Title
Quantification of Coronary Atherosclerosis in the Assessment of Coronary Artery Disease.

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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 (ΔPB/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 ΔPB/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 ΔPB/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.

Diagnosis and management strategies of coronary artery disease (CAD) have resulted in a ≈50% decline in cardiovascular mortality from 1980 to 2000, 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. However, data suggest that patients with nonobstructive CAD, usually defined as <50% diameter stenosis and hence not fulfilling the current guidelines, have a risk of myocardial infarction (MI) and death similar to that of patients with single-vessel obstructive disease. This implies that the risk from CAD does not abruptly increase with the continuous extent of atherosclerosis plaque burden (PB), which is not fully reflected by the conventional angiographic assessment of CAD.

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

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.

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. The study protocol was approved by the institutional review boards at all participating sites, and the patients 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. 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). 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...
model for coronary artery segment classification. 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. Patients with obstructive CAD were further categorized as having 1-, 2-, or 3-vessel disease to reflect the angiographic CAD extent, and segment involvement score (SIS) was also calculated. Quantitative analysis of the entire coronary tree was conducted for each patient. Vessel volume (mm³) and plaque volume (mm³) of all segments analyzable at both CCTA-1 and -2 were obtained from the entire coronary tree and then added to generate vessel volume and plaque volume on the per-patient level. PB was defined as (plaque volume/vessel volume)×100%. To determine progression or regression of coronary artery atherosclerosis, annual change in PB (ΔPB/y) was defined as follows: ([ΔPB]/[interval between CCTA examinations (years)])×100%. Patients were divided into 2 groups by using the median value of ΔPB/y: nonrapid progressors (<median value of ΔPB/y) and rapid progressors (≥median value of ΔPB/y).

HRP was defined as plaque with ≥2 of the following features: positive arterial remodeling, low-attenuation plaque, and spotty calcification. 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. Spotty calcification was defined as presence of calcification <3 mm in any direction within a plaque.

Primary and Secondary End Points
The primary end point was rapid plaque progression, defined as ≥the median value of ΔPB/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 χ² 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 ΔPB/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. 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. A standard bootstrap method was applied to generate the corresponding CIs for this estimate.

Cumulative event rates as a function of time and combination of medial value of baseline PB and ΔPB/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-
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 [0.580–0.581]; 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];
Addition of PB to the conventional angiographic CAD assessment resulted in bet-

er 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).

**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 2. Baseline CTA Characteristics**

<table>
<thead>
<tr>
<th>Model</th>
<th>C Statistics (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1: clinical risk factors*</td>
<td>0.581 (0.580–0.581)</td>
<td>...</td>
</tr>
<tr>
<td>Model 2: model 1+PIS</td>
<td>0.679 (0.678–0.679) vs model 1 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Model 3: model 2+baseline PB</td>
<td>0.687 (0.686–0.687) vs model 2 0.001</td>
<td></td>
</tr>
<tr>
<td>Model 4: model 3+any HRP†</td>
<td>0.689 (0.688–0.689) vs model 3 &lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

CCTA indicates coronary computed tomography angiography; CI, confidence interval; HRP, high-risk plaque; PB, plaque burden; and PIS, 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.
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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 provable 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-

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

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

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.

**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.**
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, 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.

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