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ORIGINAL  
RESEARCH

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# Visualization of Internal Carotid Artery Atherosclerotic Plaques in Symptomatic and Asymptomatic Patients: A Comparison of Optical Coherence Tomography and Intravascular Ultrasound

**BACKGROUND AND PURPOSE:** OCT has been reported as a high-resolution imaging tool for characterizing plaque in the coronary arteries. The present study aimed to evaluate the ability of OCT to visualize carotid artery plaques compared with that of IVUS in asymptomatic and symptomatic patients.

**MATERIALS AND METHODS:** OCT was performed for 34 plaques (17 symptomatic, 17 asymptomatic) in 30 patients during CAS under a proximal cerebral protection method. OCT was performed before balloon angioplasty and after stent placement. IVUS was also performed just after OCT.

**RESULTS:** No technical or neurologic complications were encountered by using OCT. An inner catheter was used in 12 of 34 procedures (35.3%) for advancing the OCT image wire beyond the site of stenosis. OCT clearly visualized intraluminal thrombus in 15 of 34 plaques (44.1%), whereas IVUS detected a thrombus in 1 plaque (2.9%,  $P < .001$ ). Neovascularization was demonstrated in 13 of 34 plaques (38.2%) by OCT, but not by IVUS (0%,  $P < .001$ ). Intraluminal thrombus was more frequently observed in symptomatic plaques (13 of 17, 76.5%) than in asymptomatic plaques (2 of 17, 11.8%;  $P < .001$ ). Interobserver and intraobserver variability with OCT diagnosis was excellent for thrombus, ulceration, neovascularization, and lipid pool.

**CONCLUSIONS:** The present findings suggest that OCT can safely and precisely visualize human carotid plaques during CAS and that intraluminal thrombus and neovascularization are more frequently detected in symptomatic plaques.

**ABBREVIATIONS:** CAS = carotid artery stenting; HDL = high-density lipoprotein; IVUS = intravascular ultrasound; LDL = low-density lipoprotein; OCT = optical coherence tomography; SAPHIRE = Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy; VH = virtual histology-intravascular

One of the mechanisms underlying acute stroke is the disruption of atherosclerotic plaques in major cerebral vessels, including the carotid arteries. However, visualizing arterial wall changes is sometimes difficult by using conventional imaging techniques such as angiography, MR imaging, or duplex sonography.<sup>1</sup> In particular, intraluminal thrombus is difficult to detect clearly during catheter interventions such as CAS, even with use of IVUS.<sup>2</sup>

Intravascular OCT has recently been proposed as a high-resolution imaging tool for plaque characterization. OCT is a noncontact light-based imaging method using newly developed fiber-optic technology. The typical OCT image has an axial resolution of 10  $\mu\text{m}$ , approximately 10 times higher than that of any other clinically available diagnostic imaging technique such as IVUS, with a resolution of 80  $\mu\text{m}$ .<sup>3</sup> Therefore, despite the need for removing blood from the FOV, in vivo

application of OCT has been reported for the coronary arteries<sup>4-7</sup> and, more recently, in the carotid artery.<sup>8,9</sup> The present study evaluated the ability of OCT to visualize structures of the carotid artery wall in comparison with IVUS and to evaluate differences between symptomatic and asymptomatic plaques.

## Materials and Methods

### Study Population

A total of 30 patients with a mean age of  $70.1 \pm 9.4$  years (range, 41–83 years) undergoing CAS at our facility were enrolled between November 2009 and December 2010. OCT and IVUS were performed for 34 lesions in 30 patients during the CAS procedure, with 4 patients undergoing bilateral CAS. We defined carotid plaques as “symptomatic” if they were associated with transient ischemic attack or cerebral infarction within the past 180 days. Plaques were defined as “asymptomatic” if they did not cause truly ipsilateral ischemic lesions or had not caused ipsilateral ischemic lesions within the past 180 days.<sup>10</sup> Grade of carotid stenosis was assessed by using angiography,<sup>11</sup> and indications for CAS were based on the SAPHIRE trial.<sup>12</sup> OCT examination was performed only when CAS was planned under proximal protection methods, due to the need for continuous injection of saline through the guiding catheter to remove blood from the FOV. Because OCT is approved only for coronary arteries, the application to human carotid arteries was approved by our institutional ethics committee (No. 21-108), and the study protocol was submitted to an open-access

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Table 1: Patient characteristics (N = 30)	
Characteristics	Data
Male, No. (%)	25 (83.3)
Age (yr)	71 ± 9
Degree of stenosis %	83 ± 9
History	
Ischemic heart disease, No. (%)	12 (40.0)
Hypertension, No. (%)	21 (70.0)
Diabetes mellitus type 2, No. (%)	12 (40.0)
Hyperlipidemia, No. (%)	16 (53.3)
Smoking, No. (%)	7 (23.3)
Medications	
Aspirin, No. (%)	27 (90.0)
Ticlopidine, No. (%)	1 (3.0)
Clopidogrel, No. (%)	23 (76.7)
Cilostazol, No. (%)	8 (26.7)
Statins, No. (%)	19 (63.3)
Calcium channel blockers, No. (%)	7 (23.3)
ARBs, No. (%)	14 (46.7)
Laboratory parameters	
Total cholesterol (mg/dL)	186 ± 31
Triglycerides (mg/dL)	145 ± 49
HDL cholesterol (mg/dL)	46 ± 11
LDL cholesterol (mg/dL)	112 ± 31
C-reactive protein (mg/dL)	0.21 ± 0.21
Hemoglobin A1C (mg/dL)	6.2 ± 1.1

**Note:**—ARBs indicates angiotensin II receptor blockers.

Table 2: OCT and VH-IVUS findings for corresponding lesions			
	OCT	VH-IVUS	P Value
Prestenting (n = 34)			
Thrombus, No. (%)	15 (44.1)	1 (2.9)	<.001
Neovascularization, No. (%)	13 (38.2)	0 (0)	<.001
Ulceration, No. (%)	3 (8.8)	0 (0)	.24
Calcification, No. (%)	13 (38.2)	34 (100) <sup>a</sup>	<.001
Lipid, No. (%)	28 (82.4)	30 (88.2) <sup>b</sup>	.73
Poststenting (n = 34)			
Plaque protrusion, No. (%)	6 (17.6)	0 (0)	.032

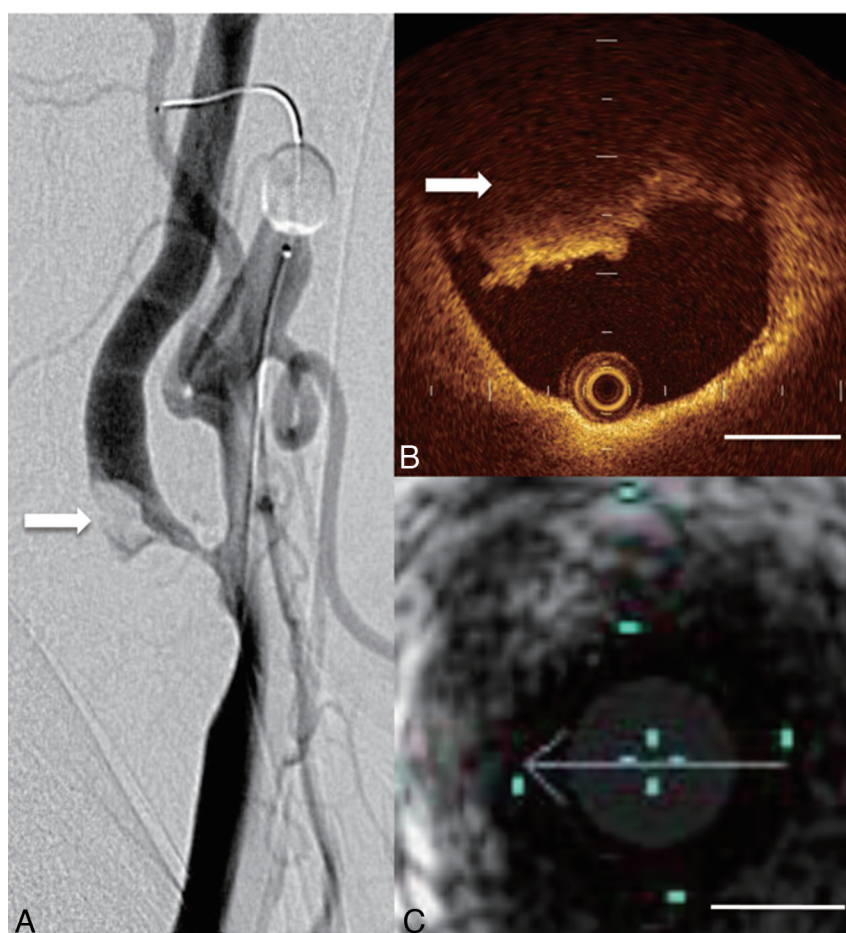
<sup>a</sup> Shown as densely calcified.

<sup>b</sup> Shown as fibrofatty and/or necrotic core on VH-IVUS.

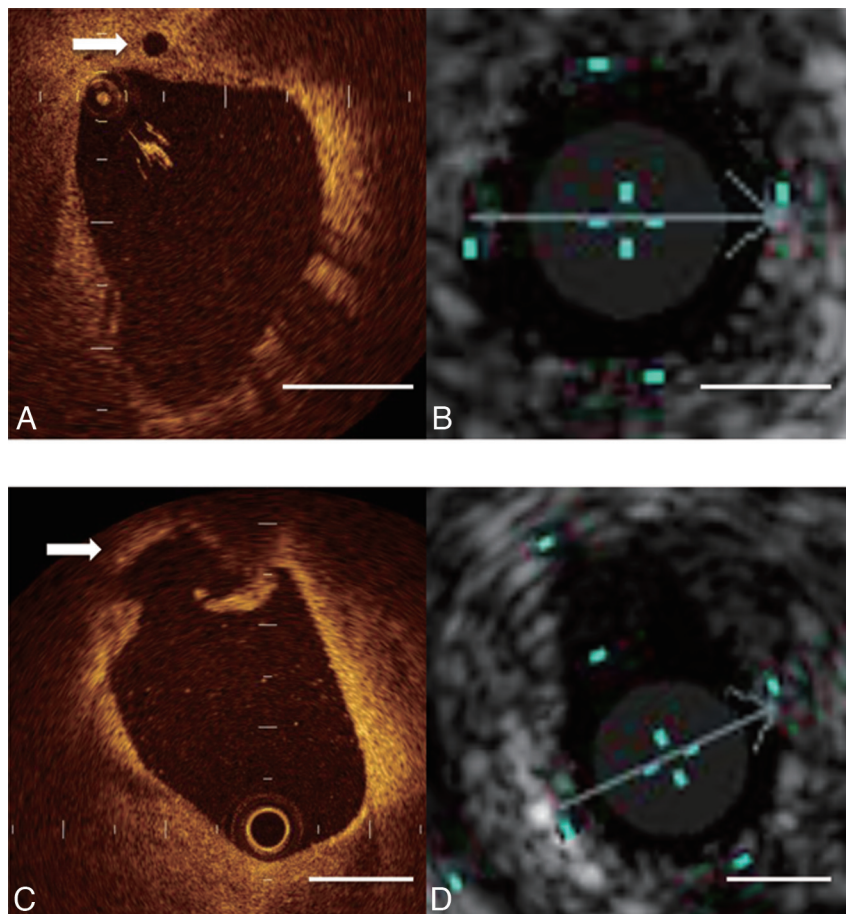
data base (University Hospital Medical Information Network; the trial number is UMIN 000002808). Informed consent was obtained from all patients before participation.

### Procedures and Data Acquisition of OCT and IVUS

A 9F guiding catheter with an occlusion balloon was navigated into the common carotid artery, and a guidewire with an occlusion balloon (GuardWire; Medtronic, Minneapolis, Minnesota) was introduced into the external carotid artery. An OCT (M2 OCT Imaging system; LightLab Imaging, Westford, Massachusetts) imaging wire (ImageWire, LightLab Imaging) was advanced into the carotid artery beyond the stenotic site, which was scanned by using a built-in automatic pullback system from the distal portion at 1 mm/s while both



**Fig 1.** Thrombus in the carotid lumen detected by OCT. *A*, Carotid angiography shows severe cervical carotid artery stenosis in a patient who presented with sudden left hemiparesis (arrow). *B*, Intraluminal thrombus is clearly detected by OCT as a backscattering protrusion into the carotid lumen with signal-intensity-free shadowing (arrow). *C*, Corresponding images from IVUS show an eccentric low-echoic plaque but do not discriminate the thrombus from other tissue components. Bar = 1 mm.



**Fig 2.** Representative images of neovascularization and ulceration of symptomatic carotid artery stenosis before CAS. *A*, OCT demonstrates neovascularization as a no-signal-intensity microchannel structure without connection to the vessel lumen that was present in >3 continuous cross-sections of OCT images (arrow). *B*, The corresponding image from IVUS does not show these findings. *C*, OCT demonstrates a small ulceration as a cavity with a lacerated superficial intimal layer (arrow). *D*, The corresponding image from IVUS does not depict this lesion. Bar = 1 mm.

common and external carotid arteries were occluded by using the balloons. During scanning, saline was infused continuously into the carotid arteries from the guiding catheter at a rate of 3 mL/s by using a motor-driven injector. All images were recorded digitally and analyzed by 2 readers. The “lipid component” was defined as a homogeneous diffusely bordered signal-intensity-poor region with an overlying signal-intensity-rich band corresponding to a fibrous cap.<sup>4</sup> “Calcification” was defined as a heterogeneous sharply delineated signal-intensity-poor or signal-intensity-rich region or alternating signal-intensity-poor and signal-intensity-rich regions.<sup>4</sup> “Thrombus” was defined as a backscattering protrusion into the carotid lumen with signal-intensity-free shadowing.<sup>13</sup> “Ulceration” was defined as a cavity with a lacerated superficial intimal layer. A “lipid-rich plaque” was defined when a lipid pool was present in  $\geq 2$  quadrants in the lesions. “Neovascularization” was defined as a no-signal-intensity microchannel structure without a connection to the vessel lumen that was present in >3 continuous cross-sections of OCT images.<sup>14</sup> Tissue characterization of carotid lesions was performed according to the consensus decision of 2 readers.

After OCT examination, occlusion balloons were deflated and the stenotic site was again scanned by VH-IVUS with a 2.9F 20-MHz phased-array IVUS catheter (Eagle Eye Gold; Volcano Therapeutics, Rancho Cordova, California) in a regular blood flow. After OCT and IVUS, CAS was performed by using a Precise stent (Cordis, Miami Lakes, Florida) or carotid Wallstent (Boston Scientific, Natick, Mas-

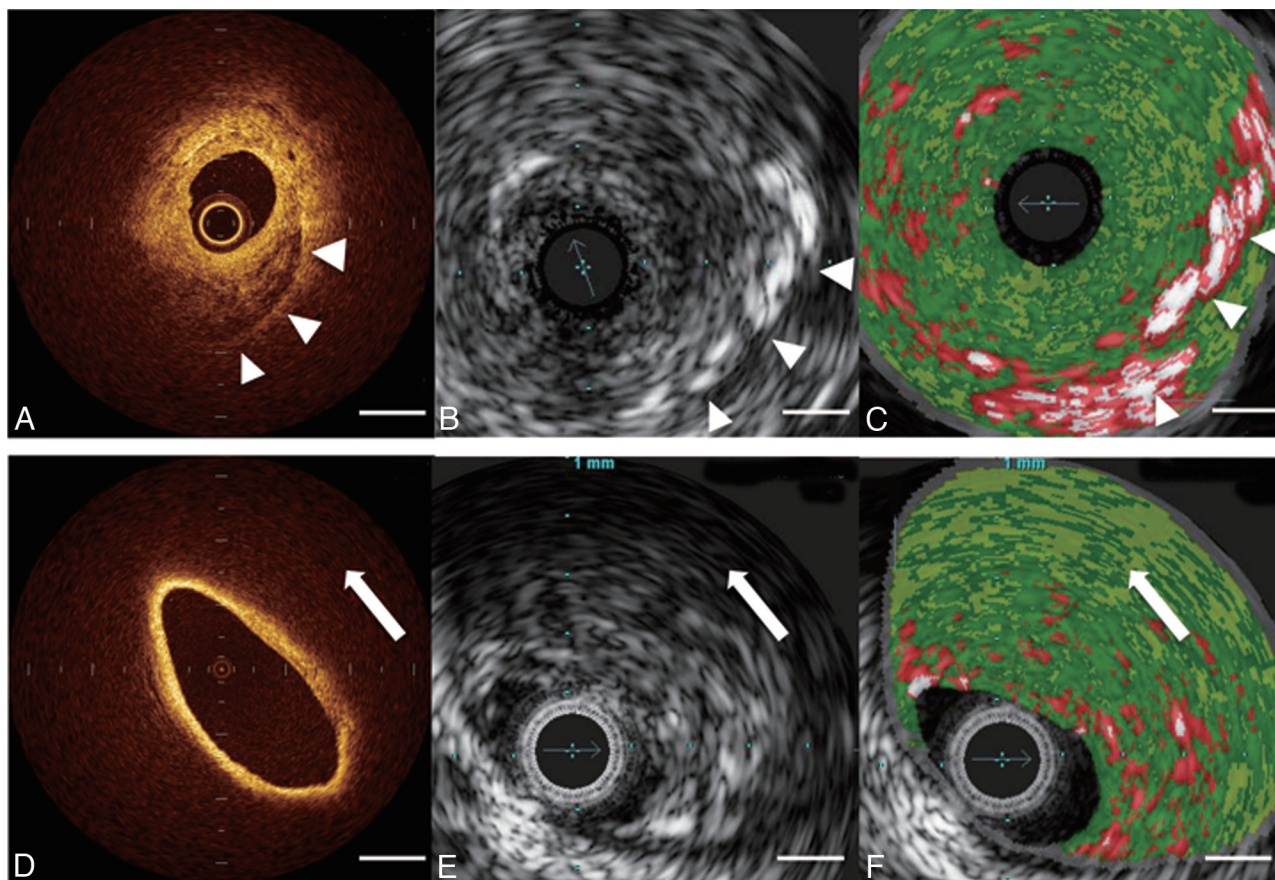
sachusetts); then the lesion was scanned again by using OCT and IVUS. To match the images obtained with OCT and those with IVUS, we selected IVUS images first and selected the same segments of OCT by using the distance from the bifurcation between the internal and external carotid arteries because imaging construction was possible at every 0.03 mm in both IVUS and OCT by using an auto-pullback device. Calcification was used as a reference marker to ensure that the sites of IVUS and OCT were the same.

Interobserver variability of OCT and IVUS diagnosis was determined in 40 randomly selected recordings that were assessed by 2 observers in a blinded fashion. Likewise, intraobserver variability of OCT and IVUS diagnosis was determined in 40 randomly selected recordings that were assessed twice by the same observer within a 7-day interval.

### Statistical Analysis

Continuous values are expressed as the mean  $\pm$  SD. Categorical data are summarized as percentages and were compared by using the Fisher exact test. Comparisons of continuous variables between cohorts were performed with unpaired Student *t* tests, because variances between cohorts did not differ significantly. Values of  $P < .05$  were indicative of statistically significant differences. Inter- and intraobserver variabilities were quantified by using Cohen  $\kappa$  test of concordance. A  $\kappa$  value of 0.61–0.80 indicated good agreement, and 0.81–1.0 indicated excellent agreement.<sup>15</sup> Statistical analyses were performed





**Fig 3.** Representative images of a calcification and lipid-rich component before stent placement. *A*, OCT demonstrates calcification as a heterogeneous, sharply delineated mixed-signal-intensity region (arrowheads). *B*, The corresponding image from IVUS shows calcification (arrowheads) as an echo-bright area with acoustic shadowing, but unclear borders. *C*, Corresponding VH-IVUS reveals white calcifications (arrows). *D*, OCT demonstrates a large lipid pool (arrow) as a homogeneous diffusely bordered signal-intensity-poor region with an overlying signal-intensity-rich band corresponding to a fibrous cap. However, OCT does not demonstrate the entire arterial wall due to the limited penetration depth. *E*, Corresponding IVUS shows the plaque as heterogeneous with an echolucent core (arrow). *F*, Corresponding VH-IVUS reveals a large light-green lipid core (arrow). Bar = 1 mm.

by using StatView software, Version 5.0 (SAS Institute, Cary, North Carolina).

## Results

### Patient Characteristics and OCT Procedures

The clinical characteristics of patients are provided in Table 1. Among the 34 lesions, 17 were symptomatic and 17 were asymptomatic. OCT examination was performed in all 34 procedures. CAS was successfully performed in 33 procedures, but carotid endarterectomy was performed in 1 patient instead of CAS after a large thrombus occupying more than half of the carotid lumen was clearly detected on OCT. Among the 34 OCT procedures, a 3.3F inner catheter was used in 12 procedures (35.3%) for advancing the OCT image wire beyond the site of stenosis. The longitudinal length of OCT images with good quality that were adequate for tissue characterization was  $22 \pm 5$  mm. No technical or neurologic complications were encountered during or after OCT, though transient carotid artery occlusion and continuous infusion of saline were necessary during the time required for imaging (mean duration,  $25 \pm 6$  seconds; range, 17–34 seconds).

### Findings of OCT in Comparison with IVUS

OCT and VH-IVUS findings for corresponding lesions are summarized in Table 2. Among prestenosis findings, intralu-

menal thrombus and neovascularization were significantly more frequently detected by OCT than by VH-IVUS ( $P < .001$ , Figs 1 and 2). Ulceration also tended to be more frequently detected by OCT than by IVUS, but the difference was not significant (Table 2 and Fig 2). Conversely, calcification was less frequently detected by OCT than by IVUS ( $P < .001$ , Table 2 and Fig 3). No difference in the frequency of the lipid component was seen between OCT and IVUS (Table 2 and Fig 3).

Regarding differences in OCT findings between symptomatic and asymptomatic carotid plaques (Table 3), intraluminal thrombus was more frequently observed in symptomatic plaques (76.5%) than in asymptomatic plaques (11.8%,  $P < .001$ ). Neovascularization was also more often observed in symptomatic plaques (58.8%) than in asymptomatic plaques (17.6%,  $P = .03$ ). In contrast, no significant differences were seen in the incidence of other findings such as calcification, lipid-rich component, ulceration, and plaque protrusion after stent placement between groups.

### Findings after CAS

Plaque protrusion after stent placement was clearly demonstrated by OCT, but not by IVUS with ChromaFlo (Volcano Therapeutics) (Fig 4).<sup>16</sup> Plaque protrusion was observed in 4

**Table 3: Laboratory and OCT findings of symptomatic and asymptomatic lesions**

	Symptomatic (n = 17)	Asymptomatic (n = 17)	P Value
Male, No. (%)	14 (82.4)	15 (88.2)	>.99
Age (yr)	72 ± 10	68 ± 10	.19
Degree of stenosis (%)	84 ± 12	79 ± 7	.26
Laboratory parameters			
Total cholesterol (mg/dL)	183 ± 35	184 ± 30	.89
Triglycerides (mg/dL)	153 ± 54	135 ± 42	.31
HDL cholesterol (mg/dL)	45 ± 12	46 ± 11	.84
LDL cholesterol (mg/dL)	107 ± 35	111 ± 30	.78
C-reactive protein (mg/dL)	0.25 ± 0.23	0.24 ± 0.26	.93
Hemoglobin A1C (mg/dL)	6.1 ± 1.0	6.4 ± 1.2	.59
Medications			
Aspirin, No. (%)	16 (94.1)	14 (82.4)	.6
Ticlopidine, No. (%)	0 (0)	1 (5.9)	>.99
Clopidogrel, No. (%)	15 (88.2)	12 (70.6)	.39
Cilostazol, No. (%)	3 (17.6)	6 (35.3)	.44
Statins, No. (%)	10 (58.8)	12 (70.6)	.72
Calcium channel blockers, No. (%)	4 (23.5)	6 (35.3)	.71
ARBs, No. (%)	8 (47.1)	7 (41.2)	>.99
OCT findings			
Thrombus	13 (76.5)	2 (11.8)	<.001
Neovascularization	10 (58.8)	3 (17.6)	.03
Ulceration	3 (17.6)	0 (0)	.23
Calcification	7 (41.2)	6 (35.3)	>.99
Lipid-rich component	16 (94.1)	12 (70.6)	.17
Plaque protrusion	4 (23.5)	2 (11.8)	.66

**Note:**—ARBs indicates angiotensin II receptor blockers.

of 17 symptomatic (23.5%) and in 2 of 17 asymptomatic lesions (11.8%, Table 3).

#### Inter- and Intraobserver Variability

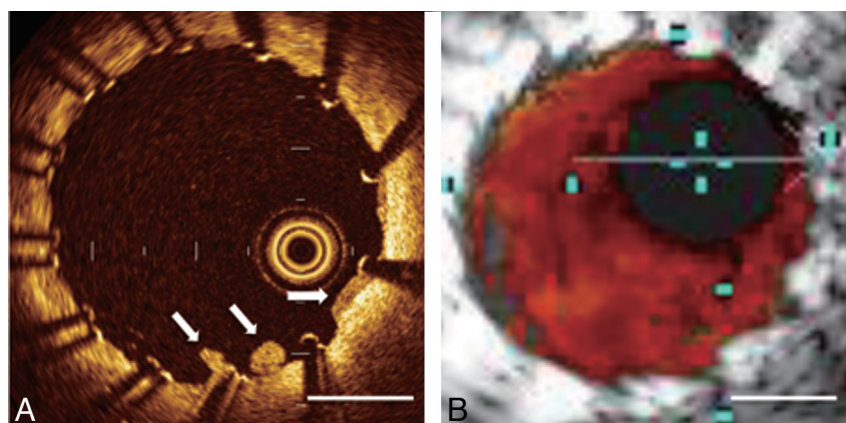
Interobserver variability with OCT diagnosis was excellent for ulceration ( $\kappa = 1.00$ ), thrombus ( $\kappa = 0.88$ ), lipid pool ( $\kappa = 0.86$ ), and neovascularization ( $\kappa = 0.84$ ) and good for calcification ( $\kappa = 0.79$ ). Interobserver variability with IVUS for calcification and lipid-rich component were 0.83 and 0.68, respectively. Intraobserver variability with OCT was excellent for ulceration ( $\kappa = 1.00$ ), calcification ( $\kappa = 1.00$ ), neovascularization ( $\kappa = 0.92$ ), thrombus ( $\kappa = 0.88$ ), and lipid pool ( $\kappa = 0.88$ ). Interobserver variability with IVUS for calcification and lipid-rich component were 0.93 and 0.86, respectively.

#### Discussion

The present study demonstrated that intravascular OCT imaging allowed safe visualization of tissue components of carotid plaques. Intraluminal thrombus and neovascularization were detected more frequently by OCT than by IVUS. Symptomatic carotid plaques showed intraluminal thrombus more frequently than asymptomatic plaques. To date, limited information has been available regarding the tissue characteristics of human carotid arteries on OCT.<sup>8</sup> The present study provides important information on the findings of carotid plaques by using OCT in relation to ischemic symptoms.

MR imaging reportedly identified more ischemic brain lesions after CAS in symptomatic patients than in asymptomatic patients.<sup>17</sup> This finding may have been attributable to a high prevalence of thrombotic plaques in symptomatic patients.<sup>18</sup> Thus, preoperative information about an intraluminal thrombus should be important to avoid a distal embolism during CAS. In the SAPHIRE trial, the presence of intraluminal thrombus was defined as an exclusion criterion.<sup>12</sup> However, it has often been reported that neither angiography nor IVUS can reliably demonstrate the presence of a thrombus. Appropriate methods to detect intraluminal thrombus before and during CAS have yet to be established. In the present study, OCT demonstrated intraluminal thrombi more clearly than IVUS or angiography without any complications. Furthermore, it was reported that red and white coronary arterial thrombi could be differentiated by using OCT.<sup>11</sup> OCT images of red thrombi are characterized as highly backscattered protrusions with signal-intensity-free shadowing. OCT thus offers significant information for evaluating intraluminal thrombi, which are at high risk for CAS. In the present study, plaque protrusion after stent placement was clearly demonstrated by OCT but was overlooked by IVUS. This finding may also be important for preventing embolic complications after CAS.

In the present study, the incidence of thrombus was significantly higher in symptomatic plaques (76.5%) than in asymptomatic plaques (11.8%;  $P < .001$ ). This finding suggests that the presence of thrombus is related to ischemic symptoms, similar to the mechanism underlying acute coronary syndrome. An angioscopic study in coronary arteries found a gradual disappearance of thrombus during the follow-up period, and several thrombi were still found on the ruptured



**Fig 4.** Representative images of plaque protrusion in a patient with symptomatic internal carotid artery stenosis after CAS. A, OCT demonstrates tissue protrusion from the spaces between stent struts (arrows). B, Corresponding image from IVUS with Chromaflo does not clearly show this finding. Bar = 1 mm.



plaque after 12 months of follow-up.<sup>19</sup> Knowing how long a carotid thrombus takes to disappear would represent interesting and potentially useful information. OCT may allow investigation of time-dependent changes.

Neovascularization was also more frequently detected in symptomatic plaques (Table 3). This finding is interesting because carotid plaque neovascularization has also been evaluated by contrast-enhanced sonography and has recently been regarded as a surrogate marker of atherosclerosis due to associations with plaque echolucency and ischemic symptoms.<sup>20–22</sup> Comparing findings of neovascularization between contrast-enhanced ultrasonography and OCT would be important in future examinations.

Regarding the potential of OCT to characterize the plaque morphology of fibrous or fatty components, a postmortem study on coronary arteries demonstrated that OCT image criteria for differentiating lipid-rich plaques achieved a high sensitivity (90%–94%) and specificity (90%–92%).<sup>5</sup> However, there might be false-negative diagnoses for lipid-rich plaques due to the limited penetration depth of OCT, and some thick-capped large lipid pools could be misinterpreted as fibrous.<sup>5</sup> Extrapolation of data from coronary arteries to carotid arteries is not always pertinent because the OCT criteria were developed for coronary arteries. We should be aware that criteria of coronary plaques that cause acute coronary syndrome are different from those of carotid plaques that cause cerebral infarction.

The current limitations of OCT compared with those of IVUS are the interference by blood flow and the degree of tissue penetration. To obtain a bloodless FOV, the proximal protection method by using occlusion balloons for the common carotid and external carotid arteries is required for the application of OCT to the cervical carotid artery. Also, the scanning length of OCT is 3.25–3.4 mm in normal saline. The diameter of the carotid arteries is normally larger than that of the coronary arteries. Therefore, plaque components located on the far side of the luminal surface are sometimes not visualized by OCT due to its limited penetration depth. In contrast, 1 advantage of OCT is the ability to visualize the near side of the vessel luminal surface with a high resolution. The axial resolution in OCT ranges from 12 to 18  $\mu\text{m}$ , compared with 150–200  $\mu\text{m}$  for VH-IVUS (Eagle Eye Gold), and the lateral resolution in OCT is typically 20–90  $\mu\text{m}$  compared with 150–300  $\mu\text{m}$  for VH-IVUS. As shown in the present study, even a small thrombus or a plaque protrusion through the stent struts can be visualized clearly by OCT. Thus, use of both OCT and IVUS would be helpful to assess total plaque morphology.

Several limitations to the present study should be considered. First, the findings obtained by OCT were not confirmed by histopathologic analysis. Although plaque characterization has been performed by using coronary and postmortem carotid plaques in the past, the relationship between in vivo OCT observation of the carotid plaque and pathologic analysis should be performed in the next study. Second, because the proximal protection method is essential for the application of OCT to the cervical carotid artery, OCT is only applicable during CAS. A new generation of OCT devices requiring less time for scanning may resolve this limitation in the near future.

## Conclusions

The present findings suggest that OCT allows safe and precise visualization of human carotid plaques during CAS and that intraluminal thrombus and neovascularization are more frequently detected in symptomatic plaques.

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