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Source / Izvornik: **The International Journal of Cardiovascular Imaging, 2018, 34, 1647 - 1655**

Journal article, Accepted version
Rad u časopisu, Završna verzija rukopisa prihvaćena za objavljivanje (postprint)

https://doi.org/10.1007/s10554-018-1376-3

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:105:358436

Medaković P., Biloglav Z., Padjen I., Pristaš I., Jukić M., Žuvela F., Ivanac G., Brkljačić B., Jukić T., Turk L. (2018) ***Quantification of coronary atherosclerotic burden with coronary computed tomography angiography: adapted Leaman score in Croatian Patients.*** **The International Journal of Cardiovascular Imaging, 34 (10). pp. 1647-1655. ISSN 1569-5794**

http://link.springer.com/journal/10554

http://dx.doi.org/10.1007/s10554-018-1376-3

http://medlib.mef.hr/3503

Quantification of coronary atherosclerotic burden with coronary computed tomography angiography - adapted Leaman score in Croatian patients

Authors: Petar Medaković[1], Zrinka Biloglav[2], Ivan Padjen[3,7], Ivan Pristaš[4], Mladen Jukić[1], Franko Žuvela[5], Gordana Ivanac[6,7], Boris Brkljačić[6,7], Tena Jukić[7], Lana Turk[7]

Affiliations:

[1]Department of Radiology, Polyclinic Sunce, Zagreb, Croatia

[2]Department of Medical Statistics, Epidemiology and Medical Informatics, School of Public Health Andrija Stampar, University of Zagreb, School of Medicine, Zagreb, Croatia

[3]Division of Clinical Immunology and Rheumatology, Department of Internal Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

[4]Croatian Institute for Public Health, Zagreb, Croatia

[5]Ministry of Defence of the Republic of Croatia

[6]Department of Diagnostic and Interventional Radiology, University Hospital Dubrava, Zagreb, Croatia

[7]University of Zagreb, School of Medicine, Zagreb, Croatia

Corresponding author:

Petar Medaković, Polyclinic Sunce, Trnjanska cesta 108, 10000 Zagreb, Croatia

Tel. Number: 00 385 1 549 74 00, e-mail: petar.medakovic@sunce.hr, eranio@gmx.at

FUNDING STATEMENT: This study is an investigator initiated project and did not receive any specific grants from funding agencies in the public, commercial or not-for-profit sectors.

ABSTRACT

Purpose: The aim of the study was to quantify the total coronary atherosclerotic burden in patients with suspected coronary artery disease (CAD) defined by coronary computed tomography adapted Leaman score (CT-LeSc) and to estimate its cut-off level for high coronary atherosclerotic burden.

Methods: We enrolled 434 consecutive patients referred to coronary computed tomography angiography, of which 261 patients fulfilled the study inclusion criteria. Demographic and clinical characteristics, as well as CAD risk factors were obtained. CAD pre-test probabilities were estimated by the Diamond-Forrester model and Morise score. The coronary atherosclerotic burden was estimated using CT-LeSc. As a cut-off for a high coronary atherosclerotic burden, we used 3rd tercile (Tc3) (CT-LeSc≥5.52). We evaluated the association of clinical characteristics and risk factors with Tc3 in univariate and multivariate analysis.

Results: There were 60.9% males and 39.1% females, 81% of patients had above-normal weight, 68.2% hypertension, 54.0% dyslipidemia, 15.3% diabetes mellitus, 12.3% positive smoking history and 11.9% had a family history of CAD. According to the Diamond-Forrester model and Morise score the majority of patients had intermediate risk, 59.7% and 52.8%, followed by the high-risk group, 36.0% and 34.4%, respectively. Age, dyslipidaemia, hypertension and pre-test risk scores in the univariate analysis significantly predicted Tc3. In the multivariate analysis, male sex (p=0.004), dyslipidaemia (p=0.002) and coronary calcium score (<0.001) were identified as predictors of Tc3.

Conclusion: CT-LeSc quantified the total coronary atherosclerotic burden and showed an association of risk factors and pre-test probabilities with Tc3.

Keywords: *coronary CT angiography, CT-adapted Leaman score, coronary atherosclerotic burden, pre-test probability*

INTRODUCTION

Cardiovascular diseases (CVD) are the major cause of death in Europe. Despite the decrease in mortality observed during the last decade, coronary artery disease (CAD) is the leading cause of death [1]. In Croatia, modest decline in mortality may be attributed to combination of primary prevention and easy access to invasive coronary angiography (ICA), as well as subsequent revascularisation in patients with obstructive CAD. Unlike ICA that predominately provides insight into the coronary artery lumen, coronary computed tomography angiography (cCTA) as a noninvasive imaging method allows comprehensive and multifaceted assessment of the coronary artery lumen and vessel walls including atherosclerotic plaques, with high diagnostic performance for the detection and exclusion of CAD [2]. Therefore, cCTA is increasingly being used as a method for accurate cardiovascular risk stratification by the total coronary artery plaque burden based on specific scores. Some of these scores have already been developed and validated for cCTA, such as segment involvement score (SIS) and segment stenosis score (SSS) [3]. The original Leaman score was developed almost four decades ago for ICA to

quantify the burden of obstructive CAD [4]. It served as a foundation for the recent development and validation of the comprehensive measure of the total coronary atherosclerotic burden – the cCTA-adapted Leaman score (CT-LeSc) [5]. Despite the existence of the aforementioned radiological scores aimed at the precise assessment of coronary atherosclerotic burden, commonly used pre-test probability (PTP) composite scores (based on atherosclerotic risk factors) are still considered the mainstay of risk assessment by the majority of cardiologists. However, none of the PTP scores have been validated for use in association with cCTA as the sole diagnostic test. The morphologic heterogeneity within the cardiovascular continuum maintains the need for precise quantification and accurate risk stratification of CAD patients.

The major objective of the study is to quantify the total coronary atherosclerotic burden in patients with suspected CAD defined by CT-LeSc and to estimate its cut-off level for high coronary atherosclerotic burden. The second objective is to assess the association of cardiovascular risk factors, PTP scores and coronary artery calcium score (CACS) with high coronary atherosclerotic burden.

MATERIALS AND METHODS

Study population

This single center cross-sectional study was conducted using data from the clinical database of Polyclinic Sunce, Zagreb, Croatia in 2017. From January to June 2008 we scanned 434 consecutive patients ≥18 years of age referred to cCTA for a variety of clinical indications: suspected or previously undiagnosed CAD in patients with abnormal or inconclusive stress test results, chest pain symptoms, presence of multiple CAD risk factors, atrial fibrillation and other arrhythmias, evaluation prior to coronary artery bypass graft surgery or valve replacement, follow-up of previous coronary artery bypass graft surgery and implanted coronary stents, evaluation of the great cardiac vessels, cerebrovascular and peripheral artery disease, as well as chronic renal disease. Patients were excluded if they had: (1) history of previous myocardial infarction with or without coronary revascularization (coronary bypass and/or percutaneous coronary intervention (PCI)) or previous PCI with coronary stent implantation (n=76), (2) chronic renal disease (glomerular filtration rate < 15 mL/min/1.73m^2 and dialysis) (n=8), (3) cCTA performed as a part of the evaluation of great cardiac vessels or valvular disease (n=46), (4) atrial fibrillation and other arrhythmias (n=25), and (5) previously known cerebrovascular and/or peripheral artery disease (n=18). The total number of excluded patients was 173. Finally, 261 patients with the following clinical presentations were evaluated: (1) stable chest pain with one or more CAD risk factors, (2) positive, inconclusive or discordant stress test, and (3) absent chest pain but presence of multiple CAD risk factors. Figure1 describes patient selection and study design.

The study design was approved by the institutional ethics committee.

Acquisition of clinical data and calculation of pre-test probability for CAD

Prior to cCTA, the patients' medical documentation was reviewed and a structured interview was conducted by two cardiologists. They collected clinical and demographic data, assessed the cardiac risk profile (cardiovascular risk factors), evaluated symptoms associated with CAD and performed a physical examination. Diabetes mellitus was defined as fasting glucose ≥7 mmol/L or the use of insulin or oral hypoglycaemic agents. Dyslipidemia was

defined as a total cholesterol level ≥5 mmol/l or treatment with lipid-lowering medications [6]. Systemic arterial hypertension was defined as systolic blood pressure ≥140 mmHg regardless of antihypertensive therapy [7]. Obesity was defined as body mass index ≥30 kg/m^2 [8]. Current smokers and patients that smoked within a year prior to observation were considered to have a positive smoking history [5]. Family history of CAD was considered positive if there was a history of myocardial infarction, coronary bypass or angioplasty, or sudden death in first-degree relatives at the age <55 years for males and <65 years for females [5]. PTP for CAD was assessed using the Morise and Diamond-Forrester (DF) scores. The Morise score includes age, gender, estrogen status, cardiovascular risk factors and chest pain symptoms. According to the Morise score, patients were divided into low (0-8), intermediate (9-15), and high (≥16) risk groups (9). The DF score takes into account age, sex, and type of chest pain (typical, atypical or non-anginal) and classifies patients into low, intermediate and high-risk categories [10].

Scan protocol

All patients were scanned on a 64-slice dual-source CT scanner (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany). Scanning parameters were as follows: detector collimation 2×2×0.6 mm^3, slice collimation 2×64 0.6 mm^3 by means of a z-flying focal spot, gantry rotation time 330 ms, and pitch of 0.2-0.5 depending the heart rate [11, 12]. Images were acquired in the mid-diastole and individually adjusted position of the reconstruction window, and, if necessary, additionally reconstructed in the end-systole. For the purpose of analysis, we used the data-set of axial slices, multiplanar reformations, and thin-slab maximum intensity projections, such as 5-mm thickness and 1-mm increments. Patients with a heart rate ≥60 beats/min were administered intravenously up to four doses of 5 mg metoprolol to lower the heart rate. Patients with a systolic blood pressure ≥100 mmHg received nitroglycerin 0.8 mg sublingually for coronary vasodilatation.

Coronary artery calcium scoring (CACS) was performed in all study patients, according to a previously described protocol, and the Agatston score was used to quantify total coronary calcium per patient [13, 14].

Contrast timing was tested by an initial bolus-timing scan using 20 mL of contrast (Iopamiro 370, Bracco S.p.a, Milan, Italy), iodine content 37 mg/mL, followed by a 50 mL saline chaser. The contrast-enhanced scan was obtained using 80-140 mL of contrast individually adapted to the selected table feed and scan range at a rate of 4-6 mL/s followed by a 50mL saline chaser.

Radiation dose

The effective radiation dose of the CACS and cCTA scan was estimated by the product of the total dose length product from the dose report of the CT scanner and a European Commission conversion factor for the chest 0.014 mSv·mGy^{-1}·cm^{-1} (effective dose (mSv) = total dose length product (mGycm) x 0.014 mSv·mGy^{-1}·cm^{-1}) [15].

Image analysis

The images were analysed by two trained radiologists (L.P. and P.M.) experienced in cardiac CT and cCTA analysis. In case of disagreement, a joint reading was performed, and a consensus decision was reached. Coronary atherosclerotic lesions were quantified for stenosis by visual estimation. The proportion of coronary artery lumen tree was segmented according to the modified American Heart Association (AHA) classification

[16]. Each segment with a diameter ≥1.5 mm was evaluated visually for the level of luminal narrowing, and then categorized semi-quantitatively into four groups: <25%, 25-49%, 50-74%, and ≥75%. Obstructive coronary artery disease was defined as stenosis of 50% or more of the diameter of the left main coronary artery, and stenosis of 70% or more of the diameter of a major epicardial or branch vessel that was >2.0 mm in diameter. The luminal diameter of the normal appearing vessel site directly proximal to the plaque served as a reference for comparison.

Classification of patients according to quantitative scores based on cCTA

Using the presence and extent of CAD, each patient was categorized as having no CAD or having non-obstructive (<50% stenosis) and obstructive disease (≥50% stenosis) [17].

CACS was categorized by employing the previously described scoring system as follows: no calcification (0), low (1-100), moderate (101-400) and severe (>400).

The total coronary atherosclerotic burden was quantified by CT-LeSc, which employs three sets of weighting (multiplication) factors using an 18-segment coronary model: (1) localization of plaques, accounting for dominance [left main (right dominance×5, left dominance×6), LAD (proximal LAD × 3.5, mid LAD × 2.5, and distal LAD×1) etc.]; (2) type of plaque, with a multiplication factor of 1 for calcified plaques and of 1.5 for non-calcified and mixed plaques; and (3) degree of stenosis, with a multiplication factor of 0.615 for non-obstructive and <50% stenosis, and a multiplication factor of 1 for ≥50% lesions [5]. The CT-LeSc on the individual level was calculated as the sum of the partial CT-LeSc of all evaluable coronary segments. Since there were no previously validated cut-offs for the CT-LeSc, the obtained scores were divided into terciles. The upper tercile (Tc3) of the CT-LeSc distribution within the total patient sample was considered equivalent to high coronary atherosclerotic burden.

Statistical analysis including the prediction of high coronary atherosclerotic burden

Results were presented numerically and graphically. Continuous variables were expressed as means and 95% confidence intervals or medians. Categorical variables were expressed as frequencies with percentages. The Kolmogorov-Smirnov test was used to assess normality of distribution. The independent samples t-test was employed to compare means of continuous variables, and the Pearson χ^2 test was used to evaluate differences in frequencies of categorical variables. Differences were regarded significant when $p<0.05$ (2-tailed).

In the univariate analysis, single atherosclerotic risk factors, PTP scores and CACS were compared between patients with and without high coronary atherosclerotic burden (defined as mentioned above). The predictive role of the same variables was assessed in a multivariate logistic regression model, where high coronary atherosclerotic burden was used as the outcome variable. All analyses were performed with statistical package IBM SPSS Statistics version 23, licence owned by the Croatian Institute of Public Health.

RESULTS

In our study population of 261 patients, there were 159 (60.9%) males and 102 (39.1%) females. CAD risk factors were highly prevalent (Table 1).

Chest pain was detected in 211 patients, 88 (41.7%) had typical angina, 103 (48.6%) had atypical angina, while 21 (9.9%) exhibited non-anginal chest pain. The remaining 50 patients reported no chest pain.

Both PTP scores (DF and Morise) classified the majority of symptomatic patients into the intermediate risk group as presented in Figure 2.

More than two thirds of patients were diagnosed with CAD (188 patients, 72%). Within this group, non-obstructive CAD was more frequently observed than its obstructive counterpart (57.4% vs. 42.6%).

The median CACS was 16.7 among CAD patients: 192.7 in the obstructive in contrast to only 2.5 in the non-obstructive CAD subgroup. The median CACS was 61.9 and 50.3 in high-risk patients according to the Morise and DF score, respectively. Patients with no chest symptoms had a median CACS of 33.3. CACS categories in relation to CAD subgroups are presented in Figure 3.

The median CT-LeSc in the study population (n=261) was 3.22. In patients with CAD (n=188) the median CT-LeSc was 5.22: 3.22 in the non-obstructive and 7.4 in the obstructive CAD subgroup. In the total study sample (n=261), the cut-off between the central and highest tercile (Tc) was 5.52. Patients with a CT-LeSc above this cut-off (i.e. categorized into the highest tercile, Tc3) were considered to have a high coronary atherosclerotic burden. The distribution of the CT-LeSc terciles in the study sample was as follows: Tc1 (0 - 0.92), Tc2 (0.93 - 5.51) and Tc3 (5.52 - 16.25).

Among 188 patients with CAD, 88 (46.8%) had a high coronary atherosclerotic burden (Tc3). The majority of patients with non-obstructive disease (n=87, 80.5%) were allocated into the lower two terciles, while the remaining 19.5% (n=21) had a high total coronary atherosclerotic burden (CT-LeSc≥5.52). Conversely, the majority of obstructive CAD patients, 84.9% (n=67), were allocated into the highest CT-LeSc tercile. The median CT-LeSc was slightly higher in males compared to females (3.63 vs. 2.61, respectively).

The univariate analysis revealed a positive association between higher age, dyslipidaemia, and hypertension with a high coronary atherosclerotic burden. (Table 2).

The same set of variables (with the exception of PTP scores) was included in the multivariate model to identify the predictors of high coronary atherosclerotic burden (Table 3). PTP scores were not included in the multivariate model to avoid collinearity, since they are composite measures of single variables already included in the model. Mean effective radiation dose was 21.9 mSv (95% confidence interval 20.9 - 22.8).

DISCUSSION

A high prevalence of CAD risk factors was observed in our study population, including dyslipidemia (54%), hypertension (68.2%), and above normal weight (81%). The smoking prevalence was rather low (12.3%) compared to the study by Vrazic et al. with 42.6% smokers among CAD patients [18]. Although cigarette smoking is a major risk factor for CAD, its lacking association with high coronary atherosclerotic burden can probably be ascribed to low prevalence in our study population. Overall, these results are suggestive of a high prevalence of CAD risk factors in the general population.

The cardiac risk assessment based on traditional risk factors represents the first step in predicting cardiovascular outcomes, but the ideal formula for integration of risk factors and their permutation leading to the score with accurate pre-test probability is still unknown. Some of the risk scores are used more frequently based on their

verified clinical benefit, easy implementation, low cost and easy access, but there is widespread use of different scores with their advantages, such as good definition of broad categories, but also downsides, such as poor identification of the intermediate risk population [10, 19, 20]. In our study we used the Diamond Forrester and Morise pre-test probability models which are firmly established in clinical practice and research. The majority of participants, according to the Morise score, were in the intermediate risk group (52.8%), followed by high (34.4%) and low (12.6%) risk groups. The distribution was similar with the Diamond Forrester pre-test probability model. The highest proportion of participants was categorised into the intermediate risk group (59.9%), followed by high-risk group (35.8%).

Despite the fact that these pre-test scores overestimate the CAD prevalence, the majority of coronary artery events occur on a substrate of moderate to severe atherosclerosis [21-23]. Most of the standard pre-test risk scores fail to predict major cardiac events in 75% of patients, thus underlining the need for a more accurate stratification tool [24]. Compared with conventional risk assessment methods, cCTA together with CACS has the ability to reclassify the patients at risk for CAD [25]. Prior to the introduction of more advanced coronary arterial plaque assessment methods, CACS had been an indirect determinant of the overall coronary plaque burden. It has been associated with an increased risk of myocardial infarction and death, as well as increased proximal stenosis burden [26]. However, measurement of the CACS as the only method of atherosclerotic burden assessment has limitation, because it does not anticipate the portion of the burden ascribable to low calcium density plaques. This diagnostic limitation was demonstrated in studies reporting coronary artery events and coronary obstructive disease in patients with a calcium score of zero [27].

In our study, the median CACS was 16.7 in the CAD group, 192.7 in the obstructive and 2.5 in the non-obstructive CAD group. Almost one quarter of patients in the low CACS group had obstructive CAD. Conversely, more than one fifth in the severe CACS group had non-obstructive CAD. Findings of a calcium score being a predictor of high coronary atherosclerotic burden are in line with the results of a pre-coronary-CT era large histological study confirming a high correlation between the overall coronary calcium and atherosclerotic plaque burden [28]. Increased coronary calcium and atherosclerotic plaque burden have been associated with an increased risk of mortality and coronary events on the patient level, however it is still unclear whether higher or lower calcium density more accurately correlates with the (increased) risk of coronary events on the plaque level [28-30]. This is due to the still unclear relationship between plaque calcification and its vulnerability or propensity of plaque towards rupture. Coronary calcium might even play a protective role against plaque vulnerability, so it can be postulated that a pattern of high atherosclerotic burden in concert with a low calcium score (high burden/low calcium pattern) may be associated with a higher risk of coronary events compared to the high burden/high calcium pattern.

CCTA is a suitable method for more accurate cardiovascular risk stratification by the total coronary artery plaque burden based on specific scores. Some scores have been developed and validated for cCTA, such as SIS and SSS, but concerning their ability to correctly reclassify the patients at risk, they have limitations compared with CT-LeSc [3, 31]. CT-LeSc uses plaque localization, degree of stenosis, plaque composition and takes into account the anatomical blood supply dominance of the coronary tree, enabling standardized assessment of the total coronary atherosclerotic burden. Given the lack of previously validated values, the 3rd tercile has been used as a cut-off for high coronary atherosclerotic burden (Tc3≥5.52). CT-LeSc has some limitations since it does not take into account the features of high-risk plaque, such as positive remodelling, low attenuation plaque and

napkin-ring sign, which influence the outcomes [32]. CT-LeSc improved the prognostic stratification and is an independent long-term predictor of hard cardiac events [33].

Our study revealed that almost one fifth of the patients with non-obstructive CAD had CT-LeSc in the highest tercile and, conversely, 15.1% with obstructive CAD had CT-LeSc in lower terciles. These findings are in line with the previous study from de Araujo Gonçalves et al. [5], and emphasise the variety of CAD and the need for exact quantification in order to accurately stratify patients with increased risk for future cardiac events. Quantification of coronary atherosclerotic burden with non-invasive coronary imaging seems to provide a better insight into the complex morphology of coronary atherosclerosis compared to conventional coronary classification. While the ICA-based classification of coronary artery obstruction relies on the percentage of luminal stenosis and considers significant obstruction of coronary arteries higher of 50%, cCTA can precisely detect high-risk plaque features, such as positive remodelling, necrotic core, napkin ring sign and spotty calcification. The requirement to substitute conventional coronary angiography with CT in low and intermediate PTP patients with suspected CAD becomes increasingly visible in clinical cardiology practice [33-35].

Limitations

Despite the fact that data analysis was performed in 2017, the extent and quality of data obtained in 2008 (stored in the clinical database), as well as stored original CT records, allowed us to calculate the required pre-test scores as well as the CT-LeSc. The time of observation was limited to the study period in 2008 because during that time the Polyclinic Sunce had a contract with the Croatian Health Insurance Fund (CHIF), a mandatory national health insurance covering the expenses of all diagnostic procedures. Complete coverage of costs by the national health insurance enabled us to recruit patients from the general population. The study could not have been extended thereafter since the contract with CHIF was not renewed. Nevertheless, studies with the larger sample size might more precisely quantify the association of classical cardiovascular risk factors and coronary atherosclerotic burden.

Conclusion

CT-LeSc enabled the quantification of the total coronary atherosclerotic burden and precise cut-off value for high coronary atherosclerotic burden among patients with suspected CAD, including obstructive and non-obstructive subgroups. CT-LeSc revealed that non-obstructive plaques can be associated with a high coronary atherosclerotic burden; conversely, a single obstructive plaque can be quantified as a low atherosclerotic burden. These results accentuate the heterogeneity of the CAD and a more careful approach especially to non-obstructive CAD.

Table 1 Baseline demographic and clinical characteristics

Variable	Value
Mean age (years) Males/Females	58.9, CI 57.6-60.3 62.3/56.7
Males/Females	159 (60.9%)/102 (39.1%)
Hypertension (mmHg)	178 (68.2%)
Diabetes mellitus	40 (15.3%)
Smoking	32 (12.3%)
Body mass index kg/m^2	28.6, CI 28.1-29.1
<25 (normal weight)	49 (19%)
25-30 (overweight)	126 (48.8%)
>30 (obese)	83 (32.2%)
Dyslipidemia	141 (54%)
Family history of CAD$^+$	31 (11.9%)

All data expressed as no., (%) or mean with confidence interval (CI)

$^+$coronary artery disease

Table 2 Univariate predictors of high coronary atherosclerotic burden (CT LeSc T3)

Variable	Value	CT LeSc T1+T2	CT LeSc T3	p-value
Age		56.8	63.1	p=0.026*
Male **Female**		98 (56.6%) 75 (43.4%)	61 (69.3%) 27 (30.7%)	p=0.470
Body mass index	<25 25-30 >30	37 (21.6%) 83 (48.5%) 51 (29.8%)	12 (13.8%) 43 (49.4%) 32 (36.8%)	p=0.253
Diabetes	yes no	24 (13.8%) 149 (86.1%)	16 (18.2%) 72 (81.8%)	p=0.361
Hypertension	yes no	109 (63.0%) 64 (37.0%)	69 (78.4%) 19 (21.6%)	p=0.012*
Dyslipidemia	yes	80 (46.2%)	61 (69.3%)	p<0.001*

	no	93 (53.8%)	27 (30.7%)	
Smoking	yes no	20 (11.6%) 153 (88.4%)	12 (13.6%) 76 (86.4%)	p=0.629
Family history of CAD^{+}	yes no	19 (11.0%) 154 (89.0%)	12 (13.6%) 76 (86.4%)	p=0.531
Coronary artery calcium score	>100 <100	15 (8.7%) 158 (91.3%)	64 (72.7%) 24 (27.3%)	p<0.001*
Morise score	<8 8-16 ≥ 16	28 (16.2%) 96 (55.5%) 49 (28.3%)	5 (5.7%) 42 (47.7%) 41 (46.6%)	p=0.003*
Diamond Forrester model	None Low (<30%) Intermediate (30-70%) High (≥70%)	34 (19.7%) 8 (4.6%) 92 (53.2%) 39 (22.5%)	15 (17%) 1 (1.1%) 35 (39.8%) 37 (42.0%)	p=0.007*

$^{+}$coronary artery disease

*statistically significant p<0.05

Table 3 Multivariate predictors of high coronary atherosclerotic burden (CT-LeScT3)

Variables	Odds ratio (95% CI)	p-value
Age	1.031 (0.992-1.072)	0.118
Male sex	3.501 (1.497-8.188)	0.004*
Body mass index	0.944 (0.859-1.037)	0.231
Diabetes	0.599 (0.208-1.729)	0.344
Hypertension	1.145 (0.506-2.593)	0.745
Dyslipidemia	3.380 (1.563-7.306)	0.002*
Smoking	1.351 (0.472-3.869)	0.575
Family history of CAD^{+}	1.430 (0.502-4.073)	0.503
CACS**	1.010 (1.007-1.014)	<0.001*

$^{+}$coronary artery disease

**coronary artery calcium score

*statistically significant p<0.05, Cox & Snell R^2=0.401

Figure 1 Patient selection and study design. cCTA – coronary computed tomography angiography; CABG – coronary artery bypass graft; PCI – percutaneous coronary intervention; N – number of patients; *consecutive sample of patients (January to June, 2008)

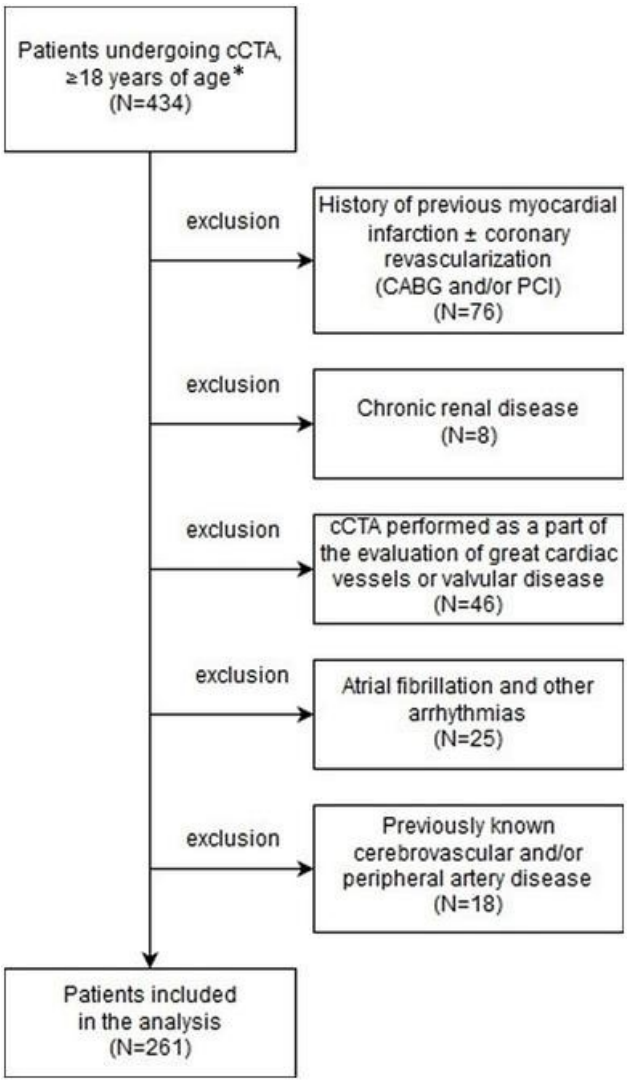
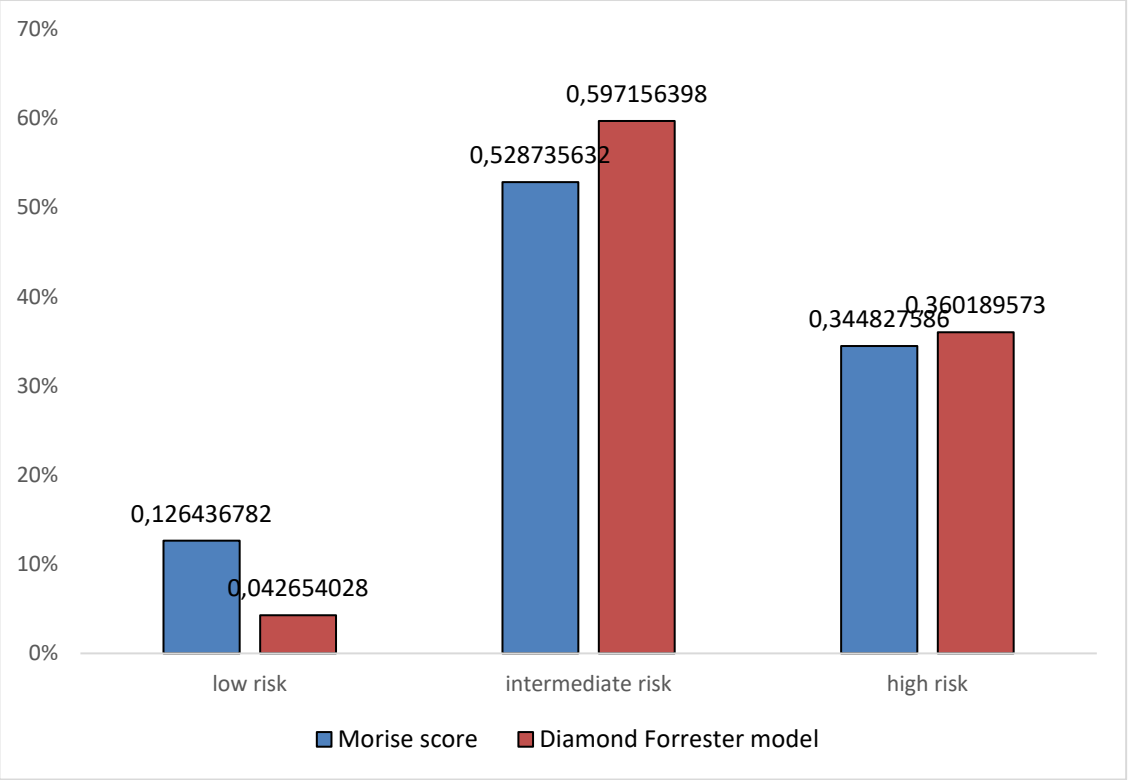
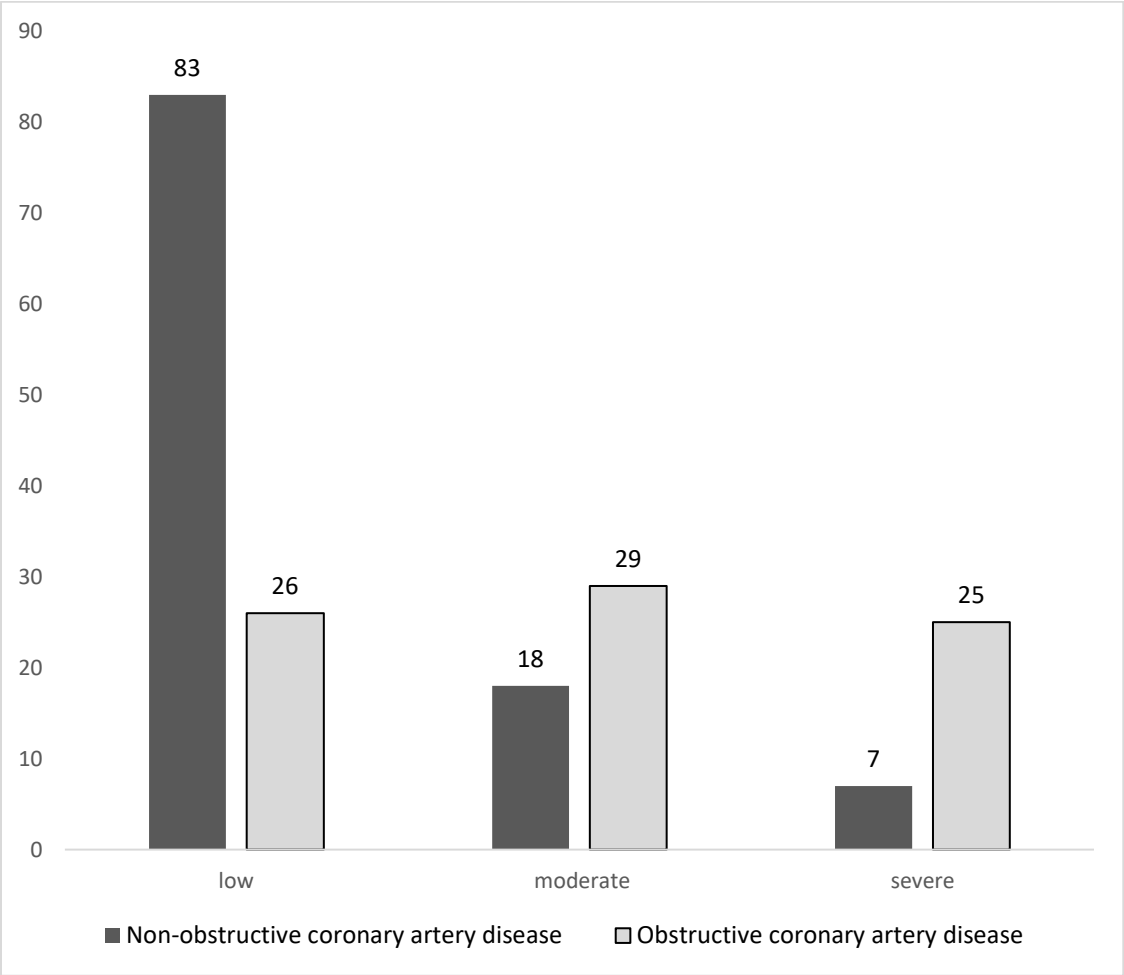


Figure 2 Risk categories according to Morise and Diamond Forrester pre-test probabilities for CAD[+]



[+]coronary artery disease

Figure 3 Coronary artery calcium score categories in relation to CAD[+] subgroups



[+]coronary artery disease

**coronary artery calcium score

ETHICAL APPROVAL

The study was conducted according to the Declaration of Helsinki. It was approved by the institutional Ethical Committee.

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