Long-Term Prognostic Effect of Coronary Atherosclerotic Burden

Validation of the Computed Tomography-Leaman Score

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Background—Computed tomography–adapted Leaman score (CT-LeSc) was developed to quantify coronary CT angiography information about atherosclerotic burden (lesion localization, stenosis degree, and plaque composition). The objective of the study is to evaluate CT-LeSc long-term prognostic value in patients with suspected coronary artery disease (CAD).

Methods and Results—Single-center prospective registry including 1304 consecutive patients undergoing coronary CT angiography for suspected CAD. High CT-LeSc was defined by upper tertile (score, >5) cutoff. Segment involvement score and segment stenosis score were also evaluated. Hard cardiac events (cardiac death and nonfatal acute coronary syndromes) were considered for analysis. Different Cox regression models were used to identify independent event predictors. Kaplan–Meier event-free survival was evaluated in 4 patient subgroups stratified by obstructive (≥50% stenosis) versus nonobstructive CAD and a high (>5) versus a low (≤5) CT-LeSc. Of 1196 patients included in the final analysis (mean follow-up of 52±22 months), 125 patients experienced 136 hard events (18 cardiac deaths and 118 nonfatal myocardial infarction). All atherosclerotic burden scores were independent predictors of cardiac events (hazard ratios of 3.09 for segment involvement score, 4.42 for segment stenosis score, and 5.39 for CT-LeSc). Cumulative event-free survival was 76.8% with a high CT-LeSc and 96.0% with a low CT-LeSc. Event-free survival in nonobstructive CAD with high CT-LeSc (78.6%) was similar to obstructive CAD with high CT-LeSc (76.5%) but lower than obstructive CAD with low CT-LeSc (80.7%).

Conclusions—CT-LeSc is an independent long-term predictor of hard cardiac events. Patients with nonobstructive CAD and high CT-LeSc had hard event-free survival similar to patients with obstructive CAD. **(*Circ Cardiovasc Imaging*. 2015;8:e002332. DOI: 10.1161/CIRCIMAGING.114.002332.)**

Key Word: computed tomography ■ coronary artery disease ■ prognosis

In recent years, studies supporting the prognostic value of coronary computed tomographic angiography (CCTA), including some meta-analyses and a large multicenter registry, have been published.[1,2] According to these data, CCTA is able to risk stratify patients, whereas the absence of identifiable plaques in the coronary tree demonstrated by this imaging tool is associated with an excellent prognosis. Across these studies, it has also been consistently demonstrated that the identification of nonobstructive lesions, a unique feature of CCTA as a noninvasive coronary imaging modality, has also prognostic value. This has clinical implications because many patients fall in this category, as reflected by the high proportion of patients with atherosclerotic plaques in many CCTA databases.[3–6]

See Clinical Perspective
See Editorial by Arbab-Zadeh

We have previously reported on the long-term prognostic value of CCTA in patients with suspected coronary artery disease (CAD)[6] and once again, the identification of nonobstructive lesions conveyed prognostic information. Nevertheless because nonobstructive CAD is a heterogeneous and prevalent condition, there is the need for tools to quantify total coronary atherosclerotic burden to risk stratify these patients better.

We have previously developed a score, the CT-adapted Leaman score (CT-LeSc), using the comprehensive information on lesion localization, plaque composition, and degree of stenosis provided by CCTA. This allowed the quantification of the total coronary atherosclerotic burden and enabled us

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to demonstrate a significant association of the CT-LeSc with some traditional demographic and clinical risk factors as well as scores for pretest CAD probability and cardiovascular risk.[7]

The aim of this study is to validate the CT-LeSc as a long-term prognostic tool in patients undergoing CCTA for suspected CAD.

Methods

Population

The study population has been previously described.[6] Briefly, a total of 3421 consecutive patients undergoing CCTA between February 2005 and March 2008 because of suspected CAD were included in a single-center prospective registry. Patients were excluded (n=2117) because of (1) known CAD (n=1242), (2) other cardiovascular diseases (n=535), (3) contraindications to contrast agents or inability to sustain a 15-s breath hold (n=195) and (5) cardiac arrhythmias compromising image quality (n=145). Thus, a total of 1304 patients were prospectively enrolled in this study. Figure 1 describes patient selection and study design.

The institution's scientific and ethical committees approved the study, and all patients gave written informed consent. A structured interview was conducted and clinical history acquired, evaluating chest pain, medical therapy and the following cardiac risk factors: diabetes mellitus, hypercholesterolemia, hypertension, positive family history of CAD, and current smoking, and these were classified as per commonly accepted definitions.[5,8]

The classic Diamond–Forrester was used for the assessment of the pretest CAD probability, as previously described.[9]

Scan Protocol and Image Reconstruction

β-blocker (metoprolol) was administered intravenously before CCTA in patients with heart rate >65 bpm. In all patients, CCTA was performed using a 64-slice scanner, (64×0.625 mm collimation, 330-ms gantry rotation time, VCT; GE Medical Systems, Milwaukee, WI).

Dose modulation was attained with ECG gating for a maximum gantry delivery between 40% and 80% during the R–R interval. A bolus of 80 mL of high concentration contrast (Iomeron 400 mg/mL; Bracco Imaging, Milan, Italy) was administered intravenously at 5 mL/s, followed by 50 mL of saline injected at the same infusion rate. The scan was initiated according to the bolus-tracking technique. The coronary calcium score was assessed with dedicated software (CaScore Package; GE Healthcare, Milwaukee, WI), and Agatston score was recorded. Image data sets were analyzed using volume rendering and multiplanar reconstruction on postprocessing workstations (CardioQ3 package, Advantage Workstation version 4.2; GE Healthcare).

Coronary Artery Analysis

Two expert readers unaware of patient clinical status evaluated all CCTA examinations and in case of disagreement, a joint reading was performed and a consensus decision was reached. The American Heart Association 16-segment classification was used[10] and in each evaluated coronary artery segment, coronary atherosclerosis was defined as a tissue structure >1 mm^2 that existed either within the coronary artery lumen or adjacent to the coronary artery lumen that could be discriminated from the surrounding pericardial tissue, epicardial fat, or the vessel lumen itself.[8] Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. Percentage obstruction of coronary artery lumen was based on a comparison of the luminal diameter of the segment exhibiting obstruction to the luminal diameter of the most normal-appearing site immediately proximal to the plaque. Plaque type was classified as noncalcified, calcified, or mixed.

Patients were divided into 3 groups, such as normal (no coronary plaques identified), nonobstructive CAD (plaques with <50% diameter stenosis), and obstructive CAD (plaques with ≥50% diameter stenosis).

The segment involvement score (SIS), ranging from 0 to 16, was calculated as the total number of segments with plaque (any degree of stenosis); the segment stenosis score (SSS), ranging from 0 to 48, was obtained by grading the stenosis severity of each segment with plaque, as was previously described.[8] For both the SIS and the SSS, the prognostically validated cutoffs (>5) were used.[6,8]

CCTA-Adapted Leaman Score

The methodology for the CT-LeSc has been previously described[7] and is presented in Table 1. Briefly, for this score, 3 sets of weighting factors are used: (1) localization of the coronary plaques, accounting for dominance, (2) type of plaque, with a multiplication factor of 1 for calcified plaques and of 1.5 for noncalcified and mixed plaques, and (3) degree of stenosis, with a multiplication factor of 0.615 for nonobstructive (<50% stenosis) and a multiplication factor of 1 for obstructive (≥50% stenosis) lesions.

The CT-LeSc on a patient level was calculated as the sum of the partial CT-LeSc of all evaluable coronary segments.

Clinical Follow-Up

Follow-up, either clinical visit or telephone interview, was performed, and hospital records were screened for clinical events to confirm the

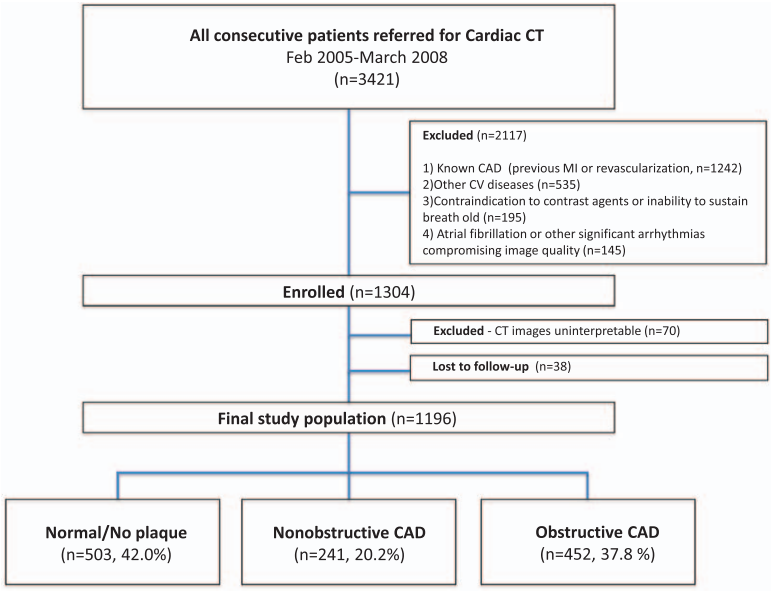


Figure 1. Patient selection and study design. CAD indicates coronary artery disease; CT, computed tomography; CV, cardiovascular; and MI, myocardial infarction.

Table 1. CT-adapted Leaman Score (CT-LeSc) Weighting Factors

	Localization		
Segment	Right Dominance	Left Dominance	Balanced
RCA proximal	1	0	0.5
RCA mid	1	0	0.5
RCA distal	1	0	0.5
PDA	1	na	0.5
Left main	5	6	5.5
LAD proximal	3.5	3.5	3.5
LAD mid	2.5	2.5	2.5
LAD distal	1	1	1
First diagonal	1	1	1
Second diagonal	0.5	0.5	0.5
LCx proximal	1.5	2.5	2.0
First obtuse marginal	1	1	1
LCx distal	0.5	1.5	1
Second obtuse marginal	1	1	1
PDA from LCA	na	1	na
PL branch from LCA	na	0.5	0.5
PL branch from RCA	0.5	na	na
Intermediate branch	1	1	1
Stenosis severity*			
Obstructive CAD		1	
Nonobstructive CAD		0.615	
Plaque composition†			
Noncalcified or mixed		1.5	
Calcified		1	

CAD indicates coronary artery disease; CCTA, coronary computed tomographic angiography; LAD, left anterior descending; LCA, left coronary artery; LCx, left circumflex; na, not applicable; PDA, posterior descending artery; PL, posterolateral; and RCA, right coronary artery.

*The multiplication factor for the degree of stenosis reflects the relative proportion of hazard ratios for mortality in the large CCTA registry CONFIRM in which the prognostic effect of nonobstructive CAD was demonstrated.

†The higher multiplication factor for noncalcified or mixed plaques reflects the assumption of their higher vulnerability as compared with predominantly calcified plaques.

obtained information. In this analysis, we included only hard cardiac events: cardiac death and nonfatal myocardial infarction. The diagnosis of nonfatal myocardial infarction was based on the presence of typical chest pain, elevated cardiac enzymes, and typical ECG changes.[11] Cardiac enzymes used for the diagnosis were troponine-I and mass creatine kinase (CK)–MB. Revascularizations were not included as hard events. Similarly, periprocedural myocardial infarctions associated with revascularization procedures were also not included in the analysis. Death was classified as cardiac when the cause was an acute myocardial infarction, ventricular arrhythmia, or refractory heart failure.

Statistical Analysis

Continuous variables are presented as mean±SD or median (interquartile range) and categorical variables as frequencies with percentages.

The nonparametric Mann–Whitney or Kruskal–Wallis tests were used to compare continuous variables, and the χ^2 or Fisher exact tests were used to evaluate differences in frequencies. Differences were regarded significant when $P<0.05$ (2 tailed).

For the CT-LeSc, the population was divided in tertiles and a high CT-LeSc was defined with the cutoff for the third tertile (a score, >5; range, 5.1–21.8; median, 9.0). The performance of the Leaman score was evaluated using 4 metrics, such as area under the curve (AUC), the Brier score, reclassification tables, and Net Reclassification Indexes (NRIs). Discrimination was studied with the AUC assessment. Comparison of AUC among CT-LeSC, SIS, and SSS was done with the De Long method.[12] The Brier score assessed the accuracy, which is the average-squared difference between the predicted probability and the true occurrence of operative mortality. A Brier score should be as close to 0 as possible, with 0.25 as an acceptable upper cutoff.[13] The comparison between performance of CT-LeSc, SSS, and SIS was further quantified by a reclassification table and its NRI.[14] The NRI focuses on reclassification tables constructed separately for participants with and without events, and quantifies the correct movement in categories—upward for events and downward for nonevents as follows: NRI=(percentage of events moved to higher risk category in event group−percentage of events moved to lower risk category in event group)−(percentage of nonevents moved to higher risk category in nonevent group−percentage of nonevents moved to lower risk category in nonevent group).[15] The categories used for the NRI were CT-LeSc ≤5%, >5% to 10%, and >10%. Because not all people had the same follow-up, our reclassification was based on the expected number of case and control patients calculated by using the Kaplan–Meier estimator. Multivariate analyses (Cox regression model) were performed to identify independent predictors of hard cardiac events, using variables included in Table 2 with $P<0.05$ in univariate analysis. To avoid overfitting and multicollinearity issues, we developed 4 different models: model 1 included all the clinical variables that were significant in univariate analysis (aged >65, men, diabetes mellitus, hypertension, dyslipidemia) and a high pretest CAD probability; models 2, 3, and 4 included the same clinical variables plus each additional atherosclerotic burden score dichotomized (SIS, SSS, or CT-LeSc, respectively).

Cumulative event-free survival rates as a function over time were obtained by the Kaplan–Meier method. The cumulative survival curves are by categories of CAD/CT-LeSc (no CAD, CAD ≤50%/CT-LeSc ≤5, CAD ≤50%/CT-LeSc >5, CAD >50%/CT-LeSc ≤5, CAD >50%/CT-LeSc >5). Hard cardiac event-free survival curves to assess differences across these categories were compared using the log-rank test.

SPSS version 21.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses.

Results

Patient Characteristics

Of the 1304 consecutive patients included, 70 were excluded because the CCTA was considered uninterpretable and 38 were lost to follow-up. Apart from being older and more hypertensive, patients lost to follow-up had no significant differences in baseline characteristics and CCTA results.

In 1136 patients (95%), the follow-up was obtained by clinical visit, and in 60 patients (5%) by telephone interview. In the final 1196 patients included in the analysis (mean follow-up, 52±22 months; ≤76 months), 125 patients experienced a total of 136 hard events (18 cardiac deaths and 118 nonfatal myocardial infarction).

Indications for CCTA were chest pain (43%), multiple cardiac risk factors (28%) or equivocal or abnormal stress tests

Table 2. Distribution of the Demographic, Clinical, and CCTA Characteristics of the Study Population According to the Presence of a High (CT-LeSc>5) Coronary Atherosclerotic Burden

	CT-LeSc≤5 (n=796)	CT-LeSc>5 (n=400)	*P* Value
Demographic and clinical			
Age >65 y	308 (38.7)	229 (57.3%)	<0.001
Men	458 (57.5)	324 (81.0%)	<0.001
Diabetes mellitus	63 (8.5)	61 (16.7)	<0.001
Hypertension	422 (53.5)	281 (71.0)	<0.001
Dyslipidemia	291 (39.4)	206 (56.3)	<0.001
Smoking	210 (28.4)	120 (32.8)	0.143
Family history of premature CAD	260 (34.1)	131 (33.7)	0.948
Chest pain	376 (50.8)	180 (50.1)	0.847
High pretest CAD probability	165 (20.7)	140 (35.0)	<0.001
CCTA results			
Normal/No plaque	503 (63.2)	-	-
Nonobstructive CAD	184 (23.1)	57 (14.3)	<0.001
Obstructive CAD	109 (13.7%)	343 (85.8)	<0.001
1. vessel	92 (11.6)	110 (27.5)	<0.001
2. vessel	11 (1.4)	113 (28.3)	<0.001
3. vessel	5 (0.6)	98 (24.5)	<0.001
Left main	2 (0.3)	21 (5.3)	<0.001
Atherosclerotic burden scores			
SIS	0 (0–1)	4 (3–6)	<0.001
SIS>5	0 (0)	103 (25.8)	<0.001
SSS	0 (0–1)	7 (5–11)	<0.001
SSS>5	18 (2.3)	268 (67.0)	<0.001
CT-LeSc	0 (0–2.2)	9 (6.8–11.8)	<0.001

Values are n (%) or median (25th to 75th percentile). CAD indicates coronary artery disease; CCTA, coronary computed tomographic angiography; CT-LeSc, CT-adapted Leaman score; SIS, segment involvement score; and SSS, segment stenosis score.

(29%). Mean pretest probability of CAD was 42.5±9.9%. Patients with a high (>5) CT-LeSc were older, more often men, had a higher prevalence of traditional risk factors (diabetes mellitus, hypertension, and dyslipidemia), and more often were classified as having a high pretest likelihood of CAD. Patients with a high CT-LeSc had also a higher prevalence of obstructive CAD and other markers of high coronary atherosclerotic burden (as reflected by the prevalence of multivessel and left main disease and higher median SIS and SSS; Table 2). The prevalence of active medication with statins in CAD patients was the following: 22% (40/183 patients) in patients with nonobstructive CAD and low CT-LeSc, 31% (18/58 patients) in patients with nonobstructive CAD and high CT-LeSc, 33% (35/105 patients) in patients with obstructive CAD and low CT-LeSc, and 42% (143/336 patients) in patients with obstructive CAD and high CT-LeSc.

CCTA Results and Distribution of Hard Events

The majority of the patients had a normal (no plaque) CCTA (n=503; 42.0%), obstructive CAD was present in 452 (37.8%) patients and 241 (20.2%) patients had nonobstructive lesions (Figure 1). The distribution of hard cardiac events in CT-LeSc tertiles was T1, 1.0% (n=398; range, 0–0; median, 0; 4 events); T2, 7.0% (n=398; range, 0–5; median, 2.2; 28 events; and T3, 23.3% (n=400; range, 5.1–21.8; median, 9.0; 93 events). The CT-LeSc receiver-operating characteristics curve for hard cardiac events (AUC, 0.808; 95% confidence interval [CI], 0.785–0.830) is depicted in Figure 2. About the AUCs for hard events, these were 0.811 (95% CI, 0.780–0.841) for the SIS and 0.820 (95% CI, 0.776–0.842) for the SSS, which were similar to the AUC of the CT-LeSc (0.808; 95% CI, 0.785–0.830). The Brier score was 0.10 for all the 3 scores. Reclassifications are summarized in Tables 3 and 4. The CT-LeSc improved the risk classification by 38% compared with SSS ($P<0.01$) and by 19% compared with SIS. The improvement was related to better identification of patients with lower risk compared with both SSS (proportion of patients without events going to lower risk categories=43%) and SIS (proportion of patients without events going to lower risk categories=20%). The 3 scores similarly identified patients at higher risk.

The distribution of patients with hard events according to the different coronary atherosclerotic burden scores is shown in Figure 3. Of the 125 patients experiencing a hard cardiac event, 93, 75, and 31 had a high coronary atherosclerotic burden as evaluated by the CT-LeSc, the SSS, and the SIS, respectively. All the patients with hard events and an SIS>5 (n=31) had also a CT-LeSc>5, and only 4 of the patients with an SSS>5 did not have a CT-LeSc>5.

In addition, 62 events (corresponding to 49.6% of the total events) occurred in patients with a high (>5) CT-LeSc but with a low (≤5) SIS. The proportion of events in this subgroup was 26.4% (62 of 235). Similar results were obtained for SSS, as 22 events (17.6% of the total events) occurred in patients with a high CT-LeSc but with a low SSS. The proportion of events in this subgroup was 20.0% (22 of 110).

The percentage of patients undergoing a coronary revascularization procedure (which were not considered as an hard event) across the different groups was the following: nonobstructive CAD (17.4%; 42 of 241 patients); obstructive CAD (72.1%; 326 of 452 patients); SIS>5 (77.7%; 80 of 103 patients); SIS>4 (72.5%; 124 of 171 patients); SSS>5 (78.7%; 225 of 286 patients); and CT-Le>5 (68.3%; 273 of 400 patients).

Univariate Predictors and Multivariate Predictors of Hard Events

Predictors of hard cardiac events are presented in the Table I in the Data Supplement. From the clinical variables, diabetes mellitus was the only risk factor that was consistently an independent predictor across the different multivariable models. The coronary atherosclerotic burden indexes were independent predictors of hard cardiac events with hazard ratios of 3.09 (95% CI, 2.00–4.75), 4.42 (95% CI, 2.97–6.57), and 5.39 (95% CI, 3.49–8.33) for SIS, SSS, and CT-LeSc, respectively.

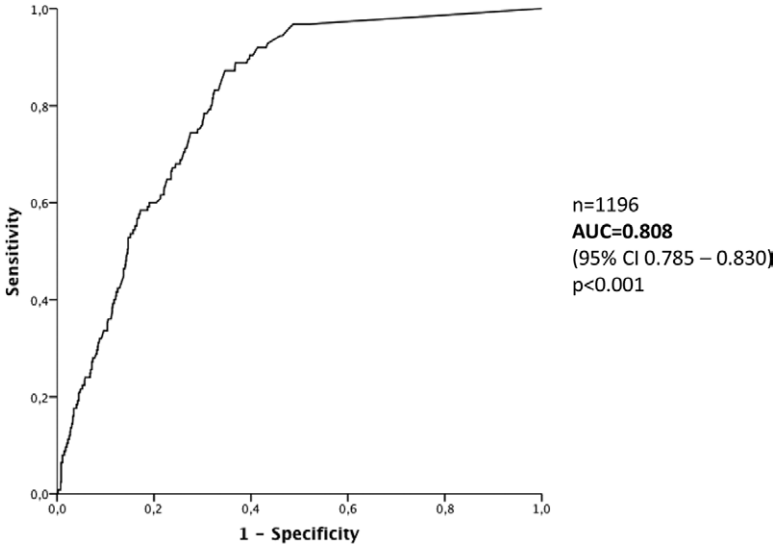


Figure 2. Receiver-operating characteristics curve of the coronary atherosclerotic burden score CT-LeSc for the prediction of hard cardiac events. AUC indicates area under the curve; CI, confidence interval; and CT-LeSc, CT-adapted Leaman score.

Survival Analysis

Cumulative event-free survival was 76.8% in patients with CT-LeSc>5 and 96.0% with CT-LeSc ≤5 (log-rank *P*<0.001; Figure 4).

We further evaluated event-free survival in patients with nonobstructive versus obstructive disease using the respective established cutoff values for the CT-LeSc. As expected, patients with normal (no plaque) coronary arteries had the highest event-free survival, followed by patients with nonobstructive CAD and a low (CT-LeSc ≤5) coronary atherosclerotic burden.

The event-free survival for the subset of patients with nonobstructive CAD and a high (>5) CT-LeSc (78.6%) was similar to that of patients with obstructive CAD and a high CT-LeSc (76.5%; log-rank, *P*=0.627) and was even numerically lower than that of patients with obstructive CAD and a low CT-LeSc (80.7%; log-rank, *P*=810; Figure 5).

Discussion

The main findings of this study are (1) the CT-LeSc is an independent long-term predictor of hard cardiac events and (2) Patients with nonobstructive CAD and a high (CT-LeSc>5) atherosclerotic burden had an event-free survival similar to patients with obstructive CAD.

High Prevalence of Nonobstructive Lesions and the Need for Atherosclerotic Burden Scores

When CCTA identifies obstructive CAD, patients are immediately classified in a high-risk category and, depending on the clinical setting or the presence of ischemia, they are likely candidates for a revascularization procedure. On the contrary, when patients have only nonobstructive lesions at CCTA evaluation, which are not usually associated with myocardial ischemia, as a rule they are not referred for revascularization and, as a group, their prognosis is better. Nevertheless, the event-free survival for patients with nonobstructive CAD is lower than that of patients without plaques. Indeed, they belong to a heterogeneous subset of patients for whom further stratification is of utmost clinical importance. Previous studies showed that it is not uncommon to find atherosclerotic plaques in the coronary artery tree and many patients evaluated by CCTA fall in this intermediate category of nonobstructive CAD.[3,4,6,8] In the large CONFIRM registry, 34% of the patients had only nonobstructive lesions.[5] In a recent study evaluating the relationship between Framingham risk score and atherosclerotic plaque burden, Pen et al[3] reported that coronary atherosclerosis was detected by CCTA in 63.5% of the patients without a history of diabetes mellitus or myocardial infarction and only a minority (11.7%) of patients with a high Framingham risk score had no evidence of plaque on CCTA.

Even taking in account only the burden of calcified plaques, these are expected to be found in the coronary artery tree in most adult patients, according to published nomograms for calcium scoring, with the 50th percentile being ≥1 for most men aged >40 years and for women aged >55 years.[16]

Besides being highly prevalent, it has been consistently demonstrated that nonobstructive CAD has also prognostic implication, with an intermediate risk of events between normal (with no plaque) patients and obstructive CAD.[5,6]

Therefore, there is a clear need for tools to quantify coronary atherosclerotic burden to identify patients at risk for future cardiac events better.

Some indexes have already been developed,[8] like the SIS and the SSS, reflecting some of the information obtained with CCTA like the number of lesions (SIS) and the number of lesions plus the degree of stenosis (SSS) and proved to carry important prognostic information.[5,6,8]

With respect to the metrics that we used to perform this analysis, there was a significant higher accuracy for the CT-LeSc score versus SIS and SSS. Moreover, it has been argued that these parameters are insensitive to systematic errors in calibration, such as differences in average outcome. Therefore, and of high importance for risk prediction is whether a new model can more accurately stratify individuals into higher or lower risk categories. We used the methodology described previously, which balances the reclassification of a new score subtracting, from a better risk grouping, a penalty if it lowers the estimated risk category of a patient with event or raises the estimated risk category of a patient without event. The overall NRI of 0.17 and 0.38 (*P*<0.01) indicates that, respectively,

Table 3. Reclassification Table Comparing 46 Months Hard Cardiac Events Risk Strata for Models that include CT-LeSc and SSS Scores.

Model With SSS	Model With CT-LeSc			
0%–5%	<5%	>5%–10%	>10%	Total
Persons included	93*	0†	0†	93*
Hard cardiac events	0*	0†	0†	0*
Event-free	93*	0†	0†	93*
Observed risk, %‡	0*	0†	0†	0*
>5%–10%				
Persons included	461§	169*	58†	688*
Hard cardiac events	0§	0*	0†	0*
Event-free	461§	169§	58†	688*
Observed risk, %‡	0§	0*	0†	0*
>10%				
Persons included	3§	37§	375*	415*
Hard cardiac events	0§	0§	40.9*	40.9*
Event-free	3§	37§	334.1*	374.1*
Observed risk, %‡	0§	0§	10.9*	9.8*
Total				
Persons included	557*	206*	433*	1196*
Hard cardiac events	0*	0*	40.9*	40.9*
Event-free	557*	206*	392.1*	1155.1*
Observed risk, %‡	0*	0*	9.4*	3.5*

CT-LeSc indicates CT-adapted Leaman score; and SSS, segment stenosis score.

*Patients who had the same classification. In patients who had events, the CT-LeSc reclassification was neutral. In nonevent patients, the new model was better in 20% compared with SSS model. The net reclassification index was 0.38 (P<0.01) when CT-LeSc was applied over SSS.

†Patients classified as at higher risk by CT-LeSc.

‡Observed risk at 46 months is estimated from the Kaplan–Meier curve by using observations in each cell.

§Patients at lower risk by CT-LeSc.

Table 4. Reclassification Table Comparing 46 Months Hard Cardiac Events Risk Strata for Models that include CT-LeSc and SIS Scores.

Model With Anatomic SIS	Model With CT-LeSc			
0%–5%	<5%	>5%–10%	>10%	Total
Persons included	351*	0†	4†	355*
Hard cardiac events	0*	0†	0†	0*
Event-free	351*	0†	4†	355*
Observed risk, %‡	0*	0†	0†	0*
>5%–10%				
Persons included	188§	159*	37†	384*
Hard cardiac events	0§	0*	0†	0*
Event-free	188§	159*	37†	384*
Observed risk, %‡	0§	0*	0†	0*
>10%				
Persons included	2§	49§	406*	457*
Hard cardiac events	0§	0§	42.2*	42.2*
Event-free	2§	49§	363.8*	414.7*
Observed risk, %‡	0§	0§	10.4*	9.2*
Total				
Persons included	541*	208*	447*	1196*
Hard cardiac events	0*	0*	42.2*	42.2*
Event-free	541*	208*	404.8*	1153.7*
Observed risk, %‡	0*	0*	9.4*	3.5*

CT-LeSc indicates CT-adapted Leaman score; and SIS, segment involvement score.

*Patients who had the same classification. In patients who had events the CT-LeSc reclassification was neutral. In nonevent patients, the new model was better in 22% compared with SIS model. The net reclassification index was 0.17 (P<0.01) when CT-LeSc was applied over SIS.

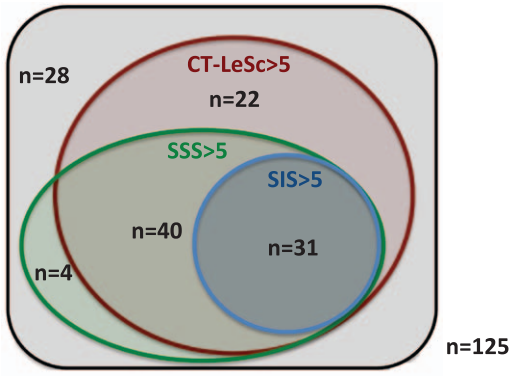
†Patients classified as at higher risk by CT-LeSc.

‡Observed risk at 46 months is estimated from the Kaplan–Meier curve by using observations in each cell.

§Patients at lower risk by CT-LeSc.

17% and 38% of patients had a net better classification for higher and lower risk categories using the CT-LeSc. The high-risk prediction was comparable, but the CT-LeSc was able to identify patients at lower risk better.

The CT-LeSc has been recently described as a more comprehensive score, including information on lesion localization, degree of stenosis, and plaque composition, all noninvasively provided by CCTA. In our study, the hazard ratio for the CT-LeSc (5.4) was higher than for the SSS (4.4), which, in turn, was higher than the SIS (3.1) for predicting hard cardiac events. In addition, many of the patients experiencing an event in the follow-up had a high CT-LeSc but either a low SIS or a low SSS (49.6% and 17.6% of the patients with events, respectively). Recently, Bittencourt et al[17] used a lower cutoff for the SIS (>4) to define extensive disease and was able to demonstrate that among patients with nonobstructive CAD, an SIS>4 can identify a subgroup with an hard (cardiovascular death or myocardial infarction) event rate similar to patients with obstructive CAD. Although using different definitions of extensive CAD burden (SIS>4 in the work of Bittencourt



Patients with hard events (n=125)	CT-LeSc ≤5 (n=32)	CT-LeSc >5 (n=93)
SIS ≤5 (n=94)	32	62
SIS>5 (n=31)	0	31
SSS≤5 (n=50)	28	22
SSS>5 (n=75)	4	71

Figure 3. Distribution of patients with hard events according to the different coronary atherosclerotic burden scores. The **top** diagram depicts the distribution of patients with hard events in the different atherosclerotic burden scores using the respective cutoffs. In the table, the white boxes refer to the number of events where there was concordance between the scores and in boxes highlighted with colors are the cases of discordance between the CT-adapted Leaman score (CT-LeSc) and the other 2 atherosclerotic burden scores (segment involvement score [SIS] and segment stenosis score [SSS]). Among patients experiencing a hard event, 93, 75, and 31 had a high coronary atherosclerotic burden as evaluated by the CT-LeSc, the SSS, and the SIS, respectively. All of the patients with an SIS>5 (n=31) had also a CT-LeSc>5 (no cases in blue box). Of note, 62 events (corresponding to 49.6% of the total events) occurred in patients with a high (>5) CT-LeSc and low (≤5) SIS (red box). Similar results were obtained for SSS, as 22 events (17.6% of the total events) occurred in patients with a high CT-LeSc and low SSS (red box). In only 4 patients with a high SSS experiencing an event, the CT-LeSc was ≤5 (green box).

et al[17] and CT-LeSc>5 in this article), and different populations (higher prevalence of obstructive CAD and cardiovascular risk in our cohort) both works are in line with the concept that computed tomographic angiography can help to identify a subset of patients with nonobstructive CAD that are at a high risk of hard cardiovascular events. This is of potential clinical benefit because it has been shown that these findings on CCTA are associated with downstream intensification of prognostically beneficial therapies,[18] which are expected to lead to an improvement in cardiovascular outcomes.

CT-LeSc as a Prognostic Tool

In this study, we have demonstrated that the CT-LeSc is an independent long-term predictor of hard cardiac events. The observation that the patients in the nonobstructive CAD subgroup with a high (>5) CT-LeSc had a higher hard event rate than patients with obstructive CAD and with a low CT-LeSc is of interest and deserves scrutiny. This finding can, in part, be explained by the fact that revascularizations, which are more often performed in patients with obstructive lesions in CCTA, were not included as hard events. Nevertheless, the CT-LeSc by reflecting total coronary atherosclerotic burden can still convey strong prognostic information and be a useful tool to identify nonobstructive CAD patients at a high risk of events, for whom more aggressive primary prevention measures are deserved because their prognosis can be even worse than that of some patients with obstructive CAD.

It has been demonstrated in earlier studies that acute coronary events can arise from previous nonobstructive lesions.[19] In a recent study, evaluating the degree of residual stenosis after thrombus aspiration in the setting of primary percutaneous coronary intervention, the median quantitative coronary angiography stenosis was <50% in 31% of the cases, meaning that nonobstructive lesions can be the culprit in many ST-segment–elevation myocardial infarctions.[20] It has also been possible to establish a relationship between some CCTA plaque features of vulnerability and the future development of events, some of which are not related to the degree of stenosis.[21–23]

Because nonobstructive lesions are more prevalent than their obstructive counterparts, even if their relative risk of disruption is lower, acute events will often arise from nonobstructive lesions.[24–26] Therefore, the risk at the patient level, as the sum of the individual risks associated with each individual plaque, will be directly proportional to the extent of the coronary atherosclerotic burden and in this way, scores that

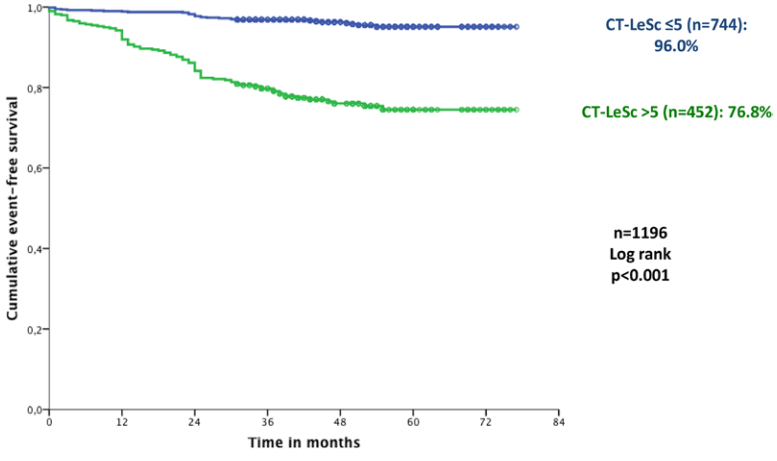


Figure 4. Kaplan–Meier survival curves for hard cardiac events stratified by coronary atherosclerotic burden (CT-LeSc >5 vs ≤5). CT-LeSc indicates CT-adapted Leaman score.

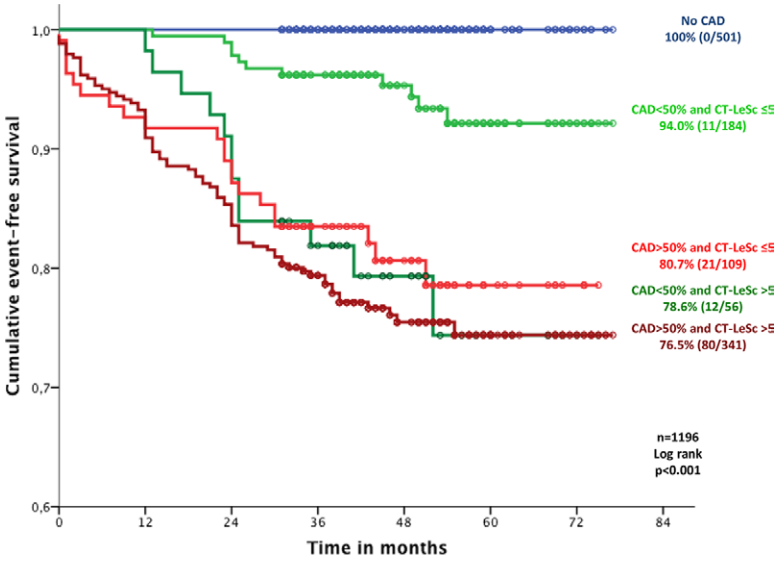


Figure 5. Kaplan–Meier survival curves for hard cardiac events stratified by CAD severity (obstructive vs nonobstructive) and coronary atherosclerotic burden (CT-LeSc >5 vs ≤5). CAD indicates coronary artery disease; and CT-LeSc, CT-adapted Leaman score.

reflect this burden are expected to convey strong prognostic information.

Finally, and although our work is in line with others demonstrating that CAD burden scores enhanced risk assessment beyond clinical evaluation,[6,17] it remains to prove whether more aggressive treatment of patients with nonobstructive CAD but with a high coronary atherosclerotic burden (like a CT-LeSc>5) leads to improved outcomes. In addition, although the more comprehensive CAD burden score CT-LeSc reflecting information on plaque localization, composition and degree of stenosis is expected to be a more accurate predictor of events, other indexes like the SIS might become more easily adopted in clinical practice.

Limitations

There are many limitations related to this report. First, this is a study performed on data originating from a single center and the study population included a subset of patients who had high pretest CAD probability. Thus, they might not represent the more usual patients with low-to-intermediate CAD likelihood usually referred for CCTA. Second, 8% of patients were excluded from the analysis, although in most cases because of low-image quality, rather than to being lost to follow-up (<5%). Third, revascularizations were not included as an end point in this analysis. Because patients with obstructive lesions are more likely to undergo a revascularization procedure, this analysis relying only on hard cardiac events could have lead to an overestimation of scores that reflect nonobstructive CAD burden (CT-LeSc) as opposed to scores with a strong weight for the degree of stenosis (like SSS). Finally, the CT-LeSc does not take in consideration some of the more advanced plaque features, like positive remodeling, low attenuation plaque, and napkin-ring sign, which have also been linked to outcomes.

Conclusions

The coronary atherosclerotic burden index CT-LeSc is an independent long-term predictor of hard cardiac events. Patients with nonobstructive CAD and a high CT-LeSc had an event-free survival similar to patients with obstructive CAD.

Disclosures

Drs Andreini and Pontone are on speaker bureau of GE Healthcare. Dr Pontone is on speaker bureau of Bayer, HeartFlow, and Medtronic. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

A large literature have demonstrated that the presence of coronary artery disease (CAD), including nonobstructive disease, at coronary computed tomographic angiography, is associated with an increased risk of cardiac events and mortality. However, a better characterization of coronary artery lesions, particularly of nonobstructive stenosis, associated with poor prognosis is needed. The computed tomography-adapted Leaman score (CT-LeSc) has been recently described as a comprehensive score, including information on lesion localization, degree of stenosis, and plaque composition, all noninvasively provided by coronary computed tomographic angiography. This study evaluated the CT-LeSc long-term prognostic value in patients with suspected CAD, showing that cumulative event-free survival was 76.8% with high CT-LeSc (defined by upper tertile cutoff, score >5) and 96.0% with low CT-LeSc. Moreover, the event-free survival in nonobstructive CAD with high CT-LeSc (78.6%) was similar to obstructive CAD with high CT-LeSc (76.5%) but lower than obstructive CAD with low CT-LeSc (80.7%). So, the main finding of this study is that CT-LeSc is an independent long-term predictor of hard cardiac events and that patients with nonobstructive CAD and a high (CT-LeSc>5) atherosclerotic burden had an event-free survival similar to patients with obstructive CAD.