11-15-2021

Prognostic significance of plaque location in non-obstructive coronary artery disease: from the CONFIRM registry

Donghee Han

Billy Chen

Heidi Gransar

Stephan Achenbach

Mouaz H. Al-Mallah

See next page for additional authors

Authors

Donghee Han, Billy Chen, Heidi Gransar, Stephan Achenbach, Mouaz H. Al-Mallah, Matthew J. Budoff, Filippo Cademartiri, Erica Maffei, Tracy Q. Callister, Kavitha Chinnaiyan, Benjamin J.W. Chow, Augustin DeLago, Martin Hadamitzky, Joerg Hausleiter, Philipp A. Kaufmann, Todd C. Villines, Yong-Jin Kim, Jonathon Leipsic, Gudrun Feuchtner, Ricardo C. Cury, Gianluca Pontone, Daniele Andreini, Hugo Marques, Ronen Rubinshtein, Hyuk-Jae Chang, Fay Y. Lin, Leslee J. Shaw, James K. Min, and Daniel S. Berman

ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2021) **00**, 1–8
https://doi.org/10.1093/ehjci/jeab223

ORIGINAL PAPER

Prognostic significance of plaque location in non-obstructive coronary artery disease: from the CONFIRM registry

Donghee Han[1], Billy Chen[1], Heidi Gransar [1], Stephan Achenbach[2], Mouaz H. Al-Mallah [3], Matthew J. Budoff[4], Filippo Cademartiri [5], Erica Maffei[5], Tracy Q. Callister[6], Kavitha Chinnaiyan[7], Benjamin J.W. Chow[8], Augustin DeLago[9], Martin Hadamitzky[10], Joerg Hausleiter[11], Philipp A. Kaufmann[12], Todd C. Villines[13], Yong-Jin Kim[14], Jonathon Leipsic[15], Gudrun Feuchtner [16], Ricardo C. Cury[17], Gianluca Pontone[18], Daniele Andreini[18], Hugo Marques[19], Ronen Rubinshtein[20], Hyuk-Jae Chang [21], Fay Y. Lin[22], Leslee J. Shaw[23], James K. Min[24], and Daniel S. Berman [1]*

[1]Department of Imaging, Cedars Sinai Medical Center, 8700 Beverly Blvd, Los Angeles, CA 90048 USA; [2]Department of Medicine, University of Erlangen, Schloßplatz 4, 91054 Erlangen, Germany; [3]Department of Medicine, Wayne State University, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202 USA; [4]Department of Medicine, Harbor UCLA Medical Center, 1000 W Carson St, Torrance, CA 90502, USA; [5]Department of Radiology/Centre de Recherche, Montreal Heart Institute/Unniversitè de Montreal, Montreal, 5000 Rue Bélanger, Montréal, QC H1T 1C8, Canada; [6]Department of Cardiology, Tennessee Heart and Vascular Institute, 353 New Shackle Island Rd Hendersonville, TN 37075 USA; [7]Department of Cardiology, William Beaumont Hospital, 3535 W 13 Mile Rd #742, Royal Oak, MI 48073, USA; [8]Department of Medicine and Radiology, University of Ottawa, 40 Ruskin St, Ottawa, ON K1Y 4W7, Canada; [9]Capitol Cardiology Associate, 7 Southwoods Blvd, Albany, NY 12211 USA; [10]Department of Radiology and Nuclear Medicine, German Heart Center Munich, Lazarettstraße 36, 80636 München, Germany; [11]Department of Radiology, Medizinische Klinik I der Ludwig-Maximilians-Universität München, Ziemssenstraße 1, 80336 München, Germany; [12]Department of Nuclear Medicine, University Hospital of Zurich, Rämistrasse 100, 8091 Zürich, Switzerland; [13]Department of Medicine, Walter Reed Medical Center, 4494 Palmer Rd N, Bethesda, MD 20814, USA; [14]Department of Medicine, Seoul National University Hospital, Jongno-gu, Seoul 03080, South Korea; [15]Department of Medicine and Radiology, University of British Columbia, 1081 Burrard Street Vancouver, BC V6Z 1Y6, Canada; [16]Department of Radiology, Medical University of Innsbruck, Christoph-Probst-Platz 1, Innrain 52 A, Fritz-Pregl-Straße 3, 6020 Innsbruck, Austria; [17]Department of Radiology, Miami Cardiac and Vascular Institute, 8900 N Kendall Dr, Miami, FL 33176, USA; [18]Department of Cardiology, Centro Cardiologico Monzino, IRCCS Milan, Via Carlo Parea, 4, 20138 Milano, MI, Italy; [19]Department of Surgery, Curry Cabral Hospital, R. da Beneficência 8, 1050-099 Lisbon, Portugal; [20]Department of Cardiology at the Lady Davis Carmel Medical Center, The Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, 3200003, Israel; [21]Division of Cardiology, Department of Internal Medicine, Severance Cardiovascular Hospital and Severance Biomedical Science Institute, Yonsei University College of Medicine, Yonsei University Health System, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, 03722, South Korea; [22]Dalio Institute of Cardiovascular Imaging, Department of Radiology, New York-Presbyterian Hospital and the Weill Cornell Medicine, 428 East, 72nd Street, New York, NY 10021; [23]Department of Population Health Science, Blavatnik Women's Health Research Institute, Mount Sinai School of Medicine, NY, USA; and [24]Cleerly, Inc., 101 Greenwich St, New York, NY 10006, USA

Received 9 July 2021; editorial decision 8 October 2021; accepted 11 October 2021

Aim Obstructive coronary artery disease (CAD) in proximal coronary segments is associated with a poor prognosis. However, the relative importance of plaque location regarding the risk for major adverse cardiovascular events (MACE) in patients with non-obstructive CAD has not been well defined.

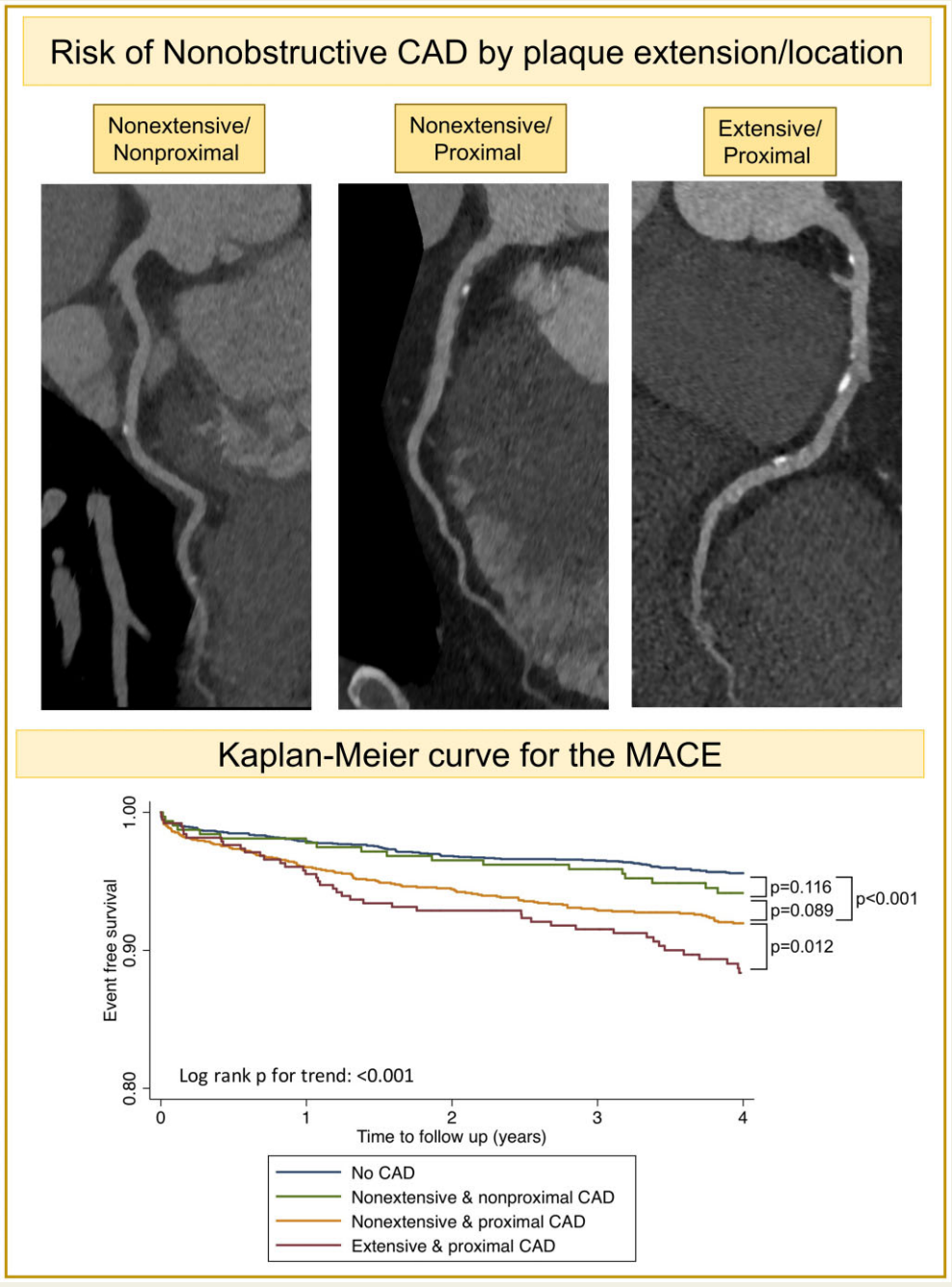
Methods and results From the Coronary CT Angiography Evaluation for Clinical Outcomes: An International Multicenter (CONFIRM) registry, 4644 patients without obstructive CAD were included in this study. The degree of stenosis was classified as 0 (no) and 1–49% (non-obstructive). Proximal involvement was defined as any plaque present in the left main or the proximal segment of the left anterior descending artery, left circumflex artery, and right coronary artery. Extensive CAD was defined as segment involvement score of >4. During a median follow-up of 5.2 years (interquartile range 4.1–6.0), 340 (7.3%) MACE occurred. Within the non-obstructive CAD group ($n = 2065$), proximal involvement was observed in 1767 (85.6%) cases. When compared to non-obstructive 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 non-obstructive CAD was associated

* Corresponding author. Tel: +1 310 423 4223. E-mail: daniel.berman@cshs.org

with increased MACE risk [hazard ratio (HR) 1.90, 95% confidence interval (CI) 1.47–2.45, $P < 0.001$] after adjusting for extensive CAD and conventional cardiovascular risk factors; however, non-proximal non-obstructive CAD did not increase MACE risk (HR 1.26, 95% CI 0.79–2.01, $P = 0.339$).

Conclusions Independent of plaque extent, proximal coronary involvement was associated with increased MACE risk in patients with non-obstructive CAD. The plaque location information by coronary computed tomography angiography may provide additional risk prediction over CAD extent in patients with non-obstructive CAD.

Graphical Abstract



Keywords coronary artery disease • non-obstructive • plaque location • prognosis • computed tomography

Introduction

Coronary computed tomography angiography (CCTA) is a non-invasive imaging technique that allows for accurate detection and assessment of coronary artery disease (CAD).[1,2] One feature of CAD evaluation by CCTA is that it provides information on the presence, quantity, and distribution of non-obstructive coronary atherosclerotic lesions. Previous studies reported that a significant proportion of patients, up to 70%, who underwent CCTA were found to have non-obstructive CAD.[3–5] Presence of non-obstructive 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 with the consequence of acute coronary events.[9,10] Furthermore, 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 the incidence of cardiovascular events is associated with stenosis severity, a substantial proportion of cardiac events arise from non-obstructive coronary lesions.[11–13] While the prognostic significance of proximally located plaque in obstructive CAD by CCTA is well established,[4,14–16] the contribution of proximal plaque location to MACE in patients with non-obstructive CAD is not fully defined. In an international multicentre CCTA registry, we examined MACE risk in relation to the location of non-obstructive 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, multicentre, 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 centres 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 ($n = 7914$), missing stenosis severity information ($n = 440$), missing plaque location information ($n = 1216$), prior history CAD or revascularization ($n = 992$), and obstructive CAD ($n = 1975$) (*Figure 1*). Finally, a total of 4644 patients were included in the current analysis. All study

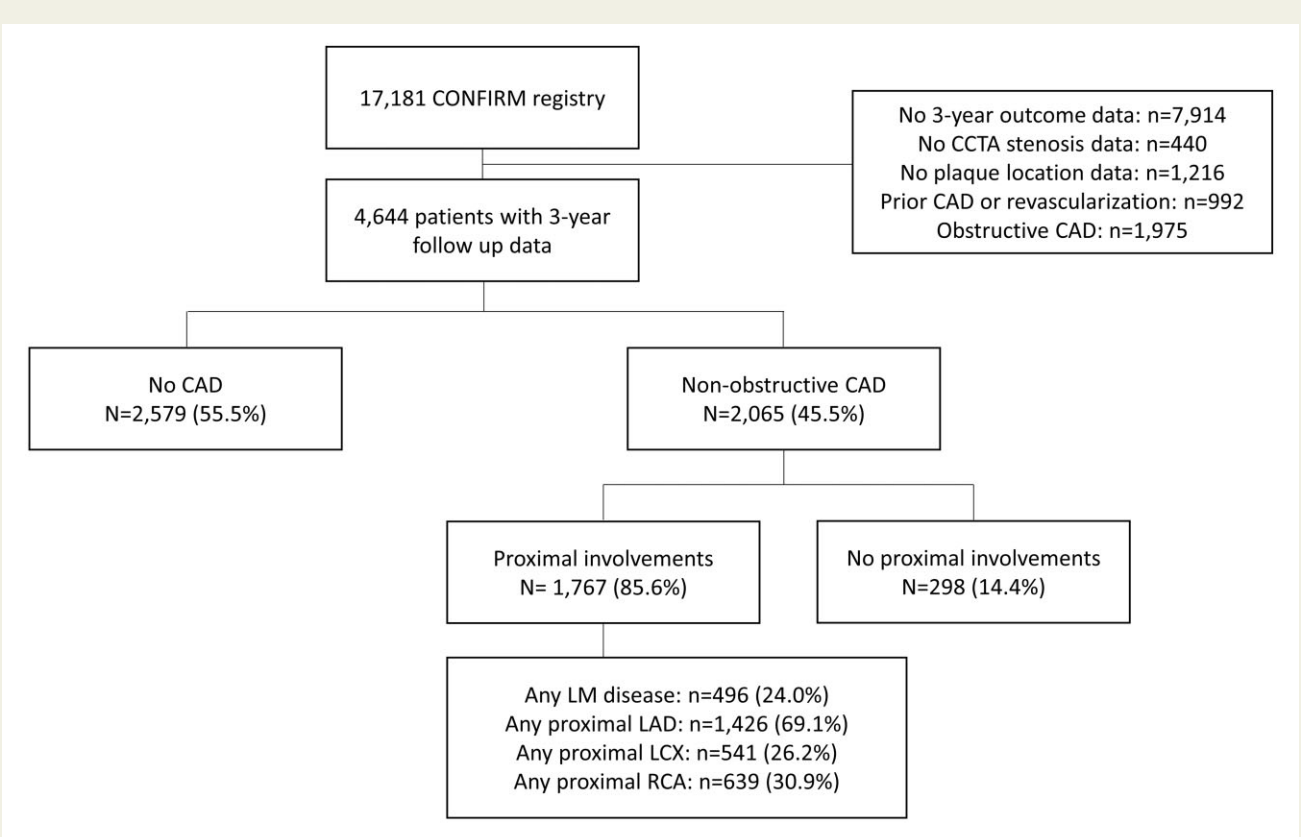


Figure 1 Study flow. CAD, coronary artery disease; CCTA, coronary computed tomography angiograpy; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; RCA, right coronary artery.

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 computed tomography (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, hyperlipidaemia, 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) and 1–49% (non-obstructive CAD). Proximal involvement was defined as any plaque present in the left main (LM) or the proximal segment of the left anterior descending artery (LAD), left circumflex artery (LCX), and right coronary artery (RCA). Extensive CAD was defined as a segment involvement score (SIS) >4.[6]

Study endpoint

The primary outcome of the current study was MACE, which was defined as all-cause mortality (ACM) and myocardial infarction (MI). Follow-up procedures were approved by all study centres' institutional review boards. Ascertainment of ACM and MI events was 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, and categorical variables are reported as counts with proportions. Continuous variables are compared using unpaired Student's *t*-test and categorical variables are compared using Pearson's χ^2 test. 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, dyslipidaemia, smoking, 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*-value <0.05 was considered statistically significant.

Results

The mean age of the study population was 56.7 ± 12.1 years and 54.8% were male. Baseline characteristics according to CCTA stenosis are shown in *Table 1*. There were 2579 (55.5%) and 2065 (44.5%) patients who had no and non-obstructive CAD by CCTA, respectively. The prevalence of hypertension, diabetes, and dyslipidaemia were increased in patients with non-obstructive CAD. The proportion of patients with family history of CAD and current smoker did not differ between stenosis groups.

Table 1 Baseline characteristics by CCTA stenosis

	No CAD (*n* = 2579)	Non-obstructive CAD (*n* = 2065)	*P*-value
Age (years)	53.3 ± 12.2	61.0 ± 10.5	<0.001
Male	1258 (48.9)	1282 (62.1)	<0.001
BMI	27.4 ± 5.2	27.9 ± 5.2	0.005
Hypertension	1110 (43.2)	1161 (56.6)	<0.001
Diabetes	286 (11.1)	280 (13.6)	0.010
Dyslipidaemia	1067 (41.7)	1188 (57.8)	<0.001
Current smoking	421 (16.5)	355 (17.3)	0.440
Family history of CAD	804 (31.6)	609 (29.7)	0.170
Framingham risk score	9.6 ± 7.8	14.3 ± 10.3	<0.001
Low (<10)	1678 (65.8)	869 (42.5)	<0.001
Intermediate (10–20)	643 (25.2)	751 (36.7)	<0.001
High (>20)	228 (8.9)	427 (20.9)	<0.001

Values are mean ± standard deviation or number (percentage).
BMI, body mass index; CAD, coronary artery disease; CCTA, coronary computed tomography angiography.

Of the 2065 patients with non-obstructive CAD, 1767 (85.6%) patients had proximal segment involvement. Patients with non-obstructive CAD with proximal involvement were older ($P = 0.019$) and the prevalence of hypertension and dyslipidaemia were greater than patients without proximal involvement (all $P < 0.05$, *Table 2*). The proportion of male and patients with diabetes, current smoker and family history did not differ between proximal involvement and non-proximal CAD patients. The Framingham risk score was higher

Table 2 Baseline characteristics of patients with non-obstructive CAD according to proximal involvement

	With proximal disease (*n* = 1767)	Without proximal disease (*n* = 298)	*P*-value
Age (years)	61.2 ± 10.6	59.7 ± 10.5	0.019
Male	1097 (62.2)	185 (62.1)	0.981
BMI	28.0 ± 5.2	27.5 ± 5.0	0.139
Hypertension	1021 (58.2)	140 (47.1)	<0.001
Diabetes	244 (13.9)	36 (12.1)	0.412
Dyslipidaemia	1041 (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
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
Non-extensive CAD (SIS ≤ 4)	1415 (80.1)	297 (99.7)	<0.001
Extensive CAD (SIS > 4)	352 (19.9)	1 (0.3)	<0.001

Values are mean ± standard deviation or number (percentage).
BMI, body mass index; CAD, coronary artery disease; SIS, segment involvement score.

in patients with proximal involvement. Extensive CAD (SIS > 4) was observed in 19.9% of patients with proximal involvement, while was only 0.3% (1/298) in non-proximal CAD patients.

During the median 5.2 years (interquartile range 4.1–6.0) of study follow-up, 340 (7.3%) MACE occurred (195 ACM and 145 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 non-obstructive CAD group (*Table 3*). When patients with non-obstructive CAD were further stratified by proximal involvement, the annualized MACE rate was 1.3 (95% CI 0.8–2.0) and 2.2 (95% CI 1.9–2.5) for non-obstructive CAD without proximal involvement and with proximal involvement, respectively. In 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 non-obstructive CAD without proximal involvement ($P = 0.122$). Patients with non-obstructive CAD that was both extensive (more than four segments) and included proximal involvement had greater probability for MACE compared to patients with non-obstructive CAD that was non-extensive but included proximal involvement or with non-extensive and non-proximal involvement (log-rank $P < 0.001$ for trend, *Figure 3*).

In Cox regression analysis, the presence of any non-obstructive CAD was associated with higher MACE risk compared to patients with no apparent CAD (HR 2.24, 95% CI 1.79–2.81, $P < 0.001$). After adjustment for conventional cardiovascular risk factors and the presence of extensive CAD, non-obstructive CAD with proximal involvement was a significant predictor of MACE (HR 1.90, 95% CI 1.47–2.45, $P < 0.001$; *Table 4*). In contrast, non-obstructive CAD without proximal involvement did not significantly increase MACE risk (HR 1.26, 95% CI 0.79–2.01, $P = 0.339$). When compared to non-obstructive non-proximal CAD, proximal involvement was associated with numerically increased MACE risk with borderline significance (HR 1.52, 95% CI 0.98–2.36, $P = 0.060$, Supplementary data online, *Table S1*). When further stratified by type of event (ACM or MI), non-obstructive CAD with proximal involvement significantly increased the risk of both ACM and MI ($P = 0.018$ and 0.001, respectively; Supplementary data online, *Table S2*). Non-obstructive 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 $P < 0.05$).

Table 3 Incidence of MACE

	Number of patients	Number of MACE (%)	Annualized MACE rate (95% CI)
Overall	4644	340 (7.3)	1.4 (1.3–1.6)
No CAD	2579	125 (4.9)	0.9 (0.8–1.1)
Non-obstructive CAD	2065	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	1767	193 (10.9)	2.2 (1.9–2.5)

CAD, coronary artery disease; CI, confidence interval; MACE, major adverse cardiovascular events.

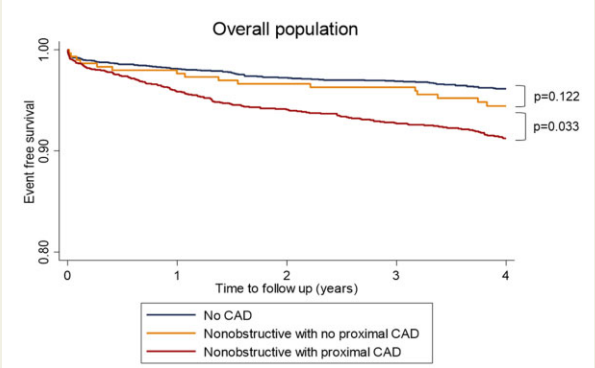


Figure 2 Kaplan–Meier curve for MACE according to stenosis severity and proximal involvement. CAD, coronary artery disease.

Statin use information was available in 73% of the study population ($n = 3374$). When further adjustment for the statin use in multivariate Cox regression analysis, proximal involvement was still a significant predictor of MACE (HR 2.25, 95% CI 1.60–3.18, $P < 0.001$; Supplementary data online, *Table S3*).

Discussion

In this prospective observational multicentre registry, we demonstrated that the presence of non-obstructive plaque in proximal coronary segments was associated with a two-fold higher risk of MACE compared to patients without 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 non-obstructive CAD. Non-obstructive 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 non-obstructive 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 CCTA 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 non-obstructive CAD by CCTA have mainly focused on characterizing the extent of affected coronary segments by non-obstructive plaque. Lin *et al.*[6]

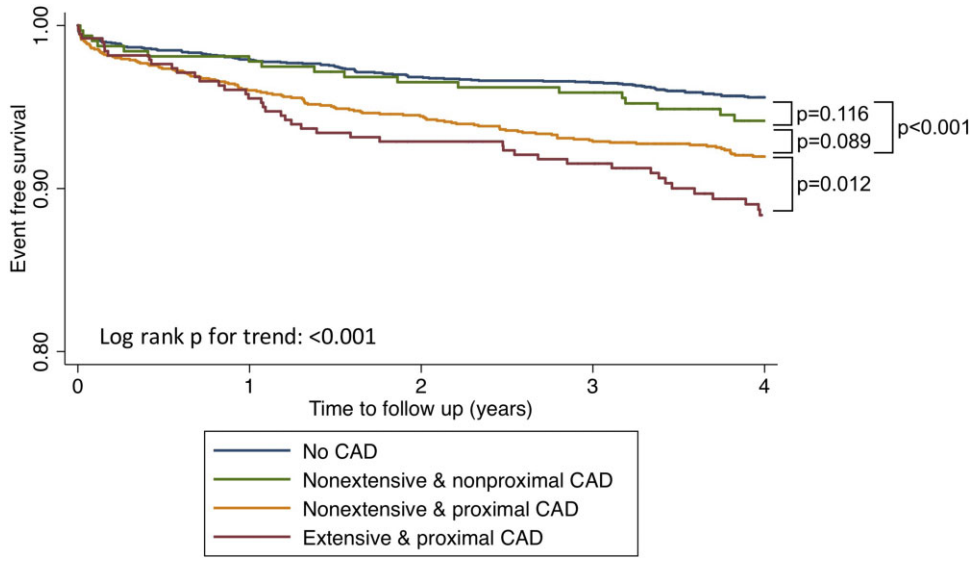


Figure 3 Kaplan–Meier curve for MACE according to extensive CAD and proximal involvement in non-obstructive CAD. CAD, coronary artery disease; MACE, major adverse cardiovascular events.

Table 4 Cox regression analysis

	Univariate			Multivariate		
	HR	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
Clinical characteristics						
Age (years)	1.05	1.04–1.05	<0.001	1.04	1.03–1.05	<0.001
Male	0.97	0.78–1.21	0.784	1.04	0.83–1.31	0.731
BMI (>30 kg/m^2)	1.71	1.38–2.13	<0.001	1.88	1.50–2.36	<0.001
Hypertension	1.67	1.33–2.08	<0.001	1.21	0.95–1.53	0.117
Diabetes	1.81	1.38–2.38	<0.001	1.48	1.11–1.96	0.007
Dyslipidaemia	0.82	0.65–1.02	0.069	0.64	0.51–0.80	<0.001
Current smoking	1.28	0.98–1.67	0.067	1.45	1.11–1.91	0.007
Family history of CAD	0.78	0.61–1.00	0.051	0.97	0.75–1.25	0.804
CCTA characteristics						
SIS > 4	2.31	0.71–3.12	<0.001	1.23	0.84–1.81	0.293
Non-obstructive CAD	2.24	1.79–2.81	<0.001	1.75	1.36–2.25	<0.001
Without proximal	1.45	0.91–2.31	0.115	1.26	0.79–2.01	0.339
With proximal	2.39	1.90–3.00	<0.001	1.90	1.47–2.45	<0.001

BMI, body mass index; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CI, confidence interval; HR, hazard ratio; SIS, segment involvement score.

examined mortality risk in relation to the extent of non-obstructive CAD in 2583 patients and found that the risk of mortality was significantly increased as the number of segments with non-obstructive plaques increased. In another study, Bittencourt *et al.*[7] reported that the presence of extensive non-obstructive disease, defined as SIS >4, was associated with an increased rate of MACE events, whereas non-extensive non-obstructive CAD was not. Few prior studies demonstrated that assessing the number of proximal segments with any plaques or non-obstructive LM disease improved the prediction of adverse cardiovascular outcomes.[15,24,25] In addition, Weir-McCall *et al.*[26] reported the presence of non-obstructive LM disease was associated with greater plaque progression and higher prevalence of high-risk plaque compared to those without LM involvement. However, these studies did not explore the prognostic significance of proximal involvement in non-obstructive CAD. One study by Mushtaq *et al.*[27] reported that a detailed scoring system weighting more risk in the LM, proximal LAD, and LCX was independently associated with increased cardiovascular risk. Our findings confirm

Table 5 Cox regression analysis[a] 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

BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main, RCA, right coronary artery.
[a]Adjustment for age, BMI, sex, hypertension, diabetes, dyslipidaemia, smoking, family history of CAD, and extensive CAD (SIS > 4).

and expand these prior observations by demonstrating the proximal involvement of non-obstructive 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 non-obstructive CAD.

One of the 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 non-obstructive disease.[28] In the current study, there are heterogeneities in MACE risk in patients with non-obstructive 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 non-obstructive 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 non-obstructive CAD should be performed. The relatively small sample size of patients with non-obstructive non-proximal CAD may cause our results to be underpowered in detecting differences in prognosis according to proximal involvement in non-obstructive CAD. The clinical endpoint examined was ACM and clinically recorded MI. Cardiovascular mortality which would be expected to be more strongly associated with the atherosclerotic burden was not available in this population. Despite this, the use of all-cause death may lower the possibility of bias due to misreporting or misclassification of death, which can often be the case when utilizing cause-specific mortality.[29] When stratified by type of event, proximal involvement in non-obstructive CAD was a significant predictor of MI events which are more specifically related to atherosclerotic burden. 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 non-proximal non-obstructive 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 non-obstructive CAD. Localization of coronary plaques by CCTA may provide additional prognostic value for MACE risk prediction in patients with non-obstructive CAD.

Supplementary data

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

Funding

This work was supported in part by the Dr Miriam and Sheldon G. Adelson Medical Research Foundation.

Conflict of interest: J.K.M. receives funding from the Dalio Foundation, National Institutes of Health, and GE Healthcare; has serves on the scientific advisory board of Arineta and GE Healthcare; and has an equity interest in Cleerly. B.J.W.C. receives research grant support from TD Bank, Artrya, Siemens, and AusculSciences and has an equity interest in GE healthcare. P.A.K.'s nuclear department at the University Hospital Zurich holds research agreement with GE Healthcare. G.P. receives honorarium as speaker and research institutional grant from GE, Bracco, Boehringer, and HeartFlow. All other authors declared no conflict of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E *et al.* Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol* 2008;**52**:1724–32.
2. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I *et al.* Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med* 2008;**359**:2324–36.
3. Hulten EA, Carbonaro S, Petrillo SP, Mitchell JD, Villines TC. Prognostic value of cardiac computed tomography angiography: a systematic review and meta-analysis. *J Am Coll Cardiol* 2011;**57**:1237–47.
4. Min JK, Dunning A, Lin FY, Achenbach S, Al-Mallah M, Budoff MJ *et al.* Age- and sex-related differences in all-cause mortality risk based on coronary computed tomography angiography findings results from the International Multicenter CONFIRM (Coronary CT Angiography Evaluation for Clinical Outcomes: an International Multicenter Registry) of 23,854 patients without known coronary artery disease. *J Am Coll Cardiol* 2011;**58**:849–60.
5. Wang ZJ, Zhang LL, Elmariah S, Han HY, Zhou YJ. Prevalence and prognosis of nonobstructive coronary artery disease in patients undergoing coronary angiography or coronary computed tomography angiography: a meta-analysis. *Mayo Clin Proc* 2017;**92**:329–46.
6. 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.

7. Bittencourt MS, Hulten E, Ghoshhajra B, O'Leary D, Christman MP, Montana P *et al.* Prognostic value of nonobstructive and obstructive coronary artery disease detected by coronary computed tomography angiography to identify cardiovascular events. *Circ Cardiovasc Imaging* 2014;**7**:282–91.
8. Leipsic J, Taylor CM, Gransar H, Shaw LJ, Ahmadi A, Thompson A *et al.* Sex-based prognostic implications of nonobstructive coronary artery disease: results from the international multicenter CONFIRM study. *Radiology* 2014;**273**: 393–400.
9. Wang JC, Normand SL, Mauri L, Kuntz RE. Coronary artery spatial distribution of acute myocardial infarction occlusions. *Circulation* 2004;**110**:278–84.
10. Gibson CM, Kirtane AJ, Murphy SA, Karha J, Cannon CP, Giugliano RP *et al.* Distance from the coronary ostium to the culprit lesion in acute ST-elevation myocardial infarction and its implications regarding the potential prevention of proximal plaque rupture. *J Thromb Thrombolysis* 2003;**15**:189–96.
11. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M *et al.* Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 1988;**12**:56–62.
12. Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT *et al.* Nonobstructive coronary artery disease and risk of myocardial infarction. *JAMA* 2014;**312**:1754–63.
13. Chang HJ, Lin FY, Lee SE, Andreini D, Bax J, Cademartiri F *et al.* Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol* 2018;**71**: 2511–22.
14. 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.
15. Cho I, Al'Aref SJ, Berger A, B OH, Gransar H, Valenti V *et al.* Prognostic value of coronary computed tomographic angiography findings in asymptomatic individuals: a 6-year follow-up from the prospective multicentre international CONFIRM study. *Eur Heart J* 2018;**39**:934–41.
16. Andreini D, Pontone G, Mushtaq S, Bartorelli AL, Bertella E, Antonioli L *et al.* A long-term prognostic value of coronary CT angiography in suspected coronary artery disease. *JACC Cardiovasc Imaging* 2012;**5**:690–701.
17. 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.
18. Raff GL, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ *et al.*; Society of Cardiovascular Computed Tomography. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *J Cardiovasc Comput Tomogr* 2009;**3**:122–36.
19. Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001;**285**:2486–97.
20. Valgimigli M, Rodriguez-Granillo GA, Garcia-Garcia HM, Malagutti P, Regar E, de Jaegere P *et al.* Distance from the ostium as an independent determinant of coronary plaque composition in vivo: an intravascular ultrasound study based radiofrequency data analysis in humans. *Eur Heart J* 2006;**27**:655–63.
21. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH *et al.* Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *J A Coll Cardiol* 2007;**49**:1860–70.
22. Lahti SJ, Feldman DI, Dardari Z, Mirbolouk M, Orimoloye OA, Osei AD *et al.* The association between left main coronary artery calcium and cardiovascular-specific and total mortality: the Coronary Artery Calcium Consortium. *Atherosclerosis* 2019;**286**:172–8.
23. Ferencik M, Pencina KM, Liu T, Ghemigian K, Baltrusaitis K, Massaro JM *et al.* Coronary artery calcium distribution is an independent predictor of incident major coronary heart disease events: results from the Framingham Heart Study. *Circ Cardiovasc Imaging* 2017;**10**:e006592.
24. Hadamitzky M, Achenbach S, Al-Mallah M, Berman D, Budoff M, Cademartiri F *et al.* Optimized prognostic score for coronary computed tomographic angiography: results from the CONFIRM registry (COronary CT Angiography EvaluatioN For Clinical Outcomes: an InteRnational Multicenter Registry). *J Am Coll Cardiol* 2013;**62**:468–76.
25. 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.
26. Weir-McCall JR, Blanke P, Sellers SL, Ahmadi AA, Andreini D, Budoff MJ *et al.* Impact of non-obstructive left main disease on the progression of coronary artery disease: a PARADIGM substudy. *J Cardiovasc Comput Tomogr* 2018;**12**:231–7.
27. Mushtaq S, De Araujo Gonçalves P, Garcia-Garcia HM, Pontone G, Bartorelli AL, Bertella E *et al.* Long-term prognostic effect of coronary atherosclerotic burden: validation of the computed tomography-Leaman score. *Circ Cardiovasc Imaging* 2015;**8**:e002332.
28. Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, Flather M *et al.*; SCOT-HEART Investigators. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med* 2018;**379**:924–33.
29. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol* 1999;**34**:618–20.