

iREVIEWS

STATE-OF-THE-ART PAPER

Plaque Composition by Intravascular Ultrasound and Distal Embolization After Percutaneous Coronary Intervention

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Distal embolization after percutaneous coronary intervention occurs in 15% to 70% of patients, depending on the sensitivity of the diagnostic modality used, and is associated with a poor prognosis after elective and primary percutaneous coronary intervention. It has been hypothesized that imaging of the plaque composition can identify coronary artery lesions that are predisposed to causing distal embolization. This review report aims to summarize all currently available published data on the use of assessment of atherosclerotic plaque composition by virtual histology intravascular ultrasound (VH-IVUS) to predict the occurrence of distal embolization. A systematic review of the literature was performed. We searched Medline, ISI Web of Knowledge, and the Cochrane Library from January 2002 until March 2011. When a study was found to be relevant, the manuscript was obtained and reviewed. A total of 11 studies were identified investigating the relationship between plaque composition assessed by VH-IVUS and distal embolization. Although all studies used the same equipment to perform and analyze VH-IVUS, there was considerable heterogeneity in patient characteristics, outcome definitions, and reporting of VH-IVUS findings. Nevertheless, the necrotic core plaque component—either by itself or as a constituent of a VH thin cap fibroatheroma—was associated with distal embolization in all but 2 of the 11 reviewed studies. Therefore, identification of lesions with large amounts of necrotic core on VH-IVUS could identify lesions that might benefit from the selective use of embolic protection devices. (J Am Coll Cardiol Img 2012;5:S111–8) © 2012 by the American College of Cardiology Foundation

umen gain during the treatment of coronary artery disease with percutaneous coronary intervention (PCI) is the result of vessel stretching and plaque dissection, redistribution, or (especially in the unstable clinical setting) embolization into the distal microvasculature leading to ischemia at the myocardial tissue level

(1–3). Depending on the imaging modality used, the incidence of distal embolization ranges from 15% with coronary angiography to as high as 70% with contrast-enhanced cardiac magnetic resonance imaging (4,5). This undesirable side effect of PCI is associated with poor functional recovery and adverse outcomes (4,5).

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Plaque composition may be an important contributing factor in the occurrence and extent of distal embolization after PCI. Virtual histology intravascular ultrasound (VH-IVUS) (Volcano Corp., Rancho Cordova, California) is a widely available technique allowing real-time determination of plaque composition in vivo using radiofrequency analysis of the backscattered ultrasound signal. VH-IVUS can distinguish among 4 different plaque components: fibrotic plaque, fibrofatty plaque, necrotic core, and dense calcium. These are represented as green, light green, red, and white, respectively. Thus, VH-IVUS provides additional information by offering an accurate assessment of plaque composition on top of the 3-dimensional anatomical assessment provided by grayscale IVUS (6,7). We performed a systematic review of all currently available data on the ability of plaque composition by VH-IVUS to predict distal embolization after PCI.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CK = creatine kinase

CK-MB = creatine kinase-myocardial band

cTnl = cardiac troponin I

HITS = high-intensity transient signals

OCT = optical coherence tomography

OR = odds ratio

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

VH-IVUS = virtual histology intravascular ultrasound

VH-TCFA = virtual histology thin cap fibroatheroma(s)

Study Search Strategy

We searched Medline, ISI Web of Knowledge, and the Cochrane Library with various combinations of the terms “virtual histology,” “intravascular ultrasound,” “embolization,” “no-reflow,” “infarction,” “microvascular,” “obstruction,” and/or “injury” in the abstract and/or title. Articles eligible for further review were selected after screening abstracts and titles. We searched the aforementioned data sources for possible studies from January 2002 until March 2011. The starting date of 2002 was chosen because the first clinical case with VH-IVUS was performed in that year. When a study was found to be relevant, the manuscript was obtained and

reviewed; and the references were searched for relevant articles. Figure 1 shows a flowchart of the study search strategy. A total of 11 studies were identified that described the relationship between plaque composition assessed by VH-IVUS and distal embolization assessed by a variety of techniques and definitions both in stable and unstable patients (Table 1).

Literature Review

Table 1 summarizes all studies included in this systematic review (8–18). The necrotic core plaque component either by itself or as a constituent of a

virtual histology-thin cap fibroatheroma (VH-TCFA) was associated with distal embolization in all but 2 of the 11 reviewed studies. Figure 2 summarizes the various quantitative measurements of necrotic core plaque in the studies included in this systematic review (8,10,12–17). Studies by Kawamoto *et al.* (9), Bose *et al.* (11), and Yamada *et al.* (18) were not included in this figure, as they did not use a dichotomous definition of distal embolization.

Kawaguchi *et al.* (8) and Kawamoto *et al.* (9) were the first to investigate the relationship between VH-IVUS plaque characteristics and the occurrence of distal embolization. Kawaguchi *et al.* (8) performed VH-IVUS in a cohort of 71 patients with ST-segment elevation myocardial infarction (STEMI). Thrombus aspiration was performed in all patients before VH-IVUS imaging was performed, and stents were implanted in all patients immediately after VH-IVUS. The primary endpoint of ST-segment re-elevation occurred in 11 patients (15.5%). Receiver-operating characteristic curve analysis showed a strong association between necrotic core volume and ST-segment re-elevation. A cutoff value of 33.4 mm³ predicted ST-segment re-elevation with a sensitivity of 81.7% and a specificity of 63.6%. Total plaque volume was not associated with an increased risk of distal embolization in this study.

In a study of 44 patients, Kawamoto *et al.* (9) investigated the relationship between pre-intervention VH-IVUS assessed plaque characteristics and small embolic particles detected using a Doppler guidewire during elective stent implantation. Patients were divided into tertiles according to the number of high-intensity transient signals (HITS) detected by the Doppler guidewire. In this relatively small study, necrotic core area was identified as an independent predictor of the tertile with the greatest number of HITS after multivariate logistic regression. Moreover, there was a significant negative correlation between the number of HITS and coronary flow velocity reserve immediately after stenting.

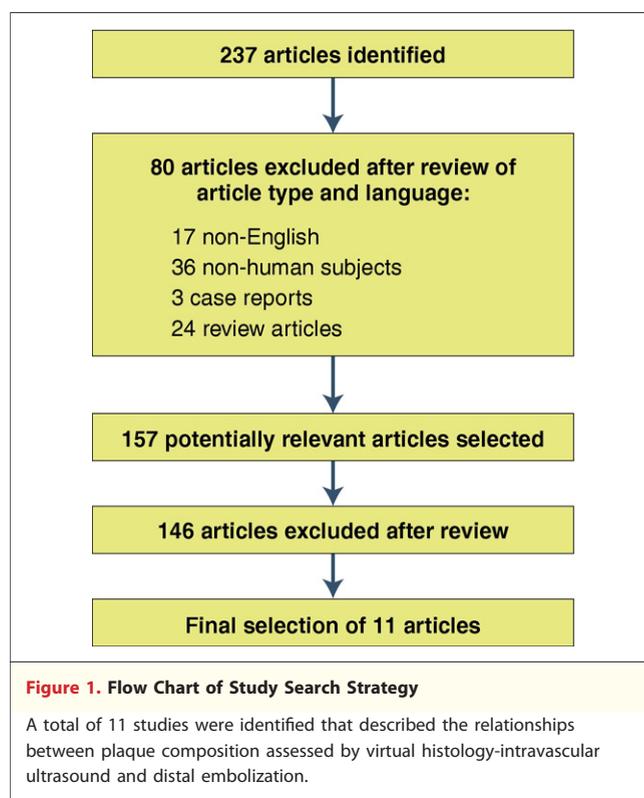
After these initial observations, a number of other research groups published results of similar studies (10–18). Studies by Nakamura *et al.* (15) and Bae *et al.* (10) in cohorts of 50 STEMI patients and 57 acute coronary syndrome (ACS) patients, respectively, did not find a relationship between necrotic core and distal embolization. Nakamura *et al.* (15) reported that the presence of a “marblelike” image, consisting of fibrofatty and fibrous plaque,

was associated with angiographic no-reflow ($p = 0.02$). It should be noted that VH-IVUS analysis of the percentage of necrotic core can be compromised by the presence of thrombus; thrombus has a VH-IVUS appearance of fibrotic or fibrofatty plaque depending on its age (19). For example, in the study by Nakamura et al. (15) in STEMI patients, the marblelike image may represent a mixed red and white thrombus to explain the relationship between the VH-IVUS appearance and angiographic no-reflow.

A large number of other publications did find a relationship between necrotic core and distal embolization. For example, Higashikuni et al. (12) performed VH-IVUS measurements in 47 patients with ACS (acute myocardial infarction or unstable angina) preceded by thrombus aspiration if thrombus was detected angiographically or by IVUS before stent implantation. In 9 patients (18.4%) with no-reflow (defined as a decrease in Thrombolysis In Myocardial Infarction [TIMI] flow grade after mechanical dilation compared with before), the percentage of necrotic core at the minimal lumen area site was significantly increased compared with patients without no-reflow ($22.3 \pm 11.0\%$ vs. $11.8 \pm 0.3\%$, $p \leq 0.01$). Similarly, in an analysis of the entire culprit lesion, patients with no-reflow had a larger percentage of necrotic core volume ($22.1 \pm 9.3\%$ vs. $11.7 \pm 7.9\%$, $p < 0.01$) and a smaller percentage of fibrotic plaque volume ($59.6 \pm 11.2\%$ vs. $68.3 \pm 10.2\%$, $p = 0.03$).

Bose et al. (11) performed VH-IVUS before stent implantation in 55 patients who underwent elective PCI for a single de novo coronary artery lesion. Serum creatine kinase (CK) and cardiac troponin I (cTnI) were measured before PCI and at 6, 12, and 24 h after PCI. Strong correlations between different measurements of necrotic core (necrotic core volume, necrotic core volume per 10-mm-long lesion segment, and percentage necrotic core volume) and the maximum increase in cardiac biomarkers were observed ($r = 0.64, 0.66$, and 0.52 , respectively; all $p < 0.01$).

The largest investigation to date of plaque composition and no-reflow was performed in a cohort of 190 consecutive ACS patients by Hong et al. (13). This study group also investigated the presence of the VH-TCFA phenotype (defined as necrotic core $\geq 10\%$ of plaque area in at least 3 consecutive frames without overlying fibrous tissue in the presence of $\geq 40\%$ plaque burden) (20). No-reflow, defined as TIMI flow grade ≤ 2 after stenting, occurred in 12.6% of patients. Patients



with no-reflow had a significantly greater absolute and percentage necrotic core area at the minimum lumen area site ($16.2 \pm 1.2 \text{ mm}^2$ vs. $0.9 \pm 0.8 \text{ mm}^2$, $p < 0.01$, and $24.5 \pm 14.3\%$ vs. $16.1 \pm 10.6\%$, $p < 0.01$). Absolute necrotic core volume and percentage necrotic core volume were also larger in patients with no-reflow ($30 \pm 24 \text{ mm}^3$ vs. $16 \pm 17 \text{ mm}^3$, $p < 0.01$; and $22 \pm 11\%$ vs. $14 \pm 8\%$, $p < 0.01$). After multivariable analysis, the percentage necrotic core volume remained an independent predictor of no-reflow (odds ratio [OR]: 1.13, $p < 0.01$). Moreover, at least 1 VH-TCFA, as well as multiple VH-TCFA, were significantly more common in patients with no-reflow (71% vs. 36%, $p < 0.01$, for at least 1 VH-TCFA and 38% vs. 15%, $p < 0.01$, for multiple VH-TCFA). Other studies by Ohshima et al. (16) and Yamada et al. (18) also reported that lesions containing a VH-TCFA are more likely to cause distal embolization after PCI (16,18).

Another publication by Hong et al. (14), but with a different cohort of patients studied at a different institution at a different time, investigated the impact of plaque composition on cardiac cTnI release after PCI. The results from this study of 80 patients (29 with stable angina, 51 with unstable angina) with normal pre-PCI cTnI

Table 1. Summary of Studies Investigating Plaque Characteristics by VH-IVUS and Distal Embolization

First Author (Ref. #)	Year	N	Elective/ACS/STEMI	Pre-Stent Thrombectomy	Primary Outcome	NC Associated With Distal Embolization				
						NC Volume	% NC Volume	NC Area	% NC Area	VH-TCFA
Kawaguchi <i>et al.</i> (8)	2007	71	STEMI	Yes, 100%	ST-segment re-elevation	+	n/a	n/a	n/a	n/a
Kawamoto <i>et al.</i> (9)	2007	44	Elective	No	High-intensity transient signals	n/a	n/a	+	n/a	n/a
Nakamura <i>et al.</i> (15)	2007	50	STEMI	Yes, 75%	Decrease in TIMI flow grade	n/a	-	n/a	n/a	n/a
Bae <i>et al.</i> (10)	2008	57	ACS	Yes, 14%	TIMI flow grade ≤ 2	-	n/a	n/a	-	n/a
Higashikuni <i>et al.</i> (12)	2008	49	ACS	Yes, 67%	Decrease in TIMI flow grade	n/a	+	n/a	+	n/a
Bose <i>et al.</i> (11)	2008	55	Elective	No	CK/cTnI elevation $\geq 3 \times$ ULN	+	+	n/a	n/a	n/a
Hong <i>et al.</i> (13)	2011	190	ACS	No	TIMI flow grade ≤ 2	+	+	+	+	+
Hong <i>et al.</i> (14)	2009	80	Elective and ACS	No	cTnI $\geq 3 \times$ ULN	+	+	+	+	n/a
Ohshima <i>et al.</i> (16)	2009	44	STEMI	Yes, 100%	TIMI flow grade ≤ 2	-*	-*	n/a	n/a	+
Yamada <i>et al.</i> (18)	2010	29	Elective	No	Index of microvascular resistance	n/a	n/a	n/a	n/a	+
Shin <i>et al.</i> (17)	2011	112	Unstable angina	No	CK-MB elevation \geq ULN	+	n/a	+	+	n/a

*However, summation of fibrofatty plaque and NC volumes and fibrofatty plaque and percentage NC volumes were associated with distal embolization.
ACS = acute coronary syndrome(s); CK = creatine kinase; cTnI = cardiac troponin I; IVUS = intravascular ultrasound; MB = myocardial band; n/a = not available; NC = necrotic core; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction; TCFA = thin-cap fibroatheroma(s); ULN = upper limit of normal; VH = virtual histology.

confirmed and extended their previous observations. Post-PCI cTnI elevation $\geq 3 \times$ the upper limit of normal was present in 38 patients (47%). Absolute and percentage necrotic core volumes and absolute and percentage necrotic core area at the minimum lumen site and at the largest necrotic core site were significantly greater in patients with post-PCI cTnI elevation $\geq 3 \times$ the upper limit of normal ($n = 38$, 47%) than in patients without post-PCI cTnI elevation $\geq 3 \times$ the upper limit of normal. After multivariable analysis, absolute necrotic core area at the minimum lumen site remained an independent predictor of post-PCI cTnI elevation $\geq 3 \times$ the upper limit of normal (OR: 1.32, $p < 0.01$).

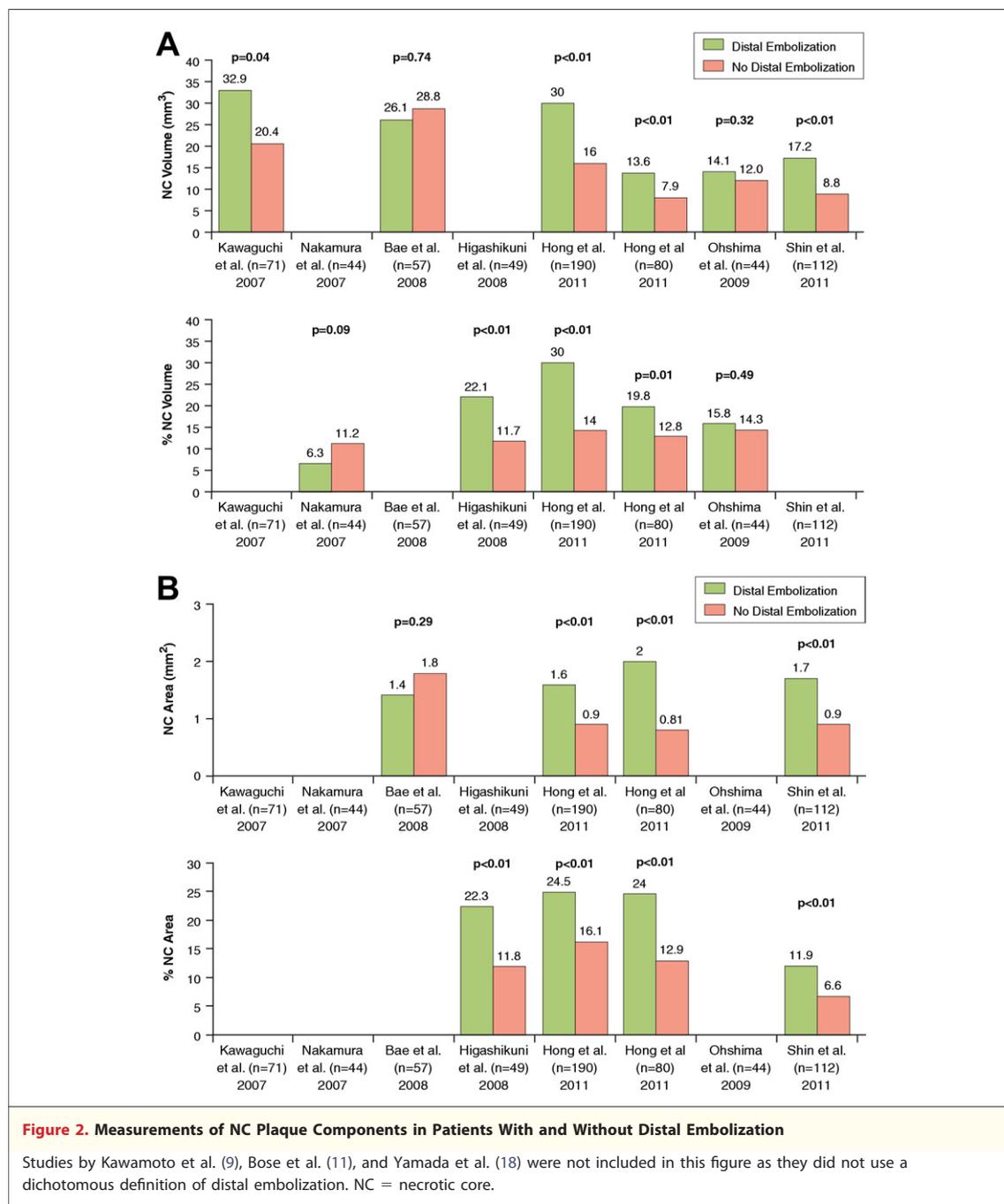
Finally, in a recent study by Shin *et al.* (17) reported an association between area, percentage area, and volume of necrotic core and creatine kinase-myocardial band (CK-MB) elevation of $>1 \times$ upper limit of normal in a cohort of 112 consecutive patients with unstable angina. After multivariate analysis, dense calcium volume and percentage necrotic core were the only independent predictors of post-PCI CK-MB elevation.

Plaque Composition Using Other Imaging Modalities and Distal Embolization

Studies using different image modalities such as integrated backscatter IVUS, near-infrared spectroscopy, and optical coherence tomography (OCT) have also reported an association between necrotic core and distal embolization (21–23). Uetani *et al.*

(23) performed integrated backscatter IVUS measurements in 114 patients undergoing elective PCI. By receiver-operating characteristic analysis, they identified a cutoff of 45.6 mm³ of lipid volume as a predictor of myocardial injury defined as a post-procedural rise in troponin T $\geq 3 \times$ the upper limit of normal (23). Yonetsu *et al.* (22) performed OCT measurements in 125 consecutive patients undergoing PCI. After multivariate analysis, the presence of OCT-TCFA (defined as a lipid-rich plaque with a fibrous cap thickness $<70 \mu\text{m}$) was an independent predictor of a post-procedural rise in CK-MB $\geq 3 \times$ the upper limit of normal (OR: 4.68, $p < 0.01$) (22). A study by Tanaka *et al.* (24) showed that OCT-derived lipid arc can predict no-reflow after PCI in patients with non-STEMI. As compared with VH-IVUS, OCT offers the advantage of a higher resolution ($\sim 10 \mu\text{m}$ compared with $\sim 100 \mu\text{m}$ for IVUS), which enables imaging of coronary endothelium and thin fibrous caps. Moreover, IVUS is not a reliable technique to image thrombus, whereas OCT is. This also holds true for mural thrombi, which are not only found in unstable but also stable angina pectoris patients. On the other hand, OCT has relatively poor penetration through tissue and blood, which limits the ability of OCT to evaluate the extent of coronary plaque volume. Also, there are conflicting reports concerning the accuracy of OCT to classify plaque composition (25,26).

Recently, Goldstein *et al.* (21) described 4 cases of distal embolization after balloon dilation of



lipid-rich plaques detected by the novel imaging technique of near-infrared spectroscopy. Near-infrared spectroscopy illuminates tissue with near-infrared light with a wavelength between 780 and 2,500 nm. As different types of chemical bonds absorb light with differing wavelengths, the resulting absorbance spectrum reflects the chemical makeup of the imaged tissue. As a result, this technique is very effective in detecting lipid-laden plaque (27,28). The device used in the study by

Goldstein et al. (21) combines the near-infrared spectroscopy lipid plaque detection technology with grayscale IVUS.

Clinical Implications

There seems to be an important relationship between the necrotic core plaque component assessed using VH-IVUS or other imaging modalities and the occurrence of distal embolization.

Figure 2 shows that the extent of necrotic core was larger in patients with distal embolization regardless of whether it was reported as volume, percentage volume, area, or percentage area. Furthermore, 3 studies reported that VH-TCFA, which contain a large amount of necrotic core, were more common in patients with distal embolization (13,16,18). Pathologists have postulated TCFA to be the precursor lesion of plaque rupture, although a recent trial showed that only a minority of VH-TCFA cause cardiovascular events (29–33). The VH-IVUS diagnosis of a TCFA must be inferred because pathologists have defined a TCFA as a necrotic core with an overlying fibrous cap measuring $<65 \mu\text{m}$, less than the resolution of IVUS (33).

Thus, lesions containing large lipid-rich necrotic cores are predisposed to iatrogenic distal embolization. The use of pre-intervention statins, vasodilators, or embolic protection devices could be particularly suited for these high-embolic-risk patients. Although the concept of embolic protection seems especially appealing, distal and proximal embolic protection devices have failed to show a treatment benefit in several randomized clinical trials in native coronary artery lesions not stratified by their composition, even in patients with ACS (34–36). Prior trials examining embolic protection devices have shown clinical benefit only in situations where the amount of debris is largest, such as in saphenous vein grafts. To the best of our knowledge, no trial has yet been published or presented investigating pre-procedural lesion assessment to guide the decision whether or not to randomize a patient. The randomized CANARY (Coronary Assessment by Near-Infrared of Atherosclerotic Rupture-Prone Yellow) trial will investigate whether a distal protection device can reduce distal embolization in patients with lesions containing a large lipid core plaque as assessed by near-infrared spectroscopy. The current review indicates that a similar trial using VH-IVUS to risk-stratify lesions prior to stent implantation might be warranted.

Several factors complicate direct interstudy comparisons in this review. Although all studies used the same equipment to perform and analyze VH-IVUS, there was considerable heterogeneity in patient characteristics, use of pre-stent throm-

bectomy, outcome definitions, and reporting of VH-IVUS findings (Table 1). Six studies enrolled only ACS patients, 3 studies enrolled only elective patients, and 1 study enrolled both. As there is no consensus on how to measure distal embolization, outcome definitions included invasive measurement of embolizing particles by Doppler guidewire, measurement of index of microvascular resistance, ST-segment re-elevation, measurements of TIMI flow, and cardiac biomarkers. These endpoints were all surrogates for distal embolization of atherosclerotic plaque material after PCI. However, although distal embolization was definitely a contributing factor in the aforementioned endpoints, it may not have been the sole contributing factor. For example, acute obstruction of blood flow to the distal vasculature has also been shown to cause capillary damage resulting in slow flow, especially in ACS patients (37). Finally, VH-IVUS measurements were not reported uniformly in the reviewed studies. A consensus document published in 2009 recommended reporting absolute and relative VH-IVUS parameters (fibrofatty plaque, fibrotic plaque, necrotic core, and dense calcium) at the site of minimum lumen area as well as averaged over the entire lesion (20). However, most studies were performed prior to publication of the consensus document, and only 2 studies reported VH-IVUS findings in the recommended manner (13,14).

Conclusions

Observational studies show a clear relationship between the amount of necrotic core and distal embolization on VH-IVUS imaging and alternative imaging modalities (integrated backscatter IVUS, OCT, near-infrared spectroscopy). The results of randomized trials will have to be awaited to determine whether imaging of plaque composition in combination with adjunctive pharmacological or device-based interventions reduces the incidence of distal embolization.

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■ percutaneous coronary
intervention ■ virtual histology
intravascular ultrasound.