

Impact of Gender and Age on In Vivo Virtual Histology–Intravascular Ultrasound Imaging Plaque Characterization (from the global Virtual Histology Intravascular Ultrasound [VH-IVUS] Registry)

Jie Qian, MD^a, Akiko Maehara, MD^{a,*}, Gary S. Mintz, MD^a, M. Paulina Margolis, MD, PhD^b, Amir Lerman, MD^c, Jason Rogers, MD^d, Shuel Banai, MD^e, Samer Kazzuha, MD^f, Celia Castellanos, MD^a, Lokesh Dani, BS^a, Martin Fahy, MSc^a, Gregg W. Stone, MD^a, and Martin B. Leon, MD^a

Virtual histology intravascular ultrasound (VH-IVUS) analyses were performed in the first 990 patients enrolled in the 3,000+ patient global VH-IVUS Registry to assess the impact of gender and age on in vivo VH-IVUS plaque characterization. The 990 patients were divided into 3 age group terciles (<58, 58 to 68, and >68 years) and again divided according to gender. In conclusion, (1) both women and men had an increase in plaque with increasing age; (2) at any age, men had more plaque than women; (3) percentages of dense calcium and necrotic core increased with increasing patient age in both men and women; and (4) gender differences were lowest in the oldest tercile (>68 years). © 2009 Elsevier Inc. All rights reserved. (Am J Cardiol 2009;103:1210–1214)

Grey-scale intravascular ultrasound (IVUS) provided limited information regarding the components of atherosclerotic plaques.^{1–6} Virtual histology (VH) IVUS uses spectral analysis of radiofrequency ultrasound backscatter to characterize plaque as fibrous tissue, fibrofatty plaque, dense calcium, and a lipid-rich necrotic core with diagnostic accuracy of 93.4% for fibrous tissue, 94.6% for fibrofatty plaque, 95.1% for necrotic core, and 96.8% for dense calcium, with sensitivities and specificities ranging from 89% to 99%.⁷ Gender and age were well-established risk factors for coronary heart disease. Pathologic studies showed that plaque composition varied with patient age and was also different in men and women.^{8–11} In general, coronary plaques in women were more cellular than those in men, especially in the premenopausal years. Up to age 70 years, plaque burden and plaque calcium were also lower in women who died with severe coronary atherosclerosis, and plaques of premenopausal women showed relatively little necrotic core and calcification in comparison to both men and postmenopausal women, possibly reflecting the protective effect of estrogen. However, the impact of gender and age on in vivo plaque characterization has not been evalu-

ated. This study described the impact of age and gender on plaque composition assessed using VH-IVUS.

Methods

From August 2004 to July 2006, a total of 990 patients in 33 centers were enrolled in the prospective multicenter nonrandomized global VH-IVUS Registry. This represented the entire group of the first 990 patients studied. Patients >18 years old without contraindication to IVUS undergoing diagnostic or interventional coronary procedures were enrolled in this study. Other than age <18 years, there were no exclusion criteria. The ethics committee at each participating institution approved the protocol, and written informed consent was obtained from all patients.

Lipid disorder was defined as total cholesterol ≥ 200 mg/dl, low-density lipoprotein cholesterol ≥ 100 mg/dl, high-density lipoprotein cholesterol <50 mg/dl, triglycerides ≥ 150 mg/dl, or medication use. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg, or use of an antihypertensive drug. A positive family history was defined as documented myocardial infarction, angiographic documentation of coronary artery disease, angina pectoris, or sudden cardiac death in first- or second-degree relatives (parents, siblings, grandparents, or blood-related aunts and uncles) ≤ 55 years of age.

A phased-array 20-MHz IVUS catheter (Eagle Eye; Volcano Corp., Rancho Cordova, California) was placed distally in the vessel, and motorized catheter pullback to the aorta was performed at 0.5 mm/s. Only nonintervened segments (or preintervention) were analyzed. Average length of nonintervened arteries imaged was 4.9 cm. If multiple pullbacks were performed, only the first was analyzed, and if multiple arteries were imaged, the culprit-containing ar-

^aCardiovascular Research Foundation and Columbia University Medical Center, New York, New York; ^bVolcano Corporation, Rancho Cordova, California; ^cMayo Clinic, Rochester, Minnesota; ^dUniversity of California, Sacramento, California; ^eTel Aviv Medical Center, Tel Aviv, Israel; ^fMount Clemens Regional Medical Center, Mt Clemens, Michigan. Manuscript received December 26, 2008; revised manuscript received and accepted January 13, 2009.

Drs. Mintz, Leon, Rogers, and Stone are consultants of Volcano Corp., and Dr. Margolis is an employee of Volcano Corp.

*Corresponding author: Tel: 212-851-9371; fax: 212-851-9230.

E-mail address: amaehara@crf.org (A. Maehara).

Table 1
Baseline patient and lesion characteristics (n = 990)

Variable	
Age (yrs)	62 ± 11
Men	61 ± 11
Women	66 ± 11
Men	747 (75.5%)
Hypertension	629 (63.5%)
Hyperlipidemia	645 (65.2%)
Diabetes mellitus	214 (21.6%)
Current smoking	255 (25.8%)
Family history of coronary heart disease	427 (43.1%)
Previous myocardial infarction	272 (27.5%)
Previous bypass surgery	61 (6.2%)
Heart failure	65 (6.6%)
Acute coronary syndrome	402 (40.6%)
Unstable angina pectoris	215 (21.7%)
Non-Q-wave myocardial infarction	106 (10.7%)
Acute myocardial infarction	81 (8.2%)
Target coronary vessel	
Left main	31 (3.1%)
Right	288 (29.1%)
Left anterior descending	483 (48.8%)
Left circumflex	172 (17.4%)
Other	16 (1.6%)

tery was analyzed. During pullback, continuous grey-scale IVUS was recorded. Radiofrequency data were captured at the top of the R wave using a commercially available system (In-Vision Gold; Volcano Corp.). Off-line volumetric reconstruction of the entire imaged segment was performed using pcVH 2.1 software (Volcano Corp.). Grey-scale measurements included external elastic membrane, plaque and media (P&M), and lumen cross-sectional areas (CSAs). VH-IVUS measurements included absolute and relative amounts of fibrous tissue, fibrofatty plaque, dense calcium, and necrotic core.

Statistical analysis was performed using SPSS, version 13.0 (SPSS Inc., Chicago, Illinois). Continuous data were reported as mean ± 1 SD. Independent 2-sample *t*-test or 1-way analysis of variance (ANOVA) with post hoc Student-Newman-Keuls test was used to test differences between ≥2 sets of data. The proportion of each plaque type was expressed as mean percentage and compared between men and women using multivariate ANOVA. A probability value <0.05 was considered statistically significant.

Results

A total of 747 men (75.5%) and 243 women (24.5%) were included in this analysis (Table 1). The 990 patients were divided into 3 age-group terciles (<58, 58 to 68, and >68 years) and subdivided according to gender, resulting in 6 subgroups.

With increasing patient age, women (who were overall older than men) showed significant increases in mean P&M CSA, especially in the oldest tercile (Figure 1). However, the relation between P&M CSA and age was not seen in men, although for each age tercile, men had more plaque compared with women. Conversely, when we analyzed plaque burden (P&M/external elastic membrane CSA, which normal-

ized plaque for vessel area), men showed a significant increase in plaque burden with increasing patient age (pANOVA = 0.0015), whereas a similar comparison in women did not reach significance (pANOVA = 0.18).

The predominant plaque component for all patients was fibrous tissue, followed by fibrofatty plaque, necrotic core, and dense calcium (Table 2). Overall, the proportion of each of these 4 plaque components was significantly different between men and women (p < 0.0001; Figure 2). Within the age and gender subgroups, mean percentages of dense calcium and necrotic core increased with increasing patient age in both men and women. Conversely, mean percentage of fibrous tissue plaque decreased significantly with increasing patient age in men, but not women. Finally, there was a significant age-related difference in mean percentage of fibrous tissue in women, but not men (Figure 3).

Discussion

In the present study, plaque areas increased with increasing patient age in women, but not men. However, when we compared plaque burden (plaque area normalized for vessel area), plaque burden increased with increasing patient age in men, but not in women statistically. Overall, we may summarize that (1) depending on the variable used, both women and men had an increase in plaque with increasing age; (2) at any age, men had more plaque than women; and (3) gender differences were lowest in the oldest tercile. This was consistent with data from Olmsted County indicating that although the prevalence of significant coronary atherosclerosis at postmortem examination was high in both genders, it was higher in men compared with women, with narrowing of the gender gap with increasing age of the decedents. In persons >60 years at death, the prevalence of coronary atherosclerosis was 70% in men compared with 56% in women.¹² One epidemiologic study showed that women developed clinical coronary atherosclerosis approximately 10 years later than men and had their first myocardial infarction 20 years later.^{13,14} Finally, before menopause, women had the protective effect of estrogen; but after menopause, atherosclerotic progression accelerated and caught up to men.

The second finding of this study was that in both men and women, dense calcium increased with increasing patient age, but the gender gap in coronary calcium narrowed with increasing patient age. One autopsy study of patients with severe coronary disease showed that radiographic coronary calcification was present in 46% of men and women aged <40 years, 79% of men and women aged 40 to 49, 90% of men and women aged 50 to 60, and 100% of men and women >60. Another pathologic study also showed more calcified atherosclerosis in older patients.^{15,16} Calcification in women showed a 10-year lag compared with men, with equalization by the eighth decade.

The third finding of this study was that in both men and women, necrotic core increased with increasing patient age, with a gender gap in only the middle and oldest age groups. Necrotic core was present in approximately 25% of plaques with <50% plaque burden, and this frequency increased with increasing disease severity. Higher than the 70% plaque bur-

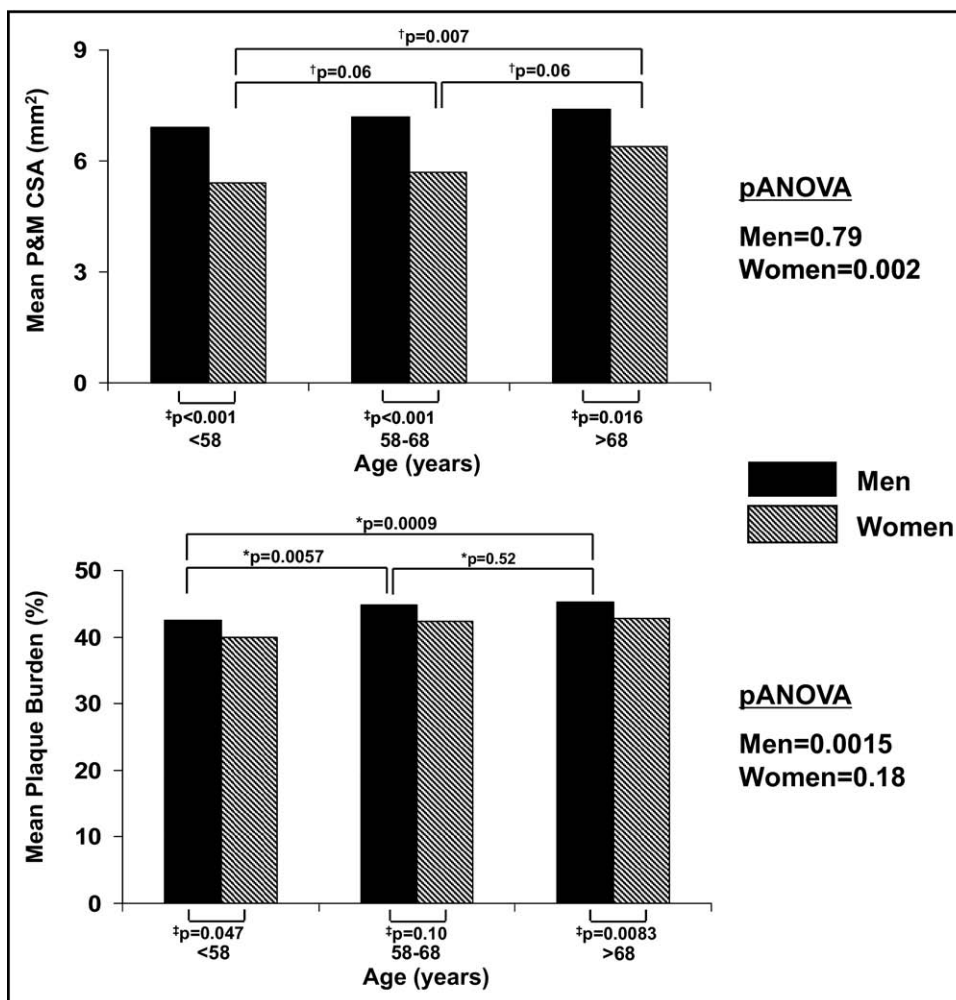


Figure 1. P&M CSAs increased significantly in the 3 age subgroups in women (pANOVA = 0.002), but not men (pANOVA = 0.79). Plaque burden (P&M/external elastic membrane CSA) increased significantly in the 3 age subgroups in men (pANOVA = 0.0015), but not women (pANOVA = 0.18). However, within each age subgroup, men still had a larger P&M CSA than women. *One-way ANOVA test post hoc SNK result for men. †One-way ANOVA test post hoc SNK result for women. ‡Independent 2-sample *t* test.

Table 2

Proportions of the four virtual histology intravascular ultrasound plaque components according to age and gender

Variable	Age Group (yrs)					
	Men (n = 747)			Women (n = 243)		
	<58 (n = 284)	58–68 (n = 246)	>68 (n = 217)	<58 (n = 61)	58–68 (n = 67)	>68 (n = 115)
Dense calcium (%)	7 ± 6	8 ± 6	9 ± 7	7 ± 7	11 ± 9	12 ± 9
Necrotic core (%)	11 ± 7	12 ± 6	12 ± 7	12 ± 10	14 ± 7	15 ± 7
Fibrofatty plaque (%)	20 ± 10	20 ± 9	20 ± 9	21 ± 14	16 ± 9	17 ± 9
Fibrous tissue (%)	62 ± 8	60 ± 7	59 ± 9	60 ± 13	59 ± 11	56 ± 9

Values expressed as mean ± 1 SD.

den, approximately 75% of plaques showed a necrotic core.¹⁷ One autopsy study of patients who died suddenly of severe coronary disease showed a smaller proportion of plaques with necrotic cores in younger compared with older women.¹¹ Two

other autopsy studies showed that men had more necrotic cores than women, especially in comparison to premenopausal women, presumably reflecting the protective effects of estrogen on the formation of large necrotic cores in premenopausal

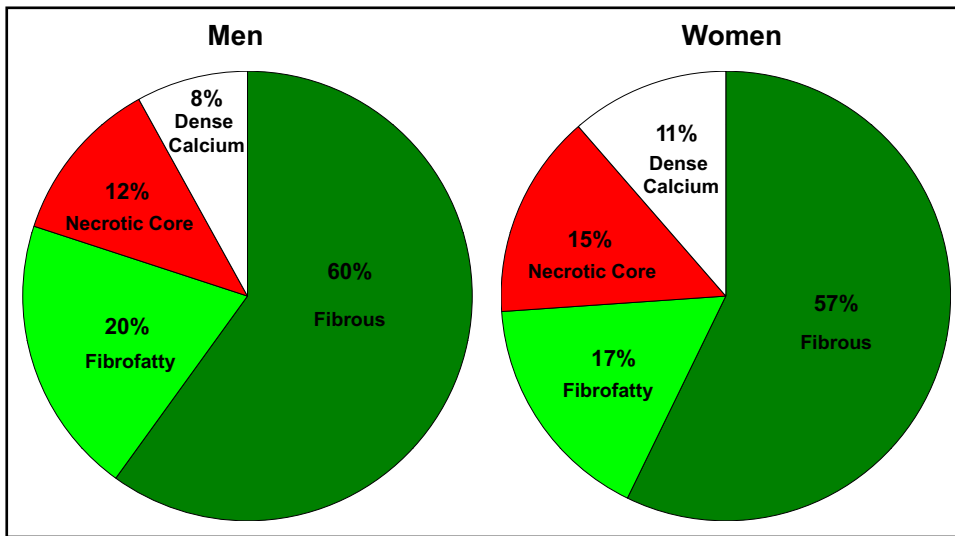


Figure 2. The proportion of relative amounts of the 4 VH-IVUS plaque types in men and women, shown using mean percentages.

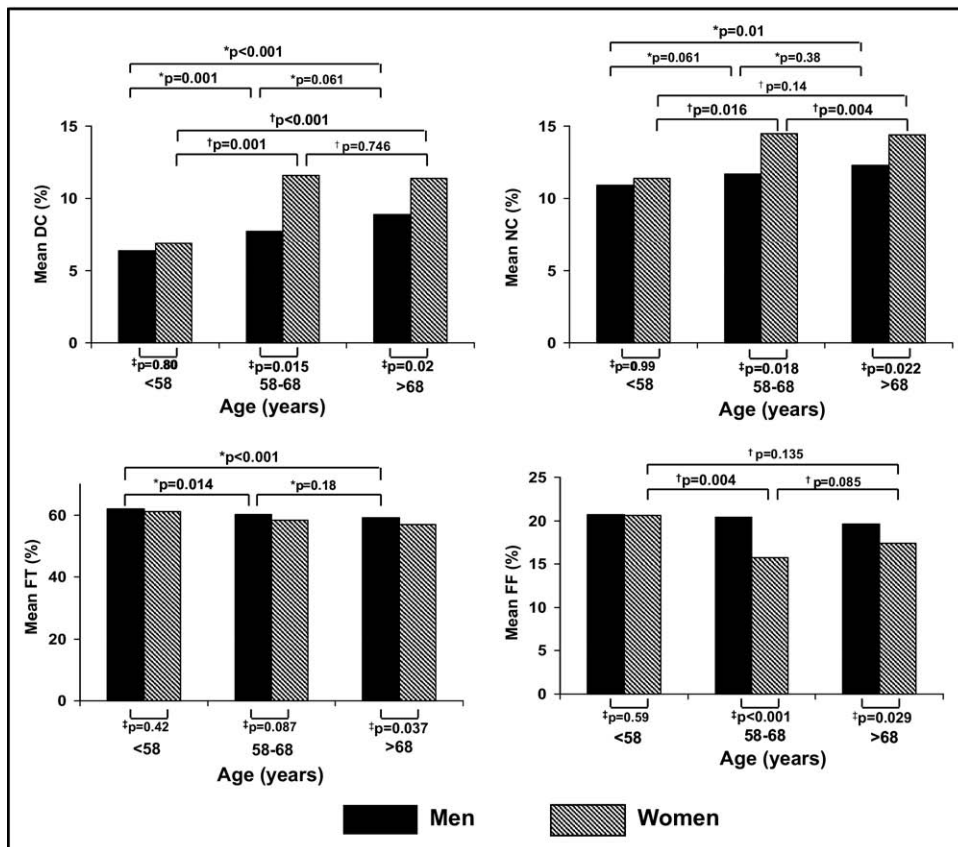


Figure 3. In both men and women, increasingly older age subgroups showed significant increases in percentages of dense calcium (DC; $pANOVA < 0.0001$ for both genders) and necrotic core (NC; $pANOVA = 0.027$ for men and 0.012 for women). However, the difference between men and women with regard to percentages of DC and NC was seen in the only middle and oldest age tertiles. Conversely, there were age-related decreases in percentage of fibrous tissue (FT) in men ($pANOVA = 0.001$) and a trend in women ($pANOVA = 0.084$), whereas there were age-related changes in the percentage of fibrofatty plaque (FF) in women ($pANOVA = 0.016$), but not men ($pANOVA = 0.42$). *One-way ANOVA test post hoc SNK result of men. †One-way ANOVA test post hoc SNK result of women. ‡Independent 2-sample t test.

women.^{9,10} Pathologic studies indicated that a large necrotic core was associated with plaque vulnerability and myocardial infarction.^{18,19} This was presumably reflected in an increasing annual coronary event rate with increasing patient age, with the

difference between men and women decreasing with increasing patient age.²⁰

The present study had limitations. This was neither a whole-vessel nor lesion-specific analysis. Rather, it was

an analysis of the entire segment of vessel imaged using IVUS. The inclusion criteria were broad; culprit and nonculprit and treated and nontreated arteries were imaged.

1. Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, Santamore WP. Can coronary angiography predict the site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? *Circulation* 1988;78:1157-1166.
2. Ambrose JA, Tannenbaum MA, Alexopoulos D, Hjemdahl-Monsen CE, Leavy J, Weiss M, Borricco S, Gorlin R, Fuster V. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 1988;12:56-62.
3. Potkin BN, Bartorelli AL, Gessert JM, Neville RF, Almagor Y, Roberts WC, Leon MB. Coronary artery imaging with intravascular high-frequency ultrasound. *Circulation* 1990;81:1575-1585.
4. Peters RJ, Kok WE, Havenith MG, Rijsterborgh H, van der Wal AC, Visser CA. Histopathologic validation of intracoronary ultrasound imaging. *J Am Soc Echocardiogr* 1994;7:230-241.
5. Palmer ND, Northridge D, Lessells A, McDicken WN, Fox KA. In vitro analysis of coronary atheromatous lesions by intravascular ultrasound; reproducibility and histological correlation of lesion morphology. *Eur Heart J* 1999;20:1701-1706.
6. Rasheed Q, Dhawale PJ, Anderson J, Hodgson JM. Intracoronary ultrasound-defined plaque composition: computer-aided plaque characterization and correlation with histologic samples obtained during directional coronary atherectomy. *Am Heart J* 1995;129:631-637.
7. Nair A, Margolis MP, Kuban BD, Vince DG. Automated coronary plaque characterization with intravascular ultrasound backscatter: ex vivo validation. *Eurointervention* 2007;3:113-120.
8. Burke AP, Farb A, Malcom GT, Liang Y, Smialek J, Virmani R. Effect of risk factors on the mechanism of acute thrombosis and sudden coronary death in women. *Circulation* 1998;97:2110-2116.
9. Dollar AL, Kragel AH, Fericola DJ, Waclawiw MA, Roberts WC. Composition of atherosclerotic plaques in coronary arteries in women less than 40 years of age with fatal coronary artery disease and implications for plaque reversibility. *Am J Cardiol* 1991;67:1223-1227.
10. Mautner SL, Lin F, Mautner GC, Roberts WC. Comparison in women versus men of composition of atherosclerotic plaques in native coronary arteries and in saphenous veins used as aortocoronary conduits. *J Am Coll Cardiol* 1993;21:1312-1318.
11. Burke AP, Farb A, Malcom G, Virmani R. Effect of menopause on plaque morphologic characteristics in coronary atherosclerosis. *Am Heart J* 2001;141(suppl):S58-S62.
12. Roger VL, Weston S, Killian JM, Pfeifer EA, Belau PG, Kottke TE, Frye RL, Bailey KR, Jacobsen SJ. Time trends in the prevalence of atherosclerosis: a population-based autopsy study. *Am J Med* 2001; 110:267-273.
13. Wenger NK. The natural history of coronary artery disease in women. In: Charney P, ed. *Coronary Artery Disease in Women*. Philadelphia: American College of Physicians, 1999:3-35.
14. Charney P, Walsh JM, Nattinger AB. Update in women's health. *Ann Intern Med* 1998;129:551-558.
15. Burke AP, Weber DK, Kolodgie FD, Farb A, Taylor AJ, Virmani R. Pathophysiology of calcium deposition in coronary arteries. *Herz* 2001;26:239-244.
16. Mautner GC, Mautner SL, Froehlich J, Feuerstein IM, Proschan MA, Roberts WC, Doppman JL. Coronary artery calcification: assessment with electron beam CT and histomorphometric correlation. *Radiology* 1994;192:619-623.
17. Burke AP, Virmani R, Galis Z, Haudenschild CC, Muller JE. Task force #2—what is the pathologic basis for new atherosclerosis imaging techniques? *J Am Coll Cardiol* 2003;41:1874-1876.
18. Kragel AH, Reddy SG, Wittes JT, Roberts WC. Morphometric analysis of the composition of atherosclerotic plaques in the four major epicardial coronary arteries in acute myocardial infarction and in sudden coronary death. *Circulation* 1989;80:1747-1756.
19. Kragel AH, Reddy SG, Wittes JT, Roberts WC. Morphometric analysis of the composition of coronary arterial plaques in isolated unstable angina pectoris with pain at rest. *Am J Cardiol* 1990;66:562-567.
20. Stokes J 3rd, Kannel WB, Wolf PA, Cupples LA, D'Agostino RB. The relative importance of selected risk factors for various manifestations of cardiovascular disease among men and women from 35 to 64 years old: 30 years of follow-up in the Framingham Study. *Circulation* 1987;75:65-73.