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Rate of Progression of Coronary Atherosclerotic Plaque in Women

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Objectives The purpose of this study was to determine the relationship between gender and the extent of coronary atherosclerosis assessed by intravascular ultrasound (IVUS) and its rate of progression in subjects treated with established medical therapies.

Background It is uncertain whether the pathophysiology of coronary artery disease (CAD) differs between genders.

Methods A systematic analysis was performed of 978 subjects who participated in serial studies of atheroma progression. Genders were compared with regard to the extent of coronary atheroma at baseline and subsequent change in response to use of established medical therapies.

Results Women were more likely to have a history of hypertension and higher levels of body mass index, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, C-reactive protein, and systolic and diastolic blood pressure. Despite this, women had less plaque in terms of percent atheroma volume (PAV) (33.9 ± 10.2% vs. 37.8 ± 10.3%, $p < 0.001$) and total atheroma volume (TAV) (148.7 ± 66.6 mm^3 vs. 194.7 ± 84.3 mm^3, $p < 0.001$). With medical therapy, the rate of change of PAV (0.7 ± 0.6% vs. 0.7 ± 0.5%, $p = 0.92$) and TAV (−2.3 ± 3.2 mm^3 vs. −1.9 ± 2.9 mm^3, $p = 0.84$) did not differ between genders. In the setting of intensive risk factor modification, there was no significant difference between genders with regard to the rates of plaque progression or regression.

Conclusions Despite the presence of more risk factors, the extent of atheroma in women with angiographic CAD is less than in men in subjects participating in clinical trials that employed serial assessments with IVUS. The finding that the rate of plaque progression or regression does not differ between genders in the setting of intensive risk factor modification supports the use of established medical therapies in women with CAD. (J Am Coll Cardiol 2007; 49:1546–51) © 2007 by the American College of Cardiology Foundation

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A suboptimal degree of attention has focused on the detection and management of coronary artery disease (CAD) in women until recently. Although many women do not perceive heart disease as a significant health risk, CAD is the leading cause of mortality of women in most developed nations (1–3). It remains uncertain whether the pathophysiology of CAD differs in women (4). Although women have a lower prevalence of obstructive disease (5–8), they tend to experience a higher frequency of chest pain (9–11). Their outcome after a clinical event tends to be worse (6,12–14), a discrepancy that is accentuated with age, owing to greater prevalence of comorbidities (15). Women are typically under-represented in clinical trials and are less likely to be investigated and receive established therapies in the setting of acute coronary syndromes (11,16–19).

Although women have less obstructive disease on angiography, it remains to be determined whether their absolute burden of atherosclerotic plaque differs from men. A number of imaging modalities have demonstrated gender differences with regard to the extent of surrogate markers of plaque burden (20–26). Intravascular ultrasound (IVUS), which precisely quantifies atheroma burden, has enhanced our understanding of the factors that influence the natural history of atherosclerosis and its response to the use of medical therapies that modify established risk factors. The purpose of this study is to determine whether the burden of atherosclerosis and associated pattern of arterial remodeling is influenced by gender in a cohort of subjects with angiographic CAD and whether

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gender influences the effect of anti-atherosclerotic therapies on the rate of plaque progression.

Methods

Selection of subjects. All subjects who participated in serial IVUS studies of coronary plaque progression (REVERSAL [Reversing Atherosclerosis With Aggressive Lipid Lowering (27)], CAMELOT [Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis (28)], and ACTIVATE [ACAT Intravascular Atherosclerosis Treatment Evaluation (29)]) were included in the current analysis. Gender was incorporated into the matching process for randomization to treatment groups in each of these studies. The subjects therefore represented a cohort with established CAD receiving best medical therapy. Because the active treatment in ACTIVATE was associated with a potentially detrimental effect on plaque progression, these subjects were excluded from analysis. The IVUS images were acquired with a standardized methodology and analyzed by the IVUS core laboratory at the Cleveland Clinic Foundation. The inclusion criteria for these studies have been described in detail previously. Subjects were ages 30 to 75 years and had angiographic CAD comprising at least 1 stenosis of a major epicardial coronary artery >20%. A segment containing no stenosis >50% for at least 30 mm in a vessel that had not undergone percutaneous intervention was studied. Biochemical analysis was performed in a central laboratory (Medical Research Laboratory, Highland Heights, Kentucky).

Acquisition and analysis of IVUS images. The details of IVUS acquisition and analysis have been described in detail previously (27–29). The IVUS catheter was advanced after the administration of intracoronary nitroglycerin to position the transducer distal to a side branch. Images were obtained during catheter pullback by an automatic pullback device at a rate of 0.5 mm/s and recorded on videotape at 30 frames/s. Observers, blinded to the experimental details, analyzed cross-sectional images, spaced 1 mm apart in the pullback from a distal to proximal fiduciary site, defined by the presence of arterial side branches. The leading edges of the lumen and external elastic membrane (EEM) were traced by manual planimetry with the National Institutes of Health Image (version 1.62, National Institutes of Health public domain software, Bethesda, Maryland).

Total atheroma volume (TAV) was determined by summation of the plaque area, defined as the difference between EEM and lumen area, for all evaluable images (30).

$$\text{TAV}\ (\text{mm}^3) = \sum (\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})$$

The TAV was subsequently normalized to the length corresponding to the median number of comparable slices for each treatment group in view of the variability in the length of pullback analyzed between subjects, because this is determined by the anatomic location of the side branches, which define the fiduciary points (30).

$$\text{TAV}_{\text{Norm}}\ (\text{mm}^3) = \frac{\sum (\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})}{\text{Number of slices in pullback}} \times \text{Median number of slices in study population}$$

The extent of atherosclerosis was also expressed as percent atheroma volume (PAV), calculated as the percentage of the sum of EEM areas occupied by TAV (30).

$$\text{PAV}\ (\%) = \frac{\sum (\text{EEM}_{\text{area}} - \text{Lumen}_{\text{area}})}{\sum (\text{EEM}_{\text{area}})} \times 100$$

The atheroma volume in the most and least diseased 10-mm segments was also determined by summating the plaque areas in the 10 consecutive images that contained the most and least amount of plaque, respectively.

Normalized volumes occupied by the EEM and lumen were calculated in a similar fashion as TAV. A remodeling index was also calculated at the individual slice that contained the greatest plaque area in each pullback. The index was determined as the ratio of the EEM area at the most diseased site compared with the EEM area at a reference point, defined as the slice within the proximal 10 mm that contained the lowest plaque area. Remodeling at that site was defined as constrictive (index <0.95) or expansive (index >1.05) (31).

Statistical analysis. Continuous variables are expressed as mean ± SD (median), and categorical variables are expressed as percentages. Results for C-reactive protein (CRP) are expressed as median (interquartile range). Estimates of atheroma burden at baseline and changes in plaque burden for women compared with men adjusting for covariates were examined with both a fixed- and random-effect model to account for the heterogeneity across trials. Adjusted changes are expressed as least square mean and SEM from the random-effects model (32) after controlling for factors related to plaque burden and progression (baseline atheroma burden, age, history of hypertension, history of diabetes, on-treatment low-density lipoprotein (LDL) cholesterol, on-treatment LDL cholesterol). This model also included investigating for a statistical interaction between genders with regard to the relationship between the change in PAV and changes in LDL cholesterol, systolic blood pressure, or CRP. A p value <0.05 was considered significant. All statistical analyses were performed with SAS software (version 8.0, SAS Institute, Cary, North Carolina).

Clinical characteristics. Clinical characteristics of subjects participating in clinical trials that employed serial assessments by IVUS at baseline are summarized in Table 1. In this study women were less likely to be Caucasian (83.9% vs. 92.4%, p = 0.001), had a higher body mass index (31.7 ±

Abbreviations and Acronyms

- **CAD** = coronary artery disease
- **CRP** = C-reactive protein
- **EEM** = external elastic membrane
- **HDL** = high-density lipoprotein
- **IVUS** = intravascular ultrasound
- **LDL** = low-density lipoprotein
- **PAV** = percent atheroma volume
- **TAV** = total atheroma volume

6.8 kg/m^2 vs. 29.9 ± 5.2 kg/m^2, p < 0.001), lower body surface area (1.88 ± 0.20 m^2 vs. 2.10 ± 0.19 m^2, p < 0.001), and more likely to have history of hypertension (80.5% vs. 63.4%, p < 0.001). Women were older (58.0 ± 9.0 years vs. 56.8 ± 9.9 years, p = 0.09) and more likely to have diabetes (23.1% vs. 18.0%, p = 0.08), although these failed to meet statistical significance. There were no differences between genders with regard to use of established antiatherosclerotic therapies at baseline. Female subjects also had higher baseline levels of total cholesterol (221.3 ± 47.0 mg/dl vs. 199.1 ± 43.8 mg/dl, p < 0.001), LDL cholesterol (133.8 ± 41.5 mg/dl vs. 123.3 ± 37.9 mg/dl, p = 0.001), HDL cholesterol (48.7 ± 13.2 mg/dl vs. 39.5 ± 9.2 mg/dl, p < 0.001), triglycerides (195.9 ± 96.6 mg/dl vs. 184.9 ± 107.5 mg/dl, p = 0.02), systolic blood pressure (133.9 ± 17.7 mm Hg vs. 130.9 ± 16.4 mm Hg, p = 0.015), and CRP (4.8 mg/l vs. 2.6 mg/l, p < 0.001).

Baseline atheroma burden. The influence of gender on the extent of atheroma at baseline is summarized in Table 1. Women had less atheromatous plaque, reflected by a lower PAV (33.9 ± 10.2% vs. 37.8 ± 10.3%, p < 0.001), TAV (148.7 ± 66.6 mm^3 vs. 194.7 ± 84.3 mm^3, p < 0.001), and percentage of images that contained plaque (71.2 ± 29.3% vs. 83.2 ± 23.2%, p < 0.001). Percent atheroma volume (33.0 ± 2.1% vs. 37.9 ± 2.0%, p < 0.0001) and TAV (153.2 ± 9.7 mm^3 vs. 189.9 ± 8.6 mm^3, p < 0.0001) remained lower after adjustment in a multivariate model that included differences between genders in terms of body surface area, race, risk factors, and medication use.

Baseline arterial wall remodeling. There was no difference between genders with regard to arterial remodeling at the site that contained the greatest amount of plaque (0.96 ± 0.22 vs. 0.95 ± 0.21, p = 0.59). Women were just as likely to undergo constrictive remodeling (remodeling index <0.95, 46.3% vs. 48.7%, p = 0.53) and expansive remodeling (remodeling index >1.05, 28.9% vs. 28.0%, p = 0.79) at the most diseased site. Women had smaller vessels, demonstrated by a lower EEM volume (435.4 ± 133.8 mm^3 vs. 512.4 ± 163.9 mm^3, p < 0.001) and lumen volume (276.8 ± 93.0 mm^3 vs. 301.7 ± 108.1 mm^3, p = 0.002) (Table 2).

Effect of risk factor modification on plaque progression. The use of antiatherosclerotic therapies and degree of risk factor control on therapy are summarized in Table 3. On therapy, women had higher levels of total cholesterol (178.5 ± 33.8 mg/dl vs. 167.7 ± 33.7 mg/dl, p < 0.001), HDL cholesterol (49.8 ± 12.3 mg/dl vs. 41.5 ± 9.7 mg/dl, p < 0.001), systolic blood pressure (131.9 ± 13.0 mm Hg vs. 129.1 ± 12.8 mm Hg, p = 0.003), and CRP (4.0 mg/l

Table 1 Clinical Characteristics and Atheroma Burden of Subjects at Baseline Stratified According to Gender

Parameter	Female (n = 251)	Male (n = 727)	p Value
Age (yrs)	58.0 ± 9.0 (57)	56.8 ± 9.9 (56)	0.09
Caucasian (%)	83.9	92.4	0.001
Body mass index (kg/m^2)	31.7 ± 6.8 (30.5)	29.9 ± 5.2 (29.0)	<0.001
Body surface area (m^2)	1.88 ± 0.20 (1.85)	2.10 ± 0.19 (2.10)	<0.001
Hypertension (%)	80.5	63.4	<0.001
Diabetes (%)	23.1	18.0	0.08
Metabolic syndrome (%)	37.5	34.9	0.47
Dyslipidemia (%)	94.0	93.7	0.84
Smoker (%)	26.3	23.5	0.38
Previous MI (%)	30.7	36.2	0.12
Previous CABG (%)	6.0	3.6	0.10
Previous PCI (%)	58.2	62.9	0.18
Statin use (%)	40.6	44.4	0.30
Beta-blocker use (%)	71.3	70.3	0.76
Aspirin use (%)	91.2	91.2	0.99
ACE inhibitor use (%)	33.5	34.0	0.88
Total cholesterol (mg/dl)	221.3 ± 47.0 (220.1)	199.1 ± 43.8 (202)	<0.001
LDL cholesterol (mg/dl)	133.8 ± 41.5 (137)	123.3 ± 37.9 (127.4)	0.001
HDL cholesterol (mg/dl)	48.7 ± 13.2 (46.3)	39.5 ± 9.2 (38.6)	<0.001
Triglycerides (mg/dl)	195.9 ± 96.6 (180)	184.9 ± 107.5 (158)	0.02
Systolic blood pressure (mm Hg)	133.9 ± 17.7 (132)	130.9 ± 16.4 (129.3)	0.015
Diastolic blood pressure (mm Hg)	77.1 ± 9.8 (79)	78.2 ± 9.8 (79)	0.12
C-reactive protein (mg/l)	4.8 (2.0, 7.8)	2.6 (1.1, 5.4)	<0.001
Percent atheroma volume (%)	33.9 ± 10.2 (33.3)	37.8 ± 10.3 (37.4)	<0.001
Total atheroma volume (mm^3)*	148.7 ± 66.6 (139.5)	194.7 ± 84.3 (183.7)	<0.001
Percent abnormal images (%)†	71.2 ± 29.3 (81)	83.2 ± 23.2 (94.7)	<0.001

Continuous variables are expressed as mean ± SD (median) and categorical variables as percentages. C-reactive protein result expressed as median (interquartile range). *Total atheroma volume is normalized to account for heterogeneity of segment length between subjects. †Abnormal image defined as having a maximal plaque thickness >0.5 mm.

ACE = angiotensin-converting enzyme; CABG = coronary artery bypass graft; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Table 2 Baseline Remodeling of Subjects at Baseline Stratified According to Gender

Parameter	Female (n = 251)	Male (n = 727)	p Value
Remodeling index	0.96 ± 0.22 (0.96)	0.95 ± 0.21 (0.95)	0.59
EEM volume (mm^3)	435.4 ± 133.8 (421.1)	512.4 ± 163.9 (488.8)	<0.001
Lumen volume (mm^3)	276.8 ± 93.0 (260.4)	301.7 ± 108.1 (284.6)	0.002

Results are expressed as mean ± SD (median). Remodeling index calculated as the ratio of the external elastic membrane (EEM) area at the site containing the greatest plaque area to the EEM area at a reference site containing the least amount of plaque within the proximal 10 mm.

vs. 2.0 mg/l, $p < 0.001$). In addition, women had a lower diastolic blood pressure (76.1 ± 6.6 mm Hg vs. 77.3 ± 7.2 mm Hg, $p = 0.047$). The influence of gender on the rate of progression of atherosclerotic plaque and remodeling is summarized in Table 4. When adjusted for differences between genders that might influence plaque progression there remained no difference between genders with regard to the change in PAV (0.7 ± 0.6% vs. 0.7 ± 0.5% in women and men, respectively, $p = 0.92$) and TAV (−2.3 ± 3.2 mm^3 vs. −1.9 ± 2.9 mm^3 in women and men, respectively, $p = 0.84$), when controlling for clinical trial. Women were no more likely to undergo substantial progression (defined as at least a 5% increase in PAV, relative risk [RR] 1.04 [95% confidence interval (CI) 0.88 to 1.23], $p = 0.62$) or substantial regression (defined as at least a 5% increase in PAV, RR 1.02 [95% CI 0.77 to 1.34], $p = 0.89$) throughout the pullback.

Intensive risk factor modification and plaque progression. The effect of intensive pharmacological modification of a number of risk factors on plaque progression is summarized in Figure 1. Female subjects were just as likely as male subjects to undergo substantial regression (defined as >5% reduction in PAV compared with baseline) in the event that LDL cholesterol was lowered below 80 mg/dl (26.0% vs. 25.0%, $p = 0.86$), systolic blood pressure below 120 mm Hg (20.4% vs. 21.9%, $p = 0.81$), and CRP below 2 mg/l (19.2% vs. 22.1%, $p = 0.58$). There was no statistical interaction between gender and the relationship between changes in PAV and either LDL cholesterol ($p = 0.97$), systolic blood pressure ($p = 0.56$), or CRP ($p = 0.92$).

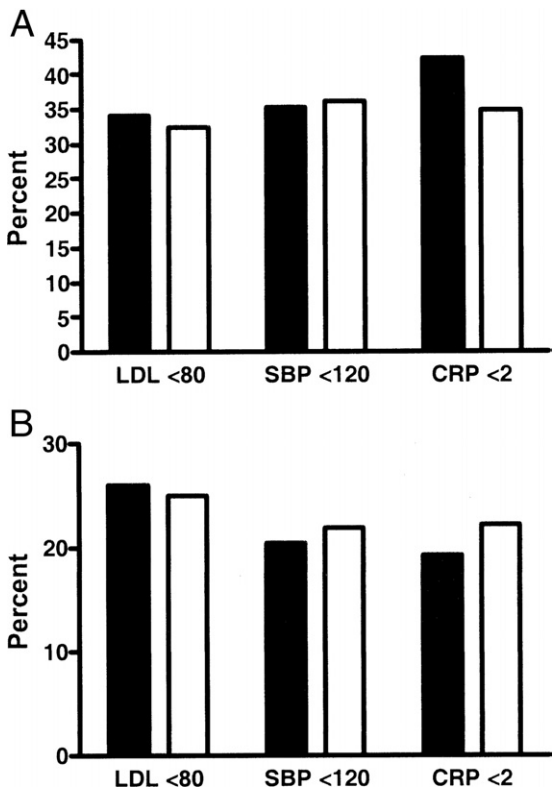

Figure 1 Rate of Progression and Regression With Intensive Risk Factor Modification

Percentage of female **(solid squares)** and male **(open squares)** subjects who underwent plaque progression **(A)** or regression **(B)** with intensive modification of a number of risk factors resulting in low-density lipoprotein (LDL) <80 mg/dl, systolic blood pressure (SBP) <120 mm Hg, or C-reactive protein (CRP) <2 mg/l.

Table 3 Use of Established Medical Therapies and Degree of Risk Factor Control of Subjects Stratified According to Gender

Parameter	Female (n = 251)	Male (n = 727)	p Value
Therapy			
Statin (%)	97.2	95.9	0.27
Beta-blocker (%)	77.7	76.0	0.52
Aspirin (%)	91.2	96.3	0.0002
ACE inhibitor (%)	38.8	41.3	0.41
On-treatment parameters			
Total cholesterol (mg/dl)	178.5 ± 33.8 (176.8)	167.7 ± 33.7 (165)	<0.001
LDL cholesterol (mg/dl)	95 ± 28.8 (93)	93.3 ± 27.5 (91.7)	0.39
HDL cholesterol (mg/dl)	49.8 ± 12.3 (47.8)	41.5 ± 9.7 (40.5)	<0.001
Triglycerides (mg/dl)	171 ± 98.2 (151.3)	166.6 ± 98.8 (141.6)	0.17
Systolic blood pressure (mm Hg)	131.9 ± 13 (131)	129.1 ± 12.8 (128)	0.003
Diastolic blood pressure (mm Hg)	76.1 ± 6.6 (76)	77.3 ± 7.2 (77)	0.047
C-reactive protein (mg/l)	4.0 (1.0, 7.0)	2.0 (1.0, 5.0)	<0.001

Results are expressed as mean ± SD (median) and categorical variables as percentages. C-reactive protein result expressed as median (interquartile range). Abbreviations as in Table 1.

Table 4 Serial Changes in Atheroma Burden and Remodeling of Subjects in Response to a High Use of Established Medical Therapies Stratified According to Gender

Parameter	Female (n = 251)	Male (n = 727)	p Value
Percent atheroma volume (%)	1.20 ± 4.56 (0.57)	0.87 ± 4.06 (0.68)	0.28
Adjusted percent atheroma volume (%)*	0.55 ± 0.28	0.86 ± 0.16	0.35
Total atheroma volume (mm^3)	2.04 ± 25.1 (0.60)	−0.05 ± 26.8 (−1.14)	0.28
Adjusted total atheroma volume (mm^3)*	−2.49 ± 1.81	−0.45 ± 1.02	0.33
Atheroma volume worst 10 mm (mm^3)	−1.10 ± 10.8 (−0.72)	−2.02 ± 11.9 (−2.07)	0.29
Atheroma volume best 10 mm (mm^3)	2.26 ± 8.0 (1.25)	1.64 ± 9.4 (1.0)	0.36
Remodeling index	−0.03 ± 0.17 (−0.03)	−0.03 ± 0.15 (−0.03)	0.88

Results are expressed as mean ± SD (median). *Adjusted changes in percent atheroma volume and total atheroma volume take into account differences in factors that influence plaque progression (baseline atheroma burden, age, history of hypertension, history of diabetes, on-treatment low-density lipoprotein cholesterol, on-treatment high-density lipoprotein cholesterol, and study) expressed as least-squares mean ± SEM.

Discussion

The current findings provide important insights into our understanding of the impact of gender on the natural history of atherosclerosis. The results demonstrate that despite the greater prevalence of risk factors, women contain less atherosclerotic plaque within their coronary arteries. Further, with the use of established medical therapies, women derive a similar benefit on plaque progression from intensive risk factor modification.

These results have implications for the elucidation of the factors that influence cardiovascular disease in women. It remains to be established whether there are any gender-specific differences in the pathophysiology of atherosclerosis. The traditional view has proposed that clinical events typically begin later in life in women, which is attributed to the protective influence of endogenous estrogen. However, a number of studies that have employed either direct measures or surrogate markers have demonstrated the presence of coronary atherosclerosis in many premenopausal women (20–26). In the current study of subjects with angiographically evident CAD, women harbored less coronary atheroma. It remains to be determined whether the relative contribution of plaque extent and activity to the incidence of clinical events differs between genders.

The current finding suggests that the relationship between the risk factor profile and plaque burden might differ between genders. Given that the correlation between individual risk factors and the extent of coronary atheroma is not strong (33), it is likely that a cluster of risk factors is more important. Despite the greater prevalence of established risk factors, women harbored less plaque. This raises the possibility that the potential atherogenicity of specific risk factors or their clusters differs between genders. It is unlikely that substantial differences in arterial remodeling contributed to the difference in amount of atheroma. Despite the finding that vessel size was predictably smaller in women, PAV, which expresses plaque burden as a proportion of vessel size, remained smaller. Furthermore, the pattern of arterial remodeling at the site that contained the greatest amount of plaque did not differ between genders.

This study also demonstrated that women are likely to derive similar benefit from the use of medical therapies that result in intensive risk factor modification. Women are less likely to seek medical attention and to receive established therapies in the settings of acute coronary syndromes (11,16–19). The current finding that women receive the same benefit of intensive risk factor modification on plaque progression supports the recently reported evidence-based guidelines for cardiovascular disease prevention in women by the American Heart Association (11).

A number of important caveats should be noted. The current analysis is derived from a post hoc study of 3 separate clinical trials in combination. However, every IVUS pullback was analyzed in the same core laboratory with a standardized protocol. All subjects, by definition, had angiographic CAD. Although the current findings relate to the use of medical therapies for secondary prevention, there is no evidence to support a restriction of primary prevention strategies in women. Similarly, all subjects met the criteria and had consented to participate in a clinical trial. It is uncertain whether the same findings would be observed in the general population presenting for diagnostic angiography. Only 1 coronary artery was studied in each subject. It is possible that the extent of atheroma throughout the coronary tree is not uniform and that the extent of plaque demonstrated in an artery does not reflect the patient's plaque burden in general. It is also not known whether the rate of progression of atherosclerosis is linear or characterized by abrupt changes in atheroma burden. The requirement for an invasive procedure limits the number of times that IVUS can be performed. It would be of interest to perform future studies with evolving noninvasive imaging modalities such as computer tomography and magnetic resonance imaging. The studies are also susceptible to selection bias. It is possible that women required more risk factors to warrant an indication to proceed to coronary angiography. In addition, IVUS is limited in its ability to characterize plaque composition. As a result, it is not possible to determine whether gender influenced either the composition of plaque at baseline or its modification in response to established antiatherosclerotic therapies. The individual trials differed widely with regard to collection of data with regard to menopausal status, exogenous hormone use, or hormone levels. The potential influence of estrogen on the observed findings should also be considered and warrants further investigation. Similarly, it is uncertain

whether the genders differed with regard to the duration of use of established medical therapies before enrollment in the clinical trials.

In summary, the current study of patients with angiographic CAD demonstrated that women harbor less atherosclerotic plaque within their coronary arteries, despite the greater prevalence of atherogenic risk factors. Furthermore, intensive risk factor modification in response to the use of established medical therapies has a similar influence on plaque progression in both men and women. These results add further support for the promotion of aggressive preventive measures to prevent morbidity and mortality from atherosclerotic cardiovascular disease in women.

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