

# Association Between IVUS Findings and Adverse Outcomes in Patients With Coronary Artery Disease

## The VIVA (VH-IVUS in Vulnerable Atherosclerosis) Study

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**OBJECTIVES** The purpose of this study was to determine whether thin-capped fibroatheromata (TCFA) identified by virtual histology intravascular ultrasound (VH-IVUS) are associated with major adverse cardiac events (MACE) on individual plaque or whole patient analysis.

**BACKGROUND** Post-mortem studies have identified TCFA as the substrate for most myocardial infarctions. However, little is known about the natural history of individual TCFA and their link with MACE. VH-IVUS provides a method of identifying plaques in vivo that are similar (although not identical) to histologically defined TCFA, and has been validated in human atherectomy and post-mortem studies.

**METHODS** One hundred seventy patients with stable angina or troponin-positive acute coronary syndrome referred for percutaneous coronary intervention (PCI) were prospectively enrolled and underwent 3-vessel VH-IVUS pre-PCI and also post-PCI in the culprit vessel. MACE consisted of death, myocardial infarction, or unplanned revascularization.

**RESULTS** In all, 30,372 mm of VH-IVUS were analyzed. Eighteen MACE occurred in 16 patients over a median follow-up of 625 days (interquartile range: 463 to 990 days); 1,096 plaques were classified, and 19 lesions resulted in MACE (13 nonculprit lesions and 6 culprit lesions). Nonculprit lesion factors associated with nonrestenotic MACE included VHTCFA (hazard ratio [HR]: 7.53,  $p = 0.038$ ) and plaque burden  $>70\%$  (HR: 8.13,  $p = 0.011$ ). VHTCFA (HR: 8.16,  $p = 0.007$ ), plaque burden  $>70\%$  (HR: 7.48,  $p < 0.001$ ), and minimum luminal area  $<4 \text{ mm}^2$  (HR: 2.91,  $p = 0.036$ ) were associated with total MACE. On patient-based analysis, the only factor associated with nonrestenotic MACE was 3-vessel noncalcified VHTCFA (HR: 1.79,  $p = 0.004$ ).

**CONCLUSIONS** VH-IVUS TCFA was associated with nonrestenotic and total MACE on individual plaque analysis, and noncalcified VHTCFA was associated with nonrestenotic and total MACE on whole-patient analysis, demonstrating that VH-IVUS can identify plaques at increased risk of subsequent events. The preservation of the association between VHTCFA and MACE despite various analyses emphasizes its biological importance. (J Am Coll Cardiol Img 2011;4:894–901) © 2011 by the American College of Cardiology Foundation

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The majority of myocardial infarctions (MIs) are caused by specific subtypes of coronary atherosclerotic plaque. Thus, the substrate for 60% to 70% of MIs are “thin-capped fibroatheromata” (TCFA), where a thin fibrous cap (<65  $\mu\text{m}$ ) separates a necrotic core from the lumen, frequently without significant vessel stenosis (1,2). Cap rupture exposes intraplaque material, resulting in intravascular thrombosis and vessel occlusion.

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Although fibroatheromata can be identified at post-mortem, identifying high-risk plaque subtypes before an event remains a major challenge.

Radiofrequency, or “virtual histology” intravascular ultrasound (VH-IVUS) is based upon spectral analysis of ultrasound backscatter, with different plaque components exhibiting a defined spectrum (3). The radiofrequency signal is mathematically transformed into a color-coded representation, including lipid, fibrous tissue, calcification, and necrotic core (4); IVUS pullback allows reconstitution in 3 dimensions. VH-IVUS spectral analysis correlates well with histopathology (predictive accuracy 87.1%, 87.1%, 88.3%, and 96.5% for fibrous, fibrofatty, necrotic core, and dense calcium, respectively) (5,6). VH-IVUS can also identify VHTCFA (7) and other plaque subtypes, and follow plaque composition after treatment (8).

Although VH-IVUS is promising, little is known about the link between VH-IVUS-defined plaque classification or plaque composition and long-term outcome, a crucial requirement for VH-IVUS to be used for risk stratification and assessing interventions, with the recently published PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study being the only other study (9). Furthermore, as major adverse cardiac events (MACE) are often driven by disease in nontarget vessels after percutaneous coronary intervention (PCI), it is unclear whether 3-vessel VH-IVUS is more strongly associated with outcome than plaque-based VH-IVUS analysis.

## METHODS

**Patients.** The VIVA (Virtual Histology in Vulnerable Atherosclerosis) study protocol was approved by the Cambridgeshire Research and Ethics Committee-3 (ref 07/Q0106/47); all participants gave written informed consent before enrollment. Patients undergoing PCI with either stable angina

or troponin-positive acute coronary syndrome (ACS) were prospectively enrolled. Exclusion criteria were: 1) prior revascularization or unsuitable for 3-vessel VH-IVUS; and 2) ACS, active inflammatory condition, or any form of surgery up to 3 months before enrollment.

VH-IVUS was performed in all main coronary arteries (target vessels before and after PCI and also nontarget vessels) after administration of glyceryl trinitrate. Data were acquired with 20 MHz Eagle-Eye Gold catheters (Volcano Corporation, Rancho Cordova, California) using motorized pull-back at 0.5 mm/s from the most distal safe position to the guide catheter. Data were captured on S5 consul software version 3.1 (Volcano Corporation), and analysis was performed offline by Krakow Cardiovascular Research Institute core laboratory, using the Volcano Image Analysis Software version 3.0.394. Consequently, VH-IVUS analysis did not influence PCI procedure or subsequent management.

Blood was drawn immediately pre-PCI and 24 h post-PCI. Core laboratory analysis of samples was performed for troponin-I (cTnI), interleukin-6 (IL-6), interleukin-18 (IL-18), high-sensitivity C-reactive protein (hsCRP), neopterin, soluble intracellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein-1 (MCP-1).

**Plaque classification.** We utilized the following plaque classification (Fig. 1), consistent with subsequently published VH-IVUS classifications (10): 1) Plaque: plaque burden of >40% vessel cross-sectional area for 3 consecutive frames. 2) Fibroatheroma (VHFA): plaque burden >40%, confluent necrotic core >10% plaque cross-sectional area, all for 3 consecutive frames. 3) Thin-capped fibroatheroma (VHTCFA): fibroatheroma (above) with the confluent necrotic core (>10% of plaque cross-sectional area) in contact with vessel lumen for 3 consecutive frames. VHTCFA were subdivided into calcified VHTCFA (dense calcium >10% plaque cross-sectional area in 3 consecutive frames) and noncalcified VHTCFA. 4) Thick-capped fibroatheroma (VHThCFA): fibroatheroma not fulfilling VHTCFA conditions. VHThCFA were subdivided into calcified VHThCFA (dense calcium >10% plaque cross-sectional area in 3 consecutive frames) and noncalcified VHThCFA. 5) Fibrocalcific plaque (VHFCa): plaque with dense calcium >10% plaque cross-sectional area in 3

### ABBREVIATIONS AND ACRONYMS

**ACS** = acute coronary syndrome

**BMS** = bare metal stent

**CI** = confidence interval

**DES** = drug-eluting stent

**ISR** = in-stent restenosis

**MACE** = major adverse cardiac events

**MI** = myocardial infarction

**MLA** = minimal luminal area

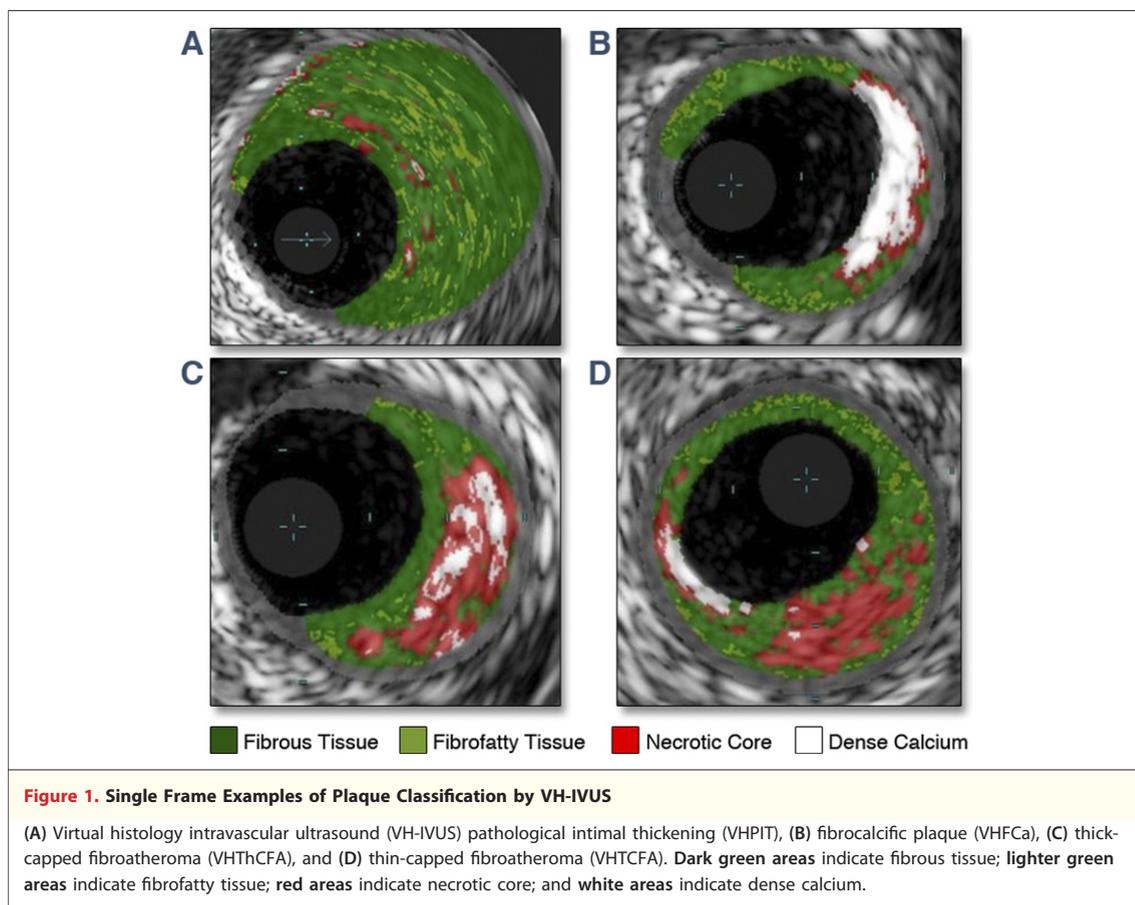
**NCL** = nonculprit lesion

**VH-IVUS** = virtual histology intravascular ultrasound

**VHTCFA** = virtual histology intravascular ultrasound-identified thin-capped fibroatheromata

**VHFA** = virtual histology intravascular ultrasound-identified fibroatheromata

**VHThCFA** = virtual histology intravascular ultrasound-identified thick-capped fibroatheromata



consecutive frames, not meeting fibroatheroma definition. 6) Pathological intimal thickening (VHPIT): plaque not meeting VHFA or VHFCa plaque definitions and predominantly fibrous tissue.

Culprit lesions were defined according to electrocardiographic criteria (ST-segment shift or T-wave inversion) and angiographic appearances (point of angiographic maximal stenosis, luminal irregularities consistent with ulceration, or filling defects consistent with thrombus) at PCI. Complete coverage by stent was also confirmed on IVUS. Remodeling index, thrombus, and plaque rupture were determined according to established definitions (11).

**Follow-up and study endpoints.** Patients were followed up for 3 years from enrollment of the first patient by clinic visits, telephone interview, clinical databases, and clinical notes. The composite primary endpoint of (total) MACE comprised death, myocardial infarction, and unplanned revascularization (PCI and coronary artery bypass surgery, driven by nonrestenotic lesions and in-stent restenosis [ISR]). Nonrestenotic MACE comprised a combined endpoint of death, myocardial infarction, or unplanned revascularization, excluding in-stent restenosis-driven events.

**Statistical analysis. LESION-BASED ANALYSIS.** To assess the effect of NCL factors on nonrestenotic MACE, a series of Cox proportional hazard regression models were fitted. Because these analyses contained several lesions per patient, analyses were stratified by patient. This allows patients to have a different baseline hazard, but within strata, the effects of lesion characteristics on time to event were assumed common to all patients. The MACE events occurring without angiographic follow-up were classified as “indeterminant” and were excluded. A second analysis was planned to examine associations between culprit lesion factors and ISR-driven MACE (excluding de novo plaque-driven MACE). However, the number of ISR-driven MACE endpoints was too low for a valid Cox proportional Hazard regression analysis. We therefore analyzed the association between all lesions at baseline (NCL and culprit lesions) with all MACE endpoints (nonrestenotic and ISR-driven) using univariate Cox proportional hazard regression stratified by patient as above.

**PATIENT-BASED ANALYSIS.** All variables (clinical, PCI-related, NCL grayscale IVUS, and VH-IVUS

parameters) were tested for association with nonre-stenotic MACE using univariate Cox proportional hazard regression. All p values <0.05 were considered significant.

**BIOMARKERS.** Biomarker levels at baseline and also the stenting-related rise in biomarkers (24 h post-PCI minus immediately pre-PCI) were tested for association with nonrestenotic MACE using univariate Cox proportional hazard regression. All p values <0.05 were considered significant.

Statistical analysis was performed using SPSS version 17.0 (SPSS Inc, Chicago, Illinois). MACE rates in similarly mixed stable angina and ACS patient cohorts suggested a 5.8% drug-eluting stent (DES) and 28.8% bare-metal stent (BMS) 1-year MACE rate (12). Our recent stent usage ratio was 2 DES:1 BMS. Given the projected 18-month median follow-up, we expected 20 MACE per 100 patients recruited. Power calculations suggested that 100 patients would be required to detect a 20% difference in VHTCFA with 80% power and an alpha = 0.05. Recruitment of 170 patients was set to allow for lower than expected MACE rates.

## RESULTS

**Study recruitment and adverse events.** One hundred seventy patients (100 stable angina and 70 troponin-positive ACS) underwent 3-vessel VH-IVUS. There were 18 MACE in 16 patients: 14 revascularizations (11 PCI and 3 coronary artery bypass grafting), 2 MIs and 2 deaths. Three patients' data (all ACS) were excluded from analysis after corruption of archived VH-IVUS recordings. Median follow-up of the remaining 167 patients was 625 days (interquartile range: 463 to 990 days). In all, 30,372 mm of VH-IVUS were analyzed. There were no adverse events related to IVUS pullbacks.

**Lesion-based analysis.** Both patients who died lacked angiographic follow-up and, therefore, were excluded from the lesion-based analysis. In total, 1,096 lesions were analyzed; 19 lesions resulted in MACE (13 nonrestenotic MACE and 6 ISR-driven MACE). The number of lesions resulting in MACE by lesion type (culprit lesion vs. NCL) is shown in Table 1. Of the 13 NCLs that resulted in nonrestenotic MACE, 9 were in different vessels from the original stent, and 4 were in the same vessel: 2 were <10 mm from the original stent (1 BMS and 1 DES), and 2 were >40 mm from the original stent (1 BMS and 1 DES). One of the MI MACE was due to ISR. The other MI did not result in further PCI.

**Table 1. Total Number of MACE According to Plaque Subtype**

	Nonculprit Lesion MACE/Total	Culprit Lesion MACE/Total	Log-Rank p Value
VHPIT	1/132 (0.8%)	0/17 (0%)	0.30
VHFCa	1/92 (1.1%)	0/8 (0%)	0.54
Noncalcified VHThCFA	2/100 (2%)	1/17 (5.9%)	0.43
Calcified VHThCFA	1/46 (2.2%)	0/8 (0%)	0.93
Noncalcified VHTCFA	5/175 (2.9%)	3/35 (8.6%)	0.045
Calcified VHTCFA	3/386 (0.8%)	2/80 (2.5%)	0.16
Total	13/931 (1.4%)	6/165 (3.6%)	0.003

Values are n/N (%).  
 MACE = major adverse cardiac event; VHFCa = virtual histology intravascular ultrasound fibrocalcific plaque; VHPIT = virtual histology intravascular ultrasound pathological intimal thickening; VHTCFA = virtual histology intravascular ultrasound thin-capped fibroatheroma; VHThCFA = virtual histology intravascular ultrasound thick-capped fibroatheroma.

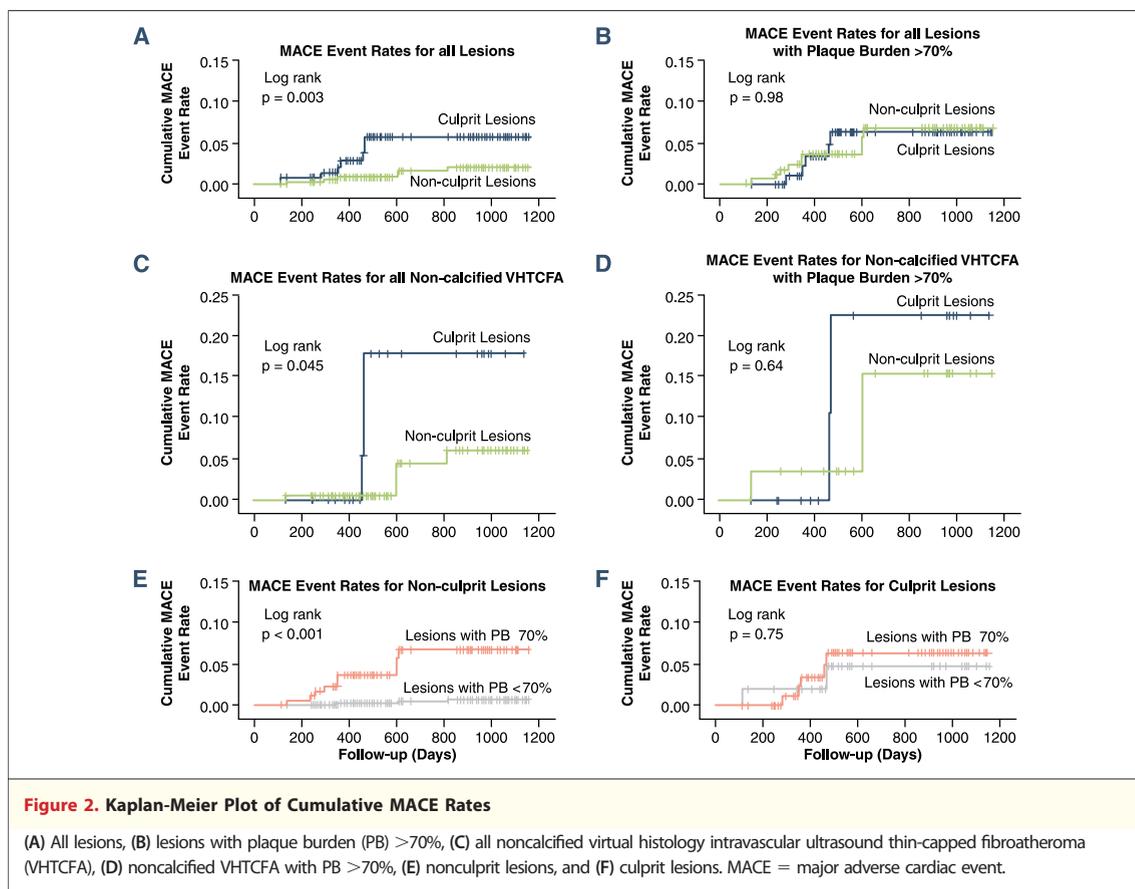
There were 931 NCLs, of which 13 resulted in MACE over a median follow-up of 625 days (1.4%). Six of the 165 culprit lesions resulted in MACE (3.6%). The following plaque characteristics were greater or more frequent in NCLs that caused nonrestenotic MACE: noncalcified VHTCFA (5 [38%] vs. 169 [18.4%]), p = 0.025), MLA <4 mm<sup>2</sup>, plaque burden >70%, and remodeling index (Table 2).

The MACE rate was greater for culprit lesions than for NCL (p = 0.003) (Fig. 2A), but this difference was lost when plaque burden was >70% (Fig. 2B). Similarly, the MACE rate for noncalcified VHTCFAs was greater for culprit lesions than for NCL (log-rank p = 0.045) (Fig. 2C), with the difference lost again when plaque burden was >70% (Fig. 2D). The MACE rate for NCLs was greater for lesions with a plaque burden >70% (log-rank p < 0.001) (Fig. 2E), but there was no difference in rates for culprit lesions with plaque burdens at baselines above or below 70% (Fig. 2F).

**Table 2. Comparison of NCL Parameters for Nonrestenotic MACE**

NCL Parameters	No MACE (n = 918)	Nonrestenotic MACE (n = 13)	Log-Rank p Value
VHPIT	131 (14.3%)	1 (8%)	0.54
VHFCa	91 (9.9%)	1 (8%)	0.78
Noncalcified VHThCFA	101 (11.0%)	2 (15%)	0.78
Calcified VHThCFA	45 (4.9%)	1 (8%)	0.79
Noncalcified VHTCFA	169 (18.4%)	5 (38%)	0.025
Calcified VHTCFA	381 (41.5%)	3 (23%)	0.32
MLA <4 mm <sup>2</sup>	251 (27%)	7 (54%)	0.021
Plaque burden >70%	169 (18%)	9 (69%)	<0.001
Remodeling index	1.00 (0.13)	1.14 (0.13)	0.014
Plaque volume, mm <sup>3</sup>	51 (21-127)	196 (106-430)	0.004
Thrombus	13 (1.4%)	0 (0%)	0.67
Ruptured plaque	13 (1.4%)	0 (0%)	0.67

Values are n (%), mean (SD), or median (interquartile range).  
 MLA = minimum luminal area; NCL = nonculprit lesion; other abbreviations as in Table 1.



**Associations between NCL and nonrestenotic MACE.** VHTCFA was the only NCL plaque subtype associated with nonrestenotic MACE on univariate analysis (HR: 7.53 [95% confidence interval [CI]: 1.12 to 50.55],  $p = 0.038$ ) (Fig. 3A). Plaque-based factors associated with nonrestenotic MACE included plaque burden >70% (HR: 8.13 [95% CI: 1.63 to 40.56],  $p = 0.011$ ) and remodeling index (HR: 2686 [95% CI: 1.94 to  $3.72 \times 10^6$ ],  $p = 0.032$ ) (Fig. 3B).

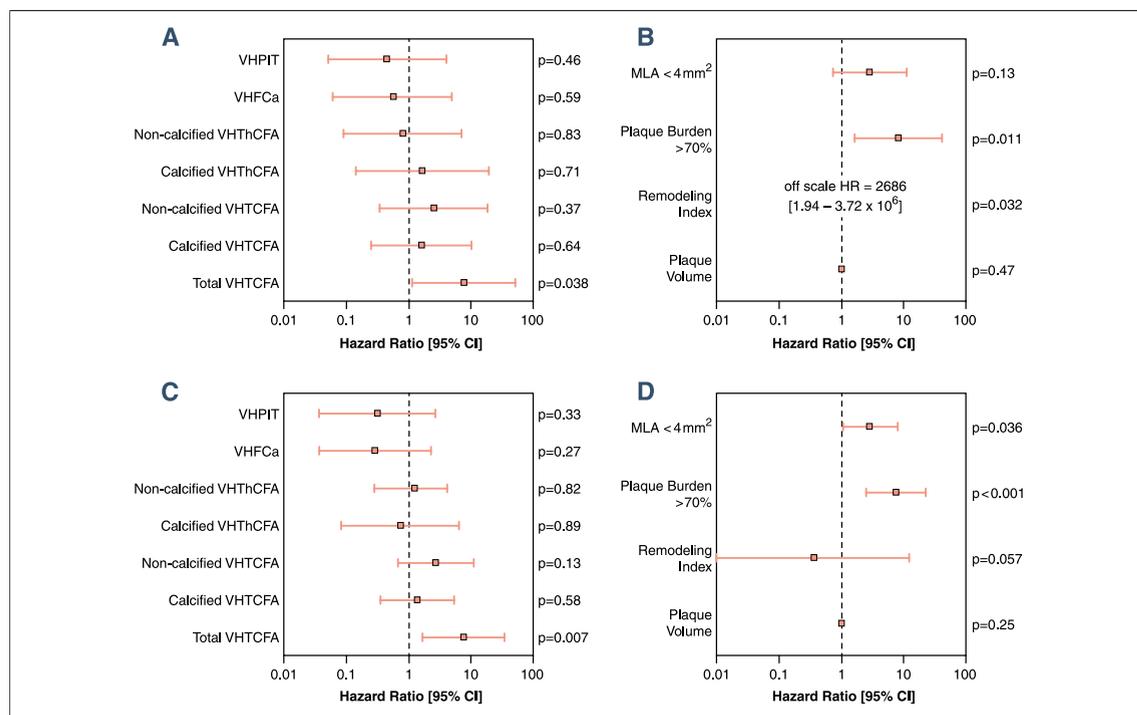
**Associations between all plaques (culprit and NCL) and total MACE events (nonrestenotic and ISR-driven events).** VHTCFA was the only VH-IVUS plaque subtype associated with total MACE on univariate analysis (HR: 8.16 [95% CI: 1.78 to 37.32],  $p = 0.007$ ) (Fig. 3C). Plaque-based factors associated with total MACE included plaque burden >70% (HR: 7.48 [95% CI: 2.50 to 22.31],  $p < 0.001$ ), MLA <4 mm<sup>2</sup> (HR: 2.91 [95% CI: 1.07 to 7.91],  $p = 0.036$ ), and the plaque being a culprit lesion, as opposed to NCL (HR: 4.43 [95% CI: 1.50 to 13.18],  $p = 0.007$ ) (Fig. 3D).

**Patient-based analysis of association between NCL factors and nonrestenotic MACE.** No patient-based clinical factors were associated with nonrestenotic MACE (Fig. 4A). Similarly, no stent-related or gray-

scale IVUS parameters were associated with nonrestenotic MACE (Fig. 4B). On whole patient-based analysis, the only NCL factor associated with nonrestenotic MACE was 3-vessel noncalcified VHTCFA (HR: 1.79 [95% CI: 1.20 to 2.66],  $p = 0.004$ ) (Fig. 4C). Biomarker levels measured immediately pre-PCI were not associated with nonrestenotic MACE. However, the PCI-related rise in interleukin-6 and high-sensitivity C-reactive protein were associated with nonrestenotic MACE on univariate analysis (Fig. 4D).

## DISCUSSION

The ability to identify plaque anatomy and composition in vivo is potentially a powerful method of predicting subsequent patient outcome. Despite the wealth of data on the substrate for MI from post-mortem studies (1,2,10) or animal models (11), methods that prospectively identify plaques that subsequently rupture are needed. VH-IVUS identifies plaque composition and potentially classifies plaques into low-risk and high-risk subtypes. However, to date, the potential prognostic relevance of VH-IVUS findings to clinical outcomes in patients undergoing PCI has received limited study.



**Figure 3. Univariate Lesion-Based Analyses of Associations Between Plaque Subtype or Characteristics and MACE**

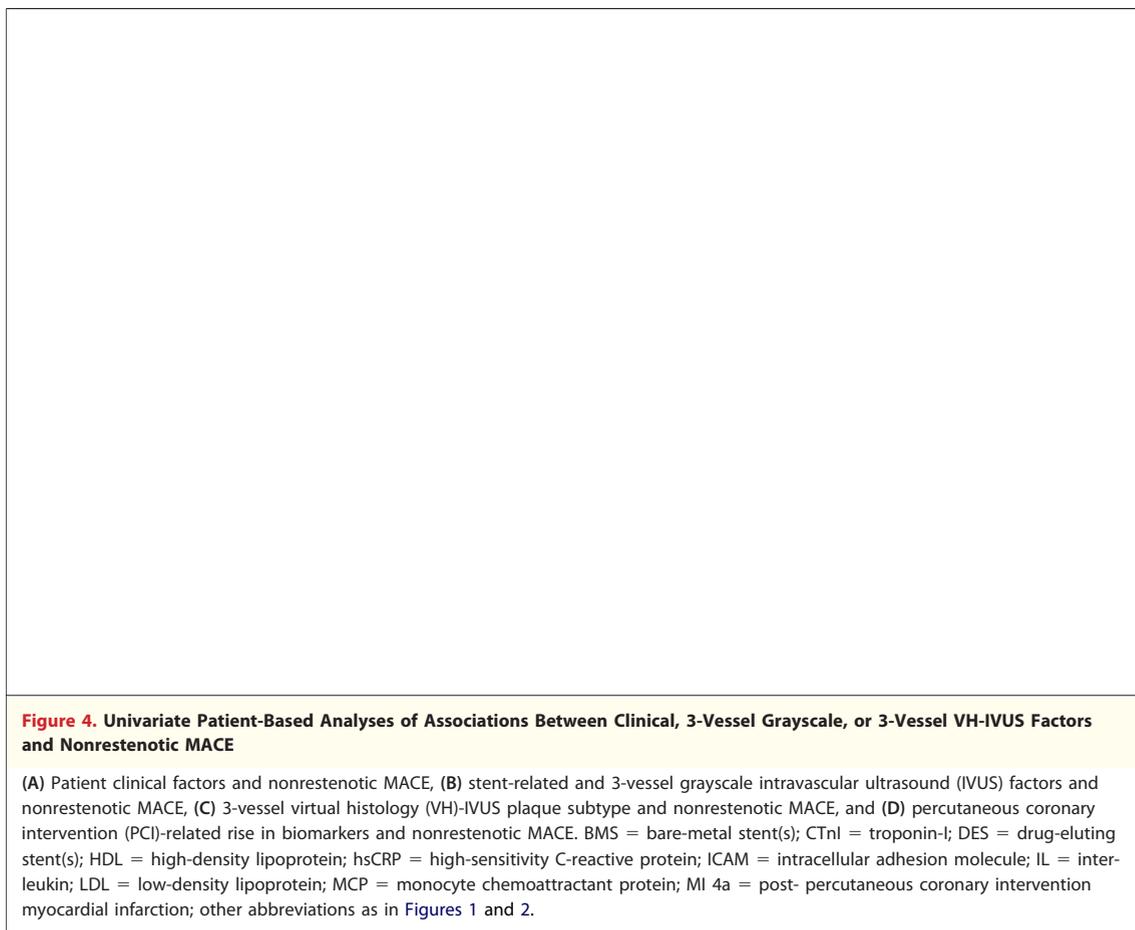
(A) Nonculprit lesion (NCL) plaque subtype and nonrestenotic MACE, (B) NCL plaque characteristics and nonrestenotic MACE, (C) all plaque subtypes (NCL and culprit lesions) and total MACE, and (D) characteristics of all plaques (NCL and culprit lesion) and total MACE. CI = confidence interval; HR = hazard ratio; MLA = minimum luminal area; other abbreviations as in Figures 1 and 2.

In this prospective study of patients undergoing 3-vessel coronary artery VH-IVUS, NCL VHTCFA was associated with nonrestenotic MACE, both on an individual plaque and whole-patient analysis. Although similar findings have recently been reported from the PROSPECT study on an individual plaque basis (9), this is the first report of an association between VH-IVUS–based plaque classification and nonrestenotic MACE on a whole-patient basis. This is also the first report of an association between VH-IVUS–identified plaque classification and total MACE. The preservation of this association between VHTCFA and MACE on a number of different analyses emphasizes the biological importance of this association, and indicates that VH-IVUS can identify plaques at increased risk of subsequent events. In addition, NCL plaque burden >70% and remodeling index were also both strongly associated with nonrestenotic MACE.

Nonrestenotic MACE rates for noncalcified VHTCFA were less for NCL than for culprit lesions (2.9% vs. 8.6%,  $p = 0.045$ ) (Table 1). Despite this difference the greater number of NCLs meant that 68% of MACE occurred because of NCLs, emphasizing that even in a PCI study, the majority of MACE occur because of NCL.

The low number of ISR-driven MACE made an analysis of the association between culprit lesion factors at baseline and subsequent ISR-driven MACE impossible. However, a pooled analysis of all plaques (culprit and NCL) and total MACE showed that VHTCFA remained associated with MACE. This finding suggests that culprit VHTCFA are associated with increased ISR-driven MACE, although a study with sufficient ISR MACE endpoints would be required for confirmation. We also found that 3-vessel noncalcified VHTCFA number was the only NCL factor associated with nonrestenotic MACE on patient-based analysis. This finding, in a population too small to permit conventional risk factors from predicting MACE, suggests that VH-IVUS plaque identification may be a more useful predictor of MACE, perhaps as it is a “downstream” marker of risk.

There are a number of important differences between our study (VIVA) and the recently reported PROSPECT study (9). First, VIVA contains both stable angina and ACS patients whereas PROSPECT contained only patients with ACS. Second, although both studies had protocol-driven 3-vessel VH-IVUS, we acquired data both before and after PCI, to permit inclusion or exclusion of



the culprit lesions in analyses. Third, MACE definitions differed between studies (death, MI, or unplanned revascularization in the VIVA study vs. “composite of death from cardiovascular causes, cardiac arrest, MI, or rehospitalization due to unstable or progressive angina” in the PROSPECT study). The inclusion of rehospitalization in the PROSPECT study is likely to result in higher MACE rates. Fourth, the VHTCFA definitions are different between studies. The PROSPECT study required the confluent necrotic core of  $>10\%$  plaque area to be in contact with the lumen for  $\geq 30^\circ$  arc for 3 consecutive frames, resulting in a higher proportion of NCL being defined as VHTCFA in the VIVA study than in the PROSPECT study (561 of 931 [60.2%] vs. 595 of 2,709 [22.0%], respectively). Fifth, the VIVA study was performed using a later iteration of the VH-IVUS software (S5 consul software version 3.1 [Volcano Corporation, Rancho Cordova, California]) with analysis performed by our core laboratory (KCRI), using the Volcano Image Analysis Software (Volcano Corporation) version 3.0.394, whereas the PROSPECT study

used pcVH 2.1 software (Volcano Corporation). Our findings also extend those reported in the PROSPECT study. We performed whole-patient analysis of both NCL and nonrestenotic MACE, and total plaques (culprit plus NCL) and total MACE, which were not reported in the PROSPECT study.

Despite these differences, the VIVA and PROSPECT studies show remarkably similar findings. Both studies find that VHTCFA was the only nonculprit lesion subtype associated with MACE (VIVA HR: 7.53 vs. PROSPECT HR: 3.90). Both studies also found that plaque burden  $>70\%$  was strongly associated with nonrestenotic MACE (VIVA HR: 8.13 vs. PROSPECT HR: 8.72). Both studies report that VHTCFA are common: VIVA 561 of 931 (60.2% of NCL) versus PROSPECT 595 of 2,709 (22.0% of NCL). Importantly, despite the increased vulnerability of VHTCFA compared to other plaque subtypes, the absolute event rate per individual VHTCFA remained low. There are a number of possible explanations for this. First, technological limitations (in particular axial resolution) limit the ability of VH-IVUS to closely replicate histology-

defined TCFA. Second, events for which plaque rupture is not critical (revascularization for the VIVA study and hospitalization with progressive angina for the PROSPECT study) made up the majority of MACE endpoints. Finally, the lack of routine angiographic follow-up means that some deaths in which TCFA rupture is likely will be excluded from the analysis.

**Study limitations.** Although VHTCFA number was associated with MACE, VH-IVUS findings were not associated with death or MI. In this modern era of aggressive interventional and pharmacotherapeutic strategies, MACE rates in PCI studies are predominantly driven by revascularization rather than by MI or death (12), and a larger study would be required to provide sufficient statistical power for these endpoints. Although MACE numbers observed were relatively small, they are consistent with our understanding of the pathophysiology of MACE, and we believe that use of rigorous study protocols and core laboratories for analysis adds robustness to our conclusions. Although we employed a number of univariate analyses, our power calculation supports a significant difference for VHTCFA only. Thus, our power calculation does not support analyses for many of the presented results and these should be viewed as exploratory findings. Finally, the number of endpoints was too small to allow reliable usage of multivariable regression.

VH-IVUS has some technological limitations, particularly the axial resolution of 100  $\mu\text{m}$  to 150  $\mu\text{m}$  (7), so that VH-IVUS TCFA definitions cannot exactly

replicate histopathologic definitions. In particular, VH-IVUS will tend to over-estimate TCFA numbers compared to histology, and some histologic ThCFAs will be classified as VHTCFAs. However, it is not claimed that VH-IVUS-identified TCFA are exactly equivalent to histologically defined TCFA, rather that VH-IVUS classification is valid and important if it provides prospective prognostic information to determine the natural history of each plaque subtype.

## CONCLUSIONS

VHTCFA was associated with nonrestenotic and total MACE on individual plaque analysis, and non-calcified VHTCFA was associated with nonrestenotic and total MACE on whole-patient analysis. We demonstrate that VH-IVUS can identify plaques at increased risk of subsequent events, raising the possibility of better risk stratification at the time of PCI.

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**Key Words:** major adverse cardiac event ■ necrotic core ■ thin-capped fibroatheroma ■ troponin ■ virtual histology intravascular ultrasound.