Coronary atherosclerosis scoring with semiquantitative CCTA risk scores for prediction of major adverse cardiac events: propensity score -based analysis of diabetic and non -diabetic patients

Hoogen, I.J. van den; Rosendael, A.R. van; Lin, F.Y.; Lu, Y.; Dimitriu-Leen, A.C.; Smit, J.M.; ... ; Bax, J.J.

Journal of Cardiovascular Computed Tomography 14 (2020) 251–257

Contents lists available at ScienceDirect

Journal of Cardiovascular Computed Tomography

journal homepage: www.elsevier.com/locate/jcct

Research paper

Coronary atherosclerosis scoring with semiquantitative CCTA risk scores for prediction of major adverse cardiac events: Propensity score-based analysis of diabetic and non-diabetic patients

Inge J. van den Hoogen[a,b], Alexander R. van Rosendael[a,b], Fay Y. Lin[b], Yao Lu[c], Aukelien C. Dimitriu-Leen[a], Jeff M. Smit[a], Arthur J.H.A. Scholte[a], Stephan Achenbach[d], Mouaz H. Al-Mallah[e], Daniele Andreini[f], Daniel S. Berman[g], Matthew J. Budoff[h], Filippo Cademartiri[i], Tracy Q. Callister[j], Hyuk-Jae Chang[k], Kavitha Chinnaiyan[l], Benjamin J.W. Chow[m], Ricardo C. Cury[n], Augustin DeLago[o], Gudrun Feuchtner[p], Martin Hadamitzky[q], Joerg Hausleiter[r], Philipp A. Kaufmann[s], Yong-Jin Kim[t], Jonathon A. Leipsic[u], Erica Maffei[v], Hugo Marques[w], Pedro de Araújo Gonçalves[w], Gianluca Pontone[f], Gilbert L. Raff[l], Ronen Rubinshtein[x], Todd C. Villines[y], Heidi Gransar[z], Erica C. Jones[b], Jessica M. Peña[b], Leslee J. Shaw[b], James K. Min[b], Jeroen J. Bax[a,*]

[a] Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands
[b] Dalio Institute of Cardiovascular Imaging, Department of Radiology, New York-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY, USA
[c] Department of Healthcare Policy and Research, New York-Presbyterian Hospital and the Weill Cornell Medical College, New York, NY, USA
[d] Department of Cardiology, Friedrich-Alexander-University Erlangen-Nuremburg, Germany
[e] King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Center, King AbdulAziz Cardiac Center, Ministry of National Guard, Health Affairs, Riyadh, Saudi Arabia
[f] Centro Cardiologico Monzino, IRCCS, Milan, Italy
[g] Department of Imaging and Medicine, Cedars Sinai Medical Center, Los Angeles, CA, USA
[h] Department of Medicine, Los Angeles Biomedical Research Institute, Torrance, CA, USA
[i] Cardiovascular Imaging Center, SDN IRCCS, Naples, Italy
[j] Tennessee Heart and Vascular Institute, Hendersonville, TN, USA
[k] Division of Cardiology, Severance Cardiovascular Hospital and Severance Biomedical Science Institute, Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea
[l] Department of Cardiology, William Beaumont Hospital, Royal Oak, MI, USA
[m] Department of Medicine and Radiology, University of Ottawa, ON, Canada
[n] Department of Radiology, Miami Cardiac and Vascular Institute, Miami, FL, USA
[o] Capitol Cardiology Associates, Albany, NY, USA
[p] Department of Radiology, Medical University of Innsbruck, Innsbruck, Austria
[q] Department of Radiology and Nuclear Medicine, German Heart Center Munich, Munich, Germany
[r] Medizinische Klinik I der Ludwig-Maximilians-UniversitätMünchen, Munich, Germany
[s] Department of Nuclear Medicine, University Hospital, Zurich, Switzerland and University of Zurich, Switzerland
[t] Seoul National University Hospital, Seoul, South Korea
[u] Department of Medicine and Radiology, University of British Columbia, Vancouver, BC, Canada
[v] Department of Radiology, Area Vasta 1/ASUR Marche, Urbino, Italy
[w] UNICA, Unit of Cardiovascular Imaging, Hospital da Luz, Lisboa, Portugal
[x] 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
[y] Cardiology Service, Walter Reed National Military Center, Bethesda, MD, USA
[z] Department of Imaging, Cedars Sinai Medical Center, Los Angeles, CA, USA

ARTICLE INFO

Keywords:
Computed tomography (CT)
Atherosclerosis

ABSTRACT

Aims: We aimed to compare semiquantitative coronary computed tomography angiography (CCTA) risk scores – which score presence, extent, composition, stenosis and/or location of coronary artery disease (CAD) – and their

* Corresponding author. Department of Cardiology, Leiden University Medical Center Albinusdreef 2, 2333 ZA, Leiden, Postal zone, 2300, RC, the Netherlands.
E-mail address: j.j.bax@lumc.nl (J.J. Bax).

https://doi.org/10.1016/j.jcct.2019.11.015
Received 15 January 2019; Received in revised form 20 November 2019; Accepted 27 November 2019
Available online 05 December 2019
1934-5925/

Diabetes mellitus
Risk stratification
Prognostic application

prognostic value between patients with and without diabetes mellitus (DM). Risk scores derived from general chest-pain populations are often challenging to apply in DM patients, because of numerous confounders.

Methods: Out of a combined cohort from the Leiden University Medical Center and the CONFIRM registry with 5-year follow-up data, we performed a secondary analysis in diabetic patients with suspected CAD who were clinically referred for CCTA. A total of 732 DM patients was 1:1 propensity-matched with 732 non-DM patients by age, sex and cardiovascular risk factors. A subset of 7 semiquantitative CCTA risk scores was compared between groups: ***1)*** any stenosis ≥50%, ***2)*** any stenosis ≥70%, ***3)*** stenosis-severity component of the coronary artery disease-reporting and data system (CAD-RADS), ***4)*** segment involvement score (SIS), ***5)*** segment stenosis score (SSS), ***6)*** CT-adapted Leaman score (CT-LeSc), and ***7)*** Leiden CCTA risk score. Cox-regression analysis was performed to assess the association between the scores and the primary endpoint of all-cause death and non-fatal myocardial infarction. Also, area under the receiver-operating characteristics curves were compared to evaluate discriminatory ability.

Results: A total of 1,464 DM and non-DM patients (mean age 58 ± 12 years, 40% women) underwent CCTA and 155 (11%) events were documented after median follow-up of 5.1 years. In DM patients, the 7 semiquantitative CCTA risk scores were significantly more prevalent or higher as compared to non-DM patients ($p \leq 0.022$). All scores were independently associated with the primary endpoint in both patients with and without DM ($p \leq 0.020$), with non-significant interaction between the scores and diabetes (interaction $p \geq 0.109$). Discriminatory ability of the Leiden CCTA risk score in DM patients was significantly better than any stenosis ≥50% and ≥70% ($p = 0.003$ and $p = 0.007$, respectively), but comparable to the CAD-RADS, SIS, SSS and CT-LeSc that also focus on the extent of CAD ($p \geq 0.265$).

Conclusion: Coronary atherosclerosis scoring with semiquantitative CCTA risk scores incorporating the total extent of CAD discriminate major adverse cardiac events well, and might be useful for risk stratification of patients with DM beyond the binary evaluation of obstructive stenosis alone.

1. Introduction

Diabetes mellitus (DM) is a well-established risk factor for coronary artery disease (CAD) as described by global guidelines.[1,2] Patients with DM exhibit higher burden of coronary plaque and have higher adverse event-rates as compared to patients without DM.[3,4] Risk scores derived from general chest-pain populations are often challenging to use in DM patients, because of many confounders that are associated with CAD.[1] For example, the universal percentiles of coronary artery calcium from the Multi-Ethnic Study of Atherosclerosis (MESA) do not directly apply to diabetic patients.[5] Coronary computed tomography angiography (CCTA) allows for non-invasive detailed characterization of CAD, and this modality has proven its superiority to functional stress testing as an initial diagnostic test in DM patients.[6–9] Coronary plaque characteristics by CCTA (e.g. presence, extent, composition, stenosis and location) can be used for further optimization of risk stratification.[10–14] Recently, it has been demonstrated that the Leiden CCTA risk score, which grades all the aforementioned features of coronary atherosclerosis, improves prediction and reclassification of adverse events as compared to the stenosis severity component of the coronary artery disease-reporting and data system (CAD-RADS).[15] However, it remains uncertain if comprehensive atherosclerotic scores derived from general chest-pain populations apply well to a specific cohort of DM patients. Therefore, the aim of the current study is to compare a subset of semiquantitative CCTA risk scores and their prognostic value between patients with and without DM.

2. Methods

2.1. Study design and population

Out of a 14,895-patient cohort from the Leiden University Medical Center (LUMC) and the COronary CT Angiography EvaluatioN For Clinical Outcomes: an InteRnational Multicenter (CONFIRM) registry at 17 sites in 9 countries with 5-year follow-up data, we performed a secondary analysis in 2,900 DM patients with suspected CAD who were clinically referred for CCTA between 2002 and 2015.[15,16] Diagnosis of DM was defined as fasting glucose ≥126 mg/dL and/or treatment with insulin or hypoglycemic medication.[1] Demographic and clinical data were prospectively collected from departmental electronic information systems and retrospectively analyzed, which was approved by institutional review boards or ethics committees at each participating site. All patients provided written informed consent, except for the patients at the LUMC where this need was waived by the institutional review board. For the present study, the following additional exclusion criteria were applied: ***1)*** an uninterpretable CCTA examination, ***2)*** prior percutaneous coronary intervention or coronary artery bypass grafting, ***3)*** CCTA in the setting of suspected acute coronary syndrome, ***4)*** missing coronary plaque data for score calculation, and ***5)*** missing follow-up data (n = 2,168). Thus, 732 DM patients were included and 1:1 propensity-matched with non-DM patients from the original cohort.

2.2. CCTA acquisition and image analysis

Patients were scanned with ≥64-slice CT scanners, and protocols with regard to the acquisition and post-processing of scans were previously published.[6,15,16] At the LUMC, scans were analyzed according to a 17-segment modified American Heart Association (AHA) model of the coronary artery tree by consensus of experienced physicians.[10] Qualitative analysis of all diseased segments was performed.[13] Coronary plaque composition was defined as calcified for plaques with high density, non-calcified for plaques with lower density than the contrast-enhanced lumen and mixed for plaques with both characteristics. Stenosis severity was categorized as normal, <30%, 30–50%, 50–70%, 70–99% and 100%. System dominance was determined upon the origin of the posterior descending artery as part of either the right coronary artery or left circumflex artery. For the CONFIRM registry, image analysis was systematically performed according to the Society of Cardiovascular Computed Tomography (SCCT) guidelines at the time.[17,18]

2.2.1. Semiquantitative CCTA risk scores

For all patients, a subset of 7 semiquantitative CCTA risk scores was calculated: ***1)*** any stenosis ≥50%, ***2)*** any stenosis ≥70%, ***3)*** stenosis severity component of the CAD-RADS, ***4)*** segment involvement score (SIS), ***5)*** segment stenosis score (SSS), ***6)*** CT-adapted Leaman score (CT-LeSc), and ***7)*** Leiden CCTA risk score. Any stenosis ≥50% or ≥70% was scored in a binary fashion. The stenosis severity component of the CAD-RADS was stratified into 3 groups according to previously published methods for reasons of uniformity and sample size[15]: no to minimal CAD (i.e. CAD-RADS 0–1), moderate CAD (i.e. CAD-RADS 2–3) and severe CAD (i.e. CAD-RADS 4–5). No high-risk plaque features were incorporated into this classification as these were not consistently evaluated in this study population. The SIS corresponded to the total number of diseased segments, irrespective of stenosis severity (range 0–17).[19] The SSS graded stenosis severity from 0 to 3 in each individual segment and summed this into a continuous score (range 0–48).[19] The CT-LeSc graded composition, stenosis and location in each individual segment and merged this into a continuous score (range 0–33).[14,20] The Leiden CCTA risk score graded in each individual segment in consecutive order: presence and composition (i.e. plaque weight factor, range 0–1.3), stenosis (i.e. stenosis weight factor, range 1.0–1.4) and location according to system dominancy, major epicardial artery and distance from ostium (i.e. location weight factor, range 0–6) (Appendix Supplement 1, online calculator available at http://18.224.14.19/calcApp/).[15] The 3 weight factors were multiplied to compute individual segment scores, and summation of these scores resulted in a continuous score (range 0–42). Further, this continuous score was stratified into 3 groups that were proven to discriminate adverse events best: 0–5, 6–20 and > 20.[15] Moreover, plaque weights, stenosis weights and location weights were summed to create per-patient weight scores. Per-patient weight scores were divided by the number of segments with coronary plaque to create per-segment weight scores (only when plaque was observed).

2.3. Study endpoints

The primary endpoint was a composite of all-cause death and non-fatal myocardial infarction (MI). Non-fatal MI was defined according to standard definitions and/or current guidelines.[21,22] Methodology on how mortality and follow-up data were documented was previously reported.[15]

2.4. Statistical analysis

2.4.1. Propensity-matching

Propensity-matching of DM and non-DM patients was performed in a 1:1 ratio in order to detect the pure effect of diabetes on the CCTA risk scores. A propensity score was calculated to predict DM from the probabilities of a multivariable logistic regression model including age, sex, cardiovascular risk factors and medication. In case of missing variables, relaxed models were used to create as many matches as possible. A total of 732 DM patients was matched to 732 non-DM patients with this propensity score by the Matchit nearest-neighbor matching algorithm.[23,24] In all matched patients the balancing property was satisfied.

2.4.2. General

Continuous data are reported as means ± standard deviations (SD), independent upon distribution for reasons of uniformity. Categorical data are reported as counts with percentages. Continuous data were compared with the paired T test or paired Wilcoxon Signed Rank test, where appropriate. Categorical data were compared with the McNemar's test. Uni and multivariable Cox-regression analysis was performed to assess the association between the 7 semiquantitative CCTA risk scores and the primary endpoint. To avoid overfitting of the multivariable model, backward selection with the Akaïke information criterion was used for selection of clinical variables. In DM-patients, also area under the receiver-operating characteristics curves (AUC) between the scores were compared with the DeLong's test to evaluate discriminatory ability. With regard to the Leiden CCTA risk score, also survival analysis with the Kaplan-Meier method was performed. Event-free survival curves were compared with the log-rank test. All statistical tests were 2-sided and a p-value of <0.05 indicated statistical significance. All analyses were performed with R (version 3.3.2, R Development Core Team, Vienna, Austria) and SPSS software (version 25, SPSS IBM Corp., Armonk, New York).

Table 1
Baseline characteristics of study population.

	DM patients	Non-DM patients	p-value
	n = 732	n = 732	
	Mean ± SD or n (%)		
Age, years	58 ± 12	58 ± 13	0.303
Male	446 (61)	436 (60)	0.614
BMI, kg/m^2	28.3 ± 5.1	27.7 ± 5.1	**0.011**
Symptoms			**<0.001**
Typical angina	76 (11)	93 (13)	
Atypical angina	175 (24)	255 (35)	
Non-cardiac	92 (13)	129 (18)	
Asymptomatic	383 (53)	251 (35)	
Cardiovascular risk factors			
Hypertension*	464 (63)	448 (61)	0.356
Hypercholesterolemia†	425 (58)	373 (51)	**0.001**
Family history of CAD‡	266 (36)	259 (35)	0.739
Smoking current	172 (24)	168 (23)	0.847
Cardiovascular medication			
ACE inhibitors	203 (29)	187 (26)	0.240
Aspirin	198 (28)	202 (28)	1.000
Beta blockers	165 (23)	203 (28)	0.092
Calcium channel blockers	81 (12)	89 (12)	1.000
Statins	375 (53)	330 (45)	**0.004**

Abbreviations: ACE, angiotensin converting enzyme-inhibitor; BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus. Definitions: * Blood pressure ≥140/90 mmHg and/or treatment with antihypertensive medication; † Total cholesterol ≥230 mg/dL or triglycerides ≥200 mg/dL and/or treatment with lipid-lowering medication; ‡ Presence of coronary artery disease in first-degree family members at age <55 years in males and <65 years in females.

3. Results

3.1. Study population

A total of 1,464 DM and non-DM patients (mean age 58 ± 12 years, 40% women) underwent CCTA and had a median follow-up of 5.1 years (interquartile range 2.2–6.2 years). The primary endpoint was documented in 155 (11%) patients, of which 95 (7%) and 60 (4%) in patients with and without DM, respectively. DM patients were largely comparable to non-DM patients with regard to age, sex, cardiovascular risk factors and medication, except for the prevalence of hypercholesterolemia and statin therapy (Table 1). However, on CCTA, patients with DM demonstrated more obstructive CAD than patients without DM, whilst no or non-obstructive CAD was less frequently observed ($p < 0.001$) (Table 2).

3.2. Semiquantitative CCTA risk scores

All binary or categorized CCTA risk scores were significantly more

Table 2
CCTA findings of study population.

	DM patients	Non-DM patients	p-value
	n = 732	n = 732	
	n (%)		
No or non-obstructive CAD	428 (59)	502 (69)	**<0.001**
Obstructive CAD	304 (42)	230 (31)	**<0.001**
1-vessel	139 (19)	117 (16)	0.141
2-vessel	87 (12)	61 (8)	**0.027**
3-vessel or LM	78 (11)	52 (7)	**0.022**

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

prevalent in DM patients ($p \leq 0.022$) (Table 3). Also, all continuous CCTA risk scores were significantly higher in this group (for SIS 3.7 ± 3.6 vs. 2.6 ± 3.1, $p < 0.001$; for SSS 5.3 ± 5.8 vs. 3.8 ± 5.1, $p < 0.001$; for CT-LeSc 6.5 ± 6.3 vs. 5.0 ± 5.5, $p < 0.001$; and for Leiden CCTA risk score 9.2 ± 8.6 vs. 7.0 ± 7.7, $p < 0.001$). With regard to the Leiden CCTA risk score, it was observed that all per-patient weights scores were higher, whereas the per-segment location weight score was lower in patients with DM ($p < 0.001$ and $p = 0.019$, respectively) (Table 4).

3.3. Prediction of major adverse cardiac events

3.3.1. Cox-regression analysis

In univariable analysis, all semiquantitative CCTA risk scores were significantly associated with the primary endpoint in patients with and without DM ($p < 0.001$) (Table 5). In multivariable analysis, the scores remained independent predictors of events in both groups ($p \leq 0.020$). More importantly, a non-significant interaction between DM and the scores was observed ($p \geq 0.109$) (Appendix Supplement 2). For instance, this was demonstrated by a similar elevation in risk for Leiden CCTA risk scores of >20 over scores of 6–20: HR 3.90 (95% CI 1.88–8.09) ($p < 0.001$) versus HR 2.38 (95% CI 1.28–4.44) ($p = 0.006$) in DM patients, and HR 3.02 (95% CI 1.27–7.22) ($p = 0.013$) versus HR 2.18 (95% CI 1.11–4.28) ($p = 0.024$) in non-DM patients.

3.3.2. Discriminatory ability

In DM patients, the AUC for discrimination of the primary endpoint was 0.636 (95% CI 0.585–0.688) for any stenosis ≥50%, 0.623 (95% CI 0.572–0.675) for any stenosis ≥70%, 0.679 (95% CI 0.630–0.729) for the CAD-RADS, 0.696 (95% CI 0.643–0.748) for the SIS, 0.704 (95% CI 0.652–0.757) for the SSS, 0.704 (95% CI 0.651–0.757) for the CT-LeSc and 0.704 (95% CI 0.651–0.757) for the Leiden CCTA risk score (Fig. 1). The discriminatory ability of the Leiden CCTA risk score was significantly better than any stenosis ≥50% and ≥70% ($p = 0.003$ and $p = 0.007$, respectively), but comparable to the CAD-RADS, SIS, SSS and CT-LeSc ($p \geq 0.265$).

4. Discussion

The present study is a propensity score-based analysis of 1,464 DM and non-DM patients with suspected CAD, who were clinically referred for CCTA and followed for all-cause death and non-fatal MI during a median of 5.1 years. We compared 7 semiquantitative CCTA risk scores – which score presence, extent, composition, stenosis and/or location of coronary atherosclerosis – and their prognostic value between both groups. All scores were independently associated with the primary endpoint in both patients with and without DM, with non-significant interaction between the scores and diabetes. Particularly, the discriminatory ability of semiquantitative CCTA risk scores that weighted stenosis and incorporated the full extent of CAD, such as the CAD-RADS, SIS, SSS, CT-LeSc and Leiden CCTA risk score, was superior to the binary evaluation of obstructive stenosis in patients with DM. These findings might be clinically useful for risk stratification of this specific patient population.

4.1. Semiquantitative CCTA risk scores in DM

Prior studies evaluated semiquantitative CCTA risk scores in diabetic patients, mainly the presence of obstructive stenosis, the SIS and the SSS.[4,25] Hadamitzky et al. studied 1,922 patients without known CAD who underwent a clinically indicated CCTA at a single center: 140 patients with DM and 1,782 patients without DM.[25] By analyzing both groups, more obstructive CAD (48% vs. 26%, $p < 0.001$) and a higher SIS (5.2 ± 3.7 vs. 2.9 ± 3.2, $p < 0.001$) were observed in DM patients as compared to non-DM patients. After a mean follow-up of 33 months, the SIS remained independently predictive of the primary endpoint of all-cause death, non-fatal MI and unstable angina requiring hospitalization in all patients. In addition to this, in a previous analysis of the CONFIRM registry, Rana et al. selected 11,110 patients without known CAD who underwent CCTA.[4] A total of 3,370 patients with DM were 1:2 propensity-matched with 6,740 patients without DM by age, sex and cardiovascular risk factors. DM patients demonstrated less no or non-obstructive CAD (63% vs. 73%, $p = 0.041$), more obstructive CAD (37% vs. 27%, $p < 0.001$), a higher SIS (2 vs. 1, $p < 0.001$) and a higher SSS (3 vs. 2, $p < 0.001$) as compared to non-DM patients. Our results, which ***1)*** included additional patients from the LUMC to the CONFIRM registry, and ***2)*** had greater restrictions with regard to system dominancy, composition, stenosis and location for score calculation, were overall very consistent with the aforementioned findings.

Only a few studies investigated the CT-LeSc next to the presence of obstructive stenosis, the SIS and the SSS in diabetic patients. For instance, Gonçalves e*t al.* evaluated 581 patients without known CAD who underwent CCTA at a single center: 85 patients with DM and 496 patients without DM.[26] Comparable to the abovementioned findings and our analysis, DM patients demonstrated less no or non-obstructive CAD (68% vs. 90%, $p < 0.001$), more obstructive CAD (32% vs. 10%, $p < 0.001$) and a higher prevalence of SIS>5 (37% vs. 13%, $p < 0.001$), SSS>5 (25% vs. 5%, $p < 0.001$) and CT-LeSc>8.3 (41% vs. 16%, $p < 0.001$) as compared to non-DM patients. Whether these CCTA risk scores were predictive of adverse events was not tested in this study. However, the long-term prognostic value of the CT-LeSc with regard to hard endpoints (e.g. non-fatal MI, all-cause death, cardiac death) has been established in other patient populations, such as a general chest-pain population and patients with non-obstructive CAD.[14,20]

No prior studies evaluated the Leiden CCTA risk score in diabetic patients. Recently, van Rosendael et al. established the prognostic importance of the Leiden CCTA risk score for adverse events (i.e. all-cause death, non-fatal MI) in a large observational study of 2,134 patients with suspected but without known CAD.[15] When the Leiden CCTA risk score was added to a selection of classical cardiovascular risk factors, both the discrimination of adverse events (AUC 0.768 vs. 0.742, $p = 0.001$) and reclassification of patients (net reclassification improvement 12.4%, $p < 0.001$) increased compared to the stenosis severity component of the CAD-RADS plus the same risk factors. Also, this discriminatory ability was reproduced in an external validation cohort. To this end, we hypothesized that the Leiden CCTA risk score might not be applicable to DM patients, because of various confounders that are associated with CAD.[1,5] Our analysis proved that the Leiden CCTA risk score was independently predictive of adverse events, and importantly,

Table 3
Semiquantitative CCTA risk scores stratified by DM.

	DM patients	Non-DM patients	p-value
	n = 732	n = 732	
	Mean ± SD or n (%)		
Any stenosis ≥50%	304 (42)	230 (31)	**<0.001**
Any stenosis ≥70%	136 (19)	107 (15)	**0.022**
CAD-RADS			**0.001**
CAD-RADS 0-1	212 (29)	269 (37)	
CAD-RADS 2-3	372 (51)	351 (48)	
CAD-RADS 4-5	148 (20)	112 (15)	
SIS	3.7 ± 3.6	2.6 ± 3.1	**<0.001**
SSS	5.3 ± 5.8	3.8 ± 5.1	**<0.001**
CT-LeSc	6.5 ± 6.3	5.0 ± 5.5	**<0.001**
Leiden CCTA risk score	9.2 ± 8.6	7.0 ± 7.7	**<0.001**

Abbreviations: CAD-RADS, coronary artery disease-reporting and data system; CCTA, coronary computed tomography angiography; CT-LeSc, CT-adapted Leaman score; DM, diabetes mellitus; SIS, segment involvement score; SSS, segment stenosis score.

Table 4
Leiden CCTA risk score and weight scores stratified by DM.

	DM patients	Non-DM patients	p-value
	n = 732	n = 732	
	Mean ± SD or n (%)		
Leiden CCTA risk score category			**<0.001**
CCTA risk score 0-5	332 (45)	416 (57)	
CCTA risk score 6-20	314 (43)	268 (37)	
CCTA risk score >20	86 (12)	48 (7)	
Per-patient weight scores			
Plaque weight score	4.4 ± 4.4	3.2 ± 3.7	**<0.001**
Stenosis weight score	4.1 ± 4.1	3.0 ± 3.5	**<0.001**
Location weight score	6.8 ± 6.2	5.2 ± 5.5	**<0.001**
Per-segment weight scores			
Plaque weight score	1.2 ± 0.1	1.2 ± 0.1	0.431
Stenosis weight score	1.1 ± 0.1	1.1 ± 0.1	0.160
Location weight score	2.1 ± 0.7	2.2 ± 0.8	**0.019**

Abbreviations: CCTA, coronary computed tomography angiography; DM, diabetes mellitus.

that this predictive value did not differ in the presence or absence of DM. Also, the Leiden CCTA risk score and per-segment and per-patient weight scores were evaluated in DM and non-DM patients, in order to determine the contribution of its components to the total score. By doing so, it was demonstrated that the Leiden CCTA risk score and all the per-patient weight scores were significantly higher in patients with DM, whilst the per-segment location weight score was lower. This discrepancy in significance between the per-patient and per-segment weight scores was explainable by the higher amount of diseased segments (SIS 3.7 ± 3.6 vs. 2.6 ± 3.1, p < 0.001) in DM patients.[27–30] For example, per-patient weight scores will increase in case of more diseased segments, as they are by definition the sum of all plaque weights, stenosis weights and location weights within a patient. When normalized for the total extent of CAD, only the per-segment location weight score remained significantly lower in diabetic patients. Though, this difference was numerically very modest.

4.2. Clinical implications

DM is an important risk factor for the development of cardiovascular disease, accounting for abundant morbidity, mortality and public health costs.[31–34] Accordingly, current global guidelines underlined that patients with DM should be considered at high-risk for cardiovascular disease, and at very high-risk with ≥1 other cardiovascular risk factors or end organ damage.[1,35] Hence, multiple studies declared DM as an equivalent of CAD.[2,3,36,37] These statements were evaluated through a large systematic review and meta-analysis by Bulugahapitiya et al.[38] In this analysis, 13 cohort- and observational studies involving 45,108 patients were included: 21,675 DM patients and 23,433 non-DM patients. This study, with mean follow-up of 13.4 years, demonstrated that for DM patients without prior MI the risk for fatal or non-fatal MI was 43% lower than in non-DM patients with prior MI. Thus, they did not support the hypothesis of DM as a CAD-equivalent. Although our results showed that patients with DM exhibited higher overall burden of coronary atherosclerosis, all semiquantitative CCTA risk scores were still able to predict the primary endpoint of all-cause death and non-fatal MI accurately. Especially scores incorporating the total extent of CAD performed particularly well. Additional results with regard to the extent atherosclerotic disease and the survival of diabetic and non-diabetic patients are available in Appendix Supplement 3.

4.3. Limitations

First, this was a nested case-control study with all the intrinsic limitations of an observational cohort study like unmeasured confounding factors and selection bias. Second, the event-rate of the primary endpoint was relatively low, and therefore the present study was underpowered to enter a multitude of variables into the multivariable model. Though, by employing the backward selection method overfitting of this model was avoided. Third, we only performed qualitative analysis or visual categorization of all diseased segments within patients. Quantitative analysis of coronary plaque might capture the full extent of atherosclerotic disease more precisely or will provide additional information.[39] Fourth, recent studies addressed the value of serial CCTA to detect not only coronary plaque growth but also the progression of high-risk or vulnerable plaques in order to evaluate the natural history of the atherosclerotic process in patients with DM.[40] Our study only ascertained scans at a single timepoint.

5. Conclusion

In summary, coronary atherosclerosis scoring with semiquantitative

Table 5
Cox-regression analysis stratified by DM.

	DM patients				Non-DM patients			
	Univariable		Multivariable*		Univariable		Multivariable†	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Any stenosis ≥50%	3.16 (2.02–4.94)	**<0.001**	2.08 (1.27–3.39)	**0.003**	5.37 (3.03–9.51)	**<0.001**	3.41 (1.87–6.21)	**<0.001**
Any stenosis ≥70%	4.08 (2.61–6.36)	**<0.001**	2.44 (1.50–3.97)	**<0.001**	4.58 (2.65–7.90)	**<0.001**	3.03 (1.65–5.56)	**<0.001**
CAD-RADS	Overall	**<0.001**	Overall	**<0.001**	Overall	**<0.001**	Overall	**<0.001**
CAD-RADS 0-1	Reference category		Reference category		Reference category		Reference category	
CAD-RADS 2-3	4.31 (1.84–10.13)	**0.001**	2.64 (1.10–6.35)	**0.030**	3.58 (1.38–9.31)	**0.009**	2.03 (0.76–5.37)	0.156
CAD-RADS 4-5	10.99 (4.60–26.26)	**<0.001**	5.07 (1.99–12.89)	**0.001**	12.17 (4.62–32.03)	**<0.001**	5.84 (2.08–16.41)	**0.001**
SIS	1.16 (1.11–1.22)	**<0.001**	1.10 (1.03–1.16)	**0.002**	1.21 (1.13–1.29)	**<0.001**	1.12 (1.04–1.21)	**0.003**
SSS	1.09 (1.06–1.12)	**<0.001**	1.06 (1.02–1.10)	**0.002**	1.11 (1.08–1.15)	**<0.001**	1.07 (1.03–1.11)	**0.001**
CT-LeSc	1.10 (1.07–1.14)	**<0.001**	1.07 (1.04–1.11)	**<0.001**	1.11 (1.07–1.16)	**<0.001**	1.06 (1.01–1.11)	**0.011**
Leiden CCTA risk score	1.08 (1.05–1.10)	**<0.001**	1.05 (1.03–1.08)	**<0.001**	1.09 (1.06–1.12)	**<0.001**	1.05 (1.01–1.08)	**0.007**
Leiden CCTA risk score category	Overall	**<0.001**	Overall	**<0.001**	Overall	**<0.001**	Overall	**0.020**
CCTA risk score 0-5	Reference category		Reference category		Reference category		Reference category	
CCTA risk score 6-20	4.01 (2.21–7.27)	**<0.001**	2.38 (1.28–4.44)	**0.006**	3.64 (1.91–6.93)	**<0.001**	2.18 (1.11–4.28)	**0.024**
CCTA risk score >20	7.15 (3.63–14.07)	**<0.001**	3.90 (1.88–8.09)	**<0.001**	7.56 (3.38–16.89)	**<0.001**	3.02 (1.27–7.22)	**0.013**

Abbreviations: BMI, body mass index; CAD-RADS, coronary artery disease-reporting and data system; CCTA, coronary computed tomography angiography; CT-LeSc, CT-adapted Leaman score; DM, diabetes mellitus; SIS, segment involvement score; SSS, segment stenosis score. Definitions: In the multivariable models with backward selection adjusted for: * age, sex, BMI, current smoking status, beta blockers, statins; † age, hypercholesterolemia, current smoking status, statins.

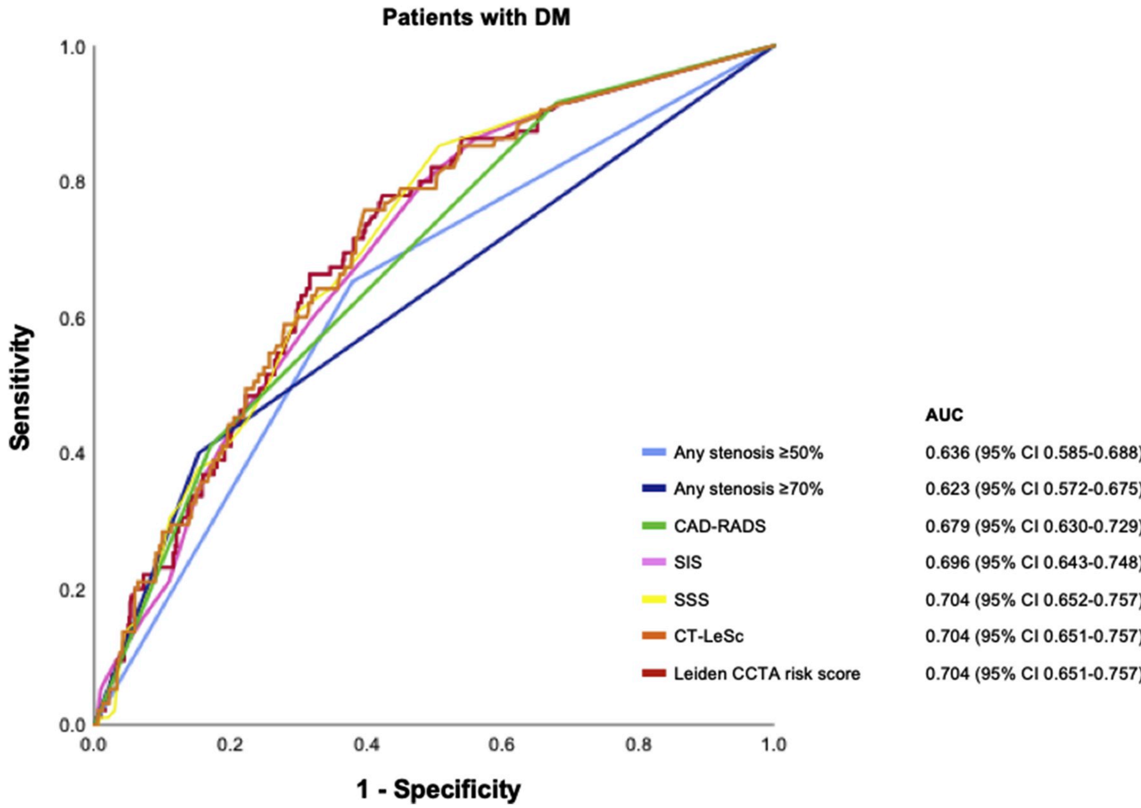

Fig. 1. Discriminatory ability of semiquantitative CCTA risk scores in DM patients.
Abbreviations: AUC, area under the receiver-operating characteristics curves; CAD-RADS, coronary artery disease-reporting and data system; CCTA, coronary computed tomography angiography; CT-LeSc, CT-adapted Leaman score; DM, diabetes mellitus; SIS, segment involvement score; SSS, segment stenosis score.

CCTA risk scores incorporating the total extent of CAD, might be useful for risk stratification of patients with DM beyond the binary evaluation of obstructive stenosis alone.

Funding

The research reported in this publication was funded, in part, by the National Institute of Health (Bethesda, MD, USA) under award number R01 HL115150. This research was also supported, in part, by the Dalio Institute of Cardiovascular Imaging (New York, NY, USA) and the Michael Wolk Foundation (New York, NY, USA).

Declaration of competing interest

Dr. James K. Min receives funding from the Dalio Foundation, National Institutes of Health, and GE Healthcare. Dr. Min serves on the scientific advisory board of Arineta and GE Healthcare, and has an equity interest in Cleerly. The Department of Cardiology of the Leiden University Medical Center received research grants from Biotronik, Medtronic, Boston Scientific and Edwards Lifesciences. Arthur J.H.A. Scholte received consulting fees from GE Healthcare and Canon.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcct.2019.11.015.

References

1. Authors/Task Force M, Ryden L, Grant PJ, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). *Eur Heart J.* 2013;34(39):3035–3087.
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(7):1588–1593.
3. Haffner SM, Lehto S, Ronnemaa 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(4):229–234.
4. Rana JS, Dunning A, Achenbach S, 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(8):1787–1794.
5. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation.* 2006;113(1):30–37.
6. de Graaf FR, Schuijf JD, van Velzen JE, et al. Diagnostic accuracy of 320-row multidetector computed tomography coronary angiography in the non-invasive evaluation of significant coronary artery disease. *Eur Heart J.* 2010;31(15):1908–1915.
7. Gao D, Ning N, Guo Y, Ning W, Niu X, Yang J. Computed tomography for detecting coronary artery plaques: a meta-analysis. *Atherosclerosis.* 2011;219(2):603–609.
8. Meijboom WB, Meijs MF, Schuijf JD, et al. Diagnostic accuracy of 64-slice computed tomography coronary angiography: a prospective, multicenter, multivendor study. *J Am Coll Cardiol.* 2008;52(25):2135–2144.
9. Sharma A, Coles A, Sekaran NK, et al. Stress testing versus CT angiography in patients with diabetes and suspected coronary artery disease. *J Am Coll Cardiol.* 2019;73(8):893–902.
10. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc committee for grading of coronary artery disease, council on cardiovascular surgery, American heart association. *Circulation.* 1975;51(4 Suppl):5–40.
11. Carrigan TP, Nair D, Schoenhagen P, et al. Prognostic utility of 64-slice computed tomography in patients with suspected but no documented coronary artery disease. *Eur Heart J.* 2009;30(3):362–371.
12. Hadamitzky M, Achenbach S, Al-Mallah M, 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(5):468–476.
13. van Werkhoven JM, Schuijf JD, Gaemperli O, et al. Incremental prognostic value of multi-slice computed tomography coronary angiography over coronary artery calcium scoring in patients with suspected coronary artery disease. *Eur Heart J.* 2009;30(21):2622–2629.

14. Mushtaq S, De Araujo Goncalves P, Garcia-Garcia HM, et al. Long-term prognostic effect of coronary atherosclerotic burden: validation of the computed tomography-Leaman score. *Circ Cardiovasc Imag.* 2015;8(2):e002332.
15. van Rosendael AR, Shaw LJ, Xie JX, et al. Superior risk stratification with coronary computed tomography angiography using a comprehensive atherosclerotic risk score. *JACC Cardiovasc Imag.* 2019;12(10):1987–1997.
16. Min JK, Dunning A, Lin FY, 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(2):84–92.
17. Abbara S, Arbab-Zadeh A, Callister TQ, et al. SCCT guidelines for performance of coronary computed tomographic angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr.* 2009;3(3):190–204.
18. Raff GL, Abidov A, Achenbach S, et al. SCCT guidelines for the interpretation and reporting of coronary computed tomographic angiography. *J Cardiovasc Comput Tomogr.* 2009;3(2):122–136.
19. Min JK, Shaw LJ, Devereux RB, et al. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol.* 2007;50(12):1161–1170.
20. Andreini D, Pontone G, Mushtaq S, et al. Long-term prognostic impact of CT-leaman score in patients with non-obstructive CAD: results from the COronary CT angiography EvaluatioN for clinical Outcomes InteRnational multicenter (CONFIRM) study. *Int J Cardiol.* 2017;231:18–25.
21. Roffi M, Patrono C, Collet JP, et al. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European society of Cardiology (ESC). *G Ital Cardiol.* 2015;17(10):831–872 2016.
22. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Glob Heart.* 2012;7(4):275–295.
23. Ho DE, Imai K, King G, Stuart EA. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Political Anal.* 2007;15(3):199–236.
24. Ho DE, Imai K, King G, Stuart EA. MatchIt: nonparametric preprocessing for parametric causal inference. *J Stat Softw.* 2011;42(8).
25. Hadamitzky M, Hein F, Meyer T, et al. Prognostic value of coronary computed tomographic angiography in diabetic patients without known coronary artery disease. *Diabetes Care.* 2010;33(6):1358–1363.
26. Goncalves PD, Garcia-Garcia HM, Carvalho MS, et al. Diabetes as an independent predictor of high atherosclerotic burden assessed by coronary computed tomography angiography: the coronary artery disease equivalent revisited. *Int J Cardiovasc Imaging.* 2013;29(5):1105–1114.
27. Kim JJ, Hwang BH, Choi IJ, et al. Impact of diabetes duration on the extent and severity of coronary atheroma burden and long-term clinical outcome in asymptomatic type 2 diabetic patients: evaluation by Coronary CT angiography. *Eur Heart J Cardiovasc Imag.* 2015;16(10):1065–1073.
28. Maffei E, Seitun S, Martini C, et al. Prognostic value of CT coronary angiography in diabetic and non-diabetic subjects with suspected CAD: importance of presenting symptoms. *Insights Imag.* 2011;2(1):25–38.
29. Nadjiri J, Hausleiter J, Deseive S, et al. Prognostic value of coronary CT angiography in diabetic patients: a 5-year follow up study. *Int J Cardiovasc Imaging.* 2016;32(3):483–491.
30. Van Werkhoven JM, Cademartiri F, Seitun S, et al. Diabetes: prognostic value of CT coronary angiography–comparison with a nondiabetic population. *Radiology.* 2010;256(1):83–92.
31. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA.* 1979;241(19):2035–2038.
32. Nathan DM, Meigs J, Singer DE. The epidemiology of cardiovascular disease in type 2 diabetes mellitus: how sweet it is ... or is it? *Lancet.* 1997;350(Suppl 1):SI4–9.
33. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the U.S. population, 1971-1993. *Diabetes Care.* 1998;21(7):1138–1145.
34. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2013 update: a report from the American Heart Association. *Circulation.* 2013;127(1):e6–e245.
35. Fox CS, Golden SH, Anderson C, et al. Update on prevention of cardiovascular disease in adults with type 2 diabetes mellitus in light of recent evidence: a scientific statement from the American heart association and the American diabetes association. *Circulation.* 2015;132(8):691–718.
36. Hajar R. Diabetes as "coronary artery disease risk equivalent": a historical perspective. *Heart Views.* 2017;18(1):34–37.
37. Juutilainen A, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. *Diabetes Care.* 2005;28(12):2901–2907.
38. Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. *Diabet Med.* 2009;26(2):142–148.
39. Chang HJ, Lin FY, Lee SE, et al. Coronary atherosclerotic precursors of acute coronary syndromes. *J Am Coll Cardiol.* 2018;71(22):2511–2522.
40. Kim U, Leipsic JA, Sellers SL, et al. Natural history of diabetic coronary atherosclerosis by quantitative measurement of serial coronary computed tomographic angiography: results of the PARADIGM study (progression of atherosclerotic plaque determined by computed tomographic angiography imaging). *JACC Cardiovasc Imag.* 2018;11(10):1461–1471.