의학석사 학위논문

관상동맥 전산화 단층 촬영 혈관 조영술의 전 관상동맥 경화반 정량화를 통한 예후 예측

2020 년 2 월

서울대학교 대학원

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양 석 훈

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A thesis of the Master's degree

Prognostic Implications of Comprehensive Whole Vessel Plaque Quantification Using Coronary Computed Tomography Angiography in Patients with Coronary Artery Disease

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Aims: We aimed to investigate the prognostic implications of whole vessel plaque quantification using coronary CT angiography (CCTA).

Methods and Results: A total of 1,013 vessels (643 patients) with fractional flow reserve (FFR) measurement and available CCTA were analyzed. The primary endpoint was the vessel-oriented composite outcome (VOCO, a composite of cardiac death, target vessel myocardial infarction or target vessel revascularization) at 5 years. Minimum lumen area $<4mm^2$, plaque burden $\geq 70\%$, low attenuating plaque, positive remodeling, spotty calcification, and napkin-ring sign were defined as high risk plaque characteristics (HRPC). In a target vessel, total plaque volume $\geq 306.5mm^3$, fibrofatty and necrotic core volume $\geq 4.46mm^3$, or percent total atheroma volume $\geq 32.2\%$, based on corresponding optimal cut-off values for 5-year VOCO, was

defined as high risk vessel characteristics (HRVC). In predicting FFR ≤0.80, whole vessel plaque quantification had incremental predictability in addition to % diameter stenosis and HRPC. Among 517 deferred vessels (368 patients) based on FFR >0.80, the components of HRVC had higher information gain than those of HRPC in predicting VOCO. The number of HRVC was significantly associated with the risk of VOCO (HR 2.54, 95% CI 1.77-3.64). In a landmark analysis at 2 years, the number of HRVC showed sustained prognostic implications beyond 2 years (HR 2.49, 95% CI 1.59-3.90) but the number of HRPC did not. The number of HRVC can discriminate the prognosis in subgroups with either ≥3 HRPC or <3 HRPC.

Conclusion: Whole vessel plaque quantification can provide incremental predictability for low FFR and has prognostic value in deferred vessels with high FFR.

Key Words: coronary artery disease; coronary CT angiography; ischemia; fractional flow reserve; prognosis.

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Abbreviations

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

FFNC = fibrofatty and necrotic core

FFR = fractional flow reserve

HR = hazard ratio

HRPC = high risk plaque characteristics

HRVC = high risk vessel characteristics

MLA = minimum lumen area

VOCO = vessel-oriented composite outcome

Introduction

The atherosclerotic burden or disease extent in entire epicardial coronary arteries is a prognostic indicator in patients with coronary artery disease (CAD). (1-3) Nevertheless, the current framework of evaluating CAD has been largely focused on identifying significant local stenosis and its revascularization.

Coronary CT angiography (CCTA) is an evolving noninvasive modality in the diagnosis of CAD and its incremental prognostic value over clinical risk factors has been well demonstrated in previous studies. (4,5) Beyond the assessment of severity and extent of obstructive CAD, CCTA provides detailed information on qualitative and quantitative plaque characteristics. (6) Previous studies demonstrated that high risk or adverse plaque characteristics on CCTA have a prognostic value in the prediction of future clinical events. (7-11) Furthermore, CCTA can also provide 2-dimensional and 3-dimensional quantification of total plaque and the individual component of atherosclerotic plaque of an entire vessel beyond the target lesion or plaque. (10,12)

Considering the diversity of coronary atherosclerosis, a reasonable approach to identify high risk patients for future clinical events would be the assessment of both target lesion and whole vessel atherosclerotic burden. However, CCTA-based whole vessel plaque quantification requires additional medical resources, and its role in defining functional significance of CAD or in risk assessment after deferral of revascularization according to fractional flow reserve

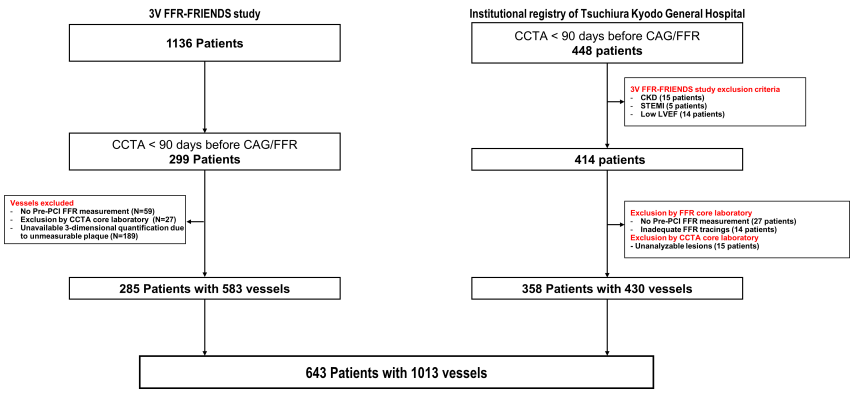
(FFR) has not been thoroughly assessed. In this regard, we sought to investigate the clinical implications of CCTA-based whole vessel plaque quantification over conventional plaque assessment in defining the functional significance of target vessel and risk stratification for patients with high FFR.

Methods

Study population

The study population was derived from the 3V FFR-FRIENDS study (3-vessel fractional flow reserve for the assessment of total stenosis burden and its clinical impact in patients with coronary artery disease, NCT01621438) and institutional registry of Tsuchiura Kyodo General Hospital. For this study, patients who underwent CCTA within 90 days of FFR measurement were included (Fig. 1).

Figure 1. Study flow



All data were collected at the core laboratories and independent screening and analyses were performed for FFR, angiographic, and CCTA data. The study protocol was approved by the Institutional Review Board or Ethics Committee at each participating center, and all patients provided written informed consent (Clinical Trial Registration Information: NCT04037163). CCTA was performed as part of routine clinical practice for patients with suspected CAD. Patients with depressed left ventricular systolic function (ejection fraction <35%), acute ST-elevation myocardial infarction (MI) within 72 hours, previous coronary artery bypass graft surgery (CABG), chronic kidney disease, abnormal epicardial coronary flow (TIMI flow <3) or planned CABG after diagnostic angiography were excluded. A part of the current study population was included in another published study. (11)

Coronary CT Angiography and Analysis of Plaque Characteristics

CCTA images were obtained in accordance with the Society of Cardiovascular Computed Tomography (SCCT) Guidelines on Performance of CCTA, with 64- or higher detector row scanner platforms. The CCTA images were analyzed at a core laboratory (Severance Cardiovascular Hospital, Seoul, Korea) in a blinded fashion. CCTA analysis was performed in 3 steps. First, qualitative

plaque characteristics was analyzed according to the definitions from previous studies. (6,7,11) The presence of the following adverse plaque characteristics was identified in a core laboratory: 1) low-attenuation plaque (average density ≤30 Hounsfield unit [HU] from 3 random region-of-interest measurements with approximately 0.5 to 1.0mm^2 in noncalcified low CT attenuation portion of the plaque); 2) positive remodeling (remodeling index ≥1.1); 3) spotty calcification (average density >130 HU, diameter <3 mm in any direction, and length of the calcium <1.5 times the vessel diameter, and width of the calcification less than two-thirds of the vessel diameter); and 4) napkin-ring sign (ring-like attenuation pattern with peripheral high attenuation tissue surrounding a central lower attenuation portion). Second, cross-sectional quantitative analysis of target stenosis, including minimum lumen area (MLA), plaque burden, and area stenosis, was performed as previously described. (11) Third, 3-dimensional plaque quantification was performed for both target stenosis and target vessels, (10,13) using semiautomated plaque analysis software (QAngioCT Research Edition version 2.1.9.1, Medis Medical Imaging Systems, Leiden, the Netherlands) with appropriate manual correction. For each segment of the 18-segment SCCT model with a diameter ≥ 2 mm, quantitative analysis was performed on every 1-mm cross-section to measure vessel length, vessel volume, atheroma volume, mean plaque burden, and plaque composition using pre-defined HU thresholds: necrotic core (-30 to 30 HU), fibrofatty (30 to 130 HU), fibrous (131 to 350 HU), and calcified plaque (≥350

HU). (10)

The semi-automated method to quantify plaque volume has been validated with intravascular ultrasound (IVUS) images as reference. (13,14) Quantitative CCTA analysis and IVUS with virtual histology were significantly correlated in previous studies. (15,16) The software provided automatically drawn centerline from the ostium to the distal part of the coronary artery. Then, multi-planar images were constructed, and the borders of the lumen and vessels were identified in four different cut planes. These lines were modified by the independent level III-experienced observers who were blinded to clinical and invasive angiographic data if needed. (12-14) Intraobserver, interobserver, and interscan reproducibility of the quantitative CCTA analysis in the core laboratory has been demonstrated. (17) In particular, the reproducibility and reliability of the 2-dimensional and 3-dimensional plaque analysis of the core laboratory were validated and showed consistency in the analysis for 2 paired different CCTA scans within 90 days, regardless of tube voltages used. (12)

Angiographic Analysis and Coronary Physiologic Measurements

Coronary angiography was performed utilizing standard techniques. Continuous intravenous infusion of adenosine (140 μg/kg/min) or ATP (160 μg/kg/min) was administered to induce

hyperemia for FFR measurement. Hyperemic proximal aortic pressure and distal arterial pressure were obtained. FFR was estimated as the lowest average of 3 consecutive beats during adenosine infusion. All pressure readings were gathered and validated at the core laboratory in a blinded fashion.

Patient Follow Up, Outcome Measurements and Adjudication of Clinical Events

Clinical data were obtained at outpatient clinic visits or by telephone contact when needed. An independent clinical events committee whose members were unaware of clinical, angiographic and physiologic data adjudicated all events. The primary outcome was the vessel-oriented composite outcome (VOCO), which included cardiac death, vessel-related myocardial infarction (MI), or vessel-related ischemia-driven revascularization. (11,18)

Definitions of High Risk Plaque Characteristics and High Risk Vessel Characteristics

For target stenosis or plaque, HRPC was defined as a plaque with MLA $<4mm^2$, plaque burden $\geq 70\%$, low attenuation plaque, positive remodeling, spotty calcification, or napkin-ring sign, based on previous literature. (2,3,6,7,9,11) For plaque quantification in whole vessel, total plaque volume, fibrofatty and necrotic core (FFNC) component volume, and percent total atheroma volume were selected

as clinically relevant parameters from previous studies. (10,19,20) high risk vessel characteristics (HRVC) were defined as a vessel with total plaque volume per vessel ≥306.5 mm^3, FFNC component volume per vessel ≥4.46 mm^3 or percent total atheroma volume ≥32.2%, based on binary classification using the corresponding optimal cut-off values to predict VOCO at 5 years.

Statistical Analysis

Categorical variables were presented as numbers and relative frequencies (percentages), and continuous variables as means and standard deviations or median with interquartile range (Q1-Q3) according to their distribution, which was checked by the Kolmogorov-Smirnov test. Categorical variables were compared using the Chi-square test and continuous variables, by the Student's t-test or Wilcoxon rank sum test as appropriate. The analysis consisted of two parts. First, using total cohort (1,013 vessels from 643 patients), discrimination ability of % diameter stenosis from CCTA, HRPC, and whole vessel plaque quantification for defining functionally significant stenosis (FFR ≤0.80) was evaluated. In order to assess incremental discrimination ability, the likelihood ratio test was performed. Incremental predictability was defined as an increase in global chi-square value. Second, prognostic implications of CCTA-derived HRVC was evaluated among 517 deferred vessels from 368 patients based on FFR >0.80. For this, an information gain analysis was used to examine the relative importance of each component of HRPC or

HRVC in predicting VOCO at 5 years. Parameters with a higher information gain value can be assumed to have higher predictability for VOCO than ones with lower information gain. (21) A bootstrapping technique with 10,000 replicates was used as a sensitivity analysis. In order to separately analyze the prognostic impact of HRPC and HRVC according to different time frames, exploratory landmark analysis at 2 years was performed. To investigate the additive clinical implications of HRVC, the risk of VOCO according to number of HRVC was compared in the subgroups of ≥3 HRPC and <3 HRPC. Optimal cut-off values of parameters from whole vessel plaque quantification to discriminate the occurrence of VOCO were calculated using a method of maximally selected log-rank statistics. Data were analyzed on a per-vessel basis for comparison of lesion characteristics, physiologic indices, and vessel-specific clinical outcomes. Correlation coefficient was measured using Pearson correlation or Spearman correlation, as appropriate. In comparisons of clinical outcomes between groups, event rates were calculated based on Kaplan-Meier censoring estimates and presented with the cumulative incidence, and the log-rank test or the Breslow test was used to compare survival curves between groups. Marginal Cox proportional hazard regression was used to calculate hazard ratio and 95% confidence interval to compare between-group differences for a per-vessel comparison of cumulative incidence of target vessel-related events. The assumption of proportionality was assessed graphically by log-minus-log plot, and Cox proportional hazard

models for all clinical outcomes satisfied the proportional hazards assumption. All probability values were two-sided and p-values <0.05 were considered statistically significant. All analyses were performed using R language version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of Patients and Lesions

Baseline patient and lesion characteristics are shown in Table 1. Most patients presented with stable coronary artery disease (80.6%). The mean angiographic % diameter stenosis and FFR were 48.5±17.4%, and 0.81±0.14, respectively. Mean or median value of MLA, total plaque volume, and percent total atheroma volume were 3.2±2.2mm^2, 143.5mm^3 (Q1-Q3: 65.1-257.1) and 21.9% (Q1-Q3: 11.4-32.5), respectively.

Table 1. Baseline patient and lesion characteristics

	Total	Deferred with FFR > 0.80
Patients	**N=643**	**N=368**
General characteristics		
Age (years)	66.1 ± 10.0	65.9 ± 9.6
Male	481 (74.8)	255 (69.3)
Previous MI	33 (5.1)	12 (3.3)
Ejection fraction	64.0 ± 7.5	63.7 ± 7.2

Cardiovascular risk factors		
Hypertension	445 (69.2)	246 (66.8)
Diabetes mellitus	228 (35.5)	129 (35.1)
Hypercholesterolemia	369 (57.4)	209 (56.8)
Current smoker	163 (25.4)	83 (22.6)
Clinical presentations		
Stable coronary artery disease	518 (80.6)	304 (82.6)
Unstable angina	72 (11.2)	45 (12.2)
NSTEMI	53 (8.2)	19 (5.2)
Lesions	**N=1,013**	**N=517**
Location		
Left anterior descending artery	544 (53.7)	200 (38.7)
Left circumflex artery	204 (20.1)	138 (26.7)
Right coronary artery	265 (26.2)	179 (34.6)
Quantitative coronary angiographic findings		
Diameter stenosis, %	48.5 ± 17.4	40.0 ± 15.0
Lesion length, mm	13.0 ± 9.5	10.0 ± 7.0
Minimal lumen diameter, mm	1.5 ± 0.6	1.9 ± 0.6
Reference diameter, mm	2.9 ± 0.6	3.0 ± 0.6
CCTA parameters		
Minimal lumen area, mm^2	3.2 ± 2.2	4.1 ± 2.4
Plaque burden, %	64.8 ± 18.9	57.4 ± 18.1
Distance from coronary ostium to MLA, mm	38.3 ± 22.9	39.5 ± 24.8
Area stenosis, %	56.4 ± 22.8	48.1 ± 21.0
Remodeling index	1.09 ± 0.43	1.06 ± 0.36

Plaque burden ≥ 70%	453 (44.7)	147 (28.4)
Minimal lumen area < 4 mm^2	744 (73.4)	303 (58.6)
Adverse plaque characteristics		
Low attenuation plaque	219 (21.6)	71 (13.7)
Positive remodeling	432 (42.6)	195 (37.7)
Spotty calcification	129 (12.7)	64 (12.4)
Napkin -ring sign	11 (1.1)	2 (0.4)
Whole vessel plaque quantification		
Total plaque volume, mm^3	143.5 [65.1, 257.1]	104.2 [47.2, 211.5]
FFNC component volume, mm^3	17.0 [2.6, 50.7]	7.8 [0.5, 33.3]
Percent total atheroma volume, %	21.9 [11.4, 32.5]	17.1 [7.9, 27.2]

Values are n (%) for categorical variables and mean ± SD or median [Interquartile] for continuous variables.

Abbreviations: CCTA, coronary computed tomography angiography; FFNC, fibrofatty and necrotic core; FFR, fractional flow reserve; HRPC, high risk plaque characteristics; MLA, minimum lumen area; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction

Association of CCTA Parameters with Functional Significance

Vessels with FFR≤0.80 showed significantly lower MLA, and higher plaque burden, area stenosis, the proportion of HRPC except for spotty calcification, total plaque volume per vessel, FFNC component volume per vessel, and percent total atheroma volume (Table 2).

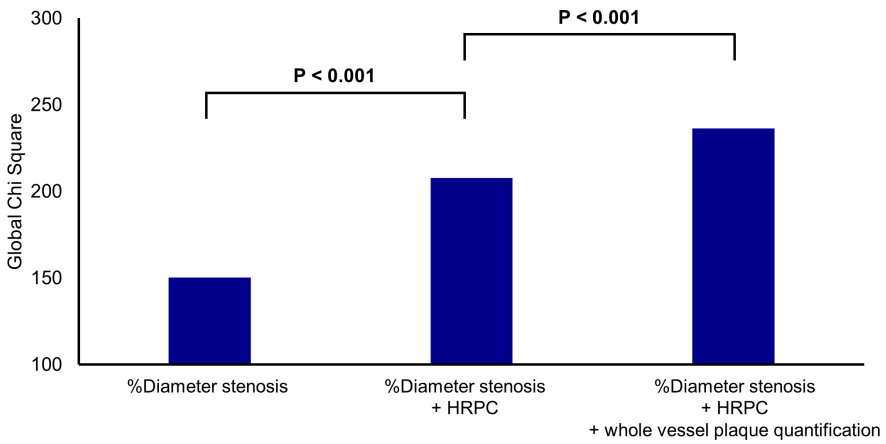
Table 2. Lesion characteristics according to functional significance

	FFR > 0.80 (N=576)	FFR ≤ 0.80 (N=437)	p-value
CCTA parameters			
Minimum lumen area, mm^2	4.0 ± 2.4	2.3 ± 1.4	<0.01
Plaque burden, %	58.6 ± 18.1	72.9 ± 16.9	<0.01
Distance from coronary ostium to MLA, mm	39.3 ± 24.5	37.0 ± 20.6	0.10
Area stenosis, %	49.5 ± 21.2	65.6 ±21.4	<0.01
Remodeling index	1.07 ± 0.37	1.12 ± 0.48	0.04
Plaque burden ≥70%	176 (30.6)	277 (63.4)	<0.01
Minimum lumen area <4 mm^2	352 (61.1)	392 (89.7)	<0.01
Adverse plaque characteristics			
Low attenuation plaque	87 (15.1)	132 (30.2)	<0.01
Positive remodeling	220 (38.2)	212 (48.5)	0.01
Spotty calcification	70 (12.2)	59 (13.5)	0.59
Napkin-ring sign	2 (0.3)	9 (2.1)	0.02
Whole vessel plaque quantification			
Total plaque volume, mm^3	111.3 [52.2;215.5]	188.7 [98.7;296.8]	<0.01
FFNC component volume, mm^3	9.5 [0.8;35.6]	27.8 [9.2;69.2]	<0.01
Percent total atheroma volume, %	17.6 [8.4, 27.4]	27.1 [17.4, 37.6]	<0.01

Abbreviations: CCTA, coronary computed tomography angiography; FFNC, fibrofatty and necrotic core; FFR, fractional flow reserve; HRPC, high risk plaque characteristics; MLA, minimum lumen area.

There were significant correlations between FFR and total plaque volume (r= -0.228, P<0.001), FFNC component volume (r= -0.287, P<0.001), and percent total atheroma volume (r= -0.332, P<0.001). In the prediction of functional significance by FFR ≤0.80, the addition of HRPC showed significantly increased discrimination ability than % diameter stenosis alone. The addition of parameters from whole vessel plaque quantification showed further increased discrimination ability than % diameter stenosis and HRPC (Fig. 2).

Figure 2. Additive predictive value of whole vessel plaque quantification over % diameter stenosis and HRPC for functional significance.



Prognostic Implications of High Risk Plaque and Vessel Characteristics

Among the 517 deferred vessels with FFR > 0.80, plaque burden ≥70%, total plaque volume ≥306.5 mm^3, FFNC component volume ≥4.46 mm^3, and percent total atheroma volume ≥32.2% were predictors of VOCO at 5 years after multivariable adjustment. (Table 3).

Table 3. Risk of VOCO according to atherosclerotic features

	N (%)	Unadjusted HR (95% CI)	p -value	Adjusted HR (95% CI)[a]	p -value
HRPC					
Low attenuation plaque	71 (13.7)	2.51 (0.93-6.77)	0.07	2.37 (0.93-6.05)	0.07
Positive remodeling	195 (37.7)	1.83 (0.85-3.96)	0.13	2.25 (0.96-5.28)	0.06
Spotty calcification	64 (12.4)	0.91 (0.28-3.02)	0.88	0.74 (1.92-2.84)	0.66
Napkin-ring sign	2 (0.4)	NA	NA	NA	NA
Plaque burden ≥ 70%	147 (28.4)	3.24 (1.43-7.35)	0.01	3.43 (1.33-8.86)	0.01
MLA < 4 mm^2	303 (58.6)	1.92 (0.79-4.64)	0.15	1.35 (0.59-3.10)	0.47
Number of HRPC	-	1.80 (1.22-2.67)	<0.01	1.82 (1.14-2.90)	0.01
HRVC					

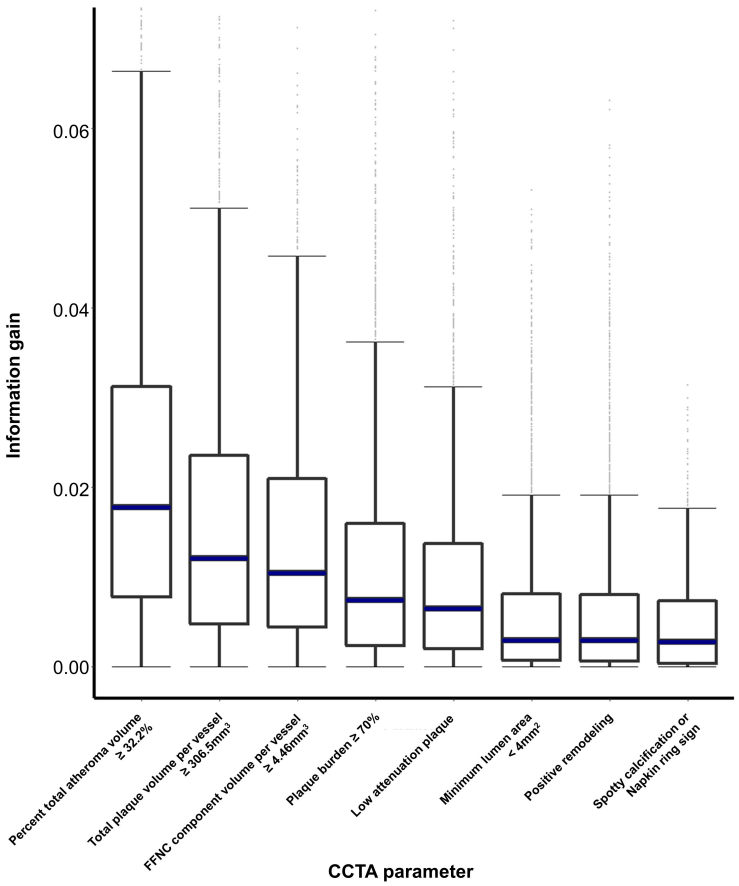
Total plaque volume ≥ 306.5 mm^3	58 (11.2)	4.51 (1.78–11.39)	<0.01	3.63 (1.39–9.50)	<0.01
FFNC component volume ≥ 4.46 mm^3	302 (58.4)	3.90 (1.36–11.18)	0.01	3.57 (1.26–10.07)	0.02
Percent total atheroma volume ≥ 32.2%	82 (15.9)	5.33 (2.20–12.91)	<0.01	4.66 (1.88–11.59)	<0.01
Number of HRVC	-	2.61 (1.78–3.81)	<0.01	2.54 (1.77–3.64)	<0.01

[a], Adjusted for the number of clinical risk factors (age ≥ 65 years, history of diabetes mellitus, hypertension, hyperlipidemia, myocardial infarction, current smoking), FFR and % diameter stenosis.

Abbreviations: CI, confidence interval; FFR, fractional flow reserve; HR, hazard ratio; HRPC, high risk plaque characteristics; HRVC, high risk vessel characteristics; MLA, minimum lumen area; VOCO, vessel-oriented composite outcome.

By information gain ranking criteria, percent total atheroma volume ≥32.2% showed the highest information gain followed by total plaque volume ≥306.5 mm^3, FFNC component volume ≥4.46 mm^3, plaque burden ≥70%, and the presence of low attenuation plaque in the prediction of VOCO at 5 years (Fig. 3).

Figure 3. Relative importance among HRVCs and HRPCs in deferred vessels with FFR >0.80.



The cumulative risk of VOCO increased according to the number of HRPC (3.8%, 4.8%, 6.5%, and 18.8%, log-rank P<0.001 in the vessel with 0, 1, 2, and ≥3 HRPC, respectively) and the number of HRVC (1.7%, 5.5%, 27.5% in vessels with 0, 1, and ≥2 HRVC, respectively, log-rank P<0.001) (Fig. 4 and Table 4).

Figure 4. Prognostic implications of the number of HRVC.

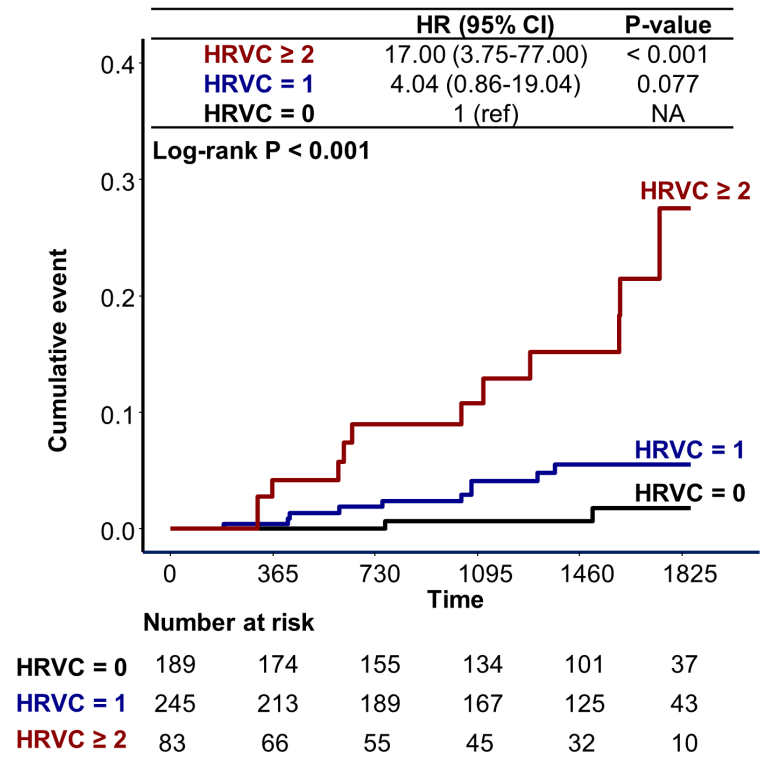


Table 4. VOCO according to the number of HRVC

	HRVC = 0 (n=189)	HRVC = 1 (n=245)	HRVC ≥2 (n=83)	p-value
Vessel-related ischemia-driven revascularization	1.7% (2)	4.6% (8)	24.7% (10)	<0.01
Vessel-related myocardial infarction	1.7% (2)	2.7% (5)	0.0% (0)	0.36
Cardiac death	0.0% (0)	1.0% (2)	3.4% (2)	0.08
VOCO	1.7% (2)	5.5% (10)	27.5% (12)	<0.01

The cumulative incidence of clinical outcomes was presented as Kaplan-Meier estimates. Log-rank p value was presented.
Abbreviations: HRVC, high risk vessel characteristics; VOCO, vessel-oriented composite outcome.

Additive Prognostic Value of HRVC

The addition of the number of HRVC to % diameter stenosis and the number of HRPC significantly increased the predictability for 5-year VOCO (area under curve 0.755 vs 0.655, P=0.024). In the landmark analysis at 2 years, both the number of HRPC and the number of HRVC were predictors of VOCO at 2 years (HR 2.53, 95% CI 1.17-5.48, P=0.019 for the number of HRPC; HR 2.81, 95% CI 1.60-4.95, P<0.001 for the number of HRVC). However, in the prediction of VOCO after 2 years, only the number of HRVC was significantly associated with the risk of VOCO (HR 2.49, 95% CI 1.59-3.90, P < 0.001) (Table 5).

Table 5. Landmark analysis at 2 years according to the number of HRPC and HRVC

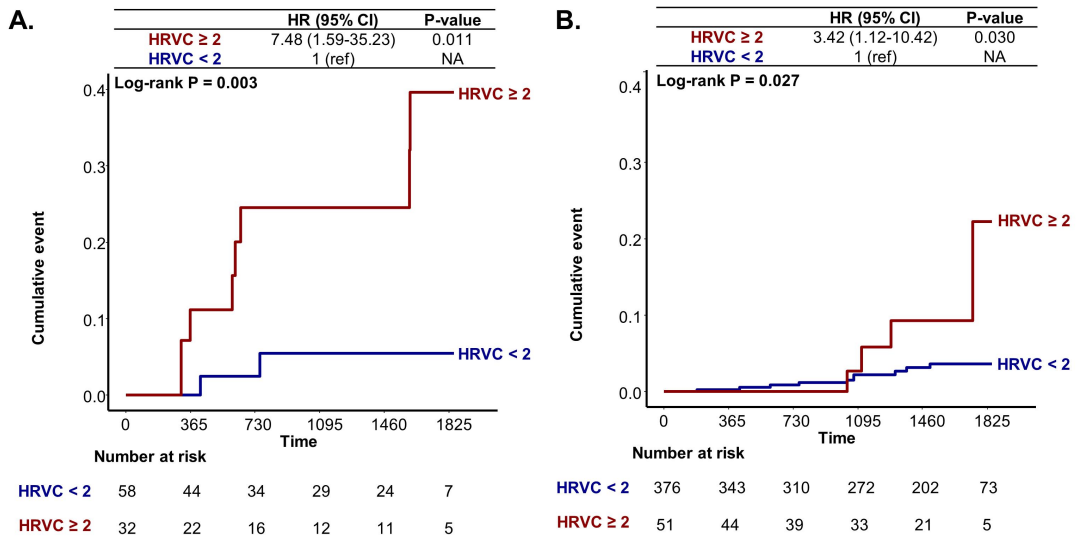
	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)[a]	p-value
VOCO at 2 years				
Number of HRPC	2.60 (1.50-4.53)	<0.01	2.53 (1.17-5.48)	0.02
Number of HRVC	3.25 (1.83-5.77)	<0.01	2.81 (1.60-4.95)	<0.01
VOCO after 2 years				
Number of HRPC	1.32 (0.82-2.13)	0.26	1.37 (0.81-2.30)	0.24

Number of HRVC	2.22 (1.39-3.54)	<0.01	2.49 (1.59-3.90)	<0.01

[a], Adjusted for the number of clinical risk factors (age ≥ 65 years, history of diabetes mellitus, hypertension, hyperlipidemia, myocardial infarction, current smoking), FFR and % diameter stenosis.
Abbreviations: CI, confidence interval; FFR, fractional flow reserve; HR, hazard ratio; HRPC, high risk plaque characteristics; HRVC, high risk vessel characteristics; VOCO, vessel-oriented composite outcome.

When the vessels were divided into 2 groups according to the number of HRPC, the number of HRVC was a still significant predictor of VOCO at 5 years in vessels with ≥3 HRPC (HR 2.55, 95% CI 1.27-5.10, P=0.008), and the risk of VOCO was significantly higher in vessels with ≥2 HRVC (HR 7.48, 95% CI 1.59-35.23, P=0.011) than vessels with <2 HRVC (Fig. 5A). Similarly, in vessels with HRPC <3, the number of HRVC was a significant predictor of VOCO at 5 years (HR 2.34, 95% CI 1.51-3.65, P<0.001), and the risk of VOCO was higher in vessels with ≥2 HRVC (HR 3.42, 95% CI 1.12-10.42, P=0.030) than vessels with <2 HRVC (Fig. 5B).

Figure 5. Cumulative incidence of VOCO according to the number of HRVC in vessels with (A) ≥3 HRPC and (B) <3 HRPC.



Discussion

The current study investigated the clinical relevance of whole vessel plaque quantification using CCTA in predicting the functional significance defined by FFR and the risk of future cardiovascular events in the deferred vessels with high FFR. The main findings were as follows. First, whole vessel plaque quantification showed incremental predictability for functional significance defined by FFR ≤0.80 over % diameter stenosis and HRPC. Second, the number of HRVC had an independent prognostic value for 5-year VOCO in deferred vessels with FFR >0.80. Each component of HRVC showed

higher information gain than the individual component of HRPC in predicting the occurrence of VOCO. Third, the number of HRVC was a significant predictor of VOCO, both within and beyond 2 years, in the landmark analysis.

Whole Vessel Plaque Quantification and Presence of Myocardial Ischemia

Presence of ischemia is a key prognostic factor in patients with CAD. (22,23) FFR is one of the standard indices used to define ischemia-causing stenosis and guide revascularization in a cardiac catheterization laboratory. (24) There have been several investigations for relevance of anatomical severity or plaque compositional characteristics from CCTA to predict the presence of vessel-related ischemia and stenosis severity, plaque geometry, and plaque compositional characteristics as the predictors of FFR. (20,25-27) Driessen, et al. reported that local plaque features such as positive remodeling, low attenuation, and non-calcified volume were significantly associated with decreased hyperemic myocardial blood flow or FFR (28), and most of the other studies also focused on the influence of local plaque characteristics on FFR. However, FFR itself is a per-vessel index that represents the physiologic disease burden of a whole vessel. (29) In this regard, we investigated the role of whole vessel plaque quantification using CCTA in defining the presence of ischemia assessed by FFR $\leq$0.80. In our study, vessels with FFR $\leq$0.80 had a significantly higher total plaque volume,

FFNC volume, and percent atheroma volume, and all these parameters showed a significant negative correlation with FFR. Furthermore, the addition of parameters from whole vessel plaque quantification improved the discrimination ability for FFR ≤0.80 compared to % diameter stenosis and HRPC. These results support the additive role of whole vessel plaque and its component quantification in prediction of the presence of ischemia over lesion-level analysis.

Prognostic Implications of Whole Vessel-Level Plaque Quantification Using CCTA in Deferred Patients with High FFR

As clinical events still occur after deferral of revascularization according to FFR (30), it is clinically important to identify the population prone to future events among patients with FFR >0.80. Although plaque analysis using CCTA has been regarded as a robust tool in prognostication of CAD (5,7,10), most studies did not incorporate the information on the functional significance of a target vessel. Like a recent study by Lee et al., (11) the present study also showed that the number of HRPC was a predictor of VOCO in vessels with high FFR. Beyond lesion-level plaque characteristics, our study focused on the prognostic implications of whole vessel plaque quantification in vessels with high FFR. We hypothesized that plaque quantification of target-vessel beyond target stenosis might have better prognostic implications. For this, 3 features of target

vessel-related quantitative parameters were selected, and HRVC was defined as a composite of absolute plaque volume, lipid-rich plaque volume, and relative atherosclerotic burden in the target vessel. In our study, all the components of HRVC showed higher information gain than those of HRPC, and the number of HRVC was a significant predictor of VOCO, even after adjustment for % diameter stenosis and FFR. These results are in line with the CAPIRE (Coronary Atherosclerosis in outlier subjects: Protective and novel Individual Risk factors Evaluation) study which showed that total plaque volume and non-calcified plaque volume were the most significant predictors in 522 patients with suspected CAD. (31)

Differential Prognostic Implications of HRPC and HRVC

Recent studies showed the long-term prognostic value of CCTA findings in patients with CAD. (4,5,32) However, the differential predictability of various CCTA parameters for early or late events has not been well defined. In the present study, the number of HRPC was a significant predictor of early events (<2 years) rather than late events (≥2 years). Our finding is line with the post-hoc analysis of SCOT-HEART trial, which showed that the presence of adverse plaque was associated with acute coronary syndrome or coronary heart disease death at 2 years but not at 5 years. (8) In a study by Motoyama, et al., time to acute coronary syndrome event was shorter in the group with positive remodeling or low attenuation

plaque (mean 1.7±1.8 years) than those without (mean 3.4±2.4 years). It is interesting to note that in the subgroup with <3 HRPC, the difference in the risk for VOCO between vessels with HRVC ≥2 and <2 was mainly driven by late events (≥ 2 years). (7)

Considering that total atherosclerotic burden beyond the target lesion was a marker of rapid plaque progression in a recent study which evaluated patients who underwent repeated CCTA >2 years apart, (33) our study results support the clinical relevance of comprehensive assessment of atherosclerotic disease burden and components of target-vessel as well as target-lesion using CCTA. These results imply that systematic treatment for atherosclerosis, including meticulous secondary prevention, would be more important than the identification and revascularization of ischemia-causing stenosis alone.

Limitations

First, this study population was from 2 different cohorts, and the influence of potential selection bias could not be completely excluded. However, all data were managed by the same independent core laboratories, and all the events were independently adjudicated by the clinical events adjudication committee. Second, invasive intravascular imaging, such as IVUS or optical coherence tomography, was not systematically performed. Third, investigators were not blinded to initial per-vessel FFR values during follow-up. However, all vessels had FFR >0.80 at the time of index procedure, and the

outcome adjudication were performed in a blind fashion. Fourth, as the current study included patients with deferred revascularization based on FFR >0.80 for outcome analysis, further study is warranted to clarify whether the main results and cutoff values for HRVC of the current study would be applied to the population with higher anatomical disease burden.

Conclusion

Whole vessel plaque quantification using CCTA had an incremental value over lesion-level plaque characteristics in defining the presence of myocardial ischemia and predicting future VOCO in patients with high FFR. Therefore, comprehensive atherosclerotic evaluation of the whole vessel, in addition to the target lesion using CCTA, could provide better risk stratification of patients with CAD.

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Figure Legends

Figure 1. Study flow

Abbreviations: CAG, coronary angiography; CCTA, coronary CT angiography; CKD, chronic kidney disease; LVEF, Left ventricular ejection fraction; FFR, fractional flow reserve; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction.

Figure 2. Additive predictive value of whole vessel plaque quantification over % diameter stenosis and HRPC for functional significance.

HRPC was defined as low attenuation plaque, positive remodeling, spotty calcification, napkin-ring sign, MLA < 4 mm^2 or plaque burden $\geq$ 70%. Whole vessel plaque quantification included the measurement of total plaque volume, FFNC volume, and percent total atheroma volume.

Abbreviations: FFNC, fibrofatty and necrotic core; HRPC, high risk plaque characteristics. MLA, minimum lumen area.

Figure 3. Relative importance among HRVCs and HRPCs in deferred vessels with FFR >0.80.

HRVC was defined as a vessel with total plaque volume per vessel $\geq$306.5 mm^3, FFNC component volume per vessel $\geq$4.46 mm^3 or percent total atheroma volume $\geq$32.2%. The definition of HRPC was

same as in Figure 2.

Abbreviations: FFR, fractional flow reserve; FFNC, fibrofatty and necrotic core; HRPC, high risk plaque characteristics; HRVC, high risk vessel characteristics.

Figure 4. Prognostic implications of the number of HRVC.

The definition of HRVC was same as in Figure 3.

Abbreviations: CI, confidence interval; FFR, fractional flow reserve; HR, hazard ratio; HRVC, high risk vessel characteristics.

Figure 5. Cumulative incidence of VOCO according to the number of HRVC in vessels with (A) ≥3 HRPC and (B) <3 HRPC.

The definition of HRVC and HRPC was same as in Figure 3.

Abbreviations: CI, confidence interval; FFR, fractional flow reserve; HR, hazard ratio; HRVC, high risk vessel characteristics.

관상동맥 전산화 단층 촬영 혈관 조영술의 전 관상동맥 경화반 정량화를 통한 예후 예측

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서론: 관상 동맥 질환 환자에서 주된 치료 방침은 협착 정도가 가장 심한 병변을 찾고 재 관류술을 시행하는데 초점이 맞춰져 있다. 그러나 이전 연구들에 의하면 협착 병변을 포함하여 전 관상동맥 경화반의 정도를 확인하는 것 또한 예후를 예측하는데 중요한 것으로 알려져 있다. 이에 본 연구는 관상동맥 전산화 단층 촬영 혈관 조영술을 이용하여 비 침습적으로 전 관상동맥의 경화반을 정량화하고 이를 통해 관상동맥 환자의 예후를 예측하고자 하였다.

방법 및 결과: 침습적 분획혈류예비력 (FFR)을 측정하고 측정 전 90일 이내에 관상동맥 전산화 단층 촬영 혈관 조영술 (CCTA)을 시행받은 643 명의 관상동맥 환자로 구성된 다국가, 다기관 참여 CCTA-FFR 레지스트리 (NCT04037163)로부터 독립적인 CCTA 분석 기관 (세브란스 병원)에서 전 관상동맥 경화반 및 성분의 2차원, 3차원 정량화를 시행하였고 독립적인 committee 로부터 5년간의 심혈관 관련 질환 (심인사, 심근 경색, 재관류술) 발생을 조사하였다. 기존 연구에 근거하여, 고 위험 병변의 특성은 minimum lumen area $<4mm^2$, plaque burden $\geq 70\%$, low attenuating plaque, positive remodeling, spotty calcification, and

napkin-ring sign 의 6 가지로 정의하였다. 전 관상동맥 경화반 정량화로부터 고 위험 혈관 특성은 total plaque volume ≥306.5mm^3, fibrofatty and necrotic core volume ≥4.46mm^3, or percent total atheroma volume ≥32.2% 의 3가지로 정의하였다. 허혈성 병변 (FFR ≤0.80)을 예측하는 데 있어 % diameter stenosis, 고 위험 병변 특성에 전 관상동맥 경화반 정량화 변수를 추가할 경우 그 예측력이 유의하게 증가함을 확인하였다. 또한 FFR >0.80에 근거하여 재관류술을 시행하지 않은 517 혈관 (368명 환자)에서 5년간의 심혈관 질환 발생을 예측하는 데에 information gain을 비교하였을 때 고 위험 혈관 특성의 모든 3가지 지표가 고 위험 병변의 6가지 지표보다 우수하였다. 고 위험 혈관 특성의 개수가 증가할수록 5년 심혈관 질환 발생률이 유의하게 증가하였다 (hazard ratio [HR] 2.54, 95% confidence interval [CI] 1.77-3.64). 2년을 기준으로 한 landmark analysis에서 고위험 혈관 특성은 2년 이후의 심혈관 질환 발생 위험도를 예측하였으나 (HR 2.49, 95% CI 1.59-3.90) 고 위험 병변 특성은 예측하지 못하였다. 고 위험 혈관 특성은 고 위험 병변 특성이 3개 이상, 미만인 하위 그룹에서도 심혈관 질환 발생 위험도를 예측할 수 있었다.

결론: 관상동맥 전산화 단층 촬영 혈관 조영술을 이용하여 전 관상동맥 경화반을 정량화하는 것은 허혈성 병변을 예측하고 FFR >0.80으로 재관류술을 시행하지 않은 환자에서 예후를 예측하는 데에 추가적인 예측력을 보였다. 따라서 이를 임상에서 적용할 경우 관상동맥 환자에게 적절한 치료 방침을 제공하는 데에 도움을 줄 수 있을 것이다.

핵심 단어: 관상 동맥 죽상반; 관상 동맥 전산화 단층 촬영 혈관 조영

술; 허혈성 병변; 분획예비혈류력; 예후

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