ORIGINAL RESEARCH

Prognostic Implications of Comprehensive Whole Vessel Plaque Quantification Using Coronary Computed Tomography Angiography

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ABSTRACT

BACKGROUND The prognostic value of whole vessel plaque quantification has not been fully understood.

OBJECTIVES We aimed to investigate the clinical relevance of whole vessel plaque quantification on coronary computed tomography angiography.

METHODS In a total of 1,013 vessels with fractional flow reserve (FFR) measurement and available coronary computed tomography angiography, high-risk plaque characteristics (HRPC) included minimum lumen area <4 mm^2, plaque burden ≥70%, low attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign; and high-risk vessel characteristics (HRVC) included total plaque volume ≥306.5 mm^3, fibrofatty and necrotic core volume ≥4.46 mm^3, or percent total atheroma volume ≥32.2% in a target vessel, based on corresponding optimal cutoff values. Survival analysis for vessel-oriented composite outcome (VOCO) (a composite of cardiac death, target vessel myocardial infarction, or target vessel revascularization) at 5 years was performed using marginal Cox proportional hazard models.

RESULTS Whole vessel plaque quantification had incremental predictability in addition to % diameter stenosis and HRPC (P < 0.001) in predicting FFR ≤0.80. Among 517 deferred vessels based on FFR >0.80, the number of HRVC was significantly associated with the risk of VOCO (HR: 2.54; 95% CI: 1.77-3.64) and enhanced the predictability for VOCO of % diameter stenosis and the number of HRPC (P < 0.001). In a landmark analysis at 2 years, the number of HRVC showed sustained prognostic implications beyond 2 years, but the number of HRPC did not.

CONCLUSIONS Whole vessel plaque quantification can provide incremental predictability for low FFR and additive prognostic value in deferred vessels with high FFR over anatomical severity and lesion plaque characteristics. (CCTA-FFR Registry for Risk Prediction; NCT04037163) (JACC: Asia 2021;1:37–48) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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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 computed tomography angiography (CTA) 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, coronary CTA provides detailed information on qualitative and quantitative plaque characteristics (6). Previous studies demonstrated that high-risk or adverse plaque characteristics on coronary CTA have prognostic value in the prediction of future clinical events (7-11). Furthermore, coronary CTA can also provide 2- 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, coronary CTA-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 coronary CTA-based whole vessel plaque quantification over conventional plaque assessment in defining the functional significance of a target vessel and risk stratification for patients with high FFR.

METHODS

This is a substudy of the CCTA-FFR registry (9). 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 the institutional registry of Tsuchiura Kyodo General Hospital. For this study, patients who underwent coronary CTA within 90 days of FFR measurement were included. Patients with depressed left ventricular systolic function (ejection fraction <35%), acute ST-segment elevation myocardial infarction (MI) within 72 h, previous coronary artery bypass graft surgery, chronic kidney disease, abnormal epicardial coronary flow (TIMI [Thrombolysis In Myocardial Infarction] flow grade <3) or planned coronary artery bypass graft surgery after diagnostic angiography were excluded. All data were collected at the core laboratories, and independent screening and analyses were performed for FFR, angiographic, and coronary CTA data. The study protocol was approved by the institutional review board or ethics committee at each participating center.

CORONARY CTA AND WHOLE VESSEL PLAQUE QUANTIFICATION. Coronary CTA was performed as a part of routine clinical practice for patients with CAD. The coronary CTA images were analyzed at a core laboratory (Severance Cardiovascular Hospital, Seoul, Korea) in a blinded fashion. Coronary CTA analysis was performed in 3 steps. First, qualitative plaque characteristics were analyzed according to the definitions from previous studies (6,7). Second, cross-sectional quantitative analysis of target stenosis, including minimum lumen area (MLA) and plaque burden, was performed as previously described (9,11). Third, 3-dimensional plaque quantification of whole vessel was performed (10,13) using semiautomated plaque analysis software (QAngioCT Research Edition version 2.1.9.1, Medis Medical Imaging Systems) with

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TABLE 1 Baseline Lesion Characteristics			
	Total (N = 1,013)	Deferred Vessels With FFR >0.80 (n = 517)	Deferred Vessels With FFR ≤0.80 or Revascularized Vessels (n = 496)
Location			
Left anterior descending artery	544 (53.7)	200 (38.7)	344 (69.4)
Left circumflex artery	204 (20.1)	138 (26.7)	66 (13.3)
Right coronary artery	265 (26.2)	179 (34.6)	86 (17.3)
Quantitative coronary angiographic findings			
Diameter stenosis, %	48.5 ± 17.4	40.0 ± 15.0	57.4 ± 15.2
Lesion length, mm	13.0 ± 9.5	10.0 ± 7.0	16.1 ± 10.8
Reference diameter, mm	2.9 ± 0.6	3.0 ± 0.6	2.8 ± 0.6
Coronary CTA findings			
High-risk plaque characteristics			
Plaque burden ≥70%	453 (44.7)	147 (28.4)	306 (61.7)
Minimal lumen area <4 mm^2	744 (73.4)	303 (58.6)	441 (88.9)
Low attenuation plaque	219 (21.6)	71 (13.7)	148 (29.8)
Positive remodeling	432 (42.6)	195 (37.7)	237 (47.8)
Spotty calcification	129 (12.7)	64 (12.4)	65 (13.1)
Napkin-ring sign	11 (1.1)	2 (0.4)	9 (1.8)
Whole vessel plaque quantification			
Total plaque volume, mm^3	143.5 (65.1-257.1)	104.2 (47.2-211.5)	184.5 (96.0-294.5)
FFNC component volume, mm^3	17.0 (2.6-50.7)	7.8 (0.5-33.3)	27.0 (9.2-69.4)
Percent total atheroma volume, %	21.9 (11.4-32.5)	17.1 (7.9-27.2)	26.1 (17.1-37.1)

Values are n (%), mean ± SD, or median (interquartile range).

CTA = computed tomography angiography; FFNC = fibrofatty and necrotic core; FFR = fractional flow reserve; PCI = percutaneous coronary intervention.
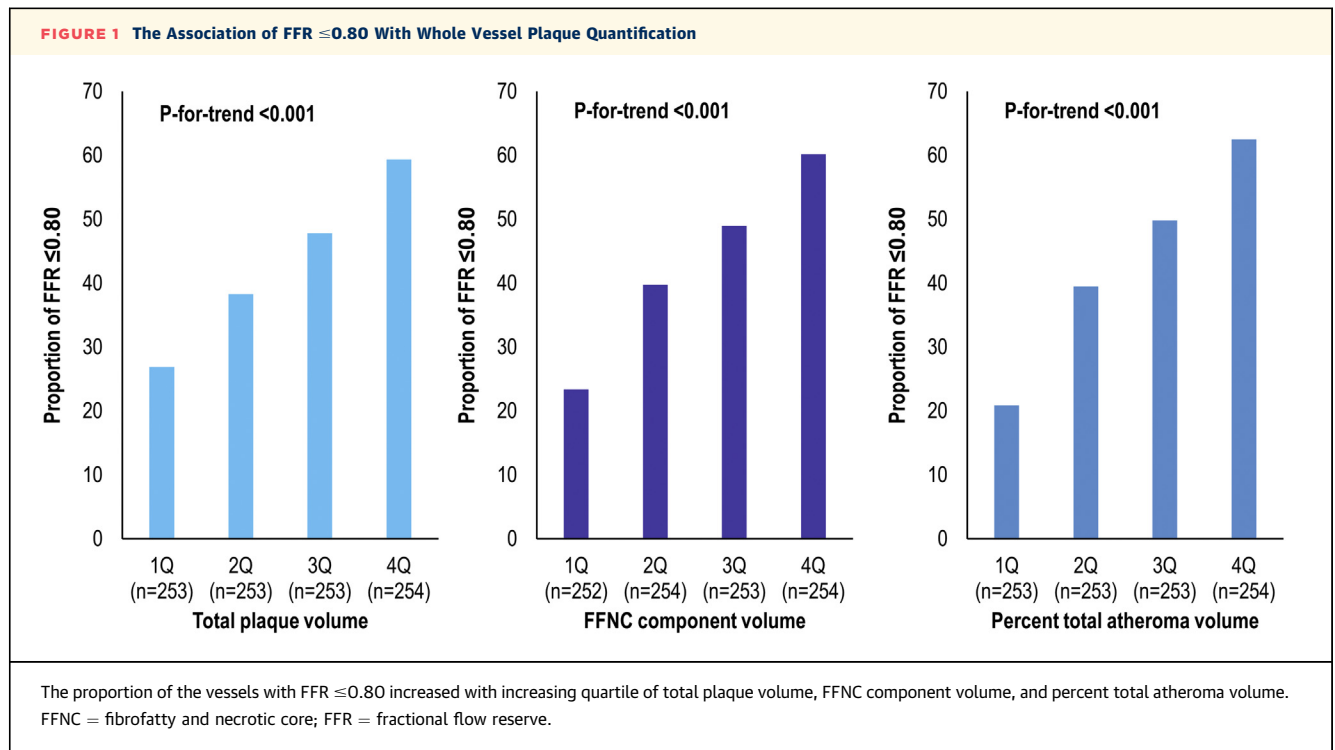
appropriate manual correction (14). Plaque composition was identified using predefined HU thresholds: necrotic core (−30 to 30 HU), fibrofatty (30-130 HU), fibrous (131-350 HU), and calcified plaque (≥350 HU) (10).

INVASIVE CORONARY ANGIOGRAPHY AND CORONARY PHYSIOLOGICAL 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. The pressure-temperature sensor guidewire was adjusted to zero and equalized to aortic pressure, and then was positioned at the distal segment of a target vessel. 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.

DEFINITIONS OF HIGH-RISK PLAQUE CHARACTERISTICS AND HIGH-RISK VESSEL CHARACTERISTICS. For target stenosis or plaque, high-risk plaque characteristics (HRPC) was defined as a plaque with MLA <4 mm^2,

plaque burden ≥70%, low attenuation plaque (average density ≤30 Hounsfield units [HU]), positive remodeling (remodeling index ≥1.1), spotty calcification (average density >130 HU, diameter <3 mm in any direction with the length of the calcium <1.5 times the vessel diameter and width of the calcification less than two-thirds of the vessel diameter), or napkin-ring sign (ring-like attenuation pattern with peripheral high attenuation tissue that surrounds a central lower attenuation portion), based on previous literature (2,3,6,7,11). 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 (10,15,16). High-risk vessel characteristics (HRVC) were defined as a vessel with total plaque volume ≥305.5 mm^3, FFNC component volume ≥4.46 mm^3, or percent total atheroma volume ≥32.2%, based on binary classification using the corresponding optimal cutoff values to predict vessel-oriented composite outcome (VOCO) at 5 years.
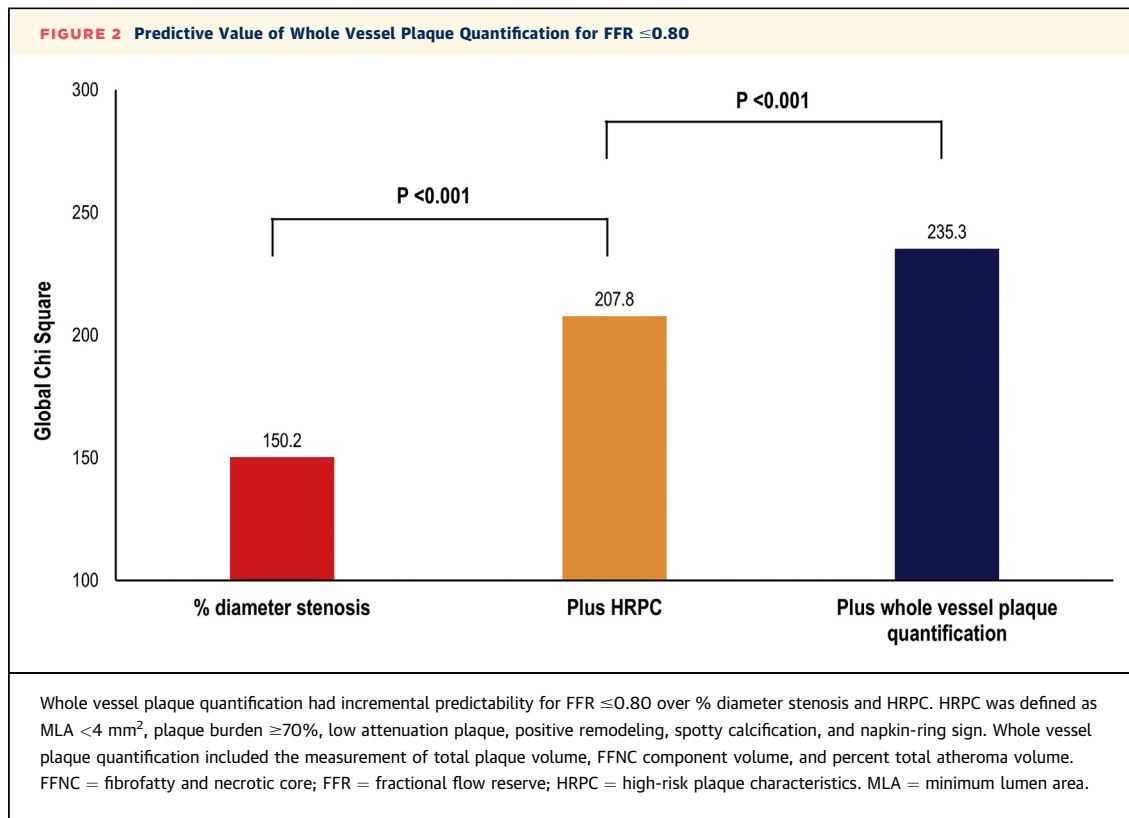
CLINICAL OUTCOME MEASUREMENTS AND ADJUDICATION OF EVENTS. Clinical data were obtained at outpatient

FIGURE 1 The Association of FFR ≤0.80 With Whole Vessel Plaque Quantification

The proportion of the vessels with FFR ≤0.80 increased with increasing quartile of total plaque volume, FFNC component volume, and percent total atheroma volume.
FFNC = fibrofatty and necrotic core; FFR = fractional flow reserve.

clinic visits or by telephone contact. An independent clinical events committee whose members were unaware of clinical, angiographic, and physiological data adjudicated all events. The primary outcome was VOCO, which included cardiac death, vessel-related MI, or vessel-related ischemia-driven revascularization (11). All clinical outcomes were defined in accordance with the Academic Research Consortium, including the addendum to the definition of MI (17). All deaths were regarded as cardiac in nature unless an undisputable noncardiac cause was present. The definition of MI was following the third universal definition of MI (18). Periprocedural MI was not included into a clinical outcome. Ischemia-driven revascularization was defined as revascularization with at least 1 of the following: 1) recurrence of angina; 2) positive noninvasive test; and 3) positive invasive physiological test.

STATISTICAL ANALYSIS. Categorical variables were presented as numbers and relative frequencies (percentages) and continuous variables as means and SDs or median with interquartile range (Q1-Q3) according to their distribution, which was checked by the Kolmogorov-Smirnov test. Data were analyzed on a per-vessel basis for comparison of lesion characteristics, physiological indexes, and vessel-specific clinical outcomes. The analysis consisted of 2 parts.

First, using the total cohort (1,013 vessels from 643 patients), the discrimination ability of % diameter stenosis from coronary CTA, HRPC, and whole vessel plaque quantification for defining FFR ≤0.80 was evaluated on a per-vessel basis. The chi-square test for trend in proportions was performed to investigate the significance of trends of the proportion of FFR ≤0.80 according to the quartile of total plaque volume, FFNC component volume, and percent total atheroma volume. The correlation coefficient between continuous FFR values and continuous values of whole plaque quantification was estimated using Pearson correlation, and the alternative hypothesis that correlation is not equal to 0 was used for the *P* value in Pearson correlation. The likelihood ratio chi-square test was used to explore the significance of addition of whole vessel plaque quantification to a model with % diameter stenosis and HRPC in prediction of vessels with FFR ≤0.80. The incremental predictive value for FFR ≤0.80 was defined as a significant increase in global chi-square value. Second, the prognostic implications of HRVC were evaluated among 517 deferred vessels from 368 patients based on FFR >0.80. Survival analysis was performed based on a per-vessel level. Marginal Cox proportional hazard regression was used to calculate the HR and

FIGURE 2 Predictive Value of Whole Vessel Plaque Quantification for FFR ≤0.80

Whole vessel plaque quantification had incremental predictability for FFR ≤0.80 over % diameter stenosis and HRPC. HRPC was defined as MLA <4 mm², plaque burden ≥70%, low attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign. Whole vessel plaque quantification included the measurement of total plaque volume, FFNC component volume, and percent total atheroma volume. FFNC = fibrofatty and necrotic core; FFR = fractional flow reserve; HRPC = high-risk plaque characteristics. MLA = minimum lumen area.

95% CI to account for a per-vessel correlation within a patient, and the individual patient was specified to assess robust sandwich variance estimates of the co-efficients. Optimal cutoff 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 (19). To separately analyze the prognostic impact of HRPC and HRVC according to different time frames, exploratory landmark analysis at 2 years was per-formed. The additive predictive value for VOCO of the number of HRVC over the number of HRPC was compared based on global chi-square value, and the risk of VOCO according to number of HRVC was compared in the subgroups of ≥3 and <3 HRPC. As sensitivity analyses, comparison of c-statistics based on receiver-operating characteristic curves between the model with and without whole vessel plaque quantification in the whole data set and the subsets with 80% random sampling, and additional analysis with consideration of HRPC by excluding spotty calcification and napkin-ring sign were performed to demonstrate the additive value of whole plaque quantification. All probability values were 2-sided,

and *P* values <0.05 were considered statistically sig-nificant. All analyses were performed using R lan-guage version 3.5.2 (R Foundation for Statistical Computing).

RESULTS

CHARACTERISTICS OF PATIENTS AND LESIONS. Baseline patient and lesion characteristics are shown in **Table 1** and Supplemental 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, respec-tively. Mean or median value of total plaque volume, FFNC component volume, and percent total atheroma volume were 143.5 mm³ (Q1-Q3: 65.1-257.1 mm³), 17.0 mm³ (Q1-Q3: 2.6-50.7 mm³), and 21.9% (Q1-Q3: 11.4%-32.5%), respectively.

ASSOCIATION OF CORONARY CTA PARAMETERS WITH FUNCTIONAL SIGNIFICANCE. The proportions of vessels with FFR ≤0.80 in those with 0, 1, 2, and ≥3 HRPC were 15.1%, 28.1%, 41.1%, and 66.5%, respec-tively (*P* for trend <0.001). The proportion of the vessels with FFR ≤0.80 proportionally increased in

FIGURE 3   Cumulative Incidence of VOCO by Each Component of HRVC
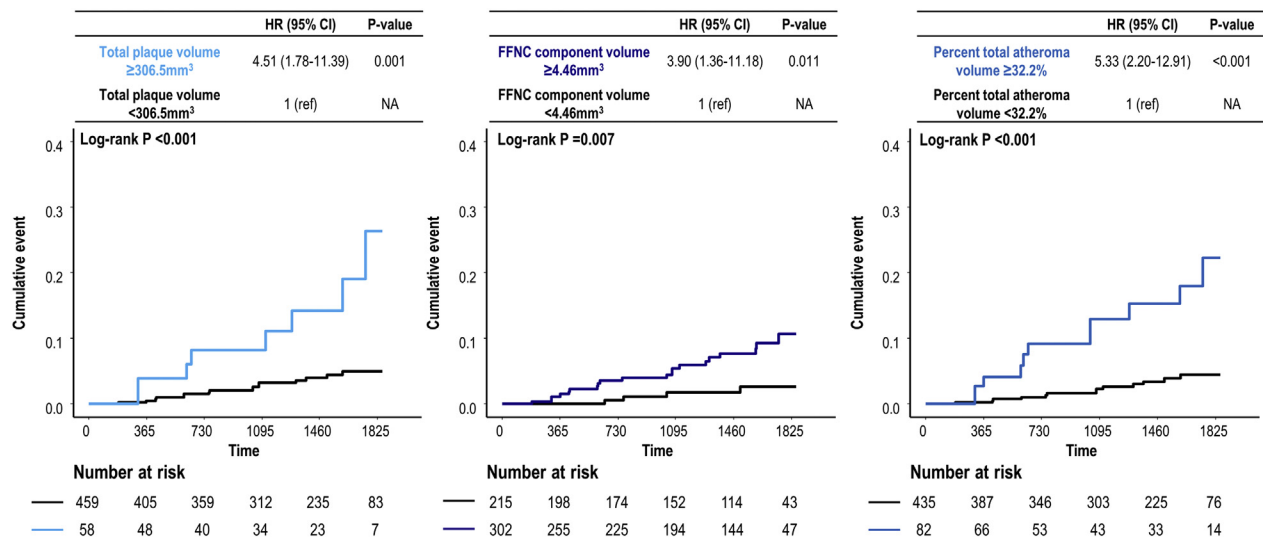
Each component of HRVC discriminated 5-year VOCO in the deferred vessels with FFR >0.80. HRVC was defined as a vessel with total plaque volume ≥306.5 mm³, FFNC component volume ≥4.46 mm³, and percent total atheroma volume ≥32.2%. HRVC = high-risk vessel characteristics; VOCO = vessel-oriented composite outcome; other abbreviations as in **Figure 2**.

the order of 1st, 2nd, 3rd, and 4th quartile of total plaque volume, FFNC component volume, or percent total atheroma volume (**Figure 1**). There were significant correlations between continuous FFR value and continuous values of 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 prediction of 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 (**Figure 2**).

PROGNOSTIC IMPLICATIONS OF HIGH-RISK PLAQUE AND VESSEL CHARACTERISTICS. Among a total of 1,013 vessels, the 517 (51.0%) vessels were deferred from revascularization with FFR >0.80. Of the deferred vessels with FFR >0.80, the cumulative incidence of 5-year VOCO was significantly higher in the vessels with total plaque volume ≥306.5 mm³, FFNC component volume ≥4.46 mm³, or percent total atheroma volume ≥32.2% than those without (**Figure 3**). These results were similar after adjustment for clinical risk factors, % diameter stenosis, and FFR (**Table 2**).

The cumulative risk of VOCO increased according to the number of HRPC (3.8%, 4.8%, 6.5%, and 18.8% in vessels with 0, 1, 2, and ≥3 HRPC, respectively; log-rank P < 0.001) (Supplemental Figure 1) and the number of HRVC (1.7%, 5.5%, and 7.5% in vessels with 0, 1, and ≥2 HRVC, respectively; log-rank P < 0.001) (**Figure 4,** Supplemental Table 2). The prognostic implications of the number of HRPC and HRVC were consistent in the multivariate analysis (**Table 2**).

ADDITIVE PROGNOSTIC VALUE OF HRVC OVER HRPC. In the deferred vessels with FFR >0.80, the addition of the number of HRVC to % diameter stenosis and the number of HRPC significantly increased the predictability for 5-year VOCO (**Figure 5**). In the landmark analysis at 2 years, both the number of HRPC and the number of HRVC were associated with 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 3**). When the vessels were divided into 2 groups according to the number of HRPC, the risk of VOCO was significantly higher in vessels with ≥2

TABLE 2 Risk of VOCO According to Atherosclerotic Features in the Deferred Vessels With FFR >0.80

	Number of Each Atherosclerotic Feature (%)	Unadjusted HR (95% CI)	*P* Value	Adjusted HR (95% CI)*	*P* Value
HRPC					
Plaque burden ≥70%	147 (28.4)	3.24 (1.43-7.35)	0.005	3.43 (1.33-8.86)	0.011
Minimal lumen area <4 mm^2	303 (58.6)	1.92 (0.79-4.64)	0.149	1.35 (0.59-3.10)	0.473
Low attenuation plaque	71 (13.7)	2.51 (0.93-6.77)	0.069	2.37 (0.93-6.05)	0.071
Positive remodeling	195 (37.7)	1.83 (0.85-3.96)	0.125	2.25 (0.96-5.28)	0.062
Spotty calcification	64 (12.4)	0.91 (0.28-3.02)	0.883	0.74 (1.92-2.84)	0.659
Napkin-ring sign	2 (0.4)	NA	NA	NA	NA
Number of HRPC	—	1.80 (1.22-2.67)	0.003	1.82 (1.14-2.90)	0.013
HRVC					
Total plaque volume ≥306.5 mm^3	58 (11.2)	4.51 (1.78-11.39)	0.001	3.63 (1.39-9.50)	0.009
FFNC component volume ≥4.46 mm^3	302 (58.4)	3.90 (1.36-11.18)	0.011	3.57 (1.26-10.07)	0.016
Percent total atheroma volume ≥32.2%	82 (15.9)	5.33 (2.20-12.91)	<0.001	4.66 (1.88-11.59)	<0.001
Number of HRVC	—	2.61 (1.78-3.81)	<0.001	2.54 (1.77-3.64)	<0.001

Values are n (%) unless otherwise indicated. Optimal cutoff of HRVC was estimated based on maximal log-rank statistics. *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.

HRPC = high-risk plaque characteristics; HRVC = high-risk vessel characteristics; VOCO = vessel-oriented composite outcome; other abbreviations as in Table 1.
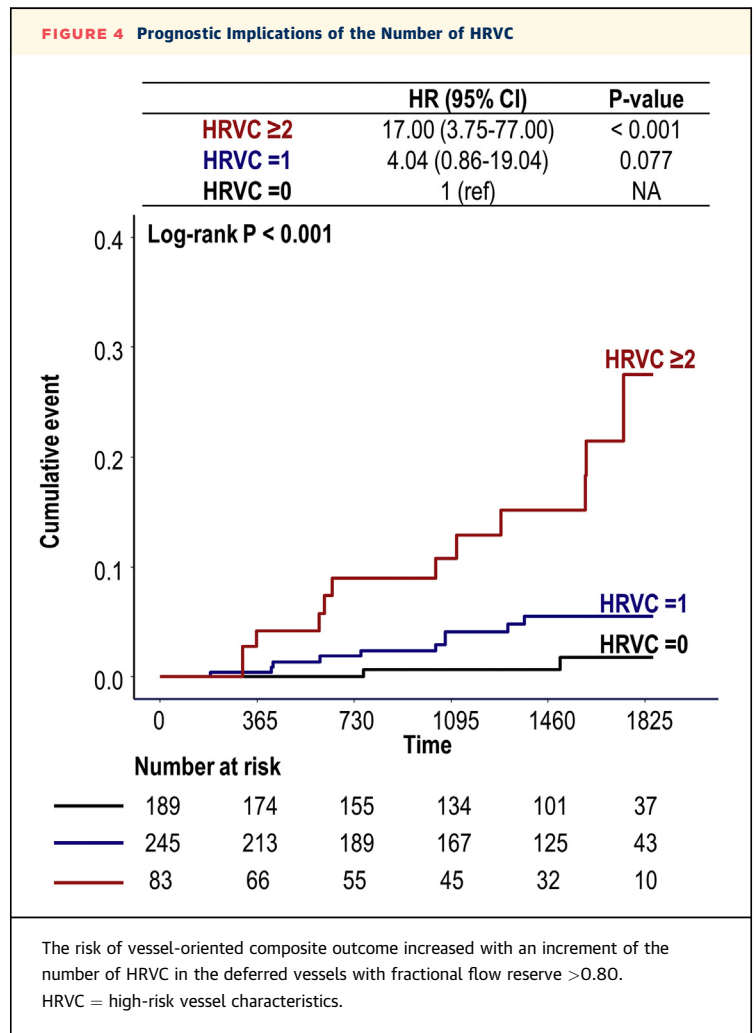
HRVC (HR: 7.48; 95% CI: 1.59-35.23; *P* = 0.011) than vessels with <2 HRVC in the subgroups with ≥3 HRPC (Supplemental Figure 2A). Similarly, in vessels with HRPC <3, the risk of VOCO was higher in vessels with ≥2 HRVC (HR: 3.42; 95% CI: 1.12-10.42; *P* = 0.030) than vessels with <2 HRVC (Supplemental Figure 2B). In whole vessels, the number of HRVC also showed incremental prognostic value relative to % diameter stenosis, the number of HPRC, and FFR in prediction of VOCO (Supplemental Figure 3).
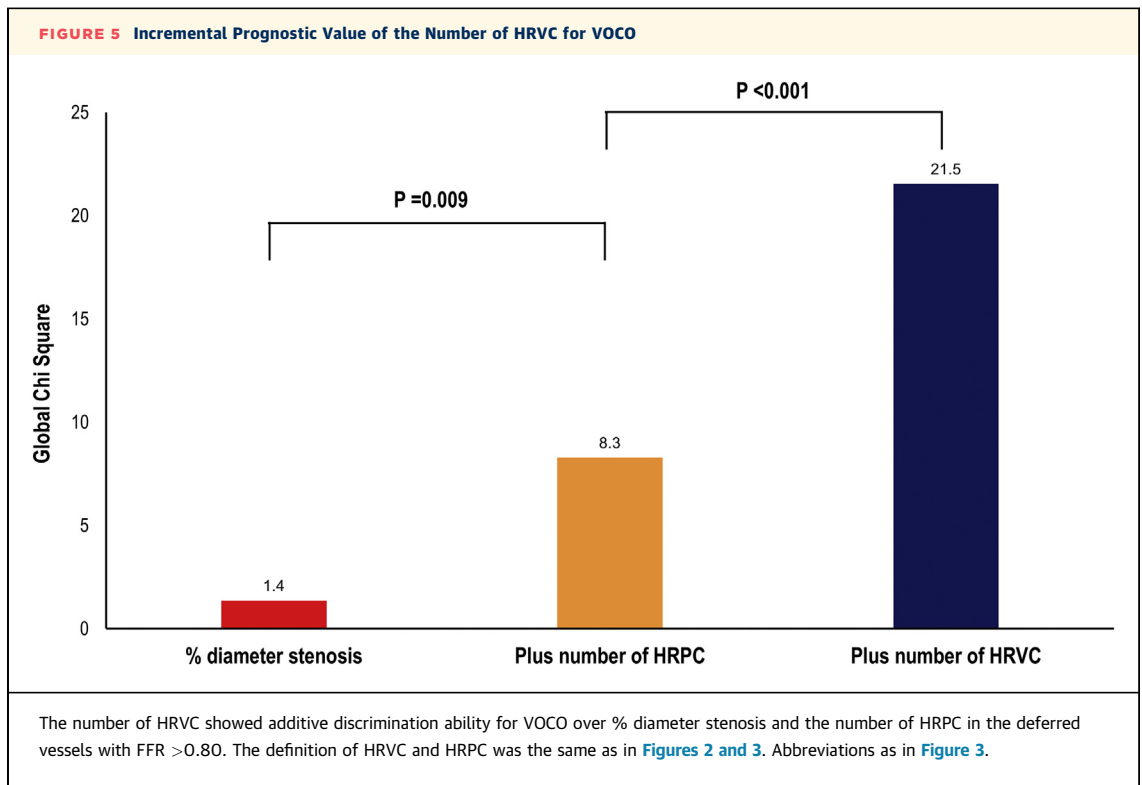
In a sensitivity analysis with c-statistics comparison, the incremental value of whole plaque quantification over % diameter stenosis and HRPC was consistent in predicting FFR ≤0.80 and 5-year VOCO in the deferred vessels with FFR >0.80 (Supplemental Figures 4 and 5), and the results were similar in the subsets with 80% random sampling (Supplemental Table 3). Moreover, the additive value of HRVC was still constant when spotty calcification and napkin-ring sign were excluded from HRPC (Supplemental Figure 6).

DISCUSSION

The current study investigated the clinical relevance of whole vessel plaque quantification using coronary CTA 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 FFR ≤0.80 over % diameter stenosis and HRPC. Second, the number of HRVC had independent prognostic value for 5-year VOCO in the deferred vessels

FIGURE 4 Prognostic Implications of the Number of HRVC

	HR (95% CI)	P-value
HRVC ≥2	17.00 (3.75-77.00)	< 0.001
HRVC =1	4.04 (0.86-19.04)	0.077
HRVC =0	1 (ref)	NA

Log-rank P < 0.001

Number at risk

Time	0	365	730	1095	1460	1825
	189	174	155	134	101	37
	245	213	189	167	125	43
	83	66	55	45	32	10

The risk of vessel-oriented composite outcome increased with an increment of the number of HRVC in the deferred vessels with fractional flow reserve >0.80. HRVC = high-risk vessel characteristics.

FIGURE 5 Incremental Prognostic Value of the Number of HRVC for VOCO

The number of HRVC showed additive discrimination ability for VOCO over % diameter stenosis and the number of HRPC in the deferred vessels with FFR >0.80. The definition of HRVC and HRPC was the same as in **Figures 2 and 3**. Abbreviations as in **Figure 3**.

with FFR >0.80. Third, the number of HRVC was significantly associated with VOCO, both within and beyond 2 years, in the landmark analysis (**Central Illustration**).

WHOLE VESSEL PLAQUE QUANTIFICATION AND PRESENCE OF MYOCARDIAL ISCHEMIA. Presence of ischemia is a key prognostic factor in patients with CAD (20,21). FFR is one of the standard indexes used to define ischemia-causing stenosis and guide revascularization in a cardiac catheterization laboratory. There have been several investigations into the relevance of anatomical severity or plaque compositional characteristics from coronary CTA to predict the presence of vessel-related ischemia and stenosis severity, plaque geometry, and plaque compositional characteristics as the predictors of FFR (16,22-24). Driessen et al. (25) reported that local plaque features such as positive remodeling, low attenuation, and noncalcified volume were significantly associated with decreased hyperemic myocardial blood flow or FFR, 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 physiological disease burden of a whole vessel (26). In this regard, we investigated the role of whole vessel plaque quantification using coronary CTA in defining the presence of ischemia assessed by FFR ≤0.80. In our study, the proportion of the vessels with FFR ≤0.80 correlated with the quartile of total plaque volume, FFNC component volume, and percent total atheroma volume, and all of 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 with % 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 CORONARY CTA IN DEFERRED PATIENTS WITH HIGH FFR. As clinical events still occur after deferral of revascularization according to FFR (27), it is clinically important to identify the population prone to future events among patients with FFR >0.80. Although plaque analysis using coronary CTA has been regarded as a robust tool in prognostication of CAD (6,7,10), most studies did not incorporate the
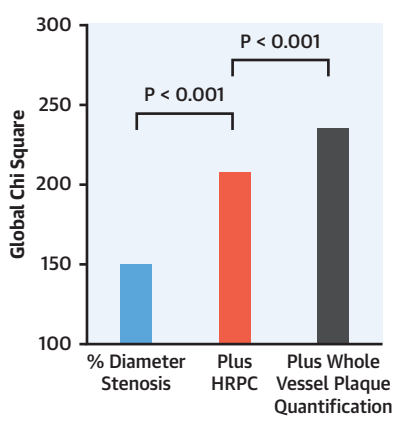
CENTRAL ILLUSTRATION Prognostic Implications of Whole Vessel Plaque Quantification Using CT Angiography

High-risk vessel characteristics (HRVC) by whole vessel plaque quantification

- Total plaque volume ≥306.5 mm^3
- FFNC component volume ≥4.46 mm^3
- Percent total atheroma volume ≥32.2%

1. Incremental predictability for functional significance

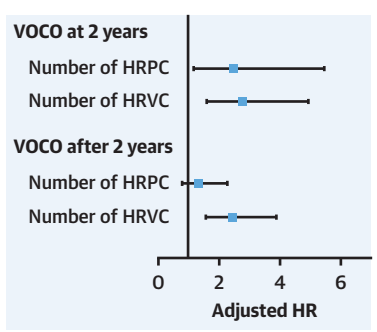**2. Prognostic value for 5-year VOCO (deferred with FFR >0.80)**

	HR (95% CI)	P-Value
HRVC ≥2	17.00 (3.75-77.00)	< 0.001
HRVC =1	4.04 (0.86-19.04)	0.077
HRVC =0	1 (ref)	NA
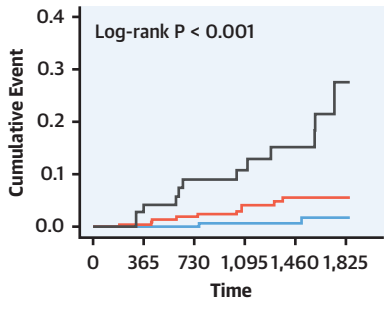
Number at risk

HRVC =0	189	174	155	134	101	37
HRVC =1	245	213	189	167	125	43
HRVC ≥2	83	66	55	45	32	10

3. Long-term (>2 years) prognostication (deferred with FFR >0.80)

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Whole vessel plaque quantification included total plaque volume, FFNC component volume, and percent total atheroma volume. It had additive predictive value for FFR ≤0.80 over lesion-level stenosis severity and HRPC. The number of HRVC discriminated clinical outcomes and provided long-term prognostication in the deferred vessels with FFR >0.80. HRPC was defined as MLA <4 mm^2, plaque burden ≥70%, low attenuation plaque, positive remodeling, spotty calcification, and napkin-ring sign. HRVC was defined as a vessel with total plaque volume ≥306.5 mm^3, percent total atheroma volume ≥32.2%, and FFNC component volume ≥4.46 mm^3.

information on the functional significance of a target vessel. Similar to a study by Lee et al. (11), the present study also showed that the number of HRPC was associated with 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, the number of HRVC was associated with 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 noncalcified plaque volume were the most significant predictors in 522 patients with suspected CAD (28).

DIFFERENTIAL PROGNOSTIC IMPLICATIONS OF HRPC AND HRVC. Recent studies showed the long-term prognostic value of coronary CTA findings in patients with CAD (4,5,29). However, the differential predictability of various coronary CTA parameters for

TABLE 3   Landmark Analysis at 2 Years According to the Number of HRPC and HRVC in the Deferred Vessels With FFR >0.80

	Unadjusted HR (95% CI)	P Value	Adjusted HR (95% CI)*	P Value
VOCO at 2 y				
Number of HRPC	2.60 (1.50-4.53)	<0.001	2.53 (1.17-5.48)	0.019
Number of HRVC	3.25 (1.83-5.77)	<0.001	2.81 (1.60-4.95)	<0.001
VOCO after 2 y				
Number of HRPC	1.32 (0.82-2.13)	0.255	1.37 (0.81-2.30)	0.237
Number of HRVC	2.22 (1.39-3.54)	<0.001	2.49 (1.59-3.90)	<0.001

*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. The definition of HRPC and HRVC was the same as in **Table 2**.

FFR = fractional flow reserve; other abbreviations as in **Table 2**.

early or late events has not been well defined. In the present study, the number of HRPC was associated with early events (<2 years) rather than late events (≥2 years). Our finding is line with the post hoc analysis of SCOT-HEART (Scottish Computed Tomography of the Heart trial) (8), 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. In a study by Motoyama et al. (7), time to acute coronary syndrome event was shorter in the group with low attenuation plaque or positive remodeling (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 ≥2 and <2 HRVC was mainly driven by late events (≥2 years) in the current study. 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 coronary CTA >2 years apart (30,31), 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 coronary CTA. 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.

STUDY 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 events were independently adjudicated by the clinical events adjudication committee. Second, invasive intravascular imaging, such as intravascular ultrasound or optical coherence tomography, was not systematically performed. Third, investigators were not blinded to initial per-vessel FFR values during follow-up. However, the outcome analysis was performed in the deferred vessels with FFR >0.80 at the time of index procedure, and the outcome adjudication was performed in a blinded 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 anatomic disease burden. Fifth, the association between plaque quantification and FFR ≤0.80 shown in the current study may be regarded as the confirmation of prior knowledge, because this finding has already been reported in previous publications. Still, our finding has strength in demonstration of this association in a large number of vessels and totally separated per-vessel index from per-lesion index to provide the practical importance of whole plaque analysis.

CONCLUSIONS

Whole vessel plaque quantification using coronary CTA 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 coronary CTA, could provide better risk stratification of patients with CAD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Whole plaque quantification of coronary arteries on coronary CTA can provide additive predictive value for functional significance and clinical outcomes over lesion-level plaque analysis.

TRANSLATIONAL OUTLOOK: Future studies are needed to investigate the implications of integrating whole vessel plaque quantification with the current diagnostic scheme and prognostic stratification of CAD in clinical practice.

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KEY WORDS atherosclerosis, coronary CT angiography, fractional flow reserve, plaque quantification

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APPENDIX For supplemental tables and figures, please see the online version of this paper.