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# Carotid Plaque Surface Irregularity Predicts Ischemic Stroke

## The Northern Manhattan Study

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**Background and Purpose**—There is scant population-based evidence regarding extracranial carotid plaque surface irregularity and ischemic stroke. Using a prospective cohort design, we evaluated the association of carotid plaque surface irregularity and the risk of ischemic stroke in a multiethnic population.

**Methods**—High-resolution B-mode ultrasound of the carotid arteries was performed in 1939 stroke-free subjects (mean age  $69 \pm 10.0$  years; 59% women; 53% Hispanic, 25% black, 22% white). Plaque was defined as a focal protrusion 50% greater than the surrounding area and localized along the extracranial carotid tree (internal carotid artery/bifurcation vs common carotid artery). Plaque surface was categorized as regular or irregular. Cox proportional hazard models were used to assess the association of surface characteristics and the risk of ischemic stroke.

**Results**—Among 1939 total subjects, carotid plaque was visualized in 56.3% (1 plaque: 21.6%, >1 plaque: 34.7%, irregular plaque: 5.5%). During a mean follow up of 6.2 years after ultrasound examination, 69 ischemic strokes occurred. Unadjusted cumulative 5-year risks of ischemic stroke were: 1.3%, 3.0%, and 8.5% for no plaque, regular plaque, and irregular plaque, respectively. After adjusting for demographics, traditional vascular risk factors, degree of stenosis, and plaque thickness, presence of irregular plaque (vs no plaque) was independently associated with ischemic stroke (Hazard ratio, 3.1; 95% CI, 1.1 to 8.5).

**Conclusions**—The presence of irregular carotid plaque independently predicted ischemic stroke in a multiethnic cohort. Plaque surface irregularities assessed by B-mode ultrasonography may help identify intermediate- to high-risk individuals beyond their vascular risk assessed by the presence of traditional risk factors. (*Stroke*. 2006;37:2696-2701.)

**Key Words:** carotid artery ■ irregular plaque ■ stroke ■ ultrasound

Large artery atherothrombosis accounts for approximately 16% of all ischemic stroke (IS) with the extracranial carotid artery being the most common site of involvement.<sup>1</sup> Presence of stenotic atherosclerotic carotid plaque is a well-established risk factor for IS.<sup>2,3</sup> Furthermore, randomized trials have demonstrated that carotid endarterectomy significantly reduces the risk of ipsilateral stroke in both asymptomatic and symptomatic patients with carotid stenosis.<sup>4-7</sup>

Besides degree of carotid stenosis, other measurements of carotid artery plaque such as plaque surface features and morphology may be powerful determinants of stroke risk. B-mode ultrasonography has been a useful noninvasive technique for identifying many of these high-risk plaque features such as echolucent plaque.<sup>8</sup> Irregular or ulcerated plaque surface morphology has also been correlated with advancing stenosis and independently with ischemic stroke in angiographic studies.<sup>9,10</sup> There is less evidence, however, regarding

plaque surface morphology in prospective cohorts using noninvasive methods such as ultrasonography.<sup>11,12</sup>

We therefore studied carotid plaque surface characteristics among stroke-free subjects in the Northern Manhattan Study (NOMAS), an ongoing multiethnic prospective cohort study of stroke risk factors and outcomes. We assessed the risk of IS as a primary outcome and the risks of myocardial infarction (MI) and vascular death (VD) as secondary outcomes in a cohort of 1939 subjects from NOMAS who underwent carotid ultrasonography. We hypothesized that irregular carotid plaque surface, as assessed by ultrasonography, increases the risk of IS.

## Methods

### Patient Selection

The methods of subject recruitment and enrollment have been previously described.<sup>13,14</sup> Briefly, 3298 subjects were enrolled be-

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tween 1993 and 1997 by random digit dialing of approximately 29 000 households. Subjects were eligible if they (1) had never been diagnosed with stroke, (2) were >40 years of age, and (3) resided in northern Manhattan for  $\geq 3$  months in a household with a telephone. The Institutional Review Board at Columbia University Medical Center approved the study.

Carotid ultrasound imaging in NOMAS was initiated after standardization of the procedure and limited to a sample of those who were not enrolled at home (89.1%). We obtained high-quality carotid ultrasonography images among 1939 subjects within 1 year of enrollment. Sensitivity analyses using imputed data for the entire cohort ( $n=3298$ ) to assess for possible selection bias did not show a significant bias.

### Baseline Evaluation

Data were collected through interviews, in-person measurements, and blood sample collection by trained research assistants, and physical and neurologic examinations were done by the study physicians, as described elsewhere.<sup>13</sup> Race–ethnicity was based on self-identification and conformed to standard definitions.<sup>15</sup> Standardized questions were adapted from the Behavioral Risk Factor Surveillance System<sup>16</sup> regarding the following conditions: hypertension, diabetes, hypercholesterolemia, transient ischemic attack, cigarette smoking, and cardiac disease such as coronary artery disease, congestive heart failure, atrial fibrillation, and valvular heart disease.

### Carotid Ultrasound Measurements

Carotid artery plaque was assessed by high-resolution B-mode ultrasound using a GE LOGIQ 700 system with a multifrequency 9 to 13 MHz linear-array transducer. All measurements were performed by technologists trained in ultrasound research according to a standard scanning and reading protocol as previously described.<sup>17</sup> Plaque was defined as a focal protrusion 50% greater than the surrounding area. Data were collected on presence of plaque (yes or no), locations of plaques (internal carotid artery including bifurcation or any common carotid artery involvement), number of plaques (0 to 4 plaques at 4 locations trichotomized as 0, 1, or >1), surface characteristics (regular or irregular), degree of stenosis (<40%, 40% to 60%, or >60%), and maximal carotid plaque thickness (MCPT). Figure 1 illustrates examples of regular and irregular plaque surfaces. In a sample of 88 stroke-free community subjects, the intraclass correlation coefficients for plaque thickness ranged from 0.87 to

0.94.<sup>18</sup> Intra- and interrater correlations of plaque surface characteristics were also greater than 0.90 in our laboratory.

### Annual Prospective Follow Up

As previously described,<sup>14</sup> all subjects were followed annually by telephone. Subjects were interviewed to detect vascular symptoms and events and to review interval hospitalizations with in-person visit for those who screened positive. Hospital surveillance provided data on mortality and morbidity not otherwise captured.

### Outcome Classifications (stroke, myocardial infarction, and death)

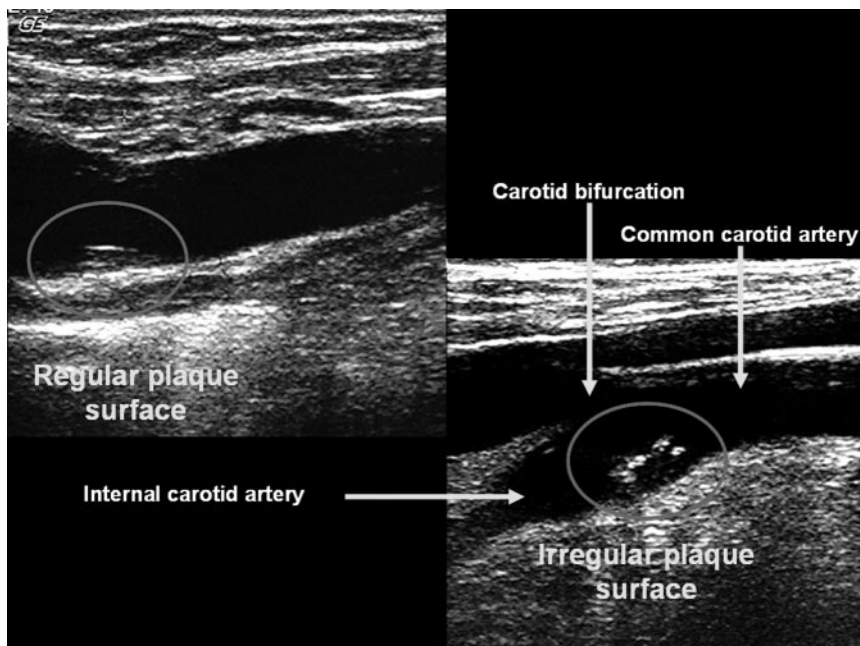
Stroke was defined as the first symptomatic occurrence of any type of stroke, including intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction, and based on the World Health Organization criteria.<sup>19</sup> Medical records of all hospitalizations were reviewed. Two neurologists classified all strokes independently after review of the data and the principal investigator adjudicated disagreements.

MI was defined by previously published criteria.<sup>20,21</sup> Deaths were classified as vascular or nonvascular. Causes of vascular death included stroke, MI, heart failure, pulmonary embolus, cardiac arrhythmia, and other vascular causes. Time to combined vascular outcome was defined as time to first ischemic stroke, MI, or vascular death.

### Statistical Analysis

The prevalence (or mean) of sociodemographic factors, conventional risk factors, potential confounders, and plaque characteristics were calculated. Demographics (age, sex, race, and education), hypertension, diabetes, any cardiac disease, hypercholesterolemia, and current cigarette smoking were included in univariate and multivariate analyses.

We estimated 5-year cumulative risks for outcomes stratified by plaque characteristic. Cox proportional hazard regression models were used to examine the association between plaque characteristics and the incidence of each outcome during follow up adjusting for other covariates. The models were adjusted for age, sex, race–ethnicity, education, current smoking, hypertension, diabetes, any cardiac disease, and hypercholesterolemia. For plaque surface irregularity, we also adjusted carotid stenosis (<40%, 40% to 60%, or >60%) and MCPT (<75th percentile or  $\geq 75$ th percentile). All



**Figure 1.** Left panel, Regular carotid plaque surface; Right panel, irregular carotid plaque surface.

statistical analyses were performed using SAS software (SAS Institute).

## Results

A group of 1939 NOMAS subjects underwent carotid ultrasonography within 1 year of enrollment. The mean age was  $68.6 \pm 10.0$  years with 41.0% male and 51.4% Hispanic. Carotid plaque was visualized in 1091 subjects (56.4%); 418 (21.6%) had one plaque, and 673 (34.7%) had more than one plaque. Median MCPT was 1.0 mm (75th percentile 1.8 mm). By plaque location, 1009 (52.0%) subjects had plaque in the internal carotid arteries or bifurcations only, whereas 82 (4.3%) had involvement of the common carotid segment; only 4 subjects had isolated common carotid artery plaque. Irregular plaque surface was recorded in 107 (5.5%) subjects, whereas 984 (51.8%) had regular plaques only. Of those with irregular surface, 36 (33.6%) were bilateral. Stenosis greater than 40% was present in only 68 subjects (3.6%). Other baseline demographic, vascular, and plaque characteristics of the cohort are presented in Table 1. During a mean follow-up time of 6.2 years, 89 subjects were diagnosed with strokes (4.6%), of which there were 69 ischemic strokes (3.6%), 102 myocardial infarctions (5.3%), 134 vascular deaths (6.9%), and 246 combined outcomes of IS, MI, or VD (12.7%).

Table 2 shows the 5-year cumulative risks of IS, MI, VD, and combined outcomes stratified by plaque characteristic. The 5-year IS risk among those with irregular plaque surface was 8.5% versus 3.0% among those with regular surface (Figure 2). Plaque surface irregularity (vs regular surface) was also associated with approximately 2 times greater 5-year cumulative risks of MI and VD, respectively. Subjects with carotid stenosis  $>60\%$  had 13.4% 5-year risk of ischemic stroke, 23.6% for MI, and 17.8% for vascular death.

After adjusting for age, sex, race-ethnicity, level of education, current smoking, diabetes, hypertension, hypercholesterolemia, and cardiac disease, plaque surface irregularity (adjusted hazard ratio [HR], 4.0; 95% CI, 1.7 to 9.4) and carotid stenosis  $>60\%$  (adjusted HR, 6.4; 95% CI, 2.2 to 18.7) significantly increased the risk for IS compared with no plaque (Table 3). Plaque number and location were not significantly predictive of ischemic stroke. However, carotid stenosis (40% to 60%: adjusted HR, 3.0; 95% CI, 1.2 to 7.4;  $>60\%$ : adjusted HR, 5.0; 95% CI, 2.2 to 11.4), presence of  $>1$  carotid plaque (adjusted HR, 1.7; 95% CI, 1.1 to 3.0), and common carotid artery plaque (adjusted HR, 2.6; 95% CI, 1.2 to 5.6) independently predicted MI. In addition, presence of common carotid artery plaque significantly elevated risk of VD (adjusted HR, 1.9; 95% CI, 1.0 to 3.6). Irregular plaque, stenosis of 40% to 60% and  $>60\%$ ,  $>1$  plaque, and common carotid artery plaque were all predictive of the combined vascular outcome.

Compared with those with regular plaque surface, irregular plaque surface increased IS risk nearly 3-fold (adjusted HR, 2.7; 95% CI, 1.3 to 5.5). Having bilateral plaque surface irregularity (adjusted HR, 3.9; 95% CI, 1.4 to 11.0) increased the risk more than unilateral irregular surface with contralateral regular surface (adjusted HR, 2.6; 95% CI, 1.1 to 6.2). Of 10 IS among 107 subjects with irregular plaque surface, 7 were ipsilateral to the lesion.

**TABLE 1. Baseline Characteristics of the Cohort (n=1939)**

Demographics	
Age in years, mean (SD)	68.6 (10.0)
Median	68
Male, n (%)	795 (41.0)
Race-ethnicity, n (%)	
White	422 (21.8)
Black	476 (24.4)
Hispanic	997 (51.4)
Other	44 (2.4)
Completed high school, n (%)	942 (48.6)
Vascular risk factors	
Hypertension, n (%)	1411 (72.8)
Diabetes, n (%)	281 (14.5)
Hypercholesterolemia, n (%)	1100 (56.7)
Current smoking, n (%)	286 (14.6)
Any cardiac disease, n (%)	439 (22.6)
Medication use	
Antithrombotic therapy	513 (26.5)
Antihypertensive therapy	845 (43.6)
Lipid-lowering therapy	253 (13.0)
Carotid artery plaque	
Any plaque, n (%)	1091 (56.4)
Number of plaques, n (%)	
1 plaque	418 (21.6)
$>1$ plaque	683 (34.7)
Surface, n (%)	
Regular	984 (50.7)
Irregular	107 (5.5)
Stenosis, n (%)	
$<40\%$	1023 (52.8)
40–60%	36 (1.9)
$>60\%$	32 (1.7)
Location, n (%)	
Internal carotid artery/BIF only	1009 (52.0)
Common carotid artery	82 (4.2)

BIF indicates bifurcation.

We further adjusted for plaque thickness and degree of stenosis to remove their potential confounding effects on the relationship between plaque surface morphology and IS risk. In a final model adjusting for demographics, vascular risk factors, MCPT ( $<$  or  $\geq 75$ th percentile), and categorical degree of stenosis ( $<40\%$ , 40% to 60%,  $>60\%$ ), irregular plaque surface remained an independent predictor of IS risk (adjusted HR, 3.1; 95% CI, 1.1 to 8.8). Compared with regular plaque, the IS risk for irregular plaque surface was attenuated (adjusted HR, 2.3; 95% CI, 1.0 to 5.4).

## Discussion

In a population-based cohort, we found that carotid plaque with irregular surface increased the risk of ischemic stroke 3-fold. The cumulative 5-year IS risk among individuals with

**TABLE 2. Unadjusted Cumulative 5-Year Risks of Vascular Events by Carotid Plaque Characteristic**

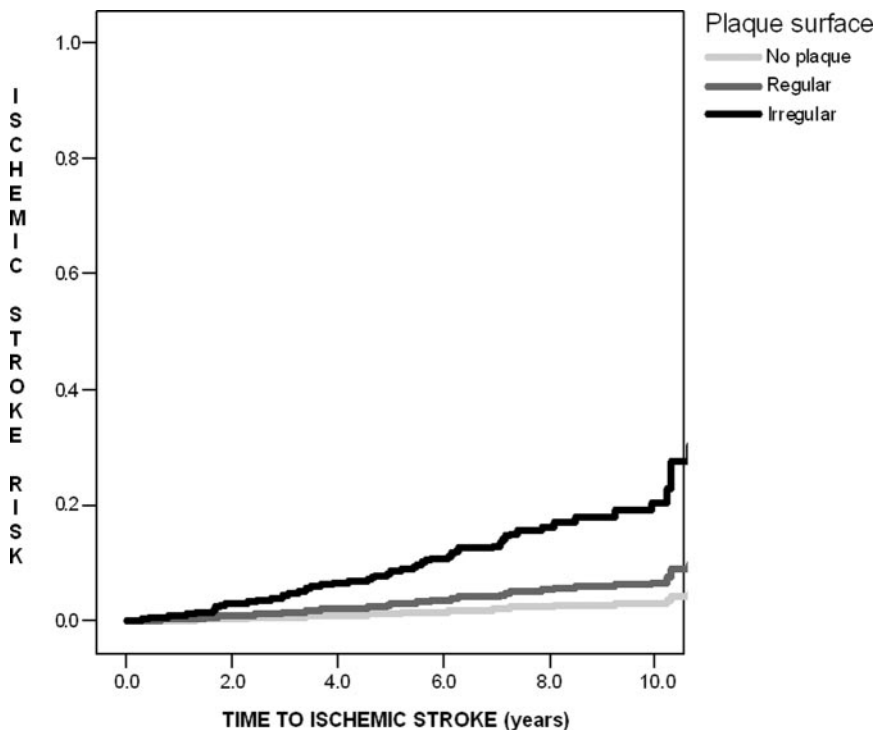
	5-Year IS		5-Year MI		5-Year VD		5-Year Combined Risk	
	N	Risk	N	Risk	N	Risk		
No plaque	17	1.3%	23	2.0%	34	2.2%	62	5.0%
Any plaque	52	3.4%	79	4.6%	100	5.0%	184	10.4%
Number of plaques								
1 plaque	18	2.8%	13	1.6%	23	2.5%	46	5.7%
>1 plaque	34	3.8%	66	6.9%	77	6.6%	138	13.5%
Surface								
Regular	42	3.0%	68	4.3%	84	4.4%	159	9.7%
Irregular	10	8.5%	11	9.5%	16	11.9%	25	16.8%
Stenosis								
<40%	45	3.2%	64	3.7%	85	4.5%	159	9.3%
40–60%	2	3.0%	7	15.4%	8	12.6%	12	23.0%
>60%	5	13.4%	9	23.6%	7	17.8%	13	35.8%
Location								
Internal carotid artery/BIF only	48	3.4%	67	4.1%	84	4.5%	158	9.6%
Common carotid artery	4	2.6%	12	11.3%	16	14.0%	26	22.5%

BIF indicates bifurcation.

an irregular plaque surface was over 8%, whereas those with regular plaque had <3% 5-year risk. These data suggest that plaque surface irregularity, even after adjusting for degree of stenosis and plaque thickness, is an independent predictor of IS. Moreover, the 5-year coronary risk (9.5%) for those with irregular plaque surface approaches the 2% annual risk commonly used to define the highest risk category.<sup>22</sup>

In addition to irregular plaque surface, we found that presence of >1 plaque, common carotid artery plaque, and carotid stenosis were predictive of the combined vascular outcome but with differences across specific vascular events.

Individuals with asymptomatic stenosis >60% carried a 13.4% 5-year IS risk and an even greater 5-year MI risk (23.6%), similar to the prior large studies.<sup>5,7</sup> Also consistent with other studies,<sup>23,24</sup> we found that presence of regular plaque surface or plaque alone increased the risks of vascular outcomes, although these associations did not reach statistical significance (perhaps because of insufficient power). Although the Rotterdam Study reported an increased IS risk among those with 5 to 6 plaques,<sup>25</sup> presence of >1 carotid plaque in our study was not significantly associated with IS but increased the risk of MI. This discrepancy may be



**Figure 2.** Cumulative risk of ischemic stroke by plaque surface type. Log-rank test:  $P < 0.01$  for homogeneity across strata.

**TABLE 3. Adjusted HR (95% CI) for Vascular Outcomes Stratified by Carotid Plaque Characteristic (reference: no plaque)\***

	Ischemic stroke	MI	VD	Combined Vascular Events
Any plaque	1.6 (0.9–2.9)	1.3 (0.8–2.2)	0.9 (0.6–1.4)	1.2 (0.9–1.7)
Number of plaques				
1 plaque	1.6 (0.8–3.1)	0.7 (0.4–1.4)	0.7 (0.4–1.2)	0.9 (0.6–1.4)
>1 plaque	1.7 (0.9–3.2)	1.7 (1.1–3.0)	1.1 (0.7–1.7)	1.4 (1.0–2.0)
Surface				
Regular	1.4 (0.8–2.7)	1.3 (0.8–2.2)	0.9 (0.6–1.3)	1.2 (0.9–1.6)
Irregular	4.0 (1.7–9.4)	1.9 (0.9–4.0)	1.6 (0.9–3.0)	1.8 (1.1–3.0)
Stenosis				
<40%	1.5 (0.8–2.7)	1.3 (0.8–2.1)	0.9 (0.6–1.3)	1.1 (0.8–1.5)
40–60%	1.8 (0.4–8.1)	3.0 (1.2–7.4)	1.6 (0.7–3.7)	2.0 (1.1–3.9)
>60%	6.4 (2.2–18.7)	5.0 (2.2–11.4)	1.7 (0.7–4.1)	3.7 (2.0–6.9)
Location				
Internal carotid artery/BIF only	1.5 (0.8–2.7)	1.2 (0.8–2.0)	0.9 (0.6–1.3)	1.1 (0.8–1.5)
Common carotid artery	1.6 (0.5–4.9)	2.6 (1.2–5.6)	1.9 (1.0–3.6)	2.4 (1.5–3.9)

\*Models adjusted for age, sex, race–ethnicity, education, current smoking, diabetes, hypertension, hypercholesterolemia, and cardiac disease.

BIF indicates bifurcation.

attributable in part to the different methods of plaque number categorization (0 to 4 in our study vs 0 to 6 in Rotterdam). Lastly, presence of common carotid artery plaque predicted MI and VD in our study.

Advancing degree of carotid stenosis is a potent risk factor for ischemic stroke.<sup>2,26</sup> Among those with asymptomatic carotid stenosis, the annual stroke risk is estimated to be 1.3% to 3.3%.<sup>27</sup> Because only a small minority with asymptomatic carotid stenosis develops stroke or transient ischemic attack, predicting who will develop ischemic symptoms remains a challenge. Furthermore, the relative mechanistic contributions of perfusion failure and artery-to-artery embolism in large artery strokes are largely unknown.<sup>9,28</sup> Analogous to MI, “rupture-prone” or “unstable” plaques may be important in the pathophysiology of large artery ischemic stroke.<sup>29</sup> Although degree of carotid stenosis may be the most powerful predictor of ischemic stroke among those with severe stenosis, there is prospective evidence that other plaque characteristics<sup>8,30,31</sup> aid in the identification of “unstable” plaques and stroke risk stratification.

Although many studies have suggested a strong correlation between carotid plaque surface irregularity and neurologic symptoms,<sup>9,32–34</sup> there have been few prospective studies.<sup>10–12</sup> In the only other large community-based prospective study using ultrasonography, markedly irregular plaque was independently predictive of IS among elderly Japanese men.<sup>12</sup> Other smaller prospective studies have suggested that large or compound ulcerations, in particular, lead to transient ischemic attack or stroke in one third of patients<sup>35</sup> with an annual stroke risk as high as 4.5% to 7.5%.<sup>36</sup> Our data corroborate this elevated risk associated with irregular plaque in a multiethnic population-based cohort.

The exact mechanisms linking irregular plaque surface and ischemic stroke are unclear. Angiographic studies have observed a strong correlation between carotid plaque surface irregularity and microscopic plaque rupture and hemor-

rhage.<sup>37</sup> Others have observed that proinflammatory markers are elevated in patients with complex or unstable carotid plaques<sup>17,37–39</sup> implying an inflammatory mechanism in plaque vulnerability and ipsilateral stroke risk. However, we were unable to show a direct ipsilateral relationship in this study. Our data support an alternate hypothesis that plaque surface irregularity may be a marker of generalized atherosclerosis rather than a potential embolic source. Such plaques may indicate an “unstable” systemic atherosclerotic state.

A major strength of this study is its population-based, multiethnic prospective cohort design with excellent follow up. There are also limitations. First, ultrasound data were not collected regarding plaque echomorphology, a known predictor of stroke.<sup>8,30</sup> Second, we included all (not just ipsilateral) ischemic strokes because we lacked sufficient power to test for laterality. Although we cannot make definitive conclusions regarding stroke mechanisms, carotid plaque with irregular surface may still serve as a useful marker of the “high-risk” patient.

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## Disclosures

None.

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