Sex Differences in Patients With Asymptomatic Carotid Atherosclerotic Plaque

In Vivo 3.0-T Magnetic Resonance Study

Hideki Ota, MD, PhD; Mathew J. Reeves, BVSc, PhD; David C. Zhu, PhD; Arshad Majid, MD; Alonso Collar, MD, FACS; Chun Yuan, PhD; J. Kevin DeMarco, MD

Background and Purpose—Stroke prevention with carotid endarterectomy in asymptomatic men with carotid stenosis is greater than in women. Men have a higher incidence of stroke <75 years of age. Sex differences in plaque characteristics may help explain this, because several plaque features, including a thin/ruptured fibrous cap, larger lipid-rich/necrotic core, and hemorrhage, are associated with increased risk of stroke. We hypothesize that MRI carotid plaque features will demonstrate sex differences indicative of higher-risk plaque in men.

Methods—One hundred thirty-one patients (men, 67; women, 64) with ≥50% asymptomatic carotid stenosis on duplex ultrasound were included. Two blinded reviewers interpreted multicontrast MRI. Presence of a thin/ruptured fibrous cap, plaque components (lipid-rich/necrotic core, hemorrhage, and calcification), and percent component volume were documented. The associations between sex and individual plaque characteristics were examined using logistic and linear regression models (2-part models) controlling for demographic characteristics and MR angiographic findings.

Results—Presence of a thin/ruptured fibrous cap (48% versus 17%, adjusted OR=4.41, $P<0.01$) and lipid-rich/necrotic core (73% versus 50%, adjusted OR=3.66, $P=0.01$) were more common in men. There was a trend for more highly prevalent hemorrhage (33% versus, 17%, adjusted OR=2.15, $P=0.07$) in men. Calcification was not significantly associated with sex. Men demonstrated larger volumes of percent lipid-rich/necrotic core (median, 7.7% versus 3.2%, $P=0.01$), and percent hemorrhage (median, 6.1% versus 1.5%, $P<0.01$).

Conclusion—In patients with asymptomatic ≥50% carotid stenosis by duplex ultrasound, men had higher-risk plaque features compared with women after controlling for potential confounders. These findings may help explain sex differences in stroke incidence and prevention. **(*Stroke*. 2010;41:1630-1635.)**

Key Words: atherosclerosis ■ magnetic resonance imaging ■ sex

In a recent heart disease and stroke statistics update, the stroke incidence rate was noted to be higher in men compared with women age <75 years.[1] Carotid endarterectomy (CEA) to prevent future stroke in asymptomatic patients with carotid stenosis is more beneficial in men than women.[2] For men, the relative risk reduction from CEA was 51% (relative risk 0.49, 95% CI 0.36 to 0.66), but for women it was only 4% (relative risk 0.96, 95% CI, 0.64 to 1.44).[2]

The exact causes or mechanisms for the sex differences in stroke incidence rate in patients <75 years of age and CEA outcomes are not fully understood. Because plaque rupture is a common precipitating event for thromboembolic events,[3–5] CEA to remove atherosclerotic plaque prone to rupture should result in reduced clinical events. Recent work has demonstrated the ability of in vivo MR images to identify "high-risk" carotid plaque features that are associated with subsequent stroke or transient ischemic attack thought to be due to plaque rupture.[6,7] Variations in these MR identified "high-risk" carotid plaque features may help explain sex differences in stroke incidence and prevention.

To our knowledge, only a few studies have examined sex differences in plaque morphology. In a study using carotid artery duplex ultrasound (DUS), Iemolo et al scanned 1686 patients recruited with vascular disease, stroke, transient ischemic attack, or asymptomatic carotid stenosis and followed them for up to 5 years; men were shown to have less carotid stenosis but more plaque area than women.[8] Carotid plaque area was found to be a stronger predictor of stroke risk than stenosis in this study. A study that used histological analysis of CEA specimens revealed several significant sex differences, including frequent atheromatous plaques (containing >40% fat), higher macrophage staining, weaker

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From the Departments of Radiology (H.O., D.C.Z., J.K.D.), Epidemiology (M.J.R.), and Neurology and Ophthalmology (A.M.), Michigan State University, East Lansing, Mich; Ingham Cardiothoracic & Vascular Surgeons (A.C.), Lansing, Mich; and the Department of Radiology (C.Y.), University of Washington, Seattle, Wash.

Correspondence to J. Kevin DeMarco, MD, Michigan State University, Department of Radiology, 184 Radiology Building, East Lansing, MI 48824-1313. E-mail jkd@rad.msu.edu

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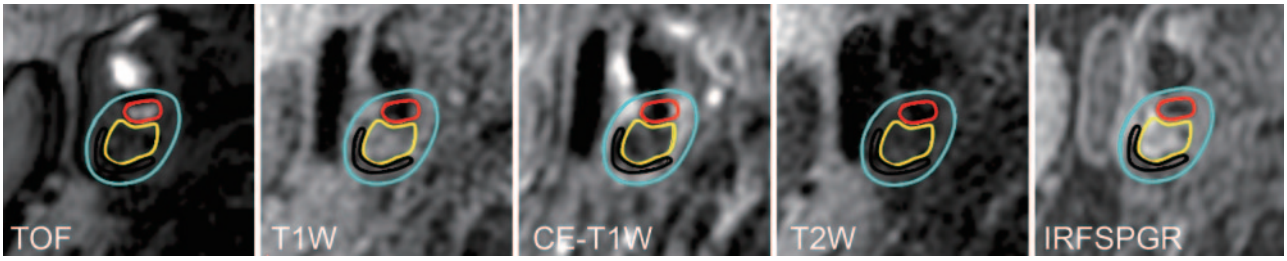

Figure 1. An example of images with overlays by MRI—plaque view. Red indicates luminal boundary; light blue, outer wall boundary; the area outlined by yellow appears iso- to hyperintense on T1-weighted image and hypoenhanced on contrast-enhanced T1-weighted image indicating LR/NC; the area inside black line appears hypointense on all the images, indicating calcification. TOF indicates time of flight; T1W, T1-weighted; CE-T1W, contrast-enhanced T1-weighted; IRFSPGR, inversion recovery fast spoiled gradient recalled.

smooth muscle cell staining, higher plaque concentration of interleukin-8, and higher matrix metalloproteinase-8 activity in men compared with women.[9] The results of this study indicated that men had more unstable carotid plaque that included more features of inflammation compared with women.[9]

In vivo carotid MRI has the ability to visualize atherosclerotic plaque components such as a lipid-rich/necrotic core (LR/NC), calcification, intraplaque hemorrhage, and fibrous cap status and has been shown to have good concordance with histology.[10–16] Previous MRI-based studies of carotid lesions demonstrated that a large LR/NC, thin/ruptured fibrous cap, intraplaque hemorrhage, and larger maximal wall thickness were associated with a higher risk of cerebrovascular ischemic events in patients with >50% stenosis on DUS.[6,7,17] However, to our knowledge, there have been no previous studies examining sex differences for carotid plaque characteristics evaluated by in vivo MRI.

The aim of this study was to test the hypothesis that carotid plaque features detected by in vivo MRI demonstrate sex differences indicative of higher-risk plaque in men compared with women in asymptomatic patients referred to subspecialists for the evaluation of >50% carotid stenosis identified on DUS or CT angiogram.

Materials and Methods

The study procedures were approved by the Community Research Institutional Review Board at Michigan State University and informed consent was obtained from all patients.

Subjects

Between March 2006 and July 2009, 208 patients (119 men, 89 women) were referred to the Department of Radiology, Michigan State University, East Lansing, Mich, for evaluation of asymptomatic moderate or severe carotid stenosis by 3-T MRI. Ninety percent were referred from a vascular interventional clinic with the remainder from either neurology or cardiology outpatient services. The vascular surgeons, neurologists, and cardiologist approached all of their patients with documented asymptomatic carotid stenosis about participation in this study. Inclusion criteria were: (1) 50% to 99% carotid stenosis as measured by DUS or CT angiography on at least 1 side; (2) no history of stroke, transient ischemic attack, or amorous fugax in the distribution of either carotid artery within 4 months before enrollment; and (3) no contraindications for MRI. Baseline clinical characteristics, including sex, age, race, body mass index, and history of hyperlipidemia, hypertension, diabetes, coronary artery disease, peripheral artery disease, statin use, and smoking, were collected by the referring physicians.

MRI Protocol

Patients were imaged with a 3-T whole-body scanner (Signa Excite; GE Healthcare, Waukesha, Wis) and a 4-channel phased-array surface coil (Pathway MRI, Seattle, Wash). The plaque multicontrast imaging protocol included the following 5 sequences: 3-dimensional time-of-flight, precontrast T1-weighted, T2-weighted, 3-dimensional inversion recovery fast spoiled gradient recalled,[18] and contrast-enhanced T1-weighted performed 5 minutes after intravenous infusion of 0.15 mmol gadobenate dimeglumine (Multihance; Bracco Diagnostic Inc, Princeton, NJ) per kilogram of body weight at a rate of 3 mL/s. The 5 sequences were obtained based on previously published protocols for a 3.0-T scanner.[18,19] Details of MRI parameters were demonstrated in Supplemental Table I(available at http://stroke.ahajournals.org). After intravenous bolus contrast injection, very high (0.28 mm^3), resolution coronal elliptical-centric carotid contrast-enhanced MR angiogram was performed with a test bolus to time the contrast arrival time.[20] Approximate scan time including patient preparation was 45 minutes.

MRI Image Review and Criteria

Before the image review, the more severely stenotic side as previously determined by DUS or CT angiography was assigned as the index carotid artery. Each patient contributed only 1 set of observations (ie, the index carotid artery) to the data set for analysis. Two experienced reviewers who were blinded to clinical outcome reviewed all MR images, and a consensus decision was reached for each plaque feature as has been previously described.[6] The quality of the overall images was scored using an image quality score rated on a 4-point scale (1=poor, 4=excellent). Arteries with an average image quality=1 were excluded from the study.[19]

The extracranial carotid bifurcation level was used as a landmark for matching the 5 different weightings. Areas of the lumen, wall, and plaque components (LR/NC, intraplaque hemorrhage, and calcification) were manually outlined (Figure 1). These plaque components were identified based on histologically validated criteria.[10–16] When a LR/NC was identified, the fibrous cap status was categorized as either a "thick" or "thin/ruptured" fibrous cap using histologically validated criteria.[11,16] Details of criteria are demonstrated in Supplemental Table II. Area measurements were obtained using an imaging analysis tool for carotid plaque MRI (MRI-Plaque View; VP Diagnostics, Seattle, Wash). This software allows: (1) to display simultaneously all the matched slices; (2) to provide in-plane registration and boundary identification so that signals inside the contours can be easily recognized; and (3) to produce a comprehensive lesion report, including sizes of the plaque components as well as the vessel wall. For plaque composition, the proportion of wall volume occupied by that feature was calculated for each artery (percent volume). This calculation normalizes compositional features to the vessel size to account for the innate differences in arterial size between subjects.

Lastly, 2 experienced reviewers, blinded to clinical information and carotid plaque findings, evaluated the level and degree of stenosis. The measurement of percent diameter carotid stenosis was based on the North American Symptomatic Carotid Endarterectomy

Trial criteria,[21] using the high-resolution carotid contrast-enhanced MR angiogram on multiplanar reformations generated using a 3-dimensional workstation (Advantage Windows version 4.3; GE Healthcare, Waukesha, Wis).

Statistical Analysis

Descriptive frequencies for categorical variables and means and medians (interquartile range) for continuous variables were generated for the overall population and for each sex. Sex differences in baseline clinical characteristics and MR angiographic findings were tested using χ^2 analysis or *t* tests. A logistic regression analysis was used to compare fibrous cap status (presence or absence of thin/ruptured fibrous cap) between sexes. A 2-part model[22] was fit to examine sex differences in the presence and size of the other plaque components, including LR/NC, intraplaque hemorrhage, and calcification. In the first part of this model, the presence/absence of a plaque component was evaluated using logistic regression analysis. In the second part, only subjects with values for component volumes (ie, values >0) are modeled using linear regression analysis. Natural log transformations were performed for all percent volume data because it was positively skewed.

Baseline characteristics demonstrating an association with sex ($P<0.20$) were considered as potential confounding factors and included in subsequent multivariable analyses. Variables were selected into the final multivariate model using a stepwise backward selection method ($P>0.10$ for removal from model). Results were expressed as adjusted OR (aOR) with 95% CIs for logistic regression models and as regression coefficients with 95% CIs for linear regression models. The regression coefficients from the linear models indicate the increase in the log percent volume in men versus women for each component. $P<0.05$ was used to designate statistical significance in the multivariate models. Computation was performed using SPSS Version 17.0 (SPSS, Chicago, Ill).

Results

Of the 208 patients initially referred for possible inclusion in this study, all had documented 50% to 99% carotid stenosis of at least 1 side by DUS or CT angiography within the past 6 months. A total 70 patients did not meet the inclusion criteria. Specifically, 7 women and 21 men were too obese/claustrophobic; 8 women and 16 men had implanted devices such as vascular stents or pacemakers that were not approved for 3-T MRI; 5 women and 9 men declined to participate in the study; 2 women and 1 man had chronic obstructive pulmonary disease or congestive heart failure that precluded their ability to lay flat for imaging; and 1 man was excluded for other reasons. Therefore, a total of 138 patients met all the inclusion and exclusion criteria.

Seven of these 138 patients with an average image quality score of 1 across all cross-sections were excluded. The remaining 131 patients consisted of 67 men (mean±SD age, 70.1±8.6 years) and 64 women (69.4±8.9 years).

Table 1 illustrates the baseline clinical characteristics and MR angiographic findings in the 131 patients. These patients demonstrated high prevalence of traditional risk factors for cerebrovascular diseases (Table 1). Prevalence of coronary artery disease was significantly higher in men than women ($P=0.02$). Although not statistically significant, higher body mass index, lower prevalence of hyperlipidemia, higher prevalence of statin use, and higher MR angiographic stenosis were seen in men compared with women ($P<0.20$). These 5 variables were therefore selected as potential confounders in the multivariable models.

Table 1. Baseline Clinical Characteristics, Degree of MR Angiographic Stenosis, and Level of Stenosis in Men and Women

Variable	Men (n=67)	Women (n=64)	*P*
Age, years	70.1±8.6*	69.4±8.9*	0.40
White patients, %	94	89	0.36
Body mass index, kg/m^2	28.3±4.5*	27.0±4.9*	0.11†
Hyperlipidemia, %	72	83	0.13†
Hypertension,%	73	78	0.51
History of coronary artery disease, %	48	28	0.02†
History of peripheral vascular disease, %	21	27	0.45
History of diabetes mellitus, %	22	19	0.61
Current statin use, %	87	75	0.10†
Ever smoked, %	74	65	0.35
Current	25	21	0.64
Past	49	44	0.53
Never	25	34	0.41
MR angiographic degree of stenosis	64.1±21.9*	58.9±18.9*	0.12†
Level of stenosis			
Common carotid, %	9	13	0.58
Carotid bulb, %	46	48	0.86
Internal carotid, %	45	39	0.60

*Mean±SD.

†Variables with $P<0.20$ were selected as potential confounders in the multivariate models.

For the presence of a thin/ruptured fibrous cap, ORs in the univariate and multivariable models remained unchanged because none of the 5 potential confounders remained in the final model. For the presence of LR/NC, statin use (aOR=0.12, 95%CI=0.03 to 0.45, $P=0.02$) was included in the final multivariable model. For the presence of hemorrhage, the MR angiographic degree of stenosis (aOR for 10% increase=1.22, 95%CI=0.98 to 1.51, $P=0.08$) was included in the final multivariable model.

The prevalence of thin/ruptured fibrous cap and LR/NC were significantly higher in men than women (Table 2). In multivariate logistic regression analyses, aORs were 4.41 (95% CI=1.97 to 9.87, $P<0.01$) for the presence of thin/ruptured fibrous cap and 3.66 (95% CI=1.67 to 8.00, $P=0.01$) for the presence of LR/NC (Figures 2 and 3). Although men had a significantly higher prevalence of hemorrhage in the univariate model, this was only marginally significant in the multivariate model (aOR=2.15, 95% CI=0.93 to 4.98, $P=0.07$), although the magnitude of OR changed little from the univariate analysis (2.36).

When subjects having individual plaque components were examined, median (25th, 75th percentile), percent component volumes in men and women were 7.66% (2.40%, 19.90%) versus 3.23% (1.15%, 6.89%) for LR/NC, 6.13% (1.97%, 10.81%) versus 1.49% (0.67%, 2.52%) for hemorrhage, and 3.13% (1.20%, 7.09%) versus 3.29% (1.52%, 6.69%) for calcification, respectively. Median with 25th and 75th of log

Table 2. Prevalence and Percent Volume of Plaque Components in Men and Women: Univariate and Multivariable

			Univariate Model			Multivariable Model		
Presence	Men, %	Women, %	OR	95% CI	*P*	aOR	95% CI	*P*
Thin/ruptured fibrous cap	48	17	4.41	1.97–9.87	<0.01	4.41*	1.97–9.87	<0.01
LR/NC	73	50	2.72	1.31–5.65	0.01	3.66†	1.67–8.00	0.01
Hemorrhage	33	17	2.36	1.03–5.38	0.04	2.15‡	0.93–4.98	0.07
Calcification	84	86	0.83	0.32–2.17	0.71	0.66‡	0.24–1.81	0.41
Log (Percent Volume)	Median (25th, 75th)	Median (25th, 75th)	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*
LR/NC (n=81)	2.04 (0.87–2.99)	1.17 (0.37–1.93)	0.79	0.23–1.36	<0.01	0.71‡	0.17–1.25	0.01
Hemorrhage (n=33)	1.81 (0.66–2.38)	0.40 (−0.40–0.92)	1.47	0.63–2.31	<0.01	1.47*	0.63–2.31	<0.01
Calcification (n=111)	1.14 (0.18–1.96)	1.19 (0.42–1.90)	−0.04	−0.48–0.40	0.86	−0.16‡	−0.58–0.26	0.45

OR or aOR by logistic regression analyses. Coefficients for log (percent volume) of patients with presence of individual plaque components by linear regression analyses.

Models also include: *none; †statin use; ‡MR angiographic degree of stenosis.

percent volumes for LR/NC, hemorrhage, and calcification in men and women are demonstrated in Table 2. The size of LR/NC and hemorrhage were both significantly larger in men than women in both univariate and multivariable models (Table 2).

For log percent LR/NC, the MR angiographic degree of stenosis (coefficient for 10% increase=0.18, 95% CI=0.06 to 0.30, P=0.01) was included as a potential confounder in the final multivariable model. For log percent hemorrhage, none of the 5 potential confounders remained in the final model.

Neither presence nor size of calcification was significantly different between men and women. In multivariate models, MR angiographic degree of stenosis was significantly associated with both the presence of calcification (aOR for 10% increase=1.28, 95% CI=1.03 to 1.59, P=0.03) and log percent calcification (coefficient for 10% increase=0.21, 95% CI=0.10 to 0.32, P<0.01).

Discussion

To our knowledge, this is the first study to reveal that carotid plaque characteristics identified by 3-T in vivo MRI differ between men and women who are referred to subspecialists for the evaluation of asymptomatic carotid stenosis seen on DUS or CT angiogram. Men tend to have carotid plaque characterized by the presence of LR/NC and thin/ruptured fibrous cap as well as larger percent volume of LR/NC and intraplaque hemorrhage as compared with women.

We determined baseline patient characteristics and MR angiographic findings as potential confounders to characterize plaque features. It is known that the prevalence of intraplaque hemorrhage is high in CEA specimens removed from severely stenotic carotid arteries,[23] and the prevalence of complicated American Heart Association Type VI carotid atherosclerotic lesions increases as the degree of stenosis increases from 1% to 15% to 80% to 99%.[24] The present study demonstrated that LR/NC and a thin/ruptured fibrous cap occurred more often in men than women even after adjusting for potential confounders. Presence of hemorrhage was also higher in men but only reached marginal significance in the multivariable analysis.

Atherosclerotic plaque that is prone to rupture because of its intrinsic composition such as intraplaque hemorrhage and a large lipid core[3–5] are associated with subsequent thromboembolic ischemic events. Takaya and colleagues used 1.5-T MRI to demonstrate that presence of a thin/ruptured fibrous cap, the presence and size of intraplaque hemorrhage, the size of LR/NC, and larger wall thickness were associated with subsequent cerebrovascular events.[6] Singh et al demonstrated MR-depicted intraplaque hemorrhage was associated with future ipsilateral cerebrovascular events.[7] Both of these studies included mostly male subjects (ie, 82% and 100%, respectively) and so did not include sex-specific analyses.

In a study of 450 consecutive patients undergoing CEA, Hellings et al demonstrated that asymptomatic women had

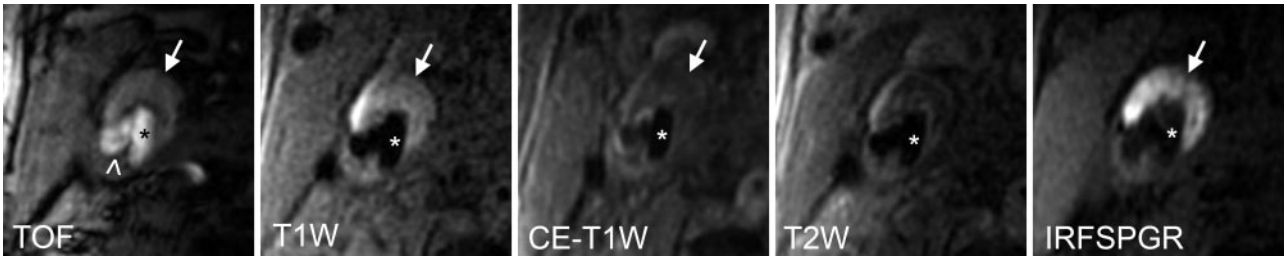

Figure 2. A representative case of large hemorrhagic LR/NC with a ruptured fibrous cap obtained from a male patient. Irregular luminal surface with protruding hyperintensity area on time of flight indicates fibrous cap rupture/ulceration (chevron). Area with hypointensity on contrast-enhanced T1-weighted and hyperintensity on inversion recovery fast spoiled gradient recalled indicates a hemorrhagic lipid-rich/necrotic core (arrows). *Lumen. TOF indicates time of flight; T1W, T1-weighted; CE-T1W, contrast-enhanced T1-weighted; IRFSPGR, inversion recovery fast spoiled gradient recalled.

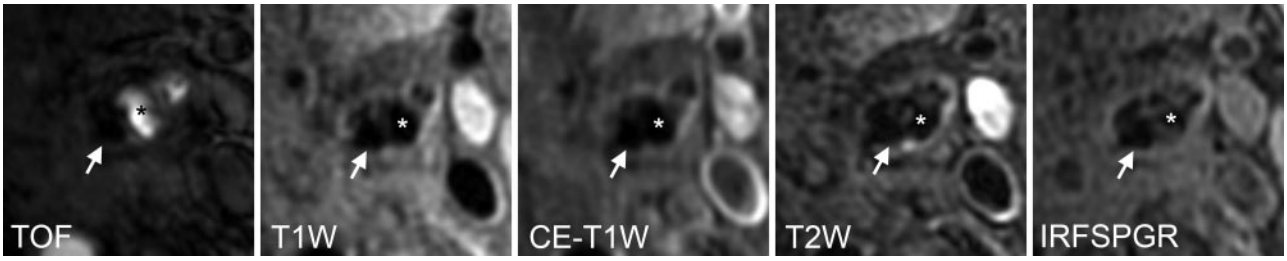

Figure 3. A representative case of calcified plaque from a female patient. Hypointensity area seen on all the images (arrows) indicates calcified plaque. *Lumen. TOF indicates time of flight; T1W, T1-weighted; CE-T1W, contrast-enhanced T1-weighted; IRFSPGR, inversion recovery fast spoiled gradient recalled.

the highest prevalence of stable plaque as determined by histological grading of plaque phenotype and biochemical features of unstable carotid plaque.[9] The results of our study are in agreement with these results and demonstrate a previously undescribed higher prevalence of a thin/ruptured fibrous cap and larger intraplaque hemorrhage in men compared with women. Previous authors have stressed the importance of corroborating these histological sex differences in preoperative testing or imaging of high-risk patients. The present results suggest that in vivo 3-T carotid plaque MRI can identify plaque phenotypes that are suggestive of high-risk patients or lesions. The increased incidence of these potentially "high-risk" carotid plaque phenotypes in men compared with women may be one reason that CEA is more effective in reducing subsequent stroke in asymptomatic men with carotid stenosis than women and is consistent with prior studies demonstrating a higher incidence of stroke in men than women age <75 years. These hypotheses would need to be tested in larger, prospective studies.

This study involved a selected group of patients with moderate to severe stenosis identified on their screening DUS or CT angiogram who were referred to subspecialists for further evaluation. Baseline characteristics in the present study appeared to be similar to those in previous CEA clinical trials and clinical studies of patients referred to vascular surgeons om which patients already have carotid stenosis[6,9,25,26] but demonstrated higher prevalence of risk factors compared with other general populations.[27] Although the present results may not be applicable to the general population, they would be applicable to clinical populations who undergo assessment for surgical treatment of carotid atherosclerotic disease.

This study has 2 major limitations. First, this is a cross-sectional study and so we were not able to demonstrate a direct association between plaque characteristics and subsequent stroke risk. Future prospective studies of noninvasive in vivo MRI are required to evaluate the role of sex-specific differences in plaque characteristics and their relationship to subsequent clinical events. Second, this is a single-center study. The results will need to be replicated in a multicenter study.

Summary

In patients with asymptomatic ≥50% carotid stenosis on the entry DUS or CT angiogram, carotid plaque characteristics differed by sex; men tended to have higher-risk plaque features compared with women. These findings may indicate a possible reason for why CEAs are more effective in asymptomatic men than women and why men age <75 years have a higher incidence of stroke than women. These results suggest the potential for the sex-specific management for patients with carotid atherosclerosis based on different plaque features. These results also suggest the need to undertake future prospective studies to determine the association between sex-specific plaque features and the risk of subsequent cerebrovascular events.

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