



**Universiteit  
Leiden**  
The Netherlands

**Prognostic significance of nonobstructive left main coronary artery disease in patients with and without diabetes: long-term outcomes from the CONFIRM registry**

Lee, J.; Shaikh, K.; Nakanishi, R.; Gransar, H.; Achenbach, S.; Al-Mallah, M.H.; ... ; Budoff, M.J.

**Citation**

Lee, J., Shaikh, K., Nakanishi, R., Gransar, H., Achenbach, S., Al-Mallah, M. H., ... Budoff, M. J. (2023). Prognostic significance of nonobstructive left main coronary artery disease in patients with and without diabetes: long-term outcomes from the CONFIRM registry. *Heart, Lung And Circulation*, 32(2), 175-183. doi:10.1016/j.hlc.2022.09.014

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](https://creativecommons.org/licenses/by/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3729546>

**Note:** To cite this publication please use the final published version (if applicable).

# Prognostic Significance of Nonobstructive Left Main Coronary Artery Disease in Patients With and Without Diabetes: Long-Term Outcomes From the CONFIRM Registry



Juhwan Lee, MD <sup>a,b</sup>, Kashif Shaikh, MD <sup>a,c</sup>, Rine Nakanishi, MD <sup>a,d</sup>, Heidi Gransar, MSc <sup>e</sup>, Stephan Achenbach, MD <sup>f</sup>, Mouaz H. Al-Mallah, MD <sup>g</sup>, Daniele Andreini, MD, PhD <sup>h</sup>, Jeroen J. Bax, MD, PhD <sup>i</sup>, Daniel S. Berman, MD <sup>e</sup>, Filippo Cademartiri, MD, PhD <sup>j</sup>, Tracy Q. Callister, MD <sup>k</sup>, Hyuk-Jae Chang, MD, PhD <sup>l</sup>, Kavitha Chinnaiyan, MD <sup>m</sup>, Benjamin J.W. Chow, MD <sup>n</sup>, Ricardo C. Cury, MD <sup>o</sup>, Augustin DeLago, MD <sup>p</sup>, Gudrun Feuchtner, MD <sup>q</sup>, Martin Hadamitzky, MD <sup>r</sup>, Joerg Hausleiter, MD <sup>s</sup>, Philipp A. Kaufmann, MD <sup>t</sup>, Yong-Jin Kim, MD, PhD <sup>u</sup>, Jonathon A. Leipsic, MD <sup>v</sup>, Erica Maffei, MD <sup>j</sup>, Hugo Marques, MD, PhD <sup>w</sup>, Pedro de Araújo Gonçalves, MD, PhD <sup>w</sup>, Gianluca Pontone, MD, PhD <sup>x</sup>, Ronen Rubinshtein, MD <sup>y</sup>, Todd C. Villines, MD <sup>z</sup>, Yao Lu, MSc <sup>A</sup>, Jessica M. Peña, MD <sup>B</sup>, Fay Y. Lin, MD <sup>B</sup>, James K. Min, MD <sup>C</sup>, Leslee J. Shaw, PhD <sup>B</sup>, Matthew J. Budoff, MD <sup>a,\*</sup>

<sup>a</sup>Department of Medicine, Lundquist Institute at Harbor-UCLA Medical Center, Torrance, CA, USA

<sup>b</sup>Department of Medicine, CHA University GUMI CHA Hospital, Gyeongsangbuk-do, South Korea

<sup>c</sup>Department of Medicine, University of Tennessee, Knoxville, Tennessee, USA

<sup>d</sup>Department of Cardiovascular Medicine, Toho University Graduate School of Medicine, Tokyo, Japan

<sup>e</sup>Department of Imaging and Medicine, Cedars Sinai Medical Center, Los Angeles, CA, USA

<sup>f</sup>Department of Cardiology, Friedrich-Alexander-University Erlangen-Nuremberg, Erlangen, Germany

<sup>g</sup>Houston Methodist DeBakey Heart & Vascular Center, Houston Methodist Hospital, Houston, TX, USA

<sup>h</sup>Centro Cardiologico Monzino, IRCCS Milan, Milan, Italy

<sup>i</sup>Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands

<sup>j</sup>Department of Radiology, Fondazione Monasterio/CNR, Pisa/Massa, Italy

<sup>k</sup>Tennessee Heart and Vascular Institute, Hendersonville, TN, USA

<sup>l</sup>Division of Cardiology, Severance Cardiovascular Hospital and Severance Biomedical Science Institute, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea

<sup>m</sup>Department of Cardiology, William Beaumont Hospital, Royal Oak, MI, USA

<sup>n</sup>Department of Medicine and Radiology, University of Ottawa, Ottawa, ON, Canada

<sup>o</sup>Department of Radiology, Miami Cardiac and Vascular Institute, Miami, FL, USA

<sup>p</sup>Capitol Cardiology Associates, Albany, NY, USA

<sup>q</sup>Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria

<sup>r</sup>Department of Radiology and Nuclear Medicine, German Heart Center Munich, Munich, Germany

<sup>s</sup>Medizinische Klinik I der Ludwig-Maximilians-Universität München, Munich, Germany

\*Corresponding author at: 1124 West Carson Street Torrance, CA 90502, USA; Email: [mbudoff@lundquist.org](mailto:mbudoff@lundquist.org); Twitter: [@BudoffMd](https://twitter.com/BudoffMd)

© 2022 Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) and the Cardiac Society of Australia and New Zealand (CSANZ).

Published by Elsevier B.V. All rights reserved.

<sup>d</sup>Department of Nuclear Medicine, University Hospital, Zurich, Zurich, Switzerland

<sup>e</sup>Seoul National University Hospital, Seoul, South Korea

<sup>f</sup>Department of Medicine and Radiology, University of British Columbia, Vancouver, BC, Canada

<sup>g</sup>UNICA, Unit of Cardiovascular Imaging, Hospital da Luz, Lisboa, Portugal

<sup>h</sup>Centro Cardiologico Monzino, IRCCS Milan, Italy

<sup>i</sup>Department of Cardiology at the Lady Davis Carmel Medical Center, The Ruth and Bruce Rappaport School of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

<sup>j</sup>Division of Cardiovascular Medicine, Department of Medicine, University of Virginia Health System, Charlottesville, VA, USA

<sup>k</sup>Department of Healthcare Policy and Research, New York-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY, USA

<sup>l</sup>Dalio Institute of Cardiovascular Imaging, Weill Cornell Medicine and NewYork-Presbyterian, New York, NY, USA

<sup>m</sup>Cleerly Inc, New York, NY, USA

Received 14 May 2022; received in revised form 21 August 2022; accepted 9 September 2022; online published-ahead-of-print 3 November 2022

## Background

Prognostic significance of non-obstructive left main (LM) disease was recently reported. However, the influence of diabetes mellitus (DM) on event rates in patients with and without non-obstructive LM disease is not well-known.

## Methods

We evaluated 27,252 patients undergoing coronary computed tomographic angiography from the COroNary CT Angiography Evaluation For Clinical Outcomes: An InteRnational Multicenter (CONFIRM) Registry. Cumulative long-term incidence of all-cause mortality (ACM) was assessed between DM and non-DM patients by normal or non-obstructive LM disease (1–49% stenosis).

## Results

The mean age of the study population was  $57.6 \pm 12.6$  years. Of the 27,252 patients, 4,434 (16%) patients had DM. A total of 899 (3%) deaths occurred during the follow-up of  $3.6 \pm 1.9$  years. Compared to patients with normal LM, those with non-obstructive LM had more pronounced overall coronary atherosclerosis and more cardiovascular risk factors. After clinical risk factors, segment involvement score, and stenosis severity adjustment, compared to patients without DM and normal LM, patients with DM were associated with increased ACM regardless of normal (HR 1.48, 95% CI 1.22–1.78,  $p < 0.001$ ) or non-obstructive LM (HR 1.46, 95% CI 1.04–2.04,  $p = 0.029$ ), while nonobstructive LM disease was not associated with increased ACM in patients without DM (HR 0.85, 95% CI 0.67–1.07,  $p = 0.165$ ) and there was no significant interaction between DM and LM status (HR 1.03, 95% CI 0.69–1.54,  $p = 0.879$ ).

## Conclusion

From the CONFIRM registry, we demonstrated that DM was associated with increased ACM. However, the presence of non-obstructive LM was not an independent risk marker of ACM, and there was no significant interaction between DM and non-obstructive LM disease for ACM.

## Keywords

Coronary computed tomographic angiography • Diabetes mellitus • Nonobstructive coronary artery disease • Left main • All-cause mortality

## Introduction

The prevalence of diabetes mellitus (DM) is increasing gradually, and DM is associated with excess cardiovascular risk [1,2]. Also, a higher prevalence of coronary artery disease (CAD) and more severe manifestations are found in patients with DM [3], and a recent study showed that patients with DM have more significant plaque progression, notably significantly higher progression in adverse plaques, defined as low attenuation plaque, spotty calcification, and positive remodelling, than those without DM [4]. Recently, a prognostic impact of non-obstructive left main (LM) disease visualised by coronary computed tomographic angiography (CCTA) has been demonstrated [5] and rapid plaque progression, as well as a high prevalence of high-risk plaques, were found in patients with non-obstructive LM disease [6]. Therefore, non-obstructive LM disease is regarded as an aggressive marker of phenotype of CAD. In daily clinical practice, CCTA frequently detects non-obstructive LM

disease. However, the impact of non-obstructive LM disease on prognosis among patients with and without DM has not been thoroughly evaluated.

Therefore, we aimed to evaluate the long-term outcomes of patients undergoing CCTA according to the diabetic status and the presence of non-obstructive LM disease detected by CCTA as well as the interaction between DM and non-obstructive LM disease in a real-world cohort.

## Methods

### Study Population

The CONFIRM Registry<sup>1</sup> is an open-label, international, multicentre observational registry designed to investigate associations between a patient's clinical data, CCTA findings, and incident adverse clinical events. The details of the study design have been described previously [7]. In this study, overall 35,281 patients who underwent CCTA

<sup>1</sup> COroNary CT Angiography Evaluation For Clinical Outcomes: An InteRnational Multicenter Registry.

between December 2002 and May 2011 were analysed. Diabetes mellitus was defined by diagnosis of a physician and/or use of diabetic medications. Hypertension was defined as a history of high blood pressure or treatment with antihypertensive medication. Hyperlipidaemia was defined as known and needed treatment according to the guideline at that time but untreated or current treatment with lipid-lowering medication. Coronary artery disease (CAD) Consortium 2 (CAD2) clinical risk scores included age, gender, symptoms, setting, DM, hypertension, hyperlipidaemia, smoking and body mass index [8].

We excluded patients with missing information on LM stenosis severity (n=3,220), obstructive LM stenosis (n=730), history of CAD, previous percutaneous coronary intervention (PCI) or coronary artery bypass graft (n=2,998), incomplete risk factors (n=976) and incomplete data of all-cause mortality (ACM) (n=105). Finally, 27,252 patients were analysed and followed up till December 2013. All sites had the approval of their respective institutional review boards and were compliant with the Health Insurance Portability and Accountability Act, where applicable. This study was consistent with the principles of the Declaration of Helsinki.

## Image Acquisition and Analysis

All CCTA exams were performed using standardised CCTA protocols as defined by guidelines of the Society of Cardiovascular Computer Tomography [9,10]. All exams were performed by at least 64-detector rows scanners, and a 16-segment coronary vascular model was used when interpreting. In each coronary artery, coronary atherosclerosis was defined as any tissue structure  $>1 \text{ mm}^2$  in size within or adjacent to the coronary artery lumen that could be discriminated from surrounding pericardial tissue, epicardial fat, or the vessel lumen itself. The luminal stenosis of coronary atherosclerosis lesions were determined by visual estimation per current guidelines [11]. Maximal stenosis severity was categorised into a four-point scale, defined as no CAD (no plaque), mild CAD (maximal stenosis 1–49%), moderate CAD (maximal stenosis 50–69%), and severe CAD ( $>70\%$  stenosis). Left main stenosis was also categorised as normal (0% stenosis) or non-obstructive (1–49% stenosis) by visual assessment. Segment involvement score (SIS), which measures the extent of plaque by semi-quantitatively, was also measured [12].

## Patient Follow-Up

Patients' events were determined at each local site by a dedicated physician and/or research nurse by interview, telephone calls and/or review of medical records. In the United States, ACM was additionally assessed by the query of the National Death Index.

## Statistical Analysis

All-cause mortality was our primary endpoint. Continuous variables are expressed as mean  $\pm$  SD, and categorical variables are presented as absolute counts and percentages. Patients were divided into four groups according to the

presence of DM and non-obstructive LM disease. Kaplan-Meier curves were compared using the log-rank test. Proportional hazard assumption was checked by graphical assessment of Schoenfeld residuals and Cox proportional hazards models were used to assess if there was an interaction between DM and LM status. We made two multivariable Cox proportional hazards models and variables were chosen by clinical decision. Age, sex, hypertension, hyperlipidaemia, current smoking, family history of premature CAD, and angina typicality were included in model 1 to adjust for baseline demographics and CAD risk factors. In model 2, SIS and the number of obstructive vessels were added to model 1 to adjust for plaque burden.

To evaluate the effects of baseline low density lipoprotein (LDL) value and medications, we performed sensitivity analysis in patients with available data. Instead of hyperlipidaemia, baseline LDL value was included in model 1 and 2. Another model, 3, was made which included covariables with model 2 and baseline medications including aspirin, beta blocker, angiotensin-converting-enzyme inhibitors/angiotensin II receptor blockers and statins. A two-tailed p-value  $<0.05$  was considered statistically significant. All statistical analyses were performed using STATA version 14 (StataCorp, College Station, TX, USA).

## Results

### Clinical and CCTA Characteristics of the Study Population

The baseline characteristics of the study population are summarised in Table 1. The mean age of the population was  $57.6 \pm 12.6$  years, and 14,860 (55%) patients were male. Of the 27,252 patients, 4,434 (16%) patients had DM, 3,561 (13%) patients had non-obstructive LM disease and 726 (3%) patients had both DM and non-obstructive LM disease. Compared to patients without DM, patients with DM were older and had more typical angina, hypertension and hyperlipidaemia ( $p < 0.001$ ). CAD2 clinical risk scores of patients with DM were two-fold higher than those of patients without DM ( $p < 0.001$ ). Non-obstructive LM disease and obstructive non-LM disease were also more common in patients with DM ( $p < 0.001$ ). Mean SIS of all patients was  $2.0 \pm 2.6$ , and patients with DM had higher SIS than patients without DM ( $2.7 \pm 2.8$  vs  $1.8 \pm 2.5$ ,  $p < 0.001$ ).

Compared to patients with normal LM, patients with non-obstructive LM were older, more male, had more hypertension, hyperlipidaemia, and DM ( $p < 0.001$ ) (Table 2). Obstructive non-LM disease was also more prevalent in patients with non-obstructive LM disease ( $p < 0.001$ ). The SIS of the patients with non-obstructive LM disease was much higher than those of patients with normal LM ( $5.4 \pm 2.9$  vs  $1.5 \pm 2.1$ ,  $p < 0.001$ ) (Table 2).

We divided the study population into four groups according to diabetic and LM status, and clinical characteristics were shown in Table 3. Baseline medication history and laboratory results from limited sites were also shown in

**Table 1** Baseline characteristics of patients with or without diabetes mellitus.

	All Patients (n=27,252)	Patients Without DM (n=22,818)	Patients With DM (n=4,434)	P-value
Age, yrs	58±13	57±13	61±11	<0.001
Male	14,860 (54.5%)	12,513 (54.8%)	2,347 (52.9%)	0.020
Hypertension	16,461 (60.4%)	12,885 (56.5%)	3,576 (80.7%)	<0.001
Hyperlipidaemia	15,468 (56.8%)	12,222 (53.6%)	3,246 (73.2%)	<0.001
Current smoking	4,857 (17.8%)	4,072 (17.9%)	785 (17.7%)	0.822
Family history of early CAD	9,785 (35.9%)	8,273 (36.3%)	1,512 (34.1%)	0.006
Typical angina	3,879 (16.4%)	3,117 (15.7%)	762 (19.9%)	<0.001
CAD2 clinical risk score	17.7±17.3	15.1±15.3	31.6±19.9	<0.001
LM status				
Normal LM	23,691 (86.9%)	19,983 (87.6%)	3,708 (83.6%)	<0.001
Nonobstructive LM (1–49%)	3,561 (13.1%)	2,835 (12.4%)	726 (16.4%)	
Extent of CAD				
No plaque	11,743 (43.1%)	10,371 (45.5%)	1,372 (30.9%)	<0.001
Nonobstructive CAD (1–49%)	9,051 (33.2%)	7,612 (33.4%)	1,439 (32.5%)	
1-vessel	3,823 (14.0%)	2,931 (12.9%)	892 (20.1%)	
2-vessel	1,710 (6.3%)	1,266 (5.6%)	444 (10.0%)	
3-vessel	925 (3.4%)	638 (2.8%)	287 (6.5%)	
SIS	2.0±2.6	1.8±2.5	2.7±2.8	<0.001

Abbreviations: CAD2, coronary artery disease Consortium 2; DM, diabetes mellitus; CAD, coronary artery disease; LM, left main; SIS, segment involvement score.

**Supplement Table 1.** Patients with DM and nonobstructive LM disease had most pronounced atherosclerosis among the four groups.

## Outcomes According to Diabetes and Left Main Disease

A total of 899 (3%) deaths occurred during the follow up of 3.6±1.9 years. **Figure 1** shows the cumulative ACM of each

group. Among the four groups, patients with DM and non-obstructive LM disease had the highest ACM rate (7.2%). Patients with non-obstructive LM disease and without DM had similar ACM compared to patients with DM and normal LM (4.6% vs 4.9%).

**Table 4** shows the uni- and multivariate hazard ratio of ACM in the four groups. In univariate analysis, compared to patients with normal LM and no DM, non-obstructive LM was associated with increased rates of ACM in patients with

**Table 2** Baseline characteristics of patients according to left main status.

	All Patients (n=27,252)	Normal LM (n=23,691)	Nonobstructive LM (n=3,561)	P-value
Age, yrs	58±13	57±13	64±10	<0.001
Male	14,860 (54.5%)	12,485 (52.7%)	2,375 (66.7%)	<0.001
Hypertension	16,461 (60.4%)	13,960 (58.9%)	2,501 (70.2%)	<0.001
Hyperlipidaemia	15,468 (56.8%)	13,106 (55.3%)	2,362 (66.3%)	<0.001
Diabetes mellitus	4,434 (16.3%)	3,708 (15.7%)	726 (20.4%)	<0.001
Current smoking	4,857 (17.8%)	4,182 (17.7%)	675 (19.0%)	0.058
Family history of early CAD	9,785 (35.9%)	8,511 (35.9%)	1,274 (35.8%)	0.863
Typical angina	3,879(16.4%)	3,386 (16.4%)	493 (16.4%)	0.973
CAD2 clinical risk score	17.7±17.3	16.5±16.6	26.0±19.2	<0.001
Extent of CAD				
No plaque	11,743 (43.1%)	11,743 (49.6%)	0 (0%)	<0.001
Nonobstructive 1–49%	9,051 (33.2%)	7,135 (30.1%)	1,916 (53.8%)	
1-vessel	3,823 (14.0%)	2,937 (12.4%)	886 (24.9%)	
2-vessel	1,710 (6.3%)	1,221 (5.2%)	489 (13.7%)	
3-vessel	925 (3.4%)	655 (2.8%)	270 (7.6%)	
SIS	2.0±2.6	1.5±2.1	5.4±2.9	<0.001

Abbreviations: CAD2, coronary artery disease Consortium 2; CAD, coronary artery disease; LM, left main; SIS, segment involvement score.

**Table 3** Baseline characteristics of patients according to left main status and diabetes mellitus.

	Normal LM+No DM N=19,983	Normal LM + DM N=3,708	Nonobstructive LM + No DM N=2,835	Nonobstructive LM + DM N=726	P-value
Age	56±13	60±11	64±11	65±9	<0.001
Male	10,617 (53.1%)	1,868 (50.4%)	1,896 (66.9%)	479 (66.0%)	<0.001
Hypertension	10,991 (55.0%)	2,969 (80.1%)	1,894 (66.8%)	607 (83.6%)	<0.001
Hyperlipidaemia	10,427 (52.2%)	2,679 (72.3%)	1,795 (63.3%)	567 (78.1%)	<0.001
Current smoking	3,533 (17.7%)	649 (17.5%)	539 (19.0%)	136 (18.7%)	0.297
Family history of early CAD	7,262 (36.3%)	1,249 (33.7%)	1,011 (35.7%)	263 (36.2%)	0.021
Typical angina	2,726 (15.6%)	660 (20.4%)	391 (16.3%)	102 (17.0%)	<0.001
CAD2 clinical risk score	14.0±14.6	30.2±19.7	22.8±17.7	39.0±19.5	<0.001
Extent of CAD					
No plaque	10,371 (51.9%)	1,372 (37.0%)	0 (0%)	0 (0%)	<0.001
Nonobstructive 1–49%	6,024 (30.2%)	1,111 (30.0%)	1,588 (56.0%)	328 (45.2%)	
1-vessel	2,241 (11.2%)	696 (18.8%)	690 (24.3%)	196 (27.0%)	
2-vessel	899 (4.5%)	322 (8.7%)	367 (13.0%)	122 (16.8%)	
3-vessel	448 (2.2%)	207 (5.6%)	190 (6.7%)	80 (11.0%)	
SIS	1.4±2.0	2.0±2.3	5.3±2.9	5.9±2.9	<0.001

Abbreviations: CAD2, coronary artery disease Consortium 2; CAD, coronary artery disease; LM, left main; SIS, segment involvement score; DM, diabetes mellitus.

DM and without DM (HR 3.15, 95% CI 2.37–4.19,  $p < 0.001$  vs HR 1.88, 95% CI 1.55–2.27,  $p < 0.001$ ). Patients with DM and non-obstructive LM had more than a three-fold increased risk of ACM compared to patients without DM and normal LM.

However, after adjusting for clinical and CAD risk factors, patients with non-obstructive LM disease and without DM did not have increased risk in ACM (HR 1.17, 95% CI 0.95–1.45,  $p = 0.139$ ) in multivariate analysis model 1. Patients with DM were associated with increased ACM regardless of normal (HR 1.58, 95% CI 1.31–1.90,  $p < 0.001$ ) or non-obstructive LM (HR 2.07, 95% CI 1.49–2.87,  $p < 0.001$ ) in model 1. In model 2, after adjusting for the SIS and the number of obstructive vessels in addition to model 1, similar results were observed. Patients with DM still had increased risk of ACM in both normal LM (HR 1.48, 95% CI 1.22–1.78,  $p < 0.001$ ), and non-obstructive LM (HR 1.46, 95% CI 1.04–2.04,  $p = 0.029$ ). Patients with non-obstructive LM disease and without DM also did not have increased risk in ACM (HR 0.85, 95% CI 0.67–1.07,  $p = 0.165$ ). There was no significant interaction between DM and LM status in model 1 (HR 0.88, 95% CI 0.59–1.32,  $p = 0.543$ ) and model 2 (HR 1.03, 95% CI 0.69–1.54,  $p = 0.879$ , [Table 5](#)). Adjusted cumulative ACM in each group by model 2 was shown in [Figure 2](#).

We also evaluated the ACM in each gender separately. In male patients, patients with DM were associated with increased ACM regardless of normal (HR 1.48, 95% CI 1.14–1.93,  $p = 0.004$ ) or non-obstructive LM (HR 1.84, 95% CI 1.22–2.78,  $p = 0.004$ ) in model 1. Patients with nonobstructive LM and without DM were not related with increased risk in ACM (HR 1.00, 95% CI 0.75–1.33,  $p = 0.995$ ) in model 1. In model 2, only patients with DM and normal LM were associated with increased ACM compared to patients with

normal LM and without DM (HR 1.40, 95% CI 1.07–1.83,  $p = 0.014$ , [Supplement Table 2](#)).

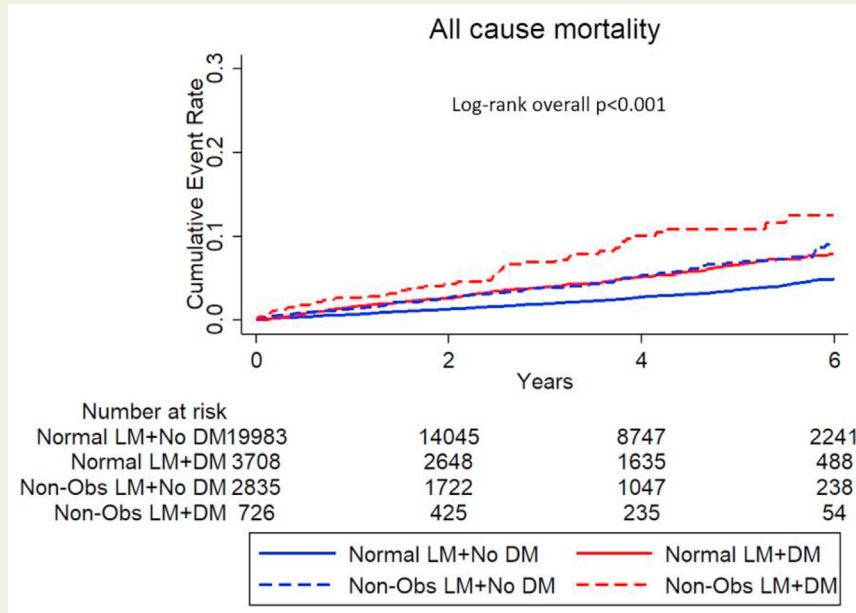
In female patients, patients with DM were also associated with increased ACM in both normal (HR 1.68, 95% CI 1.30–2.18,  $p < 0.001$ ) and nonobstructive LM (HR 2.45, 95% CI 1.44–4.16,  $p = 0.001$ ) in model 1. Contrary to male patients, patients with nonobstructive LM disease and without DM were also related with increased ACM in model 1 (HR 1.43, 95% CI 1.04–1.97,  $p = 0.027$ ). However, in model 2, only patients with DM and normal LM were associated with increased ACM compared to patients with normal LM and without DM (HR 1.54, 95% CI 1.19–2.01,  $p = 0.001$ , [Supplement Table 3](#)).

## Sensitivity Analysis

After additionally adjusting baseline LDL values and medications (model 3), patients with DM and normal LM had increased risk of ACM (HR 1.53, 95% CI 1.06–2.20,  $p = 0.022$ ). However, nonobstructive LM disease did not associated with increased risk of ACM in patients with DM and without DM (HR 1.13, 95% CI 0.57–2.22,  $p = 0.734$  vs HR 0.66, 95% CI 0.40–1.07,  $p = 0.094$ ) ([Supplement Table 4](#)).

## Discussion

In this study, we have observed that DM was associated with increased mortality regardless of the presence of non-obstructive LM disease. However, the presence of non-obstructive LM disease did not increase the risk of death, and there was no significant interaction between non-obstructive LM disease and DM. The prognostic value of CCTA in patients with DM was well evaluated in the



**Figure 1** Cumulative incidence of all-cause mortality by left main and diabetic status. Abbreviations: DM, diabetes mellitus; LM, left main; Non-Obs, nonobstructive.

previous study [13]. In the present study, we showed the outcomes of patients according to diabetic status and the presence of nonobstructive LM disease by CCTA.

Tancredi et al. [14] showed in a large cohort study, that patients with DM were associated with a two- to three-fold higher cardiovascular mortality rate compared to patients without DM. In our study, we used not only clinical risk factors but also CCTA findings, including the SIS and obstructive vessel numbers in multivariate analysis, and showed that DM was still associated with high mortality.

Plaque progression may be one of the reasons for high event rates in patients with DM and greater plaque progression in patients with DM were well demonstrated in previous studies using CCTA with quantitative plaque analysis [4,15]. Moreover, Nicholls and colleagues demonstrated greater atheroma volume progression in patients with DM using intravascular ultrasound (IVUS) [16].

Xie et al. [5] demonstrated that non-obstructive LM disease was associated with increased adverse events in females but not in males. Small luminal area of LM and more prevalent positively remodelled non-obstructive plaques were regarded as possible mechanisms of the adverse outcomes in females with non-obstructive LM. In our study, nonobstructive LM disease was also related to the increased risk of ACM in only females, but not in males in model 1. However, in model 2, nonobstructive LM disease was not associated with an increased risk of ACM in both genders. Xie’s study population was from the same CONFIRM registry, but our study population included that and was much larger than Xie’s study (27,942 vs 5,166). We evaluated the differences in baseline characteristics between Xie’s study population and the others who are added to our study population. Xie’s study population had more clinical risk factors and more

**Table 4** Univariate and multivariate hazard ratio for all-cause mortality.

	Unadjusted		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Normal LM + No DM	1.00	Ref	1.00	Ref	1.00	Ref
Normal LM + DM	1.83(1.54-2.16)	<0.001	1.58(1.31-1.90)	<0.001	1.48(1.22-1.78)	<0.001
Non-obstructive LM + No DM	1.88(1.55-2.27)	<0.001	1.17(0.95-1.45)	0.139	0.85(0.67-1.07)	0.165
Non-obstructive LM + DM	3.15(2.37-4.19)	<0.001	2.07(1.49-2.87)	<0.001	1.46(1.04-2.04)	0.029

Model 1 covariables include age, gender, hypertension, hyperlipidaemia, current smoking, family history of premature CAD, angina typicality. Model 2 covariables include those in model 1 plus the number of obstructive vessels and the segment involvement score. Abbreviations: DM, diabetes mellitus; LM, left main; CAD, coronary artery disease.

**Table 5** Univariate and multivariate hazard ratio for all-cause mortality as stratified by status of diabetes and left main status.

	Unadjusted		Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
No DM	1.00	Ref	1.00	Ref	1.00	Ref
DM	1.83(1.54-2.16)	<0.001	1.80(1.49-2.17)	<0.001	1.49(1.23-1.79)	<0.001
Normal LM	1.00	Ref	1.00	Ref	1.00	Ref
Non-obstructive LM	1.88(1.55-2.27)	<0.001	1.98(1.60-2.45)	<0.001	0.92(0.73-1.15)	0.458
Interaction	0.92(0.64-1.32)	<0.653	0.88(0.59-1.32)	0.543	1.03(0.69-1.54)	0.879

Model 1 covariables include age, gender, hypertension, hyperlipidaemia, current smoking, family history of premature CAD, angina typicality.

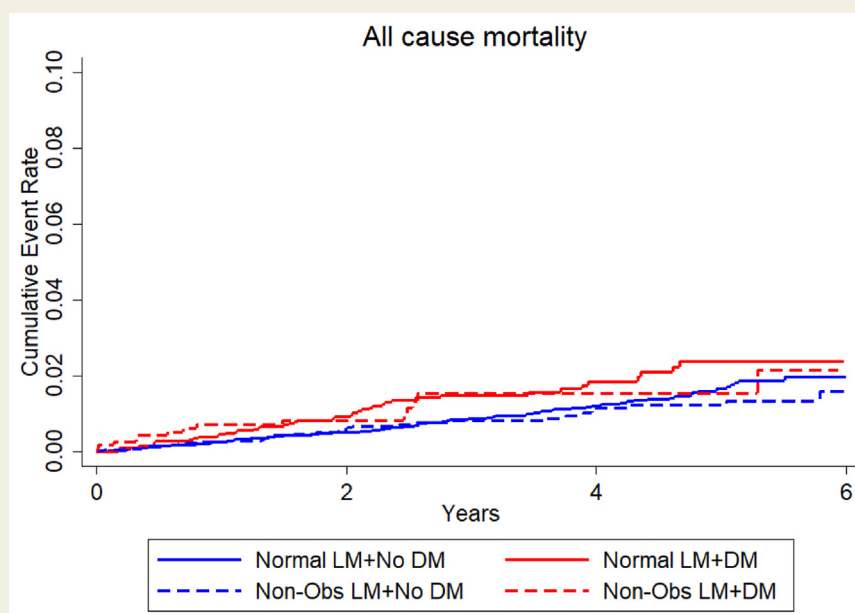
Model 2 covariables include those in model 1 plus the number of obstructive vessels and the segment involvement score.

Abbreviations: DM, diabetes mellitus; LM, left main; CAD, coronary artery disease.

obstructive coronary artery diseases than the others (Supplement Table 5).

Non-obstructive LM disease is known as a marker of severe CAD and the impact of non-obstructive LM disease on plaque progression is well documented in prior work demonstrating that patients with non-obstructive LM disease had a greater annual rate of total plaque volume progression compared to patients with normal LM ( $26.5 \pm 31.4$  vs  $14.9 \pm 20.1$  mm<sup>3</sup>/yr,  $p < 0.001$ ) [6]. Also, Ricciardi et al. [17] showed that LM disease detected by IVUS is an independent predictor of cardiac events. The authors demonstrated that angiographically silent LM disease detected by IVUS predicted worse clinical outcomes and the presence of DM had an independent impact on cardiovascular prognosis.

Recently, Bangalore et al. reported outcomes of intermediate LM disease on CCTA, International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) intermediate LM sub-study at Society of Cardiovascular Angiography and Intervention 2020. In their study patients with intermediate LM disease (defined as 25–49%) were related with significantly higher composite event rates (HR 1.31, 95% CI 1.06–1.61,  $p = 0.0123$ ), but cardiovascular death and myocardial infarction risks were not statistically significantly higher compared to those without intermediate LM disease (defined as <25%) (HR 1.24, 95% CI 0.99–1.55,  $p = 0.0574$ ). These findings are in contrast to the results of our study. Differences in study populations and the definition of nonobstructive LM might



**Figure 2** Cumulative incidence of all-cause mortality by left main and diabetic status adjusted by model 2. Model 2 covariables include age, gender, hypertension, hyperlipidaemia, current smoking, family history of premature CAD, angina typicality, the number of obstructive vessels and the segment involvement score. Abbreviations: CAD, coronary artery disease; Non-Obs, nonobstructive; LM, left main; DM, diabetes mellitus.



be one of the reasons for this discrepancy. Ricciardi et al. [17] included patients who underwent left anterior descending or left circumflex artery percutaneous coronary intervention (PCI) and defined mild LM disease as visual assessment less than 20% diameter stenosis. Bangalore defined the intermediate LM as 25–49% stenosis and patients with moderate or severe ischaemia were enrolled [18] in the ISCHEMIA trial. In contrast, in our study, 43% of the study population had no plaque at enrolment, and 1–49% stenosis in LM was regarded as non-obstructive LM. Therefore, patients with the minimal disease were possibly included in our study, and the ACM of the nonobstructive LM disease group was probably affected by those with minimal disease.

Also non-obstructive LM disease might influence the clinician to use more aggressive medical, interventional, or surgical treatment, and those also might affect the event rate. It is well established that non-obstructive disease on computed tomography (CT) angiography leads to better utilisation and adherence of preventive therapies, as shown in the Scottish Computed Tomography of the Heart (SCOT-HEART) [19–21] and the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) [22] trials, as well as numerous studies of adherence. This was one of the factors that was associated with a 41% reduction in cardiovascular events in the SCOT-HEART Trial when CT angiography was compared to functional testing. In our study, patients with nonobstructive LM disease and without DM had taken more preventive medications including statins compared to patients without nonobstructive LM disease and DM. We tried to adjust the baseline medication and lipid levels, but the data of changes of the medication and lipid levels, possibly intensification of preventive medications and improvement of lipid levels, was lacking. An additional study that evaluates the impact of changes of medication and lipid levels on the outcomes of patients of nonobstructive LM disease detected by CCTA appears warranted.

Several limitations of the current study need to be addressed. First, not all of the study population had treatment information. We could get the medication information from only limited centres and therefore we could not adjust the medication effects completely. Second, plaque progression is affected by the presence of CAD; a higher plaque burden is known to influence plaque progression [23–26]. In our study, to adjust for plaque burden, we used the SIS and number of obstructive vessels, which may be suboptimal for assessment of total atherosclerotic burden. Third, the prevalence of non-obstructive LM disease in patients with DM was relatively low.

## Conclusion

From the CONFIRM registry, we demonstrated that DM was associated with increased ACM. However, the presence of non-obstructive LM was not predictive for increased mortality.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Appendices

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.hlc.2022.09.014>

## References

- [1] Haffner SM, Lehto S, Ronnema T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339:229–34.
- [2] Whiteley L, Padmanabhan S, Hole D, Isles C. Should diabetes be considered a coronary heart disease risk equivalent?: results from 25 years of follow-up in the Renfrew and Paisley survey. *Diabetes Care*. 2005;28:1588–93.
- [3] Rana JS, Dunning A, Achenbach S, Al-Mallah M, Budoff MJ, Cademartiri F, et al. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the CONFIRM (COronary CT Angiography EvaluatioN For Clinical Outcomes): an InteRnational Multicenter Registry. *Diabetes Care*. 2012;35:1787–94.
- [4] Kim U, Leipsic JA, Sellers SL, Shao M, Blanke P, Hadamitzky M, et al. Natural history of diabetic coronary atherosclerosis by quantitative measurement of serial coronary computed tomographic angiography: results of the PARADIGM Study. *JACC Cardiovasc Imaging*. 2018;11:1461–71.
- [5] 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.
- [6] 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.
- [7] 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.
- [8] Genders TS, Steyerberg EW, Hunink MG, Nieman K, Galema TW, Mollet NR, et al. Prediction model to estimate presence of coronary artery disease: retrospective pooled analysis of existing cohorts. *BMJ*. 2012;344:e3485.
- [9] Hendel RC, Patel MR, Kramer CM, Poon M, Hendel RC, Carr JC, et al. ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American College of Radiology, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, American Society of Nuclear Cardiology, North American Society for Cardiac Imaging, Society for Cardiovascular Angiography and Interventions, and Society of Interventional Radiology. *J Am Coll Cardiol*. 2006;48:1475–97.
- [10] American College of Cardiology Foundation Task Force on Expert Consensus D, Mark DB, Berman DS, Budoff MJ, Carr JJ, Gerber TC, et al. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *Circulation*. 2010;121:2509–43.

- [11] Raff GL, Abidov A, Achenbach S, Berman DS, Boxt LM, Budoff MJ, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *J Cardiovasc Comput Tomogr*. 2009;3:122–36.
- [12] 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.
- [13] Celeng C, Maurovich-Horvat P, Ghoshhajra BB, Merkely B, Leiner T, Takx RA. Prognostic value of coronary computed tomography angiography in patients with diabetes: a meta-analysis. *Diabetes Care*. 2016;39:1274–80.
- [14] Tancredi M, Rosengren A, Svensson AM, Kosiborod M, Pivodic A, Gudbjornsdottir S, et al. Excess mortality among persons with type 2 diabetes. *N Engl J Med*. 2015;373:1720–32.
- [15] Nakanishi R, Ceponiene I, Osawa K, Luo Y, Kanisawa M, Megowan N, et al. Plaque progression assessed by a novel semi-automated quantitative plaque software on coronary computed tomography angiography between diabetes and non-diabetes patients: a propensity-score matching study. *Atherosclerosis*. 2016;255:73–9.
- [16] Nicholls SJ, Tuzcu EM, Kalidindi S, Wolski K, Moon KW, Sipahi I, et al. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials. *J Am Coll Cardiol*. 2008;52:255–62.
- [17] Ricciardi MJ, Meyers S, Choi K, Pang JL, Goodreau L, Davidson CJ. Angiographically silent left main disease detected by intravascular ultrasound: a marker for future adverse cardiac events. *Am Heart J*. 2003;146:507–12.
- [18] ISCHEMIA Trial Research Group; Maron DJ, Hochman JS, O'Brien SM, Reynolds HR, Boden WE, et al. International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial: rationale and design. *Am Heart J*. 2018;201:124–35.
- [19] Ladapo JA, Hoffmann U, Lee KL, Coles A, Huang M, Mark DB, et al. Changes in medical therapy and lifestyle after anatomical or functional testing for coronary artery disease. *J Am Heart Assoc*. 2016;5.
- [20] Adamson PD, Williams MC, Dweck MR, Mills NL, Boon NA, Daghm M, et al. Guiding therapy by coronary CT angiography improves outcomes in patients with stable chest pain. *J Am Coll Cardiol*. 2019;74:2058–70.
- [21] SCOT-HEART Investigators; Newby DE, Adamson PD, Berry C, Boon NA, Dweck MR, et al. Coronary CT angiography and 5-year risk of myocardial infarction. *N Engl J Med*. 2018;379:924–33.
- [22] Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of anatomical versus functional testing for coronary artery disease. *N Engl J Med*. 2015;372:1291–300.
- [23] Min JK, Lin FY, Gidseg DS, Weinsaft JW, Berman DS, Shaw LJ, et al. Determinants of coronary calcium conversion among patients with a normal coronary calcium scan: what is the “warranty period” for remaining normal? *J Am Coll Cardiol*. 2010;55:1110–7.
- [24] Budoff MJ, Hokanson JE, Nasir K, Shaw LJ, Kinney GL, Chow D, et al. Progression of coronary artery calcium predicts all-cause mortality. *JACC Cardiovasc Imaging*. 2010;3:1229–36.
- [25] Anand DV, Lim E, Darko D, Bassett P, Hopkins D, Lipkin D, et al. Determinants of progression of coronary artery calcification in type 2 diabetes: role of glycemic control and inflammatory/vascular calcification markers. *J Am Coll Cardiol*. 2007;50:2218–25.
- [26] Joshi FR, Rajani NK, Abt M, Woodward M, Bucerius J, Mani V, et al. Does vascular calcification accelerate inflammation?: a substudy of the dal-PLAQUE Trial. *J Am Coll Cardiol*. 2016;67:69–78.