Title

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Journal

JACC Cardiovascular Imaging, 14(1)

ISSN

1936-878X

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Publication Date

2021

DOI

10.1016/j.jcmg.2020.08.036

Peer reviewed

The Impact of Coronary Calcification on the Natural History of Coronary Artery Disease: Results from The Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging (PARADIGM) registry

Brief Title: Coronary Calcification and Natural History of Coronary Artery Disease

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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, ICT & 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.

Disclosures /Conflicts
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. 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 (MEST) (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, ART, BioSensors International, Biotronik, Boston Scientific, Celonova, Claret Medical, Cook Medical, Cordis, Edwards Lifescience, 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. All other authors have no conflicts of interest to disclose.

ACKNOWLEDGMENTS This work was supported by a grant from Research year of Inje University in 20170038.

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Abstract

BACKGROUND Coronary artery calcification is an established marker of risk of future cardiovascular events. Despite this, plaque calcification is also considered a marker of plaque stability, and increases in response to medical therapy.

OBJECTIVES To explore the impact of plaque calcification at a lesional and patient level on the natural history of coronary artery disease.

METHODS This analysis included 925 patients with 2,568 lesions from the PARADIGM (Progression of atherosclerotic plaque determined by computed tomographic angiography imaging) registry, in which patients underwent serial coronary computed tomography angiography (CCTA). Plaque calcification was examined using calcified plaque volume (CPV) and percent calcified plaque volume (PCPV), calculated as (CPV/plaque volume (PV))*100.

RESULTS CPV was strongly correlated with PV ($r = 0.780$, $p < 0.001$) at baseline, and plaque progression ($r = 0.297$, $p < 0.001$), however this association was reversed after accounting for plaque volume at baseline ($r = -0.146$, $p < 0.001$). In contrast PCPV was an independent predictor of a reduction in PV ($r = -0.11$, $p < 0.001$) in univariable and multivariable linear regression analysis. Patient-level analysis showed that CPV showed an independent association with incident MACE (HR 3.01, 95% CI:1.58-5.72), whilst an increased PCPV was an independent predictor for MACE free-survival (HR 0.529, 95% CI:0.229-0.968) in multivariable analysis.

CONCLUSIONS Calcified plaque is a marker for risk of adverse event and disease progression due to its strong association with the total plaque burden. When considered as a percentage of the total plaque volume, increasing PCPV is a marker of plaque stability and reduced risk at both a lesion and patient level.

Keywords: Coronary artery disease, coronary artery calcium, coronary artery atherosclerosis, statins, coronary computed tomography angiography, coronary artery calcium

ABBERVIATION LIST

CAC Coronary artery calcification
CAD Coronary artery disease
CCTA Coronary computed tomography angiography
CPV Calcified plaque volume
HR Hazard ratio
HRP High-risk plaque
LAP Low-attenuation plaque
PB Plaque burden
PCPV Percent calcified plaque volume
PR Positive remodeling
PV Plaque volume
SC Spotty calcification
HU Hounsfield units

Introduction

Coronary artery calcification (CAC) is indicative of the presence of coronary atherosclerosis, and is a robust marker of coronary plaque burden (1,2). Multiple studies have consistently shown that CAC is a reliable, reproducible and independent predictor of future cardiovascular events (3,4), and provides incremental information beyond traditional cardiovascular risk factors (5,6). Current guidelines endorse CAC scoring to improve cardiovascular risk assessment in asymptomatic individuals at intermediate risk to guide use of preventive therapies (7-9).

Prior studies have shown that an interval increase in coronary artery calcium is a marker of increased cardiovascular risk (10-12), yet statins induce an increase in plaque calcification despite a well-documented role in the reduction of cardiovascular events (13-15). Thus, there is an apparent paradox in our current understanding of coronary calcium where it connotes both risk and stability, with progression portending both a risk of events and a response to therapy.

The aim of the current study was to examine the relationship between coronary plaque calcification, plaque volume and progression, and downstream risk. The hypotheses tested were twofold. First, that at a patient level calcified plaque would be a marker of total plaque burden, both calcified and non-calcified, and thus a marker for risk. Second, that at a plaque lesion level, heavily calcified plaque, defined by percentage of plaque volume composed of calcium, would be a marker of stability and thus a lack of progression.

Methods

Study design and participants selection

The PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) study is an international, multicenter, observational registry prospectively collecting clinical, procedural, and follow-up data. Enrolled patients underwent clinically indicated serial CCTA with ≥64-detector rows for evaluation of CAD at ≥2-year interscan interval across 13 sites in 7 countries (Brazil, Canada, Germany, Italy, Portugal, South Korea, and the United States). The design of the study has been described in detail previously (16). PARADIGM study was approved by each of the institutional review boards at the participating sites, and all participants provided written informed consent. Among 2,252 patients enrolled from PARADIGM registry, 492 were excluded because of inadequate image quality for plaque analysis. To examine the role of calcification on the natural time course of plaque,

patients who underwent revascularization before baseline (n = 282) or their follow-up CCTA (n = 133) were excluded from the analysis as were those without calcification on baseline CCTA (n = 420), leaving 925 patients eligible for per-lesion analysis. For the outcome analysis, a further 51 patients were excluded due to missing data on clinical outcomes leaving 874 patients in this analysis (Figure 1).

Data acquisition and image analysis

All CCTA investigations were performed on ≥64 detector CT scanners. Patient preparation, acquisition, and interpretation of CTA data were performed in accordance with Society of Cardiovascular Computed Tomography guidelines (17,18). All datasets including clinical information were transferred to a single core laboratory for blinded image analysis. Independent level III-experienced readers masked to clinical results and case status performed standardized measurements using semiautomated plaque analysis software (QAngioCT Research Edition version 2.1.9.1, Medis Medical Imaging Systems, Leiden, the Netherlands) (19).

In brief, quantitative analysis was performed for each segment with a diameter ≥2 mm on every 0.5-mm cross-section based on modified 17-segment American Heart Association model (18). These measurements included vessel length, volume, mean plaque burden (PB) and PV at baseline and follow-up CCTA. PB was defined as the percentage value of plaque volume divided by vessel volume (20). Plaque composition was analysed for all atherosclerotic plaques using pre-defined Hounsfield units

(HU) thresholds: necrotic core (-30 to 30 HU), fibro-fatty (30 to 130 HU), fibrous (131 to 350 HU), and calcified plaque (≥350 HU) (18,21). In each coronary segment with plaque, we performed further qualitative evaluation for the presence of high-risk plaque (HRP) defined as coronary lesions with ≥2 of the following features: positive remodelling (PR), low-attenuation plaque (LAP), or spotty calcification (SC) (22).The presence of PR was defined as when the maximal coronary diameter at the plaque site was at least 10% larger than that of the proximal reference segment. LAP was defined as any plaque containing ≥1 voxel with ≤30 HU (22). SC was defined as presence of calcification <3 mm in any direction within a plaque (23). The napkin-ring sign was also included as HRP, which was defined as a low-attenuation plaque core surrounded by a circumferential area of higher attenuation (24)

Calcified plaque measurement and longitudinal comparison of plaque volume and clinical outcomes

Calcification was defined as any tissue ≥1 mm^3 with an attenuation over 350 HU distinct from surrounding structures and identified in ≥2 planes within or adjacent to the lumen. Coronary calcification was assessed in 2 ways:

1) Calcified plaque volume (CPV): the total volume of calcium in atherosclerotic plaque.

2) Percentage calcified plaque volume (PCPV): The degree to which the plaque is calcified, calculated as follows; PCPV = (calcified plaque volume / plaque volume) X100

Matched coronary lesions between baseline and follow-up CCTAs were used for the longitudinal analysis of changes in PV, which was calculated as an annualized rate to account for the variability in time between baseline and follow-up CCTA. For longitudinal volumetric comparisons of plaque according to degree of plaque calcification, participants were split into quartiles of PCPV. We also compared the effects of each plaque composition including CPV and PCPV on the change in PV. Development of clinical events was prospectively collected at the time of baseline and follow-up CCTA. Follow-up began at the time of the baseline examination and continued until the first clinical event, or loss to follow-up.

Study endpoints

The primary endpoint of this study was to compare the annualized per-lesion change in volume of plaque between the baseline and follow-up CCTA according to quartile of PCPV. Secondary endpoints of CCTA included the association between annualized change in PV and each composition of plaque including PCPV on the baseline CCTA, and the effect of stenosis severity on the change in PV according to quartile of PCPV. The secondary clinical endpoint was the time to major adverse cardiac events (MACE) after follow-up CCTA, the definition of which included composite of nonfatal myocardial infarction, cerebrovascular accident, coronary revascularization and cardiac death.

Statistical analysis

Continuous data were presented as means ± standard deviation. Differences in continuous variables between the quartile groups of PCPV were determined by one-way ANOVA for normal distribution and Kruskal-Wallis test for non-normal distribution. Post hoc pairwise comparison with Scheffe test was performed for variables for which there was a significant difference between groups. Categorical variables were expressed as frequencies and percentages, which were compared using the Pearson Chi-square test or Fisher exact test among four groups. The correlation of CPV with PV was analysed using Spearman's correlation test and partial correlation analysis was used to analyse the association CPV and annualized change in PV, accounting for baseline PV. Univariable and multivariable linear regression models were used to identify variables associated with the annualized change in PV. The association of calcified plaque with clinical outcomes was investigated with the Cox proportional hazards model using univariable and stepwise multivariable analysis. The univariable model was adjusted for age, gender, smoking, diabetes mellitus, hypertension, dyslipidemia and familial history of CAD. The stepwise multivariable analysis included all clinical risk factors, variables of CCTA and statin use. For this analysis, we used values of CPV and PCPV in the patient-level data, which were classified into two groups by the median value of each of these. The Cox model was used to estimate the risk of a given variable as expressed by a hazard ratio with corresponding 95% confidence interval (CI). Survival curves were generated using the Kaplan–Meier method, and the difference between curves was assessed

by the log-rank test. A p-value ≤ 0.05 was considered statistically significant. All statistical analysis was performed using SPSS (version 22, IBM SPSS, NY) and SAS 9.2 (SAS Inc., Carry, NC, USA) software.

Results

Study population

Of the 2,252 patients in the PARADIGM registry, 925 patients with 2,568 lesions were included in the final analysis. Clinical and laboratory characteristics of this cohort are shown in Table 1. Overall, mean age was 61.9 ± 8.95 years, and 59.8% were male. Baseline diabetes mellitus (DM) and dyslipidemia were present in 22.6% and 41.5% of participants, respectively. 43.7% of patients were taking statin at the time of enrollment.

Change of atherosclerotic plaque volume and coronary artery calcification

A lesion-level analysis was performed for a total of 2,586 lesions. For volumetric comparisons of plaque, participants were classified into four groups according to quartile of PCPV value in baseline CCTA. The lesion characteristics are presented in Table 2. Overall mean lesion length was 22.7± 14.8 mm and mean PV, CPV and PCPV were 48.5 ± 77.2 mm^3, 18.5 ± 37.4 mm^3, 41.2 ± 27.4 %, respectively. The average area stenosis of lesions was 32.2 ± 19.4% and high-risk plaque (HRP) was present in 14.4% of the study population. There were significant differences in all

lesion parameter including PV, degree of stenosis and frequency of HRP between the PCPV quartiles ($p < 0.01$ for all). Table 2 shows that lesions with the highest PCPV (4th quartile) were shorter lesions, with a lower volume of plaque, greater severity of stenosis, higher plaque burden and less frequent HRP compared with lower PCPV ($p < 0.05$ for all). The analysis of change in PV for the primary endpoint is shown in figure 2. Annualized change in PV was greatest in lesions with lowest PCPV (1st quartile) and decreased monotonically across the four quartiles of PCPV which was statistically significant in intergroup comparison (all $p < 0.001$) (Figure 2A). The same trend was observed in the volume of each of the plaque components including fibrous plaque, fibro-fatty plaque and necrotic core which were statistically significant in intergroup comparison (all $p < 0.001$) (Figure 2B – D). The rate of newly detected HRP on follow-up CT, similarly, was highest in the lowest PCPV quartile and also decreased across the four quartiles with increasing PCPV (Figure 2F). Change in CPV was smallest in the first quartile, but change was greatest in second quartile and decreased across 3rd and 4th quartile (Figure 2E).

These observations were robust when analysed according to the severity of stenosis (Figure 3). Regardless of stenosis severity, there were significant differences in annualized change in PV between PCPV quartile groups.

Correlation between coronary calcification, plaque volume and its change

The CPV was strongly correlated with PV at the baseline CT on correlation analysis (r = 0.780, p < 0.001). On univariable linear regression analysis, factors significantly and positively associated with change in PV were baseline CPV, lesion length, necrotic core volume, mean plaque burden, area stenosis and HRP (all p < 0.001). In contradistinction, PCPV was significantly and inversely associated with change in PV (r = - 0.11, p < 0.001) (Table 3). A partial correlation model was also used to account for baseline PV due to strong association between CPV and PV, which showed that CPV was significantly and inversely correlated with change in PV after adjustment for PV at baseline CCTA (r = -0.146, p < 0 .001). After adjustment PCPV was independently and inversely associated with change in total PV on the multivariable linear regression analysis (B [95% confidence interval (CI)]: -0.028 [-0.044 to -0.012], p = 0.002) (Table 3). Necrotic core volume, mean plaque burden and lesion length were also independently associated with change in PV. However, there was no significant association between CPV and change in PV on multivariable analysis (p = 0.327).

Coronary calcification and clinical outcomes

874 patients (58.2% male, 62.1 ± 9.1 years old) were included in the analysis of clinical outcomes. Patients were divided into two groups base on the median value of PCPV and CPV in per-lesion analysis. Baseline clinical and CCTA characteristics are shown in Table 4. Patients with high PCPV (≥ 40%) were older and more likely to be female, Caucasian, and have a history of dyslipidemia and statin use than those with low PCPV.

Over a median follow-up of 4.3 years (interquartile range: 2.6 to 6 years), 110 patients (12.6%) experienced a MACE, which was mostly driven by a difference in revascularization (n = 106, 12.1%). Patients with high PCPV had a significantly lower incidence of MACE (14.6% vs 9.4%, p = 0.022) and revascularization (14.3% vs 8.8%, p = 0.016) than those with low PCPV, with no difference in the rate of non-fatal MI and death (Table 5). When categorizing patients using PCPV and CPV, Kaplan-Meier analysis demonstrated that the survival rate free from MACE was highest in patients with a high PCPV and low CPV (log rank p < 0.001) (Figure 4).

Table 6 shows the associations of variables from quantitative analysis individually for the MACE in the univariable and adjusted univariable Cox proportional analysis. In univariable analysis, the PCPV was significantly associated with a decreased risk of MACE (hazard ratio [HR]: 0.574; 95% confidence interval [CI]: 0.349 to 0.946; p < 0.029, whereas high calcified PV, total PV, mean PB and necrotic core volume were significantly associated with incidence of MACE (all p < 0.001) (Table 6). On the multivariable Cox proportional analysis, statin use was additionally included and CCTA variables were placed in the same model. The high PCPV was significantly and inversely associated with the MACE (HR: 0.526; 95% CI: 0.286 - 0.968; P = 0.039), whereas high CPV was associated with increased risk of MACE (HR: 3.009; 95% CI: 1.582 - 5.724; P = 0.016). The risk of MACE significantly increased in high necrotic core volume (HR: 2.130; 95% CI: 1.115 – 4.069; P = 0.022) and decreased in

patients taking statins (HR: 0.526; 95% CI: 0.296 - 0.933; P = 0.028), but other variables were not significant on multivariable analysis.

Discussion

In the current study from a large prospective multinational registry of patients undergoing serial CCTA, we found that calcified plaque is a marker of risk and disease progression due to its strong association with the total plaque burden. When considered as a percentage of the total plaque volume, increasing calcification is a marker of plaque stability and reduced risk at both a lesion and patient level. The current findings highlight that a more nuanced approach to using calcified plaque change in serial imaging studies as a risk marker is required. Percent calcified plaque volume, which captures this interplay between calcified plaque and total plaque volume may be considered a marker of increasing plaque stability and should be additionally considered when assessing the patient risk, as well as treatment response.

Current paradox of coronary calcification

Coronary plaque calcification is a complex pathophysiologic process that is closely associated with the extent of atherosclerosis (1,2). Extensive investigation has demonstrated that CAC is an independent predictor of adverse events, with a significant incremental prognostic value over traditional risk stratification (3-6,25,26). It may also be useful in the decision making process for guiding and targeting the preventive use of statins and/or aspirin through improved risk stratification (27,28). However, there is still a lack of mechanistic understanding of the

association between CAC and future adverse events. To date, the majority of studies examining the role of coronary calcium in predicting CAD have used simple quantification and scoring of calcification detected on CT without considering non-calcified plaque burden. Thus, it is challenging to ascertain whether the risk of calcified plaque is correlative through its association with non-calcified plaque, or causative through the calcified lesions themselves.

Previous studies with IVUS and CCTA have demonstrated that calcified plaques are more resistant to change and progression of plaque volume (29,30). However, these studies utilized a qualitative or semi-quantitative method to evaluate the coronary calcification, and the number of patients was small. Furthermore, as mentioned earlier, these do not incorporate total plaque volume, limiting the inferences that can be derived on the effect of calcification on outcomes at a lesion and patient level.

Insights into the association between coronary calcification and the natural history of coronary artery disease

In the current study, we analysed serial CCTA from a large prospective registry with a quantitative methodology, incorporating total and compositional plaque volumes. This included both the standard volume measurement of plaque calcification, but also the novel metric of PCPV to contextualizing the CPV in the overall plaque burden in its entirety. This represents how calcified a lesion is, irrespective of total plaque volume, and is valuable to elucidate the effect of coronary calcification on the natural history of CAD, overcoming the limitation of a strong association

between the volume of calcified plaque and total plaque burden (Central illustration). The present data provides novel observations that PCPV was inversely related to change in PV and cardiovascular events, whereas CPV was positively associated with clinical outcomes and was more predictive when adjusted for PCPV. These findings are consistent with prior studies that coronary calcification is an independent risk factor for future adverse events, reflecting coronary atherosclerotic burden (3,4,31), with this plaque burden in turn positively associated with progression (30,32). However, heavily calcified plaque was found to be associated with a lower interval change in PV and improved MACE-free survival. This implies that increasing calcified plaque burden as it relates to total plaque volume may represent a marker of plaque stabilization. Importantly, this observation held true even in lesions with severe stenosis, with heavily calcified plaques with severe stenosis showing little interval progression over time. Further work is warranted to determine if a more conservative approach may be considered even in the face of a significant stenosis, when the plaque exhibits a predominantly calcified composition.

Coronary artery calcification and medical therapy

Statins reduce the risk of CVD-associated morbidity and mortality, with statins now an established treatment of atherosclerotic cardiovascular disease (33,34). Studies investigating the effect of statins on plaque composition, show that statins promote coronary calcification, with progression in the CAC score (13-15). This however seems contradictory as CAC progression has been associated with poorer clinical outcome (10-

12). Because statins impact both the volume of calcified and non-calcified plaque (13,14), measuring coronary calcification in isolation is limited in its assessment of the effects of statins. In this regard, PCPV may better reflect the beneficial effect of preventative therapies on coronary plaque. High-intensity statins increase the calcium volume but not total plaque volume, which results in a pronounced increase in PCPV. That higher PCPV is in turn predictive of lower rates of plaque progression and cardiovascular events, aligns with the expected clinical outcomes of this preventative therapy. These findings suggest that PCPV should be considered when considering risk stratification by coronary calcium quantification.

Limitations

There are several limitations to the current study. Calcium scoring was not routinely performed as part of the PRADIGM study, as a result of which the extent to which the current findings impact the translation of coronary artery calcium scoring cannot be examined. Whilst CPV is measured by direct quantification of the volume of calcium detected on CT in a manner similar to calcium scoring, it uses a different threshold for defining calcium, and does not take into account the calcium density weighting factor used to produce the Agatston score. Despite these differences, it is interesting to note that a recent post hoc analysis has shown that the calcium density is inversely related to future events (35). At 3mm thick, the images used from the non-contrast CT to calculate the

Agatston score are close to encompassing the entire diameter of the coronary arteries. As a result, the calcium density may in fact be an indirect measure of the percentage of the plaque that is calcified. Further examination of these two factors is needed to provide better understanding of coronary artery plaque calcification, density and risk. Second, this analysis focused on subjects with calcification, therefore we exclude the lesions and patients without disease or calcification on baseline CCTA. However, the importance of PCPV and CPV are clearly only a relevant concept for patients with calcified plaque, therefore current results were restricted to this population. Third, we have only examined patients with clinically indicated baseline and follow-up CCTA for the longitudinal and volumetric analysis of plaque, which will lead to a selection bias. However, this may better reflect clinical practice where follow-up CT scans are performed at the physician's discretion taking into symptoms and clinical concern. Fourth, Patients who underwent revascularization were also excluded because it could physically and hemodynamically affect the natural course of lesions. Therefore, there is a possibility that the most severe and vulnerable lesions were excluded in the analysis, and the results should be interpreted with caution in especial high-risk lesions and plaque.

Conclusion

Calcified plaque is a marker of risk and disease progression due to its strong association with the total plaque burden. When considered as a

percentage of the total plaque volume, increasing calcification is a marker of plaque stability and reduced risk at both a lesion and patient level.

Perspectives

Competency in Medical Knowledge

Coronary artery calcification is a marker of cardiovascular risk. This is due to the strong correlation of calcified plaque with total plaque volume – both calcified and non-calcified. When plaque calcification is considered as a percentage of the total plaque burden, it is a marker of stability, with slower rates of plaque progression and lower MACE rates in those with heavily calcified plaque compared to those with predominantly non-calcified plaque.

Translational Outlook

Percentage calcified plaque volume may provide for a more accurate stratification of risk than calcified plaque volume alone. Future studies examining the role of percent calcified plaque volume in assessing treatment response and association with adverse clinical outcome are warranted.

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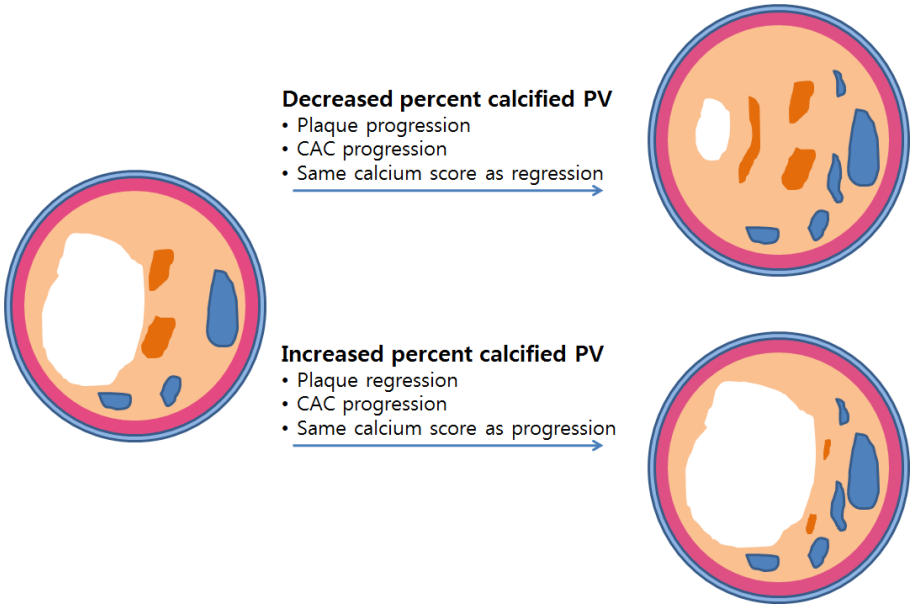
Figure Legends

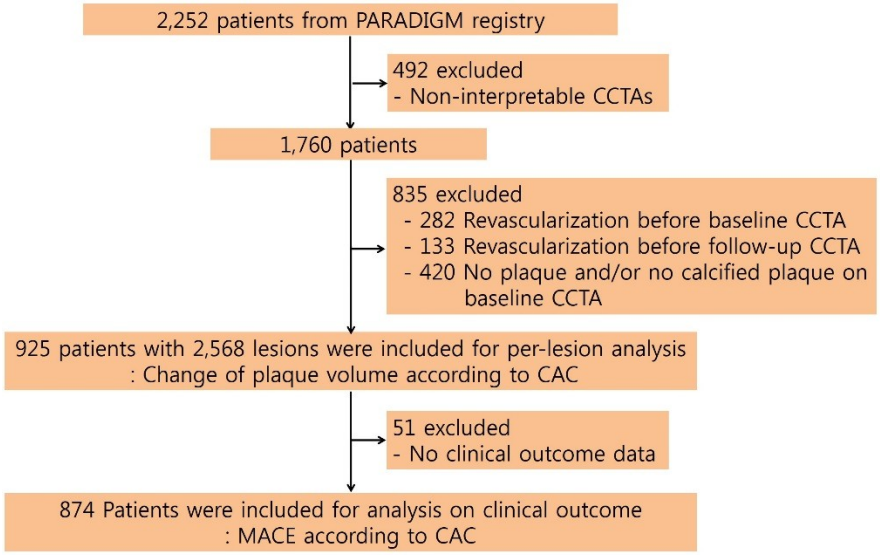
Central Illustration The role of percent calcified plaque volume in the natural history of CAD.

The percent calcified plaque volume reflects both the plaque burden and extent of lesion calcification. Despite showing the same change in plaque calcification, the character and change in lesions may be completely different. Percent calcified plaque volume delineating the natural history of coronary artery disease in lesions as representing both coronary calcification and plaque burden.



PV = plaque volume; CAC = coronary artery calcification

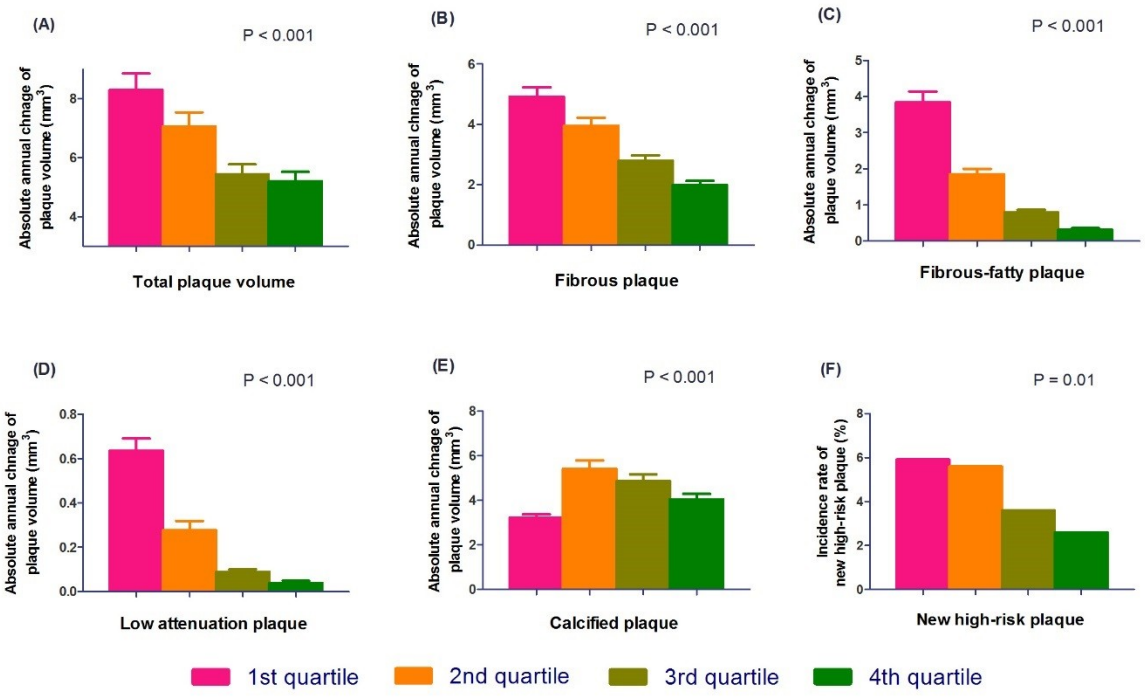
Figure 1. Flow chart of study population



CAC = coronary artery calcification; CCTA = coronary computed tomography angiography; MACE = major adverse cardiac event

Figure 2. Comparisons of volume change in plaque and its constituent elements according to percent calcified plaque volume quartile.

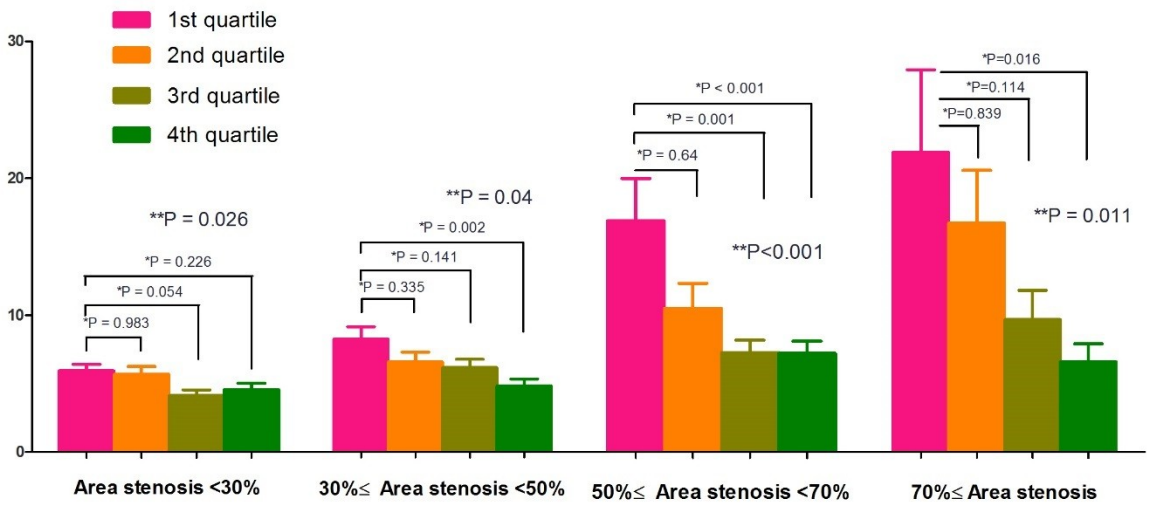
Lesions with higher PCPV were associated with lower rates of change of PV in plaque and its composition (A-D), and lower incidence of new high-risk plaque (F) across the four quartiles of PCPV



PCPV = percent calcified plaque volume

Figure 3. Severity of coronary artery disease and change in plaque volume

Regardless of disease severity, there were significant differences in PV change between quartile groups. These differences between the quartiles were the most pronounced in more severe stenosis.



*P value is for two group comparison by Scheffe's post hoc test, and **P value is for four group comparison by one-way ANOVA

PV = plaque volume

Figure 4. The survival rate free from MACE according to percent calcified plaque volume and calcified plaque volume

Kaplan-Meier analysis showed that the MACE-free survival was highest in patient with high PCPV and low CPV (97.6%, log rank p < 0.001)

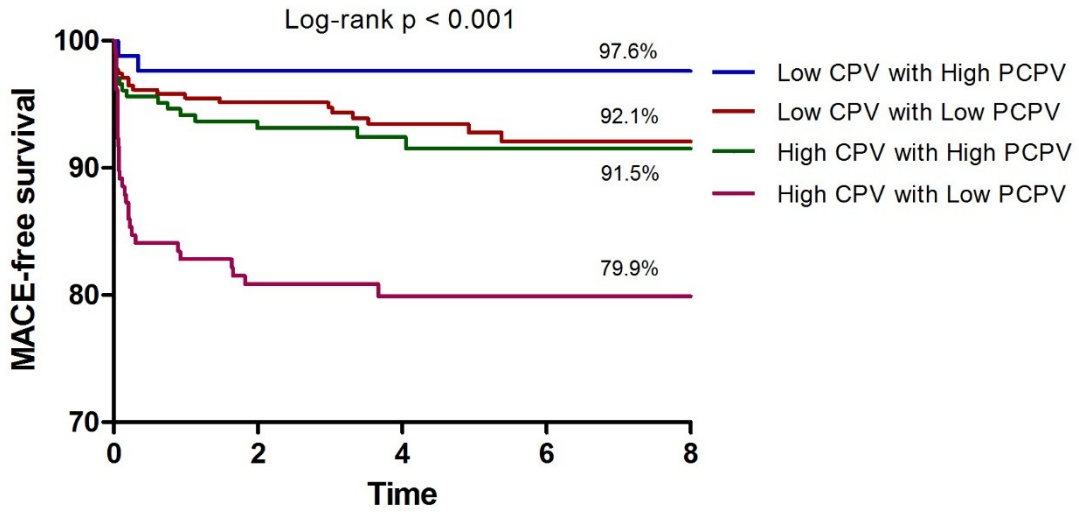


Table 1. Baseline characteristics

	Study population (n = 925)
Age, years	61.9 ± 8.95
Male gender, n (%)	553 (59.8)
Follow-up interval of CCTA, yr	3.74 ± 1.53
BMI, kg/m^2	25.4 ± 3.40
Current smoker, n (%)	176 (19.0)
Diabetes mellitus, n (%)	209 (22.6)
Hypertension, n (%)	518 (56.0)
Dyslipidemia, n (%)	384 (41.5)
Familial history of CAD, n (%)	268 (29.0)
HbA1C, %	6.38 ± 1.14
Total cholesterol, mg/dl	189.9 ± 38.7
LDL-cholesterol, mg/dl	114.5 ± 34.1
Serum Creatinine, mg/dl	1.0 ±0.52
Medication, n (%)	
Aspirin	373 (40.3)
Beta blockers	243 (26.3)
CCB	213 (23.0)
ACEI/ARB	278 (30.1)
Statins, n (%)	404 (43.7)

Values are numbers (%) or mean ± SD.

CCTA= coronary computed tomography angiography; BMI = body mass index; CAD = Coronary artery disease; HbA1c = hemoglobin A1c; LDL = low-density lipoprotein; CCB = calcium channel blocker; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker

Table 2. Coronary plaque characteristics on baseline CCTA, by Quartile of percent calcified plaque Volume

	Percent calcified plaque volume, Quartile					Total lesions (n = 2,568)
	1 (n = 642)	2 (n = 643)	3 (n = 641)	4 (n = 643)	*P value	
PCPV range (%)	0.01-17.1	17.2-40.0	40.1-63.5	63.6-99.6	<0.001	41.2 ± 27.4
Lesion length, mm	23.2 ± 13.8	23.6 ± 15.8	22.8 ± 15.6	21.2 ± 14.9	0.027	22.7 ± 14.8
Total PV, mm^3	54.2 ± 77.9	52.4 ± 83.8	47.0 ± 75.0	40.5 ± 70.9	0.007	48.5 ± 77.2
Fibrous PV, mm^3	30.6 ± 41.0	29.0 ± 45.3	19.9 ± 31.0	8.9 ± 15.8	<0.001	22.1 ± 36.2

Fibro-fatty PV, mm^3	17.8 ± 30.1	8.0 ± 16.0	2.7 ± 6.9	0.6 ± 2.4	<0.001	7.3 ± 18.7
Calcified PV, mm^3	3.7 ± 7.5	14.8 ± 25.1	24.3 ± 38.7	31.1 ± 54.8	<0.001	18.5 ± 37.4
Necrotic core volume, mm^3	2.1 ± 6.0	0.6 ± 2.0	0.2 ± 0.9	0.04 ± 0.3	<0.001	0.75 ± 3.3
Plaque burden, mm^3	39.5 ± 17.4	39.3 ± 16.6	40.7 ± 17.6	42.9 ± 16.6	<0.001	40.6 ± 17.1
Area stenosis, %	29.8 ± 18.8	31.7 ± 19.2	32.5 ± 19.4	34.6 ± 19.9	<0.001	32.2 ± 19.4
Low-attenuation plaque, n (%)	135(21.0)	36(8.4)	10(3.1)	2(0.3)	<0.001	211(8.2)
Spotty calcium, n (%)	139 (21.7)	111(17.3)	48(7.5)	18(2.8).	<0.001	316 (12.3)
Positive remodelling, n (%)	487 (75.9)	435 (67.7)	449 (70.0)	449 (69.9)	0.01	1820 (70.9)
Napkin-ring sign, n (%)	3 (0.5)	4 (0.6)	0	0	0.06	7 (0.3)
High risk plaque, n (%)	250 (9.7)	82 (12.0)	33(1.3)	4(0.2)	<0.001	369 (14.4)

Results are expressed in numbers (%) or mean ± SD. *P value is for the overall comparison among the groups by ANOVA or Pearson Chi-square test.

PCPV = percent calcified plaque volume; PV = plaque volume; CCTA = coronary computed tomography angiography

Table 3. Variables associated with the change of plaque volume in linear regression model

	Univariable		Multivariable	
	Correlation coefficient	p	Unstandardized coefficient (95% CI)	p
Percent calcified PV	-0.110	< 0.001	-0.028 (-0.044 to-0.012)	0.002
Calcified PV	0.297	< 0.001	-0.008 (-0.025 to 0.08)	0.327
Total PV	0.483	< 0.001	-*	
Necrotic core volume	0.253	< 0.001	0.281 (0.150 to 0.412)	< 0.001
Mean plaque burden	0.113	< 0.001	0.013 (0.171 to 0.452)	< 0.001
Lesion length	0.342	< 0.001	0.287 (0.245 to 0.329)	< 0.001
Area stenosis	0.173	< 0.001	-0.022 (-0.426 to 0.001)	0.057
Any HRP	0.191	< 0.001	0.032 (-1.168 to 1.231)	0.571
Spotty calcification	0.121	< 0.001		
Low attenuation plaque	0.209	< 0.001		
Positive remodelling	0.130	< 0.001		
Napkin-ring sign	0.057	0.004		

* Total PV was excluded in the multivariable model due to strong correlation with CPV

CPV = calcified plaque volume, PV = plaque volume, HRP = high-risk plaque

Table 4. Baseline clinical characteristics and CCTA findings

	Total (n = 874)	Low PCPV (PCPV < 40%, n = 533)	High PCPV (PCPV ≥ 40%, n = 341)	P value*
Age, years	62.1 ± 9.1	60.4 ± 9.1	64.8 ± 8.4	<0.001
Male, n (%)	509 (58.2)	335 (65.8)	198 (54.2)	0.001
Body mass index, kg/m^2	25.3 ± 3.3	25.6 ± 3.5	24.7 ± 2.9	<0.001
Diabetes mellitus, n (%)	225 (25.9)	136 (25.7)	89 (26.2)	0.878
Hypertension, n (%)	550 (63.4)	324 (61.2)	226 (66.9)	0.094
Dyslipidemia, n (%)	525 (60.8)	182 (34.3)	157 (47.0)	<0.001
Current smoker, n (%)	177 (20.4)	117 (22.1)	60 (17.8)	0.467
Family history of CAD, n (%)	247 (28.3)	141 (26.5)	106 (12.1)	0.120
Ethnicity				0.036
African	45 (5.1)	22 (4.1)	23 (6.7)	
Caucasian	140 (16)	74 (13.9)	66 (19.4)	
Asian	687 (78.6)	436 (81.8)	251 (36.5)	
Latin American	2 (0.2)	1 (0.2)	1 (0.3)	
Symptom				
Non cardiac CP	87 (10.0)	56 (10.5)	31 (9.2)	0.519
Atypical CP	645 (74.3)	399 (75.1)	246 (73.0)	0.481
Typical CP	48 (5.5)	31 (5.8)	17 (5.0)	0.618
Laboratory findings				
Total cholesterol, mg/dl	186.3 ± 39.1	188.1 ± 41.1	183.2±35.1	0.1
LDL cholesterol, mg/dl	113.2 ± 35.2	115.3 ± 37.2	109.6 ± 31.4	0.033

Serum Creatinine, mg/dl	0.99 ± 0.53	0.98 ± 0.33	1.01 ± 0.74	0.478
HbA1c, %	6.4 ± 1.2	6.44±1.2	6.38 ±1.1	0.643
Medication, n (%)				
Aspirin	397 (46.4)	234 (44.8)	163 (48.9)	0.239
Beta blockers	232 (27.2)	133 (25.5)	99 (29.8)	0.170
ACEI/ARB	286 (33.6)	163 (31.5)	123 (37.0)	0.093
Statins, n (%)	407 (50.2)	223 (44.5)	184 (59.5)	<0.001
Baseline CCTA findings				
% Calcified PV, %	34.7 ±25.1	17.7 ± 12.6	61.4 ± 14.2	<0.001
Lesion length, mm^3	389.3 ± 125.7	398.8 ± 121.5	374.6 ± 131.0	0.006
Total PV, mm^3	160.2 ± 203.7	141.4 ± 159.5	189.5 ± 255.5	0.002
Fibrous PV, mm^3	70.4 ± 86.6	73.8 ± 85.6	65.1 ± 88.0	0.148
Fibrous-fatty PV, mm^3	25.5 ± 39.1	36.2 ± 44.7	8.6 ± 18.1	<0.001
Calcified PV, mm^3	61.6 ±118.2	27.2 ± 44.3	115.3± 167.6	<0.001
Necrotic core volume, mm^3	2.9 ± 6.9	4.2 ± 8.4	0.75 ± 2.45	<0.001
Mean plaque burden, %	58.7 ±56.8	53.7 ± 50.4	66.5 ± 64.8	0.002
Inter-scan interval, years	3.5 ± 1.3	3.6 ± 1.3	3.2 ±1.2	0.341

Values are numbers (%) or mean ± SD. PCPV indicated percent calcified plaque volume; CAD = coronary artery disease; CP = chest pain; LDL = low density lipoprotein; HbA1c = hemoglobin A1c; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCTA = coronary computed tomography angiography; PV= plaque volume

Table 5. Clinical outcomes between two groups

	Low PCPV (n = 533)	High PCPV (n = 341)	P value*
Composite of MACE	78 (14.6)	32 (9.4)	0.022
Non-fatal myocardial infarction	1 (0.2)	0	0.424
Death from any cause	5 (0.9)	5(1.5)	0.474
Cardiac	1 (0.2)	2 (0.6)	
Noncardiac	4 (0.8)	3 (0.9)	
Revascularization	76 (14.3)	30 (8.8)	0.016
PCI	75 (14.1)	29 (8.5)	
CABG	1 (0.2)	1 (0.3)	

Values are numbers (%) MACE indicated Major adverse cardiovascular events; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft

Table 6. Predicting factors for the composite of major cardiovascular events

	Univariable analysis			
	Unadjusted		Adjusted†	
	HR (95% CI)	P value	HR (95% CI)	P value
High percent calcified PV	0.574 (0.349-0.946)	0.029	0.559 (0.331-0.942)	0.029
High calcified PV	2.598 (1.608-4.197)	<0.001	2.649 (1.600-4.386)	<0.001
High total PV	2.135 (1.341-3.399)	0.001	2.089 (1.285-3.398)	0.003
High mean plaque burden	2.744 (1.688-4.459)	<0.001	2.722 (1.639-4.518)	<0.001
High necrotic core volume	3.029 (1.838-4.991)	<0.001	3.192 (1.891-5.390)	<0.001

	Multivariable analysis††	
	HR (95% CI)	P value
High percent calcified PV	0.526 (0.286-0.968)	0.039
High calcified PV	3.009 (1.582-5.724)	0.001
High total PV	2.035 (0.964-4.296)	0.062
High mean plaque burden	1.630 (0.785-3.385)	0.190
High necrotic core volume	2.130 (1.115-4.069)	0.022
Age >70 years	1.147 (0.691-1.904)	0.595
Male	1.078(0.651-1.784)	0.335
Smoking	1.088 (0.666-1.777)	0.737
Diabetes mellitus	1.274 (0.787-2.060)	0.387
Hypertension	1.313 (0.788-2.188)	0.131
Dyslipidemia	0.815 (0.493-1.346)	0.887
Familial history of CAD	0.996(0.585-1.695)	0.988
Statin use	0.526 (0.296-0.933)	0.028

High volume of plaque and its composition were defined as above median value of each variable
The 5 separate parameters in baseline CCTA were each applied in a univariate Cox proportional hazards regression
† Models were adjusted for the following covariates: age, gender, smoking, diabetes, hypertension familial history of CAD and dyslipidemia.
†† All clinical risk factors, variables of CCTA and statin use were applied together in a multivariate Cox proportional hazards regression.

PV = plaque volume; CAD=coronary artery disease