Prognostic Value of Atherosclerotic Extent in Diabetic Patients with Non-Obstructive Coronary Artery Disease

Yipu Ding
Chinese PLA General Hospital
Zinuan Liu
Chinese PLA General Hospital
Guanhua Dou
Chinese PLA General Hospital
Xia Yang
Chinese PLA General Hospital
Xi Wang
Chinese PLA General Hospital
Dongkai Shan
Chinese PLA General Hospital
Bai He
Chinese PLA General Hospital
Jing Jing
Chinese PLA General Hospital
Yundai Chen
Chinese PLA General Hospital
Junjie Yang (fearlessyang@126.com)
Chinese PLA General Hospital

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Prognostic value of atherosclerotic extent in diabetic patients with non-obstructive coronary artery disease

Short Title: Plaque burden in DM patients with non-obstructive CAD

Concise and Informative Article Title

Yipu Ding[1,2], MD, Zinuan Liu[1,2], MD, Guanhua Dou[1], MBBS, Xia Yang[1], MD, Xi Wang[1], MBBS, Dongkai Shan[1], MD, Bai He[1], MBBS, Jing Jing[1], MBBS, Yundai Chen[1], MD, Junjie Yang[1], MD

1 Department of Cardiology, Chinese PLA General Hospital, Beijing, 100853 China

2 School of Medicine, Nankai University, Tianjin 300071, China

The first two authors contribute to the work equally.

Correspondence should be addressed to Junjie Yang; fearlessyang@126.com.

Department of Cardiology, Chinese PLA General Hospital

28 Fuxing Rd, Haidian District, Beijing 100853, P.R. China

Phone 8610-55499048, Fax 8610-55499009

ABSTRACT：

Background and Objective: Atherosclerotic extent was approved to be associated with adverse cardiac events. Risk score derived by coronary computed tomography angiography (CCTA) could identify high-risk group among patients with non-obstructive coronary artery disease (CAD) but its ability is still uncertain in the presence of diabetes mellitus (DM). The purpose of this study was to investigate the prognostic value of the plaque burden shown by CCTA in diabetic patients with non-obstructive CAD.

Methods and Results: 813 DM patients (age 58.9±9.9 years, 48.1% male) referred for CCTA due to suspect CAD in 2015-2017 were consecutively included. During a median follow-up of 31.77 months, 50 MACEs (6.15%) were experienced, including 2 cardiovascular deaths, 14 non-fatal myocardial infarction, 27 unstable angina requiring hospitalization and 7 strokes. 3 groups were defined based on coronary stenosis combined with Leidon score, as normal, non-obstructive Leidon<5, and non-obstructive Leidon≥5. Cox models was used to assess the prognosis of plaque burden within these groups. An incremental incidence of outcome event rates was observed. After adjustment for age, gender, and presence of high-risk plaque, the group of Leidon≥5 showed a higher risk than Leidon<5 in non-obstructive CAD (HR：1.88 95%CI:1.03-3.42, p＝0.039). Similar results were illustrated when segment involvement score was used for sensitivity analysis.

Conclusion: Atherosclerotic extent was associated with the prognosis of DM patients with non-obstructive coronary disease, highlighting the importance of better risk stratification and management.

Keywords: diabetes mellitus; non-obstructive coronary artery disease; risk stratification; plaque extent; management

Introduction

The rising prevalence of asymptomatic coronary artery disease (CAD) in diabetes, along with associated ischemic events, represents an important cardiac threat. Early detection of CAD in this group of patients has been the urgent requirement for the primary and secondary prevention of both fatal and non-fatal cardiac events[1, 2].

Although no definite evidence existed to support downstream benefits of imaging evaluation for CAD in diabetes[3], the current practice guideline argued that coronary computed tomography angiography（CCTA) could be an access to cardiac risk assessment in the presence of DM due to its high accuracy and acceptance[4]. In accordance with previous studies, atherosclerotic burden, derived by CCTA, has an extraordinary ability in risk stratification among non-obstructive CAD that is always underestimated due to its moderate stenosis[5]. However, few researches have been conducted on diabetic population, in which myocardial microvascular lesion is common. Using comprehensive risk score as quantitative index, we aimed to investigate the stratification capability of atherosclerotic burden in non-obstructive CAD with diabetes.

Materials and Methods

Patients

This study was approved by the local Ethics Committee and informed consent was obtained from all participants. Between 1 Jan. 2015 and 31 Dec. 2017, 2135 DM patients who had undergone CCTA for suspect CAD in our institution were prospectively enrolled. Patients with known CAD, a history of percutaneous coronary intervention or coronary bypass surgery, a history of myocardial infarction or myocarditis, revascularization driven by CCTA results within 3 months were excluded. Those with incomplete baseline data or uninterpretable CCTA results were out of further analysis (Fig 1). In addition, only mild lesion did we concern, so the obstructive CAD were excluded according to CCTA definition mentioned below.
Basic demographic data were obtained by a review of medical records or patient interview.DM was defined as fasting blood glucose ≥ 7.0 mmol/L or 2-h plasma glucose≥11.1 mmol/L during oral glucose tolerance test or A1C≥6.5% (48 mmol/mol) or the use of oral hypoglycaemic agents/insulin. The following cardiac risk factors were recorded: 1) hypertension (a systolic blood pressure ≥140mmHg or diastolic blood pressure ≥90mmHg or administration of antihypertensive therapy);2) hypercholesterolemia (known but untreated dyslipidaemia or current treatment with lipid-lowering medications);3) positive family history of CAD (presence of CAD in first-degree relatives at <55 years in men and <65 years in women);4) smoking (current smoking or cessation of smoking within 3 months of CCTA).

Image Acquisition and Analysis

Multidetector CCTA scans were performed on a dual-source CT scanner (Somatom Definition Flash CT, Siemens Medical Solutions, Forchrim, Germany). All scans were analysed using a dedicated workstation (Syngo.via, Siemens) by two experienced cardiologists. When disagreements existed on diagnosis, the final decision would be made through consultation or the intervention of a third experienced researcher.
According to modified American Heart Association classification, coronary lesions were assessed on the basis of 17-segment model visually. All segments were coded for the presence, composition and severity of coronary plaque and classified as normal, non-obstructive (1% to 49% luminal stenosis), or obstructive (>50% luminal stenosis). Calcified plaque was defined as having a density of >130HU and further specified as “spotty” if its maximum diameter of <3mm in any direction. Non-calcified plaque was defined as having an intensity below the contrasted vessel lumen. With both existing, mixed plaque was defined. “low CT attenuation plaques” were those with an average attenuation of <30HU. If the diameter of outer vessel where atherosclerotic exists was 10% greater than the mean of the diameter of the segments immediately proximal and distal to the plaque, “positive remodelling” was recognized. “napkin ring sign” was a low attenuation central area surrounded by a ring-like comparative higher attenuation plaque tissue. With at least two characteristics of “spotty”, “low CT attenuation plaques”, “positive remodelling” and “napkin ring sign”, high risk plaque (HRP) was recorded[6, 7].

Comprehensive Risk Score

A comprehensive risk score was introduced as a quantitative index of atherosclerotic burden, containing information of plaque quantity, location, stenosis, and composition as shown in Figure 1. The segment involvement score (SIS) was obtained to quantify the atherosclerotic extent for sensitivity analysis, calculated as the total number of coronary artery segments that exhibits plaque without consideration of stenosis (ranging from 0-16).

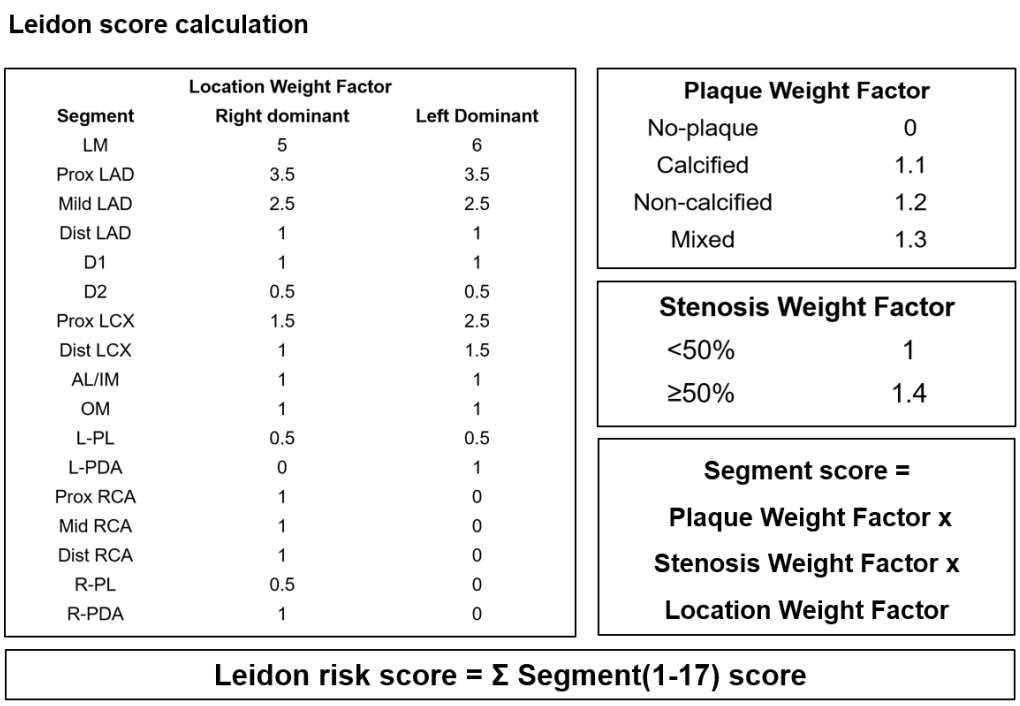

Fig 1. Schematic overview of the computed tomography angiography derived risk score.

Leidon score is calculated by summation of segment score quantified as plaque weight factor x stenosis weight factor x location weight factor, i.e., a right dominant system with a non-calcified plaque with >50% stenosis in the left main segment (5x1.2x1.4) + a non-calcified plaque with <50% stenosis in the proximal left circumflex artery (1.5x1.2x1) + a calcified plaque with >50% stenosis in the right posterior descending artery (1x1.1x1.4), so the Leidon score is 11.74. Segment involvement score (SIS) was calculated by summation of the segments exhibiting plaque, in the case above, SIS is 3.

CTA =computed tomography angiography; AL= anterolateral segment; D1 =diagonal 1; D2 = diagonal 2; IM =intermediate segment; LAD =left anterior descending coronary artery; LCA= left coronary artery; LCX= left circumflex coronary artery; LM = left main segment; L-PDA =left posterior descending artery; L-PL = left posterolateral segment; OM = obtuse marginal segment; RCA =right coronary artery; R-PDA =right posterior descending artery; R-PL =right posterolateral segment.

Follow-up and Study Endpoint

Follow-up information was obtained by phone contact or the electronic medical record system. The endpoint was cardiovascular death, non-fatal myocardial infarction, stroke, or unstable angina requiring hospitalization occurring >90 days after the CCTA examination

from 1 Jan. 2015 to 31 Aug. 2020. Each event was identified by two physicians independently. In the case of divergence, consultation would be brought in.

Statistical Analysis

Analyses were performed using SPSS version 26.0 (SPSS, IL, USA) and R version 3.6.3. Baseline characteristics were presented as mean±standard deviation or median (interquartile range, IQR) for continuous variables and as proportions for categorical variables. Prevalence of no or non-obstructive CAD were calculated and stratified by the comprehensive risk score as normal group (no CAD), non-obstructive CAD with Leidon<5 and non-obstructive CAD with Leidon≥5. Cumulative event rates were estimated using the Kaplan-Meier method and compared using the log-rank test. Cox proportional regression model was used to compute multivariable-adjusted hazard ratios for increasing CAD severity as three groups mentioned above. A p-value of <0.05 was considered as statistically significant.

Results

Baseline Characteristics

A total of 2135 DM patients who underwent CCTA for suspect CAD were enrolled, among which 51 were lost during follow-up. 1271 patients were excluded because of known CAD, revascularization, incomplete data, and other criteria. A total population of 813 diabetic patients (mean age 58.9±9.9 years; 48.1% male; median follow-up 31.77 months) was included with full demographic characteristic and CCTA information. The prevalence of hypertension, hyperlipidemia, current smoking, and a family history of CAD was 64.8%, 54.4%, 24.2% and 23.6%, respectively (Table 1). For the glucose control, 19.7% of patients solely had a diet, 80.9% only had oral hypoglycemic medication, and insulin was used in 14.3% of patients. Overall, 190(23.4%) of 813 patients had no evidence of CAD on coronary CTA. High risk plaques were found in 18(2.2%) of the patients.

Table1. Baseline characteristics.

Characteristic	Value (N=813)
Age, years	58.9±9.9
Male	391 (48.1%)
Body mass index, kg/m²	26.2±3.6
Cardiac risk factors	
Hypertension	527 (64.8%)
Hyperlipidemia	442 (54.4%)
Current smoking	197 (24.2%)

Family history of CAD	192 (23.6%)
CCTA findings	
High-risk plaque	18 (2.2%)
CAD-RADS	
0	190 (23.4%)
1	121 (14.9%)
2	502 (61.7%)
Segment Involvement Score	1 (1-1)
Segment Stenosis Score	1 (1-2)
Leidon Risk Score	2.8 (1.2-4.6)
Medication	
Anti-platelet	245 (30.1%)
Beta blocker	295 (36.3%)
ACEI/ARB	256(31.4%)
Statin	245 (30.1%)
Calcium channel blocker	145 (17.8%)
Diabetic treatment	
Diet only	160 (19.7%)
Oral hypoglycemic agent only	658 (80.9%)
Insulin	116 (14.3%)

Values are mean ± SD or n (%). CAD, coronary artery disease; CCTA, coronary computed tomography angiography

Cox Regression Analysis

In univariate analysis age (HR:1.04 95%CI:1.01-1.07) and the presence of HRP (HR:11.66 95%CI:5.45-24.95) were associated with MACEs. Compared with normal group, HR was 1.86 (95%CI: 0.70-5.00, p=0.216) for the group of non-obstructive Leidon<5, 4.06 (95%CI:1.56-10.56, p=0.004) for non-obstructive Leidon≥5, respectively.
In multivariate models, age(HR: 1.03 95%CI:1.00-1.07), and HRP(HR:10.94 95%CI:5.00-23.92) remained significance in predicting outcome events (Table 2).

Table2. Univariate and multivariate analyses of clinical profile and CCTA findings for major cardiovascular events.

	Univariable HR (95%CI)	p-Value	Leidon x CAD	
			Multivariable HR (95%CI)	p-Value
Age, yrs	1.04 (1.01-1.07)	**0.009**	1.03 (1.00-1.07)	**0.027**
Male	0.75 (0.43-1.32)	0.325	0.84 (0.47-1.51)	0.556
BMI (kg/m²)	1.03 (0.96-1.11)	0.388		
Cardiac risk factors				
Hypertension	1.23 (0.67-2.25)	0.505		
Hyperlipidemia	1.42 (0.80-2.54)	0.231		
Current smoker	0.95 (0.50-1.82)	0.876		
Family history of CAD	0.69 (0.33-1.42)	0.310		
CCTA findings				
High-risk plaque	11.66 (5.45-24.95)	**<0.001**	10.94 (5.00-23.92)	**<0.001**
Leidon Risk Score	1.06 (1.00-1.13)	0.055		
Segment involvement score	1.17 (1.00-1.36)	0.048		
CAD severity (Leidon x CAD)				
Normal	Reference		Reference	
Non-obstructive Leidon <5	1.86 (0.70-5.00)	0.216	1.56 (0.58-4.22)	0.379
Non-obstructive Leidon ≥5	4.06 (1.56-10.56)	**0.004**	2.94 (1.11-7.79)	**0.031**

CAD, coronary artery disease; CCTA, coronary computed tomography angiography

Survival Analysis

Of included 813 patients, 50 MACEs (6.15%) were experienced, including 2 cardiovascular deaths, 14 non-fatal myocardial infarction, 27 unstable angina requiring hospitalization and 7 strokes. The annual MACE rate among patients with normal group was 0.98 events per 100 person-years, and the annual MACE rate among non-obstructive Leidon<5 was 1.86 events per 100 person-years, while the rate for non-obstructive Leidon≥5 was 4.06 events per 100 person-years ($p < 0.01$).

Those experiencing MACE in the patients with non-obstructive Leidon≥5 had an unadjusted hazard ratio of 4.06 (95% CI 1.56 to 10.56, p=0.004; log-rank test: p=0.0015) (Figure 2). After adjusting for sex, gender and presence of HRP, the hazard ratio remained significant, which was 2.94 (95%CI: 1.11 to 7.79, p=0.031) and 1.88 (95%CI: 1.03 to 3.42, p=0.039), in comparison to normal group and non-obstructive Leidon<5, respectively.

Sensitivity Analysis

For further sensitivity analysis, segment involvement score (SIS) was used to quantify the atherosclerotic extent instead. A comparable distribution of event rate has been noticed (Fig 3), of which the normal group, non-obstructive SIS<3 group and non-obstructive SIS ≥3 group were 2.63%, 5.54% and 12.34%, respectively. In adjusted Cox model, patients of non-obstructive SIS ≥3 conferred a significantly higher risk than those in both normal group (HR: 3.49 95%CI:1.28-9.52) p=0.015), and non-obstructive SIS<3 group (HR: 2.14 95%CI:1.17-3.91) p=0.013).

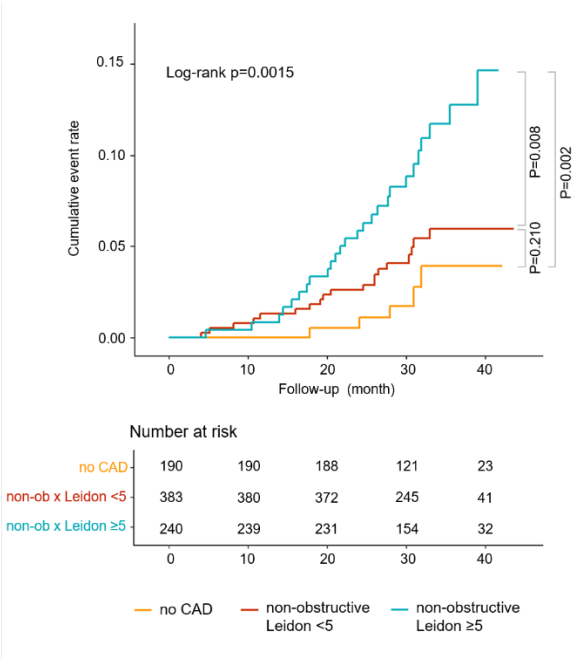

Fig 2. Cumulative risk of the composite endpoint on the basis of CAD severity with Leidon risk score. (no CAD, non-obstructive CAD with Leidon<5, and non-obstructive CAD with Leidon≥5). CAD, coronary artery disease

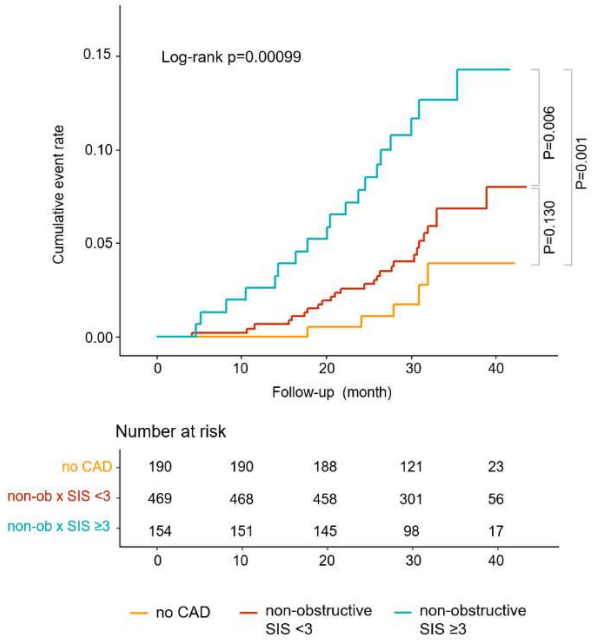

Fig 3. Cumulative risk of the composite endpoint on the basis of CAD severity with segment involvement score. (no CAD, non-obstructive with SIS<3, and non-obstructive with SIS⩾3) CAD, coronary artery disease; SIS, segment involvement score

Discussion

The main finding of this study was that in DM patients with non-obstructive CAD, higher atherosclerotic extent on CCTA provides incremental prognostic information and was associated with long term cardiovascular outcome, even after adjustment for traditional risk factors including age, gender, and high-risk plaque profiles. Our results reinforced the notion that greater efforts are needed to promote risk stratification with non-obstructive CAD, especially in the presence of DM. Segment involvement score, as well as Leidon risk score, represented an effective and reliable tool for calculating atherosclerotic extent, which have a substantial impact on clinical outcome in diabetic patients.

Our findings concur with previous cohort study[8], which demonstrated that it is possible to identify high-risk diabetic patients based on assessment of CAD revealed by CCTA. However, several disparities must be noted. A higher ratio of non-obstructive/obstructive CAD was observed in the present cohort, approximately half of them non-obstructive, presenting a comparative low-risk population, which contrasted with the previous study[9]. This may be ascribed to a direct referral to the invasive examination or revascularization driven by CCTA within 3 months, which has met the exclusion criteria, in high-risk population. Nonetheless, a slightly higher MACEs rate was present, compared with an annual events rate ranged from 1.5% to 16.9% as a meta-analysis shown[9], in which diabetes examined by CCTA were investigated. One possibility is that we broadened enrollment to MACEs with stroke and extended follow-up to a median of 31 months, which was a

sufficient duration to capture more events. Moreover, up to 80% patients received hypoglycemic therapy in baseline, indicating a potentially long duration of diabetes and higher vascular risk. Another important observation from our study is that in risk-adjusted hazard analysis, the presence of HRP was found an independent predictor with a high HR of 3.15 (95%CI:1.97-5.04). This corresponds the result from ICONIC study[10] that stressed the importance of HRP+ lesions in non-obstructive CAD, which exhibited comparable risk of becoming a culprit lesion to obstructive HRP- lesions. In view of this, we bring it into analysis, which has been done by little research before. However, after adjustment for HRP, extensive non-obstructive CAD was still found a significant indicator. This finding may inform future trials to determine the potential role of non-obstructive CAD in the setting of diabetes.

In the PROMISE (Prospective Multicenter Imaging Study for Evaluation of Chest Pain) trial, most cardiovascular deaths, or myocardial infarction (67%) occurred in patients with a normal stress test at baseline, most of which were found to have non-obstructive atherosclerotic disease by cardiac CT[11]. This suggests that we miss the opportunity to implement comprehensive preventive measures in most patients, especially in diabetic patients, by relying on stress test results. The SCOT-HEART (Scottish Computed Tomography of the Heart) trial revealed a reduction of 41% in hazard of CAD-related death or non-fatal myocardial infarction for patients who were assigned to an anatomic versus functional strategy (2.4% vs. 3.9%)[12]. This was attributed to detection of non-obstructive coronary atherosclerosis and the initiation of directed preventive treatment. Our study was partly in line with the results above, and further stress the importance of medical management in diabetic patients with extensive non-obstructive coronary artery disease. The ability of non-invasively detecting non-obstructive atherosclerotic disease by CT, thus, should be rendered as a necessary opportunity to initiate prevention earlier or intensive treatment in the process of disease, a strategy proven effective in reducing MACEs[13].

Some previous studies have evaluated the extent and distribution of atherosclerosis with semi-quantitative CCTA risk score in diabetes, mainly based on the SIS or the segment stenosis score (SSS)[14]. However, neither SIS nor SSS reflect the importance of relevant segment in coronary artery, because proximal segment in the artery holds accountability for myocardial perfusion of larger territory. In this circumstances, Leidon comprehensive risk score, being reported more strongly predictive than the SIS, integrates stenosis severity with the number and location of stenosis. A recent research from van den Hoogen IJ et al.[15] evaluated the per-segment and per-patient weight scores to determine the contribution of the stenosis, composition and location of CAD to the total score. As a result, all the per-patient weight scores were significantly higher in the setting of DM, while the per-segment location weight score was lower, which might be explained by the multi-segment disease in DM patients. We also used SIS for sensitivity analysis to stratify the extent of atherosclerotic plaque, which demonstrated the similar result and further supported our hypothesis.

Study Limitation

First, as a retrospective single center study, referral decision for CCTA was made by physicians independently and certain patients were excluded finally due to various reasons, which may introduce selection bias. Secondly, diabetes is a dynamic risk factor, lack of the diabetes duration and treatment information on baseline may cause the misinterpret of the subsequent data analysis. Thirdly, although downstream treatment and management were recorded, relative treatments were not included in the final multivariate analysis, which may lead to potential confounders and over or under-estimate the effect size of target variables.

Conclusion

In diabetic patients with non-obstructive CAD, atherosclerotic extent was associated with incremental higher risk of MACEs for about 3 years of follow-up. Efforts should be made to determine risk stratification for the management of DM patients with non-obstructive CAD.

Abbreviations:

Data Availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding Statement

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Figures

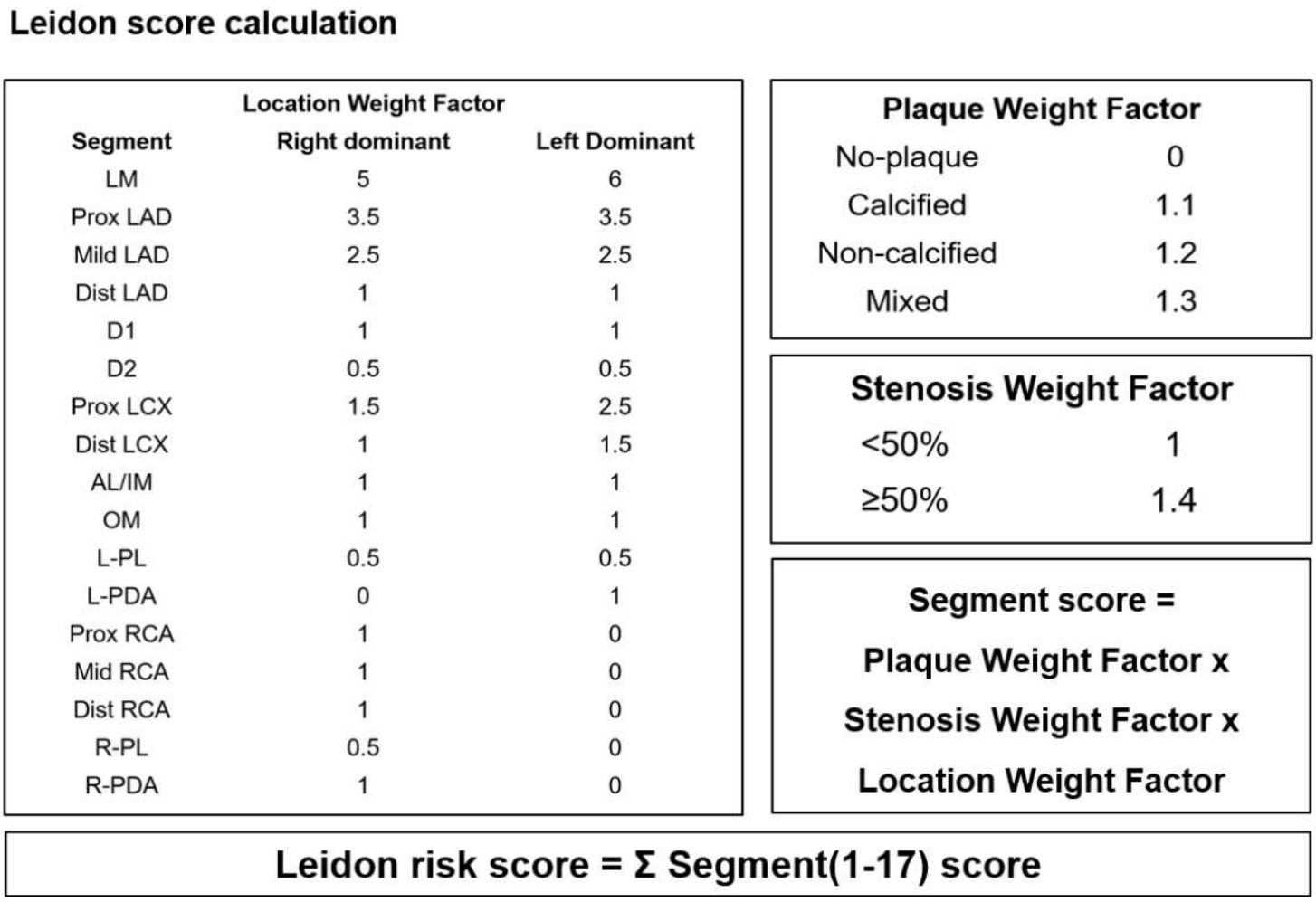

Figure 1

Schematic overview of the computed tomography angiography derived risk score. Leidon score is calculated by summation of segment score quantified as plaque weight factor x stenosis weight factor x location weight factor, i.e., a right dominant system with a non-calcified plaque with >50% stenosis in the left main segment (5x1.2x1.4) + a non-calcified plaque with <50% stenosis in the proximal left circumflex artery (1.5x1.2x1) + a calcified plaque with >50% stenosis in the right posterior descending artery (1x1.1x1.4), so the Leidon score is 11.74. Segment involvement score (SIS) was calculated by summation of the segments exhibiting plaque, in the case above, SIS is 3. CTA =computed tomography angiography; AL= anterolateral segment; D1 =diagonal 1; D2 = diagonal 2; IM =intermediate segment; LAD =left anterior descending coronary artery; LCA= left coronary artery; LCX= left circumflex coronary artery; LM = left main segment; L-PDA =left posterior descending artery; L-PL = left posterolateral segment; OM = obtuse marginal segment; RCA =right coronary artery; R-PDA =right posterior descending artery; R-PL =right posterolateral segment.

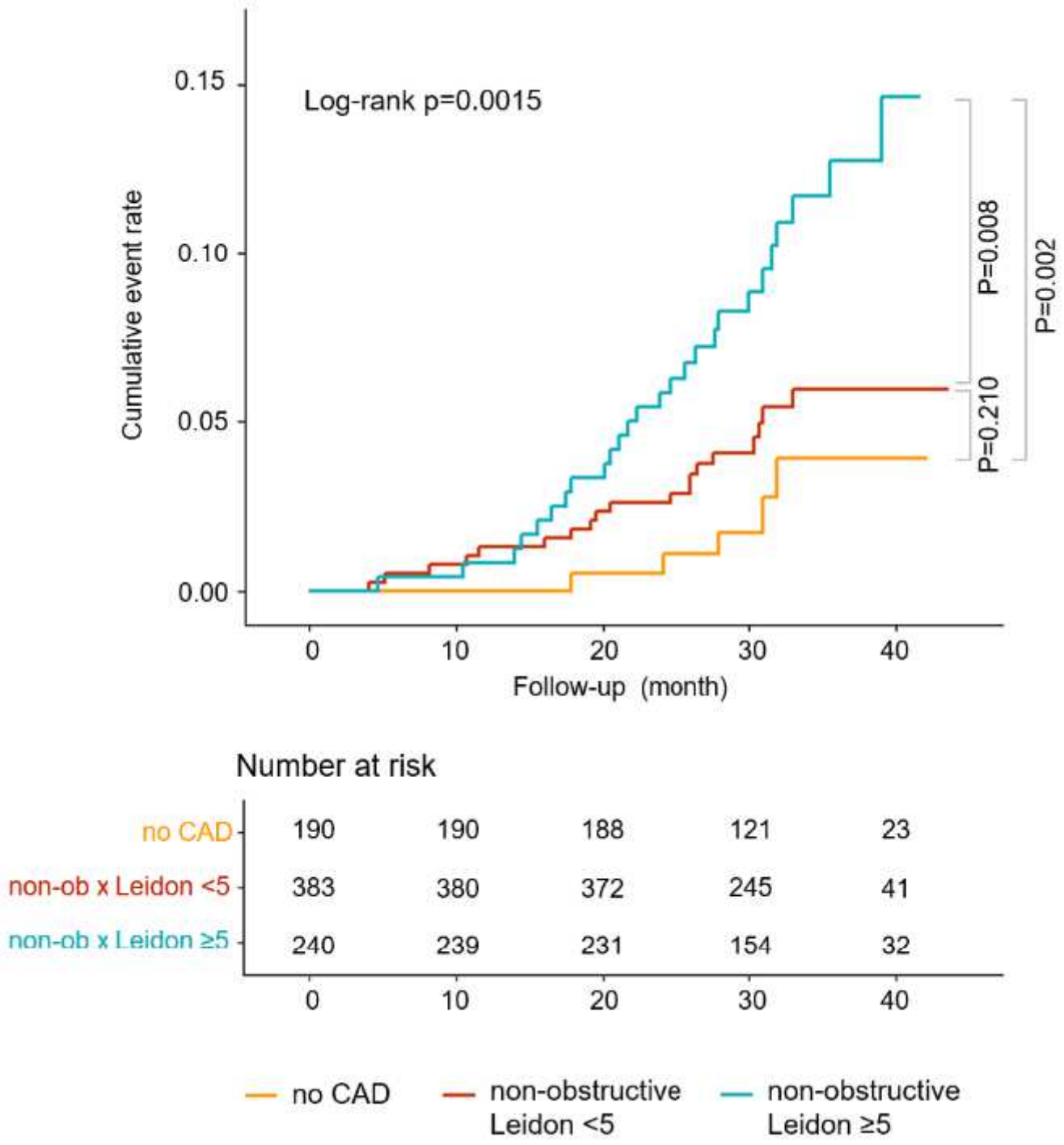

Figure 2

Cumulative risk of the composite endpoint on the basis of CAD severity with Leidon risk score. (no CAD, non-obstructive CAD with Leidon<5, and non-obstructive CAD with Leidon≥5). CAD, coronary artery disease

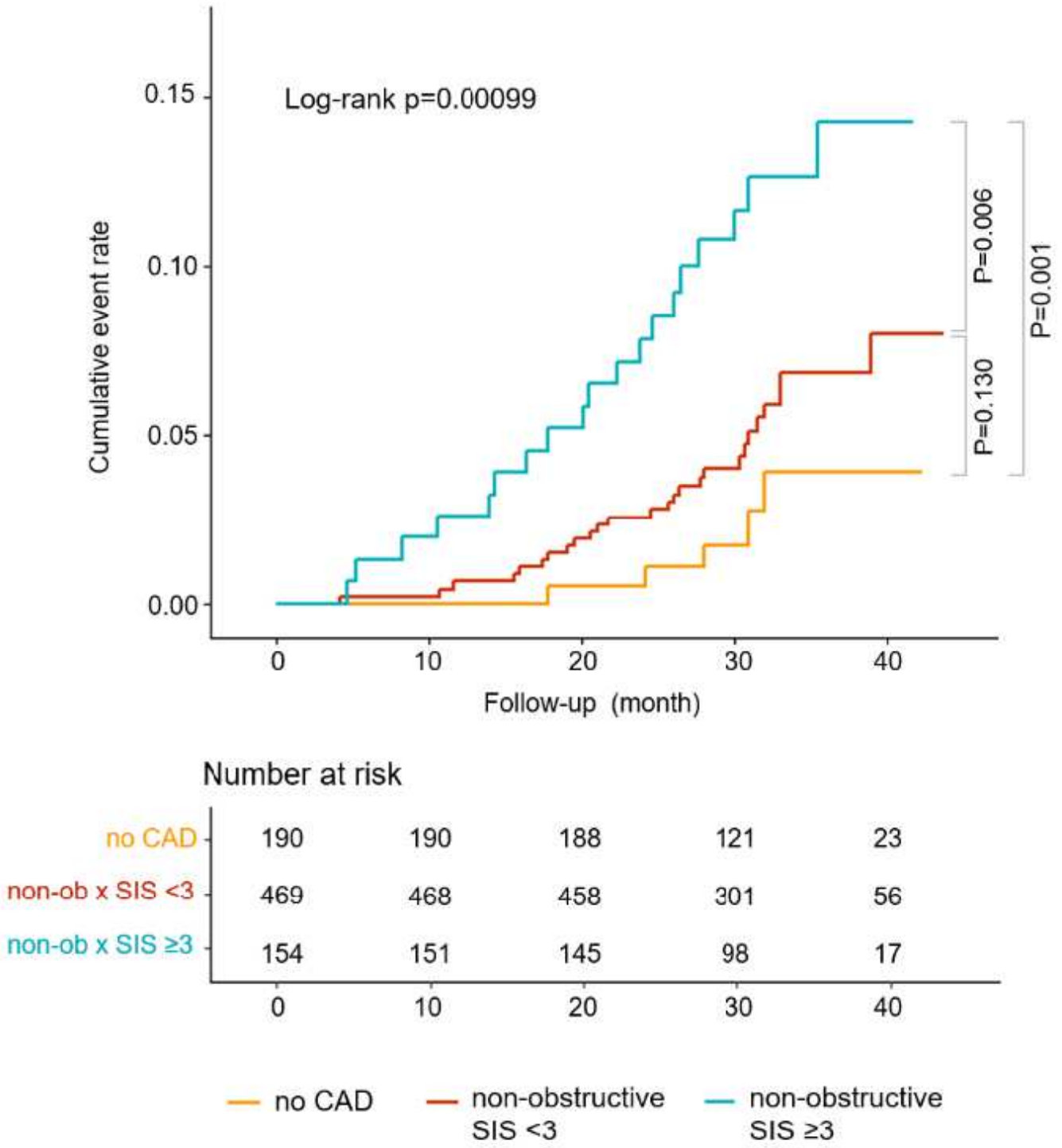

Figure 3

Cumulative risk of the composite endpoint on the basis of CAD severity with segment involvement score. (no CAD, non-obstructive with SIS<3, and non-obstructive with SIS<3) CAD, coronary artery disease; SIS, segment involvement score