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# Sex Differences in Carotid Plaque and Stenosis

Francesco Iemolo, MD; Alexandra Martiniuk, MSc; David A. Steinman, PhD; J. David Spence, MD

**Background and Purpose**—Women are relatively protected from cardiovascular events; they are 3 times as likely as men to survive to age 90 years. Although clinical trials show an excess of thrombotic events with estrogen/progestin hormone replacement therapy, much experimental and epidemiological evidence suggests that estrogen may have beneficial effects on endothelial function and atherosclerosis, raising the possibility of sex differences in arterial remodeling. We studied sex differences in carotid plaque and stenosis in relation to survival free of stroke, death, and myocardial infarction.

**Methods**—A total of 1686 patients from an atherosclerosis prevention clinic were followed annually for up to 5 years (mean,  $2.5 \pm 1.3$  years) with baseline and follow-up measurements; there were 45 strokes, 94 myocardial infarctions, and 41 deaths.

**Results**—Carotid stenosis and plaque increased with age. Women had greater stenosis compared with men ( $P=0.001$ ), whereas men had greater plaque area than did women at all ages ( $P<0.0001$ ). Stroke, myocardial infarction, and death combined were predicted significantly by plaque area ( $P=0.004$ ) but not by stenosis ( $P=0.042$ ).

**Conclusions**—Women have more stenosis but less plaque than men, suggesting that differences in sex hormones may affect remodeling of atherosclerosis. Plaque area was a stronger predictor of outcomes than was stenosis. (*Stroke*. 2004; 35:477-481.)

**Key Words:** atherosclerosis ■ carotid artery plaque ■ sex ■ stenosis ■ ultrasonography

Women enjoy protection from cardiovascular events compared with men; they are 3 times as likely to survive to age 90 years.<sup>1</sup> Although recent clinical trials do not show beneficial effects of combination hormone replacement therapy (HRT) with estrogen and progestins on events<sup>2-7</sup> or on angiographically measured coronary stenosis,<sup>8</sup> much experimental and epidemiological evidence suggests beneficial effects of estrogen on the endothelium and on atherosclerosis.<sup>9-24</sup> The discrepancy among these types of evidence raises the possibility that excess events in women taking HRT may be related not to effects of estrogen on atherosclerosis per se but to other biological processes and/or to progestins.

Furthermore, although it seems a tautology that more plaque should be associated inevitably with more stenosis, the concept of arterial remodeling suggests that arteries undergo compensatory enlargement, a form of remodeling, maintaining a normal lumen in the face of plaque development.<sup>25</sup> Since nitric oxide is produced in conditions of high shear and endothelin in conditions of low shear, one of us (J.D.S.) has hypothesized that such remodeling may be related to production of these endothelial factors.<sup>26</sup>

Estrogen influences endothelin, which is not only a vasoconstrictor but interacts with other factors to enhance coagulation and vascular proliferation.<sup>27</sup> Polderman et al<sup>28</sup> re-

ported that women have low endothelin levels and men have high endothelin levels, and when they undergo sex change surgery and hormonal therapy, their endothelin levels undergo a crossover to levels characteristic of their new sex. These observations provide new approaches to possible therapeutic effects of estrogen and phytoestrogens<sup>26</sup> and raise the possibility of sex differences in arterial remodeling.

A recent study<sup>29</sup> has highlighted a potential relationship between carotid bifurcation anatomy and the prevalence of atherosclerotic plaque, a theme that has been studied for some time.<sup>30-32</sup> The anatomy of the carotid bifurcation changes with age independently of any effect of atherosclerosis, suggesting that some of the anatomic differences observed are acquired rather than congenital. Schulz and Rothwell<sup>33</sup> found important differences between men and women in the distribution of carotid stenosis, related to differences in the anatomy of the bifurcations.

There is considerable variation (given the same systemic risk factors for atheroma) between and within individuals in the development of plaque and its specific topographic localization (eg, around bifurcations).<sup>34</sup> One possible explanation for these observations is that vessel anatomy, by determining flow patterns, may influence plaque development.

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In a previous study we showed that total carotid plaque area was a strong predictor of vascular outcomes.<sup>35</sup> We have suggested that various phenotypes of atherosclerosis, such as intima-media thickness, plaque, stenosis, and rate of progression of these parameters, may have different determinants because compensatory enlargement (remodeling) determines that stenosis is not the natural consequence of plaque enlargement but the result of a plaque event such as rupture or intraplaque hemorrhage.<sup>36</sup> Because most ultrasound laboratories measure carotid stenosis rather than plaque area, it is of interest to know whether carotid stenosis measured by Doppler velocities is as strong a predictor as plaque area. Here we compared the power of carotid plaque area and carotid stenosis as tools for evaluating the risk of the combined outcome of stroke, myocardial infarction, and vascular death. Furthermore, since there may be sex differences in plaque and stenosis, we studied sex differences in stenosis and plaque and the predictive power of these parameters in the 2 sexes.

### Subjects and Methods

As previously described,<sup>35</sup> patients were being followed in the Premature Atherosclerosis Clinic and the Stroke Prevention Clinic of the University Campus of the London Health Sciences Centre, London, Ontario, Canada.

Carotid plaque area was measured as described previously<sup>35,37</sup> with the use of a high-resolution duplex ultrasound scanner. Plaque was defined as a local thickening of the intima >1 mm in thickness. Measurements were made in magnified longitudinal views of each plaque seen in the right and left common, internal, and external carotid arteries. The plane in which the measurement of each plaque was made was chosen by panning around the artery until the view showing the largest extent of that plaque was obtained. The sum of cross-sectional areas of all plaques seen between the clavicle and the angle of the jaw was taken as total plaque area. We performed a study of interobserver reliability, in which plaque area measurements in 25 patients were repeated 1 week apart by 2 technicians using 2 different machines.

Stenosis was measured by Doppler peak frequency measurements, calibrated against angiography in 100 patients (212 arteries) measured in the North American Symptomatic Carotid Endarterectomy Trial (NASCET). The *R* for the correlation between stenosis measured by the 2 methods was 0.77.

Events were ascertained by a questionnaire at annual visits, by inspection of hospital charts for any admissions, and by death certificates, either from the hospital charts or faxed from family physicians' offices. In 2 cases family physicians had retired, and records were unavailable; in those cases cause of death was reported by the widow. (Both were sudden deaths, classified as cardiovascular death.) Determination of outcomes was not blinded in a small number of cases (ie, some strokes evaluated by J.D.S.), but in most cases outcomes occurred in settings other than the clinic. Event definitions used were those used in NASCET.<sup>38</sup>

Blood pressure results presented were the systolic and diastolic pressures at baseline in the arm with the higher diastolic pressure, measured once with an automated device (Dinamap, Critikon Inc) with the patient recumbent.

### Statistical Analyses

A prospective cohort design was used to investigate the effect of sex on carotid plaque area and carotid stenosis. On the basis of the previous literature, other risk factors for carotid plaque area and carotid stenosis were also examined: age, body mass index, lipid-lowering therapy, antihypertensive therapy, pack-years of smoking, and baseline levels of total cholesterol, triglycerides, HDL, LDL, total homocysteine, and systolic and diastolic blood pressure.

**TABLE 1. Baseline Patient Characteristics by Sex**

Characteristic	Sex	n	Mean	P Value
Age (at baseline)	M	892	56.4	0.123
	F	794	57.5	
Cholesterol	M	892	5.1	0.003
	F	794	5.2	
Triglycerides	M	760	1.9	0.017
	F	668	1.8	
HDL	M	757	1.1	0.001
	F	675	1.4	
LDL	M	731	3.3	0.013
	F	656	3.2	
Pack-years of smoking	M	892	14.8	0.359
	F	794	10.0	
Total homocysteine	M	748	13.6	0.001
	F	656	11.7	
Systolic blood pressure	M	892	140.7	0.051
	F	793	138.7	
Diastolic blood pressure	M	889	83.0	0.001
	F	786	76.9	

### Relationship Between Stenosis and Plaque

Multivariate analyses were conducted to investigate the relationships between carotid artery stenosis and plaque area. Sex was included in the original model to assess whether significant differences exist between men and women with respect to the relationship between stenosis and plaque. Models were also run separately for men and women to better understand the differences between sexes.

### Predictors of Poor Outcome

We investigated which factor (stenosis or plaque area) was a better predictor of poor outcomes. Multinomial logistic regression was used to investigate a combined outcome of stroke, myocardial infarction, and total mortality, with a median split of carotid stenosis and plaque area as fixed variables, controlling for age, sex, systolic blood pressure, pack-years of smoking, and serum cholesterol (for which complete data were available). Sex differences were investigated by running separate models for men and women.

### Results

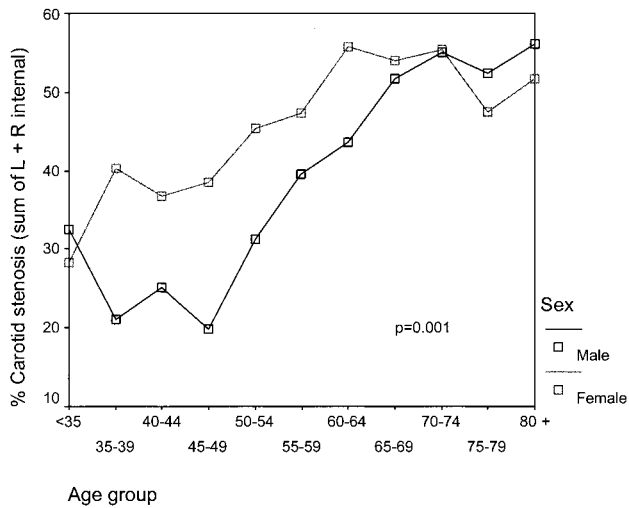
All 1686 patients with complete data for the significant variables in previous multivariate analysis of plaque<sup>35</sup> and all 1672 patients with data for stenosis (of a total study population of 1688) were included in the analyses. Baseline patient characteristics are shown in Table 1. Carotid plaque area was strongly related to age, as described previously.<sup>35</sup>

### Covariates

Baseline risk factors for which complete data were available for multivariate analyses were age, sex, pack-years of smoking, total cholesterol, and systolic blood pressure. All baseline characteristics shown in Table 1 were significantly associated with our dependent variables of interest except for diastolic blood pressure and body mass index.

### General Relationships by Sex

Women had increased carotid artery stenosis compared with men except at age 70 to 74 years ( $P=0.001$ ) (Figure 1),



**Figure 1.** Baseline carotid stenosis (sum of right [R] and left [L] internals) by age group and sex. Estimated marginal means for carotid stenosis by age group and sex are shown, with the use of the general linear model in SPSS. At any age except 70 to 74 years, women have more carotid stenosis than do men ( $P=0.001$ ).

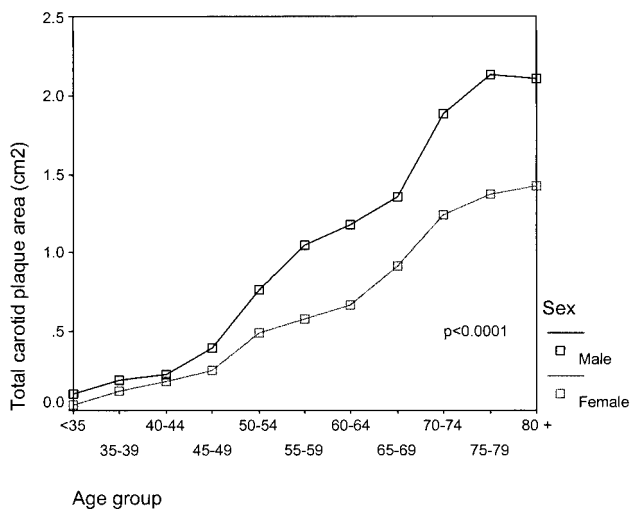
whereas at any age men had increased carotid plaque area compared with women (Figure 2) ( $P<0.0001$ ).

### Relationship Between Stenosis and Plaque

The full model including sex as an independent variable demonstrated that significant differences existed between sexes in the relationship between stenosis and plaque ( $P<0.0001$ ). The model split by sexes demonstrates that women had a lower relative risk for plaque given the same stenosis as men.

### Stenosis and Plaque Area as a Predictor of Poor Outcome

A total of 45 strokes, 94 myocardial infarctions, and 41 deaths (27 vascular, 12 due to cancer, and 2 other) occurred



**Figure 2.** Baseline carotid plaque by age group and sex. Estimated marginal means are shown, with the use of the general linear model in SPSS. At any age, men have more atherosclerotic carotid plaque than do women ( $P<0.0001$ ).

**TABLE 2. Results of Multinomial Logistic Regression for Prediction of Combined Events by a Median Split of Carotid Plaque Area or Carotid Stenosis**

Effect	Chi-Square	Significance
Total plaque area		
Intercept	0.000	
Age	0.581	0.446
Sex	21.865	0.000
Total cholesterol	0.005	0.943
Systolic pressure	1.693	0.193
Pack-years of smoking	1.458	0.227
Plaque area (median split)	8.104	0.004
Carotid stenosis		
Intercept	0.000	
Age	6.529	0.011
Sex	22.705	0.000
Total cholesterol	0.062	0.803
Systolic pressure	0.579	0.447
Pack-years of smoking	3.654	0.056
Stenosis (median split)	0.651	0.420

Combined events are stroke, myocardial infarction, or death. Median split-sum of right and left internal carotids.

during a mean follow-up of  $2.5 \pm 1.3$  years (range, 0.1 to 5 years). Survival free of events (stroke, myocardial infarction, and total mortality) was studied by multinomial logistic regression, adjusted for age, sex, pack-years of smoking, systolic blood pressure, and serum total cholesterol, with the use of a median split for both carotid stenosis and carotid plaque area (Table 2). In the total population, carotid artery plaque significantly predicted events ( $P<0.004$ ), but carotid artery stenosis did not ( $P=0.42$ ).

When the sexes were analyzed separately, plaque area was a significant predictor of stroke, myocardial infarction, or death for women ( $P=0.028$ ) and approached significance for men ( $P=0.06$ ). Stenosis did not predict the combined outcome for men ( $P=0.84$ ) or women ( $P=0.20$ ).

### Discussion

Our data revealed that stenosis and carotid plaque area increase with age in both sexes, but women had greater stenosis than men, and men had greater carotid plaque area than women. Moreover, women have a lower relative risk for plaque given the same degree of stenosis as men. In large part, these results may be driven by the use of blood velocity to measure stenosis.

We hypothesize that the apparent excess of stenosis in women may be due to differences in remodeling (compensatory enlargement) and/or to smaller arteries in women, since for a given blood flow, velocities are higher in arteries with a smaller diameter. Several studies have shown that women have significantly smaller carotid arteries than do men.<sup>39-41</sup> It is very interesting that plaque area and not stenosis is a predictor of poor outcomes for both sexes and a predictor of mortality only for men. This finding is at odds with the high risk of angiographic stenosis in previous studies<sup>38,42</sup> and

suggests that carotid stenosis measured by ultrasound, because of the dependence on velocity, may be a different biological condition than stenosis based on measurements of relative diameters of the stenosed and distal normal segments. We have observed high velocities in patients after carotid endarterectomy despite the absence of any plaque or local stenosis, apparently due to surgical reconstruction with a smaller than normal diameter.

It would be of interest to compare measurements of stenosis based on power Doppler diameter measurements with angiographic and Doppler velocity measurements of stenosis. It is important, however, to recognize that the NASCET method of measurement underestimates severe stenosis because distal collapse of the internal carotid begins at much lower levels of stenosis than is usually assumed; rather than occurring only in critical stenosis, it begins at approximately 40% stenosis and increases linearly.<sup>43,44</sup>

Figures 1 and 2 show that stenosis and carotid plaque area diverge at the age of 50 to 55 years; we speculate that this may be due to an important role of the sex hormonal system on remodeling.

Schulz and Rothwell<sup>33</sup> also found, in an angiographic study among patients with <50% stenosis, that men had more plaque than did women. They reported sex differences in the distribution of plaque related to bifurcation anatomy, with women having a higher ratio of internal carotid to common carotid diameters; this was thought to explain why women were more likely to have stenosis of the external carotid artery.

Until recently, the mechanism for apparent benefit of estrogen in experimental and epidemiological studies has been thought to be related to improvement in traditional risk factors such as lipoproteins. Bush et al,<sup>45</sup> however, reported that reduction in coronary risk in women taking estrogen could not be accounted for by changes in lipoproteins. Clarkson et al<sup>46</sup> also concluded that the protective effect of estrogen could only partially be accounted for by changes in lipoproteins, and they discussed the "residual" protective effect of estrogen, emphasizing that estrogen treatment reduces proliferation of arterial smooth muscle cells,<sup>11</sup> reduces production of collagen and elastin, and increases degradation of collagen and elastin<sup>9,10,12</sup> within arterial tissue.

Effects of estrogen on endothelial function are probably important in vascular effects of estrogen. Rosano et al<sup>13</sup> showed that estrogen acutely improved exercise-induced myocardial ischemia, implicating a vasodilator effect of estrogen.

Epidemiological literature indicates that HRT after menopause reduces the risk of heart attacks and strokes by approximately 44%.<sup>24</sup> The most recent publication from the Nurses' Health Study<sup>47</sup> indicated that an increase in postmenopausal hormone use explained a 9% decline in coronary disease between the 2-year periods 1980–1982 and 1992–1994.

Recently, retrospectively evaluated data from 1134 women with congestive heart failure in 3 randomized, double-blind, clinical trials of vesnarinone showed a significant benefit of HRT: all cause-mortality was 15% among the 237 estrogen users versus 27.1% among the 897 nonusers of estrogen;

supplemental estrogen was independently associated with improved survival.<sup>18</sup>

Contrasted with the experimental and epidemiological evidence suggesting benefit of estrogen is the complete absence of benefit of combination HRT with estrogen and progestins in clinical trials. However, there is an important change over time in the effects of HRT in these studies. The Heart and Estrogen/progestin Replacement Study (HERS)<sup>2</sup> showed an increase in events early, with little effect at 4 years. Similarly, the early increase in coronary events seen with the combination of estrogen plus progestin in the Women's Health Initiative (WHI) study was no longer significant after 4 years.<sup>48</sup> The Nurses' Health Study also showed an early increase in thrombotic events with HRT, followed by later reduction of vascular events.<sup>49</sup> This is consistent with an increase in coagulability with early thrombotic events and withdrawal of patients with hypercoagulable states. Given that the estrogen-alone arm of WHI is continuing, it seems possible that progestins rather than estrogen may be related to an increase in thrombotic events. The greatest excess of events with HRT has been an excess of deep vein thrombosis. It seems likely that the higher incidence of thrombotic events early in a small proportion of patients in the WHI estrogen-progestin study may have been related to factor V Leiden, a coagulation disorder that is aggravated by estrogen/progesterone therapy<sup>50,51</sup> and that is present in approximately 5% to 10% of women.

## Conclusions

Carotid plaque area and stenosis differed by sex; at any age men have more plaque, whereas women have more stenosis. We speculate that these differences may be related to effects of sex hormones on arterial remodeling.

Plaque area was a strong predictor of outcomes in both sexes, but stenosis measured by Doppler velocities was not. Further study of the biological bases for these differences would be of interest because such study could lead to improvements in therapy for prevention of stroke and other vascular events.

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