified Diamond Forrester) while 13.1% (341) had low pretest probability. In terms of cardiovascular risk, 49% (1,273 out of 2,597) had a 10-year ASCVD risk of 7.5% or greater. From a clinical presentation perspective, 15.3% had typical chest pain, 64.4% had atypical chest pain and 20.2% had non-cardiac chest pain. All PROMISE patients were symptomatic (75.3% had chest pain while 13.5% had dyspnea), with the remaining 11.2% of patients experienced epigastric pain, shoulder pain, palpitations, syncope, lightheadedness, or weakness as a primary symptom. Statin therapy was present in 55.2% of the study cohort at baseline, 41% were on antiplatelet therapy, while 30.6% were on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker.

Overall, baseline characteristics were not different amongst women experiencing a MACE event compared to those without an event. High-density lipoprotein cholesterol (HDL-C), on the other hand, was lower in women experiencing a MACE event (52.7 mg/dL vs. 57.9 mg/dL, p=0.036) while the mean ASCVD risk score was higher in women with a MACE event (16.5% vs. 10.4%, p=0.007). Although the prevalence of the distribution of higher CACS scores was greater among women with MACE vs no MACE, this did not meet statistical significance (Table 1). For reference, differences in patient-level characteristics between women with MACE versus men with MACE were compared in the present pooled analysis of SCOT-HEART and PROMISE (Table 1 supplement).

No CAD vs. Non-obstructive CAD:

In the setting of low-intermediate risk cohort with non-obstructive CAD, the primary endpoint event rate was 2.2% over the median follow-up interval of 32 months. Table 2 supplement shows differences in clinical characteristics in women with no CAD vs. non-obstructive CAD. Overall, women with non-obstructive CAD on coronary CTA were more likely to have the composite outcome of death/MI/revascularizations than those with no CAD on coronary CTA, adjusted HR [aHR] 2.51 95% CI (1.10–5.73); p=0.028, adjusted for age, hypertension, diabetes, obesity, smoking status and statin use at baseline (Figure 1). Findings did not change when non-obstructive CAD was defined as diameter stenosis less than 70% (similar findings were seen across subgroup analyses).

Subgroup Analysis by ASCVD:

For female patients with non-obstructive CAD, survival analysis was performed stratified by ASCVD risk score (Figure 2a). Female patients with non-obstructive CAD and ASCVD score ≥7.5% had higher risk of death/MI/revascularization than those with ASCVD score < 7.5% [3.2% vs. 1.1%, aHR 3.1 (95% CI 1.32 – 7.23), p=0.009 adjusted for statin use, CACS and BMI].

Subgroup Analysis by CACS:

When stratified by the Agatston CACS, female patients with non-obstructive CAD and CACS > 0 were more likely to experience the primary composite event of death/MI/revascularization than those with non-obstructive CAD and no CAC (CACS = 0) with a log rank P-value of 0.046 (Figure 2b). However, in a cox proportional hazard model adjusted for the ASCVD risk score, there was no statistical difference between CACS=0 and CACS>0, indicating that CACS is not an independent predictor [aHR 1.64 (95% CI 0.76 – 3.55), p=0.21].

Clinical Subgroups:

For female patients with non-obstructive CAD, survival analysis was performed stratified by age (Figure 2c). Among non-obstructive CAD cohort, women older than 60 years of age were more likely to experience major adverse cardiac events compared to younger female patients with non-obstructive CAD [2.86% vs. 1.5%, aHR 2.26 (95% CI 1.06–4.85), p= 0.035]. In addition, the risk of experiencing death/MI/revascularization for women with non-obstructive CAD increased by 5.7% for each one-year increase in age [aHR 1.057 (95% CI 1.016–1.1), p= 0.006].

Obesity, defined as BMI greater than 30 kg/m^2, statin use, diabetes mellitus and hypercholesterolemia (defined as serum cholesterol levels greater than 200 mg/dL) were not independently associated with the occurrence of a MACE event in adjusted analyses (Figure 3).

DISCUSSION

Using pooled data from two clinical trials of women with non-obstructive CAD or normal coronary arteries and symptoms suggestive of stable angina or anginal equivalent, we found that age and the ASCVD risk score were both independently associated with future risk of MACE, but not CACS. The uptake of coronary CTA as a noninvasive anatomic imaging modality has provided an important avenue for the evaluation of the distribution, burden and characteristics of atherosclerotic plaque in low to intermediate risk symptomatic individuals. As a direct consequence of this approach, the presence of non-obstructive CAD has been shown to be associated with incident MACE in numerous cohorts. Further, the higher prevalence of non-obstructive CAD coupled with the presence of atypical symptoms account for the high burden of cardiovascular morbidity and mortality in women. Thus, the detection of non-obstructive CAD should prompt implementation of intensive lifestyle and pharmacologic therapies to lower ASCVD risk.

Our analysis focused on women with non-obstructive CAD, the findings are likely independent of gender as previous other analysis using SCOT-HEART and other cohorts did not find sex-specific differences in outcomes in patients undergoing coronary CTA.[15,23] Nevertheless, there are limited data on the prognostic value of non-obstructive CAD in women on coronary CTA, and the importance of patient-level characteristics as well as coronary calcification on the occurrence of MACE. In this pooled analysis of the randomized multicenter trials of PROMISE and SCOT-HEART, we found that the presence

of non-obstructive CAD was associated with the occurrence of MACE over a median follow up of 32 months. An intermediate-high ASCVD risk score, defined as risk greater than 7.5%, was an independent predictor of MACE, while the presence of coronary calcification (defined as CACS >0) was not an independent predictor after adjusting for ASCVD risk score. Such findings highlight the influence of patient-level characteristics on the development of MACE in women with non-obstructive CAD. As such, the present analysis sheds further insight on the importance of non-obstructive plaque in women, and stresses the need to recognize atherosclerotic plaque, even when non-obstructive, as a target for prevention especially in the setting of an ASCVD risk score > 7.5%.

Previous work has established that functional coronary evaluation in symptomatic women at low to intermediate pretest probability can be less accurate as a result of limited sensitivity and specificity.[24–28] In a published meta-analysis that included 19 ECG treadmill testing studies with a total of 3,721 women, sensitivity and specificity were 61% and 70%, respectively.[29] Similarly, myocardial perfusion imaging using single photon emission computed tomography (SPECT) has been known to have limited diagnostic performance in women, including false-positive results due to breast attenuation and false-negative results due to smaller left ventricular dimensions.[27, 30] In fact, incident adverse events are prevalent in women even after a negative functional evaluation.[28, 31] This is likely explained by the fact that functional evaluation lacks the ability to detect non-obstructive CAD. In fact, in the large, multicenter, SCOT-HEART trial, an anatomical approach using coronary CTA was found to reduce the occurrence of death from coronary heart disease or nonfatal MI at 5 years (2.3% vs. 3.9%; hazard ratio, 0.59; 95% CI, 0.41 to 0.84; p=0.004). This can be partially attributable to the fact that coronary CTA can detect non-obstructive CAD, leading to incremental use of targeted medical therapy.[8] While previously considered benign, numerous analyses have held that patients with non-obstructive CAD on coronary CTA have higher incidence of MACE. The fact that a predominance of precursor lesions in the setting of ACS tend to be non-obstructive, coupled with the fact that women are more likely to have non-obstructive CAD than men, augments the significance of establishing the presence of non-obstructive CAD in women.[8, 23, 32] Although non-obstructive CAD is more common in women, large scale prospective studies investigating the prognostic value in women with non-obstructive CAD are sporadic.[12, 33]

The use of coronary CTA to diagnose the full spectrum of CAD has expanded in the last two decades, unfolding a large amount of data on plaque characteristics and calcium deposits within atherosclerotic plaques.[7] This has resulted in an ongoing debate and research on the interaction between patient-level characteristics and atherosclerotic plaque features on the occurrence of cardiac events. For instance, the occurrence of high risk plaque stipulated by the presence of positive remodeling, spotty calcification, low attenuation plaque and the napkin ring sign, as well as overall calcified plaque burden, have been shown to confer an increased risk of coronary heart disease death or nonfatal MI in a subsequent analysis of the SCOT-HEART and PROMISE cohorts.[34–36] In addition, numerous studies have revealed that plaques with high risk features on coronary CTA are strong predictors of MACE in patients with CAD, which confers greater relative risk when present in women than in men.[34, 37, 38] In subgroup analysis of SCOT-HEART, the presence of high-risk plaque was associated with a higher risk of adverse events in women, with a non-significant P value that

is likely a result of an under-powered analysis (HR 3.27; 95% CI 1.00 – 10.71; p=0.051).[34] In PROMISE, on the other hand, high-risk plaque was a stronger predictor of MACE in women (aHR, 2.41; 95% CI, 1.25–4.64) vs. men (aHR, 1.40; 95% CI, 0.81–2.39). While the present analysis did not include an assessment of high-risk plaque, we demonstrate that a global measure of cardiovascular risk, defined as an ASCVD risk score > 7.5%, is an independent predictor of adverse events in symptomatic women with non-obstructive CAD. This suggests that adverse events in lower risk symptomatic women can be better assessed using patient-level characteristics, with an adjusted hazard ratio of 3.1 (95% CI 1.32 – 7.23; p=0.009) in a pooled analysis of PROMISE and SCOT-HEART. Accordingly, combining coronary CTA findings with the commonly used ASCVD risk score can help identify symptomatic women with non-obstructive CAD who are at higher risk for adverse events and who might benefit from even more intensive preventive therapies.

Although the prognostic value of CACS is best established in asymptomatic populations, it also has strong prognostic value in patients with stable chest pain. Multiple studies demonstrated that higher CACS is associated with adverse cardiac outcomes in a graded fashion. In women, a CACS >100 identifies individuals at elevated risk of adverse events, while women with CACS >300 have similar event rate when compared to those with known stable CAD.[39] On the other hand, data from a recent meta-analysis revealed a potentially discrepant relationship between coronary calcification and adverse cardiac event.[37] The analysis suggested that calcified plaques have the weakest association with MACE, whereas the risk of future events was increased when a lesion displayed evidence of spotty calcification suggesting that the pattern and extent of intimal calcification may be an important predictor of cardiac outcomes.[37] Clearly, understanding the characteristics of calcium deposition is crucial to guide risk stratification in women with non-obstructive CAD. Nevertheless, our results are congruent with previously published analysis, as Otaki et al. had shown that an increasing number of cardiovascular risk factors in women were associated with a significant increase in non-calcified plaques only.[40] Importantly, in an analysis of quantitative plaque measures in the SCOT-HEART cohort, low-attenuation plaque burden was found to be the strongest predictor of fatal or nonfatal myocardial infarction.[9]

Our study is not without limitations. First, as expected from a prevention cohort in whom obstructive CAD was excluded, the number of events was low (2.2% over 32 months). Nevertheless, this is the largest study to date examining the prognostic value of non-obstructive CAD on coronary CTA in women. Second, neither race nor ASCVD score were reported in SCOT-HEART. To calculate the ASCVD score, the assumption was made that the predominant race was Caucasian. However, considering the official racial distribution in Scotland in 2018, we expect that this will unlikely alter the study results. Third, CACS has been extensively validated as a powerful tool for the prognostication of adverse events within asymptomatic primary prevention cohorts, while the present analysis found that CACS>0 was not an independent predictor of MACE among symptomatic women. In addition, 55.2% of the cohort had already been on Statin therapy, which could have attenuated the relationship between coronary calcification and the occurrence of MACE. Further, plaque characteristics such as non-calcified plaque burden or high-risk plaque burden might be better than CAC for risk stratification among symptomatic women

but could not be assessed in present analysis since it was not available for both PROMISE and SCOT-HEART in the publicly available dataset. Given the study design which selected for low risk women with non-obstructive CAD, it is not surprising that most patients had CACS <100, while only 7 patients had a CACS >1000. Combined with a low primary event rate, it is possible that the present analysis was underpowered to detect an association between coronary calcification and MACE. Finally, the follow up period in SCOT-HEART and PROMISE was different. Nevertheless, sensitivity analysis comparing outcomes during a 2 year follow up interval was performed without a change in the results.

In conclusion, symptomatic women with non-obstructive CAD on coronary CTA are at higher risk for MACE compared to women with normal coronaries on coronary CTA. In women with non-obstructive CAD, an ASCVD rise score >7.5% was independently associated with MACE, while CACS >0 was not an independent predictor of MACE in this symptomatic cohort. These findings highlight the importance of non-obstructive plaque in women, and stress the need to recognize atherosclerotic plaque, even when non-obstructive, as a target for prevention especially in the setting of an ASCVD score >7.5%.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosure:

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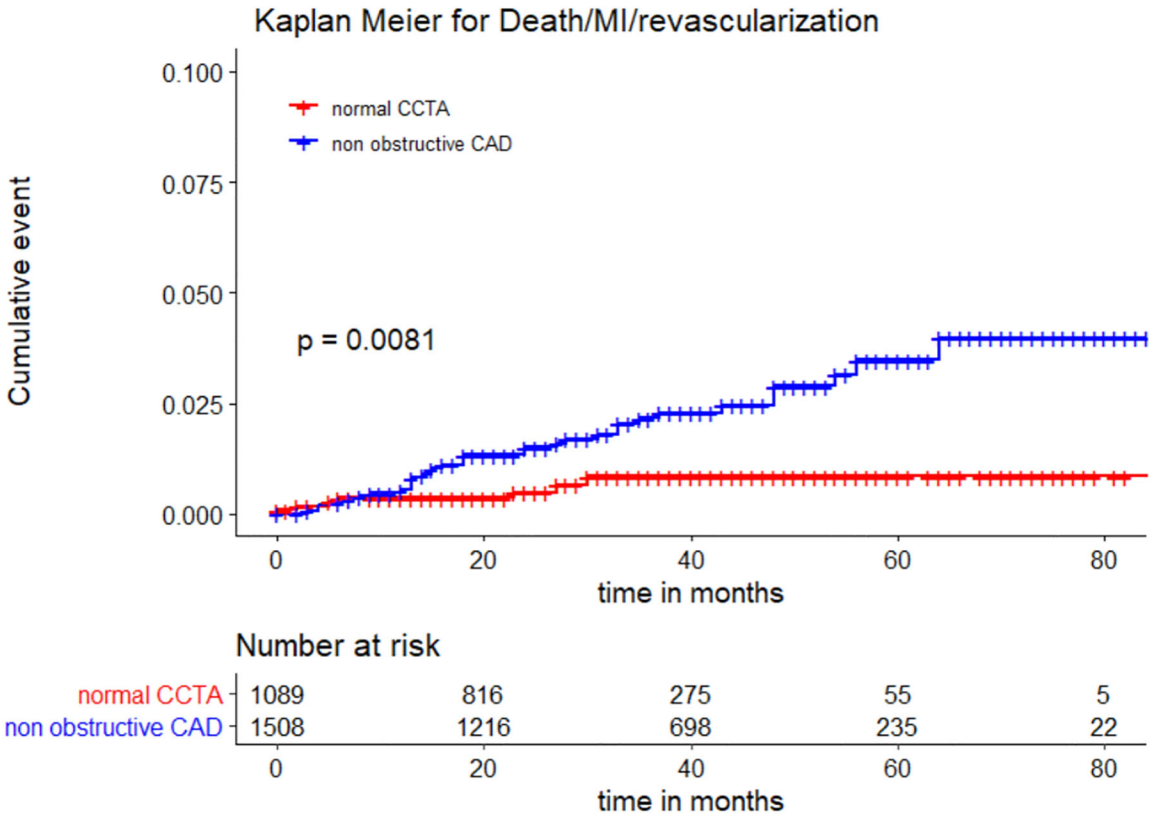
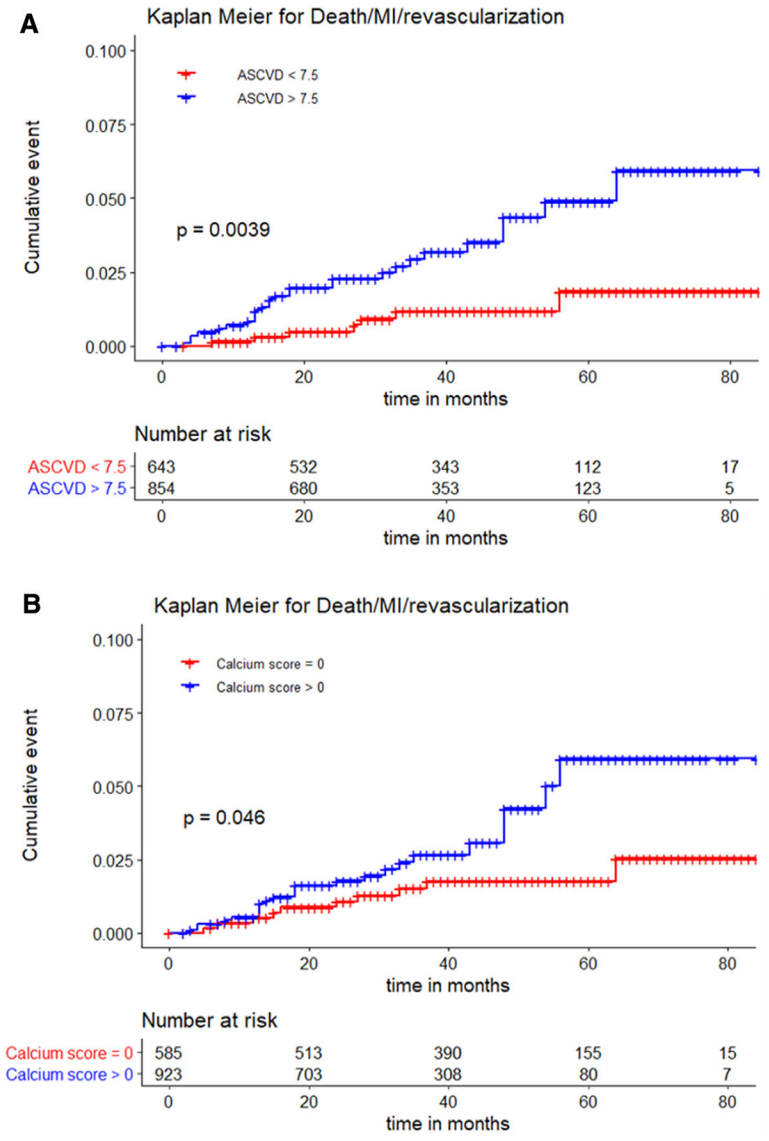


Figure 1.

Kaplan-Meier (KM) curves with log rank p-value for women with non-obstructive CAD on coronary CTA compared to those with normal coronary arteries.



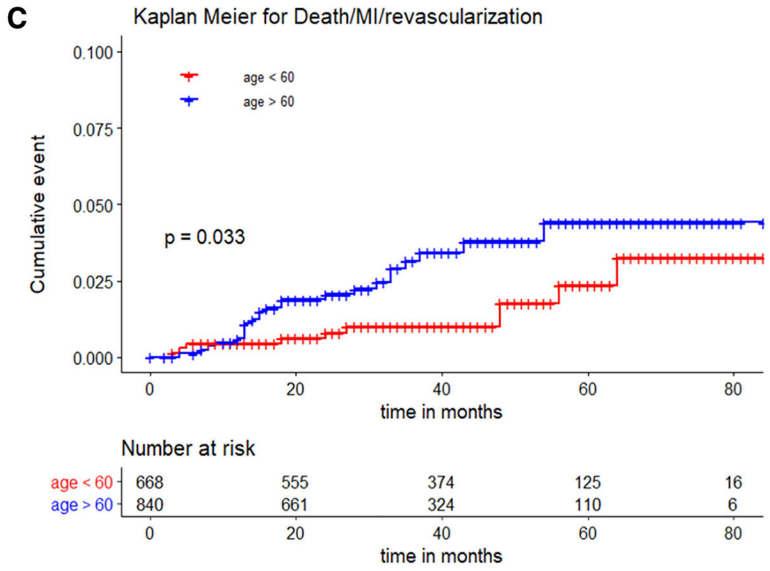


Figure 2.

(A) Kaplan-Meier (KM) curves with log rank p-value for women with non-obstructive CAD on coronary CTA stratified by ASCVD score (low risk vs. intermediate-high risk categories; n=1,497 since 11 participants did not have an ASCVD score). (B) KM curves for women with non-obstructive CAD stratified by CACS (CACS = 0 vs CACS > 0). (C) KM curves for women with non-obstructive CAD on coronary CTA stratified by age (> 60 vs < 60).

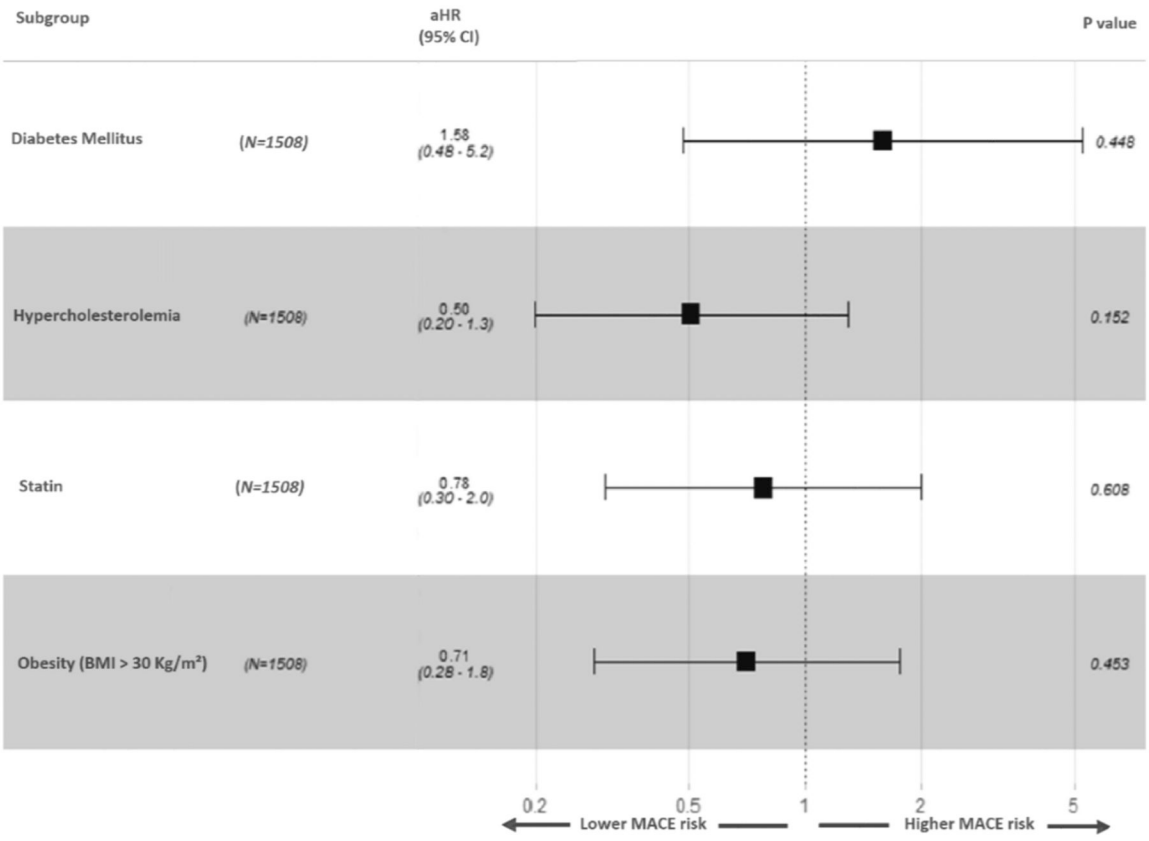


Figure 3.

Adjusted hazard ratios (aHR) for subgroups of women with non-obstructive CAD on coronary CTA. Adjusted for age, HTN and smoking status.

Table 1.

Baseline characteristics of the study cohort.

	All participants (n=2,597)	MACE (n=41)	Without MACE (n=2,556)	P value
Age (yrs. ± SD)	59.8 ± 8.3	62.7 ± 9.7	59.7 ± 8.4	0.057
BMI (Mean, Kg/m^2)	30.3 ± 6.4	29.5 ± 7.1	30.3 ± 6.4	0.51
History of CVD; n (%)	106 (4.1)	3 (7.3)	103 (4.0)	0.51
Current smoker; n (%)	398 (15.3)	14 (34.1)	384 (15.0)	0.10
Hypertension; n (%)	1,436 (55.3)	25 (61.0)	1,411 (55.2)	0.56
Diabetes Mellitus; n (%)	425 (16.4)	10 (24.4)	415 (16.2)	0.23
Serum total cholesterol, mg/dL	208.0 ± 45.6	202.5 ± 55.2	208.1 ± 45.4	0.63
HDL cholesterol, mg/dL	57.8 ± 15.9	52.7 ± 10.7	57.9 ± 16.0	0.036
Medical Therapy				
Any Statin therapy; n (%)	1,728 (66.5)	24 (58.5)	1,704 (66.7)	0.35
Statin at baseline; n (%)	1,433 (55.2)	19 (46.3)	1,414 (55.3)	0.32
Statin 6 to 8 weeks; n (%)	1,499 (57.7)	19 (46.3)	1,480 (57.9)	0.18
Anti-platelet therapy; n (%)	1,064 (41.0)	13 (31.7)	1,051 (41.1)	0.21
ACE-I or ARB; n (%)	794 (30.6)	13 (31.7)	781 (30.6)	0.23
ASCVD risk				
ASCVD score, mean	10.5 ± 9.6	16.5 ± 13.7	10.4 ± 9.5	0.007
Low risk (<7.5%)	1,306 (50.3)	9 (21.9)	1,297 (50.7)	0.14
Intermediate-high risk (≥7.5%)	1,273 (49.0)	32 (78.0)	1,241 (48.6)	0.26
Calcium Score (n=2,389)				
Calcium score = 0	1,378 (53.1)	17 (41.5)	1,361 (53.2)	0.08
Calcium score 1 – 99	757 (29.1)	15 (36.6)	742 (29.0)	0.36
Calcium score 100 – 399	210 (8.1)	6 (14.6)	204 (8.0)	0.21
Calcium score > 400	45 (1.7)	2 (4.9)	43 (1.7)	0.34
Coronary Artery disease (CAD)				
No CAD; n (%)	1089 (41.9)	7 (17.1)	1082 (42.3)	0.002
Non-obstructive CAD n (%)	1508 (58.1)	32 (78)	1476 (57.7)	0.014
Chest pain Characteristics				
Typical; n (%)	396 (15.2)	8 (19.5)	388 (15.2)	0.6
Atypical; n (%)	1676 (64.5)	23 (56.1)	1653 (64.7)	0.3
Non Cardiac; n (%)	525 (20.2)	10 (24.4)	515 (20.1)	0.6

Abbreviations: SD: standard deviation; BMI: Body mass index; CVD: cardiovascular disease; HDL: High density lipoprotein; ACEI-I: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.