Association Between Virtual Histology Intravascular Ultrasound Findings and Subsequent Coronary Events in Patients With Acute Coronary Syndrome

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Summary

Virtual histology intravascular ultrasound (VH-IVUS) was employed to compare coronary plaque characteristics between acute coronary syndrome (ACS) patients with and without subsequent coronary events.

It is critical to predict subsequent coronary events in patients treated for ACS. Coronary artery events sometimes occur in lesions that do not receive intervention.

VH-IVUS was performed in 57 patients with ACS to analyze 83 non-culprit lesions. Characteristics of plaques in the non-culprit lesions were determined. Patients were followed-up for 4.8 ± 1.8 years.

During the follow-up period, ACS and stable angina pectoris occurred in 7 patients in whom 13 non-culprit lesions had been analyzed. Seventy non-culprit lesions in 50 patients who did not experience subsequent coronary events were also analyzed. Plaque area was greater in 7 patients who had subsequent coronary events than in those who did not (11.5 ± 3.1 versus 9.1 ± 3.6 mm²/mm², \( P = 0.03 \)). However, there was no significant difference in plaque burden between the two groups (57.1 ± 8.9 versus 55.6 ± 8.7%, \( P = 0.18 \)). Areas of dense calcium (DC) and necrotic core (NC) were greater in patients who had subsequent coronary events than in those who did not (0.6 ± 0.5 versus 0.2 ± 0.3 mm³/mm², \( P < 0.001 \), and 1.8 ± 1.0 versus 1.0 ± 0.8 mm³/mm², \( P < 0.01 \), respectively). When DC area was larger (≥ 3.4% of the plaque area), the cumulative coronary event rate increased significantly (28.6 versus 6.5%, \( P < 0.01 \)). This was also true for NC area (≥ 20.9%, 31.4 versus 5.1%, \( P < 0.01 \)).

Area size of DC or NC in non-culprit plaques may be associated with subsequent coronary events in patients with ACS. (Int Heart J 2015; 56: 157-162)

Key words: Atherosclerosis, Tissue characterization, Plaque calcification

Patients with acute coronary syndrome (ACS) and stable angina can have poor clinical outcomes. Although percutaneous coronary intervention (PCI) and secondary pharmacological prevention improve clinical outcome in ACS patients, coronary events may substantially occur in lesions other than the culprit lesion receiving PCI. Therefore, it is critical to identify patients who have lesions which may cause subsequent ischemic events. Intravascular ultrasound (IVUS) studies have identified the association between subsequent major adverse cardiac events (MACE) and the characteristics of vulnerable coronary plaques, which include thin-cap fibroatheroma, a plaque burden of at least 70%, and a minimal luminal area of 4.0 mm² or less. However, the actual event rate per individual thin-cap fibroatheroma remains low. Moreover, the IVUS procedures of these studies were performed both in culprit and non-culprit vessels.

Calcification is associated with the atherosclerosis stage; for instance, spotty calcification is associated with vulnerable plaque, yet extensive calcification is associated with plaque stability. However, little is known about the correlation between plaque calcification and future coronary events in patients with ACS. Virtual histology (VH-IVUS) is a useful tool based on spectral and amplitude analysis of an IVUS radiofrequency signal, and allows in vivo determination of the characteristics of plaque components. Plaques consist of 4 components, i.e., fibrous tissue, fibro-fatty tissue, dense calcium (DC), and necrotic core (NC). VH-IVUS spectral analysis correlates well with histopathologic determination (predictive accuracy 87.1%, 87.1%, 88.3%, and 96.5% for fibrous tissue, fibro-fatty tissue, dense calcium, and necrotic core, respectively), and can quantitatively determine the area and volume of each component in plaques. The present study aimed to examine the relationship between plaque characteristics in untreated coronary segments of the culprit vessel using VH-IVUS and subsequent coronary events in ACS patients.

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Received for publication July 8, 2014. Revised and accepted August 21, 2014.
Released in advance online on J-STAGE February 23, 2015.
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**METHODS**

**Patient population:** Patients with ACS who were successfully treated with IVUS-guided primary PCI within 12 hours from the onset of symptoms between September 2005 and November 2011 constituted the study group. ACS included acute myocardial infarction with or without ST elevation and unstable angina. Diagnosis of acute myocardial infarction was based on typical chest pain lasting for >30 minutes and increased levels of cardiac enzymes (more than twice the normal creatinine kinase MB level or positive troponin T). Unstable angina was defined as new onset angina, accelerated angina, or angina at rest. Angina due to secondary causes was excluded from the study. Patients were also excluded if they were in shock, had the culprit lesion in the left main trunk, or cancer, or received hemodialysis. The study protocol was approved by the Institutional Ethics Committees of Toyama University Hospital and Saiseikai Toyama Hospital, and written informed consent was obtained from all patients.

**Coronary intravascular ultrasound imaging:** All IVUS procedures were performed after an administration of intracoronary nitrates. After successful stenting of the culprit lesion, IVUS imaging proximal to the culprit lesion was obtained. Culprit lesions were defined according to angiographic appearances, including angiographic maximal stenosis, luminal irregularities consistent with ulceration, or filling defects consistent with thrombus. A 20-MHz, 2.9 F, phased-array IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, CA, USA) was used for the IVUS procedure. After introducing an IVUS catheter to the segment just proximal to the PCI site, the catheter was pulled back to the coronary ostium using a motorized pull-back system (R-100, Volcano Corporation, Rancho Cordova, CA, USA) at a speed of 0.5 mm/second. Cine runs before and during contrast injection were performed to define the starting position for the pull back of the IVUS catheter. During pull back, gray-scale IVUS was recorded and raw radiofrequency data were captured at the top of the Rwave of electrocardiographic monitoring for reconstruction of a color-coded map by a VH-IVUS console (Volcano Corporation).

**Gray scale and VH-IVUS analyses:** The external elastic membrane and lumen borders were identified using automatic edge detection and corrected manually when necessary. The cross-sectional area (CSA) of the vessel was then determined and the difference between the vessel CSA and lumen CSA thus provided the CSA of plaque plus media. Plaque burden (%) was calculated by dividing the CSA of plaque plus media with the vessel CSA. Atherosclerotic coronary plaques were characterized as DC, NC, fibro-fatty tissue, or fibrous tissue by classification trees based on mathematical autoregressive spectral analysis of IVUS backscattered data (Figure 1). The area of each plaque component was determined using Simpson’s rule and was averaged over the length of the lesion (mm²/mm). Relative area (%) of each plaque component was obtained automatically by dividing the area of the component (mm²/mm) with the area of the plaque itself (mm²/mm) that did not contain the media. Gray scale and VH-IVUS analyses were performed by an experienced cardiologist who was blinded to the quantitative analysis data as well as baseline clinical and lesion characteristics. For the non-culprit plaques (Figure 1), we selected those that were located proximal to the culprit lesion, and had a plaque burden of >30% and a length of at least 5 mm, which was a plaque size large enough to quantitatively characterize the plaque components. We excluded those that bifurcated or had severe calcification with acoustic shadowing. When an individual patient had multiple non-culprit plaques that met the criteria mentioned above, these non-culprit plaques were all included for the following analyses.

**Subsequent coronary events:** The patients were followed up for at least 3 years following the index ACS event, and underwent diagnostic coronary angiography when necessary. Subsequent coronary events consisted of ACS and stable angina due to lesions other than the culprit lesion of the index ACS event. Stable angina was defined as angina that had stable frequency, duration, and severity of symptoms within the prior 6 weeks. In-stent restenosis was not included as a coronary event in the present study.

**Statistical analysis:** The data are presented as the mean ± standard deviation. Clinical backgrounds and IVUS parameters were compared between groups stratified by the subsequent coronary events. Continuous variables were compared with
RESULTS

A total of 57 patients (65.0 ± 11.9 years old) were included in the present study. During the mean follow-up period of 4.8 years (range, 3 to 7 years), 7 patients experienced coronary events. The characteristics of the two groups with and without subsequent coronary events are shown in Table I. Between the two groups, there were significant differences in the prevalence of hypertension, as well as acute myocardial infarction as the index ACS event. The distribution of the culprit lesions did not differ between the two groups. Analysis of 13 and 70 non-culprit lesions was performed in patients with and without subsequent coronary events, respectively (Figure 1); the distribution of non-culprit lesions did not differ between the two groups (Table I).

Table II shows the characteristics of the subsequent coronary events: ACS in 4 patients and stable angina in the other 3 patients. The culprit lesion was in a different coronary artery than the one for the index PCI procedure in two of the ACS and 3 of the stable angina patients. In one of the patients, detailed information about the culprit lesion of the subsequent acute myocardial infarction was not obtained.

The gray-scale IVUS and VH-IVUS findings are shown in Table III. A total of 83 non-culprit plaques were analyzed at the time of the index PCI procedure. Of these, 13 lesions were analyzed from patients who had subsequent coronary events, and 70 lesions from patients without subsequent events. Although plaque area was greater in patients who had subsequent coronary events compared to those without, there was no significant difference in plaque burden (plaque/vessel %) between the groups. In patients who had subsequent coronary events, the areas of DC and NC (mm²/mm) were greater than in the patients without coronary events. This was also true for the relative areas of DC and NC expressed in % (Table III). The cut-off value to predict subsequent coronary events was defined as 3.4% for the relative area of DC and 20.9% for the relative area of NC (Figure 2). The Kaplan-Meier curves for the cumulative coronary event rates are shown in Figure 3. The cumulative event rates differed significantly between the groups divided by the cut-off value shown in Figure 2. That is, when the relative area of DC was 3.4% or more, the rate of subsequent coronary events was significantly higher as compared with the relative area of DC < 3.4% (Figure 3, upper panel). This was also true for NC (Figure 3, lower panel).
**Discussion**

The major findings of the present study were as follows: when the area of DC in the non-culprit lesion was larger in patients with ACS, subsequent coronary events occurred more frequently during the average follow-up period of 4.8 years. This was also true for the area of NC in the non-culprit lesion.

**Plaque calcification and subsequent coronary events:** VH-IVUS spectral analysis can detect plaque components very precisely; in particular, calcified plaque can be detected the most accurately. Many studies have already established that coronary artery calcium is associated with atherosclerosis. Vascular calcification was associated with endothelial dysfunction; coronary segments with impaired acetylcholine-induced vasodilation had greater amounts of calcium when visualized by intracoronary ultrasonography. A post mortem study showed that the amount of calcification was greater in patients who died from acute myocardial infarction than in patients without cardiac history. Other studies have reported an association of calcification in the plaque with subsequent coronary events. The present study using VH-IVUS also supports the relation between plaque calcification and subsequent coronary events. Despite plaque burden being less than 70%, the relative area of DC was greater in patients with subsequent coronary events (Table III). However, in the present study, as in many IVUS studies, calcified plaques with acoustic shadowing were excluded due to the inability to detect the plaque characteristics in the shadow area. Therefore, the lack of analysis of the lesions with severe calcification made it unclear whether severe calcification of plaque would lead to an increase in future coronary events.

Indeed, extensive calcification decreases the risk of plaque rupture. The lengths of the calcium deposits were significantly longer in patients with stable angina than in those with acute myocardial infarction. Extensive calcification was more frequently observed in stable lesions, and noncalcified plaque and spotty calcification were more frequently observed in ACS lesions. Taken together, the severely calcified plaque may be associated with plaque stability rather than vulnerability. The VIVA study also supports this association.

**Necrotic core and subsequent coronary events:** In the present study, the area and ratio of NC were significantly greater in patients who had subsequent coronary events than in those who did not. NC is characterized by a high level of lipids, many necrotic cells, and the remnants of dead lymphocytes and foam cells, and is not mechanically stable; NC is the most vulnerable component in the coronary plaques. However, there was a critical limitation in the determination of NC volume with VH-IVUS. DC in VH analysis is known to lead to artificial overestimation of the amount of NC behind the calcium signal.

**Figure 2.** Receiver operating characteristic curves (ROC) for the relative area of dense calcium (%DC) and necrotic core (%NC). Optimal cut-offs are indicated by an arrow. A: ROC for %DC. The cut-off value was 3.4% and the area under curve (AUC) was 0.71. B: ROC for %NC. The cut-off value was 20.9% and the AUC was 0.72.

**Figure 3.** Kaplan-Meier plot of cumulative event rates. DC indicates dense calcium; and NC, necrotic core. See text for details.
Therefore, it was difficult to predict subsequent coronary events using only the NC volume, although the present study showed the association between NC area and subsequent coronary events. NC size was associated with the classification of plaque morphology,\(^{36}\) and was the largest in ruptured plaques (31.0 ± 3.6%), followed by thin-cap fibroatheroma, and then thick-cap fibroatheroma (17.2 ± 1.8%).\(^{36}\) In the present study, differences in NC area of the non-culprit lesions between patients with and without subsequent coronary events may be attributed to classification of plaque morphology; however, these plaque classifications were not made.

**Relation between dense calcium and necrotic core:** Although an influence of DC could not be ignored, the relative areas of DC and NC were significantly greater in patients with subsequent coronary events in the present study. A pathological study indicated the area of calcification had no significant correlation to extension of lipidic-necrotic core; nevertheless, both areas were significantly greater in AMI patients.\(^{33}\) VH-IVUS studies showed that an NC/DC ratio > 3 could be associated with a high risk of cardiac events.\(^{37,38}\) Although both DC and NC seemed to play an important role, the relation between DC and NC should be clarified by further studies.

**Site of IVUS procedures:** IVUS procedures of the present study differed from those in previous studies\(^{8,10}\) in which IVUS examinations were performed either in one non-culprit vessel or all 3 vessels. In contrast, IVUS examinations in the present study were performed from the PCI site to the ostium of the culprit vessel. Therefore, the examinations of the present study can be performed in daily clinical practice. Vulnerable plaques are known to be distributed widely throughout all coronary arteries.\(^{39,40}\) In the ATEROREMO-IVUS study, IVUS findings from just one non-culprit artery were correlated with the vulnerability of ACS patients.\(^{39}\) plaque characteristics of a single non-culprit lesion would reflect plaque vulnerability of other coronary arteries. Furthermore, vulnerable plaques are known to be located proximal to the culprit lesion.\(^{40}\) Although examinations in all 3 vessels may predict future coronary events more precisely, the present study supports a more simple procedure to predict subsequent coronary events in the ACS patient.

**Study limitations:** The present study has several limitations. First, the definition of “subsequent coronary events” deserves some comment. In the present study, subsequent coronary events included ACS and stable angina pectoris from lesions other than the culprit lesion of the index ACS event. In previous studies,\(^{8,10}\) subsequent coronary events were defined as MACE, including cardiac death and cardiac arrest. However, in these studies, the majority of MACE in patients required rehospitalization for unstable or progressive angina and coronary revascularizations.\(^{30,38}\) Therefore, the difference in the definition of events between the previous studies\(^{8,10}\) and the present study may not affect the present results. Second, the sample size of patients was small in the present study. Studies of a larger patient population from multiple centers are warranted to confirm the present results. Third, non-culprit lesions with bifurcation, severe calcification, and plaque burden less than 30% were excluded from the present study. Exclusion of these lesions may have affected the present results. Fourth, the subjects were patients with ACS that required PCI. Some selection bias was inevitable due to selection of just one to 3 non-culprit lesions in each patient. Fifth, the culprit lesions of the subsequent coronary events during the follow-up period were not always necessarily the same plaques that had been investigated at the time of PCI for the index ACS event. Finally, VH-IVUS could not discriminate intramural thrombi from fibrous and fibro-fatty plaque.\(^{42}\) However, evaluation of NC and DC we focused on in the present study might be unaffected by the presence of intramural thrombi.

**Conclusions:** Although limited for the reasons mentioned above, the present findings indicate that the size of DC and NC in the non-culprit plaque located proximal to the PCI site may be associated with subsequent coronary events in patients with ACS. Intensive pharmacological treatment would be mandatory for the prevention of future coronary events when ACS patients have a larger area of DC or NC on VH-IVUS findings.

**Acknowledgment**

We thank the staff of the Cardiac Catheterization Laboratory for their assistance and contributions.

**Disclosure**

Conflict of interests: The authors do not have any conflict of interests to declare.

**References**


