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Prognostic Significance of Plaque Location in Nonobstructive Coronary Artery Disease: From the CONFIRM registry

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Abstract

Introduction

Obstructive coronary artery disease (CAD) in proximal coronary segments is associated with a poor prognosis. However, the contribution of proximal plaque location to major adverse cardiovascular events (MACE) in patients with nonobstructive CAD has not been well defined. In this study, we examine MACE risk in relation to the location of nonobstructive coronary artery plaque by coronary CT angiography (CCTA).

Methods

From the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry, 6,619 patients were included in this study. The degree of stenosis was classified as 0 (no), 1-49% (nonobstructive), ≥50% (obstructive). Proximal involvement was defined as any plaque present in the LM or the proximal segment of the LAD, LCX, and RCA. Extensive CAD was defined as segment involvement score of >4. MACE was defined as a composition of all-cause death and myocardial infarction.

Results

During a median follow-up of 5.1 years (IQR 3.5-5.8), 768 (11.6%) MACE occurred. There were 2,579 (39.0%), 2,065 (31.2%) and 1,975 (29.8%) patients with no CAD, nonobstructive CAD, and obstructive CAD, respectively. Within the nonobstructive CAD group, proximal involvement was observed in 1,767 (85.6%) cases. When compared to nonobstructive CAD patients without proximal involvement, those with proximal involvement had an increased MACE risk (log rank p=0.033). Multivariate Cox analysis showed when compared to patients with no CAD, proximal nonobstructive CAD was associated with increased MACE risk (HR: 1.97, 95% CI: 1.54-2.52, p<0.001) after adjusting for extensive CAD and conventional cardiovascular risk factors; however, nonproximal nonobstructive CAD did not increase MACE risk (HR: 1.32, 95% CI:0.83-2.11, p=0.239).

Conclusions

Independent of plaque extent, proximal coronary involvement was associated with increased MACE risk in patients with nonobstructive CAD. The plaque location

information by CCTA may provide additional risk prediction over CAD extent in patients with nonobstructive CAD.

Introduction

Coronary CT angiography (CCTA) is a non-invasive imaging technique that allows for accurate detection and assessment of coronary artery disease (CAD) (1, 2). One particular feature of CAD evaluation by CCTA is it provides information on the presence and distribution of nonobstructive CAD. Previous studies reported that a significant proportion of patients, up to 70%, who underwent CCTA were found to have nonobstructive CAD (3-5). Presence of nonobstructive CAD by CCTA is associated with increased future major adverse cardiovascular events (MACE) when compared to the absence of CAD on CCTA (5-8).

Findings from early angiographic studies suggested that proximally located atherosclerotic plaques are at higher risk of erosion or rupture, which in turn lead to acute coronary events (9, 10). Further, proximal vessels supply larger portions of the myocardium, and the occurrence of acute coronary events in proximal vessels is more likely to lead to a clinically significant event. Although incidence of cardiovascular events is associated with stenosis severity, a substantial proportion of cardiac events arise from nonobstructive coronary lesions (11-13). While the prognostic significance of proximal located plaque in obstructive CAD by CCTA is well established (4, 14-16), the contribution of proximal plaque location to major adverse cardiovascular events (MACE) in patients with nonobstructive CAD is not fully defined. In an international multicenter CCTA registry, we examined MACE risk in relation to the location of nonobstructive coronary artery plaque by CCTA.

Methods

Study population

The Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry is a dynamic, international, multicenter, observational cohort study designed to evaluate the association between patient characteristics, CCTA findings and adverse clinical events. In total, 17,181 patients had been enrolled between February 2003 and May 2011 and underwent CCTA at 17 centers located in nine countries (Austria, Canada, Germany, Israel, Italy, Portugal, South Korea, Switzerland, and USA). Details of the rationale and design of the CONFIRM registry have been described previously (17). In the current study, we excluded patients with incomplete adjudication of clinical events (n=7,914), missing

stenosis severity information (n=440),missing plaque location information (n=1,216) and prior history CAD or revascularization (n=992) (**Figure 1**). Finally, a total of 6,619 patients were included in the current analysis. All study participants provided written informed consent and each of the study sites' institutional review boards approved the study protocol.

Clinical data and image acquisition

Prior to coronary CT scanning procedures, baseline information for each patient were collected, including the presence of traditional cardiac risk factors, age, sex, history of hypertension, diabetes mellitus, hyperlipidemia, smoking status, early family history of early CAD (father <55 or mother <65 years of age) and prior history of CAD. CCTA was performed using multi-detector CT scanners with more than 64 detector rows and following Society of Cardiovascular Computed Tomography guidelines (18). CCTA was interpreted onsite for the presence of coronary atherosclerotic plaque, based on a 16-segment modified SCCT coronary artery model (18). Lesions on CCTA were further categorized according to the severity of stenosis as follows: 0% (no CAD), 1-49% (nonobstructive CAD), ≥50% (obstructive CAD). Proximal involvement was defined as any plaque present in the LM or the proximal segment of the LAD, LCX, and RCA. Extensive CAD was defined as segment involvement score>4 (6).

Study endpoint

The primary outcome of the current study was major adverse cardiovascular events (MACE), which was defined as all-cause mortality and myocardial infarction (MI). Follow-up procedures were approved by all study centers' institutional review boards. Ascertainment of all-cause mortality and MI events were determined by direct/telephone interview, as well as review of medical charts, and/or query of the national medical database at each institution by a dedicated physician and/or research nurse.

Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD), and categorical variables are reported as counts with proportions. Continuous variables are compared using unpaired student t-test and categorical variables are compared

using Pearson's χ^2 test. Comparisons between CCTA stenosis groups were performed by use of a one-way analysis of variance for continuous variables (ANOVA). The Framingham risk score was calculated, and categorized as low (<10%), intermediate (10–20%), or high (>20%) risk groups (19). Cumulative MACE incidence was assessed using the Kaplan-Meier method and compared with log rank test. Cox proportional hazard regression analysis was used to calculate hazard ratio (HR) with 95% confidence interval (CI). Multivariable analysis was adjusted for cardiovascular risk factors including age, gender, body mass index, hypertension, diabetes, dyslipidemia, smoking, prior CAD history, and family history of CAD and extensive CAD. All statistical analyses were performed using STATA (version 14; StataCorp, College Station, TX, USA), and a $p<0.05$ was considered statistically significant.

Results

The mean age of the study population was 59.7±12.0 years and 62.5% were male. There were 2,579 (39.0%), 2,065 (31.2%) and 1,975 (29.8%) patients who had no, nonobstructive and obstructive CAD by CCTA, respectively. The prevalence of hypertension, diabetes, dyslipidemia, current smoker status and prior CAD history were increased in patients with higher stenosis severity (all $p<0.001$, **Table 1**). The proportion of patients with family history of CAD did not differ between stenosis groups ($p=0.377$).

Of the 2,065 patients with nonobstructive CAD, 1,767 (85.6%) patients had proximal segment involvement. Patients with nonobstructive CAD with proximal involvement were older ($p=0.019$) and the prevalence of hypertension and dyslipidemia were greater than patients without proximal involvement (All p-value<0.05, **Table 2**). The proportion of male and patients with diabetes, current smoker, prior CAD history and family history did not differ between proximal involvement and non-proximal CAD patients. The FRS was higher in patients with proximal involvement.

During the median 5.1 years (IQR: 3.5-5.8) of study follow-up, 768 (11.6%) MACE occurred (335 ACM and 433 MI). The annualized MACE rate was 0.9 (95% CI 0.8-1.1)

and 2.1 (95% CI 1.8-2.4) for the no-CAD and nonobstructive CAD group; this increased further to 5.2 (95% CI 4.7-5.7) among patients with obstructive CAD (**Table 3**). When further stratified by proximal involvement in the nonobstructive CAD group, the annualized MACE rate was 1.3 (95% CI 0.8-2.0) and 2.2 (95% CI 1.9-2.5) for nonobstructive CAD without proximal involvement and with proximal involvement, respectively. In the Kaplan Meier curve analysis, the presence of proximal involvement was associated with higher rates of MACE when compared to patients without proximal involvement (p=0.033, **Figure 2**). In contrast, no significant difference in MACE rates were found between patients with no CAD vs. patients with nonobstructive CAD without proximal involvement (p=0.122). Patients with both extensive and proximal involvement of nonobstructive CAD had greater probability for MACE compared to patients with nonextensive with proximal involvement or patients with non-extensive with non-proximal involvement CAD (log rank p<0.001 for trend, **Figure 3**).

In Cox regression analysis, nonobstructive CAD was associated with higher MACE risk compared to patients with no apparent CAD (HR: 1.87 95% CI: 1.46-2.37, p<0.001). After adjustment for the conventional cardiovascular risk factor and extensive CAD, nonobstructive CAD with proximal involvement was a significant predictor of MACE (HR: 1.97, 95% CI: 1.54-2.52, p<0.001; Table 4). In contrast, nonobstructive CAD without proximal involvement did not significantly increase MACE risk (HR: 1.32, 95% CI:0.83-2.11, p=0.239). Nonobstructive proximal involvement of the LM and the other three major epicardial coronary arteries (proximal LAD, LCX and RCA) were independently associated with increased MACE risk (**Table 5**, all p<0.05).

Discussion

In this prospective observational multicenter registry, we demonstrated that proximal involvement in nonobstructive CAD was associated with a two-fold higher risk of MACE compared to patients with no CAD as assessed by CCTA, independent of plaque extent and conventional CAD risk factors. Furthermore, patients with both extensive and proximal CAD had greater risk of MACE compared to patients with either non-extensive or non-proximal nonobstructive CAD. Nonobstructive CAD localized in the mid or distal segments did not significantly increase MACE risk when

compared to patients with no CAD. The current study findings suggest that the assessment of coronary plaque location by CCTA may enhance the utility of CCTA to risk-stratify patients with nonobstructive CAD.

Prior angiographic studies have demonstrated that plaque rupture and thrombotic occlusion tend to cluster in the proximal third of the coronary arteries (9, 10, 20). In addition, the presence and severity of CAD in the proximal coronary segments have shown to be strong predictors of prognosis. In studies with patients who underwent coronary artery calcium (CAC) scan, the presence and high burden of CAC in the LM are independently associated with increased mortality rate compared to other coronary arteries (21, 22). In another study from the Framingham Heart Study, the presence of CAC in the proximal coronary artery predicted major coronary heart disease events after adjustment for cardiovascular risk factors and Agatston CAC score (23). Several studies with coronary CT angiography have also demonstrated the prognostic significance of proximal CAD, while those studies paid more attention to risk in obstructive CAD (14-16).

Prior efforts to improve risk stratification of nonobstructive CAD by CCTA have mainly focused on characterizing the extent of affected coronary segments by nonobstructive plaque. Lin et al. examined mortality risk in relation to the extent of nonobstructive CAD in 2,583 patients and found that the risk of mortality was significantly increased as the number of segments with nonobstructive plaques increased (6). In another study, Bittencourt et al. reported that the presence of extensive nonobstructive disease, defined as segment involvement score >4, was associated with an increased rate of MACE events, whereas non-extensive nonobstructive CAD was not (7). Few prior studies demonstrated that assessing the number of proximal segments with any plaques or nonobstructive LM disease improved the prediction of adverse cardiovascular outcomes (15, 24, 25), while these studies did not explore the prognostic significance in nonobstructive CAD. One study by Mushtaq et al. reported that a detailed scoring system weighting more risk in the LM, proximal LAD, and LCX was independently associated with increased cardiovascular risk (26). Our findings confirm and expand these prior observations by demonstrating the proximal involvement of nonobstructive CAD was independently associated with increased MACE risk. Furthermore, considering both

extent and proximal involvement of CAD provided an improved risk stratification in patients with nonobstructive CAD.

One of the potential benefits of CCTA is identifying the early stages of atherosclerotic disease within the coronary arteries, allowing to identify patients who could benefit from aggressive preventive care and risk factor modification. The recent long-term follow-up in the Scottish COmputed Tomography of the HEART (SCOT-HEART) study demonstrated significant MACE reductions in the CCTA randomized arm, coupled with increased prescription of statin and aspirin for CCTA-visualized nonobstructive disease (27). In the current study, there is heterogeneities in MACE risk in patients with nonobstructive CAD according to plaque location and extension. The assessments of location and extent of plaque involvement are easy to adopt in clinical practice and may allow improved risk-stratification of patients with nonobstructive CAD.

Limitations

Our study has few limitations. Due to the observed nature of the current study, we cannot discount the possibility of unmeasured confounding factors that might affect the clinical endpoints of this study. The information regarding downstream pharmacological and/or interventional management after CCTA was unavailable. Future studies investigating the impact of medication adjustment (e.g. aspirin, statin, and beta-blockers) on outcomes in patients with nonobstructive CAD should be performed. The clinical endpoint examined was all cause mortality and clinically recorded MI. Thus, it is possible that MI events occurred in small mid or distal segments may not have been recorded as a significant clinical event. This may explain, in part, our observation of a similar MACE rates between patients with nonproximal nonobstructive CAD vs. with no CAD.

Conclusion

Independent of the extent of coronary plaque, proximal coronary involvement was associated with increased MACE risk in patients with nonobstructive CAD. Localization of coronary plaques by CCTA may provide additional prognostic value for MACE risk prediction in patients with nonobstructive CAD.

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Figure 1. Study flow

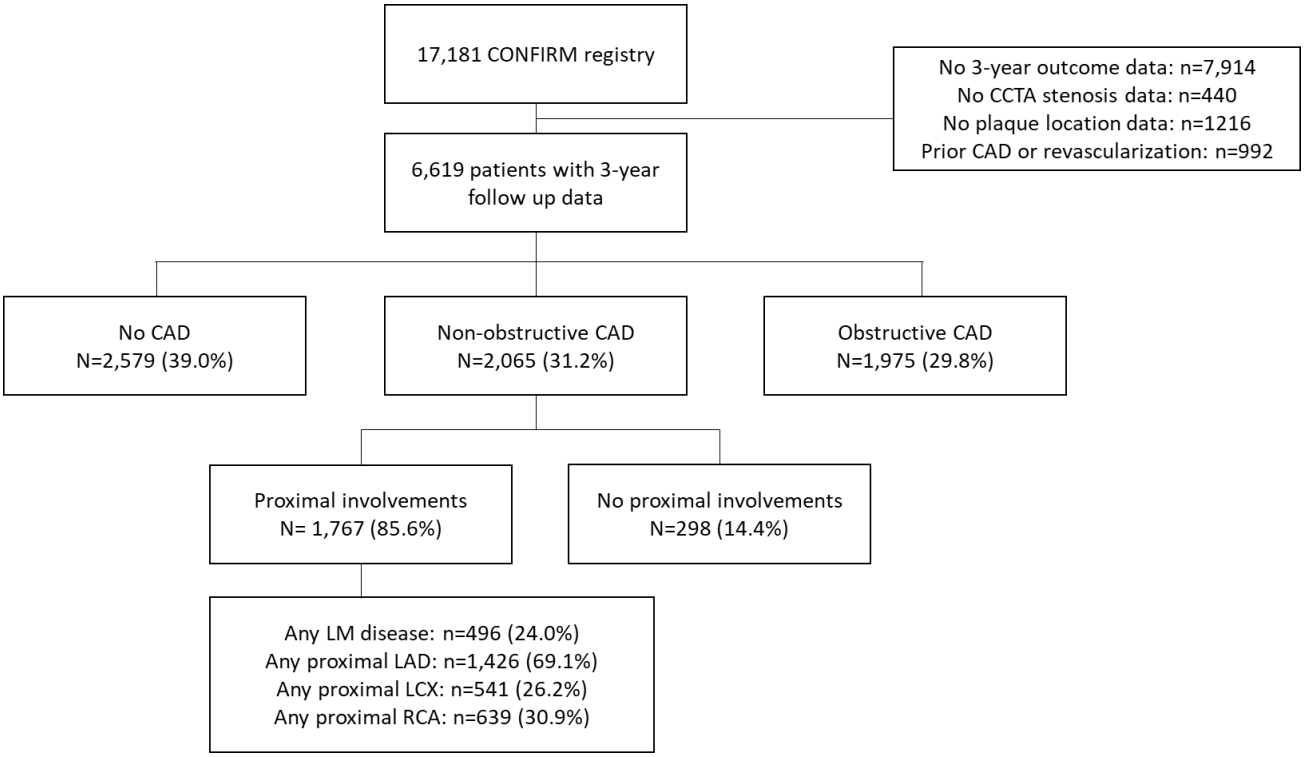

Figure 2. Kaplan-Meier curve for MACE according to stenosis severity and proximal involvement

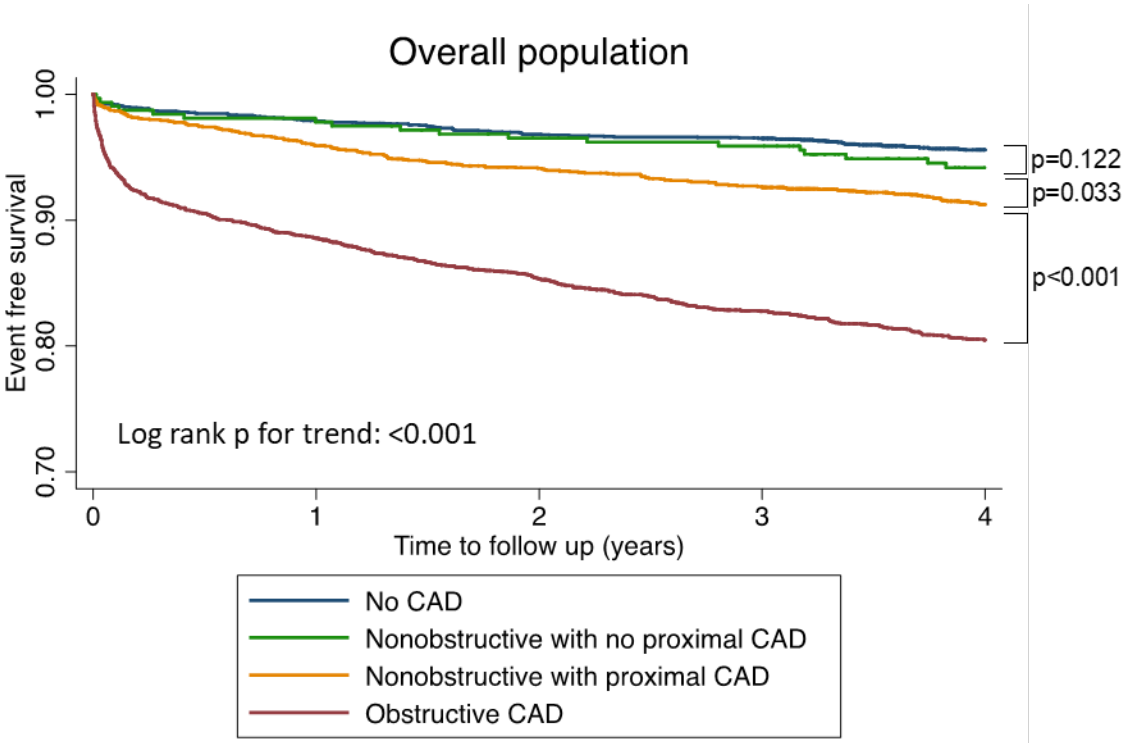

Figure 3. Kaplan-Meier curve for MACE according to extensive CAD and proximal involvement in nonobstructive CAD

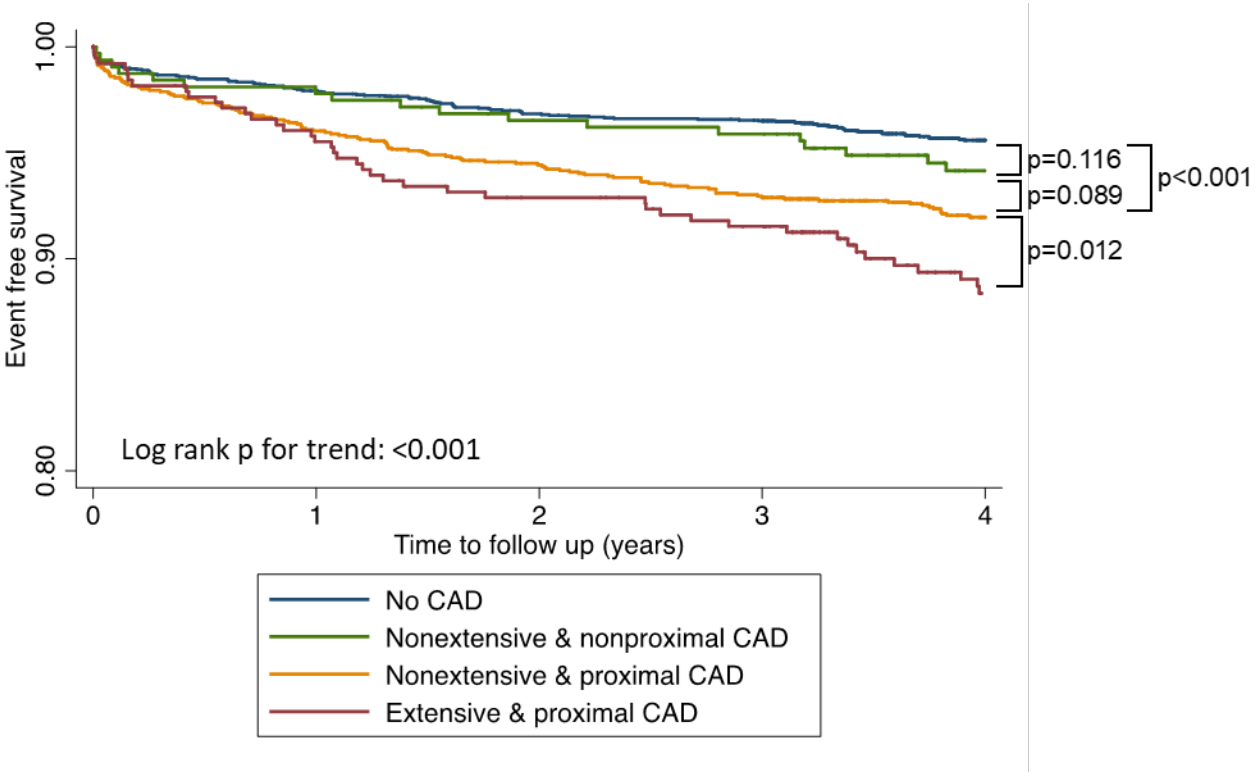

Table 1. Baseline characteristics by CCTA stenosis				
	No CAD (n=2,579)	Nonobstructive CAD (n=2,065)	Obstructive CAD (n=1,975)	p-value
Age (years)	53.3±12.2	61.0±10.5	63.9±10.1	<0.001
Male	1,258 (48.9)	1,282 (62.1)	1,428 (72.3)	<0.001
BMI	27.4±5.2	27.9±5.2	27.1±4.5	<0.001
Hypertension	1,110 (43.2)	1,161 (56.6)	1,242 (63.2)	<0.001
Diabetes	286 (11.1)	280 (13.6)	480 (24.4)	<0.001
Dyslipidemia	1,067 (41.7)	1,188 (57.8)	1,206 (61.4)	<0.001
Current smoking	421 (16.5)	355 (17.3)	479 (24.5)	<0.001
Family history of CAD	804 (31.6)	609 (29.7)	592 (30.5)	0.377
Framingham risk score	9.6±7.8	14.3±10.3	19.6±13.6	<0.001
Low (<10)	1,678 (65.8)	869 (42.5)	518 (26.5)	<0.001
Intermediate (10-20)	643 (25.2)	751 (36.7)	691 (35.3)	<0.001
High (>20)	228 (8.9)	427 (20.9)	747 (38.2)	<0.001
Values are mean ± standard deviation or number (percentage)				
Abbreviations: CCTA, coronary computed tomography angiography; CAD, coronary artery disease; BMI, body mass index				

Table 2. Baseline characteristics of patients with nonobstructive CAD according to proximal involvement

	With proximal disease	Without proximal disease	p-value
Age (years)	61.2±10.6	59.7±10.5	0.019
Male	1,097 (62.2)	185 (62.1)	0.981
BMI	28.0±5.2	27.5±5.0	0.139
Hypertension	1,021 (58.2)	140 (47.1)	<0.001
Diabetes	244 (13.9)	36 (12.1)	0.412
Dyslipidemia	1,041 (59.3)	147 (49.5)	0.002
Current smoking	300 (17.1)	55 (18.5)	0.563
Family history of CAD	526 (30.0)	83 (28.0)	0.465
Prior CAD history	129 (6.8)	21 (6.6)	0.885
Framingham risk score	14.5±10.5	13.1±9.1	0.039
Low (<10)	729 (41.7)	140 (47.1)	0.077
Intermediate (10-20)	647 (37.0)	104 (35.0)	0.518
High (>20)	374 (21.4)	53 (17.9)	0.167

Values are mean ± standard deviation or number (percentage)

Abbreviations: CCTA, coronary computed tomography angiography; CAD, coronary artery disease; BMI, body mass index

Table 3. Incidence of major adverse cardiovascular events			
	Number of patients	Number of MACE (%)	Annualized MACE rate (95% CI)
Overall	6,619	981 (12.9)	2.3 (2.2-2.5)
No CAD	2,579	125 (4.9)	0.9 (0.8-1.1)
Nonobstructive CAD	2,065	215 (10.4)	2.1 (1.8-2.4)
Without proximal disease	298	22 (7.4)	1.3 (0.9-2.0)
With proximal disease	1,767	193 (10.9)	2.2 (1.9-2.5)
Obstructive CAD	1,975	428 (21.7)	5.2 (4.7-5.7)
Abbreviations: MACE, Major adverse cardiovascular events; CAD, coronary artery disease			

Table 4. Cox regression analysis						
	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Clinical characteristics						
Age (years)	1.05	1.04-0.05	<0.001	1.03	1.02-1.04	<0.001
Male	1.06	0.91-1.23	0.459	0.88	0.75-1.04	0.135
BMI (>30 kg/m2)	1.39	1.20-1.62	<0.001	1.67	1.43-1.94	<0.001
Hypertension	1.59	1.37-1.86	<0.001	1.08	0.92-1.27	0.347
Diabetes	1.95	1.64-2.31	<0.001	1.42	1.19-1.69	<0.001
Dyslipidemia	0.95	0.92-1.10	0.518	0.71	0.61-0.83	<0.001
Current smoking	1.33	1.12-1.58	0.001	1.35	1.13-1.61	0.001
Family history of CAD	0.83	0.70-0.98	0.026	0.94	0.79-1.11	0.466
CCTA characteristics						
SIS>4	2.78	2.39-3.23	<0.001	1.26	1.05-1.50	0.011
Nonobstructive CAD	2.03	1.64-2.50	<0.001	1.87	1.46-2.37	<0.001
Without proximal	1.46	0.92-2.33	0.106	1.32	0.83-2.11	0.239
With proximal	2.37	1.89-2.99	<0.001	1.97	1.54-2.52	<0.001
Obstructive CAD	5.27	4.29-6.47	<0.001	3.77	2.94-4.82	<0.001
Abbreviations: CCTA, coronary computed tomography angiography; CAD, coronary artery disease; BMI, body mass index; HR, hazard ratio; CI, confidence interval; SIS, segment involvement score						

Table 5. Cox regression analysis according to location of proximal coronary segments

	HR	95% CI	p-value
Any LM	1.38	1.11-1.71	0.004
Any proximal LAD	1.56	1.30-1.88	<0.001
Any proximal LCX	1.41	1.16-1.72	0.001
Any proximal RCA	1.47	1.21-1.79	<0.001

* Adjustment for age, BMI, sex, hypertension, diabetes, dyslipidemia, smoking, family history of CAD, and extensive CAD (SIS>4)

Abbreviations: LM, left main, LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; CAD, coronary artery disease; HR, hazard ratio; CI, confidence interval; SIS, segment involvement score