Title

Quantification of Coronary Atherosclerosis in the Assessment of Coronary Artery Disease

Journal

Circulation Cardiovascular Imaging, 11(7)

ISSN

1941-9651

Authors

Lee, Sang-Eun
Sung, Ji Min
Rizvi, Asim
et al.

Publication Date

2018-07-01

DOI

10.1161/circimaging.117.007562

Peer reviewed

Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Quantification of Coronary Atherosclerosis in the Assessment of Coronary Artery Disease

See Editorial by Arbab-Zadeh

Sang-Eun Lee, MD, PhD
et al

BACKGROUND: Diagnosis of coronary artery disease and management strategies have relied solely on the presence of diameter stenosis ≥50%. We assessed whether direct quantification of plaque burden (PB) and plaque characteristics assessed by coronary computed tomography angiography could provide additional value in terms of predicting rapid plaque progression.

METHODS AND RESULTS: From a 13-center, 7-country prospective observational registry, 1345 patients (60.4±9.4 years old; 57.1% male) who underwent repeated coronary computed tomography angiography >2 years apart were enrolled. For conventional angiographic analysis, the presence of stenosis ≥50%, number of vessel involved, segment involvement score, and the presence of high-risk plaque feature were determined. For quantitative analyses, PB and annual change in PB (△PB/y) in the entire coronary tree were assessed. Clinical outcomes (cardiac death, nonfatal myocardial infarction, and coronary revascularization) were recorded. Rapid progressors, defined as a patient with ≥median value of △PB/y (0.33%/y), were older, more frequently male, and had more clinical risk factors than nonrapid progressors (all $P<0.05$). After risk adjustment, addition of baseline PB improved prediction of rapid progression to each angiographic assessment of coronary artery disease, and the presence of high-risk plaque further improved the predictive performance (all $P<0.001$). For prediction of adverse outcomes, adding both baseline PB and △PB/y showed best predictive performance (C statistics, 0.763; $P<0.001$).

CONCLUSIONS: Direct quantification of atherosclerotic PB in addition to conventional angiographic assessment of coronary artery disease might be beneficial for improving risk stratification of coronary artery disease.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT02803411.

The full author list is available on page 8.

Key Words: angiography ■ atherosclerosis ■ coronary artery disease ■ myocardial infarction ■ risk factors

https://www.ahajournals.org/journal/circimaging

CLINICAL PERSPECTIVE

Diagnosis and management strategies of coronary artery disease have been focused on the presence of luminal stenosis. This study sought to examine whether the direct quantification of volumetric plaque burden and plaque characteristics can provide incremental value in prediction of rapid disease progression. We found that quantitative assessment of coronary atherosclerosis using coronary computed tomography angiography can improve the prediction of rapid plaque progression and future clinical outcomes. Quantitative analysis of plaque burden had an incremental clinical value in predicting both progression of coronary artery disease and adverse clinical outcomes. A shift in focus to volumetric assessment of coronary artery atherosclerotic burden from the luminal stenosis should be considered, and future research is needed to clarify if treatment strategies considering coronary artery atherosclerotic burden would improve outcomes.

Improvements in management strategies of coronary artery disease (CAD) have resulted in a ≈50% decline in cardiovascular mortality from 1980 to 2000,[1,2] suggesting that establishing the diagnosis of CAD and identifying patients at risk of adverse events are important to further improve outcomes.

To date, angiographic categorical definitions based on luminal stenosis have been applied for diagnosing coronary heart disease and determining a suitable management strategy.[2,3] However, data suggest that patients with nonobstructive CAD, usually defined as <50% diameter stenosis and hence not fulfilling the current diagnostic criteria of CAD,[2,3] have a risk of myocardial infarction (MI) and death similar to that of patients with single-vessel obstructive disease.[4] This implies that the risk from CAD does not abruptly increase with the presence of a categorical stenosis but is related to the continuous extent of atherosclerosis plaque burden (PB), which is not fully reflected by the conventional angiographic assessment of CAD.[5–7]

Coronary computed tomography angiography (CCTA) has become a reliable noninvasive imaging modality for assessment of CAD.[8,9] The prognostic value of obstructive CAD and high-risk plaque (HRP) detected by CCTA using conventional categorical analyses has been well documented.[8,10] As technical developments have improved the image quality of CCTA while reducing the radiation dose,[11] quantification of coronary artery atherosclerosis over the entire coronary tree using CCTA has recently become possible,[12] and a possibility of serial monitoring of disease progression using CCTA has also emerged.[10,13]

However, whether addition of total PB determination per a patient to conventional CAD analysis can improve prediction of progression or regression of coronary artery atherosclerosis has not been explored, and the current guidelines do not provide recommendations on the appropriateness of repeated CCTA.[2,3,14]

Therefore, we investigated the clinical value of PB determination of the entire coronary tree using CTA in predicting progression of coronary artery atherosclerosis and clinical events.

METHODS

Study Design and Population

The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging registry is an international multicenter observational registry that prospectively collects clinical, procedural, and follow-up data on patients undergoing repeated CCTA. The detailed registry design has been described previously.[15] The study protocol was approved by the institutional review boards at all participating sites, and the participants gave informed consent.

The registry comprises 2252 patients treated across 13 sites in 7 countries (Brazil, Canada, Germany, Italy, Portugal, South Korea, and the United States) between 2003 and 2015. All consecutive patients undergoing CCTA at each participating site were enrolled if they met all the following selection criteria: (1) ≥2 clinically indicated CCTA examinations with ≥64-detector-rows for CAD evaluation and (2) ≥2-year interval between the baseline (CCTA-1) and follow-up CCTA (CCTA-2). In case of patients with ≥3 CCTA scans, the first and last CCTAs were analyzed.

After excluding patients with quantitatively nonanalyzable CCTA (n=492), CCTAs of 1760 patients were analyzed. For the primary end point, patients with known CAD before CTA-1 (n=282) and patients who experienced coronary revascularization between the 2 CTAs (n=133) were excluded, resulting in 1345 patients. For the secondary end point, patients without available clinical outcome data (n=221) were further excluded, resulting in 1124 patients (Figure 1).

Coronary Computed Tomography Angiography

Datasets from each contributing site were transferred to a core laboratory for image analysis. All procedures of testing, image acquisition, and postprocessing of CCTA data are in direct accordance with Society of Cardiovascular Computed Tomography guidelines.[16,17] All CCTA analyses were performed on axial, coronal, sagittal, cross-sectional, and curved-multiplanar reformation images by independent level III–experienced readers (blinded to clinical results) using semiautomated plaque analysis software (QAngioCT Research Edition v2.1.9.1; Medis Medical Imaging Systems, Leiden, the Netherlands).[12] Detailed method of CCTA analysis is described in the Data Supplement.

In brief, segments with a diameter ≥2 mm were evaluated using the modified 17-segment American Heart Association

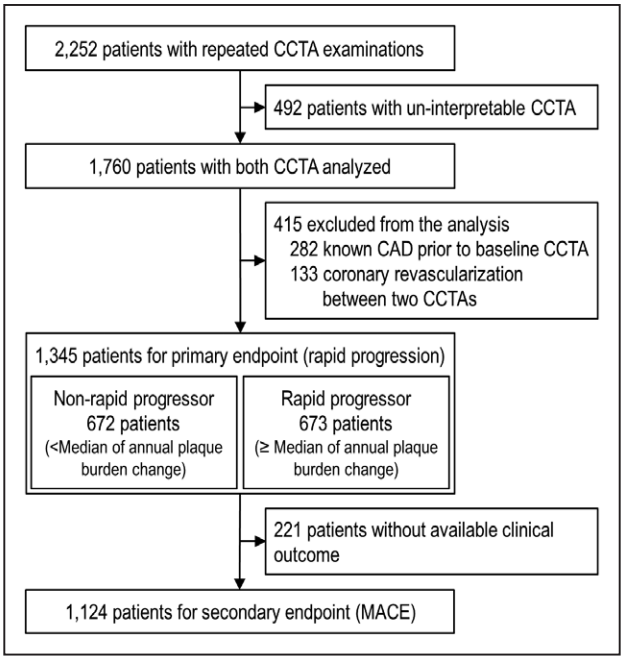

Figure 1. Consolidated standards of reporting trials flowchart.
CAD indicates coronary artery disease; CCTA, coronary computed tomography angiography; and MACE, major adverse cardiac events.

model for coronary artery segment classification.[10,17] For longitudinal assessment, segments were matched between CTA-1 and CTA-2 using branch points as landmarks, and only segments amenable to analysis for both CTA-1 and CTA-2 were considered further.

For conventional angiographic analysis, the presence of a ≥50% diameter stenosis was considered as clinically significant obstructive CAD.[2,3] Patients with obstructive CAD were further categorized as having 1-, 2-, or 3-vessel disease to reflect the angiographic CAD extent,[18] and segment involvement score (SIS) was also calculated.[19]

Quantitative analysis of the entire coronary tree was conducted for each patient. Vessel volume (mm^3) and plaque volume (mm^3) of all segments analyzable at both CCTA-1 and -2 were obtained from the entire coronary tree[20] and then added to generate vessel volume and plaque volume on the per-patient level. PB was defined as ([plaque volume/vessel volume]×100%).[20] To determine progression or regression of coronary artery atherosclerosis, annual change in PB (△PB/y, %/y) was defined as follows: ([△PB]/[interval between CCTA examinations (years)]%/y). Patients were divided into 2 groups by using the median value of △PB/y: nonrapid progressors (<median value of △PB/y) and rapid progressors (≥median value of △PB/y).

HRP was defined as plaque with ≥2 of the following features: positive arterial remodeling, low-attenuation plaque, and spotty calcification.[21] A remodeling index (maximal lesion vessel area divided by proximal reference vessel area) ≥1.1 was defined as positive arterial remodeling, and low-attenuation plaque was defined as any voxel of ≤30 HU within a region of interest.[10] Spotty calcification was defined as presence of calcification <3 mm in any direction within a plaque.[21]

Primary and Secondary End Points

The primary end point was rapid plaque progression, defined as ≥the median value of △PB/y. The secondary end point was time to major adverse cardiac events (MACE) after CCTA-2, defined as one of the following: (1) cardiac mortality, (2) nonfatal myocardial infarction, and (3) coronary revascularization (percutaneous coronary intervention or coronary artery bypass graft).

Statistical Analysis

Continuous variables are expressed as mean±SD or median (25th percentile, 75th percentile), as appropriate, and categorical variables are presented as absolute counts and percentages. Differences between categorical variables were analyzed by either the χ^2 test or Fisher exact test, whereas those between continuous variables were analyzed by the Student *t* test or Wilcoxon rank-sum test.

Hazard ratios and 95% confidence interval (CI) of the association between various measures of CCTA and MACE were calculated using Cox proportional hazard models. To compare the value added by quantitative analysis to qualitative and semiquantitative analyses of CCTA in risk prediction, various models were constructed using clinical risk factors and CCTA variables. Model 1 was constructed by only clinical risk factors, including age, sex, history of smoking, hypertension, diabetes mellitus, hyperlipidemia, family history of CAD, and statin use. For prediction of primary end point, time intervals between CCTA-1 and CCTA-2 were adjusted. Model 2 was generated by adding angiographic extent, in terms of SIS, to model 1. Baseline PB was further added to model 2 to generate model 3. For model 4, the presence of HRP was added to model 3. For prediction of clinical events, model 5 in which △PB/y was further added to model 4 was also constructed in addition to model 1 to 4, using the time to MACE after CCTA-2.

Statistical significance of the contribution of each added variable was assessed using the likelihood ratio test, consistent with recent recommendations.[22] The predictive performance of each model was assessed by Harrell C-index (area under receiver operating characteristic curve), and differences in predictive performance between models were tested using a nonparametric method.[23] A standard bootstrap method was applied to generate the corresponding CIs for this estimate.[24,25]

Cumulative event rates as a function of time and combination of medial value of baseline PB and △PB/y were calculated using the Kaplan-Meier estimator and compared using the log-rank statistic. A *P* value <0.05 was considered to indicate a statistically significant difference. All analyses were performed with SAS (version 9.4; SAS Institute Inc., Cary, NC) and R 3.3.0 (R Development Core Team, 2016).

RESULTS

Study Population and Clinical Outcomes

The study population consisted of 1345 patients; baseline characteristics and clinical outcomes are presented in Table 1. According to the calculated Framingham Risk Score, most patients were of low to intermediate risk (89%). The reason for undergoing both CTA-1 and CTA-2 was primarily ongoing and worsening or newly developed cardiac symptoms (82% and 67%, respectively). During the follow-up period after CTA-

Table 1. Summary of Baseline Characteristics and Clinical Outcomes

	Total (n=1345)	Nonrapid Progressors (n=672)	Rapid Progressors (n=673)	*P* Value
Age	60.4±9.4	58.8±9.3	62.0±9.2	<0.001
Male sex, n (%)	768 (57.1)	360 (53.6)	408 (60.6)	0.009
CCTA interval, y	3.8±1.6	4.0±1.7	3.7±1.5	<0.001
Total follow-up duration, y	7.9±2.0	8.2±1.9	7.6±2.1	<0.001
Follow-up after CCTA-2, y	4.3±2.1	4.6±2.0	4.1±2.2	<0.001
Body mass index, kg/m^2	25.4±3.4	25.2±3.3	25.5±3.4	0.038
Hypertension, n (%)	702 (52.2)	317 (47.2)	385 (57.2)	<0.001
Diabetes mellitus, n (%)	266 (19.8)	99 (14.7)	167 (54.8)	<0.001
Hyperlipidemia, n (%)	507 (37.7)	238 (35.4)	269 (40.0)	0.09
Family history of CAD, n (%)	394 (29.3)	202 (30.1)	192 (28.5)	0.54
Smoking history, n (%)	495 (36.8)	232 (34.5)	263 (39.1)	0.08
Statin, n (%)	511 (38.0)	215 (32.0)	296 (44.0)	<0.001
Anti-platelets, n (%)	480 (35.7)	201 (29.9)	279 (41.5)	<0.001
β-blockers, n (%)	502 (37.3)	209 (31.1)	293 (43.5)	<0.001
Lipid profile				
Total cholesterol, mg/dL	190.4±39.0	192.2±39.5	188.5±38.3	0.11
Low-density lipoprotein	115.7±33.8	117.2±33.9	114.2±33.6	0.13
High-density lipoprotein	51.2±14.0	52.6±14.2	49.9±13.6	<0.001
Clinical outcomes–after CCTA-2				
MACEs, n (%)	97 (8.6)	21 (4.4)	73 (12.5)	<0.001
Cardiac death	6 (0.5)	2 (0.4)	4 (0.7)	<0.001
Nonfatal MI	3 (0.3)	1 (0.2)	2 (0.3)	<0.001
Revascularization–PCI	78 (7.0)	15 (2.8)	63 (10.8)	<0.001
Revascularization–CABG	1 (0.1)	0 (0.0)	1 (0.2)	<0.001

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; MACE, major adverse cardiac events; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

2 (ranging 1–3505 days), revascularization was the most common clinical outcome, followed by minimal instances of cardiac death and nonfatal myocardial infarction.

Between the 2 CCTAs (3.8±1.6 years; range, 2.0–11.6 years), the median value of ΔPB/y was 0.33%/y. Patients were subsequently categorized into rapid progressors (n=673) and nonrapid progressors (n=672). Rapid progressors were older, more frequently male, had more clinical risk factors, and were more frequently using statins than those nonrapid progressors.

Results of CCTA Analysis

The baseline CCTA characteristics are presented in Table 2. In angiographic assessment, rapid progressors possessed more obstructive CAD, number of plaques, and SIS, than nonrapid progressors. On volumetric quantification of coronary artery atherosclerosis, rapid progressors had significantly greater total PB at baseline than nonrapid progressors. Furthermore, HRPs were more frequently observed in rapid progressors than in nonrapid progressors.

Value of Atherosclerosis Quantification for Prediction of Rapid Progression

For prediction of rapid progression, the prognostic performance of model 1, which considered only clinical risk factors, was modest (C statistics [95% CI], 0.581 [0.580–581]; Table 3). Adding SIS to model 1 improved the prognostic value (model 2, C statistics [95% CI], 0.679 [0.678–0.679]; *P*<0.001). Adding PB at baseline to SIS further increased predictive performance (models 3, C statistics [95% CI], 0.687 [0.686–0.687]; *P*<0.001). Consideration of HRP further improved prognostic value (model 4, C statistics [95% CI], 0.689 [0.688–0.689]; *P*<0.001). In model 4, hazard ratios of PB was 1.040 (95% CI, 1.029–1.051; *P*<0.001), and hazard ratios of HRP was 1.534 (95% CI, 1.300–1.817; *P*<0.001).

Value of Atherosclerosis Quantification in Prediction of MACE

For prediction of clinical outcome, adding SIS to clinical risk factors modestly improved prognostic performance (model 2, C statistics [95% CI], 0.751 [0.750–0.751];

Table 2. Baseline CTA Characteristics*

	Total (n=1345)	Nonrapid Progressors (n=672)	Rapid Progressors (n=673)	*P* Value
No. of plaques				
0–4, n (%)	1122 (83.4)	640 (95.2)	482 (71.6)	<0.001
5–9, n (%)	213 (15.8)	31 (4.6)	182 (27.0)	<0.001
>10, n (%)	10 (0.7)	1 (0.2)	9 (1.3)	<0.001
Angiography				
Presence of %DS ≥50%, n (%)	56 (4.2)	7 (1.0)	49 (7.3)	<0.001
Presence of %DS ≥70%, n (%)	3 (0.2)	0 (0.0)	3 (0.5)	0.08
Stenosis involvement score	3.1±2.9	1.6±2.0	4.5±2.8	<0.001
Angiographic CAD extent, n (%)				
No CAD	1289 (95.8)	655 (99.0)	624 (92.7)	<0.001
1-VD	55 (4.1)	7 (1.0)	48 (7.1)	<0.001
2-VD	1 (0.1)	0 (0.0)	1 (0.2)	<0.001
3-VD	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
Volumetric quantification				
Total PV, mm^3	42.5 (0–133.1)	7.7 (0.0–54.7)	96.1 (37.2–209.4)	<0.001
Total PB, %	2.0 (0.0–6.1)	0.4 (0.0–2.3)	4.7 (1.8–9.5)	<0.001
Annual PV change, mm^3/y	7.5 (0.5–20.5)	0.6 (0.0–4.1)	20.1 (11.1–38.0)	<0.001
Annual PB change, %/y	0.3 (0.0–0.9)	0.0 (0.0–0.2)	0.9 (0.6–1.5)	<0.001
High-risk plaque characterization				
Any high-risk plaque,† n (%)	359 (26.7)	107 (15.9)	252 (37.4)	<0.001
Any LAP, n (%)	268 (19.9)	89 (13.2)	179 (26.6)	<0.001
Any positive remodeling, n (%)	881 (65.5)	297 (44.2)	584 (86.8)	<0.001
Any spotty calcification, n (%)	238 (17.7)	70 (10.4)	168 (35.0)	<0.001

CAD indicates coronary artery disease; CTA, computed tomography angiography; %DS, percent diameter stenosis; LAP, low-attenuation plaque; PB, plaque burden; PV, plaque volume; and VD, vessel disease.

*Continuous values are mean±SD or median (25th percentile, 75th percentile), as appropriate.

†High-risk plaque was defined as plaque with ≥2 of low-attenuation plaque, positive arterial remodeling, and spotty calcification.

P<0.001; Table 4). Addition of PB to the conventional angiographic CAD assessment resulted in better predictive performance (models 3, C statistics [95% CI], 0.753 [0.752–0.753]; *P*=0.001), and HRP further increased prognostic performance (models 4, C statistics [95% CI], 0.756 [0.755–0.756]; *P*<0.001). When categorizing patients using PB and the presence of HRP at baseline, MACE occurred most frequently in patients with both high PB and HRP at baseline (Figure 2; log-rank *P*<0.001).

Discriminatory performance for MACE was highest among all models when annual PB progression was added (model 5, C statistics [95% CI], 0.763 [0.762–0.763]; *P*<0.001), with annual change in PB having a hazard ratios of 1.347 (95% CI, 1.121–1.619; *P*=0.002). Consistently, in Kaplan-Meier curve for MACE (Figure 3) that categorize patients into 4 groups according to combination of medial value of baseline PB (2.2%) and △PB/y, patients with both high PB and high △PB/y experienced the worst outcomes (log-rank *P*<0.001).

Table 3. Comparison of C Statistics Between CCTA Features for the Prediction of Rapid Progression (n=1345)

Model	C Statistics (95% CI)	*P* Value
Model 1: clinical risk factors*	0.581 (0.580–0.581)	…
Model 2: model 1+SIS	0.679 (0.678–0.679)	vs model 1 <0.001
Model 3: model 2+baseline PB	0.687 (0.686–0.687)	vs model 2 0.001
Model 4: model 3+any HRP†	0.689 (0.688–0.689)	vs model 3 <0.001

CCTA indicates coronary computed tomography angiography; CI, confidence interval; HRP, high-risk plaque; PB, plaque burden; and SIS, stenosis involvement score.

*Adjusted clinical risk factors: age, sex, hypertension, diabetes, hyperlipidemia, smoking, statin use, and family history of coronary artery disease.

†High-risk plaque was defined as plaque with ≥2 of low-attenuation plaque, positive arterial remodeling, and spotty calcification.

DISCUSSION

The analysis of this large, prospective observational registry demonstrated the incremental value of quantitative assessment of coronary artery atherosclerosis when compared with conventional angiographic assessment of CAD in prediction of rapid plaque progression. Direct

Table 4. Comparison of C Statistics Between CCTA Features for the Prediction of Clinical Events (n=1124)

Model	C Statistics (95% CI)	*P* Value
Model 1: clinical risk factors*	0.674 (0.673–0.675)	…
Model 2: model 1+SIS	0.751 (0.750–0.751)	vs model 1 <0.001
Model 3: model 2+baseline PB	0.753 (0.752–0.753)	vs model 2 0.001
Model 4: model 3+any HRP†	0.756 (0.755–0.756)	vs model 3 <0.001
Model 5: model 4+△PB/y	0.763 (0.762–0.763)	vs model 4 <0.001

CCTA indicates coronary computed tomography angiography; CI, confidence interval; HRP, high-risk plaque; PB, plaque burden; △PB/y, annual change in plaque burden; and SIS, stenosis involvement score.

*Adjusted clinical risk factors: age, sex, hypertension, diabetes, hyperlipidemia, smoking, statin use, and family history of coronary artery disease.

†High-risk plaque was defined as plaque with ≥2 of low-attenuation plaque, positive arterial remodeling, and spotty calcification.

quantification of CAD burden as reflected by PB was an independent predictor of disease progression that facilitated diagnosis of CAD using angiographic definition. Furthermore, analyzing CAD burden quantitatively also had additional prognostic implications for MACE in both cross-sectional and serial settings. The combination of △PB/y and baseline PB further increased the prognostic performance of the model.

To date, CAD has been defined and diagnosed based solely on angiographic evaluation, which, in turn, only focuses on the coronary lumen (ie, whether a patient has a significant obstruction, which is usually indicated by the presence of luminal stenosis >50%).[26] In this regard, the prognostic implications of obstructive CAD have been well documented.[8,10,19] Hence, current guidelines consider symptomatic patients with evidence of coronary artery atherosclerosis but without provocable ischemia or significant luminal stenosis as low-risk patients and do not offer directions for proper management.[2,3] As a consequence, studies assessing CAD progression also mostly focused on coronary artery lumen, not on the atherosclerotic plaque causing the obstruction itself.

However, it has been shown that nonobstructive and nonischemic lesions are also associated with future myocardial infarction,[27] and nonobstructive coronary artery plaques identified by CCTA also had added value in predicting outcomes.[28,29] In this regard, efforts have been made to identify risk factors of rapid disease progression, revealing that presence of HRP is an important factor associated with both progression and MACE.[8,10] However, HRP detection is still only one method of simple characterization of plaque focusing on the lesion rather than on the patient. Simple identification of HRP cannot, therefore, effectively use all the information available from CCTA, which can visualize the whole coronary tree on a patient level. Moreover, recent analyses found that, in the vast majority of cases, HRP does not demonstrate clinical instability, thereby raising doubt about the assumption that a patient with HRP is synonymous to a vulnerable patient.[6,7]

Taken together, these findings suggest that morphological characterization of plaques or simple lumi-

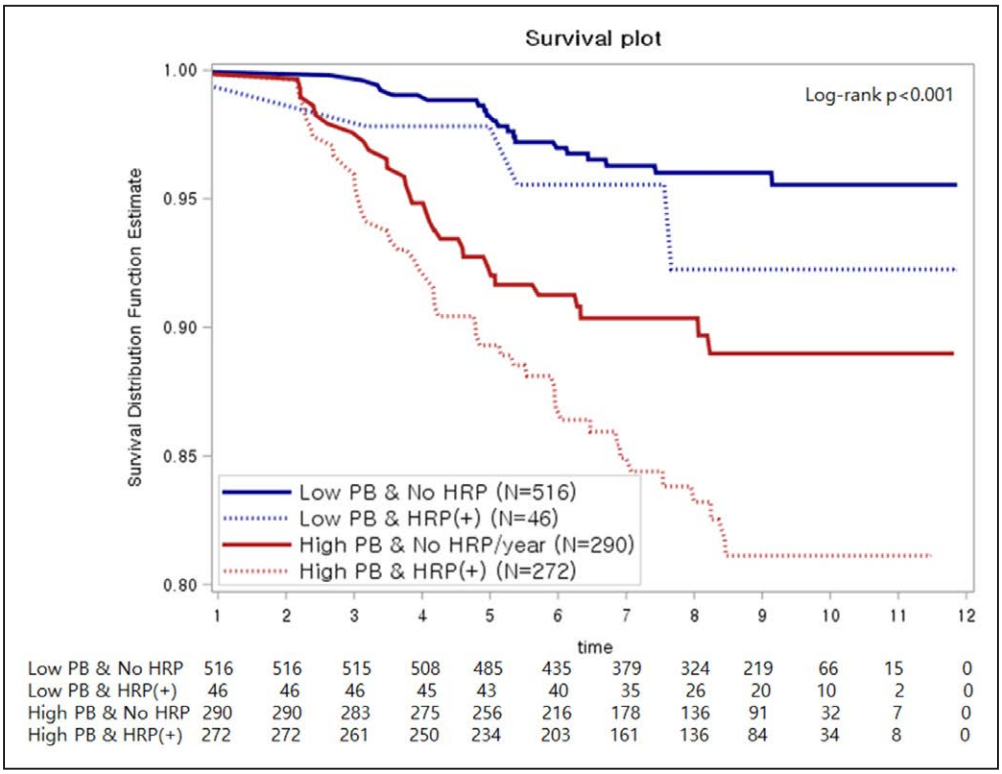

Figure 2. Event-free survival of patients with different combinations of baseline plaque burden (PB) and presence of high-risk plaque (HRP).
**HRP was defined as plaque with ≥2 of low-attenuation plaque, positive arterial remodeling, and spotty calcification.

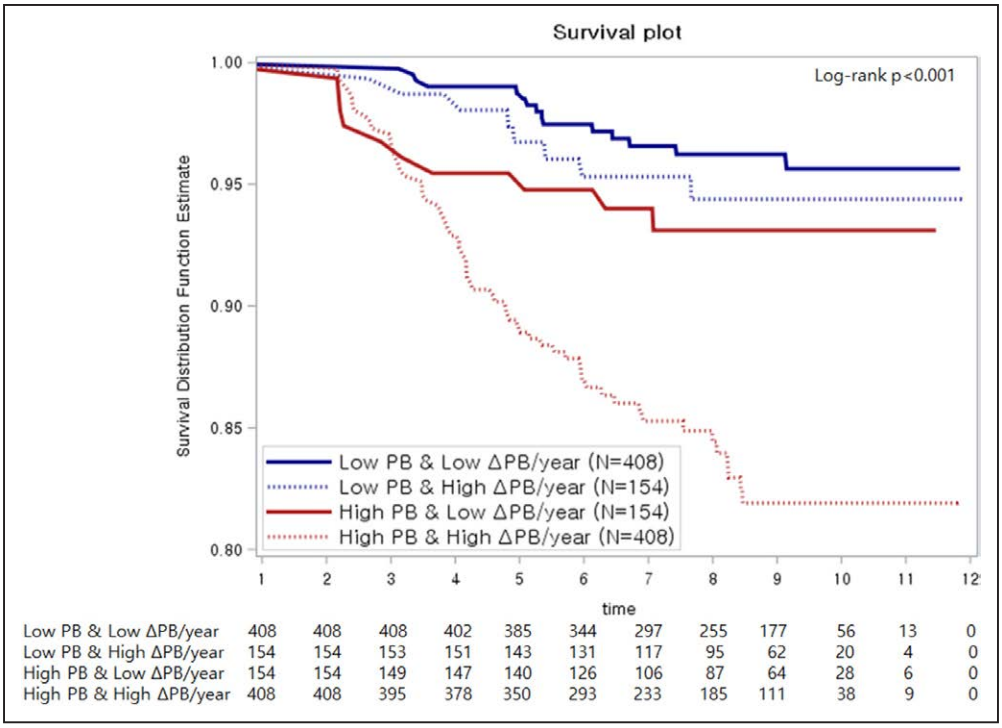

Figure 3. Event-free survival of patients with different combinations of cross-sectional and longitudinal quantitative indices.
When patients were stratified into 4 groups based on baseline plaque burden (PB) and annual progression rate of PB, patients who had both high PB and rapid progression rate experienced the worst clinical outcomes. ΔPB/y, annual progression of plaque burden.

nal assessment of CAD do not provide for complete picture. By relying entirely on conventional categorical analysis focusing on the coronary lumen, which cannot retrieve some valuable information from the image, we may miss the opportunity to implement more efficient management strategies. The results of our study and previous studies indicate that it might be the time to make a transition from a categorical view on the presence of luminal stenosis or features of individual plaques to an overall, continuous risk of coronary artery atherosclerosis as assessed by total PB.[5–7] A shift in focus from lumen to overall coronary artery atherosclerosis may help in establishing a definition of CAD that is more effective for risk stratification and improvement of outcomes. The present study provides a unique evidence-based opportunity to expand the disease spectrum of CAD and to modify risk stratification for CAD to improve clinical outcomes.

In this study, baseline PB was greater in rapid progressors than in nonrapid progressors, and PB at baseline was an independent predictor for rapid progression. These findings may simply indicate that a patient who has accrued a greater PB tends to experience faster plaque progression—meaning that the rate of CAD progression is an innate property of the patient. However, this could also convey that progression of coronary artery atherosclerosis accelerates exponentially, not linearly, as observed in a recent study where the coronary artery calcium score increased exponentially during 10 years of follow-up,[30] which implies the necessity of more frequent follow-up for patients with already advanced CAD. Further studies are warranted to clarify this notion.

The results of the present study also support the use of CCTA-based plaque quantification as a suitable and reliable risk assessment tool in patients who are at various levels of clinical risk. Precise quantification of CAD burden in all of the coronary arteries is not possible when using invasive modalities because of the characteristics of intravascular imaging and practical limitations in the extent of the coronary vasculature that can be examined.[31] Therefore, previous invasive studies were limited to specific lesions, and patients in low-risk population could not be involved in these studies, resulting in the natural history of coronary atherosclerosis in its early stage not well characterized.[32,33] By using CCTA, patients who are not subjected to invasive procedures—usually patients who have less disease burden or patients in early stages of CAD—could be enrolled. In this regard, the strength and novelty of the present study lie not only in the quantitative measure of the entire coronary tree but also in providing a unique opportunity to explore the study population that could not be fully evaluated when using invasive modalities.

Our study is not without limitations. Because only patients who had ≥2 CTA scans were enrolled, it is plausible to assume that patients with severe CAD, or normal coronary arteries at CTA-1, were omitted. In addition, patients who underwent revascularization before CTA-2 were excluded, thereby increasing selection bias. As a

result, the study population reflects patients at low-risk, as shown by the low rates of obstructive CAD and MACE, requiring caution when applying this result in high-risk population. However, as there are no recommendations on repeated CTAs in patients with suspected CAD,[2,14] an observational registry like Progression of Atherosclerotic Plaque Determined by Computed Tomographic Angiography Imaging provides a unique opportunity to assess the temporal development of CAD in low-risk populations who are not indicated for invasive studies. Whether the value of quantitative metrics of CCTA in risk stratification shown in this study would be also valuable in high-risk population remains to be proven in future large-scale trials, and the current study might be able to provide a rationale for conducting such studies.

In conclusion, quantitative analysis of coronary artery plaque using CCTA has an additional clinical value in predicting both progression of CAD and clinical events. A shift in focus to assessment of coronary artery atherosclerotic burden from evaluation of luminal stenosis alone for diagnosis and risk stratification of CAD should be considered to improve overall clinical outcome.

ARTICLE INFORMATION

Received January 10, 2018; accepted May 10, 2018.

The Data Supplement is available at https://www.ahajournals.org/journal/circimaging/doi/suppl/10.1161/CIRCIMAGING.117.007562.

Authors

Sang-Eun Lee, MD, PhD; Ji Min Sung, PhD; Asim Rizvi, MD; Fay Y. Lin, MD; Amit Kumar, MSc; Martin Hadamitzky, MD; Yong-Jin Kim, MD, PhD; Edoardo Conte, MD; Daniele Andreini, MD, PhD; Gianluca Pontone, MD, PhD; Matthew J. Budoff, MD; Ilan Gottlieb, MD, PhD; Byoung Kwon Lee, MD, PhD; Eun Ju Chun, MD, PhD; Filippo Cademartiri, MD, PhD; Erica Maffei, MD; Hugo Marques, MD; Jonathon A. Leipsic, MD; Sanghoon Shin, MD; Jung Hyun Choi, MD, PhD; Kavitha Chinnaiyan, MD; Gilbert Raff, MD; Renu Virmani, MD; Habib Samady, MD; Peter H. Stone, MD; Daniel S. Berman, MD; Jagat Narula, MD, PhD; Leslee J. Shaw, PhD; Jeroen J. Bax, MD, PhD; James K. Min, MD; Hyuk-Jae Chang, MD, PhD

Correspondence

Hyuk-Jae Chang, MD, PhD, Division of Cardiology, Yonsei-Cedars-Sinai Integrative Cardiovascular Imaging Research Center, Severance Cardiovascular Hospital, Yonsei University College of Medicine, Yonsei University Health System, 50–1 Yonsei-ro, Seodaemun-gu, Seoul 03722, South Korea. E-mail hjchang@yuhs.ac

Affiliations

Division of Cardiology, Severance Cardiovascular Hospital (H.-J.C., S.-E.L., J.M.S.), Yonsei-Cedars-Sinai Integrative Cardiovascular Imaging Research Center (H.-J.C., S.-E.L., J.M.S.), and Gangnam Severance Hospital (B.K.L.), Yonsei University College of Medicine, Yonsei University Health System, Seoul, South Korea. Dalio Institute of Cardiovascular Imaging, New York-Presbyterian Hospital and Weill Cornell Medical College (A.K., A.R., F.Y.L., J.K.M.). Department of Radiology and Nuclear Medicine, German Heart Center Munich (M.H.). Seoul National University College of Medicine, Seoul National University Hospital, South Korea (Y.-J.K.). Centro Cardiologico Monzino, Istituto di Ricovero e Cura a Carattere Scientifico Milan, Italy (E.C., G.A., G.P.). Department of Medicine, Los Angeles Biomedical Research Institute, Torrance, CA (M.J.B.). Department of Radiology, Casa de Saude São Jose, Rio de Janeiro, Brazil (I.G.). Seoul National University Bundang Hospital, South Korea (E.J.C.). Cardiovascular Imaging Center, SDN Foundation IRCCS, Naples, Italy (F.C.). Department of Radiology, Area Vasta 1/Azienda Sanitaria Unica Regionale Marche Marche, Urbino, Italy (E.M.). Hospital da Luz, Lisbon, Portugal (H.M.). Department of Radiology, St Paul's Hospital, University of British Columbia, Vancouver, Canada (J.A.L.). National Health Insurance Service Ilsan Hospital, South Korea (S.S.). Busan University Hospital, South Korea (J.H.C.). Department of Cardiology, William Beaumont Hospital, Royal Oak, MI (G.R., K.C.). Department of Pathology, CVPath Institute, Gaithersburg, MD (R.V.). Division of Cardiology, Emory University School of Medicine, Atlanta, GA (H.S., L.J.S.). Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA (P.H.S.). Department of Imaging, Burns and Allen Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA (D.S.B.). Icahn School of Medicine at Mount Sinai, Mount Sinai Heart, Zena and Michael A. Wiener Cardiovascular Institute, and Marie-Josee and Henry R. Kravis Center for Cardiovascular Health, New York, NY (J.N.). Department of Cardiology, Leiden University Medical Center, The Netherlands (J.J.B.).

Sources of Funding

This study was supported by Leading Foreign Research Institute Recruitment Program through the National Research Foundation of Korea funded by the Ministry of Science, Information and Communications Technology & Future Planning (Grant No. 2012027176) and funded in part by a generous gift from the Dalio Institute of Cardiovascular Imaging and the Michael Wolk Foundation. The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Disclosures

Dr Chang receives funding from by Leading Foreign Research Institute Recruitment Program through the National Research Foundation of Korea funded by the Ministry of Science, ICT & Future Planning (Grant No. 2012027176); Dr Min receives funding from the National Institutes of Health (Grant Nos. R01 HL111141, R01 HL115150, R01 118019, and U01 HL 105907), the Qatar National Priorities Research Program (Grant No. 09-370-3-089), and GE Healthcare. Dr Min served as a consultant to HeartFlow, serves on the scientific advisory board of Arineta, and has an equity interest in MDDX. Dr Bax receives unrestricted research grants from Biotronik, Medtronic, Boston Scientific, and Edwards Lifesciences. Dr Chun receives funding from National Research Foundation (NRF) grant funded by the Korea government (Ministry of Education, Science and Technology; NRF-2015R1D1A1A01059717). Dr Leipsic serves as a consultant and has stock options in HeartFlow and Circle Cardiovascular Imaging, and receives speaking fees from GE Healthcare. Dr Budoff receives grant support from the National Institutes of Health and GE Healthcare. Dr Samady receives grant support from Phillips/Volcano and St Jude Abbott/Medtronic/Gilead. Dr Andreini is on the Speakers Bureau for GE Healthcare and receives grant support from GE Healthcare and Bracco. Dr Pontone receives institutional research grants from GE Healthcare, HeartFlow, Medtronic, Bracco, and Bayer. Dr Berman receives software royalties from Cedars-Sinai. Dr Virmani has received institutional research support from 480 Biomedical, Abbott Vascular, Arterial Remodeling Technologies, BioSensors International, Biotronik, Boston Scientific, Celonova, Claret Medical, Cook Medical, Cordis, Edwards Lifesciences, Medtronic, MicroVention, OrbusNeich, ReCord, SINO Medical Technology, Spectranetics, Surmodics, Terumo Corporation, W.L. Gore and Xeltis. Dr Virmani also receives honoraria from 480 Biomedical, Abbott Vascular, Boston Scientific, Cook Medical, Lutonix, Medtronic, Terumo Corporation, and W.L. Gore, and is a consultant for 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore. The other authors report no conflicts.

REFERENCES

1. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. *N Engl J Med*. 2007;356:2388–2398. doi: 10.1056/NEJMsa053935.
2. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB III, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American

Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60:e44–e164. doi: 10.1016/j.jacc.2012.07.013.

3. Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, Budaj A, Bugiardini R, Crea F, Cuisset T, Di Mario C, Ferreira JR, Gersh BJ, Gitt AK, Hulot JS, Marx N, Opie LH, Pfisterer M, Prescott E, Ruschitzka F, Sabaté M, Senior R, Taggart DP, van der Wall EE, Vrints CJ, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Knuuti J, Valgimigli M, Bueno H, Claeys MJ, Donner-Banzhoff N, Erol C, Frank H, Funck-Brentano C, Gaemperli O, Gonzalez-Juanatey JR, Hamilos M, Hasdai D, Husted S, James SK, Kervinen K, Kolh P, Kristensen SD, Lancellotti P, Maggioni AP, Piepoli MF, Pries AR, Romeo F, Rydén L, Simoons ML, Sirnes PA, Steg PG, Timmis A, Wijns W, Windecker S, Yildirir A, Zamorano JL; Task Force Members; ESC Committee for Practice Guidelines; Document Reviewers. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34:2949–3003. doi: 10.1093/eurheartj/eht296.
4. Maddox TM, Stanislawski MA, Grunwald GK, Bradley SM, Ho PM, Tsai TT, Patel MR, Sandhu A, Valle J, Magid DJ, Leon B, Bhatt DL, Fihn SD, Rumsfeld JS. Nonobstructive coronary artery disease and risk of myocardial infarction. *JAMA*. 2014;312:1754–1763. doi: 10.1001/jama.2014.14681.
5. Arbab-Zadeh A, Fuster V. The risk continuum of atherosclerosis and its implications for defining CHD by coronary angiography. *J Am Coll Cardiol*. 2016;68:2467–2478. doi: 10.1016/j.jacc.2016.08.069.
6. Arbab-Zadeh A, Fuster V. The myth of the "vulnerable plaque": transitioning from a focus on individual lesions to atherosclerotic disease burden for coronary artery disease risk assessment. *J Am Coll Cardiol*. 2015;65:846–855. doi: 10.1016/j.jacc.2014.11.041.
7. Libby P, Pasterkamp G. Requiem for the 'vulnerable plaque'. *Eur Heart J*. 2015;36:2984–2987. doi: 10.1093/eurheartj/ehv349.
8. Motoyama S, Sarai M, Harigaya H, Anno H, Inoue K, Hara T, Naruse H, Ishii J, Hishida H, Wong ND, Virmani R, Kondo T, Ozaki Y, Narula J. Computed tomographic angiography characteristics of atherosclerotic plaques subsequently resulting in acute coronary syndrome. *J Am Coll Cardiol*. 2009;54:49–57. doi: 10.1016/j.jacc.2009.02.068.
9. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, Scherer M, Bellinger R, Martin A, Benton R, Delago A, Min JK. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;52:1724–1732. doi: 10.1016/j.jacc.2008.07.031.
10. Motoyama S, Ito H, Sarai M, Kondo T, Kawai H, Nagahara Y, Harigaya H, Kan S, Anno H, Takahashi H, Naruse H, Ishii J, Hecht H, Shaw LJ, Ozaki Y, Narula J. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. *J Am Coll Cardiol*. 2015;66:337–346. doi: 10.1016/j.jacc.2015.05.069.
11. Meyer M, Haubenreisser H, Schoepf UJ, Vliegenthart R, Leidecker C, Allmendinger T, Lehmann R, Sudarski S, Borggrefe M, Schoenberg SO, Henzler T. Closing in on the K edge: coronary CT angiography at 100, 80, and 70 kV-initial comparison of a second- versus a third-generation dual-source CT system. *Radiology*. 2014;273:373–382. doi: 10.1148/radiol.14140244.
12. Park HB, Lee BK, Shin S, Heo R, Arsanjani R, Kitslaar PH, Broersen A, Dijkstra J, Ahn SG, Min JK, Chang HJ, Hong MK, Jang Y, Chung N. Clinical feasibility of 3D automated coronary atherosclerotic plaque quantification algorithm on coronary computed tomography angiography: comparison with intravascular ultrasound. *Eur Radiol*. 2015;25:3073–3083. doi: 10.1007/s00330-015-3698-z.
13. Lehman SJ, Schlett CL, Bamberg F, Lee H, Donnelly P, Shturman L, Kriegel MF, Brady TJ, Hoffmann U. Assessment of coronary plaque progression in coronary computed tomography angiography using a semiquantitative score. *JACC Cardiovasc Imaging*. 2009;2:1262–1270. doi: 10.1016/j.jcmg.2009.07.007.
14. Taylor AJ, Cerqueira M, Hodgson JM, Mark D, Min J, O'Gara P, Rubin GD, Kramer CM, Berman D, Brown A, Chaudhry FA, Cury RC, Desai MY, Einstein AJ, Gomes AS, Harrington R, Hoffmann U, Khare R, Lesser J, McGann C, Rosenberg A, Schwartz R, Shelton M, Smetana GW, Smith SC Jr; American College of Cardiology Foundation Appropriate Use Criteria Task Force; Society of Cardiovascular Computed Tomography; American College of Radiology; American Heart Association; American Society of Echocardiography; American Society of Nuclear Cardiology; North American Society for Cardiovascular Imaging; Society for Cardiovascular Angiography and Interventions; Society for Cardiovascular Magnetic Resonance. ACCF/SCCT/ACR/AHA/ASE/ASNC/NASCI/SCAI/SCMR 2010 appropriate use criteria for cardiac computed tomography. A report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, the Society of Cardiovascular Computed Tomography, the American College of Radiology, the American Heart Association, the American Society of Echocardiography, the American Society of Nuclear Cardiology, the North American Society for Cardiovascular Imaging, the Society for Cardiovascular Angiography and Interventions, and the Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol*. 2010;56:1864–1894. doi: 10.1016/j.jacc.2010.07.005.
15. Lee SE, Chang HJ, Rizvi A, Hadamitzky M, Kim YJ, Conte E, Andreini D, Pontone G, Volpato V, Budoff MJ, Gottlieb I, Lee BK, Chun EJ, Cademartiri F, Maffei E, Marques H, Leipsic JA, Shin S, Choi JH, Chung N, Min JK. Rationale and design of the Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging (PARADIGM) registry: a comprehensive exploration of plaque progression and its impact on clinical outcomes from a multicenter serial coronary computed tomographic angiography study. *Am Heart J*. 2016;182:72–79. doi: 10.1016/j.ahj.2016.09.003.
16. Abbara S, Blanke P, Maroules CD, Cheezum M, Choi AD, Han BK, Marwan M, Naoum C, Norgaard BL, Rubinshtein R, Schoenhagen P, Villines T, Leipsic J. SCCT guidelines for the performance and acquisition of coronary computed tomographic angiography: a report of the society of Cardiovascular Computed Tomography Guidelines Committee: endorsed by the North American Society for Cardiovascular Imaging (NASCI). *J Cardiovasc Comput Tomogr*. 2016;10:435–449. doi: 10.1016/j.jcct.2016.10.002.
17. Leipsic J, Abbara S, Achenbach S, Cury R, Earls JP, Mancini GJ, Nieman K, Pontone G, Raff GL. SCCT guidelines for the interpretation and reporting of coronary CT angiography: a report of the Society of Cardiovascular Computed Tomography Guidelines Committee. *J Cardiovasc Comput Tomogr*. 2014;8:342–358. doi: 10.1016/j.jcct.2014.07.003.
18. Ostrom MP, Gopal A, Ahmadi N, Nasir K, Yang E, Kakadiaris I, Flores F, Mao SS, Budoff MJ. Mortality incidence and the severity of coronary atherosclerosis assessed by computed tomography angiography. *J Am Coll Cardiol*. 2008;52:1335–1343. doi: 10.1016/j.jacc.2008.07.027.
19. Min JK, Shaw LJ, Devereux RB, Okin PM, Weinsaft JW, Russo DJ, Lippolis NJ, Berman DS, Callister TQ. Prognostic value of multidetector coronary computed tomographic angiography for prediction of all-cause mortality. *J Am Coll Cardiol*. 2007;50:1161–1170. doi: 10.1016/j.jacc.2007.03.067.
20. Papadopoulou SL, Neefjes LA, Garcia-Garcia HM, Flu WJ, Rossi A, Dharampal AS, Kitslaar PH, Mollet NR, Veldhof S, Nieman K, Stone GW, Serruys PW, Krestin GP, de Feyter PJ. Natural history of coronary atherosclerosis by multislice computed tomography. *JACC Cardiovasc Imaging*. 2012;5(suppl 3):S28–S37. doi: 10.1016/j.jcmg.2012.01.009.
21. Puchner SB, Liu T, Mayrhofer T, Truong QA, Lee H, Fleg JL, Nagurney JT, Udelson JE, Hoffmann U, Ferencik M. High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. *J Am Coll Cardiol*. 2014;64:684–692. doi: 10.1016/j.jacc.2014.05.039.
22. Vickers AJ, Cronin AM, Begg CB. One statistical test is sufficient for assessing new predictive markers. *BMC Med Res Methodol*. 2011;11:13. doi: 10.1186/1471-2288-11-13.
23. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
24. Pencina MJ, D'Agostino RB. Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. *Stat Med*. 2004;23:2109–2123. doi: 10.1002/sim.1802.
25. Kang L, Chen W, Petrick NA, Gallas BD. Comparing two correlated C indices with right-censored survival outcome: a one-shot nonparametric approach. *Stat Med*. 2015;34:685–703. doi: 10.1002/sim.6370.
26. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, Naidu SS, Ohman EM, Smith PK, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK; American College of Cardiology/Americal Heart Association Task Force on Practice Guidelines; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2014 ACC/AHA/

AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Thorac Cardiovasc Surg*. 2015;149:e5–e23. doi: 10.1016/j.jtcvs2014.11.002.

27. Dedic A, Kurata A, Lubbers M, Meijboom WB, van Dalen BM, van Dalen B, Snelder S, Korbee R, Moelker A, Ouhlous M, van Domburg R, de Feijter PJ, Nieman K. Prognostic implications of non-culprit plaques in acute coronary syndrome: non-invasive assessment with coronary CT angiography. *Eur Heart J Cardiovasc Imaging*. 2014;15:1231–1237. doi: 10.1093/ehjci/jeu111.
28. Williams MC, Hunter A, Shah ASV, Assi V, Lewis S, Smith J, Berry C, Boon NA, Clark E, Flather M, Forbes J, McLean S, Roditi G, van Beek EJR, Timmis AD, Newby DE; SCOT-HEART Investigators. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. *J Am Coll Cardiol*. 2016;67:1759–1768. doi: 10.1016/j.jacc.2016.02.026.
29. Hoffmann U, Ferencik M, Udelson JE, Picard MH, Truong QA, Patel MR, Huang M, Pencina M, Mark DB, Heitner JF, Fordyce CB, Pellikka PA, Tardif JC, Budoff M, Nahhas G, Chow B, Kosinski AS, Lee KL, Douglas PS; PROMISE Investigators. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE Trial (Prospective Multicenter Imaging Study for Evaluation of Chest Pain). *Circulation*. 2017;135:2320–2332. doi: 10.1161/CIRCULATIONAHA.116.024360.
30. Carr JJ, Jacobs DR Jr, Terry JG, Shay CM, Sidney S, Liu K, Schreiner PJ, Lewis CE, Shikany JM, Reis JP, Goff DC Jr. Association of coronary artery calcium in adults aged 32 to 46 years with incident coronary heart disease and death. *JAMA Cardiol*. 2017;2:391–399. doi: 10.1001/jamacardio.2016.5493.
31. Maehara A, Stone GW. High-risk coronary atherosclerosis: is it the plaque burden, the calcium, the lipid, or something else? *Circ Cardiovasc Imaging*. 2017;10:e007116.
32. Nissen SE, Tuzcu EM, Brewer HB, Sipahi I, Nicholls SJ, Ganz P, Schoenhagen P, Waters DD, Pepine CJ, Crowe TD, Davidson MH, Deanfield JE, Wisniewski LM, Hanyok JJ, Kassalow LM; ACAT Intravascular Atherosclerosis Treatment Evaluation (ACTIVATE) Investigators. Effect of ACAT inhibition on the progression of coronary atherosclerosis. *N Engl J Med*. 2006;354:1253–1263. doi: 10.1056/NEJMoa054699.
33. Nicholls SJ, Tuzcu EM, Wolski K, Bayturan O, Lavoie A, Uno K, Kupfer S, Perez A, Nesto R, Nissen SE. Lowering the triglyceride/high-density lipoprotein cholesterol ratio is associated with the beneficial impact of pioglitazone on progression of coronary atherosclerosis in diabetic patients: insights from the PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) study. *J Am Coll Cardiol*. 2011;57:153–159. doi: 10.1016/j.jacc.2010.06.055.